KEY PATHWAY ADVISOR

Analysis report

DEXvsUNT_CE

29 NOV 2017

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CONTENTS

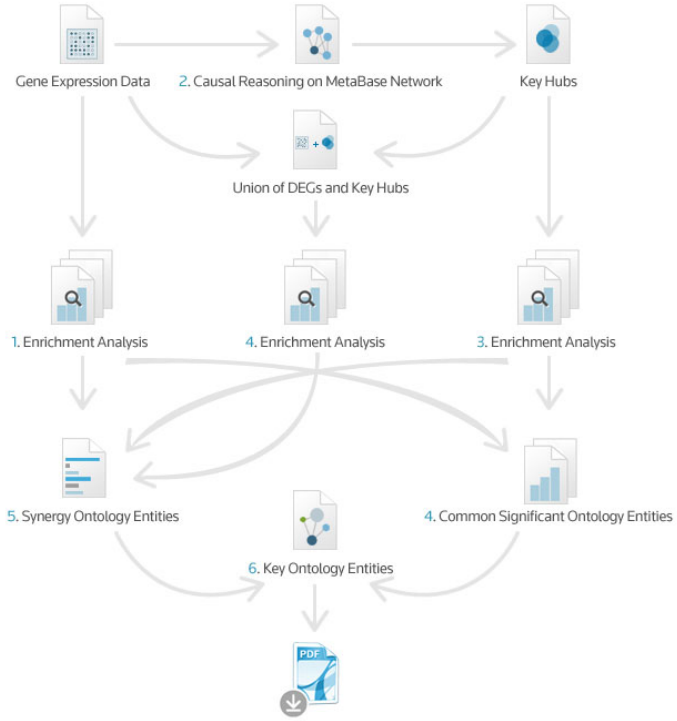
INTRODUCTION

In order to understand functional processes behind the differentially expressed gene (DEG) list, KPA represents comprehensive pathway analysis workflow.

The Causal Reasoning approach and Overconnectivity analysis help identify both key direct regulators (i.e. one step away) of the dataset and the major “master” regulators of the global protein network. Concurrent enrichment analysis of both differentially expressed genes and their ranked direct and indirect regulators (Key Hubs), allows one to reconstruct the mechanisms underlining differential gene expression more comprehensively.

We define “Key Ontology Processes” as ontology terms (i.e. pathway maps) enriched with both differentially expressed genes and corresponding Key Hubs. They are identified by the following workflow.

1. Enrichment analysis is performed for the list of differentially expressed genes. Statistically significant ontology processes (enrichment p-value < 0.05) for differentially expressed genes are identified.
2. Calculation of Key Hubs by either Causal Reasoning approach (if DEGs associated with expression values) or Overconnectivity analysis (if DEGs uploaded without expression values).
3. Enrichment analysis is performed for the corresponding list of Key Hubs. Statistically significant ontology processes (enrichment p-value < 0.05) for Key Hubs are identified.
4. Ontology processes statistically significant for both the list of differentially expressed genes and the list of corresponding Key Hubs are identified.
5. Ontology processes that display “synergistic” behaviour for the list of differentially expressed genes and the list of corresponding Key Hubs are defined (please see “Enrichment synergy” in Glossary). The final list of synergistic ontology processes includes all ontology terms with synergistic expression pattern for the union of DEGs and Key Hubs and p-value < 0.05.
6. The resulted list of key processes includes ontology terms which show significant enrichment for both lists and synergistic behaviour.



INPUT DATA AND SETTINGS

This section contains experiment file name and data format. Statistics section contains Ids that were in original file and how many of them were recognized by system and mapped on Molecular Entities. Analysis settings that were used for Key Hubs and Processes calculation steps are listed in the last section.

Analysis Overview	
Analysis Name	DEXvsUNT_CE
File Type	Gene Expression
File Content	Tag ID: Gene Symbol, Fold change
KPA Version	17.4

Statistics

IDs in File	374
Molecular Entities	459
Unrecognized IDs	17

Analysis Settings

Selected Processes Ontologies	Key Pathway Maps, Pathological Pathway Maps, Physiological Pathway Maps, Diseases, Process Networks, Pathway Groups
Key Processes p-value Threshold	0.05
Key Hubs Calculation Algorithm	Causal Reasoning Analysis
Key Hubs p-value Threshold	0.01

This report contains only top 100 key results for each ontology.

RESULTS

Key Pathway Maps

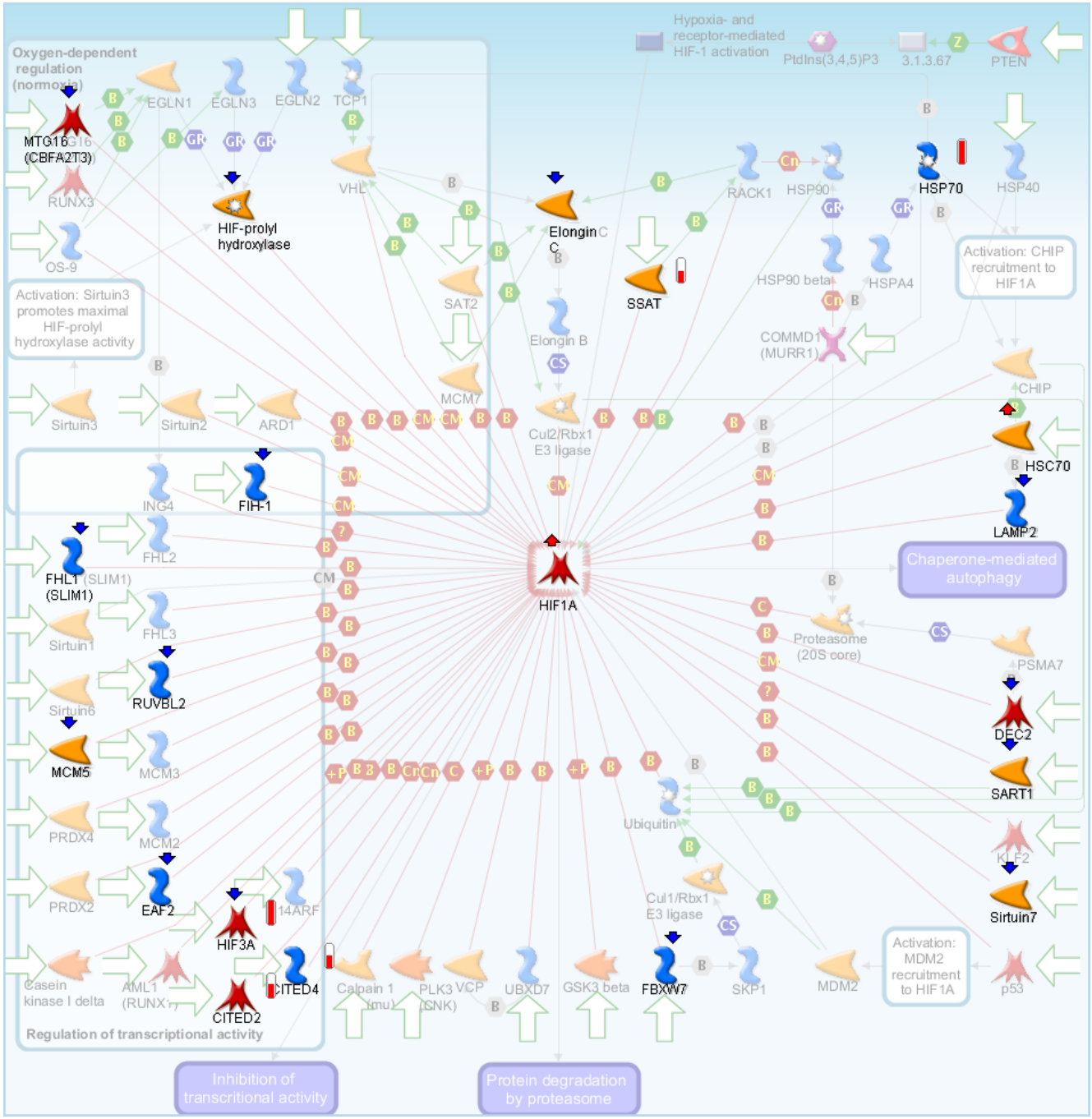
Pathway maps are graphic images representing complete biochemical pathways or signaling cascades in a commonly accepted sense. All maps listed below are enriched with both input genes and Key Hubs. The enrichment analysis was done for whole set of pathway maps including physiological and pathological processes.

Key Pathway Maps Details [45 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
1	Transcription_Negative regulation of HIF1A function	0.02617	2.712E-9	1.678E-9
2	Signal transduction_PTMs in IL-17-induced CIKS-independent signaling pathways	0.02285	4.514E-7	1.628E-7
3	Main growth factor signaling cascades in multiple myeloma cells	3.515E-4	5.439E-4	2.45E-7
4	Neurophysiological process_Receptor-mediated axon growth repulsion	8.741E-4	4.335E-5	3.035E-7
5	Role of alpha-6/beta-4 integrins in carcinoma progression	0.01957	2.475E-6	6.504E-7
6	Development_Transcription factors in segregation of hepatocytic lineage	0.006026	9.628E-5	7.014E-7
7	Putative pathways for stimulation of fat cell differentiation by Bisphenol A	0.006026	9.628E-5	7.014E-7
8	Transcription_HIF-1 targets	2.046E-5	5.085E-5	7.508E-7
9	Development_Insulin, IGF-1 and TNF-alpha in brown adipocyte differentiation	0.008241	1.591E-5	1.234E-6
10	Stimulation of TGF-beta signaling in lung cancer	9.817E-4	0.00172	2.709E-6
11	Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor	7.939E-4	4.707E-4	2.962E-6
12	Cell adhesion_Chemokines and adhesion	0.03143	1.247E-5	3.781E-6
13	Immune response_IL-7 signaling in T lymphocytes	0.01046	2.705E-4	4.057E-6
14	Development_Regulation of epithelial-to-mesenchymal transition (EMT)	0.004846	5.983E-4	4.536E-6
15	Oxidative stress_Role of Sirtuin1 and PGC1-alpha in activation of antioxidant defense system	0.002251	9.557E-4	1.785E-5
16	Development_YAP/TAZ-mediated co-regulation of transcription	4.242E-4	0.0181	2.198E-5
17	Development_Cytokine-mediated regulation of megakaryopoiesis	0.01214	2.142E-4	2.198E-5
18	Development_c-Kit ligand signaling pathway during hemopoiesis	0.014	5.145E-5	3.282E-5
19	Development_Beta adrenergic receptors in brown adipocyte differentiation	0.01155	3.252E-4	3.757E-5
20	Development_Alpha-1 adrenergic receptors signaling via Cyclic AMP	8.482E-4	0.02834	5.154E-5
21	Cell cycle_Role of Nek in cell cycle regulation	8.88E-4	0.02781	6.299E-5
22	Development_VEGF signaling and activation	0.01523	0.003093	7.968E-5
23	Translation_Non-genomic (rapid) action of Androgen Receptor	0.0166	0.003526	1.006E-4
24	Breast cancer (general schema)	0.003207	0.01806	1.259E-4

Key Pathway Maps Details [45 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
25	Development_IGF-1 receptor signaling	0.03244	0.002203	1.305E-4
26	Cell adhesion_Alpha-4 integrins in cell migration and adhesion	0.01046	0.001745	1.774E-4
27	Reproduction_Gonadotropin-releasing hormone (GnRH) signaling	0.001381	0.01357	1.867E-4
28	Development_Leptin signaling via PI3K-dependent pathway	0.02117	0.005097	1.929E-4
29	Immune response_Oncostatin M signaling via JAK-Stat	0.01626	0.008418	2.232E-4
30	Cell adhesion_ECM remodeling	0.03917	6.514E-4	2.292E-4
31	Development_WNT signaling pathway. Part 2	0.04158	0.003478	2.737E-4
32	Immune response_MIF-induced cell adhesion, migration and angiogenesis	0.02461	0.006396	2.877E-4
33	Development_Role of proteases in hematopoietic stem cell mobilization	0.009264	0.003964	4.813E-4
34	Cytoskeleton remodeling_Regulation of actin cytoskeleton organization by the kinase effectors of Rho GTPases	0.002705	0.01961	5.316E-4
35	Apoptosis and survival_NGF/ TrkA PI3K-mediated signaling	0.01108	0.007498	5.826E-4
36	Neurophysiological process_Circadian rhythm	0.02117	0.02183	9.18E-4
37	Influence of low doses of Arsenite on glucose uptake in adipocytes	0.03106	0.01975	0.001127
38	Immune response_IL-6-induced acute-phase response in hepatocytes	0.01155	0.00203	0.001164
39	High shear stress-induced platelet activation	0.004828	0.02608	0.001295
40	Transport_Macropinocytosis regulation by growth factors	0.015	0.02288	0.00264
41	Development_Role of CDK5 in neuronal development	0.008495	0.03412	0.003125
42	Role of Tissue factor in cancer independent of coagulation protease signaling	0.009445	0.03757	0.003734
43	Development_Role of G-CSF in hematopoietic stem cell mobilization	0.0143	0.04253	0.007306
44	Neurophysiological process_Ephrin-B receptors in dendritic spine morphogenesis and synaptogenesis	0.04731	0.03412	0.01324
45	Immune response_CCL2 signaling	0.04158	0.04818	0.01381

Maps and Descriptions [1 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Transcription_Negative regulation of HIF1A function	0.02617	2.712E-9	1.678E-9



Abstract:

Hypoxia-inducible factor (HIF) is an oxygen-sensitive transcription factor which regulates cellular response to changes in oxygen tension during normal development or pathologic processes. HIF activity is primarily controlled through post-translational modifications and stabilization/ destabilization of **HIF1A** protein. The main pathway that regulates **HIF1A** stabililty in oxygen-dependent manner is **HIF-prolyl hydroxylase**- and **VHL**-dependent **HIF1A** ubiquitination with subsequent degradation. However, multiple cellular pathways involving both oxygen-dependent and independent mechanisms are involved in regulation of **HIF1A** protein stability and activity.

Details:

Hypoxia-inducible factor (HIF) is an oxygen-sensitive transcription factor which regulates cellular response to changes in oxygen tension during normal development or pathologic processes. HIF activity is primarily controlled through post-translational modifications and stabilization/ destabilization of **HIF1A** protein and is regulated by a number of cellular pathways involving both oxygen-dependent and independent mechanisms [1], [2], [3], [4], [5].

Oxygen-dependent mechanisms

Under normoxic conditions, **HIF1A** is hydroxylated by **HIF-prolyl hydroxylase** (**EGLN1**, **EGLN3** and **EGLN2**, with **EGLN1** playing the most important role) [1], [3], [6], [7], [8]. **VHL** recognizes and binds to dihydroxylated form of **HIF1A** [9], [10], [11], and recruits E3 ubiquitin-protein ligase, **Cul2/Rbx1 E3 ligase**, composed of **Elongin C**/ **Elongin B**, RING box 1 (Rbx1) and Cullin 2 [1], [4], [5], [12]. **Cul2/Rbx1 E3 ligase** promotes **HIF1A** ubiquitination leading to **HIF1A** degradation by **Proteasome (20S core)** (see proteasomal protein catabolic process) [1], [4], [5], [13], [14].

The prolyl hydroxylation of **HIF1A** can be further promoted by **MTG16 (CBFA2T3)** [15] and **RUNX3** [16] binding to both **EGLN1** and **HIF1A**, and **OS-9** binding to **EGLN1**, **EGLN3** and **HIF1A** [17].

Moreover, **Sirtuin3**-mediated inhibition of reactive oxygen species (ROS) is necessary for maximal **HIF-prolyl hydroxylase** activity [18], [19], [20], while **Sirtuin2**-mediated **HIF1A** deacetylation increases binding affinity for **EGLN1**, thus increasing **HIF1A** hydroxylation and ubiquitination [21].

In addition, **SAT2** [22] and **MCM7** [23] bind to **HIF1A**, **VHL**, and **Elongin C** increasing **VHL**-**Elongin C** complex formation to promote hydroxylation-dependent ubiquitination. Moreover, interaction between **VHL** and **HIF1A** can be promoted by acetylation of **HIF1A** by the **ARD1** [24], although the role of **ARD1**-mediated acetylation of **HIF1A** is controversial [3], [25].

Finally, chaperones are required for proper E3 ubiquitin-protein ligase complex assembly. Chaperones **TCP1** and **HSP70** interact with **VHL** and together mediate its incorporation into the complex with **Elongin C**/ **Elongin B** [26], [27].

In addition to **HIF1A** stability, **HIF1A** transcriptional activity is also regulated in an oxygen-dependent manner. Asparaginyl hydroxylase **FIH-1** hydroxylates **HIF1A** under normoxia and mild hypoxia which blocks interactions between **HIF1A** and transcriptional co-activators preventing **HIF1A** activity [3], [28], [29]. Moreover, **EGLN1** can recruit **ING4**, a negative regulator of **HIF1A** transcriptional activity [30], [31].

Oxigen-independent mechanisms

In addition to "classical", normoxia-dependent, regulation of **HIF1A** stability/ activity, there are oxygen-independent mechanisms of **HIF1A** regulation.

RACK1 directly binds to **HIF1A** and competes for this binding with **HSP90**, a positive regulator of **HIF1A** stability [32]. Moreover, **RACK1** binds to **Elongin C** thus recruiting **Cul2/Rbx1 E3 ligase** to **HIF1A** in oxygen/ **HIF-prolyl hydroxylase**/ **VHL**-independent manner [32], [33]. As a result, **RACK1** promotes oxygen-independent **HIF1A** degradation [32], [33]. Moreover, **SSAT**, via binding to **HIF1A** and **RACK1**, stabilizes **RACK1**/ **HIF1A** interaction thus enhancing oxygen-independent **HIF1A** degradation [34].

In addition, **COMMD1 (MURR1)** competes with **HSP90** family member **HSP90 beta** for binding to **HIF1A**, and, together with **HSP70** protein, **HSPA4**, facilitates **HIF1A** degradation in ubiquitin-independent manner, presumably escorting **HIF1A** to **Proteasome (20S core)** [35], [36].

HSP70, as well as **HSP40**, through recruitment of the **Ubiquitin** ligase **CHIP**, promote ubiquitination and proteasomal degradation of **HIF1A** [37], [38]. Moreover, **CHIP** also triggers **HIF1A** degradation via chaperone-mediated autophagy mediated by **HSC70** and **LAMP2** [39], [40], [41].

DEC2 binds to **HIF1A** and promotes **HIF1A** proteasomal degradation via association with **PSMA7** subunit of **Proteasome (20S core)** [42].

SART1 promotes oxygen-independent ubiquitination and degradation of **HIF1A** [43], [44].

KLF2 disrupts **HSP90** interaction with **HIF1A** promoting its degradation [45].

Sirtuin7 negatively regulates **HIF1A** protein levels by a mechanism that is independent of prolyl hydroxylation and that does not involve proteasomal or lysosomal degradation [46].

p53 recruits **Ubiquitin** ligase **MDM2** to **HIF1A**, and **MDM2**, in turn, promotes **HIF1A** ubiquitination and degradation [47].

GSK3 beta phosphorylates **HIF1A** [48], [49], [50]. **FBXW7** recognizes **GSK3 beta**-phosphorylated **HIF1A** and presumably recruits **SKP1** and **Cul1/Rbx1 E3 ligase** thus leading to **HIF1A** ubiquitination and degradation [51], [52], [53].

UBXD7 binds to **HIF1A** and recruits **VCP**, which promotes **HIF1A** degradation [54].

PLK3 (CNK) phosphorylates **HIF1A** and decreases its stability [53], [55].

Calpain 1(mu) mediates a **VHL**-independent destruction of **HIF1A** [56].

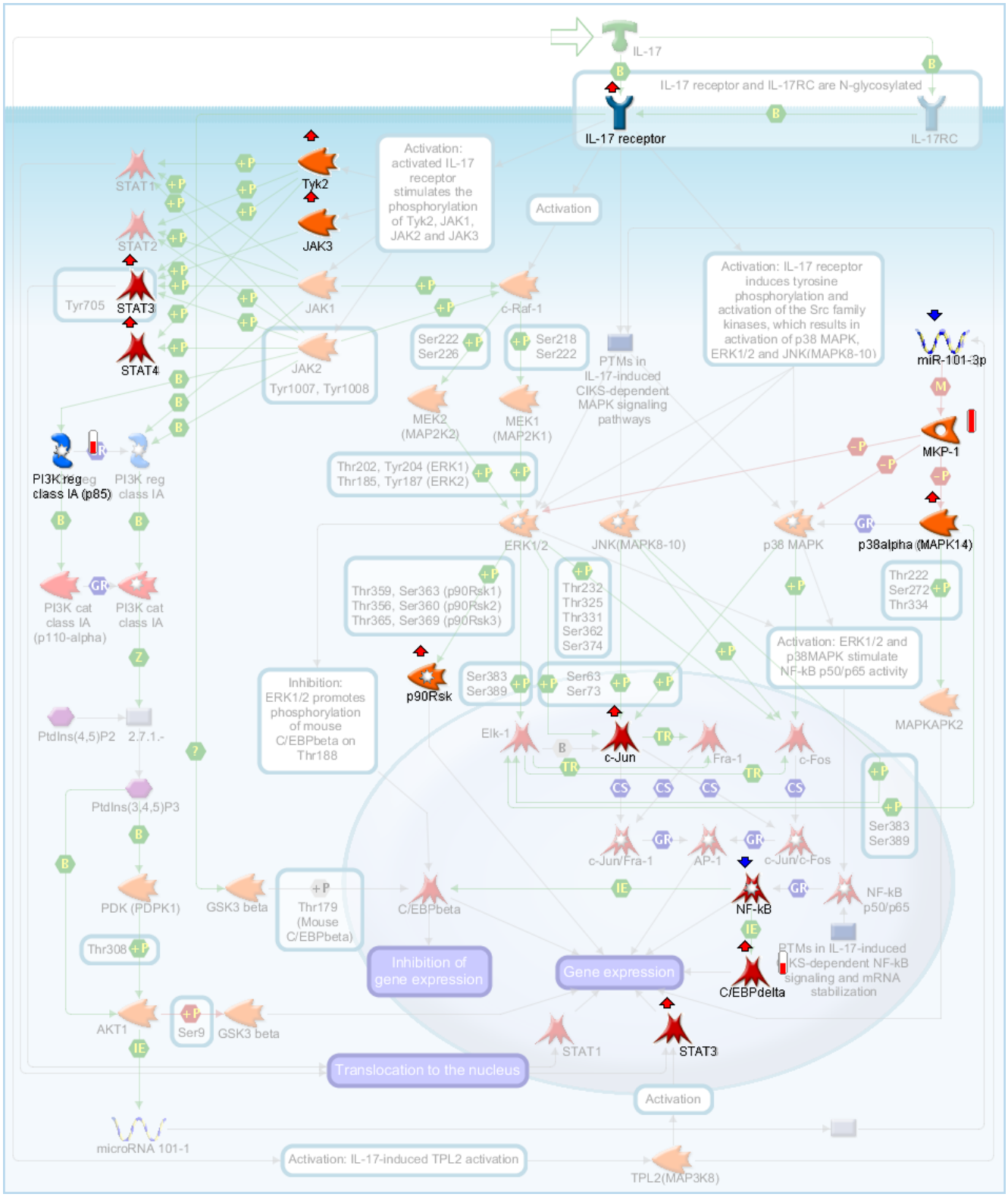
In addition to regulation of **HIF1A** protein stability, there are several regulators of **HIF1A** transcriptional activity.

Thus, **FHL1 (SLIM1)**, **FHL2** and **FHL3** directly interact with **HIF1A** and repress **HIF1A** transcriptional activity [57], [58]. **Sirtuin1** dually regulates **HIF1A** function: inhibits its transcriptional activity via blocking co-activator recruitment [59], but increases **HIF1A** stability [60], [61]. Moreover, **Sirtuin6** inhibits **HIF1A** activity [62] and **RUVBL2** negatively regulates **HIF1A** function [63]. **MCM3**, **MCM2** and **MCM5** [23], as well as **PRDX2** and **PRDX4** [64], bind to and inhibit **HIF1A** transcriptional activity. In addition, **EAF2** suppresses **HIF1A** transcriptional activity by disrupting its interaction with co-activator [65]. Furthermore, **Casein kinase I delta** phosphorylates and inhibits **HIF1A** activity without affecting its stability or nuclear accumulation [66]. **AML1 (RUNX1)** binds to **HIF1A** thus inhibiting its activity [67]. In addition, **HIF3A** binds to and functions as dominant-negative regulator of **HIF1A** inhibiting its activity [68], [69], [70]. Moreover, **p14ARF** binds to **HIF1A** inhibiting its activity [71]. Finally, **CITED2** [72], [73] and **CITED4** [74] compete with **HIF1A** for co-activator binding and thus inhibit **HIF1A** activity [70].

Finally, **PTEN** negatively regulates **HIF1A** via depletion of **PtdIns(3,4,5)P3** and thus inhibition of Phosphatidylinositol-4,5-bisphosphate 3-Kinase (PI3K) pathway (which, when active, induces **HIF1A** abundance) [75], [76].

Maps and Descriptions [2 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Signal transduction_PTMs in IL-17-induced CIKS-independent signaling pathways	0.02285	4.514E-7	1.628E-7



Abstract:

Although **IL-17** induces signaling pathways mainly through the activation of an adaptor/ E3 ubiquitin ligase TRAF3 interacting protein 2 (CIKS), **IL-17** also activates CIKS-independent signaling cascades, including activation of Janus kinases (JAKs), Signal transducer and activator of transcription (STAT) factors, Phosphatidylinositol 3-kinase (PI3K)/ v-Akt murine thymoma viral oncogene homolog (AKT) pathway, and Mitogen-activated protein kinase (MAPK) cascades. This leads to regulation of gene expression through the involvement of **AP-1**, **NF-kB p50/p65**, **C/EBPbeta** and **C/EBPdelta** transcription factors. CIKS-independent signaling pathways are poorly investigated in the **IL-17** signaling. The main post-translational modifications (PTMs) of signaling proteins that regulate the **IL-17**-induced CIKS-independent signaling cascades are phosphorylation and dephosphorylation events.

Details:

IL-17 is a proinflammatory cytokine that contributes to the pathogenesis of several inflammatory diseases. A major source of **IL-17** is a lineage of T cells known as T helper 17 (Th17) cells [1], [2], [3].

The **IL-17** molecule is composed of two monomers that are linked by intramolecular disulphide bonds on cysteine residues to form a homodimer. **IL-17** is a member of the IL-17 protein family, and is formally referred to as IL-17A. The first receptor to be identified for **IL-17** was initially referred to as **IL-17 receptor** but is now known as IL-17RA following the identification of additional receptor components that are required in order to form a functional receptor complex for **IL-17** signaling [1], [2], [3], [4].

A homo-dimeric form of **IL-17** binds to a dimeric receptor complex composed of two **IL-17 receptor** (IL-17RA) subunits or a heterogeneous receptor composed of **IL-17 receptor** (IL-17RA) and **IL-17RC** subunits [1], [2], [3], [4], [5], [6]. The heterogeneous receptor for **IL-17** contains an undetermined number of **IL-17 receptor** (IL-17RA) and **IL-17RC** subunits, although it is supposed to be at minimum trimeric complex [1]. Both receptor subunits, **IL-17 receptor** (IL-17RA) [6], [7] and **IL-17RC** [8], are N-glycosylated (see: protein N-linked glycosylation). **IL-17** binding promotes the association of **IL-17RC** with a glycosylated **IL-17 receptor** (IL-17RA) [9].

IL-17 binding to the receptor induces activation of multiple signaling proteins. Although the adaptor/ E3 ubiquitin ligase TRAF3 interacting protein 2 (CIKS, also known as Act1) is an immediate and essential signaling component downstream of **IL-17 receptor** [1], [2], [4], [10], [11], **IL-17** also induces CIKS-independent signaling pathways, including activation of Janus kinases (JAKs) and Signal transducer and activator of transcription (STAT) factors, Phosphatidylinositol 3-kinase (PI3K)/ v-Akt murine thymoma viral oncogene homolog (AKT) pathway (protein kinase B signaling) and Mitogen-activated protein kinase (MAPK) cascades (MAPK cascade) [1], [10], [11], [12], [13], [14], [15], [16], [17]. Mechanisms of CIKS-independent signaling pathways are poorly investigated.

Stimulation with **IL-17** induces a rapid tyrosine phosphorylation of **JAK1**, **JAK2**, **JAK3**, **Tyk2**, **STAT1**, **STAT2**, **STAT3**, and **STAT4** [12] (see: peptidyl-tyrosine phosphorylation; tyrosine phosphorylation of STAT protein). Usually, cytokine binding to their cognate receptors induces rapid phosphorylation of JAKs, which subsequently phosphorylate STATs. Tyrosine phosphorylated STATs dimerize and translocate to the nucleus (see: regulation of protein heterodimerization activity; regulation of protein homodimerization activity; STAT protein import into nucleus) where they regulate gene expression [18]. This canonical JAK/ STAT pathway (see: JAK-STAT cascade) has not been confirmed in the **IL-17** signaling [12].

Nevertheless, **STAT3** [14], [19], [20], [21], [22], [23], [24], [25], and **STAT1** [26], [22] are involved in the **IL-17**-induced expression of target genes. Also, **STAT3** phosphorylation on Tyr705 has been shown in the **IL-17** signaling [14], [25]. Moreover, **IL-17** can induce tyrosine phosphorylation and activation of **STAT3** via **TPL2(MAP3K8)** [25]. Probably, **IL-17** also enhances phosphorylation of **STAT4** [27].

In addition, the phosphorylation sites of **JAK1** and **JAK2** have been detected upon **IL-17** stimulation [15]. **JAK2** was phosphorylated on Tyr1007 and Tyr1008 [15], [28]. Although **JAK1** has been shown to be phosphorylated on Tyr1022 and Tyr1023 [15], **JAK1** human and mouse proteins don't contain tyrosines at 1022 and 1023 positions [29], [30]; usually, **JAK1** human protein is tyrosine phosphorylated at

Tyr1034 and Tyr1035 [29]. In addition, both **JAK1** and **JAK2** are implicated in the **IL-17** signaling and expression of target genes [15], [31], [32].

In the **IL-17** signaling, **JAK1** and **JAK2** are required for activation of the **PI3K reg class IA** (namely, **PI3K reg class IA (p85)**)/ **PI3K cat class IA** (namely, **PI3K cat class IA (p110-alpha)**)/ **PtdIns(3,4,5)P3**/ **PDK (PDPK1)**/ **AKT1**/ **GSK3 beta** pathway, that leads to expression of target genes [15]. In this pathway, phosphorylation of **AKT1** at Thr308 (in the catalytic domain) by **PDK (PDPK1)** and phosphorylation of **AKT1** at Ser473 results in **AKT1** activation [15], [33], [34], [35], [36], [37] (see: peptidyl-threonine phosphorylation; peptidyl-serine phosphorylation); in turn, phosphorylation of **GSK3 beta** at Ser9 by **AKT1** results in **GSK3 beta** inhibition [15], [38]. Several other data also confirm the involvement of the PI3K/ AKT pathway in the **IL-17** signaling [17], [39], [40], [41], [42].

In addition, **IL-17** induces activation of MAPKs, namely **p38 MAPK**, **JNK(MAPK8-10)** and **ERK1/2** [14], [16], [17], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], but signaling pathways that lead to MAPK activation remain poorly understood. Activation of MAPKs seems to include both CIKS-dependent and CIKS-independent signaling pathways [1], [10], [11], [75], [76]. Activated MAPKs phosphorylate multiple transcription factors, such as **Elk-1** and **AP-1** (including **c-Jun** and **c-Fos**), leading to expression of **IL-17** target genes [13], [57], [58], [62], [77], [78], [79]. **Elk-1** phosphorylation on Ser383 and Ser389 by **ERK1/2** [80], [81], [82], [83], **JNK(MAPK8-10)** [81], [84], [85], [86] and **p38alpha (MAPK14)** [87], [88] is required for **Elk-1** transcriptional activity [36], [83], [89]. **Elk-1** is one of the main factors that up-regulate expression of **c-Fos**, **Fra-1** and, probably, **c-Jun** [83]. Phosphorylation of **c-Jun** on Ser63 and Ser73 by **ERK1/2** [25], [43], [90], [91], **JNK(MAPK8-10)** [25], [43], [85], [92], [93] and **p38 MAPK** [25], [43], [94], [95], [96], [97], [98], and **c-Fos** by **ERK1/2** (on Thr325, Thr331, Ser362 and Ser374) [58], [25], [99], [100], [101], [102], [103], **JNK(MAPK8-10)** and **p38 MAPK** [58], [104] is responsible for **c-Jun** and **c-Fos** transcriptional activity and expression of target genes. **IL-17** induces activation of **AP-1** (including **c-Jun**, **c-Fos** and **Fra-1**), **NF-kB p50/p65**, **C/EBPbeta** and **C/EBPdelta** downstream of MAPKs [1], [13], [25], [56], [57], [58], [62], [77], [105].

The early signaling events triggered by **IL-17** involve rapid tyrosine phosphorylation and activation of catalytic activity of **c-Raf-1** serine/threonine kinase [106]. Thus, it is suggested, that activation of **c-Raf-1** can lead to the canonical **c-Raf-1**/ **MEK1(MAP2K1)** and **MEK2(MAP2K2)**/ **ERK1/2** cascade [13], [106]. In the canonical **ERK1/2** cascade, **c-Raf-1** phosphorylates **MEK1(MAP2K1)** on Ser218 and Ser222 [44], [107], [108], [109], [110], [111], and **MEK2(MAP2K2)** on Ser222 and Ser226 [44], [110], [112], that positively regulates MEK kinase activity. In turn, both **MEK1(MAP2K1)** and **MEK2(MAP2K2)** [17], [69], [113], [114] phosphorylate Thr202 and Tyr204 on ERK1 (MAPK3) [83], [113], [115], [116], and Thr185 and Tyr187 on ERK2 (MAPK1) [83], [117], [118], [119], [120], that is required for full **ERK1/2** activation and interaction with substrates [83]. It is also possible, that **JAK1** and/or **JAK2** can initiate the **ERK1/2** cascade through activation of **c-Raf-1**, probably, by phosphorylation [13], [31], [36], [121], [122].

IL-17 also induces tyrosine phosphorylation and activation of the Src family kinases resulting in phosphorylation and activation of **ERK1/2**, **JNK(MAPK8-10)** and **p38 MAPK** [13], [123].

IL-17 also stimulates the **MEK1(MAP2K1)** and **MEK2(MAP2K2)**/ **ERK1/2**/ **p90Rsk** and the **p38 MAPK** (most likely, **p38alpha (MAPK14)**)/ **MAPKAPK2** cascades to induce expression of target genes [13], [44]. **ERK1/2** phosphorylates **p90Rsk** [124], [125] on Thr359 and Ser363 (p90Rsk1) [126], Thr356 and Ser360 (p90Rsk2) [127], [128], Thr365 and Ser369 (p90Rsk3) [124], [129]. **p38 MAPK** (namely, **p38alpha (MAPK14)**) phosphorylates **MAPKAPK2** on Thr222, Ser272 and Thr334 [130], [131], [132].

In addition, **IL-17** induces **microRNA 101-1** expression via the PI3K/ **AKT1** pathway [41]. After **microRNA 101-1** processing to the mature **miR-101-3p** (see: pre-miRNA processing), **miR-101-3p**-dependent suppression of **MKP-1** phosphatase [133] results in attenuation of the inhibitory **MKP-1** action on **p38 MAPK** and **ERK1/2** followed by activation of these MAPKs [41]; functionally active **MKP-1** dephosphorylates **p38 MAPK** (including **p38alpha (MAPK14)**) and **ERK1/2** to inhibit their activities [134], [135] (see: protein dephosphorylation).

IL-17 has also been shown to activate **ERK1/2** via **TPL2(MAP3K8)** signaling [25].

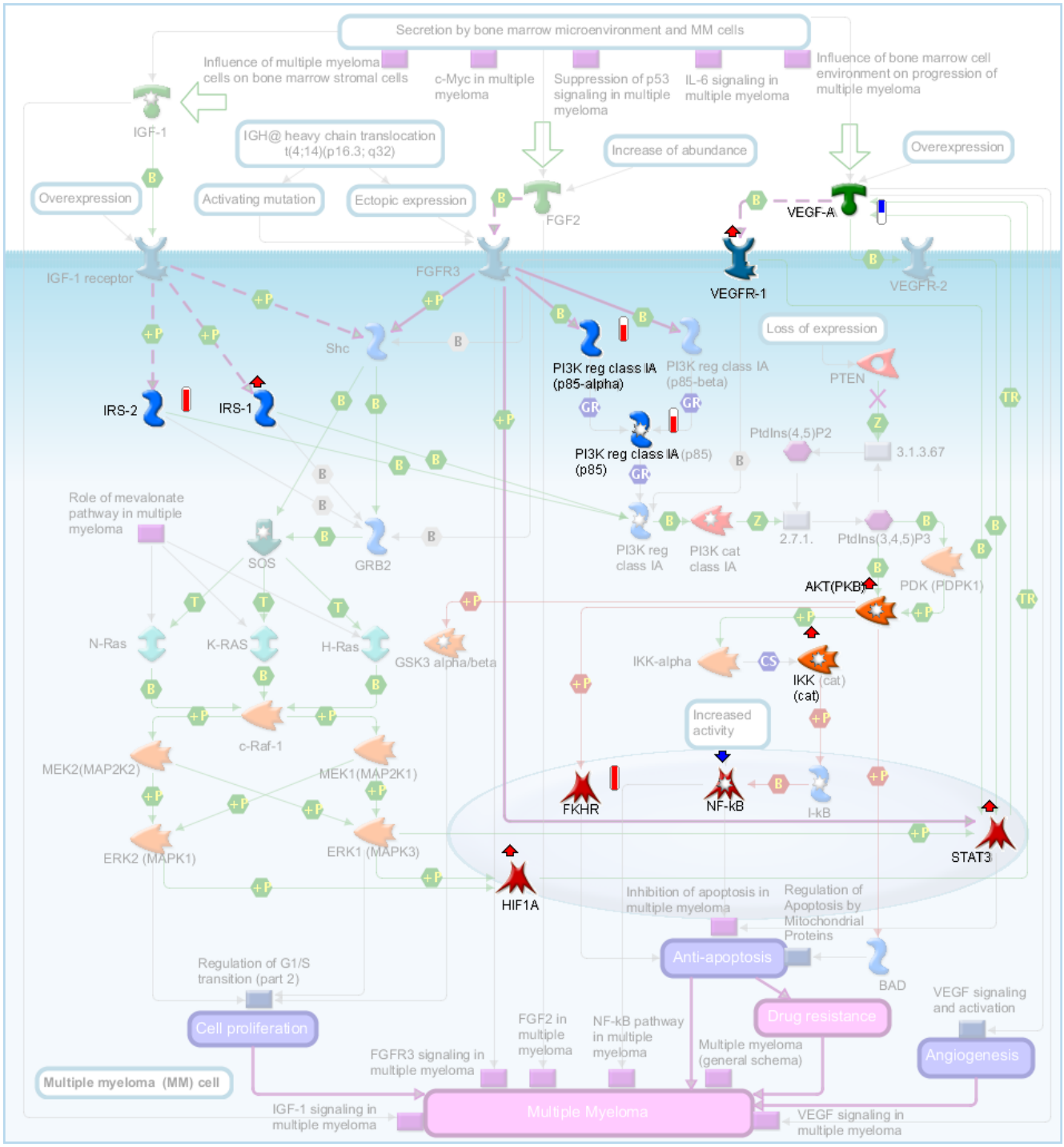
ERK1/2 plays dual roles in **C/EBPbeta**-dependent regulation of gene expression in the **IL-17** signaling [56], [58], [76], [79], [136].

