reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 73 on 10/09/2020. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMDA5MTAwNjM0MDFfNTE1Mw%3D%3D

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

Table of Contents

1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for Homo sapiens are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and Arabidopsis. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

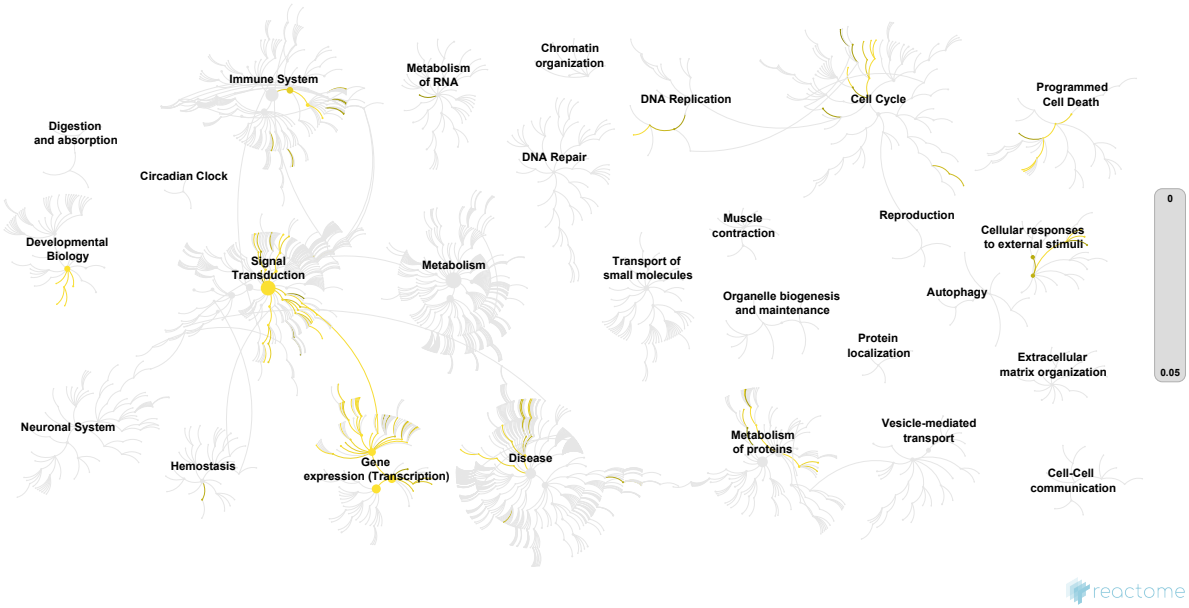
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, … Hermjakob H (2017). Reactome pathway analysis: a high-performance in-memory approach. BMC Bioinformatics, 18.

2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method.
- 24 out of 27 identifiers in the sample were found in Reactome, where 322 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMDA5MTAwNjM0MDFfNTE1Mw%3D%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

3. Genome-wide overview



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

4. Most significant pathways

The following table shows the 25 most relevant pathways sorted by p-value.

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Transcriptional regulation of pluripotent stem cells	13 / 45	0.003	1.11e-16	3.76e-14	34 / 35	0.003
Developmental Biology	23 / 1,241	0.085	2.35e-12	3.97e-10	71 / 537	0.041
Generic Transcription Pathway	24 / 1,554	0.106	2.99e-11	3.38e-09	265 / 824	0.064
POU5F1 (OCT4), SOX2, NANOG activate genes related to proliferation	6 / 21	0.001	1.29e-10	1.01e-08	16 / 16	0.001
Gene expression (Transcription)	25 / 1,851	0.126	1.67e-10	1.01e-08	292 / 996	0.077
RNA Polymerase II Transcription	24 / 1,693	0.115	1.80e-10	1.01e-08	282 / 885	0.068
Interleukin-4 and Interleukin-13 signaling	9 / 211	0.014	3.87e-08	1.86e-06	19 / 46	0.004
ESR-mediated signaling	9 / 256	0.017	1.97e-07	8.26e-06	81 / 110	0.008
Estrogen-dependent gene expression	7 / 154	0.01	9.44e-07	3.49e-05	60 / 66	0.005
Transcriptional regulation of granulopoiesis	5 / 71	0.005	4.69e-06	1.33e-04	8 / 27	0.002
Signaling by Nuclear Receptors	9 / 385	0.026	5.57e-06	1.33e-04	81 / 191	0.015
POU5F1 (OCT4), SOX2, NANOG repress genes related to differentiation	3 / 10	6.82e-04	6.06e-06	1.33e-04	7 / 7	5.40e-04
Binding of TCF/LEF:CTNNB1 to target gene promoters	3 / 10	6.82e-04	6.06e-06	1.33e-04	4 / 4	3.09e-04
Activation of PUMA and translocation to mitochondria	3 / 10	6.82e-04	6.06e-06	1.33e-04	4 / 5	3.86e-04
RUNX3 regulates WNT signaling	3 / 10	6.82e-04	6.06e-06	1.33e-04	3 / 5	3.86e-04
Repression of WNT target genes	3 / 16	0.001	2.45e-05	5.14e-04	5 / 7	5.40e-04
Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors	4 / 52	0.004	3.19e-05	6.06e-04	8 / 44	0.003
TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest	3 / 20	0.001	4.73e-05	8.44e-04	10 / 17	0.001
Signaling by Interleukins	10 / 639	0.044	5.07e-05	8.44e-04	92 / 490	0.038
Transcriptional regulation by RUNX3	5 / 118	0.008	5.27e-05	8.44e-04	9 / 47	0.004
TFAP2 (AP-2) family regulates transcription of growth factors and their receptors	3 / 21	0.001	5.46e-05	8.74e-04	5 / 18	0.001
Intrinsic Pathway for Apoptosis	4 / 61	0.004	5.90e-05	8.86e-04	9 / 62	0.005

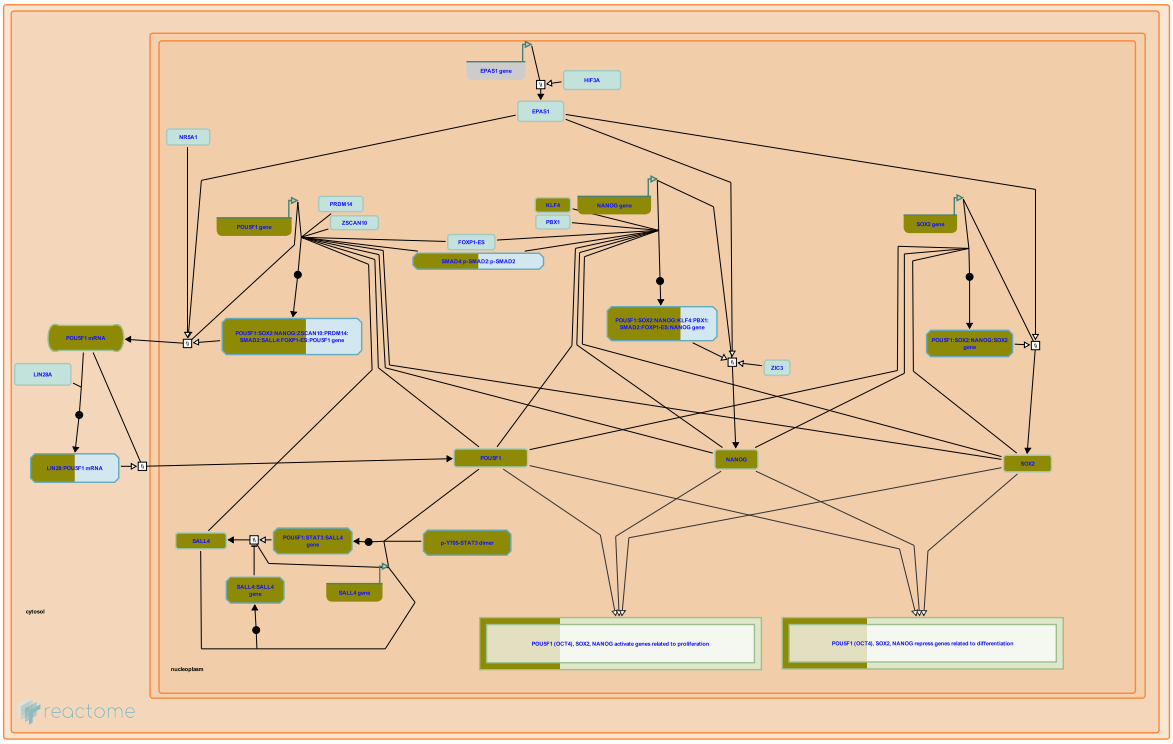
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Regulation of TP53 Expression	2 / 4	2.73e-04	9.02e-05	0.001	5 / 5	3.86e-04
Transcription of E2F targets under negative control by DREAM complex	3 / 25	0.002	9.13e-05	0.001	5 / 12	9.26e-04
PIP3 activates AKT signaling	7 / 316	0.022	9.52e-05	0.001	7 / 86	0.007

* False Discovery Rate

5. Pathways details

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Transcriptional regulation of pluripotent stem cells (R-HSA-452723)



Cellular compartments: cytosol, nucleoplasm.

Pluripotent stem cells are undifferentiated cells posessing an abbreviated cell cycle (reviewed in Stein et al. 2012), a characteristic profile of gene expression (Rao et al. 2004, Kim et al. 2006, Player et al. 2006, Wang et al 2006 using mouse, International Stem Cell Initiative 2007, Assou et al. 2007, Assou et al. 2009, Ding et al. 2012 using mouse), and the ability to self-renew and generate all cell types of the body except extraembryonic lineages (Marti et al. 2013, reviewed in Romeo et al. 2012). They are a major cell type in the inner cell mass of the early embryo in vivo, and cells with the same properties, induced pluripotent stem cells, can be generated in vitro from differentiated adult cells by overexpression of a set of transcription factor genes (Takahashi and Yamanaka 2006, Takahashi et al. 2007, Yu et al. 2007, Jaenisch and Young 2008, Stein et al. 2012, reviewed in Dejosez and Zwaka 2012).

Pluripotency is maintained by a self-reinforcing loop of transcription factors (Boyer et al. 2005, Rao et al. 2006, Matoba et al. 2006, Player et al. 2006, Babaie et al. 2007, Sun et al. 2008, Assou et al. 2009, reviewed in Kashyap et al. 2009, reviewed in Dejosez and Zwaka 2012). In vivo, initiation of pluripotency may depend on maternal factors transmitted through the oocyte (Assou et al. 2009) and on DNA demethylation in the zygote (recently reviewed in Seisenberger et al. 2013) and hypoxia experienced by the blastocyst in the reproductive tract before implantation (Forristal et al. 2010, reviewed in Mohyeldin et al. 2010). In vitro, induced pluripotency may initiate with demethylation and activation of the promoters of POU5F1 (OCT4) and NANOG (Bhutani et al. 2010). Hypoxia also significantly enhances conversion to pluripotent stem cells (Yoshida et al. 2009). POU5F1 and NANOG, together with SOX2, encode central factors in pluripotency and activate their own transcription (Boyer et al 2005, Babaie et al. 2007, Yu et al. 2007, Takahashi et al. 2007). The autoactivation loop maintains expression of POU5F1, NANOG, and SOX2 at high levels in stem cells and, in turn, complexes containing various combinations of these factors (Remenyi et al. 2003, Lam et al. 2012) activate the expression of a group of genes whose products are associated with rapid cell proliferation and repress the expression of a group of genes whose products are associated with cell differentiation (Boyer et al. 2005, Matoba et al. 2006, Babaie et al. 2007, Chavez et al. 2009, Forristal et al. 2010, Guenther 2011).

Comparisons between human and mouse embryonic stem cells must be made with caution and for this reason inferences from mouse have been used sparingly in this module. Human ESCs more closely resemble mouse epiblast stem cells in having inactivated X chromosomes, flattened morphology, and intolerance to passaging as single cells (Hanna et al. 2010). Molecularly, human ESCs differ from mouse ESCs in being maintained by FGF and Activin/Nodal/TGFbeta signaling rather than by LIF and canonical Wnt signaling (Greber et al. 2010, reviewed in Katoh 2011). In human ESCs POU5F1 binds and directly activates the FGF2 gene, however Pou5f1 does not activate Fgf2 in mouse ESCs (reviewed in De Los Angeles et al. 2012). Differences in expression patterns of KLF2, KLF4, KLF5, ESRRB, FOXD3, SOCS3, LIN28, NODAL were observed between human and mouse ESCs (Cai et al. 2010) as were differences in expression of EOMES, ARNT and several other genes (Ginis et al.2004).

References

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Assou S, Le Carrour T, Tondeur S, Ström S, Gabelle A, Marty S, ... De Vos J (2007). A meta-analysis of human embryonic stem cells transcriptome integrated into a web-based expression atlas. Stem Cells, 25, 961-73.