In murine cells, **IL-17** induces activation of **ERK1/2** and **GSK3 beta** via unknown pathways. This results in inhibition of **C/EBPbeta** by sequential phosphorylation of two sites in the regulatory 2 domain of **C/EBPbeta**. Activation of **ERK1/2** is supposed to be partially CIKS-dependent and partially CIKS-independent, downstream to **IL-17 receptor** signal transduction via a cytoplasmic motif termed a "SEFIR/TILL" domen. Activation of **GSK3 beta** is supposed to be independent of CIKS, and is mediated via a distal cytoplasmic tail of **IL-17 receptor**. **ERK1/2** phosphorylates **C/EBPbeta** (mouse protein, [137]) on Thr188 which then renders **C/EBPbeta** permissive for subsequent phosphorylation on Thr179 by **GSK3 beta**. Phosphorylation of Thr188 and Thr179 on **C/EBPbeta** negatively regulates **C/EBPbeta**-dependent expression of **IL-17**-target genes [136] (see: negative regulation of gene expression). However, it is not clear, whether inhibition of **GSK3 beta**, which is induced by **IL-17** via the PI3K/ **AKT1** signaling, is required for **C/EBPbeta**-dependent gene expression or not [15], [136].

At the same time, in other cell types, **ERK1/2** has been shown to activate **C/EBPbeta**-dependent gene expression in resonse to **IL-17** [56], [58], [76], [79]. In addition, both **ERK1/2** and **p38 MAPK** activate **NF-kB p50/p65** and **AP-1** (namely, **c-Jun**, **c-Fos** and **Fra-1**) transcription factors [56], [58], [62], [105]. **IL-17** also triggers expression of both **C/EBPbeta** and **C/EBPdelta** [76], [79], probably, via **NF-kB** activation [1], [138].

Maps and Descriptions [3 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Main growth factor signaling cascades in multiple myeloma cells	3.515E-4	5.439E-4	2.45E-7



Abstract:

Multiple myeloma (MM) is a hematologic malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow (BM). Interaction of myeloma cells with cells within the BM microenvironment results in the production of diverse cytokines and growth factors. **IGF-I**, **VEGF-A** and **FGF -2**, which are produced by myeloma cells and BM stromal cells, are important growth factor for myeloma cells. Growth factor signaling includes main RAS/ MAPK, PI3K/ AKT and **STAT3** signaling pathways which promote proliferation, survival, drug resistance and angiogenesis in MM.

Details:

Multiple myeloma (MM) is a hematologic malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow (BM). Interaction of myeloma cells with cells within the BM microenvironment results in the production of diverse cytokines and growth factors. **IGF-1**, **VEGF-A** and **FGF2**, which are produced by myeloma cells and BM stromal cells, are important growth factor for myeloma cells. Growth factors activate common RAS/ MAPK, PI3K/ **AKT(PKB)** and **STAT3** signaling pathways which promote cell proliferation, anti-apoptosis (see negative regulation of apoptotic process), drug resistance and angiogenesis in MM [1], [2], [3], [4], [5].

In MM cells **IGF-1** binds to and activates **IGF-1 receptor**, resulting in stimulation of **IRS-1**/ **IRS-2**/ **PI3K reg class IA**/ **PI3K cat class IA**/ **PtdIns(3,4,5)P3**/ **PDK (PDPK1)**/ **AKT(PKB)** cascade [6], [7], [8]. **PTEN** is a negative regulator that controls the PI3K/ **AKT(PKB)** pathway in MM cells. **PTEN** expression is lost in some MM cells thereby contributing to enhanced **AKT(PKB)** activation under **IGF-1** action [9]. **AKT(PKB)** promotes cell proliferation and anti-apoptosis (see negative regulation of apoptotic process) by several pathways in MM cells. Firstly, **AKT(PKB)** can directly phosphorylate and inhibit pro-apoptotic **BAD** and transcription factor **FKHR**, thereby promoting MM cell anti-apoptosis (see negative regulation of apoptotic process) [6], [10]. Secondly, **AKT(PKB)** can promote MM cell proliferation via phosphorylation of **GSK3 alpha/beta** [10], [7]. In addition, **AKT(PKB)** induces the **IKK-alpha**/ **IKK (cat)**/ **I-kB**/ **NF-kB** pathway which promotes anti-apoptosis (see negative regulation of apoptotic process), drug resistance and MM progression [11], [12]. Besides, **NF-kB** is constitutively active in most MM patients [13], [14].

Binding of **IGF-1** to the **IGF-1 receptor** leads to the induction of the **IRS-1**/ **IRS-2**/ **Shc**/ **GRB2**/ **SOS**/ **H-Ras**/ **c-Raf-1**/ **MEK1(MAP2K1)**, **MEK2(MAP2K2)**/ **ERK1 (MAPK3)**, **ERK2 (MAPK1)** pathway driving cell proliferation [8], [12], [15]. In turn, **ERK1 (MAPK3)** and **ERK2 (MAPK1)** activate **VEGF-A** secretion probably via **HIF1A** [12], [15]. **VEGF-A** can then induce angiogenesis and multiple myeloma progression [12], [15].

Several FGF ligands activate several FGF receptors in normal plasma and malignant MM cells, but **FGF2**/ **FGFR3** signaling is altered in MM cells. Higher abundance of **FGF2** has been observed in MM patients [16], [17] and **FGFR3** is not expressed in normal plasma cells, but IGH@-**FGFR3** translocation t(4;14)(p16.3;q32) that is present in 15% of patients leads to **FGFR3** ectopic expression [2], [18], [19], [20], [21]. t(4;14)(p16.3;q32) also promotes activating mutations of **FGFR3** [22], [23]. This mutation promotes ligand-independency of **FGFR3**, but nevertheless, FGF ligands are able to stimulate **FGFR3** signaling in multiple myeloma cells [23], [24], [25], [26], [27], [28].

Under **FGF2** action **FGFR3** binds to **Shc** and activates **Shc**/ **GRB2**/ **SOS**/ **H-Ras**, **N-Ras**, **K-RAS**/ **c-Raf-1**/ **MEK1(MAP2K1)**, **MEK2(MAP2K2)**/ **ERK1 (MAPK3)**, **ERK2 (MAPK1)** pathway stimulating MM cell proliferation [19], [29], [30], [31], [32], [33]. **ERK1 (MAPK3)** phosphorylates and activates **STAT3** [31], [34]. In addition, **FGFR3** can directly phosphorylate **STAT3** [35]. Activation of **STAT3** leads to anti-apoptosis in MM cells (see negative regulation of apoptotic process) [36], [37] and enhanced expression of **VEGF-A**, which promotes angiogenesis [38].

FGFR3 binds to and activates **PI3K reg class IA (p85-alpha)** and **PI3K reg class IA (p85-beta)**, thus stimulating kinase activity of **PI3K cat class IA** [31], [39]. **PI3K cat class IA** activates **PDK (PDPK1)**/ **AKT(PKB)** pathway promoting MM cell proliferation [31] and anti-

apoptosis (via inhibition of **FKHR**) (see negative regulation of apoptotic process) [40].

The VEGF signaling cascade is a well established mediator of angiogenesis which is enhanced in many types of cancer. However, in MM it contributes to tumor progression not only by activation of angiogenesis, but also by activation of MM cell proliferation and anti-apoptosis (see negative regulation of apoptotic process) [41], [42], [43], [44], [45], [46]. Indeed, VEGF signaling in MM has been demonstrated to be enhanced in MM cells when compared to normal plasma cells and early premalignant cell types [47], [48], [49].

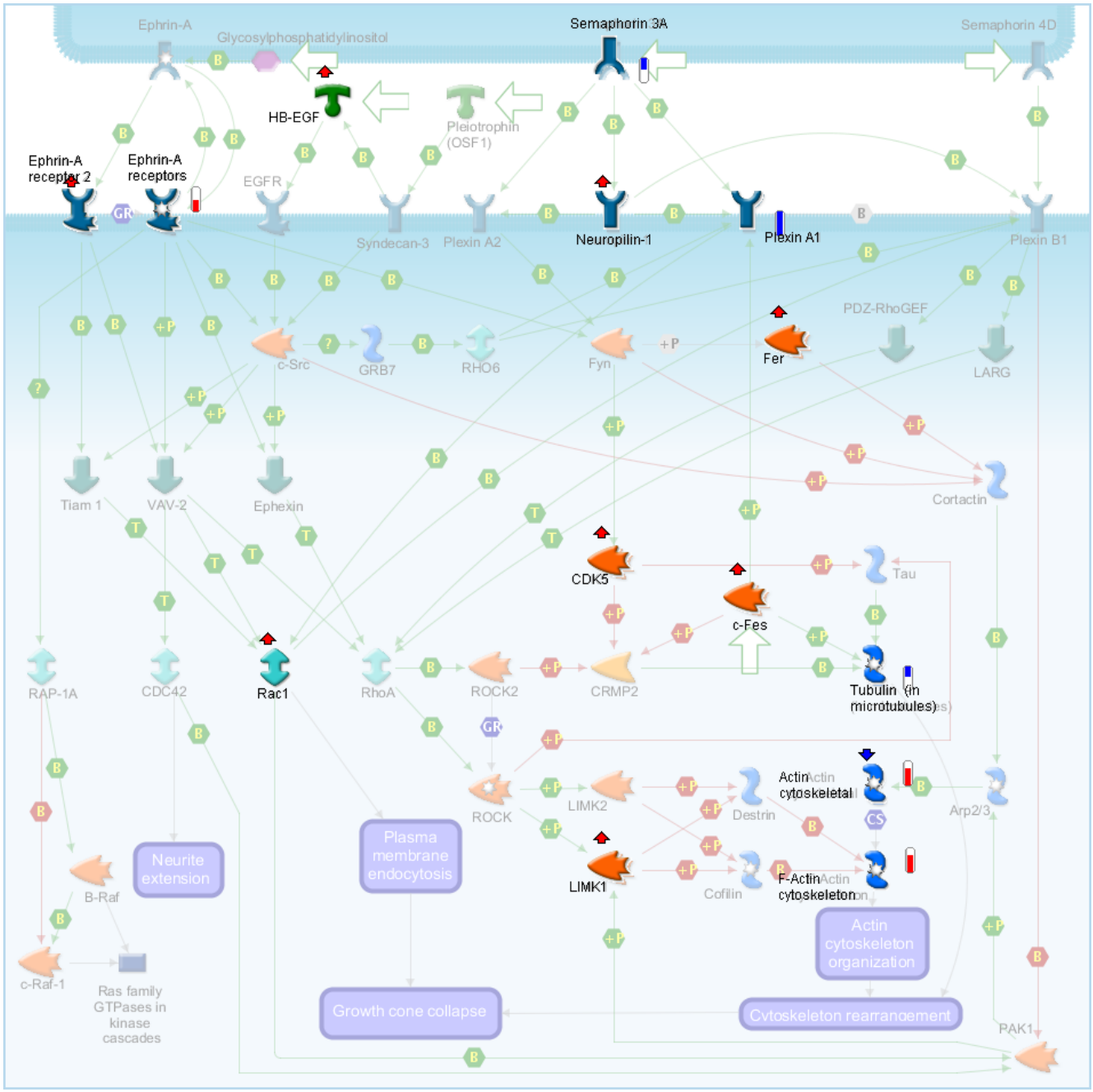
VEGF-A is overexpressed and overproduced by MM cells [41], [44], [50], [51], [52], [53].

Activation of **VEGFR-1** by **VEGF-A** and promotes the induction of the **GRB2**, **Shc**/ **SOS**/ **H-Ras**/ **c-Raf-1**/ **MEK1(MAP2K1)**, **MEK2(MAP2K2)**/ **ERK1 (MAPK3)**, **ERK2 (MAPK1)** pathway, which contributes to MM cell proliferation [40], [41], [44], [45], [53], [54], [55].

Activation of **VEGFR-1** leads to its association with **PI3K reg class IA** and activation of the **PI3K cat class IA**/ **AKT(PKB)** pathway [45], [54]. **AKT(PKB)** then phosphorylates **FKHR**, most likely contributing to anti-apoptotic effects in MM cells (see negative regulation of apoptotic process) [40]. Also, **VEGF-A** via the **VEGFR-1**, **VEGFR-2** activates **STAT3** pathway promoting anti-apoptosis in MM cells (see negative regulation of apoptotic process) [53], [56], [57], [58].

Maps and Descriptions [4 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Neurophysiological process_Receptor-mediated axon growth repulsion	8.741E-4	4.335E-5	3.035E-7



Description

Receptor-mediated axon growth repulsion

Ephrin-A proteins which are anchored in the plasma membrane through attachment of glycosylphosphatidylinositol (**GPI**) [1], are the ligands for **Ephrin-A receptors**, which belong to the membrane family of receptor tyrosine kinases [2].

In the absence of **Ephrin-A** stimulation, **Ephrin-A receptors** are shown to target **Ephexin** exchange factor to the plasma membrane. **Ephrin-A** stimulation of **Ephrin-A receptors** activates exchange factors **Ephexin** [3], **VAV-2** [4] and **Tiam 1** [5]. Src-family tyrosine kinases **c-Src** and **Fyn** are recruited to **Ephrin-A receptors** after **Ephrin-A** stimulation [6]. In response to **Ephrin-A** signaling **Ephexin** becomes phosphorylated by **c-Src** [6] and this phosphorylation enhances its activity toward Ras homolog gene family, member A (**RhoA**) [7]. **VAV-2** is rapidly phosphorylated by **c-Src** upon stimulation by **Ephrin-A** [4] and activates **RhoA** [8].

Ephrin-A receptors have also been shown to signal through the Ras-related C3 botulinum toxin substrate 1 (**Rac1**) exchange factors **Tiam1** [5] and**VAV-2** [9] to promote neurite outgrowth.

In response to **Ephrin-A1** stimulation, Ras-related protein **Rap-1A** is activated [10] and can regulate MAPK signaling cascade by reducing **c-Raf-1** activation [11] or by stimulation of **B-Raf** kinase [10], [12].

When **Ephrin-A** receptors are activated, phosphorylation of **Ephexin** promotes its GTPase activity toward **RhoA**. **RhoA** downstream effector Rho-associated kinase **ROCK** directly phosphorylates LIM-kinases **LIMK1** and **LIMK2**, which in turn phosphorylates actin-depolymerizing factor **destrin** and actin-associated protein**cofilin**. Activity of **LIMK1** is also regulated by p21-activated kinase 1 (**PAK1**) [13]. **Cofilin** and **destrin** both exhibit **actin**-depolymerizing activity followed by reorganization of the **actin** cytoskeleton [14], [15].

The F-actin-binding protein **cortactin** is an important regulator of cytoskeletal dynamics, and a prominent target of various tyrosine kinases (**c-Src**, **Fyn**, **Fer**) [6], [16]. Tyrosine phosphorylation of **cortactin** has been suggested to reduce its F-actin cross-linking capability [16].

The semaphorins family of secreted or membrane-bound proteins was identified originally as axonal guidance factors functioning during neuronal development. The class 4 semaphorin **Semaphorin 4D** utilizes **Plexin B1** (transmembrane protein) as receptor. [17] **Plexin B1** directly interacts with exchange factors **PDZ-RhoGEF** and **LARG** to regulate **RhoA** and the growth cone morphology [18].

Rho6 is a member of Rho family GTPases. It is activated by adaptor protein **Grb7 and** directly interacts with the cytoplasmic domain of **Plexin B1** in response to **Semaphorin 4D**. **Rho6** promotes the interaction between **Plexin B1** and **PDZ-RhoGEF** and thereby potentiates the **PDZ-RhoGEF**-induced **RhoA** activation [19].

PAK1 promotes activation of **actin** polymerization by phosphorylation of **Arp2/3** (complex of actin-related proteins) [20]. **c-Raf-1** kinase, a member of the MAPK pathway, is also phosphorylated and activated by **PAK1** [21]. Inhibition of **Pak1** by **Plexin B1** is believed to cause suppression of membrane protrusions, thus supporting the cell repulsion response. Furthermore, active **Rac1** was shown to promote cell surface localization of **Plexin B1 thus** enhancing **Semaphorin 4D** binding to the receptor. Thus, **Rac1** and **Plexin B1** signaling appears to be bidirectional: **Rac-1** modulates **Plexin B1** activity, and **Plexin B1** modulates **Rac-1** function [22].

Another semaphorin, **Semaphorin 3A**, binds to **Neuropilin-1**/**Plexin A1** complex and induces repulsive responses [23]. The active form of **Rac1** directly binds to **Plexin-A1. A**ctivated **Rac1** mediates endocytosis of the growth cone plasma membranes and reorganization of **F-actin** in neurons [24]. Endocytosis of plasma membranes is supposed to be an important step for growth cone collapse.

c-Fes tyrosine kinase also is implicated in **Semaphorin 3A**-induced collapse [25]. **c-Fes** directly binds to the cytoplasmic region of **Plexin A1**. In the resting state, **neuropilin-1** associates with **Plexin-A1** and blocks the binding of **c-Fes** to **Plexin A1**. **Semaphorin 3A** binding to **Neuropilin-1** permits **c-Fes** to associate with and phosphorylate **Plexin A1**. This tyrosine phosphorylation stimulates repulsive action in the receptor.

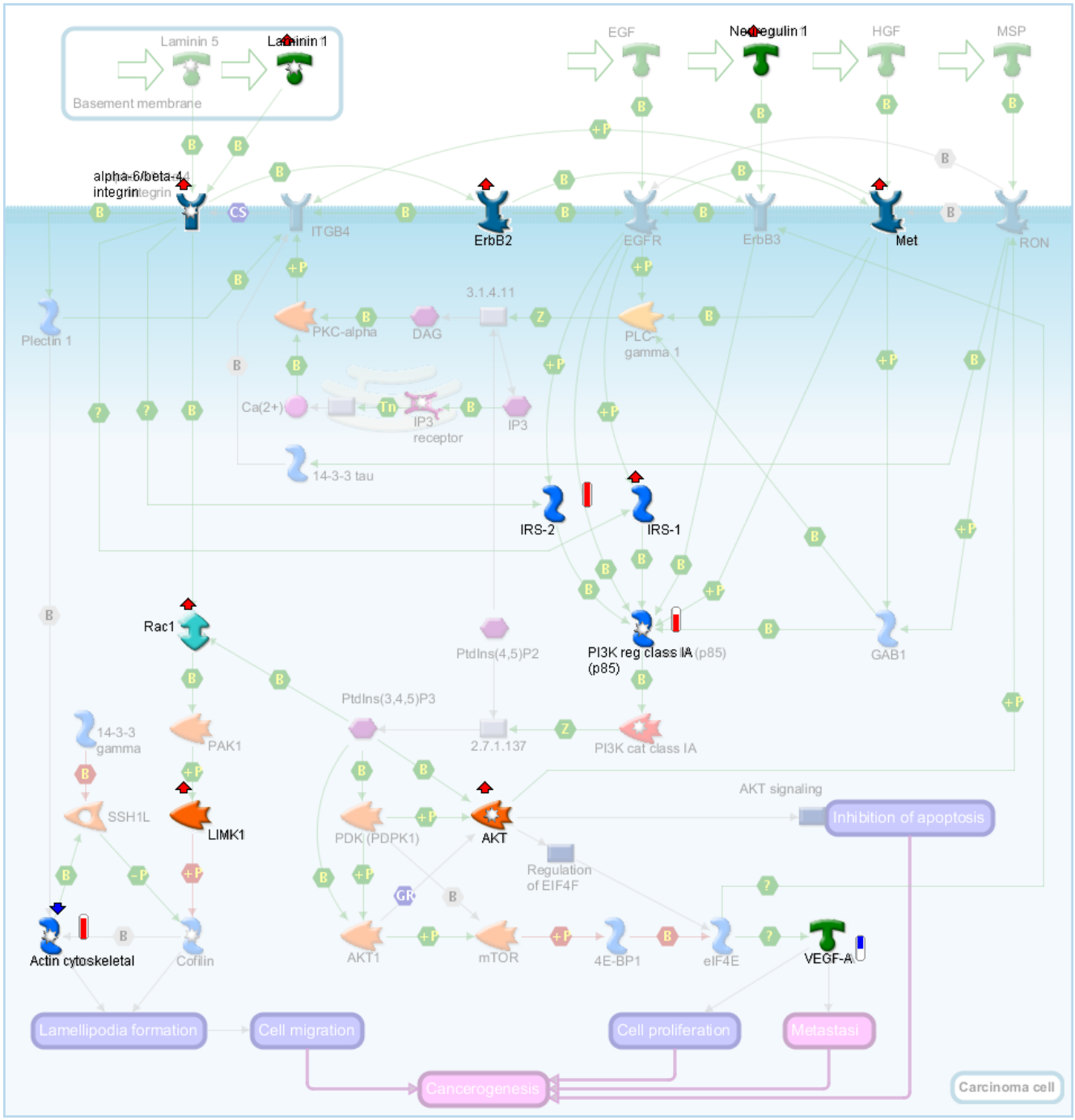
c-Fes also phosphorylates collapsin response mediator protein **CRMP2** [26].

Fyn, a member of src-family of tyrosine kinases, associates with **Plexin A2** in response to **Semaphorin 3A** and phosphorylates serine/threonine kinase **CDK5**. [27] Activated **CDK5** phosphorylates **CRMP2** [28]. **ROCK2** kinase also has been shown to phosphorylate **CRMP2** [29]. CRMP2 binds to tubulin heterodimers to promote microtubule assembly that is important for axonal growth and branching [30]. Phosphorylation of **CRMP2** reduces its tubulin-heterodimer binding and the promotion of microtubule assembly.

CDK5 also phosphorylates the microtubule-associated protein **Tau**, thereby reduces its ability to induce **tubulin** microtubule formation [31].

Maps and Descriptions [5 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Role of alpha-6/beta-4 integrins in carcinoma progression	0.01957	2.475E-6	6.504E-7



Description

Role of alpha-6/beta-4 integrins in carcinoma progression

In normal epithelia, **Alpha-6/beta-4 integrin** functions as a receptor for the laminin family of extracellular matrix proteins (such as **Laminin 1** and **Laminin 5**) and mediates the stable attachment of epithelial cells to the underlying basement membrane [1], [2]. The function of **Alpha-6/beta-4 integrin** is altered substantially as normal epithelia undergo malignant transformation and progress to invasive carcinoma [3].

In carcinoma cells, **Alpha-6/beta-4 integrin** also functions as a laminin receptor and via Intermediate filament binding protein **Plectin 1** interacts with the **Actin** cytoskeleton to promote the formation of actin-rich structures that are important for cell motility [4], [5], [6], [7], [8]. **Alpha-6/beta-4 integrin** may support cell migration on laminin to promote tumor cell invasion. **Alpha-6/beta-4 integrin**, through interaction with the Ras-related C3 botulinum toxin substrate 1 (**Rac1**), regulates **Laminin-5** matrix organization which supports cell migration along linear tracks [9]. The interaction of beta-4 integrin subunit (**ITGB4**) with **Plectin 1** stabilizes **Alpha-6/beta-4 integrin** and **Laminin-5** interaction [7].

Alpha-6/beta-4 integrin/ **Rac1** complexes induce activation of the actin-regulatory protein **Cofilin** to form an F-actin-rich lamellipodial extension in the direction of cell movement [9]. Rapid turnover of actin filaments is essential to maintain and extend the lamellipodium for cell migration [10]. Activated **Rac1** increases association of p21/Cdc42/Rac1-activated kinase 1(**PAK1**) with LIM domain kinase 1 (**LIMK1**) and increases **LIMK1**-mediated phosphorylation of **Cofilin** [11]. **Cofilin** stimulates disassembly and severance of actin filaments near the pointed ends and thereby actin monomers are continuously supplied for polymerization [12]. Slingshot homolog 1 (**SSH1L**) dephosphorylates and reactivates an inactive **Cofilin** [13]. **SSH1L** is locally activated in lamellipodia by translocation to and association with **Actin** filaments, and **14-3-3 gamma** proteins negatively regulate this activation by sequestering **SSH1L** in the cytoplasm [14]. **LIMK1** contributes to actin turnover in lamellipodia by releasing free **Actin** and **Cofilin** [15]. The dynamic and coordinated activation of **LIMK1** and **SSH1L** can accelerate the recycling of **Cofilin** and thereby promote **Actin** turnover.

Alpha-6/beta-4 integrin is a component of hemidesmosomes in normal epithelia. Growth factors associated with carcinoma progression have the potential to mobilize **Alpha-6/beta-4 integrin** from hemidesmosomes and promote its association with F-actin in lamellae and filopodia.

Epidermal growth factor (**EGF**) via Epidermal growth factor receptor (**EGFR**)/ Phospholipase C, gamma 1 (**PLC-gamma 1**)/ 1,2-Diacylglycerol (**DAG**)/ Inositol 1,4,5-trisphosphate (**IP3**)/ Calcium (**Ca(2+)**) signaling activates Protein kinase C, alpha (**PKC-alpha**) [16], [17], [18]. **PKC-alpha** phosphorylates **ITGB4** that leads to disruption of hemidesmosomes [3], [5], [18].

One mechanism that may contribute to this disruption is the binding of **14-3-3 tau** proteins to phosphoserins in **ITGB4** cytoplasmic domain, since **PKC-alpha** phosphorylation generates 14-3-3 binding sites on**ITGB4** [18], [19].

The Macrophage stimulating 1 (**MSP**) protein and its receptor **RON** via signaling adapter GRB2-associated binding protein 1 (**GAB1**) activate phosphoinositide 3-kinase (**PI3K**) and its downstream effector v-Akt murine thymoma viral oncogene homolog (**AKT**) kinase. **AKT** phosphorylates **RON** that is required for **RON** / **14-3-3 tau** interaction. Consequently, **RON** /**Alpha-6/beta-4 integrin** complex formed via **14-3-3 tau** binding displaces **Alpha-6/beta-4 integrin** from its location at hemidesmosomes and relocalizes it to lamellipodia [19].

The key signaling event mediated by **Alpha-6/beta-4 integrin**, that increases the invasive potential of carcinoma cells, is activation of **PI3K** [20]. Insulin receptor substrate 1 and 2 (**IRS-1** and **IRS-2**) has been revealed as signaling intermediates in this **Alpha-6/beta-4 integrin**-dependent **PI3K** activation [21].

Alpha-6/beta-4 integrin also can form signaling complexes with specific growth factor receptors that act synergistically to activate **PI3K** [3

], [22].

In carcinoma cells, following Hepatocyte growth factor receptor (**Met**) activation, **Alpha-6/beta-4 integrin** potentiates Hepatocyte growth factor (**HGF**)-triggered activation of **PI3K** pathway. Although **Met** can associate with **ITGB4**, **Alpha-6/beta-4 integrin** is supposed to be a functional amplifier of **Met** signaling rather than a mechanical adhesive device [23].

Cooperative signaling between **Alpha-6/beta-4 integrin** and v-Erb-b2 erythroblastic leukemia viral oncogene homologs 2 and 3 (**ErbB2** and **ErbB3**) is required to promote **PI3K** activation. **Alpha-6/beta-4 integrin** associates with **ErbB2** [24], [25]. **ErbB2** is thought to function only when it heterodimerizes with other members of the EGFR family [26]. The **ErbB2**/**ErbB3** heterodimer is the strongest stimulator of the **PI3K** activity [27]. Integrin/ EGFR family complexes facilitate key functions of carcinoma cells, including their ability to migrate, invade, and evade apoptosis [3], [25], [28].

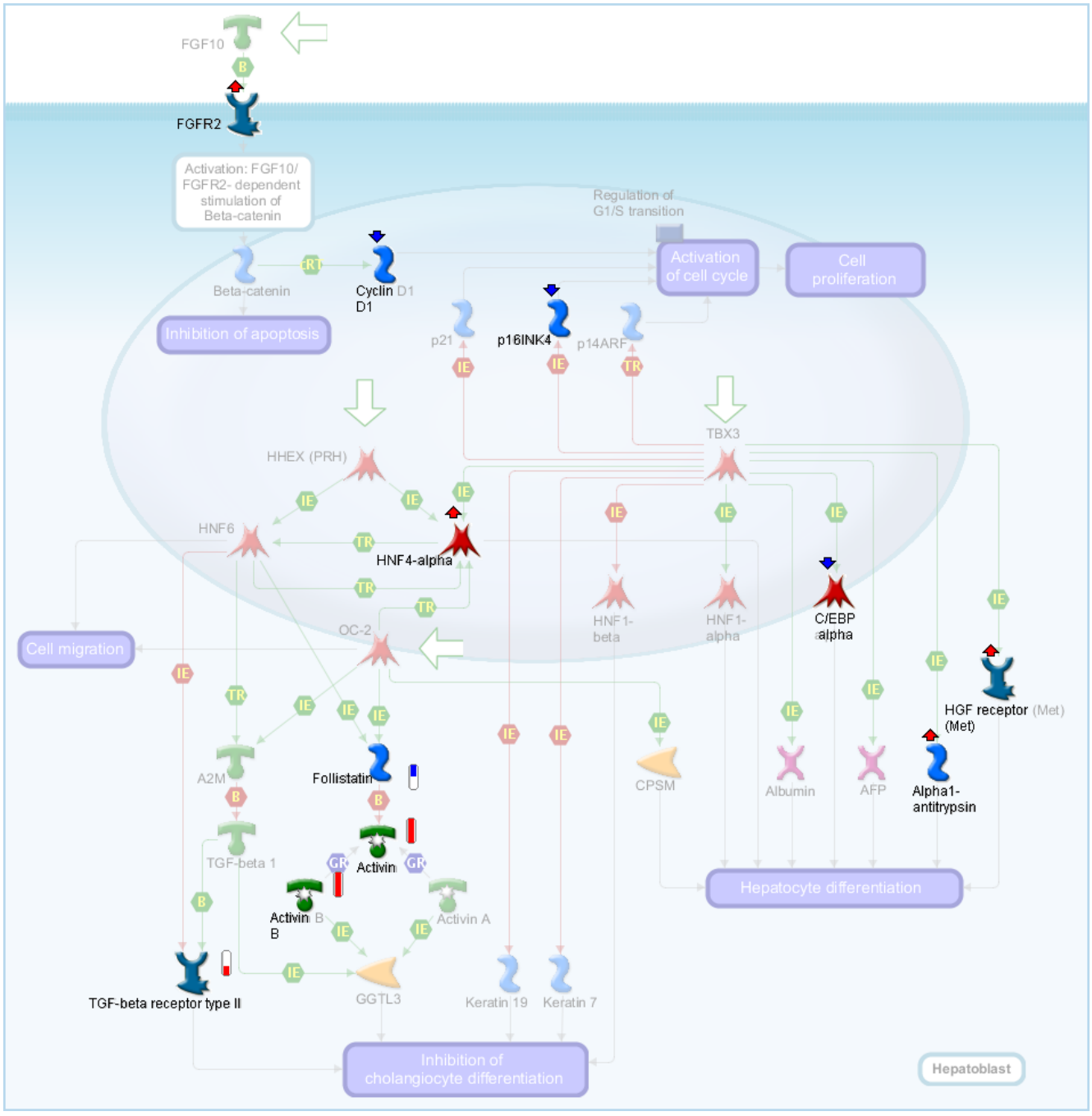
The **PI3K**/ 3-phosphoinositide dependent protein kinase-1 (**PDK (PDPK1)**)/ **AKT** signaling leads to carcinoma cell survival and tumor progression [22], [29].

The **PI3K**/ **AKT** pathway also leads to FK506 binding protein 12-rapamycin associated protein 1 (**mTOR**) activation. The phosphorylation of Eukaryotic translation initiation factor 4E binding protein 1 (**4E-BP1**) by **mTOR** disrupts the interaction between **4E-BP1** and Eukaryotic translation initiation factor 4E (**eIF4E**) [30], enabling **eIF-4E** to initiate translation of **ErbB3**, that contributes to the positive feedback loop in the **ErbB2**/**ErbB3** signaling [28].

Alpha-6/beta-4 integrin via the same signaling pathway also enhances Vascular endothelial growth factor A (**VEGF-A**) translation in carcinoma cells that leads to the tumor progression and metastases development [3], [31].

Maps and Descriptions [6 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Transcription factors in segregation of hepatocytic lineage	0.006026	9.628E-5	7.014E-7



Abstract:

After specification, hepatic progenitors (hepatoblasts) proliferate and migrate to septum transversum mesenchyme, where they give rise to the cells of bile ducts (cholangiocytes) and mature hepatocytes. **FGF10** signaling probably through **Beta-catenin** activation, induces survival and proliferation of hepatoblasts. **HNF6** and **OC-2** promote hepatoblast migration into the mesenchyme and segregation of the hepatocytic and biliary lineages via preventing **TGF-beta 1/Activin** signaling. **TBX3** signaling promotes hepatoblast proliferation and inhibits their differentiation to cholangiocytes.

Details:

After specification (see hepatoblast differentiation), the hepatic progenitors (hepatoblasts) proliferate and migrate to the septum transversum mesenchyme, where they give rise to the cells of bile ducts (cholangiocytes) and the mature hepatocytes [1], [2].
FGF10 is expressed by mesenchymal cells of liver after hepatoblast differentiation. **FGF10** signaling activates **Beta-catenin** in hepatoblasts probably via **Beta-catenin** and, thereby provides normal cell proliferation of hepatoplasts and prevents apoptotic process of hepatic cells [3]. In addition, **Beta-catenin** in hepatoblasts upregulates expression of **Cyclin D1**, the well known cell cycle regulator [4].

The transcription factor **HHEX (PRH)** activated at the time of hepatic specification (see hepatoblast differentiation) directly induces expression of **HNF6** and **HNF4-alpha** [5]. **HNF6** and **HNF4-alpha** positively regulate expression of each other in fetal liver [6], [7]. **OC-2** also positively regulates expression of **HNF4-alpha** [6].

HNF6 and **OC-2** promote migration of hepatoblasts (see positive regulation of cell migration) into the mesenchyme [8] and are required for hepatoblast segregation between the hepatocytic and biliary lineages [9]. Both **HNF6** and **OC-2** increase expression of **TGF-beta 1** antagonist **A2M** and **Activin** antagonist **Follistatin**, thereby preventing **TGF-beta 1**/ **Activin** signaling required for biliary differentiation [10]. **HNF6** inhibits expression of the **TGF-beta receptor type II** as well. Inhibition of **TGF-beta 1**/ **Activin** signaling by **HNF6** and **OC-2** downregulates expression of biliary marker **GGTL3** in hepatoblasts. At the same time **OC-2** upregulates expression of hepatocytic marker **CPSM**. Thus, **HNF6** and **OC-2** provide segregation of the hepatocytic and the biliary lineages [9].

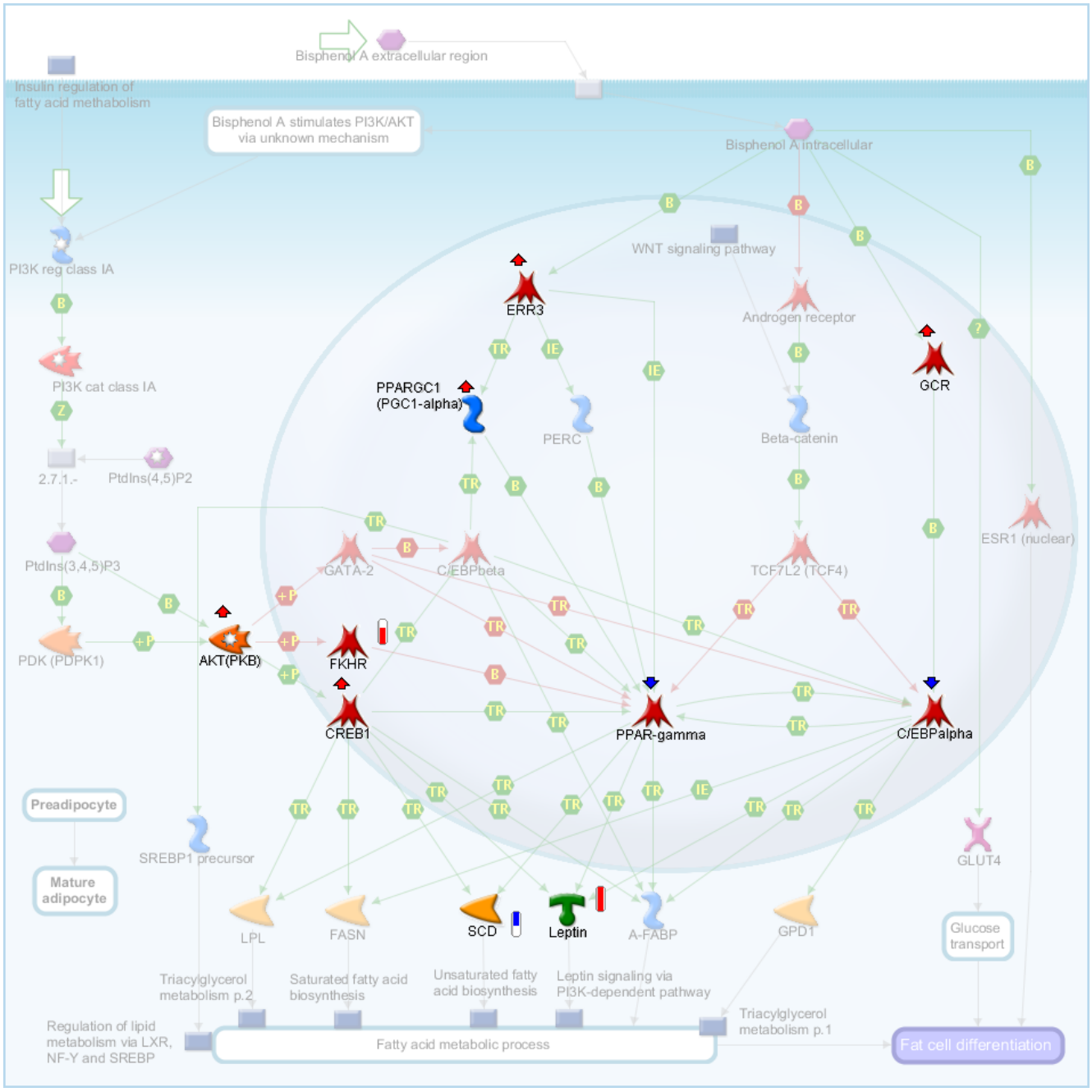
Expression of **TBX3** is strongly upregulated at the time of liver bud expansion and segregation of the hepatocytic lineage. **TBX3** suppresses expression of the cell cycle inhibitors **p14ARF** and **p16INK4** [11], products of Ink4a/Arf locus and **p21** [12]. Thus, **TBX3** promotes cell proliferation of hepatoblasts and inhibits their differentiation to cholangiocytes [11].

TBX3 also downregulates expression of genes associated with cholangiocyte differentiation such as **Keratin 19**, **Keratin 7**, **HNF1-beta**, and upregulates expression of liver-specific genes such as, **HNF4-alpha**, **HNF1-alpha**, **C/EBPalpha**, **Albumin**, **AFP**, **Alpha 1-antitrypsin** [11].

In addition, **TBX3** upregulates expression of **HGF receptor (Met)** [11] which then transduces HGF signaling required for hepatic cell differentiation and cell maturation [13].

Maps and Descriptions [7 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Putative pathways for stimulation of fat cell differentiation by Bisphenol A	0.006026	9.628E-5	7.014E-7



Abstract:

One of the putative mechanisms of **Bisphenol A** effect on body weight is stimulation of fat cell differentiation. However, the mechanisms by which **Bisphenol A** exerts its action is enigmatic.

Bisphenol A may stimulate fat cell differentiation via stimulation of **PI3K reg class IA/ AKT(PKB)**, activation of **ESR1 (nuclear)**, **ERR3**, **GCR** and/or inhibition of **Androgen receptor**. Modulation of these genes expression by **Bisphenol A** leads to activation of adipogenic marker proteins including **PPARGC1 (PGC1-alpha)**, **PERC**, **PPAR-gamma** and **A-FABP**, lipogenic proteins (**LPL**, **GPD1**, **SCD**, **FASN**, **Leptin**, **SREBP1 precursor**) and glucose transporter **GLUT4**.

Details:

Bisphenol A is a small molecule which is used as a monomer in polymerization reaction to produce polycarbonate plastics. Polycarbonates are found in numerous consumer products, including food and water containers, medical tubing, epoxy resins and dental fillings. Small amounts of **Bisphenol A** can migrate from the polymers to food or water, especially upon heating. Studies conducted in the USA, Europe and Japan, have documented widespread human exposure to **Bisphenol A**, including detectable levels in serum and breast milk. Lipophilic **Bisphenol A** also accumulates in human fat [1], [2].

Some observations link prenatal or perinatal **Bisphenol A** exposure to increased body weight [3], [4]. One of the putative mechanisms of **Bisphenol A** effect on body weight is a stimulation of fat cell differentiation [2].

The exact mechanisms of **Bisphenol A** effects on fat cell differentiation are unknown. **Bisphenol A** can accelerate conversion of preadipocytes into mature adipocytes directly [5] or in combination with Insulin [6].

It was shown that **Bisphenol A** stimulates fat cell differentiation in **PI3K reg class IA/ AKT(PKB)**-dependent manner [5].

Bisphenol A stimulates expression of **LPL** and **A-FABP** in **PI3K reg class IA/ AKT(PKB)**-dependent manner [5]. **AKT(PKB)** may activate expression of **LPL** and **A-FABP** via a certain pathway, for instance by regulation of transcription factors **GATA-2** [7], **FKHR** [8], **CREB1** [9].

GATA-2 is phosphorylated and blocked by the **PI3K reg class IA/ AKT(PKB)** signal transduction pathway [7]. It eliminates **GATA-2**-dependent inhibition of **C/EBPbeta** and **C/EBPalpha** transcription activity [10] and **PPAR-gamma** expression [7], [10], [11], [12].

FKHR is phosphorylated and blocked by **AKT(PKB)**. It eliminates **FKHR**-dependent inhibition of **PPAR-gamma** transcription activity [8]

CREB1 is phosphorylated and stimulated by **AKT(PKB)**. It was suggested that activated **CREB1** increases **PPAR-gamma**, **C/EBPbeta**, **LPL**, **SCD**, **FASN**, **Leptin** and **A-FABP** expression [9], [13], [14], [15], [16].

C/EBPbeta is an important adipogenic transcription factor which stimulates transcription of **C/EBPalpha** and **PPAR-gamma**. **C/EBPbeta**, **C/EBPalpha** and **PPAR-gamma** form a network of transcription factors that coordinate expression of proteins responsible for establishing the mature fat-cell phenotype (including, **LPL**, **SCD**, **FASN**, **Leptin** and **A-FABP** and other [17], [18]).

Bisphenol A is equipotent to estradiol in some of its effects. It is possible that **Bisphenol A** stimulates fat cell differentiation via estrogen receptors (most likely, **ESR1 (nuclear)** [19], [20], [21] and **ERR3** [22], [23]). **ESR1 (nuclear)** stimulates transcription of glucose transporter **GLUT4** [24], [25]. **ERR3** stimulates transcription of adipogenic marker genes including **PPAR-gamma** co-activators **PPARGC1 (PGC1-alpha)** [26] and **PERC**, **PPAR-gamma** and **A-FABP** [23].

Moreover, **Bisphenol A** is capable to promote fat cell differentiation through activation of the **GCR** [27], [28]. The activated **GCR** increases lipid storage [27], possibly, via **C/EBPalpha**-dependent stimulation of **Leptin** expression [29], [30].

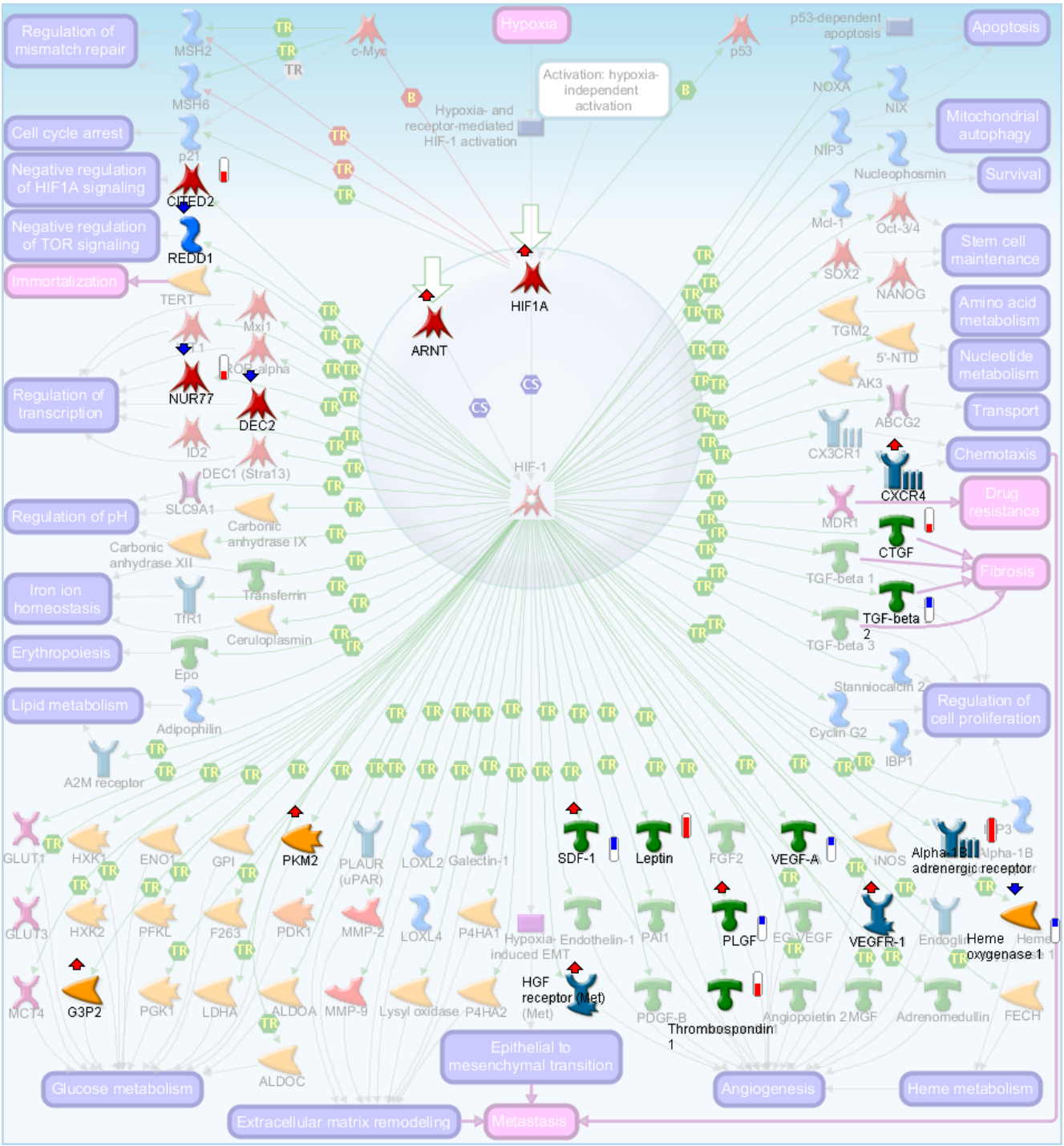
In addition, **Bisphenol A** may stimulate fat cell differentiation via inhibition of **Androgen receptor** [31]. **Bisphenol A** is likely to eliminate nuclear translocation of **Androgen receptor** complex with **Beta-catenin** and **TCF7L2 (TCF4)**. It elevates **TCF7L2 (TCF4)**-dependent inhibition of translation of **C/EBPalpha** and **PPAR-gamma** [32]. **LPL** and **GPD1** expression may be stimulated via this pathway [6], [33], [34].

Lipogenic proteins (**LPL**, **GPD1**, **SCD**, **FASN**, **Leptin**, **SREBP1 precursor** and **A-FABP**) stimulate fatty acid metabolic process, thus

contributing to the establishment of the mature fat-cell phenotype [35].

Maps and Descriptions [8 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Transcription_HIF-1 targets	2.046E-5	5.085E-5	7.508E-7



Abstract:

Hypoxia-inducible factor-1 (**HIF-1**) is an oxygen-sensitive transcription factor composed of hypoxia-regulated **HIF1A** and constitutively expressed **ARNT**. **HIF-1** directly or indirectly (via other transcription factors such as **c-Myc** and **p53**) regulates transcription of hundreds genes thus resulting in multiple physiological and pathologic processes, including glucose metabolism, angiogenesis, erythropoiesis, cell proliferation, apoptosis, survival, stem cell maintenance and metastasis.

Details:

Hypoxia-inducible factor-1 (**HIF-1**) is an oxygen-sensitive transcription factor composed of hypoxia-regulated **HIF1A** and constitutively expressed **ARNT**, which regulates cellular response to changes in oxygen tension during normal development or pathologic processes. **HIF-1** regulates multiple physiological processes, including glucose metabolic process, angiogenesis, erythropoiesis (see erythrocyte differentiation), cell proliferation, apoptosis and survival (see regulation of apoptotic process). Moreover, **HIF-1** is a critical regulator of pathologic processes such as neoplasmic survival, metastasis and invasion, and drug resistance [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12].

HIF-1 exerts its effect on cellular processes via activation/ inhibition of transcription of its target genes. **HIF-1** can regulate transcription directly or indirectly via modulation of activity of other transcription factors. In particular, **HIF1A** inhibits **c-Myc** function [13]. As **c-Myc** positively regulates transcription of mismatch repair genes **MSH2** and **MSH6**, **HIF1A** decreases **MSH2** and **MSH6** expression thus promoting genomic instability in cancers [14]. Moreover, **HIF1A** displaces **c-Myc**, a negative regulator of **p21** expression, from **p21** promoter thus increasing **p21** expression and inducing cell cycle arrest [15].

Moreover, **HIF-1** can regulate its own activity via triggering negative feedback loop and inducing its negative regulator **CITED2** [16].

In addition, **HIF-1** inhibits Target of Rapamycin (TOR) signaling (see negative regulation of TOR signaling) via induction of expression of **REDD1** [17], [18], [19].

HIF-1 activates transcription of **TERT** [20] which can contribute to cellular immortalization in cancers [10].

HIF-1 induces expression of several transcription factors including **Mxi1** [21], **WT1** [22], **ROR-alpha** [23], **NUR77** [24], [25], **DEC1 (Stra13)** and **DEC2** [26] and **ID2** [27].

HIF-1 regulates pH homeostasis (see regulation of pH) via induction of transcription of **SLC9A1** [28], **Carbonic anhydrase IX** and **Carbonic anhydrase XII** [29].

Moreover, **HIF-1** up-regulates proteins involved in cellular iron ion homeostasis, such as **Transferrin** [30], **TfR1** [31] and **Ceruloplasmin** [3], [32] and promotes erythropoiesis (see erythrocyte differentiation) via induction of **Epo** [3], [33].

HIF-1 regulates cellular lipid metabolic process via induction of genes such as **Adipophilin** [13], [34] and **A2M receptor** [35], [36].

HIF-1 is a critical regulator of glucose metabolic process which shifts cellular energy metabolism from oxidative phosphorylation and towards canonical glycolysis [7], [12]. Among other targets, **HIF-1** activates transcription of **GLUT1** [1], [3], [37], [38], **GLUT3** [1], [3], [38], [39], [40], **MCT4** [7], [41] **HXK1** and **HXK2** [1], [3], [7], [38], [42], [43], **G3P2** [2], [12], [44], **ENO1** [2], [7], [12], [45], **PFKL** [2], [12], [46], **PGK1** [2], [7], [12], [46], **GPI** [2], [12], [47], **F263** [2], [48], **LDHA** [2], [7], [12], [38], [45], **PKM2** [7], [12], [38], [49], **PDK1** [7], [12], [50], **ALDOA** [7], [12], [45], **ALDOA** [7], [12], [46].

HIF-1 induces extracellular matrix remodeling (see extracellular matrix organization), in particular, via induction of **PLAUR (uPAR)** [12], [51], [52], MMPs such as **MMP-2** and **MMP-9** [12], [53], [54], **Lysyl oxidase**, **LOXL2** and **LOXL4** [12], [55], **Galectin-1** [12], [56], **P4HA1** [57] and **P4HA2** [58], [59]. Moreover, **HIF-1** is well-known trigger of epithelial to mesenchymal transition [60].

Expression of virtually all of the critical angiogenic growth factors and regulator of angiogenesis/ vascular tone is induced by hypoxia through the transcriptional activity of **HIF-1**. In particular, **HIF-1** induces **SDF-1** [8], [10], [61], [62], **Endothelin-1** [3], [10], [63], **HGF receptor (Met)** [10], [64], [65], Leptin [10], [12], [66], **PAI1** [1], [12], [67], [68], [69], **PDGF-B** [70], [71], **FGF2** [11], [62], [72], **PLGF** [8], [62],

Thrombospondin 1 [5], [73], **VEGF-A** [1], [8], [10], [12], [62], [74], **EG-VEGF** [2], [75], **Angiopoietin 2** [8], [76], **iNOS** [2], [3], [12], [77], **VEGFR-1** [1], [12], [38], [78], **MGF** [8], [62], [79], [80], **Endoglin** [2], [81], **Adrenomedullin** [1], [3], [82] and **Alpha-1B adrenergic receptor** [2], [3], [83].

Moreover, **HIF-1** regulates heme metabolic process, in particular, via induction of **Heme oxygenase 1** [38] , [84],and **FECH** [12], [85].

HIF-1 regulates cell proliferation, in particular, via induction of **iNOS** [77], [86], **IBP1** [1], [2], [87] and **IBP3** [1], [2], [88], **Cyclin G2** [2], [89] and **Stanniocalcin 2** [90].

HIF-1 also activates transcription of pro-fibrotic and pro-proliferative **TGF-beta 1** [91], **TGF-beta 2** [92], **TGF-beta 3** [93], [94] and **CTGF** [95].

HIF-1 can promote multi-drug resistance in cancer cells via induction of **MDR1** [96], [97].

HIF-1 regulates chemotaxis of normal and cancer cells via activation of transcription of chemokine receptors such as **CXCR4** [98] and **CX3CR1** [99].

HIF-1 induces expression of pro-angiogenic **ABCG2** channel that can transport multiple molecules thus affecting cellular biology [100].

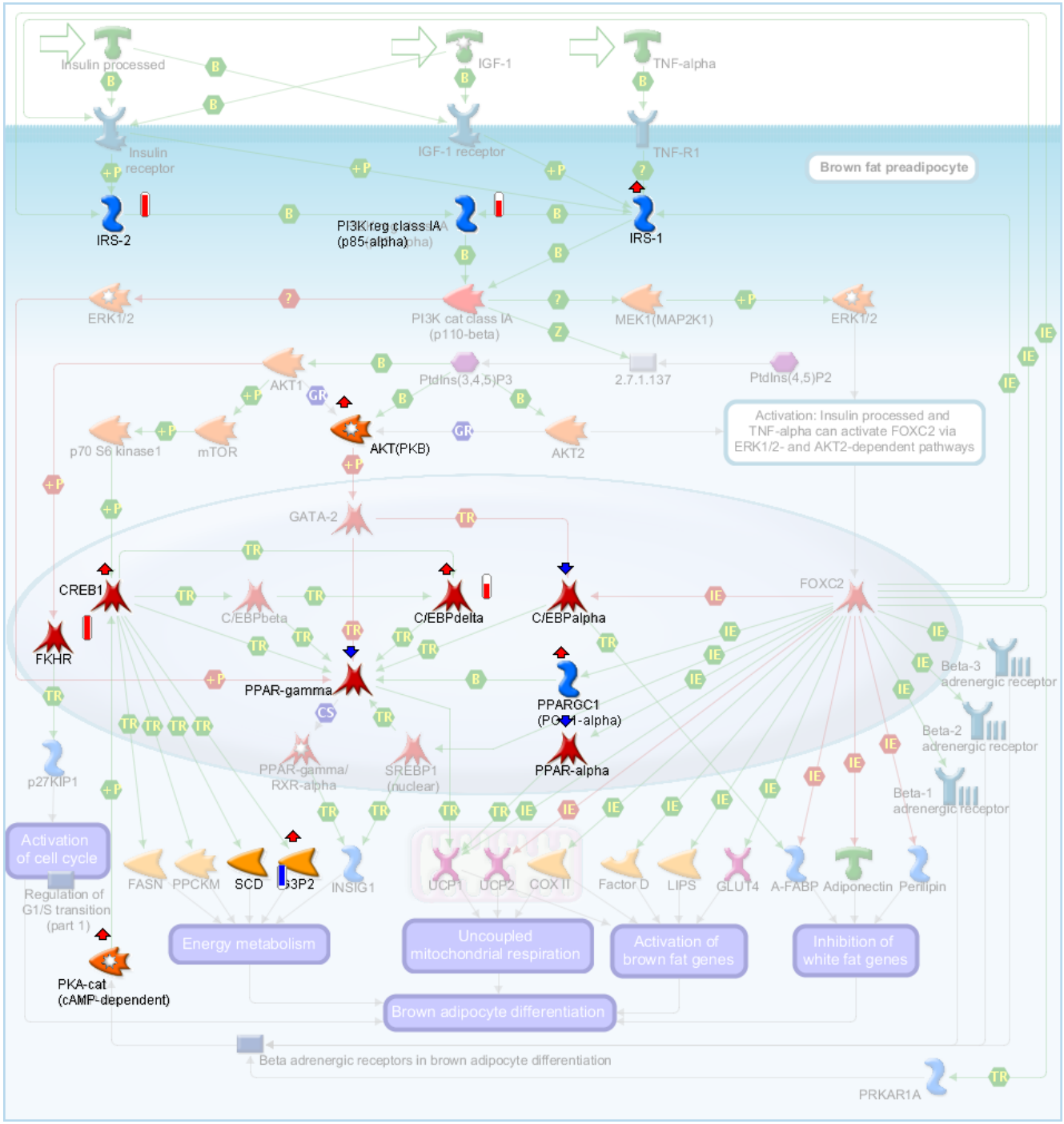
HIF-1 regulates nucleotide metabolic process via activation of transcription of **AK3** [1], [2], [3], [38], [101], [102] and **5'-NTD** [2], [103] and cellular amino acid metabolic process via **TGM2** [2], [104].

HIF-1 can support stem cell population maintenance via induction of expression of **NANOG**, **Oct-3/4** and **SOX2** [105].

HIF-1 promotes survival or triggers apoptosis (see regulation of apoptotic process) depending on cell type/ cellular context [106]. In particular, **HIF-1** can induce anti-apoptotic **Mcl-1** [107], [108] and **Nucleophosmin** [12], [109] and pro-apoptotic **NIP3**, **NIX** [110] and **NOXA** [111]. Moreover, during prolonged hypoxia **HIF1A** stabilizes **p53** [13], [112], [113] thus promoting cell apoptotic process [113], [114].

Maps and Descriptions [9 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Insulin, IGF-1 and TNF-alpha in brown adipocyte differentiation	0.008241	1.591E-5	1.234E-6



Abstract:

Regulation of energy balance is the main function of adipose tissue. There are two functionally different types of fat in mammals: white adipose tissue and brown adipose tissue. **Insulin**, **IGF-1** and **TNF-alpha** can induce adipogenesis and differentiation of brown adipocytes. Their signaling cascades activate PI3K which can both activate and inhibit **ERK1/2** pathways and stimulate **AKT** signaling. Each pathway leads to adipogenesis. PI3K-induced inhibition of **ERK1/2** attenuates its inhibitory action on **PPAR-gamma**, involved in adipogenesis. PI3K-induced activation of **ERK1/2** leads to expression of **FOXC2**. **FOXC2** represses expression of white fat genes and activates expression of brown fat genes, leading to differentiation of brown adipocytes. PI3K/ **AKT1** signaling stimulates **CREB1**, which up-regulates transcription of **PPAR-gamma** and enzymes, involved in energy metabolism. **AKT1** also inhibits **FKHR**, thereby decreasing expression of **p27KIP1**. Inhibition of **p27KIP1** activates cell cycle involved in adipogenesis.

Details:

Regulation of energy balance is the main function of adipose tissue. There are two functionally different types of fat in mammals: white adipose tissue, the primary site of triglyceride storage, and brown adipose tissue, which is specialized in energy expenditure and can counteract obesity [1].

Insulin, Insulin-like growth factor 1 (**IGF-1**) and Tumor necrosis factor (**TNF-alpha**) are potent inducers of adipogenesis and differentiation of brown adipocytes. **Insulin**, **IGF-1** and **TNF-alpha** promote differentiation by activating their cognate receptors - **Insulin receptor**, Insulin-like growth factor I receptor (**IGF-1 receptor**), and Tumor necrosis factor receptor superfamily, member 1A (**TNF-R1**), respectively [2], [3], [4]. **Insulin receptor**, **IGF-1 receptor** and **TNF-R1** stimulate Insulin receptor substrate 1 and 2 (**IRS-1** and**IRS-2**)/ Phosphoinositide-3-kinase, regulatory subunit 1 (alpha) (**PI3K reg class IA (p85-alpha)**)/ Phosphatidylinositol 3-kinase, catalytic, beta polypeptide (**PI3K cat class IA (p110-beta)**) cascade [5], [6].

Bi-directional regulation of brown fat adipogenesis by the **Insulin Receptor** via **PI3K cat class IA (p110-beta)** has been observed in brown preadipocytes [7].On the one hand, **PI3K cat class IA (p110-beta)** inhibits Mitogen activated protein kinase 1/3 (**ERK1/2**), thereby attenuating **ERK1/2** inhibitory action on Peroxisome proliferator activated receptor gamma (**PPAR-gamma**) and promoting activation of **PPAR-gamma** which stimulates adipogenesis [6]. On the other hand, **Insulin** and **TNF-alpha**-induced **PI3K cat class IA (p110-beta)** activates Mitogen-activated protein kinase kinase 1 (**MEK1(MAP2K1)**) via yet unknown mechanism. **MEK1(MAP2K1)** activates **ERK1/2**, that induces expression of another transcriptional factor required for adipogenesis, Forkhead box C2 (**FOXC2**) [3]**.**

In addition, **PI3K cat class IA (p110-beta)** activates V-akt murine thymoma viral oncogene homolog 1 (**AKT1**)/ Mechanistic target of rapamycin (**mTOR**)/ RPS6KB2 ribosomal protein S6 kinase, 70kDa, polypeptide 2 (**p70 S6 kinase1**)/ cAMP responsive element binding protein 1 (**CREB1**) pathway [8], [9]**. CREB1** stimulates adipogenesis by up-regulating transcription of Peroxisome proliferator activated receptor gamma (**PPAR-gamma**) and enzymes involved in energy metabolism, such as Fatty acid synthase (**FASN**), phosphoenolpyruvate carboxykinase 2 (**PPCKM**), stearoyl-CoA desaturase (**SCD**), and GAPDH glyceraldehyde-3-phosphate dehydrogenase (**G3P2**) [8], [10].

Insulin- and **TNF-alpha**-induced PI3K signaling also activates V-akt murine thymoma viral oncogene homolog 2 (**AKT2**) which, probably, stimulates **FOXC2** transcriptional activity [11]. **FOXC2** represses expression of white fat genes, such as CCAAT/enhancer binding protein (C/EBP), alpha (**C/EBPalpha**), Uncoupling protein 2 (mitochondrial, proton carrier) (**UCP2**), **Perilipin**, **Adiponectin** and Fatty acid binding protein 4, adipocyte (**A-FABP**) [12]. **FOXC2** activates expression of brown fat genes, such as **PPARGC1 (PGC1-alpha)**, Peroxisome proliferator activated receptor alpha (**PPAR-alpha**), Cytochrome c oxidase II, mitochondrial (**COX II**), Uncoupling protein 1 (mitochondrial, proton carrier) (**UCP1**), Lipase, hormone-sensitive (**LIPS**), Solute carrier family 2 (facilitated glucose transporter), member 4 (**GLUT4**), Complement factor D (adipsin) (**Factor D**) (that is present in both white and brown adipocytes), Protein kinase, cAMP-dependent,

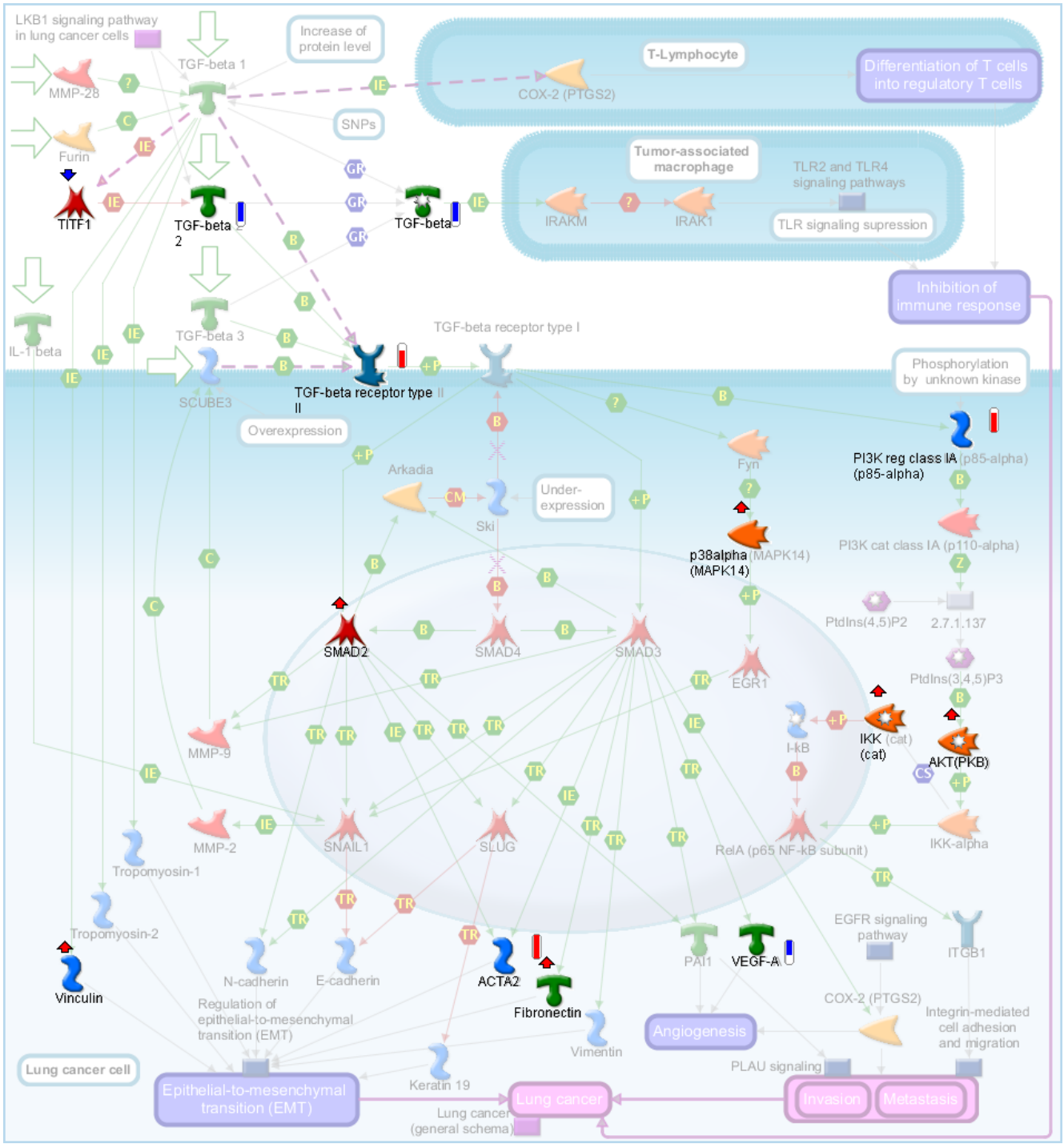
regulatory, type I, alpha (**PRKAR1A**), Sterol regulatory element binding transcription factor 1 (**SREBP1 (nuclear)**), **IRS-1** and **2**, **Insulin receptor**, **Beta-1 adrenergic receptor**, **Beta-2 adrenergic receptor** and **Beta-3 adrenergic receptor** [12]. **SREBP1 (nuclear)** activates transcription of Insulin induced gene 1 (**INSIG1**) and **PPAR-gamma** [13], [14]. In addition, **PPAR-gamma/RXR-alpha** induces transcription of **INSIG1** [14]. Besides, **FOXC2** stimulates Beta adrenergic receptor/ cAMP/ PKA/ CREB pathway via activating transcription of Protein kinase, cAMP-dependent, regulatory, type I, alpha (**PRKAR1A**) [12].

Furthermore, **AKT1** inhibits Forkhead box O1 (**FKHR**), thereby decreasing expression of Cyclin-dependent kinase inhibitor 1B (**p27KIP1**). Inhibition of **p27KIP1** activates cell cycle involved in adipogenesis [4].

In addition, **AKT** phosphorylates and inhibits activity of GATA binding protein 2 (**GATA-2**), thereby promoting activation of **PPAR-gamma** and stimulating adipogenesis [15].

Maps and Descriptions [10 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Stimulation of TGF-beta signaling in lung cancer	9.817E-4	0.00172	2.709E-6



Abstract:

Upregulation of **TGF-beta** signaling is involved in tumor progression in the late stages of lung cancer. **TGF-beta** signaling is activated via several mechanisms induced by SNP variants, and changes in gene and protein expression levels of members of **TGF-beta** signaling pathway. Ultimately, up-regulation of **TGF-beta** signaling stimulates SMADs-dependent and -independent pathways, promoting epithelial to mesenchymal transition, angiogenesis and metastasis. It leads to lung cancer progression.

Details:

Lung cancer continues to be the leading cause of cancer deaths in the United States, in Europe, and in the world. The main types of lung cancer are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC) [1], [2].

TGF-beta is a family of multifunctional cytokines with dual and paradoxical roles in cancer biology. In early stages of carcinogenesis, **TGF-beta** functions as a tumor suppressor, whereas in late stages **TGF-beta** functions as a tumor promoter [3].

Upregulation of **TGF-beta** signaling is involved in lung tumour progression and it realized via many mechanisms including:

- the presence of SNP variants of **TGF-beta 1** that are associated with higher circulating levels of **TGF-beta 1** and increased risk of NSCLC and adenocarcinoma of the lung [4], [5], [6];

- an increase of **TGF-beta 1** plasma levels in patients with lung cancer [7];

- overexpression of **TGF-beta 1** in tumor infiltrating stromal cells may regulate the occurrence of spontaneous pulmonary metastasis in NSCLC [8];

- overexpression of **SCUBE3** - a secreted glycoprotein acting as a **TGF-beta** ligand [9];

- underexpression of a negative regulator of **TGF-beta** signaling, **Ski** which enhances tumor metastasis [10];

TGF-beta signaling primarily occurs through SMAD protein dependent pathways. **TGF-beta** ligands (**TGF-beta 1**, **TGF-beta 2**, **TGF-beta 3** [11]) and/or the secreted glycoprotein **SCUBE3** [9] bind to **TGF-beta receptor type II** to induce phosphorylation and activation of **TGF-beta receptor type I**. After activation of **TGF-beta receptor type I**, phosphorylated **SMAD2** and **SMAD3** dissociate to form a heterotrimeric complex with **SMAD4** and translocate into the nucleus to regulate gene transcription. For example, transcriptional factors **SNAIL1** and **SLUG** are important targets of SMADs in epithelial to mesenchymal transition of lung cancer cells [12].

In lung cancer, **MMP-28** stimulates proteolytic processing of latent **TGF-beta 1**-complexes and increases the levels of active **TGF-beta 1** via an unknown pathway [13].

TGF-beta 1 and **TGF-beta 3** induce epithelial to mesenchymal transition of lung cancer cells via SMAD-dependent pathway, stimulating the expression of mesenchymal phenotype markers **Fibronectin**, **Vimentin**, **N-cadherin** and inhibiting the expression of the epithelial phenotype markers **E-cadherin** and **Keratin 19** [14], [15], [16]. **IL-1 beta** has synergic effects with **TGF-beta 1** in epithelial to mesenchymal transition via stimulation of **SNAIL1** transcription [16]. In addition, **TGF-beta 1** stimulates the expression of several pro-epithelial to mesenchymal transition proteins such as **Tropomyosin-1**, **Tropomyosin-2** and **Vinculin** via an unknown mechanism [17].

In addition, **TGF-beta 1** (in a synergic manner with Epidermal growth factor (EGF)) induced **COX-2 (PTGS2)** at the transcriptional and post-transcriptional levels in **SMAD3**-dependent manner [18]. Thus, **COX-2 (PTGS2)** is overexpressed in lung cancer and promotes cancer cell proliferation, angiogenesis and tumor invasion [19].

Overexpression of **SCUBE3** promotes SMAD-dependent expression of target genes involved in epithelial to mesenchymal transition, angiogenesis, tumor invasion and metastasis (such as **TGF-beta 1**, **MMP-2**, **MMP-9**, **PAI1**, **VEGF-A**, **SNAIL1** and **SLUG**) [9].

In addition, **TGF-beta** signaling may be realized via non-SMAD pathways [20].

TGF-beta 1 stimulates **Fyn**-dependent activation of **p38alpha (MAPK14)** thus inhibiting **E-cadherin** expression [21], possibly, via **EGR1** [22].

Moreover, **TGF-beta 1** acts through **PI3K reg class IA (p85-alpha)**/ **AKT(PKB)**, which in turn activates **IKK (cat)** and **RelA (p65 NF-kB**

subunit), resulting in the activation of transcription of **ITGB1** and contribute to the human lung cancer cell migration [23].
TGF-beta signaling may induce autostimulation of itself. **SMAD2** and **SMAD3** cooperate with E3 ubiquitin ligase **Arkadia** to mediate **TGF-beta**-induced degradation of negative regulation of **TGF-beta** signaling **Ski** [10]. In addition, enhancement of autocrine **TGF-beta 1** signaling may accelerate the decrease of **TITF1** expression, and conversely, **TITF1** may attenuate autocrine **TGF-beta 2** signaling [24].
As part of its tumor promoting effects, **TGF-beta** has a broad influence on the immune system. For example, in tumor-associated macrophages, **TGF-beta** stimulates expression of **IRAKM** which antagonizes Toll-like receptor signaling through inhibition of **IRAK1**. This positive regulation of macrophage tolerance induction serves as a key mechanism by which lung tumors may circumvent anti-tumor responses of macrophages, promoting tumor immune tolerance [25]. In addition, **TGF-beta** stimulation of human CD4+ T cells induces **COX-2 (PTGS2)** expression, promoting T cell differentiation (scilicet the formation of regulatory T cells, which participates in cancer-mediated immunosuppression) [26].

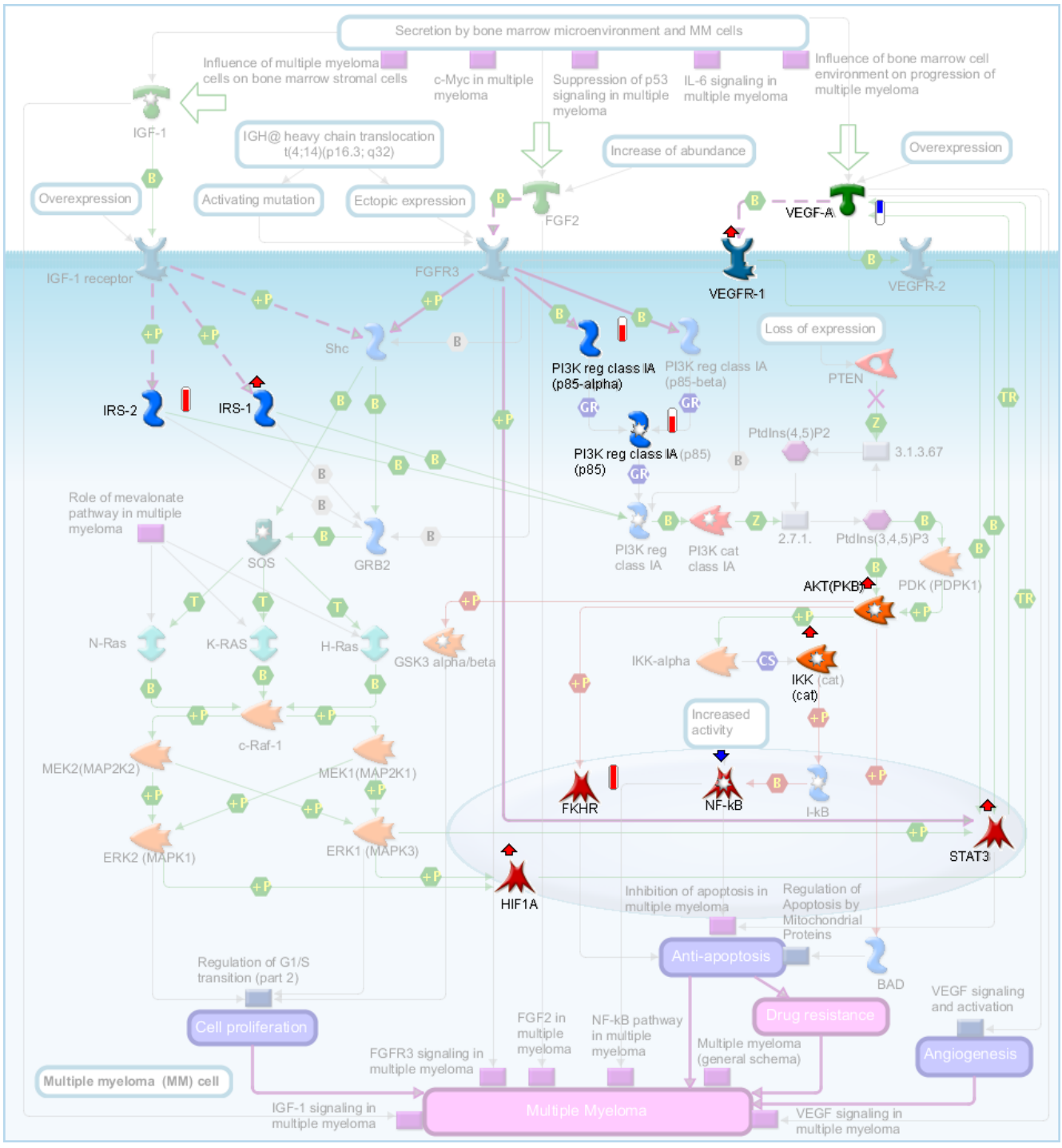
Pathological Pathway Maps

Pathological pathway maps are graphic images representing changes in biochemical pathways or signaling cascades found in pathologic cells. All maps listed below are enriched with both input genes and Key Hubs.