Babaie Y, Herwig R, Greber B, Brink TC, Wruck W, Groth D, ... Adjaye J (2007). Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. Stem Cells, 25, 500-10.

Li SS, Liu YH, Tseng CN, Chung TL, Lee TY & Singh S (2006). Characterization and gene expression profiling of five new human embryonic stem cell lines derived in Taiwan. Stem Cells Dev, 15, 532-55.

International Stem Cell Initiative, Adewumi O, Aflatoonian B, Ahrlund-Richter L, Amit M, Andrews PW, ... Zhang W (2007). Characterization of human embryonic stem cell lines by the International Stem Cell Initiative. Nat Biotechnol, 25, 803-16.

Edit history

Date	Action	Author
2010-01-16	Created	May B
2010-11-12	Edited	May B
2010-11-12	Authored	May B
2014-01-23	Reviewed	Wang J
2020-06-04	Modified	Cook J

Entities found in this pathway (7)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
KLF4	O43474	NANOG	Q9H9S0	POU5F1	Q01860
SALL4	Q9UJQ4	SMAD4	Q13485	SOX2	P48431
STAT3	P40763				

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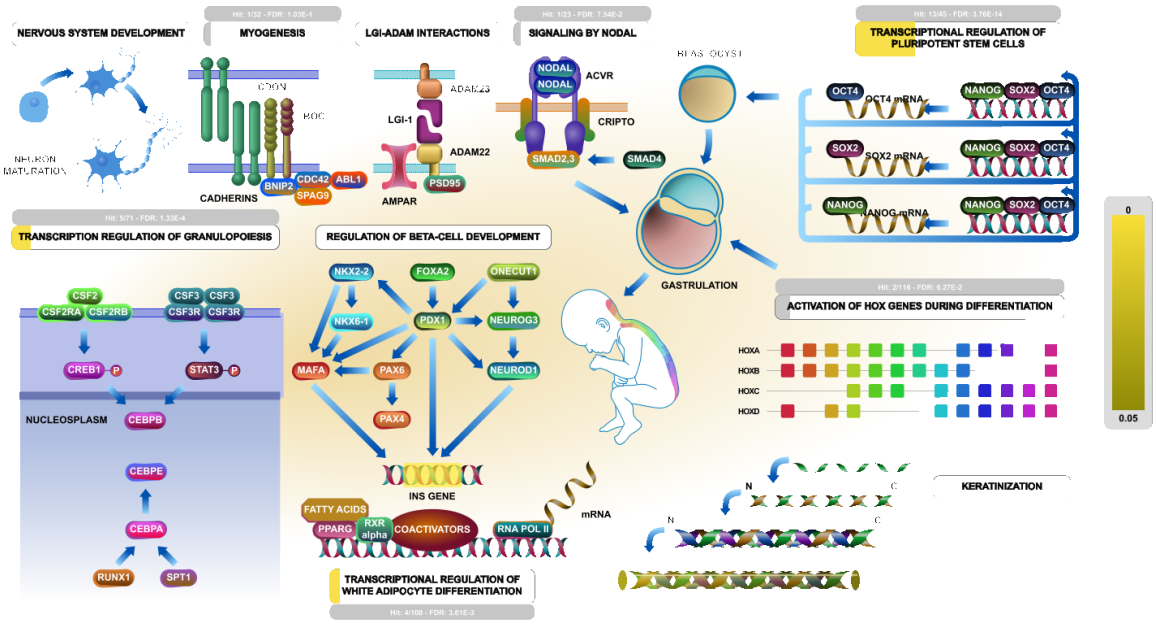
NANOG	ENSG00000111704	POU5F1	ENSG00000204531, ENST00000259915	SALL4	ENSG00000101115
SOX2	ENSG00000181449	STAT3	ENSG00000168610		

2. Developmental Biology (R-HSA-1266738)



As early steps towards capturing the array of processes by which a fertilized egg gives rise to the diverse tissues of the body, examples of ten processes have been annotated. Aspects of two processes involved in most developmental processes, **transcriptional regulation of pluripotent stem cells**, and **activation of HOX genes during differentiation** are annotated. More specialized processes include **nervous system development** , aspects of the roles of cell adhesion molecules in **axonal guidance** and **myogenesis**, of **transcriptional regulation in pancreatic beta cell**, **transcriptional regulation of granulopoeisis**, and **transcriptional regulation of white adipocyte differentiation**, molecular events of **"nodal" signaling**, **LGI-ADAM interactions**, and **keratinization**.

References

Edit history

Date	Action	Author
2011-05-06	Edited	Matthews L
2011-05-06	Created	Orlic-Milacic M
2011-08-22	Reviewed	Jensen J, Walmod PS, Maness PF, Krauss RS
2020-05-29	Modified	Cook J

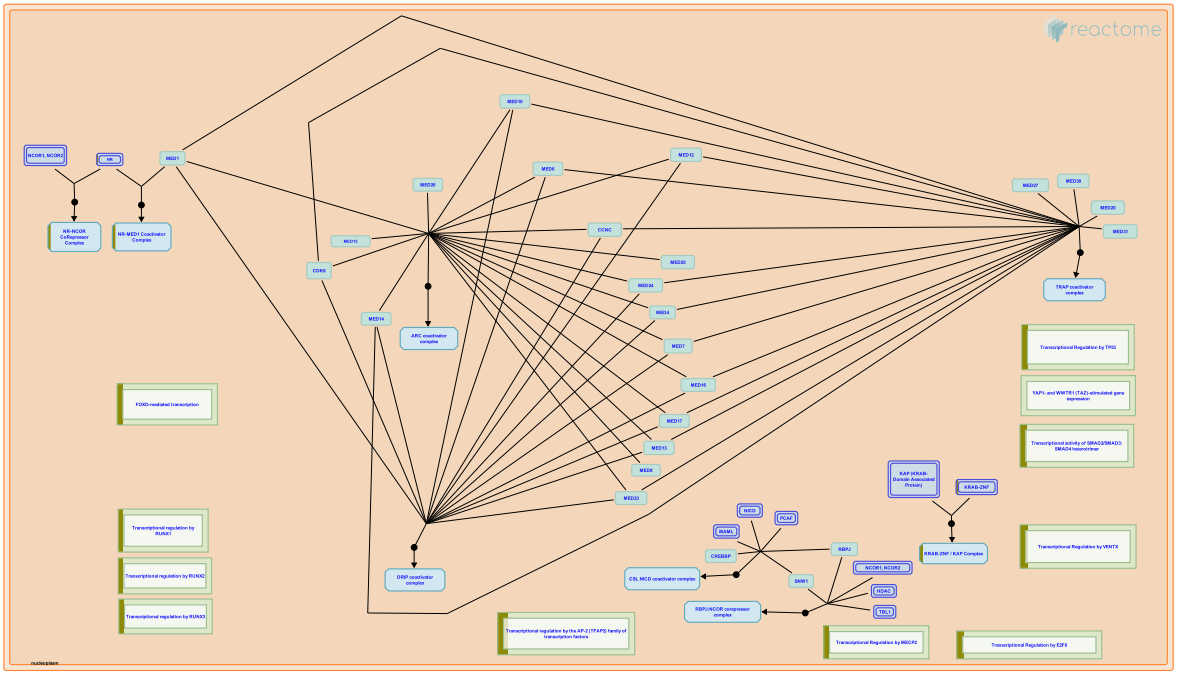
Entities found in this pathway (15)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CTCF	P49711	E2F1	Q01094	GATA2	P23769
KLF4	O43474	MYC	P01106	NANOG	Q9H9S0
POU5F1	Q01860	PPARG	P37231	RELA	Q04206
SALL4	Q9UJQ4	SMAD4	Q13485	SOX2	P48431
STAT3	P40763	TCF3	P15923	YY1	P25490

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
MYC	ENSG00000136997	NANOG	ENSG00000111704	POU5F1	ENSG00000204531, ENST00000259915

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
PPARG	ENSG00000132170	SALL4	ENSG00000101115	SOX2	ENSG00000181449
STAT3	ENSG00000168610				

3. Generic Transcription Pathway (R-HSA-212436)



OVERVIEW OF TRANSCRIPTION REGULATION:

Detailed studies of gene transcription regulation in a wide variety of eukaryotic systems has revealed the general principles and mechanisms by which cell- or tissue-specific regulation of differential gene transcription is mediated (reviewed in Naar, 2001. Kadonaga, 2004, Maston, 2006, Barolo, 2002; Roeder, 2005, Rosenfeld, 2006). Of the three major classes of DNA polymerase involved in eukaryotic gene transcription, Polymerase II generally regulates protein-encoding genes. Figure 1 shows a diagram of the various components involved in cell-specific regulation of Pol-II gene transcription.

Core Promoter: Pol II-regulated genes typically have a Core Promoter where Pol II and a variety of general factors bind to specific DNA motifs:

i: the TATA box (TATA DNA sequence), which is bound by the "TATA-binding protein" (TBP).

ii: the Initiator motif (INR), where Pol II and certain other core factors bind, is present in many Pol II-regulated genes.

iii: the Downstream Promoter Element (DPE), which is present in a subset of Pol II genes, and where additional core factors bind.

The core promoter binding factors are generally ubiquitously expressed, although there are exceptions to this.

Proximal Promoter: immediately upstream (5') of the core promoter, Pol II target genes often have a Proximal Promoter region that spans up to 500 base pairs (b.p.), or even to 1000 b.p.. This region contains a number of functional DNA binding sites for a specific set of transcription activator (TA) and transcription repressor (TR) proteins. These TA and TR factors are generally cell- or tissue-specific in expression, rather than ubiquitous, so that the presence of their cognate binding sites in the proximal promoter region programs cell- or tissue-specific expression of the target gene, perhaps in conjunction with TA and TR complexes bound in distal enhancer regions.

Distal Enhancer(s): many or most Pol II regulated genes in higher eukaryotes have one or more distal Enhancer regions which are essential for proper regulation of the gene, often in a cell or tissue-specific pattern. Like the proximal promoter region, each of the distal enhancer regions typically contain a cluster of binding sites for specific TA and/or TR DNA-binding factors, rather than just a single site.

Enhancers generally have three defining characteristics:

i: They can be located very long distances from the promoter of the target gene they regulate, sometimes as far as 100 Kb, or more.

ii: They can be either upstream (5') or downstream (3') of the target gene, including within introns of that gene.

iii: They can function in either orientation in the DNA.

Combinatorial mechanisms of transcription regulation: The specific combination of TA and TR binding sites within the proximal promoter and/or distal enhancer(s) provides a "combinatorial transcription code" that mediates cell- or tissue-specific expression of the associated target gene. Each promoter or enhancer region mediates expression in a specific subset of the overall expression pattern. In at least some cases, each enhancer region functions completely independently of the others, so that the overall expression pattern is a linear combination of the expression patterns of each of the enhancer modules.

Co-Activator and Co-Repressor Complexes: DNA-bound TA and TR proteins typically recruit the assembly of specific Co-Activator (Co-A) and Co-Repressor (Co-R) Complexes, respectively, which are essential for regulating target gene transcription. Both Co-A's and Co-R's are multi-protein complexes that contain several specific protein components.

Co-Activator complexes generally contain at lease one component protein that has Histone Acetyl Transferase (HAT) enzymatic activity. This functions to acetylate Histones and/or other chromatin-associated factors, which typically increases that transcription activation of the target gene. By contrast, Co-Repressor complexes generally contain at lease one component protein that has Histone De-Acetylase (HDAC) enzymatic activity. This functions to de-acetylate Histones and/or other chromatin-associated factors. This typically increases the transcription repression of the target gene.

Adaptor (Mediator) complexes: In addition to the co-activator complexes that assemble on particular cell-specific TA factors, - there are at least two additional transcriptional co-activator complexes common to most cells. One of these is the Mediator complex, which functions as an "adaptor" complex that bridges between the tissue-specific co-activator complexes assembled in the proximal promoter (or distal enhancers). The human Mediator complex has been shown to contain at least 19 protein distinct components. Different combinations of these co-activator proteins are also found to be components of specific transcription Co-Activator complexes, such as the DRIP, TRAP and ARC complexes described below.

TBP/TAF complex: Another large Co-A complex is the "TBP-associated factors" (TAFs) that assemble on TBP (TATA-Binding Protein), which is bound to the TATA box present in many promoters. There are at least 23 human TAF proteins that have been identified. Many of these are ubiquitously expressed, but TAFs can also be expressed in a cell or tissue-specific pattern.

Specific Coactivator Complexes for DNA-binding Transcription Factors.