Pathological Pathway Maps Details [4 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
1	Main growth factor signaling cascades in multiple myeloma cells	0.001682	0.01853	6.949E-5
2	Putative pathways for stimulation of fat cell differentiation by Bisphenol A	0.01725	0.004232	9.576E-5
3	Stimulation of TGF-beta signaling in lung cancer	0.004462	0.0469	5.679E-4
4	Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor	0.004324	0.02989	0.001023

Maps and Descriptions [1 of 4]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Main growth factor signaling cascades in multiple myeloma cells	0.001682	0.01853	6.949E-5



Abstract:

Multiple myeloma (MM) is a hematologic malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow (BM). Interaction of myeloma cells with cells within the BM microenvironment results in the production of diverse cytokines and growth factors. **IGF-I**, **VEGF-A** and **FGF -2**, which are produced by myeloma cells and BM stromal cells, are important growth factor for myeloma cells. Growth factor signaling includes main RAS/ MAPK, PI3K/ AKT and **STAT3** signaling pathways which promote proliferation, survival, drug resistance and angiogenesis in MM.

Details:

Multiple myeloma (MM) is a hematologic malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow (BM). Interaction of myeloma cells with cells within the BM microenvironment results in the production of diverse cytokines and growth factors. **IGF-1**, **VEGF-A** and **FGF2**, which are produced by myeloma cells and BM stromal cells, are important growth factor for myeloma cells. Growth factors activate common RAS/ MAPK, PI3K/ **AKT(PKB)** and **STAT3** signaling pathways which promote cell proliferation, anti-apoptosis (see negative regulation of apoptotic process), drug resistance and angiogenesis in MM [1], [2], [3], [4], [5].

In MM cells **IGF-1** binds to and activates **IGF-1 receptor**, resulting in stimulation of **IRS-1**/ **IRS-2**/ **PI3K reg class IA**/ **PI3K cat class IA**/ **PtdIns(3,4,5)P3**/ **PDK (PDPK1)**/ **AKT(PKB)** cascade [6], [7], [8]. **PTEN** is a negative regulator that controls the PI3K/ **AKT(PKB)** pathway in MM cells. **PTEN** expression is lost in some MM cells thereby contributing to enhanced **AKT(PKB)** activation under **IGF-1** action [9]. **AKT(PKB)** promotes cell proliferation and anti-apoptosis (see negative regulation of apoptotic process) by several pathways in MM cells. Firstly, **AKT(PKB)** can directly phosphorylate and inhibit pro-apoptotic **BAD** and transcription factor **FKHR**, thereby promoting MM cell anti-apoptosis (see negative regulation of apoptotic process) [6], [10]. Secondly, **AKT(PKB)** can promote MM cell proliferation via phosphorylation of **GSK3 alpha/beta** [10], [7]. In addition, **AKT(PKB)** induces the **IKK-alpha**/ **IKK (cat)**/ **I-kB**/ **NF-kB** pathway which promotes anti-apoptosis (see negative regulation of apoptotic process), drug resistance and MM progression [11], [12]. Besides, **NF-kB** is constitutively active in most MM patients [13], [14].

Binding of **IGF-1** to the **IGF-1 receptor** leads to the induction of the **IRS-1**/ **IRS-2**/ **Shc**/ **GRB2**/ **SOS**/ **H-Ras**/ **c-Raf-1**/ **MEK1(MAP2K1)**, **MEK2(MAP2K2)**/ **ERK1 (MAPK3)**, **ERK2 (MAPK1)** pathway driving cell proliferation [8], [12], [15]. In turn, **ERK1 (MAPK3)** and **ERK2 (MAPK1)** activate **VEGF-A** secretion probably via **HIF1A** [12], [15]. **VEGF-A** can then induce angiogenesis and multiple myeloma progression [12], [15].

Several FGF ligands activate several FGF receptors in normal plasma and malignant MM cells, but **FGF2**/ **FGFR3** signaling is altered in MM cells. Higher abundance of **FGF2** has been observed in MM patients [16], [17] and **FGFR3** is not expressed in normal plasma cells, but IGH@-**FGFR3** translocation t(4;14)(p16.3;q32) that is present in 15% of patients leads to **FGFR3** ectopic expression [2], [18], [19], [20], [21]. t(4;14)(p16.3;q32) also promotes activating mutations of **FGFR3** [22], [23]. This mutation promotes ligand-independency of **FGFR3**, but nevertheless, FGF ligands are able to stimulate **FGFR3** signaling in multiple myeloma cells [23], [24], [25], [26], [27], [28].

Under **FGF2** action **FGFR3** binds to **Shc** and activates **Shc**/ **GRB2**/ **SOS**/ **H-Ras**, **N-Ras**, **K-RAS**/ **c-Raf-1**/ **MEK1(MAP2K1)**, **MEK2(MAP2K2)**/ **ERK1 (MAPK3)**, **ERK2 (MAPK1)** pathway stimulating MM cell proliferation [19], [29], [30], [31], [32], [33]. **ERK1 (MAPK3)** phosphorylates and activates **STAT3** [31], [34]. In addition, **FGFR3** can directly phosphorylate **STAT3** [35]. Activation of **STAT3** leads to anti-apoptosis in MM cells (see negative regulation of apoptotic process) [36], [37] and enhanced expression of **VEGF-A**, which promotes angiogenesis [38].

FGFR3 binds to and activates **PI3K reg class IA (p85-alpha)** and **PI3K reg class IA (p85-beta)**, thus stimulating kinase activity of **PI3K cat class IA** [31], [39]. **PI3K cat class IA** activates **PDK (PDPK1)**/ **AKT(PKB)** pathway promoting MM cell proliferation [31] and anti-

apoptosis (via inhibition of **FKHR**) (see negative regulation of apoptotic process) [40].

The VEGF signaling cascade is a well established mediator of angiogenesis which is enhanced in many types of cancer. However, in MM it contributes to tumor progression not only by activation of angiogenesis, but also by activation of MM cell proliferation and anti-apoptosis (see negative regulation of apoptotic process) [41], [42], [43], [44], [45], [46]. Indeed, VEGF signaling in MM has been demonstrated to be enhanced in MM cells when compared to normal plasma cells and early premalignant cell types [47], [48], [49].

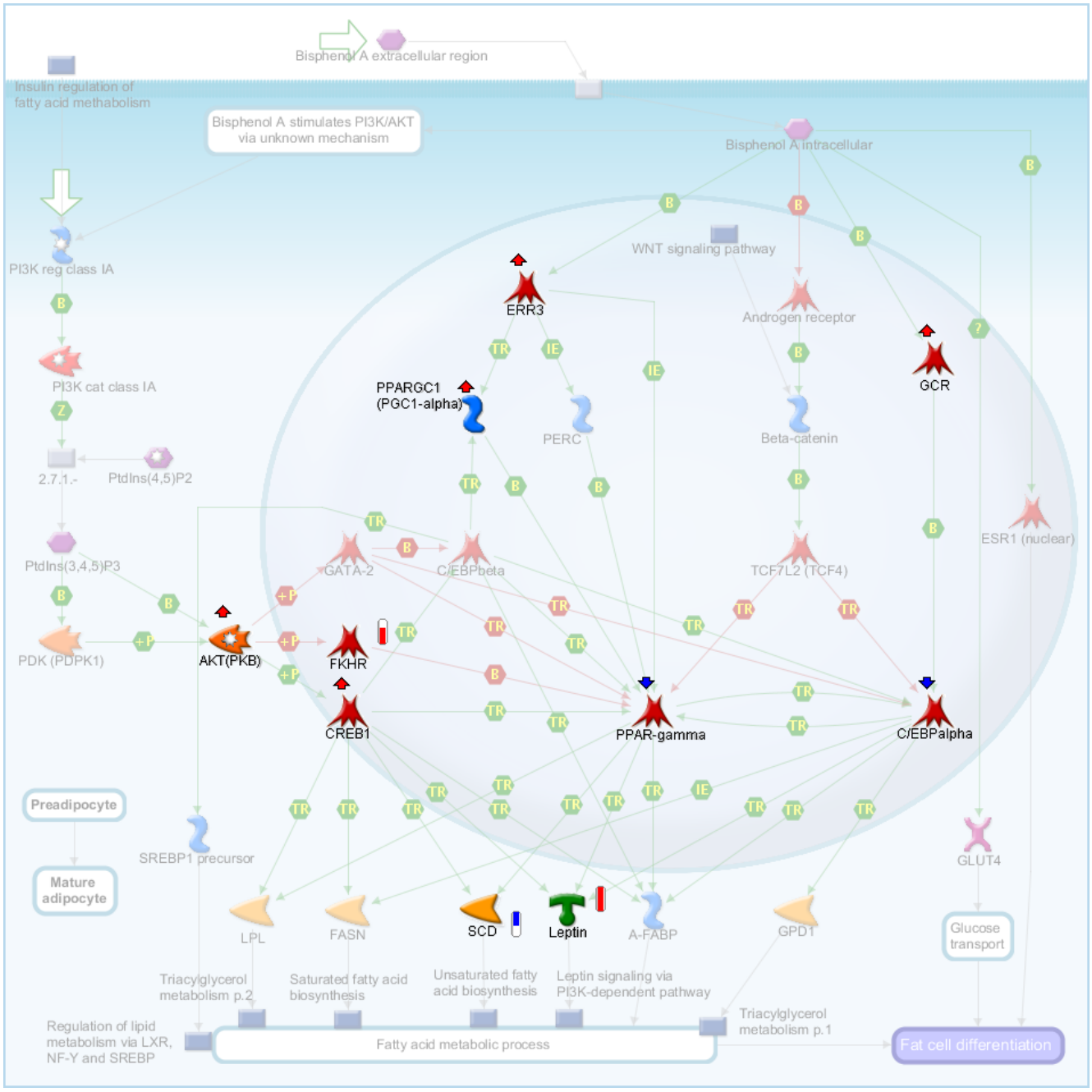
VEGF-A is overexpressed and overproduced by MM cells [41], [44], [50], [51], [52], [53].

Activation of **VEGFR-1** by **VEGF-A** and promotes the induction of the **GRB2**, **Shc**/ **SOS**/ **H-Ras**/ **c-Raf-1**/ **MEK1(MAP2K1)**, **MEK2(MAP2K2)**/ **ERK1 (MAPK3)**, **ERK2 (MAPK1)** pathway, which contributes to MM cell proliferation [40], [41], [44], [45], [53], [54], [55].

Activation of **VEGFR-1** leads to its association with **PI3K reg class IA** and activation of the **PI3K cat class IA**/ **AKT(PKB)** pathway [45], [54]. **AKT(PKB)** then phosphorylates **FKHR**, most likely contributing to anti-apoptotic effects in MM cells (see negative regulation of apoptotic process) [40]. Also, **VEGF-A** via the **VEGFR-1**, **VEGFR-2** activates **STAT3** pathway promoting anti-apoptosis in MM cells (see negative regulation of apoptotic process) [53], [56], [57], [58].

Maps and Descriptions [2 of 4]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Putative pathways for stimulation of fat cell differentiation by Bisphenol A	0.01725	0.004232	9.576E-5



Abstract:

One of the putative mechanisms of **Bisphenol A** effect on body weight is stimulation of fat cell differentiation. However, the mechanisms by which **Bisphenol A** exerts its action is enigmatic.

Bisphenol A may stimulate fat cell differentiation via stimulation of **PI3K reg class IA/ AKT(PKB)**, activation of **ESR1 (nuclear)**, **ERR3**, **GCR** and/or inhibition of **Androgen receptor**. Modulation of these genes expression by **Bisphenol A** leads to activation of adipogenic marker proteins including **PPARGC1 (PGC1-alpha)**, **PERC**, **PPAR-gamma** and **A-FABP**, lipogenic proteins (**LPL**, **GPD1**, **SCD**, **FASN**, **Leptin**, **SREBP1 precursor**) and glucose transporter **GLUT4**.

Details:

Bisphenol A is a small molecule which is used as a monomer in polymerization reaction to produce polycarbonate plastics. Polycarbonates are found in numerous consumer products, including food and water containers, medical tubing, epoxy resins and dental fillings. Small amounts of **Bisphenol A** can migrate from the polymers to food or water, especially upon heating. Studies conducted in the USA, Europe and Japan, have documented widespread human exposure to **Bisphenol A**, including detectable levels in serum and breast milk. Lipophilic **Bisphenol A** also accumulates in human fat [1], [2].

Some observations link prenatal or perinatal **Bisphenol A** exposure to increased body weight [3], [4]. One of the putative mechanisms of **Bisphenol A** effect on body weight is a stimulation of fat cell differentiation [2].

The exact mechanisms of **Bisphenol A** effects on fat cell differentiation are unknown. **Bisphenol A** can accelerate conversion of preadipocytes into mature adipocytes directly [5] or in combination with Insulin [6].

It was shown that **Bisphenol A** stimulates fat cell differentiation in **PI3K reg class IA**/ **AKT(PKB)**-dependent manner [5].

Bisphenol A stimulates expression of **LPL** and **A-FABP** in **PI3K reg class IA**/ **AKT(PKB)**-dependent manner [5]. **AKT(PKB)** may activate expression of **LPL** and **A-FABP** via a certain pathway, for instance by regulation of transcription factors **GATA-2** [7], **FKHR** [8], **CREB1** [9].

GATA-2 is phosphorylated and blocked by the **PI3K reg class IA**/ **AKT(PKB)** signal transduction pathway [7]. It eliminates **GATA-2**-dependent inhibition of **C/EBPbeta** and **C/EBPalpha** transcription activity [10] and **PPAR-gamma** expression [7], [10], [11], [12].

FKHR is phosphorylated and blocked by **AKT(PKB)**. It eliminates **FKHR**-dependent inhibition of **PPAR-gamma** transcription activity [8]

CREB1 is phosphorylated and stimulated by **AKT(PKB)**. It was suggested that activated **CREB1** increases **PPAR-gamma**, **C/EBPbeta**, **LPL**, **SCD**, **FASN**, **Leptin** and **A-FABP** expression [9], [13], [14], [15], [16].

C/EBPbeta is an important adipogenic transcription factor which stimulates transcription of **C/EBPalpha** and **PPAR-gamma**. **C/EBPbeta**, **C/EBPalpha** and **PPAR-gamma** form a network of transcription factors that coordinate expression of proteins responsible for establishing the mature fat-cell phenotype (including, **LPL**, **SCD**, **FASN**, **Leptin** and **A-FABP** and other [17], [18]).

Bisphenol A is equipotent to estradiol in some of its effects. It is possible that **Bisphenol A** stimulates fat cell differentiation via estrogen receptors (most likely, **ESR1 (nuclear)** [19], [20], [21] and **ERR3** [22], [23]). **ESR1 (nuclear)** stimulates transcription of glucose transporter **GLUT4** [24], [25]. **ERR3** stimulates transcription of adipogenic marker genes including **PPAR-gamma** co-activators **PPARGC1 (PGC1-alpha)** [26] and **PERC**, **PPAR-gamma** and **A-FABP** [23].

Moreover, **Bisphenol A** is capable to promote fat cell differentiation through activation of the **GCR** [27], [28]. The activated **GCR** increases lipid storage [27], possibly, via **C/EBPalpha**-dependent stimulation of **Leptin** expression [29], [30].

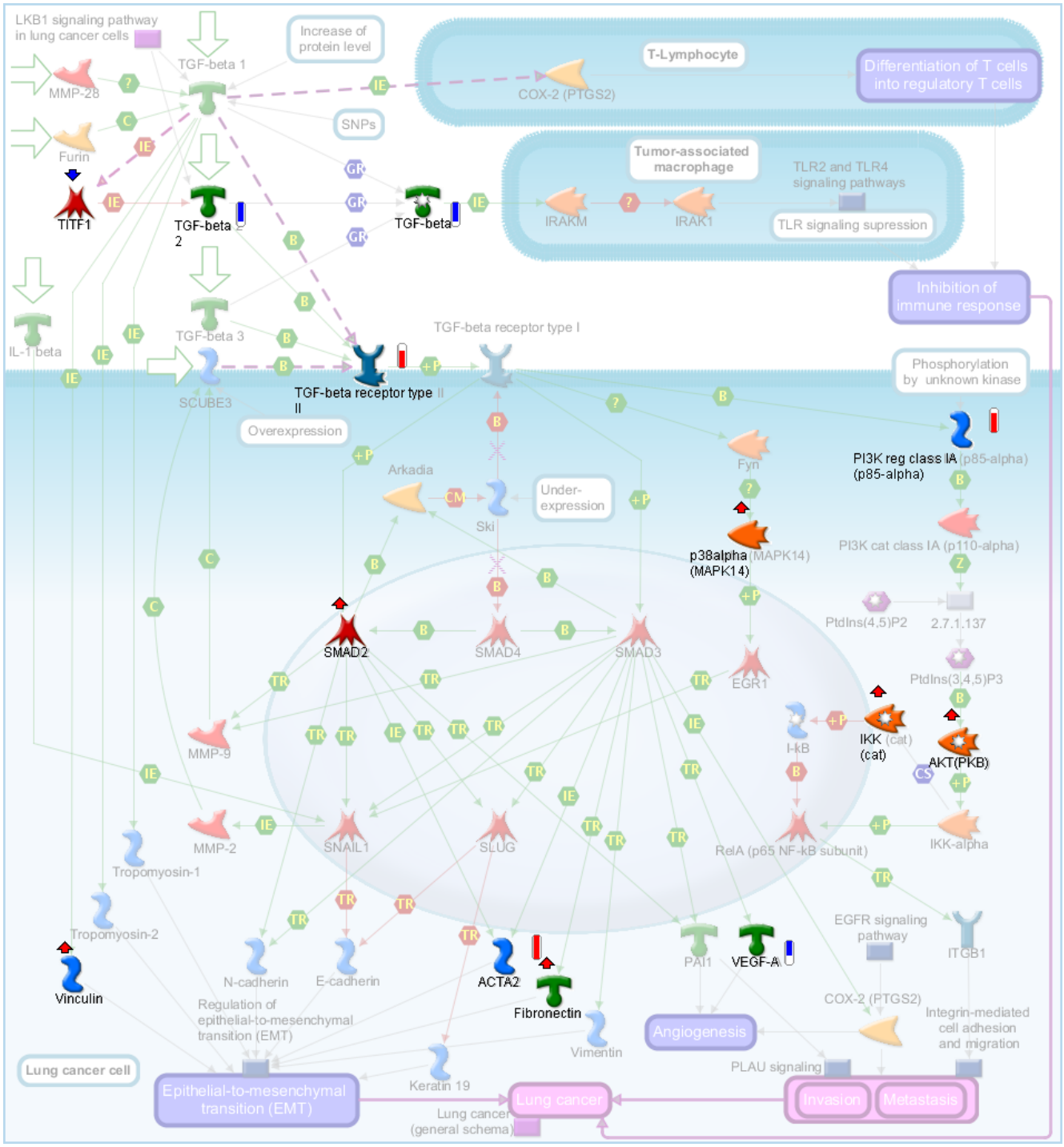
In addition, **Bisphenol A** may stimulate fat cell differentiation via inhibition of **Androgen receptor** [31]. **Bisphenol A** is likely to eliminate nuclear translocation of **Androgen receptor** complex with **Beta-catenin** and **TCF7L2 (TCF4)**. It elevates **TCF7L2 (TCF4)**-dependent inhibition of translation of **C/EBPalpha** and **PPAR-gamma** [32]. **LPL** and **GPD1** expression may be stimulated via this pathway [6], [33], [34].

Lipogenic proteins (**LPL**, **GPD1**, **SCD**, **FASN**, **Leptin**, **SREBP1 precursor** and **A-FABP**) stimulate fatty acid metabolic process, thus

contributing to the establishment of the mature fat-cell phenotype [35].

Maps and Descriptions [3 of 4]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Stimulation of TGF-beta signaling in lung cancer	0.004462	0.0469	5.679E-4



Abstract:

Upregulation of **TGF-beta** signaling is involved in tumor progression in the late stages of lung cancer. **TGF-beta** signaling is activated via several mechanisms induced by SNP variants, and changes in gene and protein expression levels of members of **TGF-beta** signaling pathway. Ultimately, up-regulation of **TGF-beta** signaling stimulates SMADs-dependent and -independent pathways, promoting epithelial to mesenchymal transition, angiogenesis and metastasis. It leads to lung cancer progression.

Details:

Lung cancer continues to be the leading cause of cancer deaths in the United States, in Europe, and in the world. The main types of lung cancer are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC) [1], [2].

TGF-beta is a family of multifunctional cytokines with dual and paradoxical roles in cancer biology. In early stages of carcinogenesis, **TGF-beta** functions as a tumor suppressor, whereas in late stages **TGF-beta** functions as a tumor promoter [3].

Upregulation of **TGF-beta** signaling is involved in lung tumour progression and it realized via many mechanisms including:

- the presence of SNP variants of **TGF-beta 1** that are associated with higher circulating levels of **TGF-beta 1** and increased risk of NSCLC and adenocarcinoma of the lung [4], [5], [6];

- an increase of **TGF-beta 1** plasma levels in patients with lung cancer [7];

- overexpression of **TGF-beta 1** in tumor infiltrating stromal cells may regulate the occurrence of spontaneous pulmonary metastasis in NSCLC [8];

- overexpression of **SCUBE3** - a secreted glycoprotein acting as a **TGF-beta** ligand [9];

- underexpression of a negative regulator of **TGF-beta** signaling, **Ski** which enhances tumor metastasis [10];

TGF-beta signaling primarily occurs through SMAD protein dependent pathways. **TGF-beta** ligands (**TGF-beta 1**, **TGF-beta 2**, **TGF-beta 3** [11]) and/or the secreted glycoprotein **SCUBE3** [9] bind to **TGF-beta receptor type II** to induce phosphorylation and activation of **TGF-beta receptor type I**. After activation of **TGF-beta receptor type I**, phosphorylated **SMAD2** and **SMAD3** dissociate to form a heterotrimeric complex with **SMAD4** and translocate into the nucleus to regulate gene transcription. For example, transcriptional factors **SNAIL1** and **SLUG** are important targets of SMADs in epithelial to mesenchymal transition of lung cancer cells [12].

In lung cancer, **MMP-28** stimulates proteolytic processing of latent **TGF-beta 1**-complexes and increases the levels of active **TGF-beta 1** via an unknown pathway [13].

TGF-beta 1 and **TGF-beta 3** induce epithelial to mesenchymal transition of lung cancer cells via SMAD-dependent pathway, stimulating the expression of mesenchymal phenotype markers **Fibronectin**, **Vimentin**, **N-cadherin** and inhibiting the expression of the epithelial phenotype markers **E-cadherin** and **Keratin 19** [14], [15], [16]. **IL-1 beta** has synergic effects with **TGF-beta 1** in epithelial to mesenchymal transition via stimulation of **SNAIL1** transcription [16]. In addition, **TGF-beta 1** stimulates the expression of several pro-epithelial to mesenchymal transition proteins such as **Tropomyosin-1**, **Tropomyosin-2** and **Vinculin** via an unknown mechanism [17].

In addition, **TGF-beta 1** (in a synergic manner with Epidermal growth factor (EGF)) induced **COX-2 (PTGS2)** at the transcriptional and post-transcriptional levels in **SMAD3**-dependent manner [18]. Thus, **COX-2 (PTGS2)** is overexpressed in lung cancer and promotes cancer cell proliferation, angiogenesis and tumor invasion [19].

Overexpression of **SCUBE3** promotes SMAD-dependent expression of target genes involved in epithelial to mesenchymal transition, angiogenesis, tumor invasion and metastasis (such as **TGF-beta 1**, **MMP-2**, **MMP-9**, **PAI1**, **VEGF-A**, **SNAIL1** and **SLUG**) [9].

In addition, **TGF-beta** signaling may be realized via non-SMAD pathways [20].

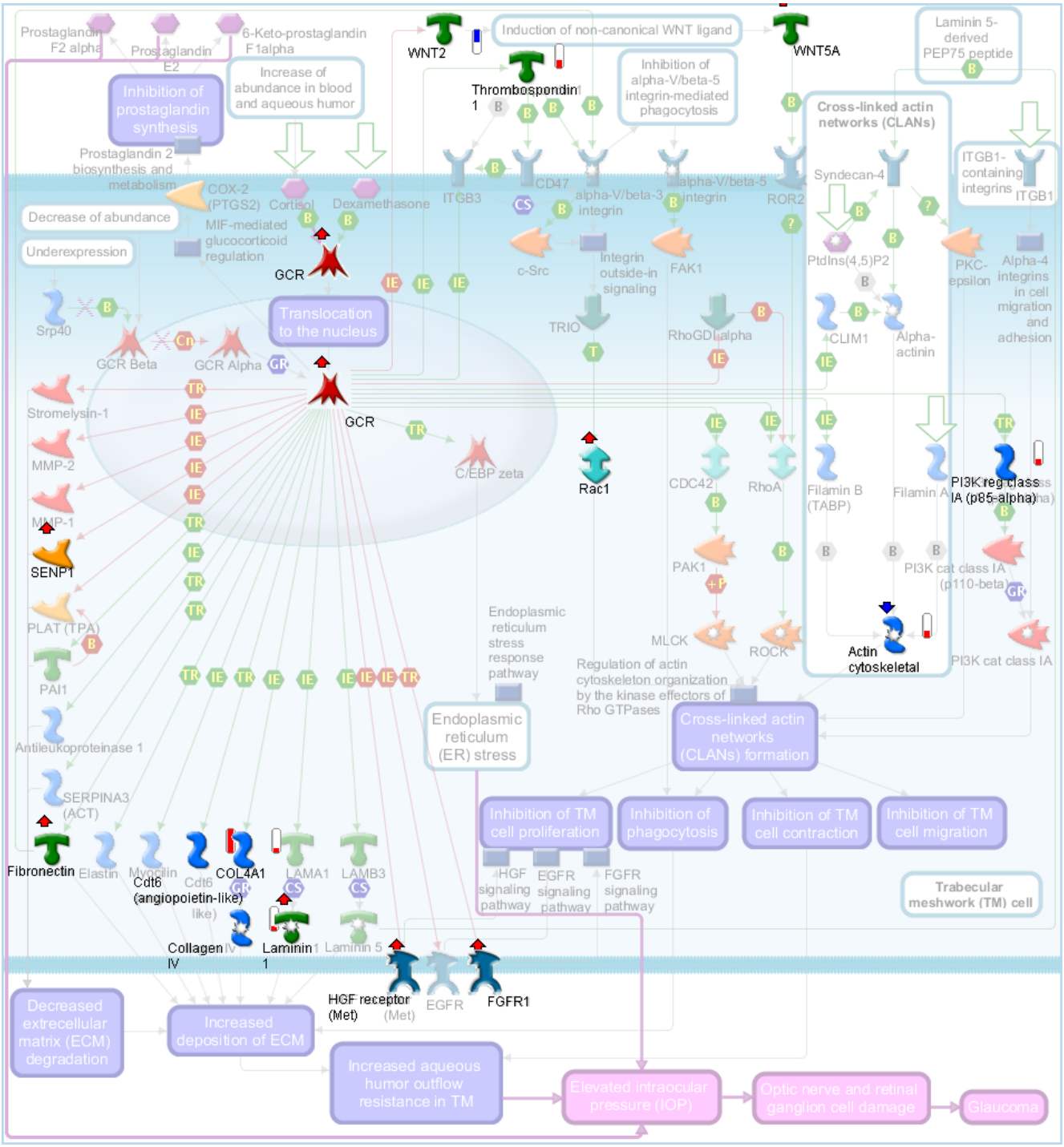
TGF-beta 1 stimulates **Fyn**-dependent activation of **p38alpha (MAPK14)** thus inhibiting **E-cadherin** expression [21], possibly, via **EGR1** [22].

Moreover, **TGF-beta 1** acts through **PI3K reg class IA (p85-alpha)**/ **AKT(PKB)**, which in turn activates **IKK (cat)** and **RelA (p65 NF-kB**

subunit), resulting in the activation of transcription of **ITGB1** and contribute to the human lung cancer cell migration [23].
TGF-beta signaling may induce autostimulation of itself. **SMAD2** and **SMAD3** cooperate with E3 ubiquitin ligase **Arkadia** to mediate **TGF-beta**-induced degradation of negative regulation of **TGF-beta** signaling **Ski** [10]. In addition, enhancement of autocrine **TGF-beta 1** signaling may accelerate the decrease of **TITF1** expression, and conversely, **TITF1** may attenuate autocrine **TGF-beta 2** signaling [24].
As part of its tumor promoting effects, **TGF-beta** has a broad influence on the immune system. For example, in tumor-associated macrophages, **TGF-beta** stimulates expression of **IRAKM** which antagonizes Toll-like receptor signaling through inhibition of **IRAK1**. This positive regulation of macrophage tolerance induction serves as a key mechanism by which lung tumors may circumvent anti-tumor responses of macrophages, promoting tumor immune tolerance [25]. In addition, **TGF-beta** stimulation of human CD4+ T cells induces **COX-2 (PTGS2)** expression, promoting T cell differentiation (scilicet the formation of regulatory T cells, which participates in cancer-mediated immunosuppression) [26].

Maps and Descriptions [4 of 4]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Glucocorticoid-induced elevation of intraocular pressure as glaucoma risk factor	0.004324	0.02989	0.001023



Abstract:

One of the form of glaucoma is so-called steroid-induced or glucocorticoid (GC)-induced glaucoma, induced by administration of exogenous GCs. GCs promote glaucoma via elevation of intraocular pressure (IOP) in GC responders. There are several mechanisms how GCs contribute to IOP elevation. GCs via **GCR** regulate expression of multiple matrix metalloproteinases, proteases, protease inhibitors and extracellular matrix (ECM) proteins in such way that degradation of ECM is inhibited while synthesis of ECM proteins is increased, what leads to ECM deposition and as a result to increased aqueous humor (AH) outflow resistance in TM and thus elevated IOP. Moreover, GCs/ **GCR** signaling pathway, via **alpha-V/beta-3 integrin** in particular, induces so-called cross-linked actin networks (CLANs) formation which leads to inhibition of TM cell functions, such as phagocytosis and cell contraction, which in turn increases deposition of ECM and AH outflow resistance, contributing to IOP elevation as well.

Details:

Glaucoma is a term describing a group of ocular disorders with multi-factorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy [1]. One of the forms of glaucoma is so-called steroid-induced or glucocorticoid (GC)-induced glaucoma, induced by administration of exogenous GCs. Its clinical presentation is similar in many ways to primary open-angle glaucoma (POAG). GCs induce glaucoma via elevation of intraocular pressure (IOP). However, only about 40% of the general population responds to GCs treatment with IOP elevation. Elevated IOP induced by GCs in steroid responders is due to increased aqueous humor (AH) outflow resistance that has been associated with morphological and biochemical changes in the trabecular meshwork (TM). In turn, elevated IOP can lead to optic nerve and retinal ganglion cell damage and subsequently to POAG. Thus, the GC responder population is at greater risk of developing POAG compared with non-responders [2].

GCs are a group of chemical compounds, both natural (such as **Cortisol**) and synthetic (such as **Dexamethasone**), which exert their effects via binding to **GCR**. GCs bind to **GCR** in cytoplasm which leads to **GCR** translocation to the nucleus where it induces transcription of target genes [3]. In addition to the fact that exogenous GCs induce IOP and subsequently can contribute to glaucoma development in responders, in patients with POAG abundance of natural GC **Cortisol** is increased in blood and AH [2], [4], [5]. Thus, similarly to administration of exogenous GCs, chronic slightly higher levels of endogenous **Cortisol** may lead to slowly progressive changes in the TM, which may eventually lead to elevated IOP and glaucoma [2].

The existence of GC responders and non-responders, as well as difference in GC response between normal individuals and POAG patients, could be due to different expression of **GCR Beta**, which acts as dominant-negative inhibitor of **GCR Alpha** transcriptional activities [3]. **GCR Beta** abundance is decreased in primary glaucomatous TM cell lines [6]. Underexpression of **Srp40**, which positively regulates expression of **GCR Beta** splice isoform of glucocorticoid receptor, could be one of the reasons of **GCR Beta** decreased abundance [7]. Decreased abundance of **GCR Beta** in POAG could explain the fact that almost all POAG patients are steroid responders [3].

There are several mechanisms how GCs/ **GCR** signaling pathway induces TM morphological and biochemical changes which result in increased AH outflow resistance in TM [2].

Dexamethasone via **GCR** decreases production of prostaglandins such as **Prostaglandin F2 alpha**, **Prostaglandin E2** and **6-Keto-prostaglandin F1alpha** [8], [9], [10], [11] probably via decreasing expression of **COX-2 (PTGS2)**, enzyme necessary for prostaglandin synthesis (see prostaglandin biosynthetic process), although other mechanisms couldn't be excluded [12], [13]. In turn, decrease of prostaglandin synthesis in TM cells presumably contributes to elevation of IOP, although the exact mechanism is unclear and some contradicting data exist in the literature [14], [15], [16], [17].

In addition, **Dexamethasone**/ **GCR** signaling decreases expression/ abundance and/ or secretion of matrix metalloproteinases and proteases including **Stromelysin-1** [18], **MMP-2** [19], **MMP-1** [20], **SENP1** [21] and **PLAT (TPA)** [18], [19], [22]. Moreover, **Dexamethasone** induces expression/ abundance of protease inhibitors such as **PAI1**, **PLAT (TPA)** inhibitor [22], **Antileukoproteinase 1** [23] and **SERPINA3 (ACT)** [21], [23]. In turn, decrease of abundances and activities of matrix metalloproteinases and proteases leads to decreased extracellular matrix (ECM) degradation (see negative regulation of extracellular matrix disassembly) and as a result to increased ECM deposition (see positive regulation of extracellular matrix assembly). ECM deposition in turn presumably increases AH outflow resistance in TM resulting in elevation of IOP [2]. Decrease of **PLAT (TPA)** level and/ or activity seems to be especially important as administration of **PLAT (TPA)** reverses the effect of GCs on induction of IOP in animal models [24], [25], [26].

In addition, **Dexamethasone** induces ECM deposition via increasing synthesis of components of ECM such as **Fibronectin** [27], [28], **Elastin** [29], **COL4A1**/ **Collagen IV** [28], [30], **LAMA1**/ **Laminin 1** [30], [31] and **LAMB3**/ **Laminin 5** [32].

Moreover, **Dexamethasone**/ **GCR** signaling induces **Myocilin** expression, although effect seems to be indirect, involving synthesis of additional proteins and activation of other transcription factor(s) [19], [23], [33], [34], [35], [36]. **Myocilin** seems to play important role in pathogenesis of glaucoma as it regulates ECM turnover and function of TM cells, although its role in glaucoma development is contradicting [37], [38], [39]. Moreover, **Dexamethasone** induces expression of **Cdt6 (angiopoietin-like)** which seems to be important for the effect of **Dexamethasone** on ECM proteins, but its role in regulation of ECM proteins is contradicting as well [40], [41].

In addition, **Dexamethasone** inhibits expression of growth factor receptors **HGF receptor (Met)**, **EGFR**, **FGFR1** thus presumably inhibiting proliferation of TM cells (see negative regulation of cell proliferation) which probably can contribute to increased AH outflow resistance in TM and elevated IOP [2].

Moreover, **Dexamethasone** induces endoplasmic reticulum (ER) stress via **C/EBP zeta** [42]. In turn, ER stress contributes to elevation of IOP and subsequently to development of glaucoma [42], [43].

Moreover, changes in cytoskeleton of TM cells with formation of so-called cross-linked actin networks (CLANs) in reponse to **Dexamethasone** are very important mechanism that contributes to increase of AH outflow resistance in TM [2], [44], [45], [46]. CLANs are **Actin cytoskeletal**-based cytoskeleton structures which contain, in particular, **Syndecan-4**, **PtdIns(4,5)P2**, **CLIM1**, **Alpha-actinin**, **Filamin A** and in some cases **Filamin B (TABP)** [47], [48]. Several **Dexamethasone**-induced pathways that lead to CLAN formation are known. **Dexamethasone**/ **GCR** signaling decreases expression of canonical WNT ligand **WNT2** what subsequently leads to induction of non-canonical WNT ligand **WNT5A** via unknown pathway. In turn, **WNT5A** via **ROR2** activates **RhoA**/ **ROCK** signaling pathway thus inducing CLANs [49]. Moreover, **Dexamethasone** increases abundance of **RhoA** and decreases abundance of its inhibitor **RhoGDI alpha**, which most probably enhances **RhoA**-mediated signaling pathway [50]. Thus, **RhoA**/ **ROCK** signaling pathway, activated presumably downstream of non-canonical WNT pathway **WNT5A**/ **ROR2**, promotes CLAN formation which results in increase of AH outflow resistance and IOP elevation [51], [52], [53], [54], [55], [56].

Another **Dexamethasone**-activated signaling pathway involved in CLAN formation is **alpha-V/beta-3 integrin**-mediated signaling pathways. **Dexamethasone** indirectly induces expression of **alpha-V/beta-3 integrin** beta subunit, **ITGB3**, and probably triggers some unknown inside-out integrin signaling pathway that promotes **alpha-V/beta-3 integrin** activation [57], [58]. Moreover, **Dexamethasone** induces expression of **Thrombospondin 1** [59] which in turn binds to and activates **CD47**/ **alpha-V/beta-3 integrin** receptor complex [60], [61], [62], [63]. Furthermore, **Dexamethasone** induces expression of multiple ECM proteins such as **Fibronectin** which activate **alpha-V/beta-3 integrin** as well [63]. In turn, activated **alpha-V/beta-3 integrin** induces **c-Src**/ **TRIO**/ **Rac1** signaling pathway to promote cytoskeleton changes and CLAN formation [57], [61]. Furthermore, activation of **alpha-V/beta-3 integrin** inhibits **alpha-V/beta-5 integrin**/

FAK1-mediated TM cell phagocytosis [63], [64].

Moreover, to induce significant CLAN formation **Dexamethasone**-induced **alpha-V/beta-3 integrin** signaling pathway presumably converges with other signaling pathways such as **Laminin 5**-derived PEP75 peptide/ **Syndecan-4**/ **PKC-epsilon** signaling [32] and/ or **ITGB1**-containing integrins/ **PI3K cat class IA** pathway [61], [63].

Furthermore, **Dexamethasone**/ **GCR** signaling induces abundance and/ or expression of several proteins involved in CLAN formation. **Dexamethasone** induces expression of **CDC42** leading to activation of **PAK1** with subsequent inhibition of **MLCK**, thus contributing to **Dexamethasone**-induced cytoskeleton rearrangements (actin cytoskeleton reorganization) [65]. Moreover, expressions of CLAN-forming proteins **CLIM1** and **Filamin B (TABP)** are also induced by **Dexamethasone** [48]. In addition, **Dexamethasone** increases expression of **PI3K reg class IA (p85-alpha)** and abundance of **PI3K cat class IA (p110-beta)**, which presumably contributes to enhancement of **ITGB1**-containing integrin signal transduction [48].

In turn, CLANs presumably inhibit multiple TM cell functions and cellular processes, such as TM cell proliferation [50], [66], phagocytosis [67], [68], cell contraction (see actin-mediated cell contraction) [63] and cell migration [2], [66]. Although it is unknown how (and if) inhibition of TM cell proliferation and migration contributes to elevation of IOP, decreased phagocytic capacity of TM cells presumably increases ECM deposition in TM thus increasing AH outflow resistance [2]. In its turn, inhibition of TM cell contractility (presumably due to increased TM cell rigidity) most probably increases AH outflow resistance as well [62].

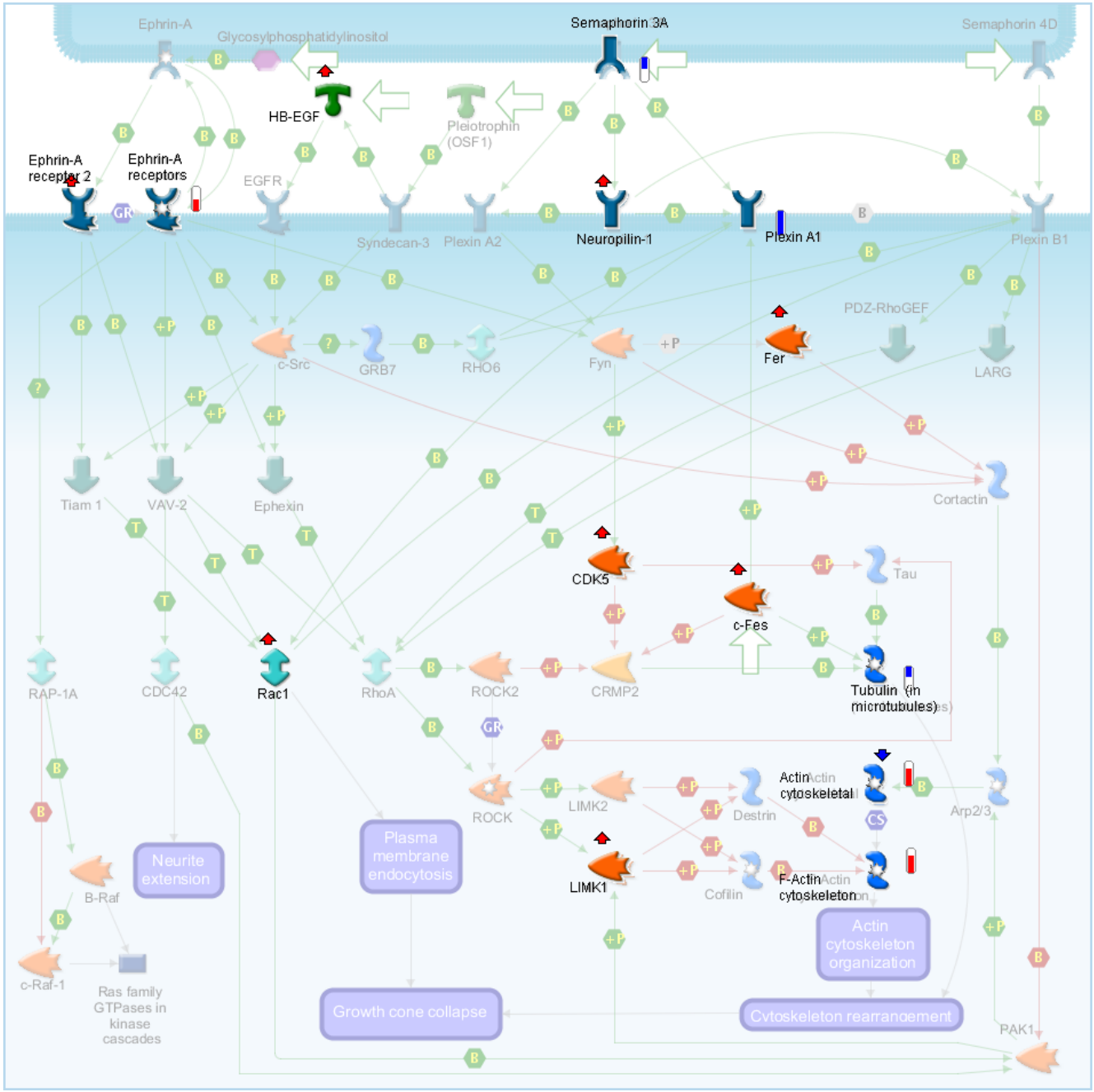
Physiological Pathway Maps

Physiological pathway maps are graphic images representing complete biochemical pathways or signaling cascades of healthy cells in a commonly accepted sense. All maps listed below are enriched with both input genes and Key Hubs.

Physiological Pathway Maps Details [16 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
1	Neurophysiological process_Receptor-mediated axon growth repulsion	0.004212	8.909E-4	2.283E-5
2	Development_Transcription factors in segregation of hepatocytic lineage	0.01755	0.001125	2.475E-5
3	Development_Insulin, IGF-1 and TNF-alpha in brown adipocyte differentiation	0.02817	4.552E-4	8.165E-5
4	Immune response_IL-7 signaling in T lymphocytes	0.02943	0.002916	1.261E-4
5	Transcription_HIF-1 targets	3.205E-4	0.002399	1.635E-4
6	Development_Regulation of epithelial-to-mesenchymal transition (EMT)	0.02048	0.009148	3.168E-4
7	Oxidative stress_Role of Sirtuin1 and PGC1-alpha in activation of antioxidant defense system	0.01015	0.01125	7.243E-4
8	Development_Beta adrenergic receptors in brown adipocyte differentiation	0.03227	0.003449	7.735E-4
9	Development_Cytokine-mediated regulation of megakaryopoiesis	0.04007	0.003732	8.697E-4
10	Development_c-Kit ligand signaling pathway during hemopoiesis	0.04557	0.001309	0.001235
11	Development_VEGF signaling and activation	0.04169	0.02081	0.001522
12	Translation_Non-genomic (rapid) action of Androgen Receptor	0.04514	0.02336	0.001874
13	Immune response_Oncostatin M signaling via JAK-Stat	0.03672	0.03258	0.002042
14	Cell adhesion_Alpha-4 integrins in cell migration and adhesion	0.02943	0.01249	0.002549
15	Development_Role of proteases in hematopoietic stem cell mobilization	0.02147	0.01627	0.003298
16	Immune response_IL-6-induced acute-phase response in hepatocytes	0.03227	0.0143	0.01115

Maps and Descriptions [1 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Neurophysiological process_Receptor-mediated axon growth repulsion	0.004212	8.909E-4	2.283E-5



Description

Receptor-mediated axon growth repulsion

Ephrin-A proteins which are anchored in the plasma membrane through attachment of glycosylphosphatidylinositol (**GPI**) [1], are the ligands for **Ephrin-A receptors**, which belong to the membrane family of receptor tyrosine kinases [2].

In the absence of **Ephrin-A** stimulation, **Ephrin-A receptors** are shown to target **Ephexin** exchange factor to the plasma membrane. **Ephrin-A** stimulation of **Ephrin-A receptors** activates exchange factors **Ephexin** [3], **VAV-2** [4] and **Tiam 1** [5]. Src-family tyrosine kinases **c-Src** and **Fyn** are recruited to **Ephrin-A receptors** after **Ephrin-A** stimulation [6]. In response to **Ephrin-A** signaling **Ephexin** becomes phosphorylated by **c-Src** [6] and this phosphorylation enhances its activity toward Ras homolog gene family, member A (**RhoA**) [7]. **VAV-2** is rapidly phosphorylated by **c-Src** upon stimulation by **Ephrin-A** [4] and activates **RhoA** [8].

Ephrin-A receptors have also been shown to signal through the Ras-related C3 botulinum toxin substrate 1 (**Rac1**) exchange factors **Tiam1** [5] and**VAV-2** [9] to promote neurite outgrowth.

In response to **Ephrin-A1** stimulation, Ras-related protein **Rap-1A** is activated [10] and can regulate MAPK signaling cascade by reducing **c-Raf-1** activation [11] or by stimulation of **B-Raf** kinase [10], [12].

When **Ephrin-A** receptors are activated, phosphorylation of **Ephexin** promotes its GTPase activity toward **RhoA**. **RhoA** downstream effector Rho-associated kinase **ROCK** directly phosphorylates LIM-kinases **LIMK1** and **LIMK2**, which in turn phosphorylates actin-depolymerizing factor **destrin** and actin-associated protein**cofilin**. Activity of **LIMK1** is also regulated by p21-activated kinase 1 (**PAK1**) [13]. **Cofilin** and **destrin** both exhibit **actin**-depolymerizing activity followed by reorganization of the **actin** cytoskeleton [14], [15].

The F-actin-binding protein **cortactin** is an important regulator of cytoskeletal dynamics, and a prominent target of various tyrosine kinases (**c-Src**, **Fyn**, **Fer**) [6], [16]. Tyrosine phosphorylation of **cortactin** has been suggested to reduce its F-actin cross-linking capability [16].

The semaphorins family of secreted or membrane-bound proteins was identified originally as axonal guidance factors functioning during neuronal development. The class 4 semaphorin **Semaphorin 4D** utilizes **Plexin B1** (transmembrane protein) as receptor. [17] **Plexin B1** directly interacts with exchange factors **PDZ-RhoGEF** and **LARG** to regulate **RhoA** and the growth cone morphology [18].

Rho6 is a member of Rho family GTPases. It is activated by adaptor protein **Grb7 and** directly interacts with the cytoplasmic domain of **Plexin B1** in response to **Semaphorin 4D**. **Rho6** promotes the interaction between **Plexin B1** and **PDZ-RhoGEF** and thereby potentiates the **PDZ-RhoGEF**-induced **RhoA** activation [19].

PAK1 promotes activation of **actin** polymerization by phosphorylation of **Arp2/3** (complex of actin-related proteins) [20]. **c-Raf-1** kinase, a member of the MAPK pathway, is also phosphorylated and activated by **PAK1** [21]. Inhibition of **Pak1** by **Plexin B1** is believed to cause suppression of membrane protrusions, thus supporting the cell repulsion response. Furthermore, active **Rac1** was shown to promote cell surface localization of **Plexin B1 thus** enhancing **Semaphorin 4D** binding to the receptor. Thus, **Rac1** and **Plexin B1** signaling appears to be bidirectional: **Rac-1** modulates **Plexin B1** activity, and **Plexin B1** modulates **Rac-1** function [22].

Another semaphorin, **Semaphorin 3A**, binds to **Neuropilin-1**/**Plexin A1** complex and induces repulsive responses [23]. The active form of **Rac1** directly binds to **Plexin-A1. A**ctivated **Rac1** mediates endocytosis of the growth cone plasma membranes and reorganization of **F-actin** in neurons [24]. Endocytosis of plasma membranes is supposed to be an important step for growth cone collapse.

c-Fes tyrosine kinase also is implicated in **Semaphorin 3A**-induced collapse [25]. **c-Fes** directly binds to the cytoplasmic region of **Plexin A1**. In the resting state, **neuropilin-1** associates with **Plexin-A1** and blocks the binding of **c-Fes** to **Plexin A1**. **Semaphorin 3A** binding to **Neuropilin-1** permits **c-Fes** to associate with and phosphorylate **Plexin A1**. This tyrosine phosphorylation stimulates repulsive action in the receptor.

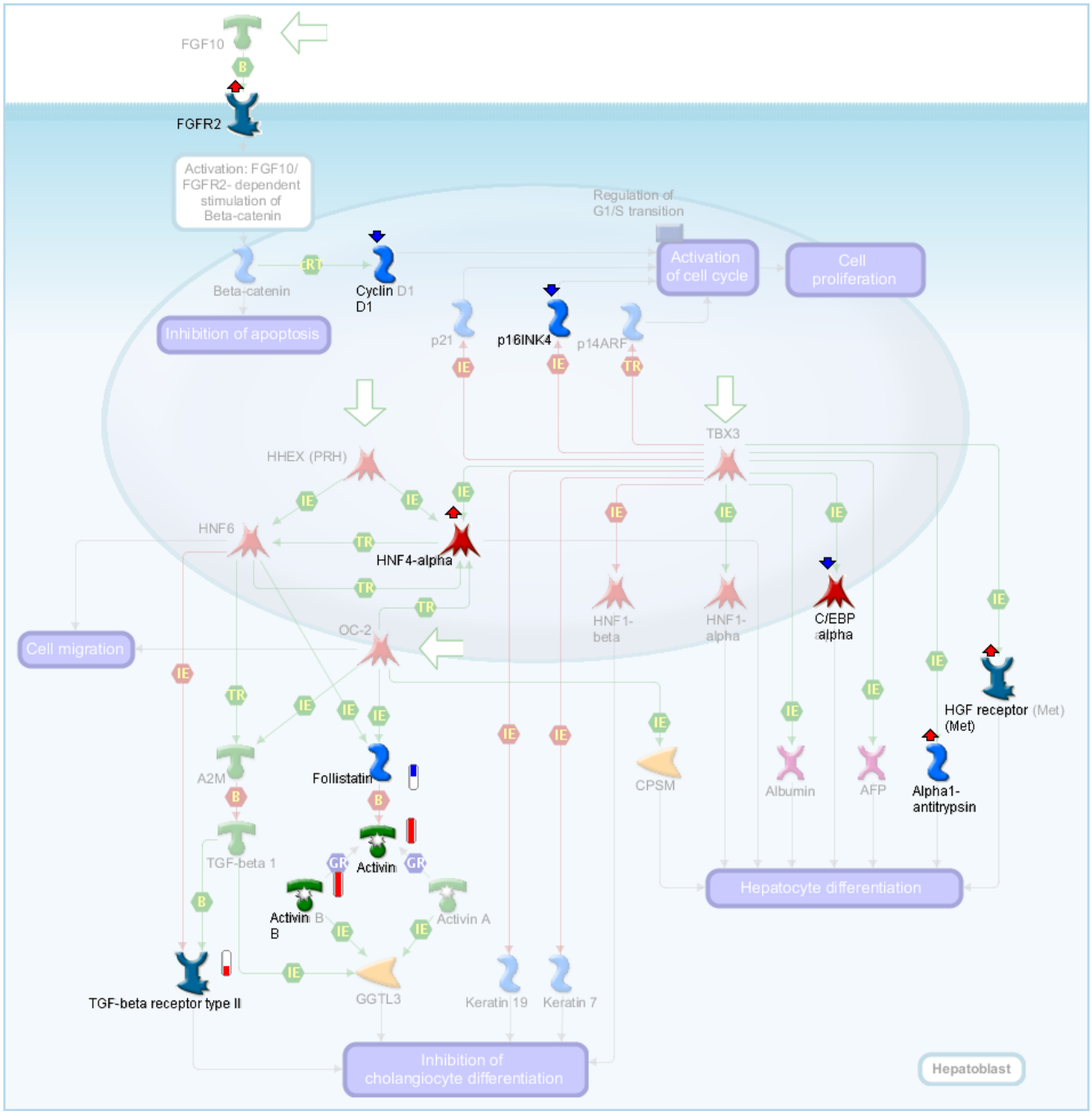
c-Fes also phosphorylates collapsin response mediator protein **CRMP2** [26].

Fyn, a member of src-family of tyrosine kinases, associates with **Plexin A2** in response to **Semaphorin 3A** and phosphorylates serine/threonine kinase **CDK5**. [27] Activated **CDK5** phosphorylates **CRMP2** [28]. **ROCK2** kinase also has been shown to phosphorylate **CRMP2** [29]. CRMP2 binds to tubulin heterodimers to promote microtubule assembly that is important for axonal growth and branching [30]. Phosphorylation of **CRMP2** reduces its tubulin-heterodimer binding and the promotion of microtubule assembly.

CDK5 also phosphorylates the microtubule-associated protein **Tau**, thereby reduces its ability to induce **tubulin** microtubule formation [31].

Maps and Descriptions [2 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Transcription factors in segregation of hepatocytic lineage	0.01755	0.001125	2.475E-5



Abstract:

After specification, hepatic progenitors (hepatoblasts) proliferate and migrate to septum transversum mesenchyme, where they give rise to the cells of bile ducts (cholangiocytes) and mature hepatocytes. **FGF10** signaling probably through **Beta-catenin** activation, induces survival and proliferation of hepatoblasts. **HNF6** and **OC-2** promote hepatoblast migration into the mesenchyme and segregation of the hepatocytic and biliary lineages via preventing **TGF-beta 1/Activin** signaling. **TBX3** signaling promotes hepatoblast proliferation and inhibits their differentiation to cholangiocytes.

Details:

After specification (see hepatoblast differentiation), the hepatic progenitors (hepatoblasts) proliferate and migrate to the septum transversum mesenchyme, where they give rise to the cells of bile ducts (cholangiocytes) and the mature hepatocytes [1], [2].
FGF10 is expressed by mesenchymal cells of liver after hepatoblast differentiation. **FGF10** signaling activates **Beta-catenin** in hepatoblasts probably via **Beta-catenin** and, thereby provides normal cell proliferation of hepatoplasts and prevents apoptotic process of hepatic cells [3]. In addition, **Beta-catenin** in hepatoblasts upregulates expression of **Cyclin D1**, the well known cell cycle regulator [4].

The transcription factor **HHEX (PRH)** activated at the time of hepatic specification (see hepatoblast differentiation) directly induces expression of **HNF6** and **HNF4-alpha** [5]. **HNF6** and **HNF4-alpha** positively regulate expression of each other in fetal liver [6], [7]. **OC-2** also positively regulates expression of **HNF4-alpha** [6].

HNF6 and **OC-2** promote migration of hepatoblasts (see positive regulation of cell migration) into the mesenchyme [8] and are required for hepatoblast segregation between the hepatocytic and biliary lineages [9]. Both **HNF6** and **OC-2** increase expression of **TGF-beta 1** antagonist **A2M** and **Activin** antagonist **Follistatin**, thereby preventing **TGF-beta 1**/ **Activin** signaling required for biliary differentiation [10]. **HNF6** inhibits expression of the **TGF-beta receptor type II** as well. Inhibition of **TGF-beta 1**/ **Activin** signaling by **HNF6** and **OC-2** downregulates expression of biliary marker **GGTL3** in hepatoblasts. At the same time **OC-2** upregulates expression of hepatocytic marker **CPSM**. Thus, **HNF6** and **OC-2** provide segregation of the hepatocytic and the biliary lineages [9].

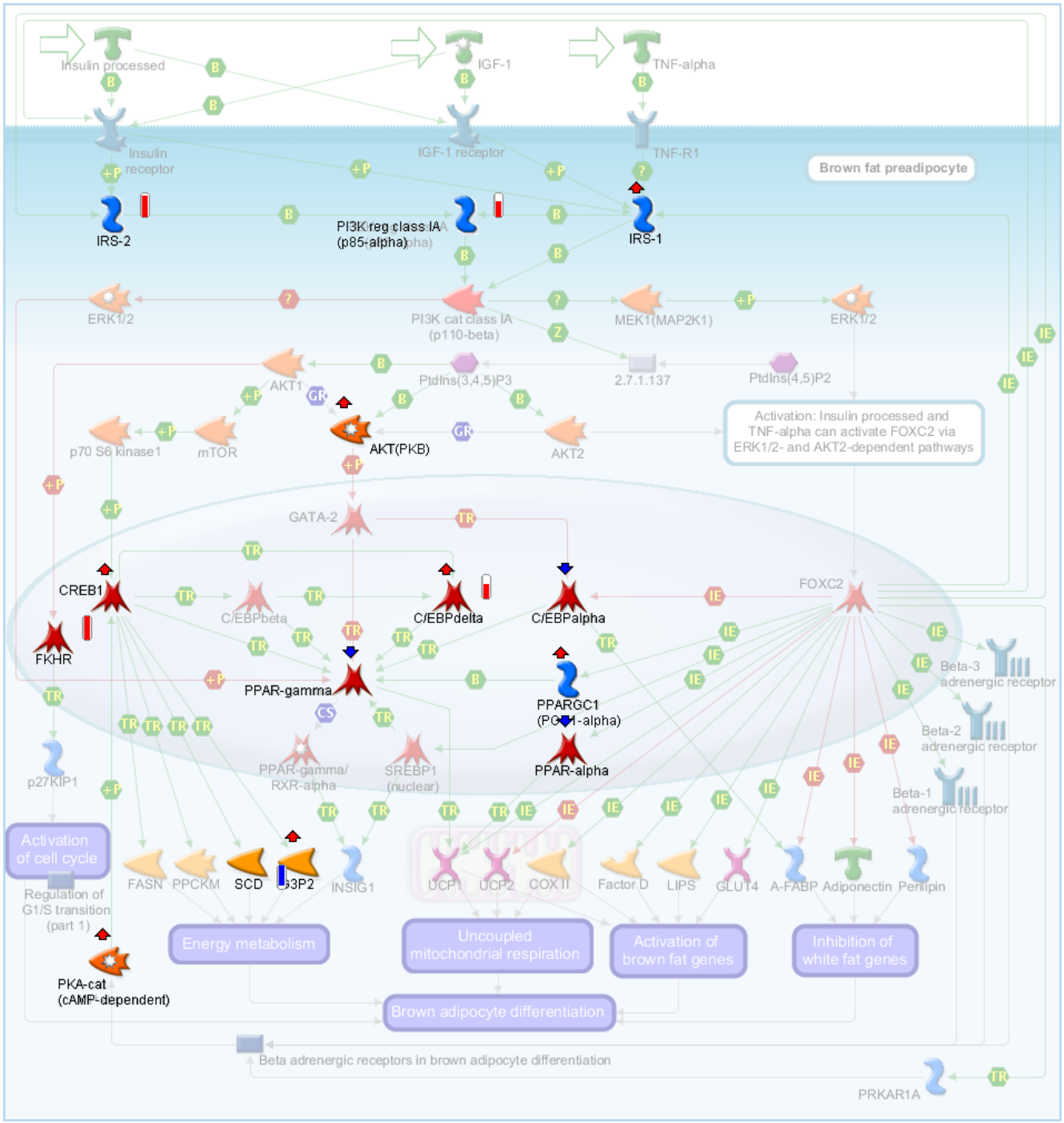
Expression of **TBX3** is strongly upregulated at the time of liver bud expansion and segregation of the hepatocytic lineage. **TBX3** suppresses expression of the cell cycle inhibitors **p14ARF** and **p16INK4** [11], products of Ink4a/Arf locus and **p21** [12]. Thus, **TBX3** promotes cell proliferation of hepatoblasts and inhibits their differentiation to cholangiocytes [11].

TBX3 also downregulates expression of genes associated with cholangiocyte differentiation such as **Keratin 19**, **Keratin 7**, **HNF1-beta**, and upregulates expression of liver-specific genes such as, **HNF4-alpha**, **HNF1-alpha**, **C/EBPalpha**, **Albumin**, **AFP**, **Alpha 1-antitrypsin** [11].

In addition, **TBX3** upregulates expression of **HGF receptor (Met)** [11] which then transduces HGF signaling required for hepatic cell differentiation and cell maturation [13].

Maps and Descriptions [3 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Insulin, IGF-1 and TNF-alpha in brown adipocyte differentiation	0.02817	4.552E-4	8.165E-5



Abstract:

Regulation of energy balance is the main function of adipose tissue. There are two functionally different types of fat in mammals: white adipose tissue and brown adipose tissue. **Insulin**, **IGF-1** and **TNF-alpha** can induce adipogenesis and differentiation of brown adipocytes. Their signaling cascades activate PI3K which can both activate and inhibit **ERK1/2** pathways and stimulate **AKT** signaling. Each pathway leads to adipogenesis. PI3K-induced inhibition of **ERK1/2** attenuates its inhibitory action on **PPAR-gamma**, involved in adipogenesis. PI3K-induced activation of **ERK1/2** leads to expression of **FOXC2**. **FOXC2** represses expression of white fat genes and activates expression of brown fat genes, leading to differentiation of brown adipocytes. PI3K/ **AKT1** signaling stimulates **CREB1**, which up-regulates transcription of **PPAR-gamma** and enzymes, involved in energy metabolism. **AKT1** also inhibits **FKHR**, thereby decreasing expression of **p27KIP1**. Inhibition of **p27KIP1** activates cell cycle involved in adipogenesis.

Details:

Regulation of energy balance is the main function of adipose tissue. There are two functionally different types of fat in mammals: white adipose tissue, the primary site of triglyceride storage, and brown adipose tissue, which is specialized in energy expenditure and can counteract obesity [1].

Insulin, Insulin-like growth factor 1 (**IGF-1**) and Tumor necrosis factor (**TNF-alpha**) are potent inducers of adipogenesis and differentiation of brown adipocytes. **Insulin**, **IGF-1** and **TNF-alpha** promote differentiation by activating their cognate receptors - **Insulin receptor**, Insulin-like growth factor I receptor (**IGF-1 receptor**), and Tumor necrosis factor receptor superfamily, member 1A (**TNF-R1**), respectively [2], [3], [4]. **Insulin receptor**, **IGF-1 receptor** and **TNF-R1** stimulate Insulin receptor substrate 1 and 2 (**IRS-1** and**IRS-2**)/ Phosphoinositide-3-kinase, regulatory subunit 1 (alpha) (**PI3K reg class IA (p85-alpha)**)/ Phosphatidylinositol 3-kinase, catalytic, beta polypeptide (**PI3K cat class IA (p110-beta)**) cascade [5], [6].

Bi-directional regulation of brown fat adipogenesis by the **Insulin Receptor** via **PI3K cat class IA (p110-beta)** has been observed in brown preadipocytes [7].On the one hand, **PI3K cat class IA (p110-beta)** inhibits Mitogen activated protein kinase 1/3 (**ERK1/2**), thereby attenuating **ERK1/2** inhibitory action on Peroxisome proliferator activated receptor gamma (**PPAR-gamma**) and promoting activation of **PPAR-gamma** which stimulates adipogenesis [6]. On the other hand, **Insulin** and **TNF-alpha**-induced **PI3K cat class IA (p110-beta)** activates Mitogen-activated protein kinase kinase 1 (**MEK1(MAP2K1)**) via yet unknown mechanism. **MEK1(MAP2K1)** activates **ERK1/2**, that induces expression of another transcriptional factor required for adipogenesis, Forkhead box C2 (**FOXC2**) [3]**.**

In addition, **PI3K cat class IA (p110-beta)** activates V-akt murine thymoma viral oncogene homolog 1 (**AKT1**)/ Mechanistic target of rapamycin (**mTOR**)/ RPS6KB2 ribosomal protein S6 kinase, 70kDa, polypeptide 2 (**p70 S6 kinase1**)/ cAMP responsive element binding protein 1 (**CREB1**) pathway [8], [9]**. CREB1** stimulates adipogenesis by up-regulating transcription of Peroxisome proliferator activated receptor gamma (**PPAR-gamma**) and enzymes involved in energy metabolism, such as Fatty acid synthase (**FASN**), phosphoenolpyruvate carboxykinase 2 (**PPCKM**), stearoyl-CoA desaturase (**SCD**), and GAPDH glyceraldehyde-3-phosphate dehydrogenase (**G3P2**) [8], [10].

Insulin- and **TNF-alpha**-induced PI3K signaling also activates V-akt murine thymoma viral oncogene homolog 2 (**AKT2**) which, probably, stimulates **FOXC2** transcriptional activity [11]. **FOXC2** represses expression of white fat genes, such as CCAAT/enhancer binding protein (C/EBP), alpha (**C/EBPalpha**), Uncoupling protein 2 (mitochondrial, proton carrier) (**UCP2**), **Perilipin**, **Adiponectin** and Fatty acid binding protein 4, adipocyte (**A-FABP**) [12]. **FOXC2** activates expression of brown fat genes, such as **PPARGC1 (PGC1-alpha)**, Peroxisome proliferator activated receptor alpha (**PPAR-alpha**), Cytochrome c oxidase II, mitochondrial (**COX II**), Uncoupling protein 1 (mitochondrial, proton carrier) (**UCP1**), Lipase, hormone-sensitive (**LIPS**), Solute carrier family 2 (facilitated glucose transporter), member 4 (**GLUT4**), Complement factor D (adipsin) (**Factor D**) (that is present in both white and brown adipocytes), Protein kinase, cAMP-dependent,

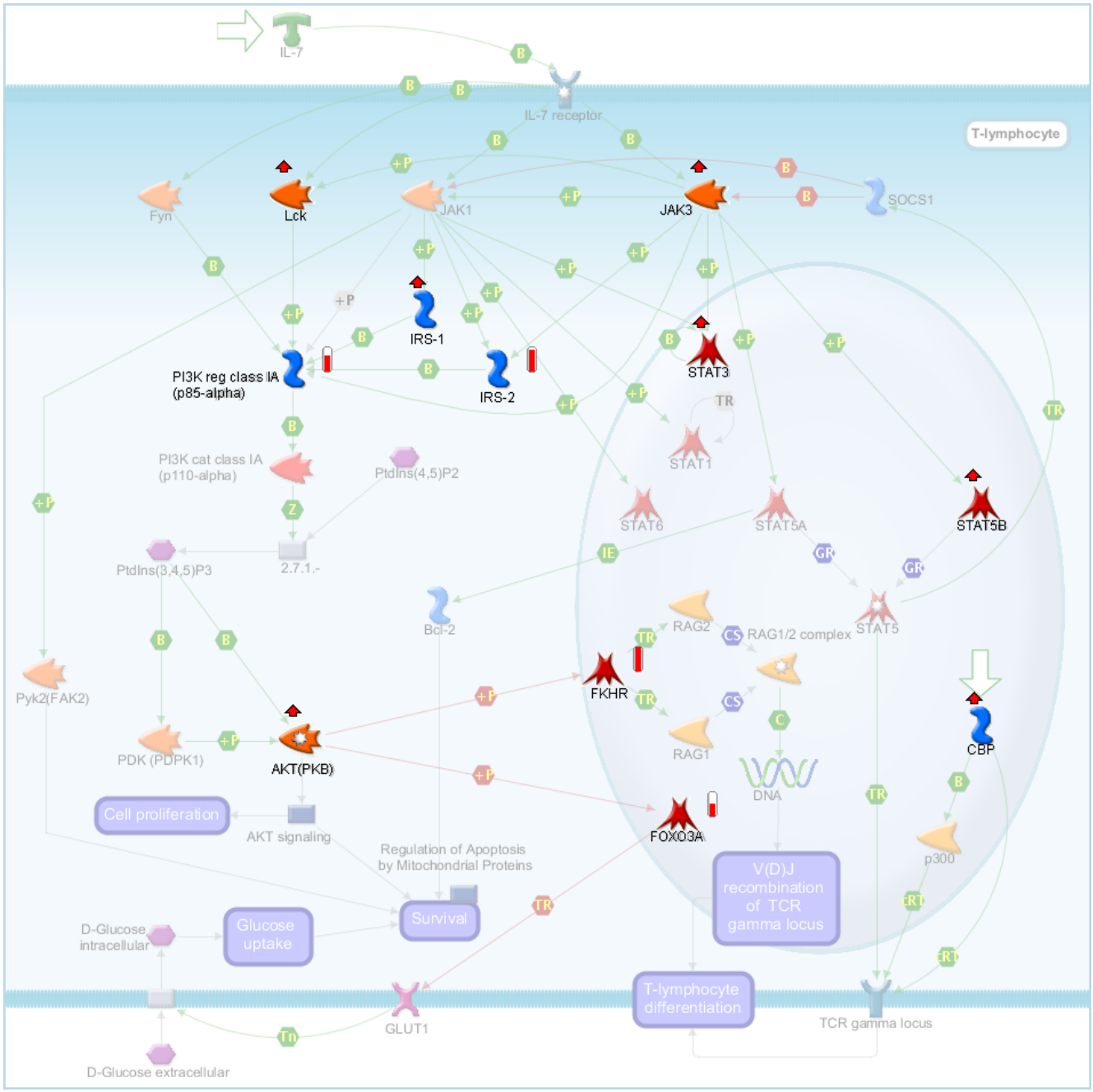
regulatory, type I, alpha (**PRKAR1A**), Sterol regulatory element binding transcription factor 1 (**SREBP1 (nuclear)**), **IRS-1** and **2**, **Insulin receptor**, **Beta-1 adrenergic receptor**, **Beta-2 adrenergic receptor** and **Beta-3 adrenergic receptor** [12]. **SREBP1 (nuclear)** activates transcription of Insulin induced gene 1 (**INSIG1**) and **PPAR-gamma** [13], [14]. In addition, **PPAR-gamma/RXR-alpha** induces transcription of **INSIG1** [14]. Besides, **FOXC2** stimulates Beta adrenergic receptor/ cAMP/ PKA/ CREB pathway via activating transcription of Protein kinase, cAMP-dependent, regulatory, type I, alpha (**PRKAR1A**) [12].

Furthermore, **AKT1** inhibits Forkhead box O1 (**FKHR**), thereby decreasing expression of Cyclin-dependent kinase inhibitor 1B (**p27KIP1**). Inhibition of **p27KIP1** activates cell cycle involved in adipogenesis [4].

In addition, **AKT** phosphorylates and inhibits activity of GATA binding protein 2 (**GATA-2**), thereby promoting activation of **PPAR-gamma** and stimulating adipogenesis [15].

Maps and Descriptions [4 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Immune response_IL-7 signaling in T lymphocytes	0.02943	0.002916	1.261E-4



Description

Interleukin-7 (**IL-7**) is an essential cytokine for proliferation, maintenance and survival of T-lymphocytes [1]. **IL-7 receptor** activates pathways that regulate lymphocyte survival, glucose uptake, proliferation and differentiation [2].

IL-7 receptor consists of the IL-7 receptor alpha chain (**IL7RA**) and the common cytokine gamma chain (**IL-2R gamma chain**) [1]. **IL-7** ligation to the **IL-7 receptor** stimulates the trans-phosphorylation of receptor associated Janus kinases 1 and 3 (**JAK1** and **JAK3**), which in turn phosphorylate tyrosine residues on the receptors themselves [3], [4], [5].

IL-7 receptor serves as docking sites for SH2 domain proteins including the Signal transducers and activators of transcription family of transcription factors (**STAT1**, **STAT3**, **STAT5** and **STAT6**) which are activated by JAK-mediated phosphorylation [6], [7]. **STAT5** promotes transcription of B-cell CLL/lymphoma 2 (**Bcl-2**) stimulating cell survival [8]. **STAT5** promotes transcription of Suppressor of cytokine signaling 1 (**SOCS1**) inducing negative feed-back on **IL-7** signaling [9], [10].

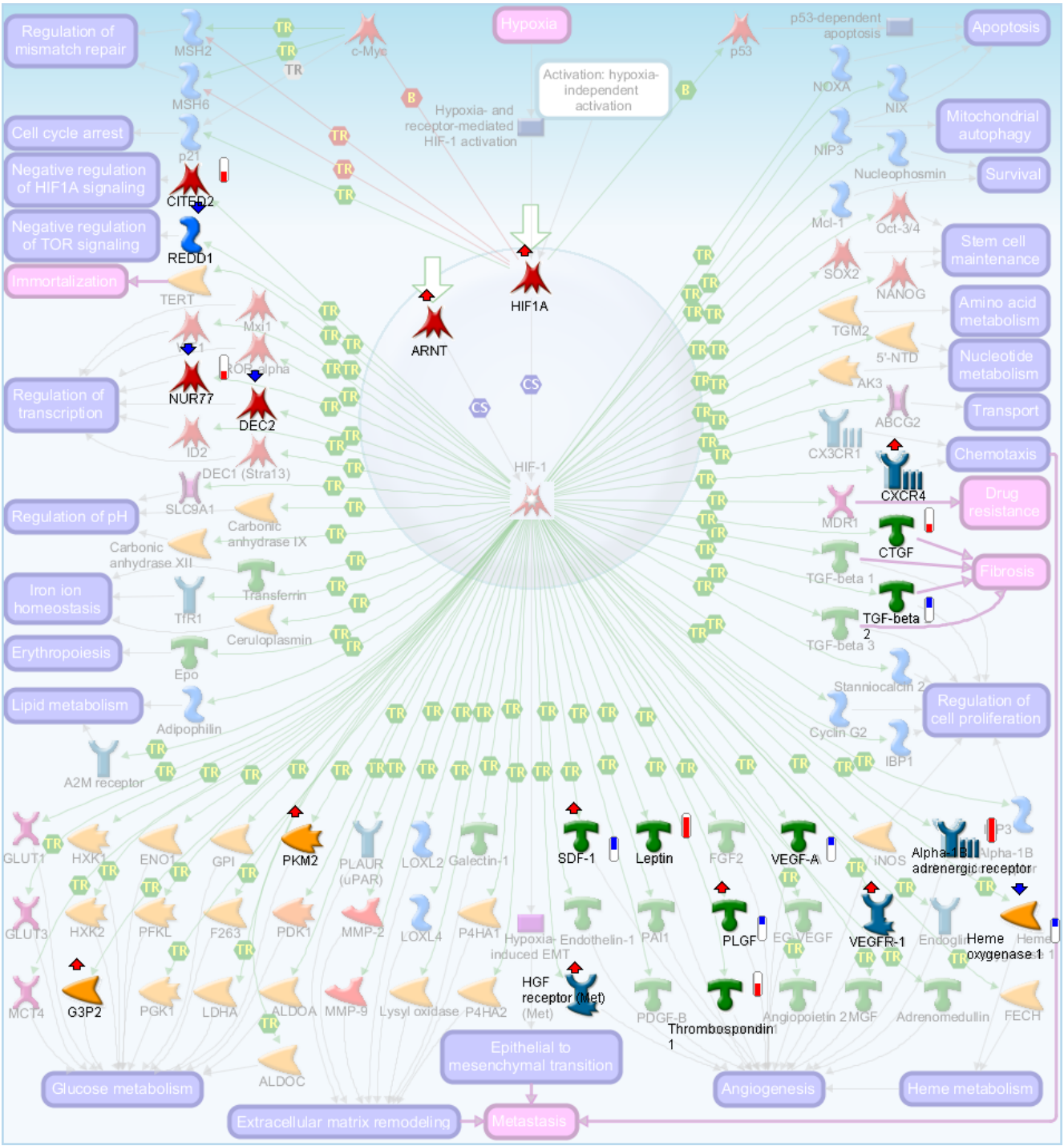
IL-7 receptor induces **JAKs/** PTK2B protein tyrosine kinase 2 beta (**Pyk2(FAK2)**) cascade that participates in activation of T cell survival [5].

Activated **IL-7 receptor** stimulatesPhosphatidylinositol 3-kinase (**PI3K**)/ V-akt murine thymoma viral oncogene (**AKT/PKB**) cascade via **JAKs/** Insulin receptor substrates 1 and 2 (**IRS-1**, **IRS-2**) [11], [12] and/or Src family kinases FYN oncogene related to SRC (**Fyn**) and Lymphocyte-specific protein tyrosine kinase (**Lck**) [4], [13]. Activated **PI3K** induces conversion from Phosphatidyl-4,5-inositol bisphosphate (**PtdIns(4,5)P2**) to Phosphatidyl-3,4,5-inositol triphosphate (**PtdIns(3,4,5)P3**). **PtdIns(3,4,5)P3** in turn induces **AKT/PKB** and 3-phosphoinositide dependent protein kinase-1 (**PDK (PDPK1)**) activation that promotes T lymphocytes proliferation and survival [14], [15]. **AKT/PKB** complex induces Solute carrier family 2 member 1 (**GLUT1**) activation inhibition of transcriptional factor Forkhead box O3 (**FOXO3A**). **GLUT1** stimulates **Glucose** uptake thus promoting cell survival [16].

IL-7 stimulates V(D)J recombination of T-cell receptor gamma chain (**TCR gamma locus)** in T cells. V(D)J recombination is assemblage of mature genes encoding the component chains of TCR and immunoglobulin proteins from germ-line arrays of variable (V), diversity (D), and joining (J) gene segments during lymphoid development [17], [18]. **STAT5** plays a key role in synthesis and V(D)J recombination of **TCR gamma locus** with participation of histone acetylases **p300** and **CBP** [19]. It is possibly, that **AKT/PKB**-dependent inhibition Forkhead box O1 (**FKHR**) stimulatesRecombination activating gene 1 and 2 (**RAG1** and **RAG2**) transcription, thus inducing V(D)J recombination of **TCR gamma locus.** The **RAG1**/ **RAG2** dimer recognizes the synapsis formed by the recognition motifs and initiates the cleavage step of V(D)J recombination [10], [17], [20].