A number of specific co-activator complexes for DNA-binding transcription factors have been identified, including DRIP, TRAP, and ARC (reviewed in Bourbon, 2004, Blazek, 2005, Conaway, 2005, and Malik, 2005). The DRIP co-activator complex was originally identified and named as a specific complex associated with the Vitamin D Receptor member of the nuclear receptor family of transcription factors (Rachez, 1998). Similarly, the TRAP co-activator complex was originally identified as a complex that associates with the thyroid receptor (Yuan, 1998). It was later determined that all of the components of the DRIP complex are also present in the TRAP complex, and the ARC complex (discussed further below). For example, the DRIP205 and TRAP220 proteins were show to be identical, as were specific pairs of the other components of these complexes (Rachez, 1999).

In addition, these various transcription co-activator proteins identified in mammalian cells were found to be the orthologues or homologues of the Mediator ("adaptor") complex proteins (reviewed in Bourbon, 2004). The Mediator proteins were originally identified in yeast by Kornberg and colleagues, as complexes associated with DNA polymerase (Kelleher, 1990). In higher organisms, Adapter complexes bridge between the basal transcription factors (including Pol II) and tissue-specific transcription factors (TFs) bound to sites within upstream Proximal Promoter regions or distal Enhancer regions (Figure 1). However, many of the Mediator homologues can also be found in complexes associated with specific transcription factors in higher organisms. A unified nomenclature system for these adapter / co-activator proteins now labels them Mediator 1 through Mediator 31 (Bourbon, 2004). For example, the DRIP205 / TRAP220 proteins are now identified as Mediator 1 (Rachez, 1999), based on homology with yeast Mediator 1.

Example Pathway: Specific Regulation of Target Genes During Notch Signaling:

One well-studied example of cell-specific regulation of gene transcription is selective regulation of target genes during Notch signaling. Notch signaling was first identified in Drosophila, where it has been studied in detail at the genetic, molecular, biochemical and cellular levels (reviewed in Justice, 2002; Bray, 2006; Schweisguth, 2004; Louvri, 2006). In Drosophila, Notch signaling to the nucleus is thought always to be mediated by one specific DNA binding transcription factor, Suppressor of Hairless. In mammals, the homologous genes are called CBF1 (or RBPJkappa), while in worms they are called Lag-1, so that the acronym "CSL" has been given to this conserved transcription factor family. There are at least two human CSL homologues, which are now named RBPJ and RBPJL.

In Drosophila, Su(H) is known to be bifunctional, in that it represses target gene transcription in the absence of Notch signaling, but activates target genes during Notch signaling. At least some of the mammalian CSL homologues are believed also to be bifunctional, and to mediate target gene repression in the absence of Notch signaling, and activation in the presence of Notch signaling.

Notch Co-Activator and Co-Repressor complexes: This repression is mediated by at least one specific co-repressor complexes (Co-R) bound to CSL in the absence of Notch signaling. In Drosophila, this co-repressor complex consists of at least three distinct co-repressor proteins: Hairless, Groucho, and dCtBP (Drosophila C-terminal Binding Protein). Hairless has been show to bind directly to Su(H), and Groucho and dCtBP have been shown to bind directly to Hairless (Barolo, 2002). All three of the co-repressor proteins have been shown to be necessary for proper gene regulation during Notch signaling in vivo (Nagel, 2005).

In mammals, the same general pathway and mechanisms are observed, where CSL proteins are bifunctional DNA binding transcription factors (TFs), that bind to Co-Repressor complexes to mediate repression in the absence of Notch signaling, and bind to Co-Activator complexes to mediate activation in the presence of Notch signaling. However, in mammals, there may be multiple co-repressor complexes, rather than the single Hairless co-repressor complex that has been observed in Drosophila.

During Notch signaling in all systems, the Notch transmembrane receptor is cleaved and the Notch intracellular domain (NICD) translocates to the nucleus, where it there functions as a specific transcription co-activator for CSL proteins. In the nucleus, NICD replaces the Co-R complex bound to CSL, thus resulting in de-repression of Notch target genes in the nucleus (Figure 2). Once bound to CSL, NICD and CSL proteins recruit an additional co-activator protein, Mastermind, to form a CSL-NICD-Mam ternary co-activator (Co-A) complex. This Co-R complex was initially thought to be sufficient to mediate activation of at least some Notch target genes. However, there now is evidence that still other co-activators and additional DNA-binding transcription factors are required in at least some contexts (reviewed in Barolo, 2002).

Thus, CSL is a good example of a bifunctional DNA-binding transcription factor that mediates repression of specific targets genes in one context, but activation of the same targets in another context. This bifunctionality is mediated by the association of specific Co-Repressor complexes vs. specific Co-Activator complexes in different contexts, namely in the absence or presence of Notch signaling.

References

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Maston GA, Evans SK & Green MR (2006). Transcriptional regulatory elements in the human genome. Annu Rev Genomics Hum Genet, 7, 29-59.

Barolo S & Posakony JW (2002). Three habits of highly effective signaling pathways: principles of transcriptional control by developmental cell signaling. Genes Dev, 16, 1167-81.

Roeder RG (2005). Transcriptional regulation and the role of diverse coactivators in animal cells. FEBS Lett, 579, 909-15.

Edit history

Date	Action	Author
2008-02-09	Created	Caudy M
2008-02-26	Reviewed	Freedman LP
2020-05-29	Modified	Cook J

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AR	P10275	E2F1	Q01094	ESR1	P03372
GATA2	P23769	KLF4	O43474	MYC	P01106

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PPARG	P37231
SOX2	P48431
TP53	P04637
ZNF384	Q8TAQ5

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RELA	Q04206
TAF1	P21675, Q8IZX4
TP63	Q9H3D4

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SMAD4	Q13485
TCF3	P15923, Q9HCS4
YY1	P25490

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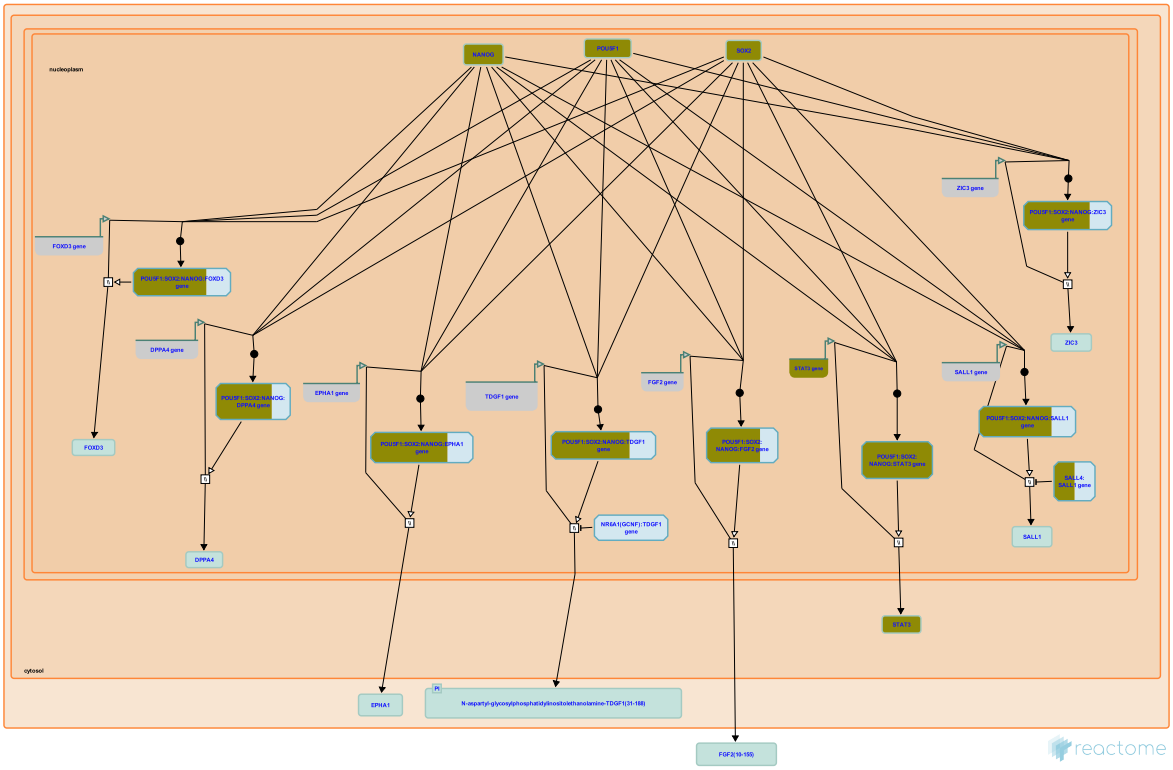
MYC	ENSG00000136997

Input	Ensembl Id
ESR1	ENSG00000091831
PPARG	ENSG00000132170

Input	Ensembl Id
KLF4	ENSG00000136826
TP53	ENSG00000141510

4. POU5F1 (OCT4), SOX2, NANOG activate genes related to proliferation (R-HSA-2892247)



Cellular compartments: nucleoplasm, cytosol, endosome membrane, extracellular region, plasma membrane.

POU5F1 (OCT4), SOX2, and NANOG bind elements in the promoters of target genes. The target genes of each transcription factor overlap extensively: POU5F1, SOX2, and NANOG co-occupy at least 353 genes (Boyer et al. 2005). About half of POU5F1 targets also bind SOX2 and about 90% of these also bind NANOG (Boyer et al. 2005). Upon binding the transcription factors activate expression of one subset of target genes and repress another subset (Kim et al. 2006, Matoba et al. 2006, Player et al. 2006, Babaie et al. 2007). The targets listed in this module are those that have been described as composing activated genes in the core transcriptional network of pluripotent stem cells (Assou et al. 2007, Chavez et al. 2009, Jung et al. 2010). Inferences from mouse to human have been made with caution because of significant differences between the two species (Ginis et al. 2004).

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Edit history

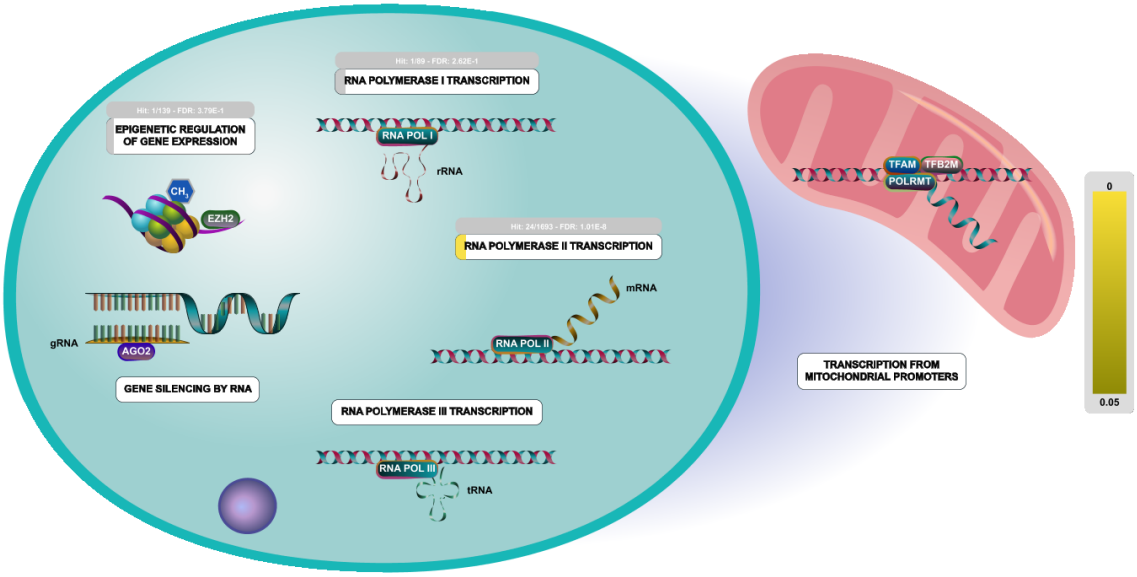
Date	Action	Author
2013-01-01	Edited	May B
2013-01-01	Authored	May B
2013-01-02	Created	May B
2014-01-23	Reviewed	Wang J
2016-09-19	Modified	May B

Entities found in this pathway (5)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
NANOG	Q9H9S0	POU5F1	Q01860	SALL4	Q9UJQ4
SOX2	P48431	STAT3	P40763		

Input	Ensembl Id
STAT3	ENSG00000168610

5. Gene expression (Transcription) (R-HSA-74160)



Gene expression encompasses transcription and translation and the regulation of these processes. RNA Polymerase I Transcription produces the large preribosomal RNA transcript (45S pre-rRNA) that is processed to yield 18S rRNA, 28S rRNA, and 5.8S rRNA, accounting for about half the RNA in a cell. RNA Polymerase II transcription produces messenger RNAs (mRNA) as well as a subset of non-coding RNAs including many small nucleolar RNAs (snRNA) and microRNAs (miRNA). RNA Polymerase III Transcription produces transfer RNAs (tRNA), 5S RNA, 7SL RNA, and U6 snRNA. Transcription from mitochondrial promoters is performed by the mitochondrial RNA polymerase, POLRMT, to yield long transcripts from each DNA strand that are processed to yield 12S rRNA, 16S rRNA, tRNAs, and a few RNAs encoding components of the electron transport chain. Regulation of gene expression can be divided into epigenetic regulation, transcriptional regulation, and post-transcription regulation (comprising translational efficiency and RNA stability). Epigenetic regulation of gene expression is the result of heritable chemical modifications to DNA and DNA-binding proteins such as histones. Epigenetic changes result in altered chromatin complexes that influence transcription. Gene Silencing by RNA mostly occurs post-transcriptionally but can also affect transcription. Small RNAs originating from the genome (miRNAs) or from exogenous RNA (siRNAs) are processed and transferred to the RNA-induced silencing complex (RISC), which interacts with complementary RNA to cause cleavage, translational inhibition, or transcriptional inhibition.