Maps and Descriptions [5 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Transcription_HIF-1 targets	3.205E-4	0.002399	1.635E-4



Abstract:

Hypoxia-inducible factor-1 (**HIF-1**) is an oxygen-sensitive transcription factor composed of hypoxia-regulated **HIF1A** and constitutively expressed **ARNT**. **HIF-1** directly or indirectly (via other transcription factors such as **c-Myc** and **p53**) regulates transcription of hundreds genes thus resulting in multiple physiological and pathologic processes, including glucose metabolism, angiogenesis, erythropoiesis, cell proliferation, apoptosis, survival, stem cell maintenance and metastasis.

Details:

Hypoxia-inducible factor-1 (**HIF-1**) is an oxygen-sensitive transcription factor composed of hypoxia-regulated **HIF1A** and constitutively expressed **ARNT**, which regulates cellular response to changes in oxygen tension during normal development or pathologic processes. **HIF-1** regulates multiple physiological processes, including glucose metabolic process, angiogenesis, erythropoiesis (see erythrocyte differentiation), cell proliferation, apoptosis and survival (see regulation of apoptotic process). Moreover, **HIF-1** is a critical regulator of pathologic processes such as neoplasmic survival, metastasis and invasion, and drug resistance [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12].

HIF-1 exerts its effect on cellular processes via activation/ inhibition of transcription of its target genes. **HIF-1** can regulate transcription directly or indirectly via modulation of activity of other transcription factors. In particular, **HIF1A** inhibits **c-Myc** function [13]. As **c-Myc** positively regulates transcription of mismatch repair genes **MSH2** and **MSH6**, **HIF1A** decreases **MSH2** and **MSH6** expression thus promoting genomic instability in cancers [14]. Moreover, **HIF1A** displaces **c-Myc**, a negative regulator of **p21** expression, from **p21** promoter thus increasing **p21** expression and inducing cell cycle arrest [15].

Moreover, **HIF-1** can regulate its own activity via triggering negative feedback loop and inducing its negative regulator **CITED2** [16].

In addition, **HIF-1** inhibits Target of Rapamycin (TOR) signaling (see negative regulation of TOR signaling) via induction of expression of **REDD1** [17], [18], [19].

HIF-1 activates transcription of **TERT** [20] which can contribute to cellular immortalization in cancers [10].

HIF-1 induces expression of several transcription factors including **Mxi1** [21], **WT1** [22], **ROR-alpha** [23], **NUR77** [24], [25], **DEC1 (Stra13)** and **DEC2** [26] and **ID2** [27].

HIF-1 regulates pH homeostasis (see regulation of pH) via induction of transcription of **SLC9A1** [28], **Carbonic anhydrase IX** and **Carbonic anhydrase XII** [29].

Moreover, **HIF-1** up-regulates proteins involved in cellular iron ion homeostasis, such as **Transferrin** [30], **TfR1** [31] and **Ceruloplasmin** [3], [32] and promotes erythropoiesis (see erythrocyte differentiation) via induction of **Epo** [3], [33].

HIF-1 regulates cellular lipid metabolic process via induction of genes such as **Adipophilin** [13], [34] and **A2M receptor** [35], [36].

HIF-1 is a critical regulator of glucose metabolic process which shifts cellular energy metabolism from oxidative phosphorylation and towards canonical glycolysis [7], [12]. Among other targets, **HIF-1** activates transcription of **GLUT1** [1], [3], [37], [38], **GLUT3** [1], [3], [38], [39], [40], **MCT4** [7], [41] **HXK1** and **HXK2** [1], [3], [7], [38], [42], [43], **G3P2** [2], [12], [44], **ENO1** [2], [7], [12], [45], **PFKL** [2], [12], [46], **PGK1** [2], [7], [12], [46], **GPI** [2], [12], [47], **F263** [2], [48], **LDHA** [2], [7], [12], [38], [45], **PKM2** [7], [12], [38], [49], **PDK1** [7], [12], [50], **ALDOA** [7], [12], [45], **ALDOA** [7], [12], [46].

HIF-1 induces extracellular matrix remodeling (see extracellular matrix organization), in particular, via induction of **PLAUR (uPAR)** [12], [51], [52], MMPs such as **MMP-2** and **MMP-9** [12], [53], [54], **Lysyl oxidase**, **LOXL2** and **LOXL4** [12], [55], **Galectin-1** [12], [56], **P4HA1** [57] and **P4HA2** [58], [59]. Moreover, **HIF-1** is well-known trigger of epithelial to mesenchymal transition [60].

Expression of virtually all of the critical angiogenic growth factors and regulator of angiogenesis/ vascular tone is induced by hypoxia through the transcriptional activity of **HIF-1**. In particular, **HIF-1** induces **SDF-1** [8], [10], [61], [62], **Endothelin-1** [3], [10], [63], **HGF receptor (Met)** [10], [64], [65], Leptin [10], [12], [66], **PAI1** [1], [12], [67], [68], [69], **PDGF-B** [70], [71], **FGF2** [11], [62], [72], **PLGF** [8], [62],

Thrombospondin 1 [5], [73], **VEGF-A** [1], [8], [10], [12], [62], [74], **EG-VEGF** [2], [75], **Angiopoietin 2** [8], [76], **iNOS** [2], [3], [12], [77], **VEGFR-1** [1], [12], [38], [78], **MGF** [8], [62], [79], [80], **Endoglin** [2], [81], **Adrenomedullin** [1], [3], [82] and **Alpha-1B adrenergic receptor** [2], [3], [83].

Moreover, **HIF-1** regulates heme metabolic process, in particular, via induction of **Heme oxygenase 1** [38] , [84],and **FECH** [12], [85].

HIF-1 regulates cell proliferation, in particular, via induction of **iNOS** [77], [86], **IBP1** [1], [2], [87] and **IBP3** [1], [2], [88], **Cyclin G2** [2], [89] and **Stanniocalcin 2** [90].

HIF-1 also activates transcription of pro-fibrotic and pro-proliferative **TGF-beta 1** [91], **TGF-beta 2** [92], **TGF-beta 3** [93], [94] and **CTGF** [95].

HIF-1 can promote multi-drug resistance in cancer cells via induction of **MDR1** [96], [97].

HIF-1 regulates chemotaxis of normal and cancer cells via activation of transcription of chemokine receptors such as **CXCR4** [98] and **CX3CR1** [99].

HIF-1 induces expression of pro-angiogenic **ABCG2** channel that can transport multiple molecules thus affecting cellular biology [100].

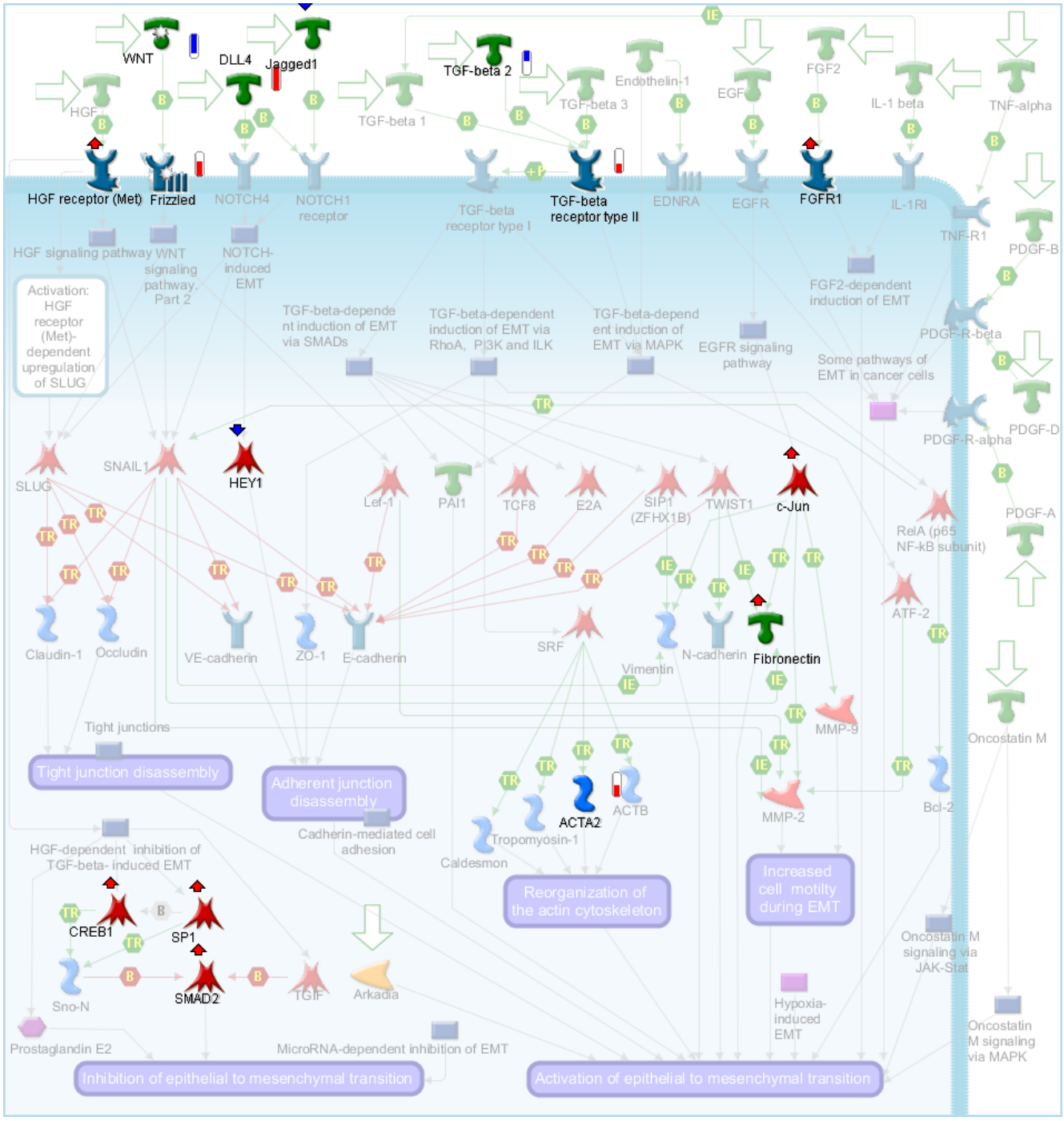
HIF-1 regulates nucleotide metabolic process via activation of transcription of **AK3** [1], [2], [3], [38], [101], [102] and **5'-NTD** [2], [103] and cellular amino acid metabolic process via **TGM2** [2], [104].

HIF-1 can support stem cell population maintenance via induction of expression of **NANOG**, **Oct-3/4** and **SOX2** [105].

HIF-1 promotes survival or triggers apoptosis (see regulation of apoptotic process) depending on cell type/ cellular context [106]. In particular, **HIF-1** can induce anti-apoptotic **Mcl-1** [107], [108] and **Nucleophosmin** [12], [109] and pro-apoptotic **NIP3**, **NIX** [110] and **NOXA** [111]. Moreover, during prolonged hypoxia **HIF1A** stabilizes **p53** [13], [112], [113] thus promoting cell apoptotic process [113], [114].

Maps and Descriptions [6 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Regulation of epithelial-to-mesenchymal transition (EMT)	0.02048	0.009148	3.168E-4



Description

The term epithelial to mesenchymal transition (EMT) describes a series of events during which epithelial cells lose many of their epithelial characteristics and take on properties that are typical of the mesenchymal cells. This process takes place during embryogenesis, wound healing and also during pathological conditions such as cancerogenesis, fibrotic diseases, and cataract. Process epithelial to mesenchymal transition modulation involves a number of signaling pathways. **E-cadherin**, **VE-cadherin**, **Claudin-1** and **Occludin** are down-regulated, while **Vimentin**, **Fibronectin**, and **N-cadherin** are up-regulated during epithelial to mesenchymal transition [1], [2].

TGF-beta is one of the major inducers of epithelial to mesenchymal transition [3]. TGF-beta can induce epithelial to mesenchymal transition via SMAD family member proteins (**SMAD2**, SMAD3 and SMAD4) [3], [4], MAPK [5], RhoA [6], PI3K [4], [7], ILK [8] and other pathways. **TGF-beta 1**-dependent secretion of **Endothelin-1** induces epithelial to mesenchymal transition, because the expression of TGF-beta is **Endothelin-1**-dependent [9]. In tubular renal cells TGF-beta-induced epithelial to mesenchymal transition is enhanced by **Arkadia**, and this process is associated with development of renal fibrosis [10], [11]. **Endothelin-1** also induces epithelial to mesenchymal transition of ovarian cancer cells [12], [13]. Integrin signaling facilitates TGF-beta-mediated induction of epithelial to mesenchymal transition in mammary epithelial cells. [14]. Expression of ITGB6 [15] and ITGB5 [16], [17] during epithelial to mesenchymal transition is believed to be TGF-beta-dependent.

WNT/Beta-catenin pathway is linked to the epithelial to mesenchymal transition process. Mainly this pathway is studied during cancer progression and in embryonic cells [18], [19], [20], [21].

EGF is also one of the modulators of epithelial to mesenchymal transition. Excessive or inadequate **EGF** stimulation leads to epithelial to mesenchymal transition during tumor development [22], [23]. **EGF** leads to epithelial to mesenchymal transition during tissue development, for example epicardial tissue [24]. Combined action of the **EGF** and hydrocortisone induces epithelial to mesenchymal transition during postovulatory functional changes in the ovarian surface epithelium [25]. **EGF** in breast cancer cells induces epithelial to mesenchymal transition via JAK/ Signal transducer and STAT3 transcription of **TWIST1** that inhibits **E-cadherin** transcription [22].

HGF signaling leads to epithelial to mesenchymal transition via **SNAIL1** [26], Rac1 [27], [28], [29], and **SLUG** activation [30], [31]. **HGF** also counteracts induction of epithelial to mesenchymal transition in kidney cells mediated by **TGF-beta 1** due to an up-regulation of **Prostaglandin E2** [32], SMAD inhibitors **TGIF** and **Sno-N** [33], [34], [35].

Activation of **NOTCH1 receptor** and **NOTCH4** induces epithelial to mesenchymal transition in endothelial cells [36].

IL-1 beta induces **FGF2** expression via PI3K in corneal cells. **FGF2** in turn also induces epithelial to mesenchymal transition via PI3K [37], [38], [39].

A number of microRNA species were found to be involved in the negative regulation of epithelial to mesenchymal transition [40], [41].

Oncostatin M participates in induction of epithelial to mesenchymal transition of renal cells via JAK/ STAT1 and STAT3 pathway. Induction of epithelial to mesenchymal transition possibly is a normal recovery process in renal cells, as indicated by the fact that it is accompanied by production of proliferating myofibroblasts. epithelial to mesenchymal transition of renal cells can lead to progression of renal fibrosis [42], [43], [44]. [45], [46].

Some of epithelial to mesenchymal transition induction mechanisms, for example **EGF** and **Endothelin-1**-dependent ones, were described in model cancer cells and are suspected to be involved in cancerogenesis.

TNF-alpha promotes epithelial to mesenchymal transition in certain cancer cells [47].

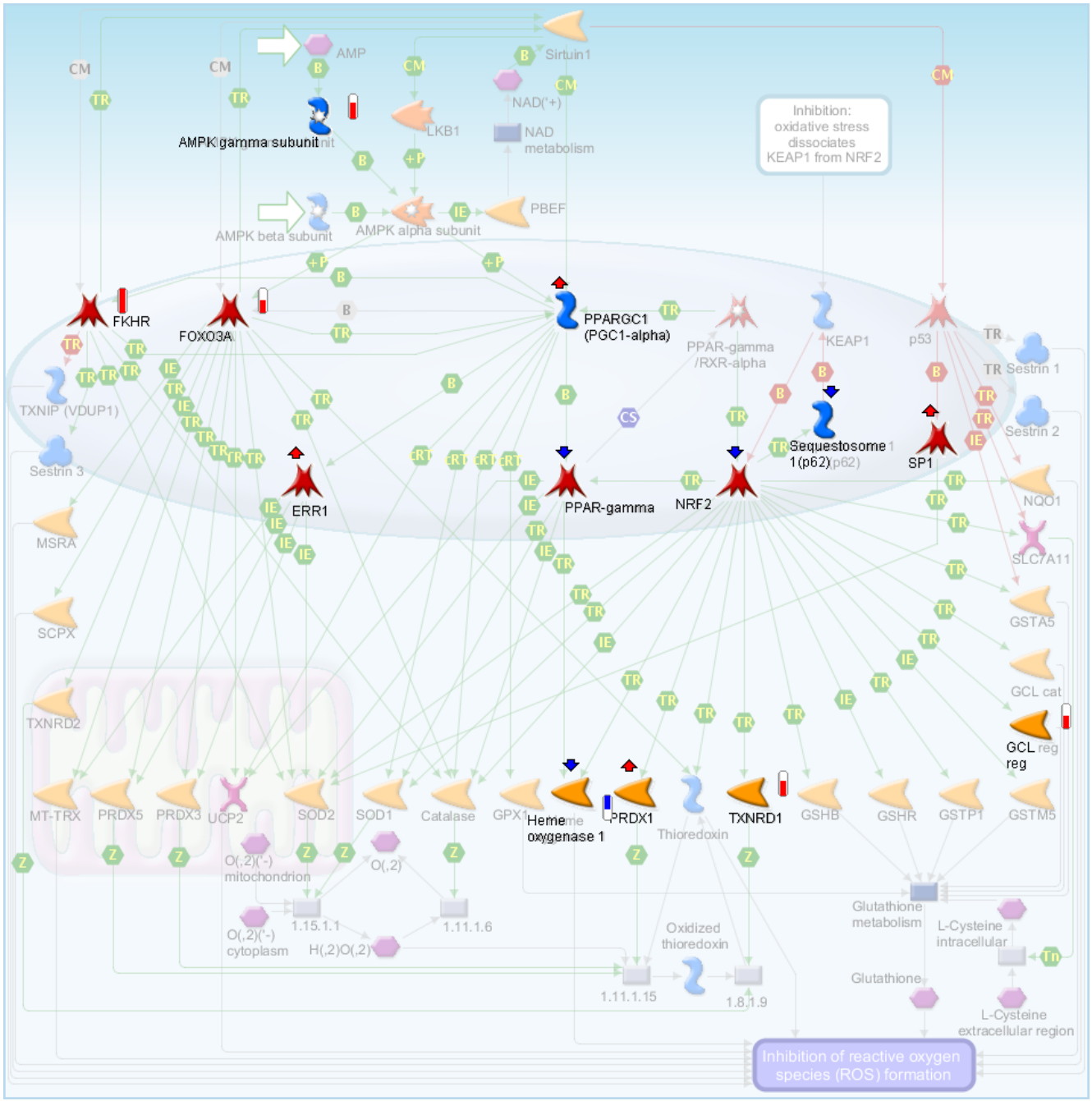
PDGF also participates in epithelial to mesenchymal transition induction or maintenance in cancer cell lines [48]. **PDGF-D** overexpression induces epithelial to mesenchymal transition in prostate carcinogenesis via mTOR/ 4E-BP1 and **RelA (p65 NF-kB subunit)**/ **Bcl-2** pathways [49].

Hypoxia can trigger epithelial to mesenchymal transition in some pathological states. Hypoxia stimulates metastases and migration during

cancer progression [50] and development of tissue fibrosis [51].

Maps and Descriptions [7 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Oxidative stress_Role of Sirtuin1 and PGC1-alpha in activation of antioxidant defense system	0.01015	0.01125	7.243E-4



Abstract:

Excess of reactive oxygen spices (ROS) constantly generated by mitochondria is neutralized by mitochondrial and cytoplasmic antioxidant defense system. Antioxidant defense system activation is mediated, in particular, by **PPARGC1 (PGC1-alpha)** and **Sirtuin1**, which promote induction of ROS detoxifying enzymes and proteins.

Details:

Excess of reactive oxygen spices (ROS) constantly generated by mitochondria is neutralized by mitochondrial and cytoplasmic antioxidant defense system [1], [2]. In particular, **PPARGC1 (PGC1-alpha)** and **Sirtuin1** play important role in activation of antioxidant defense system and thus in inhibition of ROS formation [3], [4], [5].

Sirtuin1 is NAD('+)-dependent deacetylase which regulates activity of multiple proteins [5], [6], [7], [8], [9].

Sirtuin1 deacetylates **FKHR** and **FOXO3A** transcription factors and enhances their transcriptional activity toward genes involved in inhibition of ROS formation (see negative regulation of reactive oxygen species metabolic process) and thus defense against oxidative stress [5], [10], [11], [12], [13], [14], [15], [16], [17], [18].

FKHR activates transcription of **SOD2** [11] and possibly **Catalase** [19] and **Sestrin 3** [16], [20]. **SOD2** generates **O(,2)** and **H(,2)O(,2)** from mitochondrial **O(,2)('-)** [21]. In turn, **Catalase** reduces **H(,2)O(,2)** to **O(,2)**, leading to neutralization of ROS [21]. **Sestrin 3** decreases oxidative stress as well [16], [22]. In addition, **FKHR** possibly promotes defense against oxidative stress via inhibition of **TXNIP (VDUP1)** transcription [16], [23], [24], [25].

FOXO3A activates transcription of **MSRA** [26], [27] and possibly **SCPX** [28], **TXNRD2** [29], **MT-TRX** [29], **PRDX5** [29], **PRDX3** [30], [31], [32], **UCP2** [29], **SOD2** [29], [33], [34], **Catalase** [29], [35], [36] and **Thioredoxin** [37] thus decreasing oxidative stress [16], [27], [28], [38], [39], [40]. Mitochondrial **PRDX5** and **PRDX3** decrease ROS via reducing **H(,2)O(,2)** with help of **Thioredoxin**, generating **Oxidized thioredoxin** [41]. Subsequently, mitochondrial **TXNRD2** regenerates **Oxidized thioredoxin** to **Thioredoxin** [41].

Moreover, **FKHR** and **FOXO3A** exert a positive feedback mechanism regulating **Sirtuin1** expression [5], [9], [42], [43], [44].

In addition, **FKHR** and **FOXO3A** are capable of inducing expression of **PPARGC1 (PGC1-alpha)** [29], [45], [46], [47], an important regulator of oxidative stress in cells [3], [4].

Sirtuin1 deacetylates and activates **PPARGC1 (PGC1-alpha)** [48], [49], [4], [50], [51], [52]. In addition, **Sirtuin1** possibly activates **PPARGC1 (PGC1-alpha)** as well as **FOXO3A** indirectly via AMP-activated protein kinase (AMPK) [53], [54], [55]. AMPK is composed of **AMP**-sensing **AMPK gamma subunit**, **AMPK beta subunit** and catalytic **AMPK alpha subunit** [53]. **Sirtuin1** deacetylates and activates **LKB1**, which in turn phosphorylates and activates **AMPK alpha subunit** [9], [56], [57]. Subsequently, **AMPK alpha subunit** phosphorylates and activates **FOXO3A** and **PPARGC1 (PGC1-alpha)**, thus promoting defense against oxidative stress [18], [37], [46], [58], [59], [60], [61], [62], [63], [64]. Moreover, **AMPK alpha subunit** enhances **Sirtuin1** activity possibly via induction of **PBEF** and subsequent increase in **NAD('+)** level [65], [66], [67], [68], [69], [70], [71].

PPARGC1 (PGC1-alpha) can associate with and activate multiple transcription factors including **FKHR** [72], **FOXO3A** [29], **PPAR-gamma** [73] and **ERR1** [74], [75] to regulate gene expression [73], [76], [77].

PPARGC1 (PGC1-alpha) promotes defense against oxidative stress via induction of **SOD1**, which converts cytoplasmic **O(,2)('-)** into **H(,2)O(,2)** [21], **GPX1**, which reduces ROS via oxidation of major non-enzymatic antioxidant **Glutathione** [41], [3], as well as via upregulation of **MT-TRX**, **UCP2**, **SOD2**, **Catalase** [78], [34], [36], [51] and possibly **PRDX5** and **PRDX3** [75], [79]. **ERR1** seems to be the main transcription factor involved in **PPARGC1 (PGC1-alpha)**-mediated induction of **MT-TRX**, **PRDX5**, **PRDX3** and **SOD2** [75].

PPARGC1 (PGC1-alpha)-activated **PPAR-gamma** protects cells from oxidative stress [80], [81], [82], [83] via induction of **UCP2** [84], **SOD2** [85], **SOD1** [85], [86], [87], **Catalase** [85], [87], [88] and possibly **Heme oxygenase 1** [83], [85]. Moreover, **PPARGC1 (PGC1-alpha)**-activated **PPAR-gamma**/ **PPAR-gamma/RXR-alpha** provides positive autoregulatory loop via upregulation of **PPARGC1 (PGC1-alpha)** expression [89], [90], [91], [92], [93]. In addition, **PPAR-gamma/RXR-alpha** possibly upregulates **NRF2** [94] which in turn induces

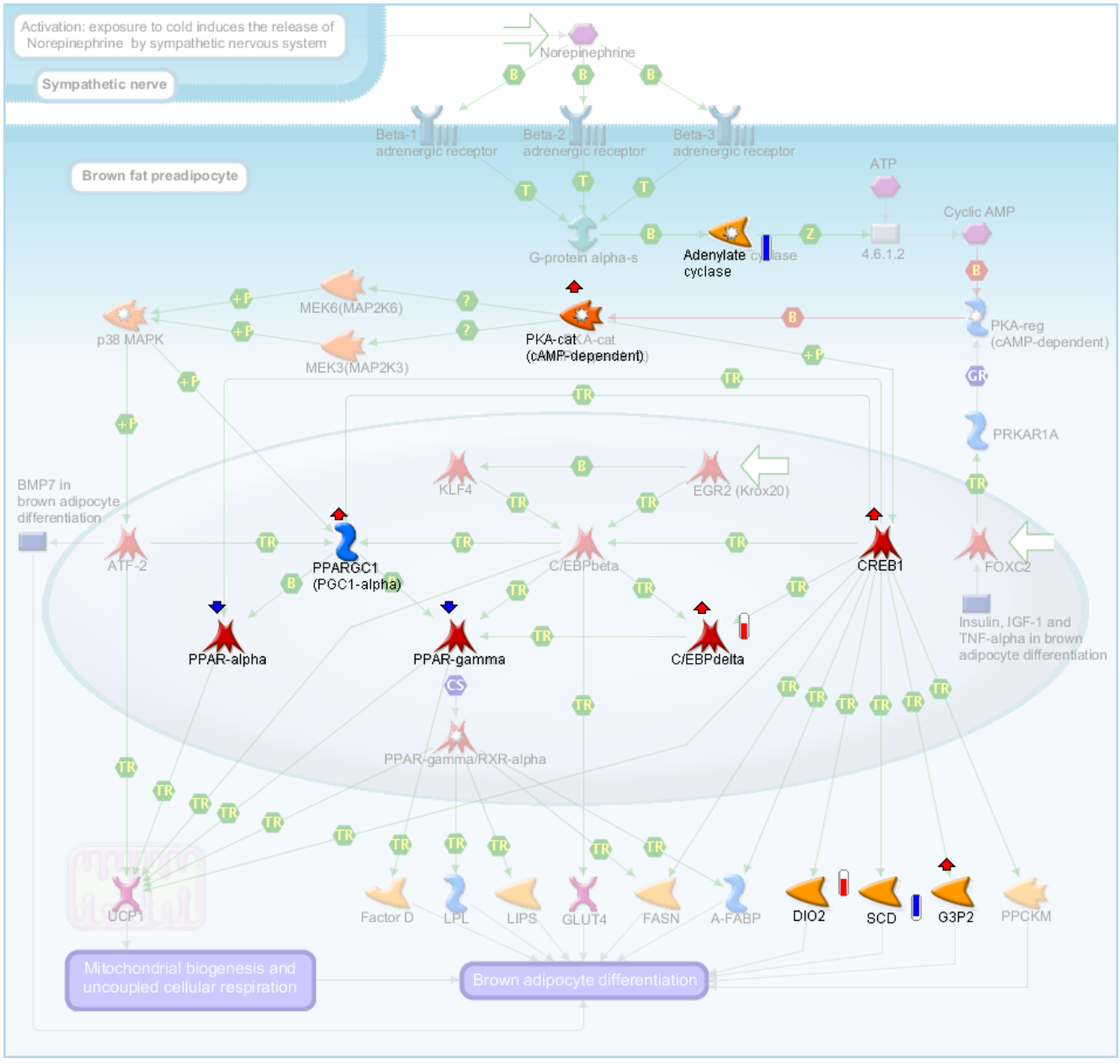
expression of **PPAR-gamma** [83], [95].

In response to oxidative stress **KEAP1** dissociates from **NRF2**, leading to **NRF2** activation [96], [97]. **NRF2** induces expression of genes involved in **Glutathione** metabolism, such as **GCL cat** [97], [98], [99], **GCL reg** [100], [101], [102], **GSTM5** [98], **GSTP1** [103], **GSHR** [100], [104], **GSHB** [79], [105] and possibly **SLC7A11**, which transports **L-Cysteine** from exracellular region to cytosol, and **GSTA5** [106]. Moreover, **NRF2** decreases oxidative stress [107], [108] via induction of **NQO1** [97], [98], [102], cytoplasmic **TXNRD1** which acts in the same manner as mitochondrial **TXNRD2** [100], **Thioredoxin** [109], cytoplasmic **PRDX1** which acts in the same manner as mitochondrial **PRDX5** and **PRDX3** [109], **Heme oxygenase 1** [97], [99], [102], [110], [111], **Catalase** [98] and possibly **SOD1** and **SOD2** [112], [113]. Finally, **NRF2** creates positive feedback loop via induction of expression of **Sequestosome 1(p62)** [114]. **Sequestosome 1(p62)** binds to **KEAP1**, sequesters it and directs its degradation, thus decreasing **KEAP1**/ **NRF2** association [114], [115], [116], which leads to **NRF2** stabilization and activation [114], [115], [116], [117], [118].

Finally, **Sirtuin1** deacetylates and inhibits **p53** [9], [49]. Inhibition of **p53** possibly enhances antioxidant defense system activity via release from repression of such **p53** targets as **Sestrin 1**, **Sestrin 2**, **NQO1**, **SLC7A11** and **GSTA5** [106], [119], [120], [121]. Inhibition of **p53** also promotes **SP1**-mediated **SOD2** expression [119], [120], [121], [122].

Maps and Descriptions [8 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Beta adrenergic receptors in brown adipocyte differentiation	0.03227	0.003449	7.735E-4



Abstract:

In mammals, there are two functionally different types of adipose tissue: white adipose tissue, the primary site of triglyceride storage, and brown adipose tissue, which is specialized in energy expenditure. Exposure to cold induces production of **Norepinephrine** by sympathetic nervous system and stimulates brown adipocyte differentiation. **Norepinephrine** activates **Beta adrenergic receptor 1**, **2** and **3**. These receptors stimulate **G-protein alpha-s** / **Adenylate cyclase/ Cyclic AMP/** PKA cascade. PKA activates **MEK3** and **MEK6/ p38 MAPK** signaling. **p38 MAPK** stimulates **ATF-2** and **PPARGC1**. **PPARGC1** is a coactivator of **ATF-2**, **PPAR-gamma** and **PPAR-alpha** in up-regulating transcription of **UCP1**, a mitochondrial uncoupling protein. **UCP1** expression leads to brown adipocyte differentiation.

KLF4 and **EGR2 (Krox20)** transactivate expression of **C/EBPbeta**, that up-regulates expression of the genes involved in differentiation of brown adipocytes. **C/EBPbeta** and **C/EBPdelta** induce transcription of **PPAR-gamma**. **PPAR-gamma/RXR-alpha** activates expression of brown adipose tissue genes, which are required for adipocyte differentiation.

In addition, **PKA** activates **CREB1** which also up-regulates expression of brown fat genes.

FOXC2 enhances Beta Adrenergic receptor/ **Cyclic AMP**/ PKA signaling pathway via activating transcription of **PRKAR1A**, a regulatory subunit of PKA.

Details:

The main function of adipose tissue is to store energy in the form of fat and to regulate the adaptive thermogenesis. There are two functionally different types of fat in mammals: white adipose tissue, the primary site of triglyceride storage and brown adipose tissue, which is specialized in energy expenditure and can counteract obesity [1].

Exposure to cold induces production of **Norepinephrine** by sympathetic nervous system and stimulates brown adipocyte differentiation [2]. **Norepinephrine** promotes the process of differentiation of brown adipocytes via activation of **Beta adrenergic receptor 1**, **2** and **3** [3].Beta adrenergic receptorsstimulate **G-protein alpha-s** / **Adenylate cyclase/ Cyclic AMP/** Protein kinase cAMP dependent (PKA) cascade [4]. PKA is composed of regulatory and catalytic subunits, **PKA-reg (cAMP-dependent)** and **PKA-cat (cAMP-dependent)**. PKA activates Mitogen-activated protein kinase kinase 3 and 6 (**MEK3** and **MEK6**) via an unknown mechanism [5]. **MEK3** and **MEK6** activate Mitogen-activated protein kinase 11-14 (**p38 MAPK**) [5], [6]. **p38 MAPK** stimulates Activating transcription factor 2 (**ATF-2**) and Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (**PPARGC1**) [7]. **PPARGC1** is a coactivator of **ATF-2** and Peroxisome proliferator activated receptor gamma (**PPAR-gamma**) in up-regulating transcription of Uncoupling protein 1 (**UCP1**) [7]. **PPARGC1** also activates Peroxisome proliferator activated receptor alpha (**PPAR-alpha**) that induces **UCP1** expression. **UCP1** is a mitochondrial transporter protein uncoupling oxidative phosphorylation from ATP synthesis in brown adipose tissue. As a result, energy is dissipated in the form of heat. Expression of **UCP1** leads to brown adipocytedifferentiation [1], [8].

In addition, Early growth response 2 (**EGR2 (Krox20)**) binds to Kruppel-like factor 4 (**KLF4)** and both factors cooperatively transactivate the same site of the CCAAT/enhancer binding protein, beta (**C/EBPbeta**) promoter [9]. Then, **C/EBPbeta** activates transcription of **PPAR-gamma**, CCAAT/enhancer binding protein, delta (**C/EBPdelta**), Solute carrier family 2 (facilitated glucose transporter), member 4 (**GLUT4**), **PPARGC1** and **UCP1**, thereby promoting brown adipocyte differentiation [9], [10], [11].

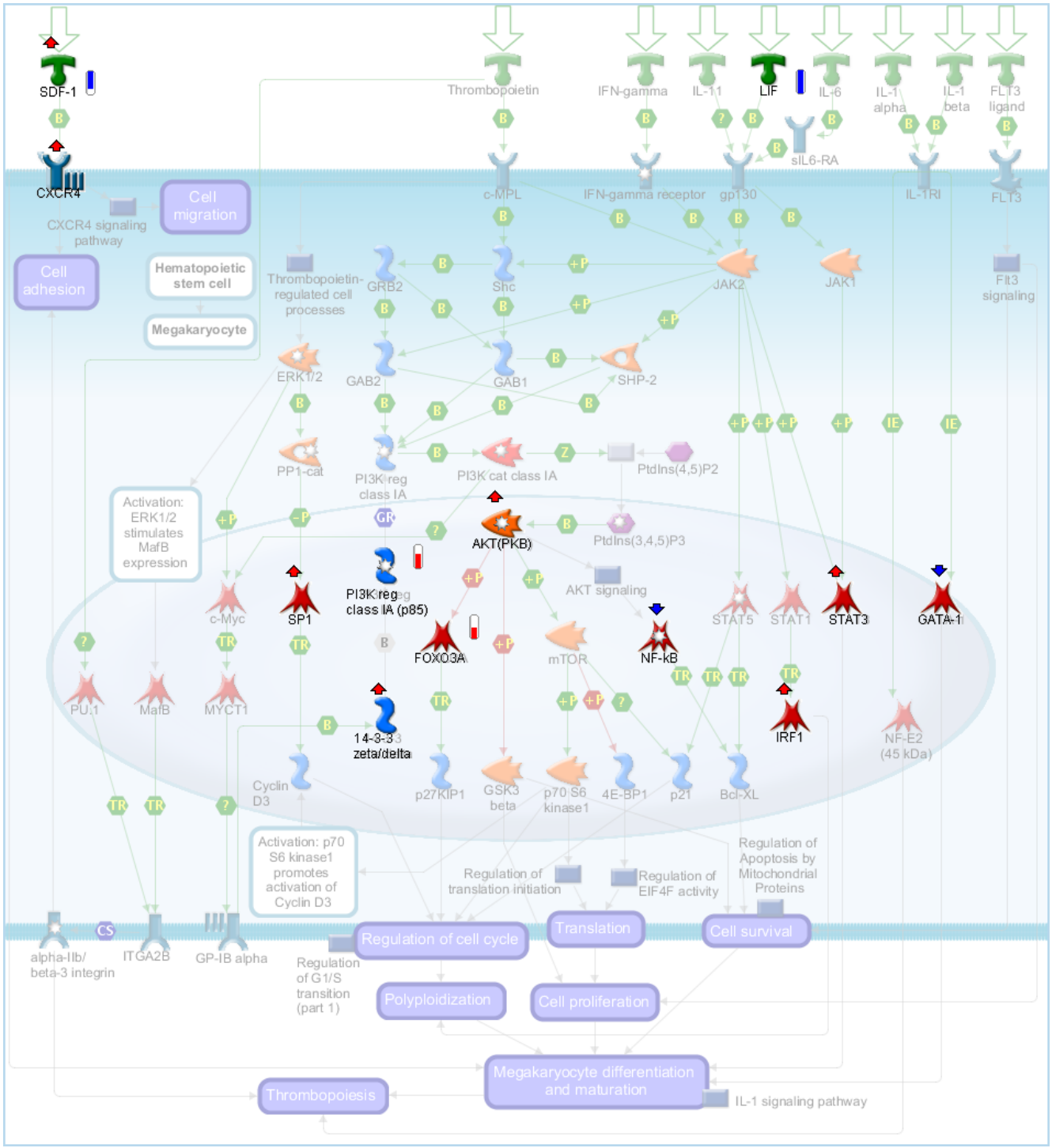
In addition, **PKA** activates cAMP responsive element binding protein 1 (**CREB1**) [5], [7]. **CREB1** activatestranscription of Phosphoenolpyruvate carboxykinase 2 (mitochondrial) (**PPCKM**), Stearoyl-CoA desaturase (**SCD**), Fatty acid binding protein 4, adipocyte (**A-FABP**), Fatty acid synthase (**FASN**), **C/EBPbeta**, CCAAT/enhancer binding protein, delta (**C/EBPdelta**) [12] and Deiodinase, iodothyronine, type II (**DIO2**) [8]. Furthermore, **CREB1**,probably, activates transcription of Glyceraldehyde-3-phosphate dehydrogenase (**G3P2**) and Peroxisome proliferator activated receptor alpha (**PPAR-alpha**) [8], [13]. **PPAR-alpha** in **PPARGC1 (PGC1-alpha)**-dependent

manner activates transcription of **UCP1** [8]. **C/EBPdelta** and **C/EBPbeta** induce transcription of **PPAR-gamma** [12].Transcriptional complex **PPAR-gamma/RXR-alpha** activates transcription of Complement factor D (adipsin) (**Factor D**), Lipase, hormone-sensitive (**LIPS**), Lipoprotein lipase (**LPL**), **A-FABP**, **FASN** and**UCP1** [6], [7], [12], [14], [15], [16].

Furthermore, Forkhead box C2 (**FOXC2**) enhances **Beta Adrenergic receptor** / **Cyclic AMP** / **PKA** pathway via activating transcription of Protein kinase, cAMP-dependent, regulatory, type I, alpha (**PRKAR1A**) [17].

Maps and Descriptions [9 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_Cytokine-mediated regulation of megakaryopoiesis	0.04007	0.003732	8.697E-4



Abstract:

Megakaryocytopoiesis is regulated by a number of cytokines, such as **Thrombopoietin**, **IFN-gamma**, **IL-6**, **IL-11**, **LIF**, **IL-1 alpha**, **IL-1 beta** , and **FLT3 ligand**, which promote megakaryocyte differentiation, proliferation, polyploidization and survival.