References

Edit history

Date	Action	Author
2003-09-11	Authored	Larsson NG, Comai L, Gustafsson CM, Reinberg D, Timmers HTM et al.
2003-09-11	Created	Proudfoot NJ, Kornblihtt AR
2008-12-03	Authored	Caudy M, Proudfoot NJ, Kornblihtt AR, D'Eustachio P
2016-12-29	Revised	D'Eustachio P
2020-05-27	Edited	Joshi-Tope G
2020-05-27	Reviewed	Paule M, Willis I, Zhao X

Date	Action	Author
2020-05-29	Modified	Cook J

Entities found in this pathway (17)

Input	UniProt Id
AR	P10275
GATA2	P23769
PPARG	P37231
SOX2	P48431
TP53	P04637
YY1	P25490

Input	UniProt Id
E2F1	Q01094
KLF4	O43474
RELA	Q04206
TAF1	P21675, Q8IZX4
TP63	Q9H3D4
ZNF384	Q8TAQ5

Input	UniProt Id
ESR1	P03372
MYC	P01106
SMAD4	Q13485
TCF3	P15923, Q9HCS4
UBTF	P17480

Input	Ensembl Id
E2F1	ENSG00000101412
MYC	ENSG00000136997

Input	Ensembl Id
ESR1	ENSG00000091831
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Input	Ensembl Id
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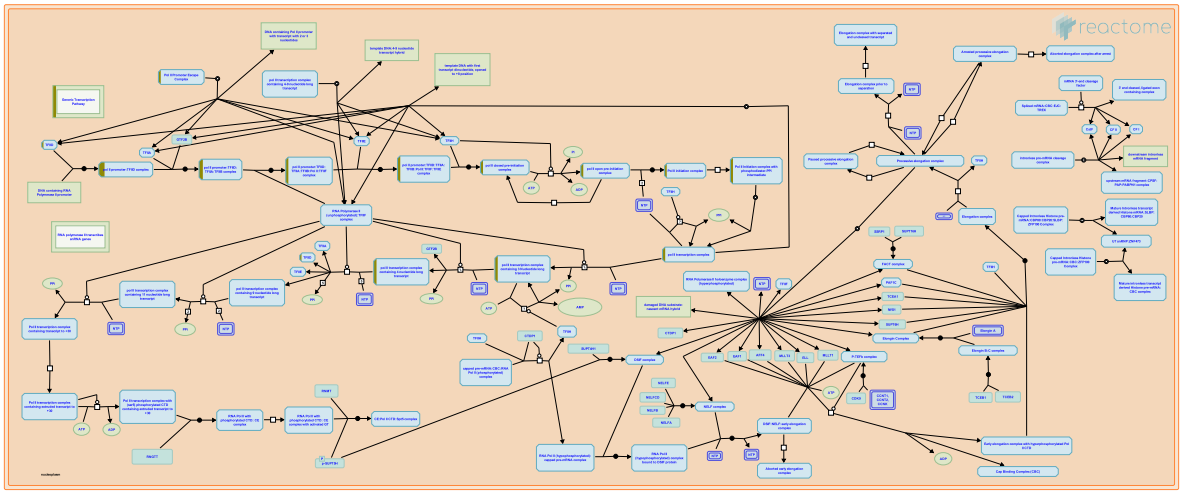
6. RNA Polymerase II Transcription (R-HSA-73857)



Cellular compartments: nucleoplasm.

RNA polymerase II (Pol II) is the central enzyme that catalyses DNA- directed mRNA synthesis during the transcription of protein-coding genes. Pol II consists of a 10-subunit catalytic core, which alone is capable of elongating the RNA transcript, and a complex of two subunits, Rpb4/7, that is required for transcription initiation.

The transcription cycle is divided in three major phases: initiation, elongation, and termination. Transcription initiation include promoter DNA binding, DNA melting, and initial synthesis of short RNA transcripts. The transition from initiation to elongation, is referred to as promoter escape and leads to a stable elongation complex that is characterized by an open DNA region or transcription bubble. The bubble contains the DNA-RNA hybrid, a heteroduplex of eight to nine base pairs. The growing 3-end of the RNA is engaged with the polymerase complex active site. Ultimately transcription terminates and Pol II dissocitates from the template.

References

Cramer P (2004). Structure and function of RNA polymerase II. Adv. Protein Chem., 67, 1-42.

Edit history

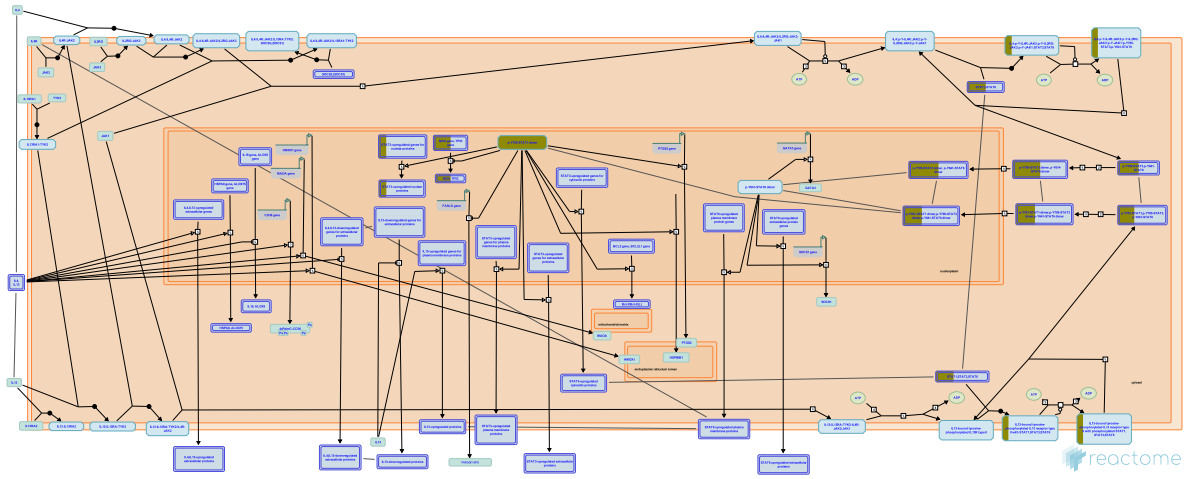
Date	Action	Author
2005-01-12	Created	Reinberg D, Timmers HTM, Conaway JW, Proudfoot NJ, Conaway RC
2020-05-29	Modified	Cook J

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AR	P10275	E2F1	Q01094	ESR1	P03372
GATA2	P23769	KLF4	O43474	MYC	P01106
PPARG	P37231	RELA	Q04206	SMAD4	Q13485
SOX2	P48431	TAF1	P21675, Q8IZX4	TCF3	P15923, Q9HCS4
TP53	P04637	TP63	Q9H3D4	YY1	P25490
ZNF384	Q8TAQ5				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
E2F1	ENSG00000101412	ESR1	ENSG00000091831	KLF4	ENSG00000136826
MYC	ENSG00000136997	PPARG	ENSG00000132170	TP53	ENSG00000141510

7. Interleukin-4 and Interleukin-13 signaling (R-HSA-6785807)



Interleukin-4 (IL4) is a principal regulatory cytokine during the immune response, crucially important in allergy and asthma (Nelms et al. 1999). When resting T cells are antigen-activated and expand in response to Interleukin-2 (IL2), they can differentiate as Type 1 (Th1) or Type 2 (Th2) T helper cells. The outcome is influenced by IL4. Th2 cells secrete IL4, which both stimulates Th2 in an autocrine fashion and acts as a potent B cell growth factor to promote humoral immunity (Nelms et al. 1999).

Interleukin-13 (IL13) is an immunoregulatory cytokine secreted predominantly by activated Th2 cells. It is a key mediator in the pathogenesis of allergic inflammation. IL13 shares many functional properties with IL4, stemming from the fact that they share a common receptor subunit. IL13 receptors are expressed on human B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, macrophages, respiratory epithelial cells, and smooth muscle cells, but unlike IL4, not T cells. Thus IL13 does not appear to be important in the initial differentiation of CD4 T cells into Th2 cells, rather it is important in the effector phase of allergic inflammation (Hershey et al. 2003).

IL4 and IL13 induce “alternative activation” of macrophages, inducing an anti-inflammatory phenotype by signaling through IL4R alpha in a STAT6 dependent manner. This signaling plays an important role in the Th2 response, mediating anti-parasitic effects and aiding wound healing (Gordon & Martinez 2010, Loke et al. 2002)

There are two types of IL4 receptor complex (Andrews et al. 2006). Type I IL4R (IL4R1) is predominantly expressed on the surface of hematopoietic cells and consists of IL4R and IL2RG, the common gamma chain. Type II IL4R (IL4R2) is predominantly expressed on the surface of nonhematopoietic cells, it consists of IL4R and IL13RA1 and is also the type II receptor for IL13. (Obiri et al. 1995, Aman et al. 1996, Hilton et al. 1996, Miloux et al. 1997, Zhang et al. 1997). The second receptor for IL13 consists of IL4R and Interleukin-13 receptor alpha 2 (IL13RA2), sometimes called Interleukin-13 binding protein (IL13BP). It has a high affinity receptor for IL13 (Kd = 250 pmol/L) but is not sufficient to render cells responsive to IL13, even in the presence of IL4R (Donaldson et al. 1998). It is reported to exist in soluble form (Zhang et al. 1997) and when overexpressed reduces JAK-STAT signaling (Kawakami et al. 2001). It's function may be to prevent IL13 signalling via the functional IL4R:IL13RA1 receptor. IL13RA2 is overexpressed and enhances cell invasion in some human cancers (Joshi & Puri 2012).

The first step in the formation of IL4R1 (IL4:IL4R:IL2RB) is the binding of IL4 with IL4R (Hoffman et al. 1995, Shen et al. 1996, Hage et al. 1999). This is also the first step in formation of IL4R2 (IL4:IL4R:IL13RA1). After the initial binding of IL4 and IL4R, IL2RB binds (LaPorte et al. 2008), to form IL4R1. Alternatively, IL13RA1 binds, forming IL4R2. In contrast, the type II IL13 complex (IL13R2) forms with IL13 first binding to IL13RA1 followed by recruitment of IL4R (Wang et al. 2009).

Crystal structures of the IL4:IL4R:IL2RG, IL4:IL4R:IL13RA1 and IL13:IL4R:IL13RA1 complexes have been determined (LaPorte et al. 2008). Consistent with these structures, in monocytes IL4R is tyrosine phosphorylated in response to both IL4 and IL13 (Roy et al. 2002, Gordon & Martinez 2010) while IL13RA1 phosphorylation is induced only by IL13 (Roy et al. 2002, LaPorte et al. 2008) and IL2RG phosphorylation is induced only by IL4 (Roy et al. 2002).

Both IL4 receptor complexes signal through Jak/STAT cascades. IL4R is constitutively-associated with JAK2 (Roy et al. 2002) and associates with JAK1 following binding of IL4 (Yin et al. 1994) or IL13 (Roy et al. 2002). IL2RG constitutively associates with JAK3 (Boussiotis et al. 1994, Russell et al. 1994). IL13RA1 constitutively associates with TYK2 (Umeshita-Suyama et al. 2000, Roy et al. 2002, LaPorte et al. 2008, Bhattacharjee et al. 2013).

IL4 binding to IL4R1 leads to phosphorylation of JAK1 (but not JAK2) and STAT6 activation (Takeda et al. 1994, Ratthe et al. 2007, Bhattacharjee et al. 2013).

IL13 binding increases activating tyrosine-99 phosphorylation of IL13RA1 but not that of IL2RG. IL4 binding to IL2RG leads to its tyrosine phosphorylation (Roy et al. 2002). IL13 binding to IL4R2 leads to TYK2 and JAK2 (but not JAK1) phosphorylation (Roy & Cathcart 1998, Roy et al. 2002).

Phosphorylated TYK2 binds and phosphorylates STAT6 and possibly STAT1 (Bhattacharjee et al. 2013).

A second mechanism of signal transduction activated by IL4 and IL13 leads to the insulin receptor substrate (IRS) family (Kelly-Welch et al. 2003). IL4R1 associates with insulin receptor substrate 2 and activates the PI3K/Akt and Ras/MEK/Erk pathways involved in cell proliferation, survival and translational control. IL4R2 does not associate with insulin receptor substrate 2 and consequently the PI3K/Akt and Ras/MEK/Erk pathways are not activated (Busch-Dienstfertig & González-Rodríguez 2013).

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Edit history

Date	Action	Author
2015-07-01	Authored	Jupe S
2015-07-01	Created	Jupe S
2016-09-02	Edited	Jupe S
2016-09-02	Reviewed	Leibovich SJ

Date	Action	Author
2020-06-04	Modified	Cook J

Entities found in this pathway (5)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MYC	P01106	NANOG	Q9H9S0	SOX2	P48431
STAT3	P40763	TP53	P04637		

Input	Ensembl Id	Input	Ensembl Id
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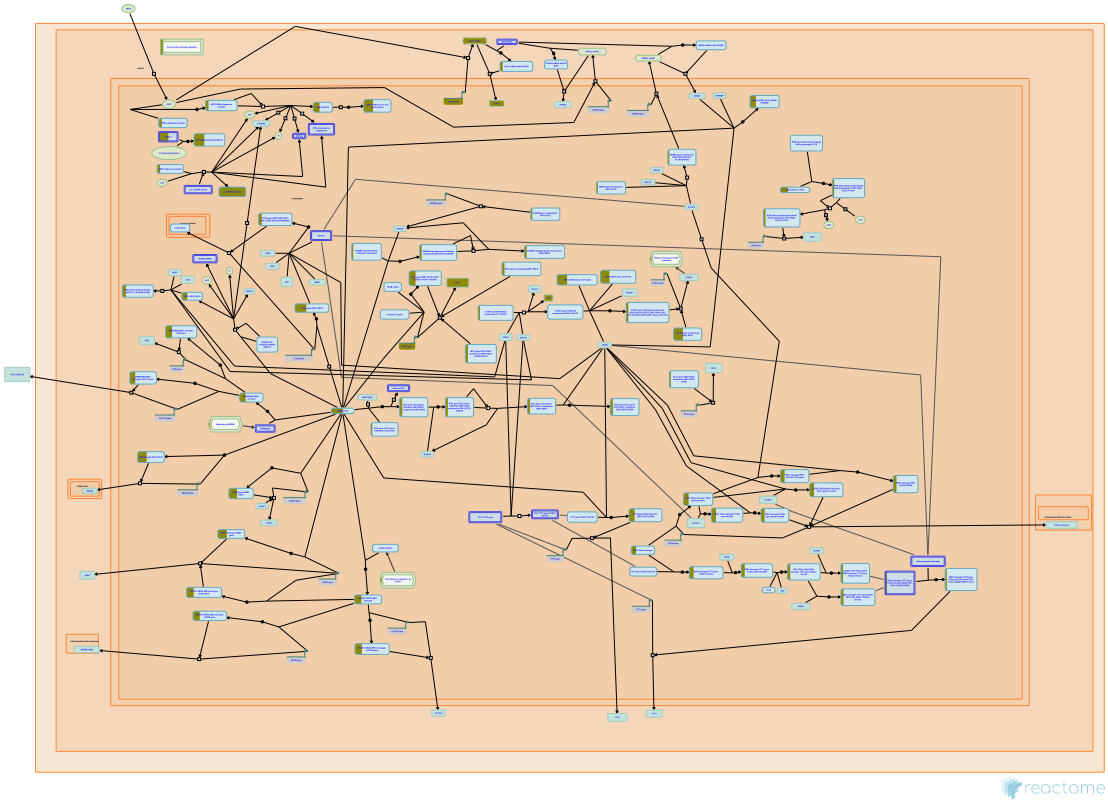
8. ESR-mediated signaling (R-HSA-8939211)



Estrogens are a class of hormones that play a role in physiological processes such as development, reproduction, metabolism of liver, fat and bone, and neuronal and cardiovascular function (reviewed in Arnal et al, 2017; Haldosen et al, 2014). Estrogens bind estrogen receptors, members of the nuclear receptor superfamily. Ligand-bound estrogen receptors act as nuclear transcription factors to regulate expression of genes that control cellular proliferation and differentiation, among other processes, but also play a non-genomic role in rapid signaling from the plasma membrane (reviewed in Hah et al, 2014;Schwartz et al, 2016).

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Haldosén LA, Zhao C & Dahlman-Wright K (2014). Estrogen receptor beta in breast cancer. Mol. Cell. Endocrinol., 382, 665-72.

Hah N & Kraus WL (2014). Hormone-regulated transcriptomes: lessons learned from estrogen signaling pathways in breast cancer cells. Mol. Cell. Endocrinol., 382, 652-64.

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Edit history

Date	Action	Author
2016-09-16	Created	Rothfels K
2017-09-29	Authored	Rothfels K

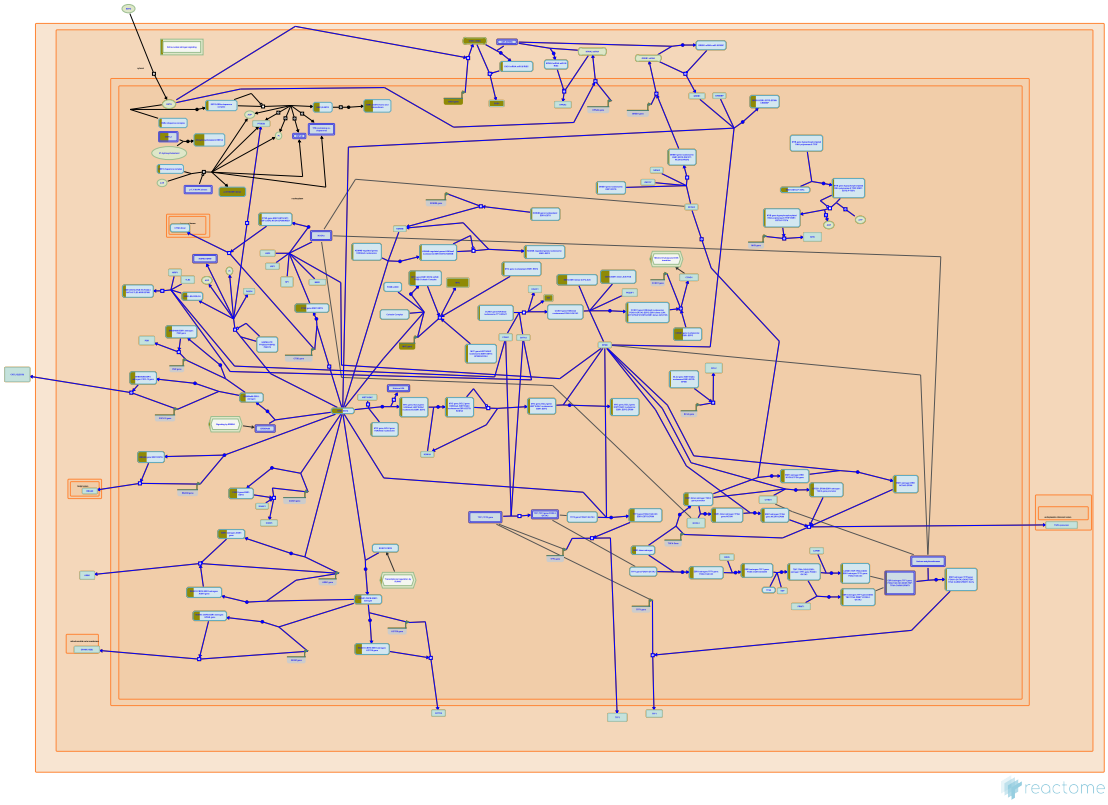
Date	Action	Author
2017-11-03	Edited	Rothfels K
2018-02-23	Reviewed	Magnani L
2020-05-29	Modified	Cook J

Entities found in this pathway (4)

Input	UniProt Id	Input	UniProt Id
CHD1	O14646	ESR1	P03372, P03372-3, P03372-4
MYC	P01106	YY1	P25490

Input	Ensembl Id	Input	Ensembl Id
CHD1	ENSG00000153922, ENST00000284049.7	MYC	ENSG00000136997

9. Estrogen-dependent gene expression (R-HSA-9018519)



Estrogens mediate their transcriptional effects through interaction with the estrogen receptors, ESR1 (also known as ER alpha) and ESR2 (ER beta). ESR1 and ESR2 share overlapping but distinct functions, with ESR1 playing the primary role in transcriptional activation in most cell types (Hah and Krauss, 2014; Haldosén et al, 2014. The receptors function as ligand-dependent dimers and can activate target genes either through direct binding to an estrogen responsive element (ERE) in the target gene promoter, or indirectly through interaction with another DNA-binding protein such as RUNX1, SP1, AP1 or NF-kappa beta (reviewed in Bai and Gust, 2009; Hah and Krause, 2014). Binding of estrogen receptors to the DNA promotes the assembly of higher order transcriptional complexes containing methyltransferases, histone acetyltransferases and other transcriptional activators, which promote transcription by establishing active chromatin marks and by recruiting general transcription factors and RNA polymerase II. ESR1- and estrogen-dependent recruitment of up to hundreds of coregulators has been demonstrated by varied co-immunoprecipitation and proteomic approaches (Kittler et al, 2013; Mohammed et al, 2013; Foulds et al, 2013; Mohammed et al, 2015; Liu et al, 2014; reviewed in Magnani and Lupien, 2014; Arnal, 2017). In some circumstances, ligand-bound receptors can also promote the assembly of a repression complex at a target gene, and in some cases, heterodimers of ESR1 and ESR2 serve as repressors of ESR1-mediated target gene activation (reviewed in Hah and Kraus, 2014; Arnal et al, 2017). Phosphorylation of the estrogen receptor also modulates its activity, and provides cross-talk between nuclear estrogen-dependent signaling and non-genomic estrogen signaling from the plasma membrane (reviewed in Anbalagan and Rowan, 2015; Halodsèn et al, 2014; Schwartz et al, 2016)

A number of recent genome wide studies highlight the breadth of the transcriptional response to estrogen. The number of predicted estrogen-dependent target genes ranges from a couple of hundred (based on microarray studies) to upwards of 10000, based on ChIP-chip or ChIP-seq (Cheung and Kraus, 2010; Kinnis and Kraus, 2008; Lin et al, 2004; Welboren et al, 2009; Ikeda et al, 2015; Lin et al, 2007; Carroll et al, 2006). Many of these predicted sites may not represent transcriptionally productive binding events, however. A study examining ESR1 binding by ChIP-seq in 20 primary breast cancers identified a core of 484 ESR-binding events that were conserved in at least 75% of ER+ tumors, which may represent a more realistic estimate (Ross-Innes et al, 2012). These studies also highlight the long-range effect of estrogen receptor-binding, with distal enhancer or promoter elements regulating the expression of many target genes, often through looping or other higher order chromatin structures (Kittler et al, 2013; reviewed in Dietz and Carroll, 2008; Liu and Cheung, 2014; Magnani and Lupien, 2014). Transcription from a number of estrogen-responsive target genes also appears to be primed by the binding of pioneering transcription factors such as FOXA1, GATA3, PBX1 among others. These factors bind to heterochromatin by virtue of their winged helix domains and promote chromatin opening, allowing subsequent recruitment of other transcription factors (reviewed in Zaret and Carroll, 2011; Fiorito et al, 2013; Arnal et al, 2017; Magnani et al, 2011)

References

Hah N & Kraus WL (2014). Hormone-regulated transcriptomes: lessons learned from estrogen signaling pathways in breast cancer cells. Mol. Cell. Endocrinol., 382, 652-64.

Haldosén LA, Zhao C & Dahlman-Wright K (2014). Estrogen receptor beta in breast cancer. Mol. Cell. Endocrinol., 382, 665-72.

Bai Z & Gust R (2009). Breast cancer, estrogen receptor and ligands. Arch. Pharm. (Weinheim), 342, 133-49.

Arnal JF, Lenfant F, Métivier R, Flouriot G, Henrion D, Adlanmerini M, ... Katzenellenbogen J (2017). Membrane and Nuclear Estrogen Receptor Alpha Actions: From Tissue Specificity to Medical Implications. Physiol. Rev., 97, 1045-1087.

Anbalagan M & Rowan BG (2015). Estrogen receptor alpha phosphorylation and its functional impact in human breast cancer. Mol. Cell. Endocrinol., 418, 264-72.