Details:

Bone marrow (BM) is a major reservoir for adult organ-specific stem cells, including hematopoietic stem cells (HSCs). Megakaryocytopoiesis (see: megakaryocyte differentiation) is the process of BM HSC development into mature megakaryocytes (MKs), which involves the commitment of multipotent hematopoietic stem cells toward MK progenitors, the cell proliferation and cell differentiation of MK progenitors, the polyploidization of MK precursors and the cell maturation of MK. In turn, MKs ultimately produce platelets, critical for hemostasis in the peripheral blood vasculature [1], [2], [3]. BM stromal cells produce **SDF-1**, the chemoattractant which induces cell adhesion, transendothelial cell migration and homing of HSCs to bone marrow microenvironment, promotes megakaryocytopoiesis (see: megakaryocyte differentiation) and also MK cell adhesion to BM endothelium by activation of **CXCR4** [4], [5], [6].

Thrombopoietin is the key cytokine that regulates megakaryopoiesis (see: megakaryocyte differentiation). **Thrombopoietin** via its cognate receptor **c-MPL** triggers multiple signaling pathways in MKs, leading to cell proliferation, cell maturation, and polyploidization of megakaryocyte progenitors and their cell differentiation into mature platelet-producing megakaryocytes. **Thrombopoietin** activates **ERK1/2** ; **JAK2**/ **Shc**/ **GRB2**/ **SHP-2**/ **GAB1**/ **GAB2**/ **PI3K reg class IA**/ **PI3K cat class IA**/ **PtdIns(4,5)P2**/ **PtdIns(3,4,5)P3**/ **AKT(PKB)** and **JAK2**/ **STAT3**/ **STAT5** signaling pathways [7], [8], [9], [10], [11], [12], [13], [14], [15]. **Thrombopoietin** increases **PU.1** protein levels, which in turn activates the expression of **ITGA2B**, a subunit of **alpha-IIb/beta-3 integrin** [16]. **alpha-IIb/beta-3 integrin** promotes MK cell migration and cell adhesion to BM endothelium and is also able to regulate thrombopoiesis (see: platelet formation) [17], [18].

Thrombopoietin activates **ERK1/2** signaling, which leads to an increase of **MafB** RNA and protein levels. In turn, **MafB** activates the expression of **ITGA2B** [19]. **Thrombopoietin** also activates **ERK1/2**/ **c-Myc** and **PI3K cat class IA**/ **c-Myc** signaling pathways in MKs [20]. In turn, **c-Myc** probably can induce **MYCT1**/ **GP-IB alpha**/ **14-3-3 zeta/delta**/ **PI3K reg class IA (p85)**/ **PI3K reg class IA**/ **AKT(PKB)** pathway and thus contributes to megakaryocytic polyploidization [21], [22], [23]. **ERK1/2**/ **PP1-cat**/ **SP1** signaling markedly upregulates expression of **Cyclin D3**, which is essential for regulation of cell cycle [24], [25], [26].

Thrombopoietin-induced **AKT(PKB)**/ **FOXO3A**/ **p27KIP1** and **AKT(PKB)**/ **GSK3 beta** pathways contribute to MK polyploidization and cell proliferation [27], [28], [29], [30]. **AKT(PKB)**/ **mTOR** signaling promotes activation of **p70 S6 kinase1** followed by nuclear relocation and activation of **Cyclin D3**, inhibition of **4E-BP1** and increase of **p21** levels, thus leading to MK cell proliferation and polyploidization [31], [13].

Thrombopoietin-activated **STAT5** stimulates **p21** expression and also contributes to MK polyploidization [32], [33], [33]. Additionally **Thrombopoietin** upregulates expression of anti-apoptotic **Bcl-XL** via both **STAT5** and **AKT(PKB)**/ **NF-kB** signaling pathways, thus implicating in MK cell survival [34].

Another cytokine, **IFN-gamma**, can activate **IFN-gamma receptor**/ **JAK2**/ **STAT1**/ **IRF1** signaling, thereby additionally promoting MK polyploidization [35], [36].

IL-11, **LIF** and **IL-6** via **sIL6-RA** are able to activate **gp130**/ **JAK1**/ **JAK2**/ **STAT3** signaling in MKs and thus contribute to megakaryopoiesis (see: megakaryocyte differentiation) [37], [38], [39], [40], [41], [42].

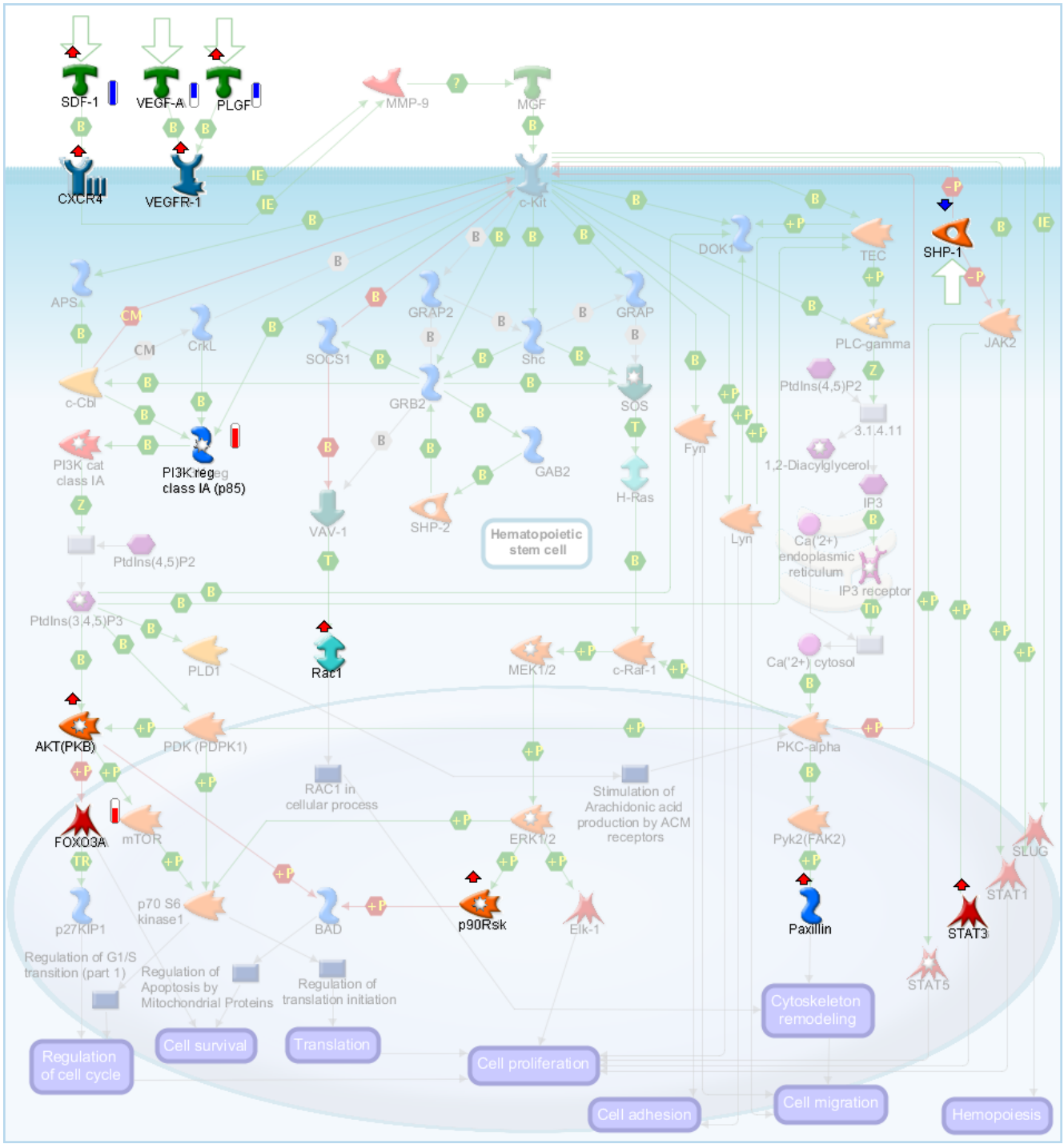
IL-1 alpha and **IL-1 beta** via **IL-1RI** signaling pathway also augment megakaryopoiesis (see: megakaryocyte differentiation) [43], [44]. Moreover, **IL-1 beta**/ **IL-1RI** activates the expression of **NF-E2 (45 kDa)** and **GATA-1** in MKs [44], [45].

FLT3 ligand/ **FLT3** signaling can promote cell proliferation and survival of MK progenitors, though it delays ultimate MK cell maturation [46], [43], [47].

Mature MKs migrate from the BM endosteal niche to the vascular-rich niche where they bind to BM endothelium and generate proplatelets [3].

Maps and Descriptions [10 of 10]

Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
Development_c-Kit ligand signaling pathway during hemopoiesis	0.04557	0.001309	0.001235



Abstract:

MGF is an important factor for cell proliferation, survival and differentiation during hemopoiesis.

Details:

c-Kit ligand **MGF** is a pleiotropic factor, which plays an important role in cell proliferation, survival and cell differentiation during hemopoiesis . **MGF** is expressed as a membrane-bound form and is cleaved and activated by **MMP-9**, which can be produced in both bone marrow stromal cells and hematopoietic stem cells (HSCs). **MMP-9** expression is stimulated by **SDF-1**/ **CXCR4** and **VEGF-A** and/ or **PLGF**/ **VEGFR-1** signaling pathways in HSCs [1], [2], [3]. Activated **MGF** binds to its cognate receptor **c-Kit**, which results in dimerization of the receptor followed by activation of its intrinsic tyrosine kinase activity [4]. **c-Kit** recruits multiple adaptor proteins to the receptor complex in HSCs, which enable spatial and sequential signaling regulation. These are **APS**, **CrkL**, **GRAP**, **GRAP2**, **Shc**, **GRB2**, **GAB2**, **DOK1** [5], [6], [7], [8], [9], [10], [11]. Activated **c-Kit** induces activation of several signaling pathways in HSCs, involved in a range of cell functions, including cell proliferation and cell survival [11], [12], [13], [14].

c-Kit activates **PI3K reg class IA (p85)**/ **PI3K cat class IA**/ **PtdIns(4,5)P2**/ **PtdIns(3,4,5)P3**/ **AKT(PKB)** signaling pathway [15], [16], [17]. **CrkL** and **c-Cbl** associate with **PI3K reg class IA (p85)** [7]. **PI3K reg class IA (p85)** signaling is also involved in activation of **PtdIns(3,4,5)P3**/ **PDK (PDPK1)** and/ or **PLD1**/ **PKC-alpha**/ **c-Raf-1**/ **MEK1/2**/ **ERK1/2** signaling pathway in HSCs [18], [19], [20], [21]. **c-Kit** -induced **PI3K cat class IA**/ **PtdIns(3,4,5)P3** signaling also activates **DOK1** and **TEC**, which directly interact with **Lyn** [9]. **AKT(PKB)** inhibits **FOXO3A**/ **p27KIP1** and **BAD** signaling and activates **mTOR**/ **p70 S6 kinase1** signals, implicated in cell survival and cell proliferation [22], [23], [11], [24], [25].

c-Kit activates **SOS**/ **H-Ras**/ **c-Raf-1**/ **MEK1/2**/ **ERK1/2**/ **Elk-1** signaling pathway [5], [6], [12], [26]. **GAB2** can link to the **ERK1/2** pathway through association with **SHP-2** [6], [27]. Downstream of **ERK1/2** the **p70 S6 kinase1** and **p90Rsk**/ **BAD** signals are activated, which contributes to cell proliferation and cell survival [22], [28].

c-Kit activates **PLC-gamma**/ **PtdIns(4,5)P2**/ **IP3**/ **IP3 receptor**/ **Ca('2+)**/ **PKC-alpha**/ **Pyk2(FAK2)** signaling pathway [13], [29], [30]. **Pyk2(FAK2)** associates with **Paxillin**, which is involved in cell cytoskeleton remodeling (see: actin cytoskeleton reorganization) [31], [32]. **c-Kit** can also activate **TEC**, which links to **PLC-gamma** signaling [33], [34].

c-Kit also activates **Lyn** and **Fyn** in HSCs, which play a role in **MGF**-mediated cell proliferation and chemotaxis [35], [36], [37].

MGF induces **c-Kit**/ **JAK2**/ **STAT1**/ **STAT3**/ **STAT5** signaling and also direct association of **c-Kit** with **STAT1**. This signaling pathway is necessary for optimal cell proliferative response to **MGF** [38], [39], [40].

Moreover, **MGF**-activated **c-Kit** stimulates the expression of **SLUG**, the important factor of hematopoietic development [41], [42].

Ligand-induced downregulation of **c-Kit** is an important phenomenon in the normal physiology. Upon **MGF** stimulation, **c-Kit** induces activation of **c-Cbl**, which in turn mediates **c-Kit** degradation [43]. **SHP-1** is another negative regulator of **c-Kit** signaling and/or **c-Kit**-activated **JAK2** pathway [44], [45]. **PKC-alpha** also negatively regulates of **c-Kit** signaling [46]. **SOCS1** is a negative regulator of **c-Kit** mitogenic signaling, while it doesn't affect cell survival. **SOCS1** interacts with **GRB2** and negatively regulates its downstream target **VAV-1**, which is involved in activation of **Rac1** signaling [47], [48].

Diseases

This ontology is created based on the classification in Medical Subject Headings (MeSH). Each disease in diseases ontology has its corresponding biomarker gene or set of genes annotated manually from the literature.

Diseases Details [Top 100 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
1	Carcinoma	6.262E-18	6.125E-54	5.649E-65
2	Adenocarcinoma	2.995E-17	6.755E-54	6.776E-64
3	Bronchial Neoplasms	2.763E-17	3.271E-48	3.964E-61
4	Carcinoma, Bronchogenic	6.907E-17	2.842E-48	1.16E-60
5	Neoplasms, Glandular and Epithelial	3.775E-21	1.388E-43	1.821E-60
6	Carcinoma, Non-Small-Cell Lung	2.926E-16	9.75E-49	3.387E-60
7	Pathological Conditions, Signs and Symptoms	1.681E-28	1.97E-28	5.308E-54
8	Pathologic Processes	2.398E-24	2.587E-31	1.845E-53
9	Neoplasms by Histologic Type	2.25E-16	1.352E-39	9.188E-52
10	Colonic Diseases	1.056E-14	3.086E-42	3.686E-51
11	Endocrine System Diseases	2.092E-18	1.015E-34	4.3E-50
12	Endocrine Gland Neoplasms	1.788E-15	3.247E-36	7.161E-49
13	Stomach Neoplasms	1.01E-17	1.719E-33	8.233E-49
14	Ovarian Neoplasms	4.265E-17	2.105E-32	8.535E-48
15	Stomach Diseases	3.517E-17	1.201E-32	2.037E-47
16	Ovarian Diseases	9.044E-18	9.989E-31	4.841E-47
17	Gonadal Disorders	4.523E-18	2.582E-30	5.079E-47
18	Adnexal Diseases	9.467E-18	1.069E-30	5.433E-47
19	Neoplasms, Ductal, Lobular, and Medullary	2.213E-11	1.724E-39	2.717E-45
20	Drug-Related Side Effects and Adverse Reactions	1.333E-25	4.092E-20	1.671E-44
21	In-house Adverse Events	6.058E-26	1.225E-19	2.815E-44
22	Carcinoma, Renal Cell	5.535E-8	1.158E-41	8.29E-44
23	Digestive System Neoplasms	8.362E-13	1.817E-36	1.404E-43
24	Liver Diseases	5.676E-11	3.72E-39	2.651E-43
25	Digestive System Diseases	8.386E-12	1.243E-37	3.854E-43
26	Chemically-Induced Disorders	2.977E-24	8.073E-20	1.52E-42
27	Carcinoma, Ductal	7.874E-10	5.886E-38	7.979E-42
28	Gastrointestinal Neoplasms	1.743E-14	9.389E-31	2.894E-41
29	Immune System Diseases	6.845E-14	1.189E-29	1.968E-40
30	Gastrointestinal Diseases	2.626E-13	4.244E-31	3.869E-40
31	Colonic Neoplasms	4.037E-11	2.713E-32	1.005E-39
32	Liver Neoplasms	3.447E-10	4.572E-34	3.368E-39
33	Pancreatic Diseases	6.072E-11	2.704E-32	4.042E-39

Diseases Details [Top 100 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
34	Cardiovascular Diseases	2.908E-20	1.968E-19	4.85E-38
35	Neoplasms, Connective and Soft Tissue	4.278E-12	3.087E-28	3.569E-37
36	Vascular Diseases	1.102E-18	9.132E-20	1.042E-36
37	Sarcoma	1.489E-12	2.647E-26	1.894E-36
38	Intestinal Neoplasms	1.831E-13	7.206E-27	1.988E-36
39	Colorectal Neoplasms	3.131E-13	5.437E-27	2.963E-36
40	Rectal Diseases	7.372E-14	6.657E-25	1.89E-35
41	Carcinoma, Ductal, Breast	7.564E-9	8.319E-32	3.963E-35
42	Intestinal Diseases	1.364E-11	1.444E-27	8.224E-35
43	Carcinoma, Hepatocellular	8.56E-8	6.57E-33	8.657E-35
44	Immunoproliferative Disorders	2.661E-11	6.475E-26	1.244E-34
45	Lymphoproliferative Disorders	7.352E-11	4.768E-26	3.261E-34
46	Hemic and Lymphatic Diseases	4.777E-11	2.357E-26	4.17E-34
47	Breast Neoplasms	2.065E-14	1.748E-20	4.718E-33
48	Breast Diseases	2.121E-14	1.81E-20	5.019E-33
49	Pancreatic Neoplasms	1.342E-9	4.827E-26	2.871E-32
50	Neoplasms, Neuroepithelial	2.704E-17	7.362E-16	4.568E-32
51	Neoplasms, Connective Tissue	2.886E-11	4.402E-23	7.436E-32
52	Lung Diseases, Obstructive	7.336E-18	1.096E-15	3.677E-31
53	Neoplastic Processes	1.729E-10	4.09E-23	7.896E-31
54	Paraproteinemias	6.166E-12	2.042E-20	1.171E-30
55	Neoplasms, Plasma Cell	1.565E-11	6.596E-21	1.171E-30
56	Multiple Myeloma	1.333E-11	1.598E-20	2.25E-30
57	Astrocytoma	6.064E-16	1.159E-15	2.393E-30
58	Nutritional and Metabolic Diseases	8.892E-19	1.125E-15	3.091E-30
59	Blood Protein Disorders	1.38E-11	2.247E-20	3.132E-30
60	Glioma	3.911E-17	2.643E-14	3.756E-30
61	Thyroid Neoplasms	1.257E-12	1.207E-19	3.951E-30
62	Nerve Sheath Neoplasms	5.394E-10	1.611E-21	4.481E-30
63	Signs and Symptoms	2.816E-24	9.422E-10	1.397E-29
64	Hypoxia	1.113E-14	7.097E-18	1.587E-29
65	Signs and Symptoms, Respiratory	9.137E-15	1.365E-17	1.962E-29
66	Hemostatic Disorders	2.026E-11	1.216E-19	2.361E-29
67	Prostatic Neoplasms	1.214E-10	1.215E-19	3.547E-29
68	Prostatic Diseases	1.268E-10	1.299E-19	3.97E-29
69	Hematologic Diseases	1.202E-10	7.984E-21	5.525E-29
70	Hemorrhagic Disorders	2.426E-11	2.73E-19	5.85E-29

Diseases Details [Top 100 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
71	Genital Neoplasms, Male	1.496E-10	1.668E-19	6.052E-29
72	Genital Diseases, Male	1.426E-10	2.009E-19	6.458E-29
73	Neoplasms, Nerve Tissue	7.769E-14	3.464E-16	1.541E-28
74	Nervous System Diseases	2.395E-13	9.103E-17	2.092E-28
75	Carcinoma in Situ	2.309E-9	3.282E-21	2.337E-28
76	Glioblastoma	5.193E-15	1.673E-14	3.551E-28
77	Wounds and Injuries	3.485E-17	1.863E-12	6.392E-28
78	Thyroid Diseases	3.637E-12	2.108E-17	1.34E-27
79	Congenital, Hereditary, and Neonatal Diseases and Abnormalities	1.768E-11	1.487E-18	1.477E-27
80	Neuroectodermal Tumors	2.442E-15	8.318E-14	1.757E-27
81	Neoplasms, Germ Cell and Embryonal	3.775E-15	7.301E-14	2.226E-27
82	Psychiatry and Psychology	3.6E-18	6.359E-12	2.246E-27
83	Metabolic Diseases	6.825E-17	2.025E-13	4.355E-27
84	Genetic Diseases, Inborn	2.75E-11	1.797E-17	7.074E-27
85	Neoplasm Metastasis	4.409E-8	4.609E-21	1.237E-26
86	Mental Disorders	4.208E-17	4.437E-12	1.342E-26
87	Pulmonary Disease, Chronic Obstructive	3.026E-14	8.488E-15	1.431E-26
88	Skin and Connective Tissue Diseases	1.133E-11	1.776E-16	1.68E-26
89	Virus Diseases	4.039E-5	5.768E-25	1.405E-25
90	Skin Diseases	4.977E-12	3.585E-15	1.716E-25
91	Connective Tissue Diseases	9.672E-11	8.514E-16	1.122E-24
92	Urogenital Neoplasms	4.719E-10	3.734E-16	2.038E-24
93	Adenoma	5.474E-12	5.65E-14	2.884E-24
94	Peripheral Nervous System Neoplasms	6.086E-8	4.063E-17	4.247E-24
95	Autoimmune Diseases	2.226E-8	2.629E-18	4.882E-24
96	Cystic Fibrosis	1.534E-9	7.224E-17	5.026E-24
97	Lymphoma	6.05E-6	3.988E-22	8.96E-24
98	Diabetes Mellitus	2.808E-20	1.529E-8	9.822E-24
99	Musculoskeletal Diseases	1.003E-16	3.937E-9	1.048E-23
100	Fibrosis	6.224E-19	2.845E-8	1.27E-23

Process Networks

A recognized series of events (interactions or biochemical reactions) accomplished by one or more ordered assemblies of molecular functions with a defined beginning and end.

Process Networks Details [24 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
1	Development_Blood vessel morphogenesis	1.499E-7	2.446E-7	3.742E-13
2	Signal transduction_NOTCH signaling	0.01902	9.663E-9	7.636E-10
3	Cell adhesion_Attractive and repulsive receptors	6.255E-7	0.00102	7.632E-9
4	Cell cycle_G1-S Growth factor regulation	0.02627	1.769E-6	1.348E-7
5	Reproduction_Progesterone signaling	4.635E-4	8.309E-5	4.725E-7
6	Signal transduction_ESR1-membrane pathway	0.004753	4.701E-6	6.996E-7
7	Development_Regulation of angiogenesis	7.27E-5	0.002371	1.178E-6
8	Reproduction_FSH-beta signaling pathway	7.307E-4	0.001047	1.334E-6
9	Cell adhesion_Integrin-mediated cell-matrix adhesion	1.272E-5	0.008294	1.358E-6
10	Development_EMT_Regulation of epithelial-to-mesenchymal transition	0.02957	5.83E-5	3.994E-6
11	Signal transduction_Androgen receptor signaling cross-talk	0.01774	1.801E-4	5.808E-6
12	Signal transduction_Leptin signaling	0.03562	3.522E-5	1.1E-5
13	Inflammation_Amphoterin signaling	0.02113	1.113E-4	1.608E-5
14	Reproduction_Feeding and Neurohormone signaling	0.007953	4.839E-4	1.767E-5
15	Development_Neurogenesis_Axonal guidance	3.519E-5	0.01621	1.868E-5
16	Signal Transduction_BMP and GDF signaling	0.0484	3.825E-4	4.176E-5
17	Cytoskeleton_Regulation of cytoskeleton rearrangement	2.613E-4	0.009737	5.5E-5
18	Cell adhesion_Amyloid proteins	0.004307	0.003276	6.9E-5
19	Inflammation_Neutrophil activation	0.02236	0.00388	3.896E-4
20	Development_Neurogenesis in general	0.02376	0.0147	7.26E-4
21	Protein folding_Response to unfolded proteins	0.01462	0.02483	7.856E-4
22	Proteolysis_ECM remodeling	0.03655	0.02555	0.001966
23	Cell cycle_Meiosis	0.03409	0.03332	0.002468
24	Inflammation_Histamine signaling	0.04548	0.03373	0.00648

Pathway Groups

The maps in the Pathway Maps ontology are grouped according to main biological processes. A map could participate in different groups if depicted pathway takes part in different main biological processes.

Pathway Groups Details [37 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
1	Cell differentiation	1.67E-14	4.236E-23	3.264E-36
2	Neurofibromatoses	1.731E-12	2.644E-23	5.343E-33
3	Prostatic Neoplasms	1.823E-8	2.611E-27	6.426E-32
4	Colorectal Neoplasms	1.189E-8	5.483E-21	3.961E-28
5	Ovarian cancer	5.861E-7	8.192E-25	4.113E-28
6	Stomach Neoplasms	1.078E-6	1.899E-24	4.418E-28
7	Carcinoma, Hepatocellular	3.862E-8	2.587E-23	6.958E-28
8	Melanoma	2.876E-5	2.313E-21	4.252E-24
9	Systemic Lupus Erythematosus	1.602E-5	8.377E-21	8.742E-24
10	Lung cancer	2.83E-7	4.046E-19	2.782E-23
11	Apoptosis	1.024E-4	7.114E-21	2.515E-22
12	Asthma	4.65E-7	4.596E-17	2.998E-22
13	Stem cells	2.719E-9	1.209E-13	1.473E-21
14	Vascular development (Angiogenesis)	3.252E-6	5.129E-17	1.181E-19
15	Glaucoma	2.819E-5	3.779E-14	2.554E-17
16	Tissue remodeling and wound repair	4.893E-8	2.604E-11	3.54E-17
17	Neurodegeneration in Multiple sclerosis	2.572E-4	3.083E-15	4.823E-17
18	Cell cycle and its regulation	5.531E-6	7.957E-14	4.844E-17
19	Hematology	2.404E-4	1.337E-15	7.445E-17
20	Breast Neoplasms	6.54E-5	5.041E-14	4.075E-16
21	Inflammatory response	1.63E-4	1.041E-13	9.386E-16
22	Depression	1.294E-5	2.754E-12	5.241E-15
23	Dermatitis, Allergic Contact	6.552E-4	2.713E-13	5.451E-15
24	Pancreatic Neoplasms	3.812E-5	3.062E-12	6.926E-15
25	Calcium signaling	1.473E-5	9.514E-11	1.909E-14
26	Immune system response	2.234E-4	1.416E-10	1.005E-12
27	Huntington Disease	5.848E-5	9.132E-10	1.834E-12
28	Protein synthesis	2.155E-4	1.178E-5	2.728E-9
29	Hypoxia response regulation	3.771E-5	3.447E-7	3.746E-9
30	Inflammatory diseases	0.002759	3.813E-6	2.335E-8
31	Pulmonary Disease, Chronic Obstructive	0.01048	4.13E-7	3.659E-8
32	Nuclear receptor signaling	0.03936	1.469E-5	2.572E-6
33	Heart Failure	0.02069	1.318E-5	3.167E-6

Pathway Groups Details [37 items]				
#	Name	Input Data p-value	Key Hubs p-value	Union p-value ▲
34	Myogenesis regulation	0.0444	2.753E-4	2.61E-5
35	Obesity	0.03965	1.15E-4	6.009E-5
36	Blood clotting	0.006728	0.004148	1.067E-4
37	Vasodilation	0.04108	0.024	0.001899

Appendix 1: Legend

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Appendix 2: Glossary

Processes Networks
A recognized series of events (interactions or biochemical reactions) accomplished by one or more ordered assemblies of molecular functions with a defined beginning and end.
Diseases
This ontology is created based on the classification in Medical Subject Headings (MeSH). Each disease in diseases ontology has its corresponding biomarker gene or set of genes.
Enrichment Analysis (EA) (also, Ontology Enrichment)
An analysis procedure that consists of mapping gene IDs of the dataset(s) of interest onto gene IDs in processes (terms) of built-in functional ontologies such as pathway maps, networks,diseases, etc. The terms in a given ontology are ranked based on “relevance” in the dataset. The statistical relevance procedure, a p-value of hypergeometric distribution, is calculated as the probability of a match to occur by chance, given the size of the ontology, the dataset and the particular process. The lower the p-value, the higher is the 'non-randomness' of finding the intersection between the dataset and the particular ontology term. That, in turn, translates into a higher ranking for the process matched. Everything equal, the more genes/proteins belong to a process/pathway, the lower the p-value. In EA we use multiple proprietary ontologies (canonical pathway maps, cellular processes, toxicities, disease biomarkers etc., and public ontologies such as Gene Ontology (cellular processes, protein functions, localizations).
Enrichment Synergy
The enrichment synergy method was offered for comparison of datasets that are functionally relevant but poorly overlapping at the gene level, for instance mutated and amplified genes in breast cancer [5]. The genes derived from different datasets may populate the very same pathway or process, which suggests that they are functionally complimentary. To determine whether two distinct gene lists cooperatively alter a certain cellular pathway or process, we calculate the synergy between them by ontology enrichment. An ontology term (pathway or process) is considered synergistic if the enrichment p-value for the non-redundant union of compared gene lists is lower than p-values for individual lists. More significant enrichment for the union reflects functional connectivity of two gene lists and their complementary effect on the pathway.
Process
An element or an term in an ontology, e.g., a given disease, or a given process, etc.
GO Localizations
A GO ontology for localization of the gene products inside or outside the cell.
GO Molecular Functions
A GO ontology of hierarchically structured molecular functions. A protein may be linked to several different molecular functions.
GO Processes
A GO ontology for biological processes. The processes are structured as hierarchical tree with branches defined according to the Gene Ontology controlled vocabulary. GO process folders are nested, i.e., each folder references all the proteins participating in its sub-processes.
Key Hub (KH)
A topologically significant molecular entity that supposed to regulate differential expression genes. KHs could be obtained by two approaches: causal reasoning network analysis and overconnectivity analysis. Using causal resoning the one could define one step KHs (transcriptional factors that statistically significant associated with experimental differential expressed genes regulation) and distant KHs (second step objects regulate one step transcriptional factors, etc, up to four steps). Overconnectivity analysis gives molecular entities that are overconnected with experimental differentially expressed genes.
Key Process
An ontology term (i.e. pathway maps) that enriched with both differentially expressed genes and corresponding key Hubs (see Introduction part for detailed workflow description).

Pathway groups
The maps in the Pathway Maps ontology are grouped according to main biological processes. A map could participate in different groups if depicted pathway takes part in different main biological processes.
Molecular Entity
A process that describes the type of molecule, e.g. kinases, transcriptional factors, receptors, etc.
Ontology
Functional ontologies developed for biological processes, toxic processes, disease biomarkers, diseases, drug targets and drug action mechanisms. Each ontology has hierarchical tree structure and each has corresponding sets of pre-built networks and pathway maps, or, in case of disease biomarkers, gene lists.
Pathway Map
Pathway maps are graphic images representing complete biochemical pathways or signaling cascades in a commonly accepted sense. They are drawn by experts using Pathway Map Creator™ tool. Typically, a map comprises 3-5 pathways. Maps are assembled into groups divided onto regulatory, metabolic, disease, toxicity and drug action sections, and thus form an ontology of their own kind. Maps are interactive and hyperlinked to annotation pages for all objects displayed on them (genes, proteins, compounds and interactions).

Appendix 3: List of Key Hubs IDs

For uploaded DEG lists, a causal reasoning test was performed to identify statistically significant molecular entities (p-value < 0.01). These proteins can be considered as topologically significant direct and indirect upstream regulators of the input genes (up to four steps from the DEG subset). First step regulators always are transcriptional factors while the other more distant regulators could be different regulatory proteins (Number of step from a significant regulator to DEG subset is defined in Calculation Distance column).

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
1	miR-495-3p	RNA	-	57/71	1.333E-07	2	View
2	ARNT	Transcription factor	+	95/133	4.125E-07	3	View
3	miR-22-3p	RNA	-	68/91	1.261E-06	2	View
4	MAP3K3	Protein kinase	+	68/91	1.261E-06	3	View
5	miR-106b-5p	RNA	-	45/56	2.689E-06	2	View
6	miR-320-3p	RNA	-	43/53	2.775E-06	2	View
7	miR-93-5p	RNA	-	66/89	2.845E-06	2	View
8	microRNA 34a	RNA	-	52/67	3.23E-06	2	View
9	HSP90 alpha	Binding protein	+	62/83	3.753E-06	2	View
10	miR-106a-5p	RNA	-	44/55	4.35E-06	2	View
11	Vinculin	Binding protein	+	61/82	5.648E-06	3	View
12	miR-429-3p	RNA	-	69/95	5.914E-06	2	View
13	miR-124-3p	RNA	-	72/100	6.29E-06	2	View
14	Lck	Protein kinase	+	70/97	7.383E-06	3	View
15	JAB1	Enzyme	+	57/76	7.418E-06	2	View
16	Gas5	RNA	-	48/62	8.714E-06	2	View
17	microRNA 17	RNA	-	77/109	9.69E-06	3	View
18	miR-1224-5p	RNA	-	78/111	1.163E-05	3	View
19	UBPY	Protease	+	65/90	1.483E-05	3	View
20	miR-378-3p	RNA	-	16/16	1.526E-05	2	View
21	miR-200c-3p	RNA	-	74/105	1.638E-05	2	View
22	microRNA 17	RNA	-	43/55	1.653E-05	2	View
23	miR-200b-3p	RNA	-	66/92	1.835E-05	2	View
24	ARNT	Transcription factor	+	58/79	1.881E-05	2	View
25	TRADD	Binding protein	-	58/79	1.881E-05	3	View
26	HSP90 alpha	Binding protein	+	84/122	1.896E-05	3	View
27	miR-495-3p	RNA	-	72/102	1.943E-05	3	View
28	NCOA1 (SRC1)	Binding protein	+	64/89	2.161E-05	2	View
29	miR-18a-5p	RNA	-	56/76	2.184E-05	2	View
30	Nucleolin	Binding protein	+	57/78	2.786E-05	2	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
31	RIP140	Binding protein	-	87/128	2.939E-05	3	View
32	E3KARP (NHERF2)	Binding protein	+	78/113	3.223E-05	3	View
33	CRY1	Transcription factor	-	61/85	3.698E-05	3	View
34	SMRT	Binding protein	-	67/95	3.902E-05	2	View
35	SHARP (SPEN)	Binding protein	-	70/100	3.925E-05	3	View
36	DAX1	Transcription factor	-	86/127	4.031E-05	3	View
37	miR-153-3p	RNA	-	41/53	4.086E-05	2	View
38	CXCR4	GPCR	+	59/82	4.358E-05	3	View
39	MUC1	Binding protein	+	90/134	4.373E-05	3	View
40	miR-4443	RNA	-	62/87	4.53E-05	3	View
41	c-Jun	Transcription factor	+	87/129	4.603E-05	3	View
42	AP-2A	Transcription factor	+	84/124	4.824E-05	3	View
43	HSP27	Binding protein	+	57/79	5.13E-05	2	View
44	SP1	Transcription factor	+	88/131	5.235E-05	3	View
45	REDD1	Protein	-	63/89	5.496E-05	3	View
46	Aprataxin	Binding protein	+	63/89	5.496E-05	3	View
47	ST13 (Hip)	Binding protein	+	66/94	5.556E-05	3	View
48	TACC3	Binding protein	+	61/86	6.519E-05	3	View
49	SYT	Binding protein	+	70/101	6.541E-05	3	View
50	HIF3A	Transcription factor	-	50/68	6.542E-05	3	View
51	miR-200b-3p	RNA	-	83/123	6.598E-05	3	View
52	miR-640	RNA	-	38/49	7.099E-05	2	View
53	MAP2K5 (MEK5)	Protein kinase	+	56/78	7.474E-05	3	View
54	DEK	Binding protein	+	84/125	7.507E-05	3	View
55	miR-410-3p	RNA	-	43/57	7.694E-05	2	View
56	Cezanne	Enzyme	+	59/83	7.728E-05	3	View
57	c-Jun	Transcription factor	+	59/83	7.728E-05	2	View
58	Flotillin-2	Binding protein	+	36/46	7.821E-05	3	View
59	miR-31-5p	RNA	-	51/70	8.302E-05	2	View
60	ErbB4(ICD)	Binding protein	+	75/110	8.619E-05	3	View
61	HSPBP1	Binding protein	-	41/54	8.756E-05	2	View
62	LAMP2	Binding protein	-	63/90	9.388E-05	3	View
63	ADAM9	Metalloprotease	-	30/37	9.554E-05	3	View
64	miR-93-5p	RNA	-	86/129	9.597E-05	3	View
65	RWDD3	Enzyme	+	44/59	0.0001019	2	View
66	Kallikrein 4	Protease	+	44/59	0.0001019	3	View