Edit history

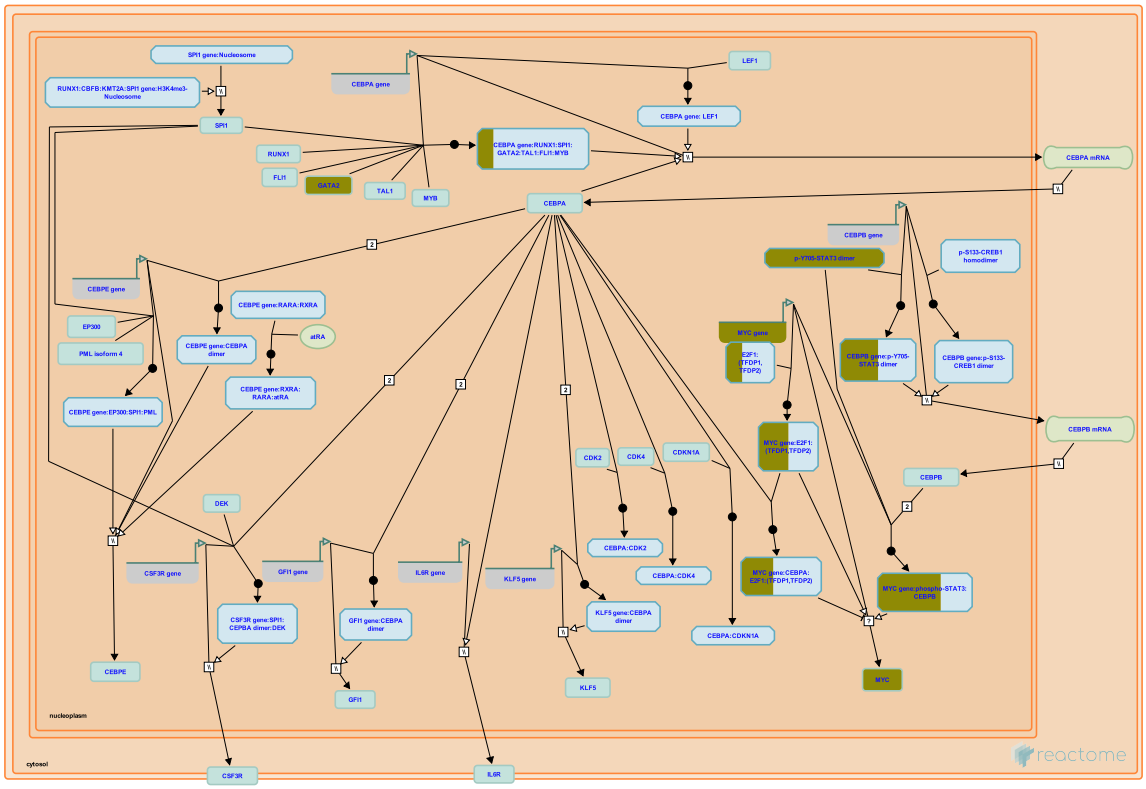
Date	Action	Author
2017-09-01	Created	Rothfels K
2017-09-29	Authored	Rothfels K
2017-11-03	Edited	Rothfels K
2018-02-23	Reviewed	Magnani L
2020-05-29	Modified	Cook J

Entities found in this pathway (4)

Input	UniProt Id	Input	UniProt Id
CHD1	O14646	ESR1	P03372
MYC	P01106	YY1	P25490

Input	Ensembl Id	Input	Ensembl Id
CHD1	ENSG00000153922, ENST00000284049.7	MYC	ENSG00000136997

10. Transcriptional regulation of granulopoiesis (R-HSA-9616222)



Neutrophilic granulocytes (hereafter called granulocytes) are distinguished by multilobulated nuclei and presence of cytoplasmic granules containing antipathogenic proteins (reviewed in Cowland and Borregaard 2016, Yin and Heit 2018). Granulocytes comprise eosinophils, basophils, mast cells, and neutrophils, all of which are ultimately derived from hemopoietic stem cells (HSCs), a self-renewing population of stem cells located in the bone marrow. A portion of HSCs exit self-renewing proliferation and differentiate to form multipotent progenitors (MPPs). MPPs then differentiate to form common myeloid progenitors (CMPs) as well as the erythrocyte lineage. CMPs further differentiate into granulocyte-monocyte progenitors (GMPs) which can then differentiate into monocytes or any of the types of granulocytes (reviewed in Fiedler and Brunner 2012). granulocytes are the most abundant leukocytes in peripheral blood.

For early granulopoiesis the CEBPA, SPI1 (PU.1), RAR, CBF, and MYB transcription factors are essential. CEBPE, SPI1, SP1, CDP, and HOXA10 transcription factors initiate terminal neutrophil differentiation.

Initially, RUNX1 activates SPI1 (PU.1), which is believed to be the key transcription factor driving the formation of MPPs and CMPs (reviewed in Friedman 2007, Fiedler and Brunner 2012). SPI1, in turn, activates expression of CEBPA, an indispensable transcription factor for granulopoiesis especially important in the transition from CMP to GMP (inferred from mouse homologs in Wilson et al. 2010, Guo et al. 2012, Guo et al. 2014, Cooper et al. 2015). CEBPA, in turn, activates the expression of several transcription factors and receptors characteristic of granulocytes, including CEBPA (autoregulation), CEBPE (Loke et al. 2018, and inferred from mouse homologs in Wang and Friedman 2002, Friedman et al. 2003), GFI1 (inferred from mouse homologs in Lidonnici et al. 2010), KLF5 (Federzoni et al. 2014), IL6R (inferred from mouse homologs in Zhang et al. 1998), and CSF3R (Smith et al. 1996). Importantly, CEBPA dimers repress transcription of MYC (c-Myc) (Johansen et al. 2001, and inferred from mouse homologs in Slomiany et al. 2000, Porse et al. 2001). CEBPA binds CDK2 and CDK4 (Wang et al. 2001) which inhibits their kinase activity by disrupting their association with cyclins thereby limiting proliferation and favoring differentiation of granulocyte progenitors during regular ("steady-state") granulopoiesis (reviewed in Friedman 2015). The transcription factor GFI1 regulates G-CSF signaling and neutrophil development through the Ras activator RasGRP1 (de la Luz Sierra et al. 2010).

Inhibitors of DNA binding (ID) proteins ID1 and ID2 regulate granulopoiesis and eosinophil production such that ID1 induces neutrophil development and inhibits eosinophil differentiation, whereas ID2 induces both eosinophil and neutrophil development (Buitenhuis et al. 2005, Skokowa et al. 2009).

Major infection activates emergency granulopoiesis (reviewed in Manz and Boettcher 2014, Hirai et al. 2015), the production of large numbers of granulocytes in a relatively short period of time. Emergency granulopoiesis is activated by cytokines, CSF2 (GM-CSF) and especially CSF3 (G-CSF, reviewed in Panopoulos and Watowich 2008, Liongue et al. 2009) which bind receptors, CSF2R and CSF3R, respectively, resulting in expression of CEBPB, which interferes with repression of MYC by CEBPA (inferred from mouse homologs in Zhang et al. 2010) and represses MYC less than CEBPA does (Hirai et al. 2006), leading to proliferation of granulocyte progenitors prior to final differentiation.Both, emergency and steady-state granulopoiesis are regulated by direct interaction of CEBPA (steady-state) or CEBPB (emergency) proteins with NAD+-dependent protein deacetylases, SIRT1 and SIRT2 (Skokowa et al. 2009). G-CSF induces the NAD+-generating enzyme, Nicotinamide phosphoribosyltransferase (NAMPT, or PBEF), that in turn activates sirtuins (Skokowa et al. 2009).

GADD45A and GADD45B proteins are essential for stress-induced granulopoiesis and granulocyte chemotaxis by activation of p38 kinase (Gupta et al. 2006, Salerno et al. 2012). SHP2 is required for induction of CEBPA expression and granulopoiesis in response to CSF3 (G-CSF) or other cytokines independent of SHP2-mediated ERK activation (Zhang et al. 2011).

Transcription of neutrophil granule proteins (e.g. ELANE, MPO, AZU1, DEFA4), that play an essential role in bacterial killing are regulated by CEBPE and SPI1 (PU.1) transcription factors (Gombart et al. 2003, Nakajima et al. 2006). RUNX1 and LEF1 also regulate ELANE (ELA2) mRNA expression by binding to its promoter (Li et al. 2003).

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Friedman AD (2007). Transcriptional control of granulocyte and monocyte development. Oncogene , 26, 6816-28.

Edit history

Date	Action	Author
2018-08-10	Edited	May B
2018-08-10	Authored	May B
2018-08-10	Created	May B
2019-03-10	Reviewed	Skokowa J
2020-05-29	Modified	Cook J

Entities found in this pathway (4)

Input	UniProt Id
E2F1	Q01094
MYC	P01106

Input	UniProt Id
GATA2	P23769
STAT3	P40763

Input	Ensembl Id
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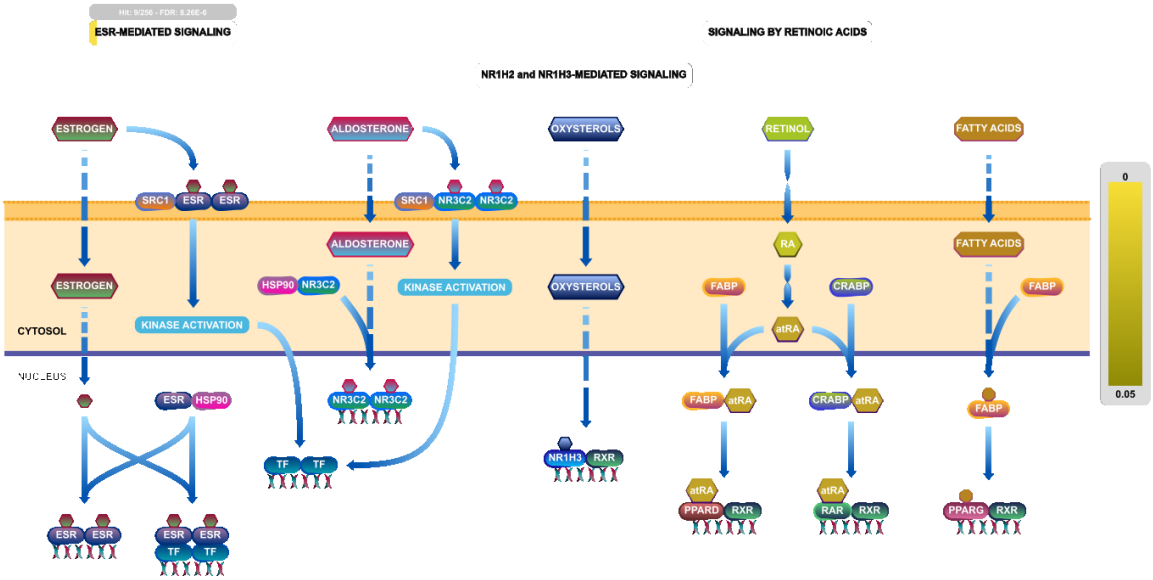
11. Signaling by Nuclear Receptors (R-HSA-9006931)



Nuclear receptors (NRs) are ligand-activated transcription factors that bind to small lipid based molecules to regulate gene expression and other cellular process. This family includes receptors for steroid hormones and derivatives (such as estrogen, progesterone, glucocorticoids, Vitamin D, oxysterols and bile acids, among others) as well as receptors for retinoic acids, thyroid hormones and fatty acids and their derivatives. These ligands are able to diffuse directly through cellular membranes as a result of their lipophilic nature (reviewed in Beato et al, 1996; Holzer et al, 2017).

The 48 human nuclear receptors share a conserved modular structure that consists of a sequence specific DNA-binding domain and a ligand-binding domain, in addition to various other protein-protein interaction domains. Upon interaction with ligand, NRs bind to the regulatory regions of target genes as homo- or heterodimers, or more rarely, as monomers. At the promoter, NRs interact with other activators and repressors to regulate gene expression (reviewed Beato et al, 1996; Simons et al, 2014; Hah and Kraus, 2010).

A number of nuclear receptors are cytoplasmic in the absence of ligand and exist as part of a heat shock protein complex that regulates their cellular location, protein stability, competency to bind steroid hormones and transcriptional activity (Echeverria and Picard, 2010). Ligand-binding to these receptors promotes dimerization and nuclear translocation. Other nuclear receptors are contstitutively nuclear and their chromatin-modifying activities are regulated by ligand binding (reviewed in Beato et al, 1996).

In addition to the classic transcriptional response, NRs also have a role in rapid, non-nuclear signaling originating from receptors localized at the plasma membrane. Ligand-binding to these receptors intitiates downstream phospholipase- and kinase-based signaling cascades (reviewed in Schwartz et al, 2016; Levin and Hammes, 2016).

Signaling by estrogen, liver X and retinoic acid receptors are currently described here.