	Key Hubs - Causal Reasoning						
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
67	Heme oxygenase 1	Enzyme	-	73/107	0.0001032	3	View
68	microRNA 26a-2	RNA	-	52/72	0.0001039	3	View
69	NCOA3 (pCIP/SRC3)	Binding protein	+	70/102	0.0001067	2	View
70	AKAP6	Binding protein	+	64/92	0.0001113	3	View
71	Sti1	Binding protein	+	64/92	0.0001113	3	View
72	miR-559	RNA	-	47/64	0.0001134	3	View
73	miR-20b-5p	RNA	-	50/69	0.0001222	2	View
74	MTF-1	Transcription factor	+	50/69	0.0001222	3	View
75	miR-27b-3p	RNA	-	53/74	0.0001282	2	View
76	miR-429-3p	RNA	-	85/128	0.0001293	3	View
77	BICC1	Binding protein	-	62/89	0.0001328	3	View
78	miR-27a-3p	RNA	-	59/84	0.0001332	2	View
79	FIH-1	Binding protein	-	59/84	0.0001332	3	View
80	14-3-3 eta	Binding protein	+	40/53	0.0001343	2	View
81	p130	Binding protein	-	51/71	0.0001516	3	View
82	JMJD1A	Enzyme	+	66/96	0.0001528	3	View
83	HIF-prolyl hydroxylase	Binding protein	-	66/96	0.0001528	3	View
84	RENT1	Binding protein	+	29/36	0.0001563	2	View
85	SET	Binding protein	-	54/76	0.0001565	2	View
86	miR-1296-5p	RNA	+	54/76	0.0001565	3	View
87	ERR1	Transcription factor	+	60/86	0.0001585	3	View
88	CCAR1	Binding protein	+	87/132	0.0001616	3	View
89	ELL	Binding protein	-	73/108	0.0001629	3	View
90	TTC5 (Strap)	Binding protein	+	77/115	0.0001755	3	View
91	BRK	Protein kinase	+	41/55	0.0001776	2	View
92	SF1	Transcription factor	+	49/68	0.000179	3	View
93	APEX	Enzyme	+	88/134	0.0001797	3	View
94	p16INK4	Binding protein	-	55/78	0.0001889	2	View
95	STAT4	Transcription factor	+	58/83	0.0001892	3	View
96	TRIP2	Transcription factor	+	58/83	0.0001892	2	View
97	Lingo1	Binding protein	-	34/44	0.0001941	3	View
98	RECK	Binding protein	-	34/44	0.0001941	3	View
99	PAK2	Protein kinase	+	75/112	0.0002105	3	View
100	LINC01139	RNA	+	62/90	0.000219	3	View
101	miR-130b-3p	RNA	-	50/70	0.0002201	2	View
102	SMAD2	Transcription factor	+	90/138	0.0002203	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
103	PKC	Protein kinase	+	59/85	0.0002236	3	View
104	ERR3	Transcription factor	+	59/85	0.0002236	3	View
105	RIP140	Binding protein	-	59/85	0.0002236	2	View
106	miR-147-3p	RNA	+	53/75	0.0002248	3	View
107	Dysbindin	Binding protein	+	56/80	0.0002258	3	View
108	LSD1	Enzyme	+	69/102	0.0002343	3	View
109	NF-kB p52/RelB	Transcription factor	-	30/38	0.000236	3	View
110	N-CoR	Binding protein	-	66/97	0.0002451	2	View
111	TRAP170	Binding protein	+	73/109	0.0002525	3	View
112	miR-149-3p	RNA	-	28/35	0.0002541	2	View
113	TRAP80	Binding protein	+	28/35	0.0002541	2	View
114	TReP-132	Transcription factor	+	48/67	0.0002608	3	View
115	MAP3K2 (MEKK2)	Protein kinase	+	51/72	0.0002675	3	View
116	Magea11	Binding protein	+	26/32	0.0002675	2	View
117	miR-221-3p	RNA	-	54/77	0.0002694	2	View
118	miR-335-5p	RNA	-	81/123	0.000278	3	View
119	miR-200c-3p	RNA	-	81/123	0.000278	3	View
120	CaMK II gamma	Protein kinase	+	74/111	0.0002851	3	View
121	PPAR-alpha	Transcription factor	-	64/94	0.000294	3	View
122	ATM	Protein kinase	+	71/106	0.000303	3	View
123	ErbB2	Receptor with enzyme activity	+	33/43	0.0003031	2	View
124	HIF1A	Transcription factor	+	58/84	0.000314	2	View
125	nNOS	Enzyme	-	49/69	0.0003181	3	View
126	CCAR1	Binding protein	+	55/79	0.0003197	2	View
127	RGS2	Regulators (GDI, GAP, GEF etc.)	-	65/96	0.0003374	3	View
128	NFKBIE	Binding protein	-	72/108	0.0003421	3	View
129	CREB1	Transcription factor	+	91/141	0.0003497	3	View
130	NCOA3 (pCIP/SRC3)	Binding protein	+	91/141	0.0003497	3	View
131	NCOA2 (GRIP1/TIF2)	Binding protein	+	62/91	0.0003527	2	View
132	IKBZ	Binding protein	-	76/115	0.0003586	3	View
133	NF-kB	Transcription factor	-	29/37	0.0003764	2	View
134	MARVELD1	Protein	-	29/37	0.0003764	3	View
135	miR-20a-5p	RNA	-	47/66	0.0003781	2	View
136	RNF4	Enzyme	-	47/66	0.0003781	2	View
137	miR-612	RNA	-	50/71	0.0003834	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
138	C/EBPdelta	Transcription factor	+	50/71	0.0003834	3	View
139	TR-beta	Transcription factor	+	66/98	0.0003849	3	View
140	ATF-4	Transcription factor	+	77/117	0.0003998	3	View
141	TRIP2	Transcription factor	+	77/117	0.0003998	3	View
142	GATA-1	Transcription factor	-	39/53	0.0004012	2	View
143	MCM5	Enzyme	-	63/93	0.000405	3	View
144	GCR	Transcription factor	+	27/34	0.0004107	1	View
145	PNRC2	Binding protein	+	27/34	0.0004107	2	View
146	EAR2	Transcription factor	-	70/105	0.0004107	3	View
147	HIF1A	Transcription factor	+	85/131	0.000416	3	View
148	NCOA1 (SRC1)	Binding protein	+	74/112	0.0004303	3	View
149	MITF	Transcription factor	+	57/83	0.0004388	3	View
150	ATF7IP	Binding protein	+	57/83	0.0004388	3	View
151	SART1	Protein	-	23/28	0.0004561	2	View
152	SP1	Transcription factor	+	48/68	0.0004572	2	View
153	BTEB1	Transcription factor	-	64/95	0.0004623	3	View
154	c-Fes	Protein kinase	+	64/95	0.0004623	3	View
155	miR-122-5p	RNA	-	32/42	0.0004703	2	View
156	NCOA2 (GRIP1/TIF2)	Binding protein	+	87/135	0.0004997	3	View
157	miR-223-3p	RNA	-	58/85	0.0005081	2	View
158	FGFR2	Receptor with enzyme activity	+	72/109	0.0005165	3	View
159	NKRF	Transcription factor	-	72/109	0.0005165	3	View
160	HNF4-alpha	Transcription factor	+	55/80	0.0005264	3	View
161	NF-kB p50/p50	Transcription factor	-	30/39	0.0005325	3	View
162	DET1	Protein	-	43/60	0.0005329	3	View
163	ADAR1	Enzyme	-	52/75	0.0005398	3	View
164	SMRT	Binding protein	-	80/123	0.0005422	3	View
165	G3P2	Enzyme	+	46/65	0.000545	2	View
166	NCOA6 (TRBP)	Binding protein	+	49/70	0.0005466	2	View
167	miR-424-5p	RNA	-	28/36	0.0005966	2	View
168	MAPKAPK5	Protein kinase	+	56/82	0.0006102	3	View
169	OBCAM	GPCR	-	33/44	0.00063	3	View
170	NUAK1	Protein kinase	+	53/77	0.0006316	3	View
171	Cyclin A1	Binding protein	+	41/57	0.0006318	2	View
172	Optineurin	Binding protein	+	44/62	0.0006495	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
173	p23 co-chaperone	Enzyme	+	44/62	0.0006495	2	View
174	CBP80	Binding protein	+	44/62	0.0006495	3	View
175	PNRC2	Binding protein	+	67/101	0.0006659	3	View
176	miR-29b-3p	RNA	-	57/84	0.0007022	2	View
177	OASIS	Transcription factor	+	57/84	0.0007022	3	View
178	Nucleolin	Binding protein	+	75/115	0.0007065	3	View
179	NF-kB	Transcription factor	-	64/96	0.0007122	3	View
180	TRAP80	Binding protein	+	64/96	0.0007122	3	View
181	TLE	Binding protein	+	24/30	0.0007155	3	View
182	SDF-1	Receptor ligand	+	31/41	0.0007252	3	View
183	EAR2	Transcription factor	-	31/41	0.0007252	2	View
184	PP5	Protein phosphatase	-	31/41	0.0007252	2	View
185	miR-34a-3p	RNA	-	39/54	0.0007481	2	View
186	DARPP-32	Binding protein	+	51/74	0.0007581	3	View
187	ATM	Protein kinase	+	51/74	0.0007581	2	View
188	PXR	Transcription factor	-	72/110	0.0007665	3	View
189	COP1	Enzyme	-	42/59	0.0007736	2	View
190	FOXK1	Transcription factor	-	45/64	0.0007814	3	View
191	Pc2	Binding protein	+	29/38	0.000829	2	View
192	microRNA 20a	RNA	-	29/38	0.000829	2	View
193	NF-kB p65/p65	Transcription factor	-	29/38	0.000829	3	View
194	STAT5B	Transcription factor	+	55/81	0.0008443	3	View
195	miR-101-3p	RNA	-	55/81	0.0008443	2	View
196	UTX	Enzyme	+	55/81	0.0008443	3	View
197	HIPK1	Protein kinase	-	55/81	0.0008443	3	View
198	miR-221-3p	RNA	-	73/112	0.0008473	3	View
199	USP19	Protease	+	62/93	0.0008564	3	View
200	NFAT-90	Transcription factor	+	66/100	0.000895	3	View
201	PREX1	Regulators (GDI, GAP, GEF etc.)	+	49/71	0.0009102	3	View
202	PABPC1	Binding protein	+	49/71	0.0009102	2	View
203	miR-613	RNA	-	49/71	0.0009102	3	View
204	RAD1	Binding protein	+	59/88	0.000912	3	View
205	miR-149-5p	RNA	-	70/107	0.0009201	3	View
206	miR-301a-3p	RNA	-	40/56	0.0009208	2	View
207	AKT(PKB)	Protein kinase	+	74/114	0.0009334	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
208	microRNA 106b	RNA	-	27/35	0.0009391	2	View
209	GCR	Transcription factor	+	63/95	0.0009622	2	View
210	RBM4	Binding protein	+	56/83	0.0009657	3	View
211	AKT(PKB)	Protein kinase	+	53/78	0.001016	2	View
212	miR-622	RNA	-	71/109	0.001017	3	View
213	Suv39H1	Enzyme	-	60/90	0.00103	3	View
214	Zac1	Transcription factor	+	50/73	0.001059	2	View
215	Sequestosome 1(p62)	Binding protein	-	50/73	0.001059	2	View
216	Rb protein	Binding protein	+	47/68	0.001093	2	View
217	DNAJC3	Binding protein	-	38/53	0.001095	3	View
218	G3P2	Enzyme	+	68/104	0.001105	3	View
219	Nibrin	Binding protein	+	30/40	0.001111	2	View
220	PRKD2	Protein kinase	-	41/58	0.001116	3	View
221	SET	Binding protein	-	76/118	0.001121	3	View
222	Ephrin-A receptor 2	Receptor with enzyme activity	+	61/92	0.001157	3	View
223	TLE2	Binding protein	+	23/29	0.001158	3	View
224	miR-18b-5p	RNA	-	65/99	0.001197	3	View
225	G-protein alpha-11	G-alpha	+	33/45	0.001229	3	View
226	EID1	Binding protein	-	48/70	0.001274	3	View
227	MBD3	Binding protein	-	48/70	0.001274	3	View
228	miR-181c-5p	RNA	-	48/70	0.001274	2	View
229	Homer 3	Binding protein	-	62/94	0.001294	3	View
230	DDB1	Binding protein	-	45/65	0.001313	3	View
231	miR-18b-5p	RNA	-	42/60	0.001335	2	View
232	HSPBP1	Binding protein	-	74/115	0.001343	3	View
233	miR-211-3p	RNA	-	59/89	0.001393	3	View
234	BART1	Binding protein	+	63/96	0.001439	3	View
235	TCOF1	Transporter	+	31/42	0.001444	3	View
236	CD164	Binding protein	+	31/42	0.001444	3	View
237	PP6C	Protein phosphatase	-	49/72	0.001471	3	View
238	HEXIM1	Binding protein	-	49/72	0.001471	2	View
239	JKAP	Protein phosphatase	-	56/84	0.001493	3	View
240	microRNA 106a	RNA	-	46/67	0.001533	3	View
241	miR-143-5p	RNA	-	60/91	0.001556	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
242	Rac1	RAS superfamily	+	60/91	0.001556	3	View
243	TTC5 (Strap)	Binding protein	+	43/62	0.001578	2	View
244	DJ-1	Enzyme	+	43/62	0.001578	2	View
245	miR-96-5p	RNA	-	43/62	0.001578	2	View
246	DAXX	Binding protein	-	53/79	0.001592	2	View
247	Beta-arrestin1	Binding protein	+	53/79	0.001592	2	View
248	HMGA2	Transcription factor	+	37/52	0.001593	2	View
249	NEK6	Protein kinase	+	64/98	0.001594	3	View
250	Pin1	Enzyme	+	64/98	0.001594	2	View
251	NF-kB1 (p105)	Transcription factor	-	68/105	0.00161	3	View
252	Hdj-2	Binding protein	+	24/31	0.001663	2	View
253	ZDHHC21	Enzyme	+	24/31	0.001663	2	View
254	ZNF370	Enzyme	+	24/31	0.001663	2	View
255	PKM2	Kinase	+	81/128	0.001687	3	View
256	IFNAR2	Receptor	+	77/121	0.001725	3	View
257	STAT3	Transcription factor	+	61/93	0.001731	2	View
258	HGF receptor (Met)	Receptor with enzyme activity	+	61/93	0.001731	3	View
259	DND1	Binding protein	+	61/93	0.001731	3	View
260	UACA	Binding protein	-	65/100	0.001759	3	View
261	PAX8	Transcription factor	+	47/69	0.001772	3	View
262	ISG15	Binding protein	-	47/69	0.001772	3	View
263	GCNF	Transcription factor	-	54/81	0.001798	3	View
264	PRC (PGC-1 related)	Binding protein	+	54/81	0.001798	3	View
265	miR-21-5p	RNA	-	54/81	0.001798	2	View
266	BAF47	Binding protein	-	54/81	0.001798	3	View
267	PKA-cat alpha	Protein kinase	+	54/81	0.001798	2	View
268	miR-493-3p	RNA	-	44/64	0.001845	3	View
269	AP-2A	Transcription factor	+	44/64	0.001845	2	View
270	HES1	Transcription factor	+	22/28	0.00186	2	View
271	HBXIP	Binding protein	+	78/123	0.001866	3	View
272	Laminin 1	Receptor ligand	+	41/59	0.001897	3	View
273	DEK	Binding protein	+	35/49	0.001901	2	View
274	microRNA 103-1	RNA	-	74/116	0.001903	3	View
275	miR-140-5p	RNA	-	74/116	0.001903	3	View
276	PIWIL4	Binding protein	+	62/95	0.001916	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
277	BRG1	Enzyme	+	51/76	0.001918	2	View
278	miR-let-7g-3p	RNA	+	51/76	0.001918	3	View
279	CDK5	Protein kinase	+	51/76	0.001918	2	View
280	microRNA 26b	RNA	-	51/76	0.001918	3	View
281	HNF3-gamma	Transcription factor	+	38/54	0.001919	3	View
282	ZNF145	Transcription factor	-	38/54	0.001919	2	View
283	MED25	Protein	+	70/109	0.001927	3	View
284	miR-513a-5p	RNA	-	66/102	0.001933	3	View
285	KLF6	Transcription factor	+	66/102	0.001933	3	View
286	MSK1	Protein kinase	+	83/132	0.001953	3	View
287	SAM68	Binding protein	+	48/71	0.002033	2	View
288	RIPK3	Protein kinase	+	48/71	0.002033	3	View
289	RUVBL2	Binding protein	-	75/118	0.002062	3	View
290	p90Rsk	Protein kinase	+	71/111	0.002098	3	View
291	miR-106b-5p	RNA	-	63/97	0.002113	3	View
292	miR-615-3p	RNA	+	45/66	0.002136	3	View
293	miR-450a-5p	RNA	+	45/66	0.002136	3	View
294	NF45 (ILF2)	Transcription factor	+	30/41	0.002162	3	View
295	miR-302b-3p	RNA	-	30/41	0.002162	2	View
296	MCM5	Enzyme	-	30/41	0.002162	2	View
297	N-CoR	Binding protein	-	80/127	0.002165	3	View
298	Cyclin A1	Binding protein	+	80/127	0.002165	3	View
299	miR-573	RNA	-	52/78	0.002167	3	View
300	Neuropilin-1	Receptor	+	52/78	0.002167	3	View
301	Connexin 43	Channel	-	52/78	0.002167	3	View
302	SHIP	Phosphatase	-	42/61	0.002222	3	View
303	miR-153-3p	RNA	-	56/85	0.002256	3	View
304	miR-506-3p	RNA	-	56/85	0.002256	2	View
305	S100A1	Binding protein	-	33/46	0.002267	3	View
306	miR-519d-3p	RNA	-	25/33	0.002276	2	View
307	BACE1	Protease	-	25/33	0.002276	3	View
308	miR-193a-3p	RNA	-	25/33	0.002276	2	View
309	miR-23b-5p	RNA	-	25/33	0.002276	3	View
310	miR-500-5p	RNA	-	36/51	0.002301	3	View
311	Sedlin (MIP-2A)	Binding protein	-	36/51	0.002301	3	View
312	MTF-1	Transcription factor	+	36/51	0.002301	2	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
313	alpha-6/beta-4 integrin	Receptor	+	36/51	0.002301	3	View
314	PSD-95	Binding protein	-	36/51	0.002301	3	View
315	BAZ1A	Binding protein	-	60/92	0.002305	3	View
316	PPARGC1 (PGC1-alpha)	Binding protein	+	60/92	0.002305	2	View
317	miR-130b-3p	RNA	-	68/106	0.002309	3	View
318	miR-141-3p	RNA	-	49/73	0.002313	2	View
319	SOCS3	Binding protein	-	64/99	0.00232	3	View
320	miR-142-3p	RNA	-	46/68	0.002452	2	View
321	Calcyclin	Binding protein	-	46/68	0.002452	3	View
322	miR-489-3p	RNA	-	57/87	0.002507	3	View
323	PHF8	Enzyme	+	57/87	0.002507	3	View
324	CRSP8 (CRSP34)	Binding protein	+	65/101	0.002539	3	View
325	EDF1	Transcription factor	+	61/94	0.002539	3	View
326	FZD2	GPCR	+	61/94	0.002539	3	View
327	microRNA 96	RNA	-	28/38	0.002549	3	View
328	PARP-16	Enzyme	+	28/38	0.002549	3	View
329	CRY1	Transcription factor	-	28/38	0.002549	2	View
330	SOCS6	Binding protein	-	28/38	0.002549	3	View
331	Flotillin-1	Binding protein	+	43/63	0.002576	3	View
332	APEX	Enzyme	+	50/75	0.002614	2	View
333	HEY1	Transcription factor	-	50/75	0.002614	3	View
334	Paxillin	Binding protein	+	31/43	0.002701	2	View
335	TARBP2	Binding protein	-	31/43	0.002701	3	View
336	BCR	Regulators (GDI, GAP, GEF etc.)	-	54/82	0.002718	3	View
337	BRK	Protein kinase	+	70/110	0.002724	3	View
338	C/EBPdelta	Transcription factor	+	37/53	0.002743	2	View
339	miR-433-3p	RNA	-	37/53	0.002743	2	View
340	SMARCA3	Transcription factor	+	34/48	0.002758	2	View
341	miR-181a-5p	RNA	-	58/89	0.002772	2	View
342	HDAC5	Enzyme	+	62/96	0.002786	3	View
343	NRF3	Transcription factor	+	47/70	0.002791	3	View
344	TRAP230	Binding protein	+	47/70	0.002791	3	View
345	microRNA let-7a-2	RNA	+	47/70	0.002791	3	View
346	CBP	Enzyme	+	75/119	0.002863	2	View
347	TMEM2L	Protein	+	51/77	0.002935	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
348	EKLF1	Transcription factor	+	51/77	0.002935	3	View
349	ANCO-1	Binding protein	-	71/112	0.002945	3	View
350	HMGI/Y	Transcription factor	+	44/65	0.002959	2	View
351	HDAC5	Enzyme	+	44/65	0.002959	2	View
352	Ephrin-A receptor 7	Receptor with enzyme activity	+	21/27	0.002962	3	View
353	Fibronectin	Receptor ligand	+	21/27	0.002962	3	View
354	MASP1	Protease	+	26/35	0.002994	3	View
355	ERR1	Transcription factor	+	26/35	0.002994	2	View
356	AKAP6	Binding protein	+	26/35	0.002994	2	View
357	miR-640	RNA	-	67/105	0.003008	3	View
358	IRF1	Transcription factor	+	85/137	0.003026	3	View
359	miR-4516	RNA	-	63/98	0.003046	3	View
360	LIMK1	Protein kinase	+	63/98	0.003046	3	View
361	miR-301a-3p	RNA	-	59/91	0.003053	3	View
362	PKA-cat alpha	Protein kinase	+	76/121	0.003075	3	View
363	miR-133b-3p	RNA	-	41/60	0.003109	2	View
364	TDG	Enzyme	+	81/130	0.003164	3	View
365	PR (nuclear)	Transcription factor	+	11/12	0.003174	1	View
366	TFCP2	Transcription factor	-	11/12	0.003174	2	View
367	miR-181a-5p	RNA	-	72/114	0.003176	3	View
368	miR-195-5p	RNA	-	29/40	0.003213	2	View
369	SKIP (Ski-interacting protein)	Binding protein	+	29/40	0.003213	2	View
370	NRF2	Transcription factor	-	68/107	0.003259	3	View
371	FBX25	Enzyme	-	35/50	0.0033	3	View
372	Suv39H1	Enzyme	-	35/50	0.0033	2	View
373	STAT5B	Transcription factor	+	35/50	0.0033	2	View
374	ATF7IP	Binding protein	+	35/50	0.0033	2	View
375	CAPON	Binding protein	-	35/50	0.0033	3	View
376	SF1	Transcription factor	+	35/50	0.0033	2	View
377	DR4(TNFRSF10A)	Receptor with enzyme activity	-	35/50	0.0033	3	View
378	PLGF	Receptor ligand	+	19/24	0.003305	3	View
379	CDX1	Transcription factor	-	64/100	0.003319	3	View
380	SH2B	Binding protein	+	64/100	0.003319	3	View
381	HMGA2	Transcription factor	+	64/100	0.003319	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
382	NP60	Binding protein	+	60/93	0.003348	3	View
383	miR-205-5p	RNA	-	45/67	0.003371	2	View
384	miR-140-5p	RNA	-	45/67	0.003371	2	View
385	p16INK4	Binding protein	-	73/116	0.003416	3	View
386	Sirtuin7	Enzyme	-	73/116	0.003416	3	View
387	miR-146b-5p	RNA	-	24/32	0.0035	2	View
388	ZNF366	Binding protein	-	69/109	0.00352	3	View
389	miR-548c-3p	RNA	-	49/74	0.003542	3	View
390	MUC1	Binding protein	+	49/74	0.003542	2	View
391	IMP3	Binding protein	+	42/62	0.003574	3	View
392	miR-4500	RNA	-	42/62	0.003574	3	View
393	miR-520a-5p	RNA	-	61/95	0.003657	3	View
394	Tyk2	Protein kinase	+	57/88	0.003672	3	View
395	miR-296-3p	RNA	-	57/88	0.003672	3	View
396	miR-424-3p	RNA	-	57/88	0.003672	3	View
397	SAFB	Binding protein	-	39/57	0.003754	2	View
398	BRG1	Enzyme	+	70/111	0.003792	3	View
399	LIG-1	Binding protein	-	46/69	0.00381	3	View
400	NRF2	Transcription factor	-	46/69	0.00381	2	View
401	microRNA let-7a-3	RNA	+	46/69	0.00381	3	View
402	IRS-1	Binding protein	+	27/37	0.003816	2	View
403	PKA-cat (cAMP-dependent)	Protein kinase	+	36/52	0.003894	2	View
404	C10orf46	Binding protein	-	36/52	0.003894	2	View
405	HNF4-alpha	Transcription factor	+	36/52	0.003894	2	View
406	FOXP2	Transcription factor	+	36/52	0.003894	3	View
407	miR-125a-5p	RNA	-	36/52	0.003894	2	View
408	Sequestosome 1(p62)	Binding protein	-	66/104	0.0039	3	View
409	LRP16	Binding protein	+	75/120	0.003923	3	View
410	miR-15a-5p	RNA	-	30/42	0.003958	2	View
411	C1q	Binding protein	-	30/42	0.003958	3	View
412	miR-211-3p	RNA	-	30/42	0.003958	2	View
413	C/EBPepsilon	Transcription factor	-	33/47	0.003971	3	View
414	Magea11	Binding protein	+	62/97	0.00398	3	View
415	Clusterin	Binding protein	-	62/97	0.00398	3	View
416	CCDC6	Binding protein	-	54/83	0.004018	3	View
417	miR-522-3p	RNA	-	22/29	0.004065	2	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
418	miR-1224-5p	RNA	-	43/64	0.004073	2	View
419	miR-133a-3p	RNA	-	43/64	0.004073	2	View
420	DAX1	Transcription factor	-	43/64	0.004073	2	View
421	E2F1	Transcription factor	+	81/131	0.004256	3	View
422	microRNA 302b	RNA	+	47/71	0.004277	3	View
423	FBX4	Binding protein	+	47/71	0.004277	3	View
424	YB-1	Transcription factor	+	47/71	0.004277	2	View
425	Adenosine A2b receptor	GPCR	-	63/99	0.004317	3	View
426	ZBP1	Binding protein	-	40/59	0.004321	3	View
427	Pellino 1	Enzyme	-	40/59	0.004321	3	View
428	miR-509-3p	RNA	-	72/115	0.004368	3	View
429	DPF3	Binding protein	+	72/115	0.004368	3	View
430	CREB1	Transcription factor	+	51/78	0.004386	2	View
431	p38alpha (MAPK14)	Protein kinase	+	59/92	0.00439	2	View
432	miR-766-3p	RNA	+	59/92	0.00439	3	View
433	TIRAP (Mal)	Binding protein	+	55/85	0.004418	3	View
434	p23 co-chaperone	Enzyme	+	77/124	0.004467	3	View
435	miR-519c-3p	RNA	-	25/34	0.004521	2	View
436	miR-1180-3p	RNA	-	25/34	0.004521	3	View
437	ERR3	Transcription factor	+	25/34	0.004521	2	View
438	NR2E3	Transcription factor	+	68/108	0.004529	3	View
439	ZBTB8A	Binding protein	-	68/108	0.004529	3	View
440	ODP2	Enzyme	+	37/54	0.004537	3	View
441	Aurora-A	Protein kinase	+	37/54	0.004537	2	View
442	LINC00277	RNA	+	37/54	0.004537	3	View
443	SP7	Transcription factor	+	64/101	0.004668	3	View
444	Gremlin	Binding protein	+	20/26	0.004678	3	View
445	WNT5A	Receptor ligand	+	20/26	0.004678	3	View
446	Glutaredoxin 1	Enzyme	+	20/26	0.004678	2	View
447	gamma-Secretase complex	Protease	-	20/26	0.004678	3	View
448	TIMP3	Binding protein	-	20/26	0.004678	3	View
449	APOA1	Receptor ligand	-	20/26	0.004678	3	View
450	CD44	Receptor	+	20/26	0.004678	2	View
451	Cyclin B1	Binding protein	-	34/49	0.0047	2	View
452	TReP-132	Transcription factor	+	34/49	0.0047	2	View
453	SP1	Transcription factor	+	34/49	0.0047	1	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
454	DLX4 (BP1)	Transcription factor	-	34/49	0.0047	2	View
455	Fer	Protein kinase	+	34/49	0.0047	2	View
456	miR-634	RNA	-	28/39	0.004738	2	View
457	Evi-1	Transcription factor	-	78/126	0.004752	3	View
458	MYST1	Enzyme	+	48/73	0.004771	2	View
459	IRS-1	Binding protein	+	60/94	0.004774	3	View
460	ATF-4	Transcription factor	+	31/44	0.00478	2	View
461	PKR	Protein kinase	+	31/44	0.00478	2	View
462	CIRBP	Binding protein	+	56/87	0.004837	3	View
463	RBB2	Enzyme	-	56/87	0.004837	3	View
464	DDX5	Enzyme	+	52/80	0.004841	2	View
465	IKK (cat)	Protein kinase	+	65/103	0.005032	3	View
466	PGAM5	Phosphatase	-	45/68	0.005169	3	View
467	miR-212-3p	RNA	-	45/68	0.005169	2	View
468	MCR	Transcription factor	-	61/96	0.005173	3	View
469	FHL1 (SLIM1)	Binding protein	-	38/56	0.005227	2	View
470	ZBTB2	Transcription factor	-	38/56	0.005227	2	View
471	FBXW7	Binding protein	-	57/89	0.005273	2	View
472	LMO2	Transcription factor	-	49/75	0.005291	3	View
473	PIMT	Enzyme	+	75/121	0.005306	3	View
474	Angiomotin (AMOT)	Binding protein	-	53/82	0.005319	3	View
475	HGF receptor (Met)	Receptor with enzyme activity	+	23/31	0.005337	2	View
476	Ataxin-1	Binding protein	+	66/105	0.005409	3	View
477	miR-96-5p	RNA	-	66/105	0.005409	3	View
478	14-3-3 eta	Binding protein	+	66/105	0.005409	3	View
479	PRMT6	Enzyme	+	66/105	0.005409	3	View
480	PMCA4	Protein	+	35/51	0.005487	3	View
481	miR-492	RNA	-	35/51	0.005487	2	View
482	RGS17	Regulators (GDI, GAP, GEF etc.)	+	35/51	0.005487	3	View
483	TITF1	Transcription factor	-	35/51	0.005487	2	View
484	NRSF	Transcription factor	-	42/63	0.005571	2	View
485	CXXC6	Binding protein	+	62/98	0.005587	3	View
486	ZFP36(Tristetraprolin)	Binding protein	-	86/141	0.005628	3	View
487	miR-298-5p	RNA	-	26/36	0.005665	2	View
488	TRIP15	Binding protein	-	26/36	0.005665	2	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
489	miR-873-5p	RNA	-	32/46	0.005676	2	View
490	PP2A cat (beta)	Protein phosphatase	-	58/91	0.005728	3	View
491	miR-622	RNA	-	29/41	0.005754	2	View
492	Cyclin D1	Binding protein	-	46/70	0.005763	2	View
493	miR-324-5p	RNA	-	54/84	0.005817	3	View
494	miR-340-5p	RNA	-	54/84	0.005817	2	View
495	Alpha-actinin 2	Binding protein	+	50/77	0.005836	3	View
496	C/EBPalpha	Transcription factor	-	50/77	0.005836	2	View
497	PDK4	Protein kinase	+	50/77	0.005836	3	View
498	MAML2	Binding protein	+	50/77	0.005836	3	View
499	MAML3	Binding protein	+	50/77	0.005836	3	View
500	YY1	Transcription factor	-	10/11	0.005859	1	View
501	TFIIIB90	Transcription factor	+	16/20	0.005909	3	View
502	miR-128-1-5p	RNA	-	39/58	0.005964	3	View
503	PSMC5	Enzyme	-	39/58	0.005964	2	View
504	Alpha 1-antitrypsin	Binding protein	+	39/58	0.005964	3	View
505	Rb protein	Binding protein	+	63/100	0.006016	3	View
506	JAK3	Protein kinase	+	63/100	0.006016	3	View
507	IMPK	Lipid kinase	+	63/100	0.006016	3	View
508	LMTK3	Protein kinase	+	59/93	0.0062	3	View
509	DDX6	Enzyme	-	68/109	0.006202	3	View
510	WWOX	Enzyme	-	43/65	0.006251	2	View
511	Reticulon 3	Binding protein	+	21/28	0.00627	3	View
512	MSN (moesin)	Binding protein	+	21/28	0.00627	3	View
513	DAXX	Binding protein	-	73/118	0.006301	3	View
514	Neuregulin 1	Receptor ligand	+	36/53	0.00633	3	View
515	ASXL3	Binding protein	-	36/53	0.00633	3	View
516	PSMD10 (Gankyrin)	Binding protein	-	78/127	0.00633	3	View
517	HB-EGF	Receptor ligand	+	55/86	0.006336	3	View
518	BAP1	Protease	+	55/86	0.006336	3	View
519	SCOP	Protein phosphatase	-	55/86	0.006336	3	View
520	miR-4458	RNA	+	47/72	0.006387	3	View
521	SUMO-2	Binding protein	-	51/79	0.006406	2	View
522	FAP-1	Phosphatase	-	51/79	0.006406	3	View
523	miR-149-3p	RNA	-	64/102	0.00646	3	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
524	PAX3	Transcription factor	+	12/14	0.00647	2	View
525	miR-498	RNA	-	12/14	0.00647	2	View
526	DEXH helicase	Enzyme	-	12/14	0.00647	3	View
527	Zimp10	Binding protein	+	33/48	0.006642	2	View
528	BAF60A	Binding protein	+	33/48	0.006642	2	View
529	STAT3	Transcription factor	+	74/120	0.006688	3	View
530	PRDX1	Enzyme	+	74/120	0.006688	3	View
531	DEC2	Transcription factor	-	40/60	0.006745	2	View
532	Homer 2	Binding protein	-	40/60	0.006745	3	View
533	GASC1	Enzyme	+	40/60	0.006745	2	View
534	HIF1A	Transcription factor	+	24/33	0.006765	1	View
535	Actin cytoskeletal	Binding protein	-	24/33	0.006765	3	View
536	Zimp7	Binding protein	+	24/33	0.006765	2	View
537	Osteopontin	Receptor ligand	+	24/33	0.006765	3	View
538	miR-488-5p	RNA	-	56/88	0.006875	3	View
539	MIR31HG	RNA	+	65/104	0.006918	3	View
540	miR-543-3p	RNA	-	27/38	0.006926	2	View
541	miR-940	RNA	-	27/38	0.006926	3	View
542	SENP1	Protease	+	44/67	0.006967	2	View
543	HUS1	Binding protein	+	52/81	0.007	3	View
544	NF-AT4(NFATC3)	Transcription factor	+	52/81	0.007	3	View
545	RGS13	Regulators (GDI, GAP, GEF etc.)	-	52/81	0.007	3	View
546	Kallikrein 3 (PSA)	Protease	+	52/81	0.007	3	View
547	miR-455-5p	RNA	-	48/74	0.00704	3	View
548	NGFR (ICD)	Binding protein	+	48/74	0.00704	3	View
549	Gamma-synuclein	Binding protein	+	61/97	0.007195	3	View
550	NUR77	Transcription factor	-	61/97	0.007195	2	View
551	PUM2	Binding protein	+	37/55	0.007227	3	View
552	HIC1	Transcription factor	-	19/25	0.007317	2	View
553	STAT3	Transcription factor	+	19/25	0.007317	1	View
554	SHP-1	Protein phosphatase	-	57/90	0.007433	3	View
555	CAR	Transcription factor	+	57/90	0.007433	3	View
556	TRF2	Binding protein	-	41/62	0.007567	3	View
557	ERK7 (MAPK15)	Protein kinase	-	41/62	0.007567	3	View
558	14-3-3 zeta/delta	Binding protein	+	41/62	0.007567	2	View

Key Hubs - Causal Reasoning							
#	Molecular Entity	Molecular Function	Predicted Activity	Correct/total network predictions	Activity prediction p-value ▲	Calculation Distance	View Network
559	PPAR-gamma	Transcription factor	-	41/62	0.007567	2	View
560	miR-133a-5p	RNA	-	34/50	0.007673	3	View
561	SHPS-1	Binding protein	-	45/69	0.007716	3	View
562	IRF9	Transcription factor	-	45/69	0.007716	3	View
563	miR-125a-5p	RNA	-	62/99	0.007716	3	View
564	VEGFR-1	Receptor with enzyme activity	+	49/76	0.00772	3	View
565	MTG16 (CBFA2T3)	Transcription factor	-	31/45	0.008047	2	View
566	Karyopherin alpha 1	Transporter	+	31/45	0.008047	3	View
567	Necdin	Binding protein	-	31/45	0.008047	2	View
568	IRF7	Transcription factor	+	31/45	0.008047	3	View
569	Perlecan	Binding protein	-	31/45	0.008047	3	View
570	YES	Protein kinase	+	22/30	0.008062	2	View
571	CKS2	Binding protein	+	38/57	0.008174	3	View
572	miR-1181	RNA	-	63/101	0.008253	3	View
573	ATAD2	Binding protein	+	54/85	0.008254	3	View
574	MJD (ataxin-3)	Enzyme	+	25/35	0.008337	3	View
575	TBLR1 (DC42)	Binding protein	+	25/35	0.008337	2	View
576	EPC1	Binding protein	+	25/35	0.008337	2	View
577	NCOA4 (ARA70)	Binding protein	+	25/35	0.008337	2	View
578	JMJD2B	Enzyme	+	68/110	0.008373	3	View
579	CDK5RAP3	Binding protein	-	68/110	0.008373	3	View
580	MSK1/2 (RPS6KA5/4)	Protein kinase	+	50/78	0.008427	3	View
581	miR-548d-5p	RNA	+	50/78	0.008427	3	View
582	RAD9A	Binding protein	+	42/64	0.008429	3	View
583	GHR	Receptor	+	46/71	0.008497	3	View
584	Importin (karyopherin)-beta	Transporter	-	59/94	0.008605	3	View
585	CD28	Receptor	+	35/52	0.008767	3	View
586	miR-324-5p	RNA	-	35/52	0.008767	2	View
587	TBX5	Transcription factor	+	35/52	0.008767	3	View
588	USP25	Protease	-	35/52	0.008767	3	View
589	IL-17 receptor	Receptor	+	35/52	0.008767	3	View
590	HES1	Transcription factor	+	64/103	0.008805	3	View
591	miR-101-3p	RNA	-	64/103	0.008805	3	View
592	miR-433-3p	RNA	-	69/112	0.008883	3	View
593	GCR	Transcription factor	+	85/141	0.009028	3	View

Key Hubs - Causal Reasoning							
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594	RhoE	RAS superfamily	+	51/80	0.009158	3	View
595	Jagged1	Receptor ligand	-	51/80	0.009158	3	View
596	BTEB1	Transcription factor	-	39/59	0.009169	2	View
597	DDX3X	Enzyme	+	39/59	0.009169	2	View
598	TDG	Enzyme	+	39/59	0.009169	2	View
599	BRD3	Binding protein	+	47/73	0.009309	3	View
600	HSC70	Enzyme	+	47/73	0.009309	2	View
601	NCK1	Binding protein	+	47/73	0.009309	3	View
602	CDK3	Protein kinase	+	32/47	0.009312	2	View
603	miR-299-5p	RNA	-	32/47	0.009312	2	View
604	Inversin	Binding protein	-	43/66	0.009329	3	View
605	Syntaxin 8	Transporter	-	43/66	0.009329	3	View
606	URI	Binding protein	-	43/66	0.009329	3	View
607	PMEPA1	Binding protein	-	65/105	0.00937	3	View
608	SAFB	Binding protein	-	65/105	0.00937	3	View
609	HEXIM1	Binding protein	-	65/105	0.00937	3	View
610	BAF155	Binding protein	+	70/114	0.009405	3	View
611	CUX1	Transcription factor	-	70/114	0.009405	3	View
612	MEIS1	Transcription factor	-	20/27	0.009579	2	View
613	microRNA 34c	RNA	-	20/27	0.009579	2	View
614	microRNA 185	RNA	-	20/27	0.009579	2	View
615	FGFR1	Receptor with enzyme activity	+	20/27	0.009579	2	View
616	Lck	Protein kinase	+	20/27	0.009579	2	View
617	RBM8 (Y14)	Binding protein	+	20/27	0.009579	2	View
618	RAD9	Binding protein	-	20/27	0.009579	2	View
619	TBP	Transcription factor	+	15/19	0.009605	2	View
620	miR-888-5p	RNA	-	15/19	0.009605	2	View
621	Elongin C	Enzyme	-	29/42	0.00976	3	View
622	EAF2	Binding protein	-	29/42	0.00976	2	View
623	ULK3	Protein kinase	+	29/42	0.00976	3	View
624	ELMO1	Binding protein	+	29/42	0.00976	3	View
625	DEF6	Regulators (GDI, GAP, GEF etc.)	+	29/42	0.00976	3	View
626	SP-A	Binding protein	-	29/42	0.00976	3	View
627	Calreticulin	Binding protein	-	29/42	0.00976	2	View
628	ZBTB2	Transcription factor	-	61/98	0.009845	3	View

Key Hubs - Causal Reasoning							
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629	HP1 beta	Binding protein	+	61/98	0.009845	3	View
630	RanGAP1	Regulators (GDI, GAP, GEF etc.)	-	52/82	0.009913	3	View
631	miR-320d	RNA	-	52/82	0.009913	3	View
632	miR-320e	RNA	-	52/82	0.009913	3	View
633	miR-1291	RNA	-	52/82	0.009913	3	View
634	Ataxin-1	Binding protein	+	36/54	0.009917	2	View
635	Caspase-3	Protease	-	36/54	0.009917	2	View
636	YB-1	Transcription factor	+	66/107	0.00995	3	View