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Edit history

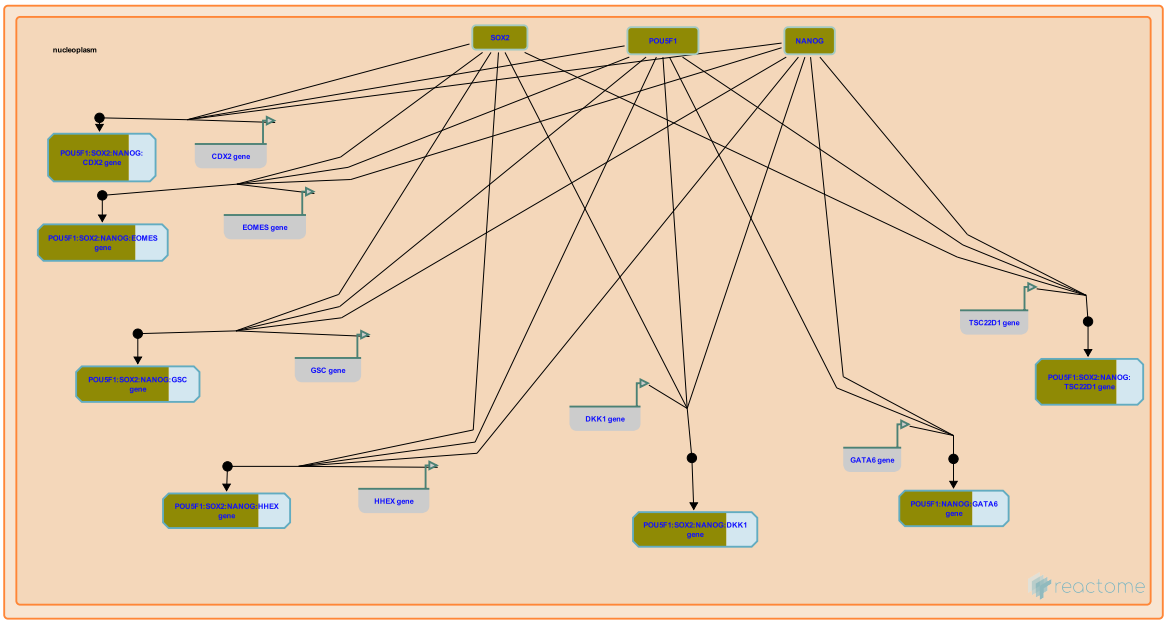
Date	Action	Author
2017-05-24	Edited	Rothfels K
2017-05-24	Authored	Rothfels K
2017-05-24	Created	Rothfels K
2017-06-22	Reviewed	D'Eustachio P
2020-05-29	Modified	Cook J

Entities found in this pathway (4)

Input	UniProt Id	Input	UniProt Id
CHD1	O14646	ESR1	P03372, P03372-3, P03372-4
MYC	P01106	YY1	P25490

Input	Ensembl Id	Input	Ensembl Id
CHD1	ENSG00000153922, ENST00000284049.7	MYC	ENSG00000136997

12. POU5F1 (OCT4), SOX2, NANOG repress genes related to differentiation (R-HSA-2892245)



Cellular compartments: nucleoplasm, cytosol, extracellular region, plasma membrane.

POU5F1 (OCT4), SOX2, and NANOG bind elements in the promoters of target genes. The target genes of each transcription factor overlap extensively: POU5F1, SOX2, and NANOG co-occupy at least 353 genes (Boyer et al. 2005). About half of POU5F1 targets also bind SOX2 and about 90% of these also bind NANOG (Boyer et al. 2005). Upon binding the transcription factors activate expression of one subset of target genes in the core transcriptional network of pluripotent stem cells and repress another subset (Kim et al. 2006, Matoba et al. 2006, Player et al. 2006, Assou et al. 2007, Babaie et al. 2007, Chavez et al. 2009, Jung et al. 2010). The target genes listed in this module are the repressed genes. Caution must be used when making inferences about human stem cells from mouse stem cells because of significant differences between the two species (Ginis et al. 2004).

References

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Player A, Wang Y, Bhattacharya B, Rao M, Puri RK & Kawasaki ES (2006). Comparisons between transcriptional regulation and RNA expression in human embryonic stem cell lines. Stem Cells Dev, 15, 315-23.

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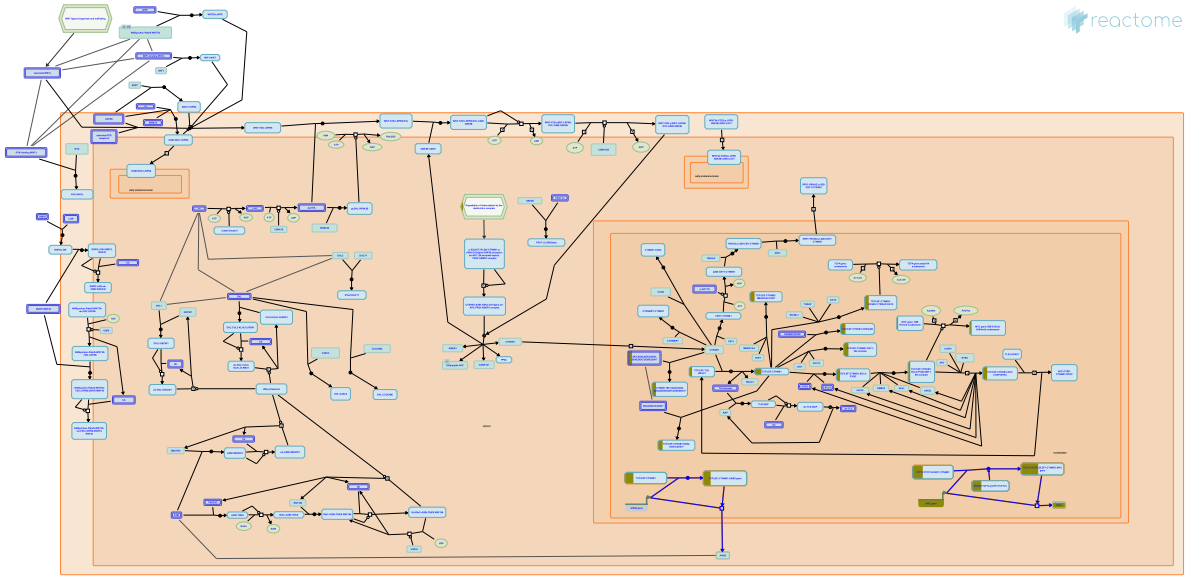
Edit history

Date	Action	Author
2013-01-01	Edited	May B
2013-01-01	Authored	May B
2013-01-02	Created	May B
2014-01-23	Reviewed	Wang J
2020-06-04	Modified	Cook J

Entities found in this pathway (3)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
NANOG	Q9H9S0	POU5F1	Q01860	SOX2	P48431

13. Binding of TCF/LEF:CTNNB1 to target gene promoters (R-HSA-4411364)



Cellular compartments: nucleoplasm.

The genes regulated by beta-catenin and TCF/LEF are involved in a diverse range of functions in cellular proliferation, differentiation, embryogenesis and tissue homeostasis, and include transcription factors, cell cycle regulators, growth factors, proteinases and inflammatory cytokines, among others (reviewed in Vlad et al, 2008). A number of WNT signaling components are themselves positively or negatively regulated targets of TCF/LEF-dependent transcription, establishing feedback loops to enhance or restrict signaling (see for instance, Khan et al 2007; Chamorro et al, 2005; Roose et al, 1999; Lustig et al, 2002). Other than a few of these general feedback targets (e.g. Axin2), most target genes are cell- and/or tissue-specific. A list of WNT/beta-catenin-dependent target genes is maintained at http://www.standford.edu/group/nusselab/cgi-bin/wnt/target_genes.

References

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Edit history

Date	Action	Author
2007-09-04	Edited	Matthews L
2013-08-24	Authored	Rothfels K
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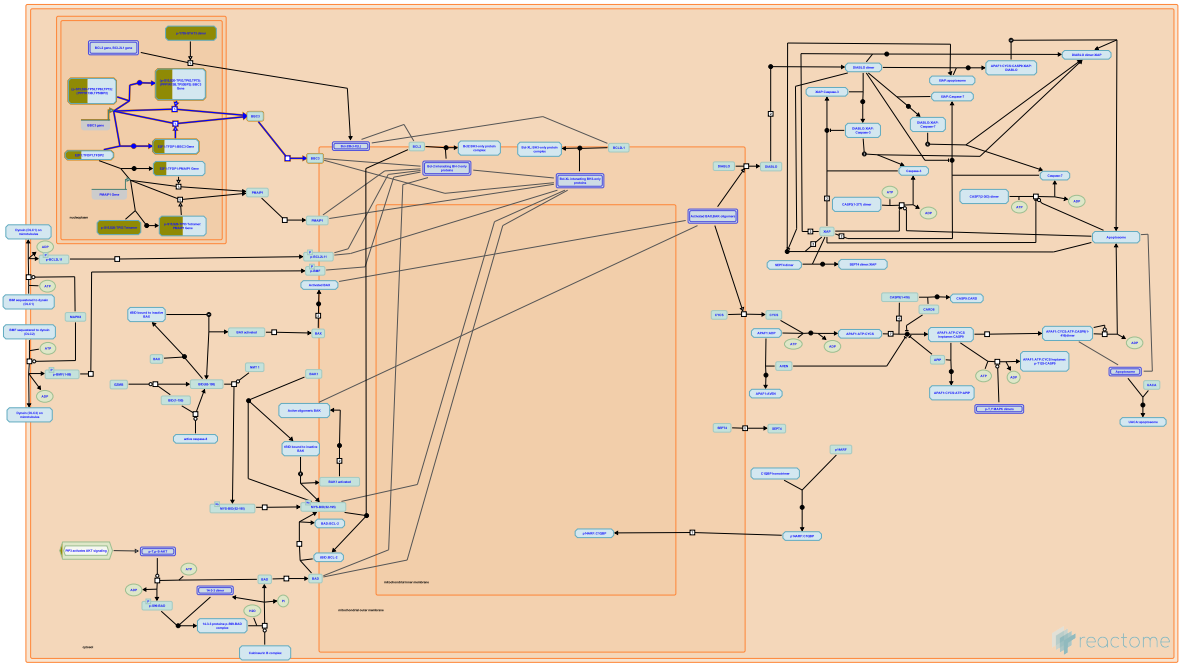
2013-10-03	Edited	Gillespie ME
2014-01-22	Reviewed	Rajakulendran N
2014-02-15	Reviewed	van Amerongen R
2014-04-22	Reviewed	Kikuchi A
2020-06-04	Modified	Cook J

Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
MYC	P01106	TCF3	Q9HCS4

Input	Ensembl Id
MYC	ENSG00000136997

14. Activation of PUMA and translocation to mitochondria (R-HSA-139915)



Cellular compartments: cytosol.

Puma is transactivated in a p53-dependent manner and by E2F1. Activated Puma is translocated to mitochondria.

References

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Hershko T & Ginsberg D (2004). Up-regulation of Bcl-2 homology 3 (BH3)-only proteins by E2F1 mediates apoptosis. J Biol Chem, 279, 8627-34.

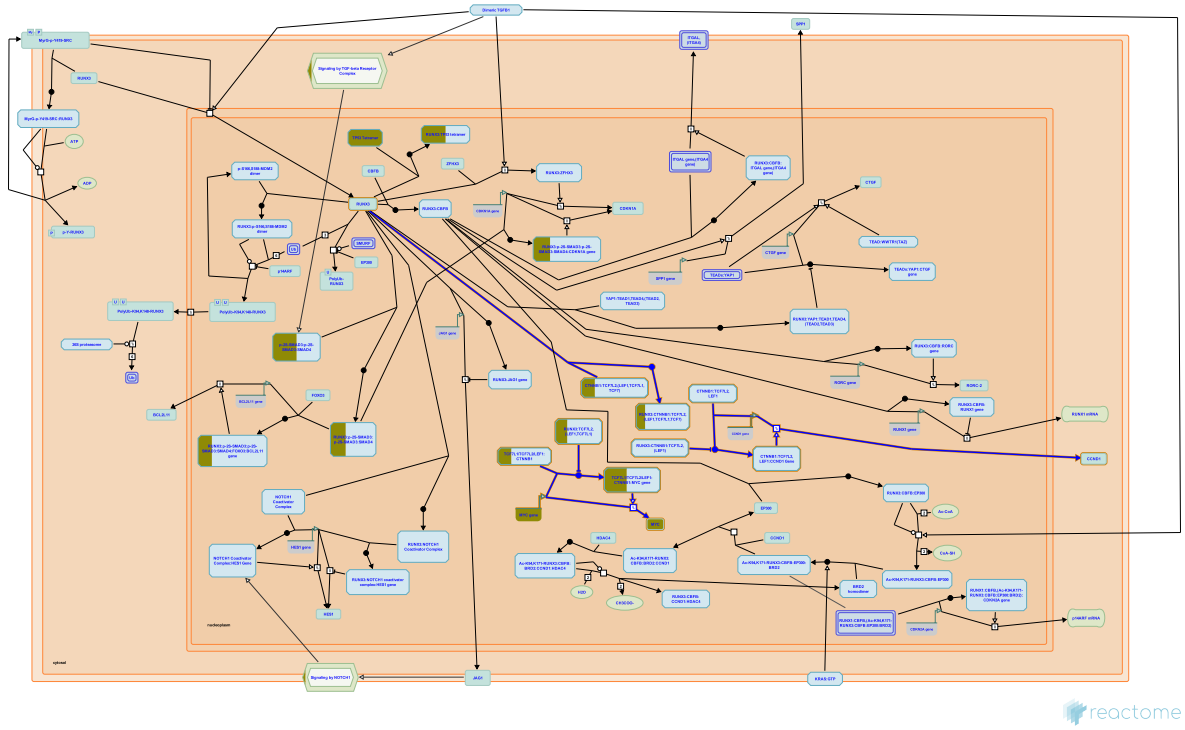
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM
2017-02-25	Modified	Orlic-Milacic M

Entities found in this pathway (3)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
E2F1	Q01094	TP53	P04637	TP63	Q9H3D4

15. RUNX3 regulates WNT signaling (R-HSA-8951430)



RUNX3 binds to complexes of beta-catenin (CTNNB1) and TCF/LEF family members. Binding of RUNX3 to CTNNB1:TCF/LEF complexes prevents their loading onto cyclin D1 (CCND1) and MYC gene promoters and interferes with WNT signaling-mediated activation of CCND1 and MYC1 transcription. RUNX3 therefore inhibits WNT-induced cellular proliferation (Ito et al. 2008).

References

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Edit history

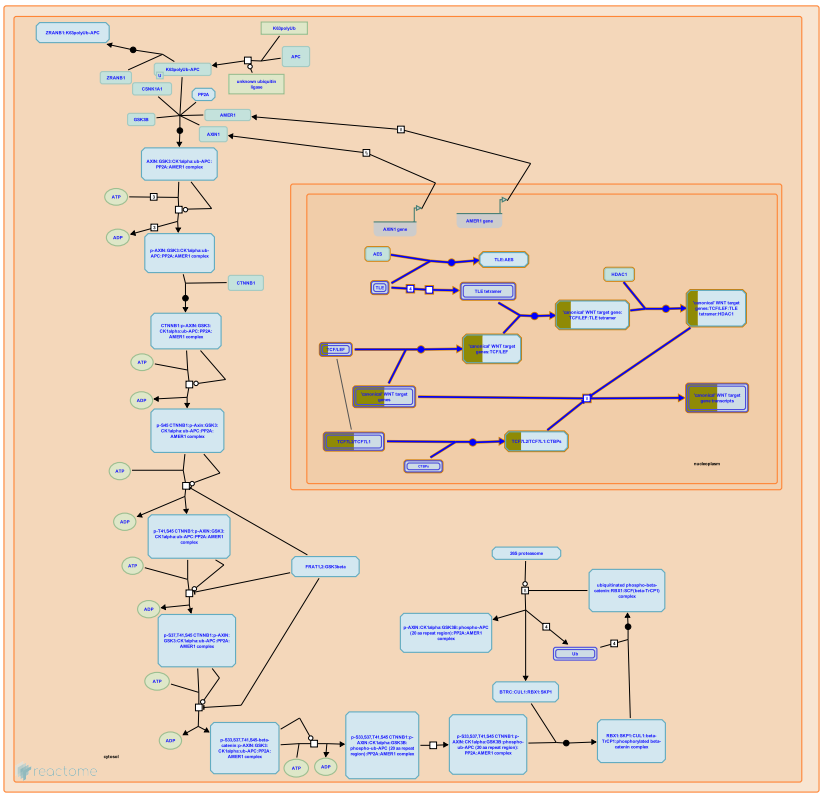
Date	Action	Author
2016-12-02	Created	Orlic-Milacic M
2016-12-13	Authored	Orlic-Milacic M
2017-01-31	Edited	Orlic-Milacic M
2017-01-31	Reviewed	Ito Y, Chuang LS
2020-06-04	Modified	Cook J

Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
MYC	P01106	TCF3	Q9HCS4

Input	Ensembl Id
MYC	ENSG00000136997

16. Repression of WNT target genes (R-HSA-4641265)



Cellular compartments: nucleoplasm.

In the absence of a WNT signal, many WNT target genes are repressed by Groucho/TLE. Groucho was initially identified in Drosophila, where it has been shown to interact with a variety of proteins to repress transcription (reviewed in Turki-Judeh and Courey, 2012). Groucho proteins, including the 4 human homologues (transducin-like enhancer of split (TLE) 1-4), do not bind DNA directly but instead are recruited to target genes through interaction with DNA-binding transcription factors including TCF/LEF (Brantjes et al, 2001; reviewed in Chen and Courey, 2000). Groucho proteins are believed to oligomerize in a manner that depends on an N-terminal glutamine-rich Q domain, and oligomerization may be important for function (Song et al, 2004; Pinto and Lobe, 1996). Groucho/TLE proteins affect levels of gene expression by interacting with the core transcriptional machinery as well as by modfiying chromatin structure through direct interaction with histones and recruitment of histone deacetylases, among other mechanisms (reviewed in Turki-Judeh and Courey, 2012). In addition to the four TLE proteins, human cells also include a truncated TLE-like protein called amino-terminal enhancer of split (AES) which contains the N-terminal Q domain but lacks much of the C-terminal sequence of TLE proteins, including the WD domain which is important for many protein-protein interactions. AES is believed to act as a dominant negative, since it is able to heter-oligomerize with full-length TLE proteins to form non-functional complexes (Brantjes et al, 2001; reviewed in Beagle and Johnson, 2010).

References

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Edit history

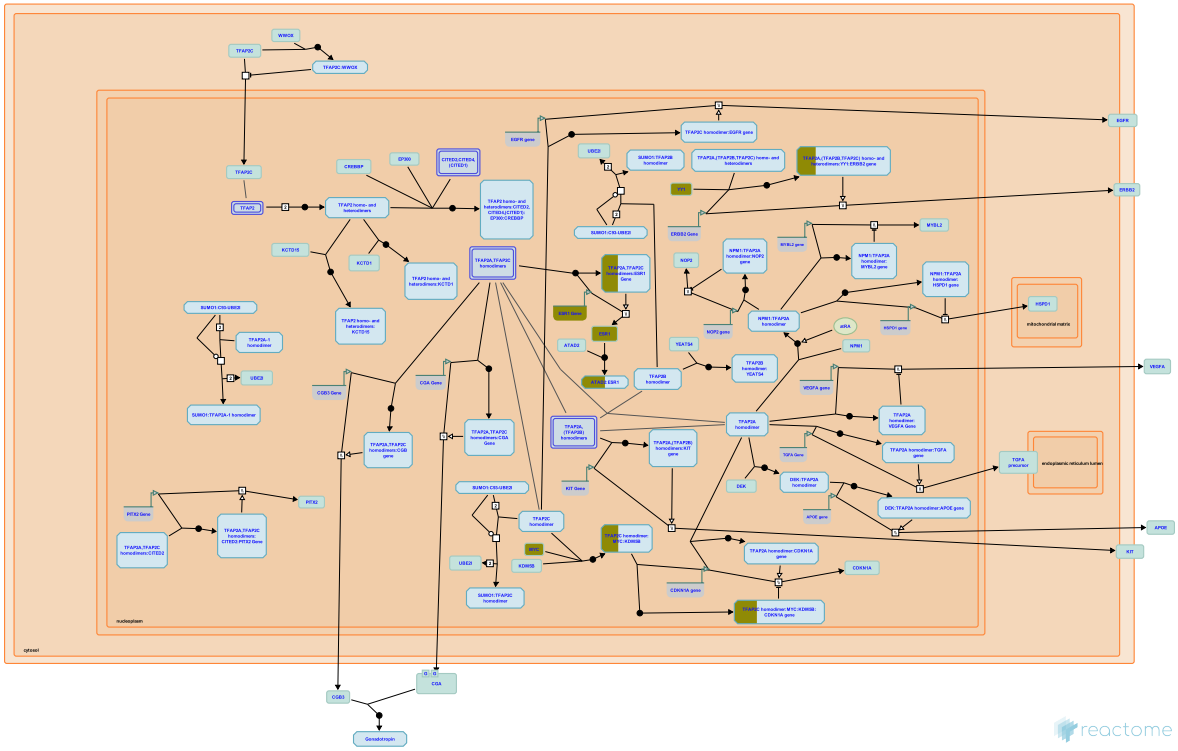
Date	Action	Author
2013-09-23	Authored	Rothfels K
2013-09-28	Created	Rothfels K
2014-01-22	Reviewed	Rajakulendran N
2014-04-03	Edited	Matthews L
2020-05-29	Modified	Cook J

Entities found in this pathway (2)

Input	UniProt Id
TCF3	Q9HCS4

Input	Ensembl Id
MYC	ENSG00000136997, ENST00000377970

17. Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors (R-HSA-8864260)



The AP-2 (TFAP2) family of transcription factors includes five proteins in mammals: TFAP2A (AP-2 alpha), TFAP2B (AP-2 beta), TFAP2C (AP-2 gamma), TFAP2D (AP-2 delta) and TFAP2E (AP-2 epsilon). The AP-2 family transcription factors are evolutionarily conserved in metazoans and are characterized by a helix-span-helix motif at the C-terminus, a central basic region, and the transactivation domain at the N-terminus. The helix-span-helix motif and the basic region enable dimerization and DNA binding (Eckert et al. 2005).

AP-2 dimers bind palindromic GC-rich DNA response elements that match the consensus sequence 5'-GCCNNNGGC-3' (Williams and Tjian 1991a, Williams and Tjian 1991b). Transcriptional co-factors from the CITED family interact with the helix-span-helix (HSH) domain of TFAP2 (AP-2) family of transcription factors and recruit transcription co-activators EP300 (p300) and CREBBP (CBP) to TFAP2-bound DNA elements. CITED2 shows the highest affinity for TFAP2 proteins, followed by CITED4, while CITED1 interacts with TFAP2s with a very low affinity. Mouse embryos defective for CITED2 exhibit neural crest defects, cardiac malformations and adrenal agenesis, which can at least in part be attributed to a defective Tfap2 transactivation (Bamforth et al. 2001, Braganca et al. 2002, Braganca et al. 2003). Transcriptional activity of AP-2 dimers in inhibited by binding of KCTD1 or KCTD15 to the AP-2 transactivation domain (Ding et al. 2009, Zarelli and Dawid 2013). Transcriptional activity of TFAP2A, TFAP2B and TFAP2C is negatively regulated by SUMOylation mediated by UBE2I (UBC9) (Eloranta and Hurst 2002, Berlato et al. 2011, Impens et al. 2014, Bogachek et al. 2014).

During embryonic development, AP-2 transcription factors stimulate proliferation and suppress terminal differentiation in a cell-type specific manner (Eckert et al. 2005).

TFAP2A and TFAP2C directly stimulate transcription of the estrogen receptor ESR1 gene (McPherson and Weigel 1999). TFAP2A expression correlates with ESR1 expression in breast cancer, and TFAP2C is frequently overexpressed in estrogen-positive breast cancer and endometrial cancer (deConinck et al. 1995, Turner et al. 1998). TFAP2A, TFAP2C, as well as TFAP2B can directly stimulate the expression of ERBB2, another important breast cancer gene (Bosher et al. 1996). Association of TFAP2A with the YY1 transcription factor significantly increases the ERBB2 transcription rate (Begon et al. 2005). In addition to ERBB2, the expression of another receptor tyrosine kinase, KIT, is also stimulated by TFAP2A and TFAP2B (Huang et al. 1998), while the expression of the VEGF receptor tyrosine kinase ligand VEGFA is repressed by TFAP2A (Ruiz et al. 2004, Li et al. 2012). TFAP2A stimulates transcription of the transforming growth factor alpha (TGFA) gene (Wang et al. 1997). TFAP2C regulates EGFR in luminal breast cancer (De Andrade et al. 2016).

TFAP2C plays a critical role in maintaining the luminal phenotype in human breast cancer and in influencing the luminal cell phenotype during normal mammary development (Cyr et al. 2015).

In placenta, TFAP2A and TFAP2C directly stimulate transcription of both subunits of the human chorionic gonadotropin, CGA and CGB (Johnson et al. 1997, LiCalsi et al. 2000).

TFAP2A and/or TFAP2C, in complex with CITED2, stimulate transcription of the PITX2 gene, involved in left-right patterning and heart development (Bamforth et al. 2004, Li et al. 2012).

TFAP2A and TFAP2C play opposing roles in transcriptional regulation of the CDKN1A (p21) gene locus. While TFAP2A stimulates transcription of the CDKN1A cyclin-dependent kinase inhibitor (Zeng et al. 1997, Williams et al. 2009, Scibetta et al. 2010), TFAP2C represses CDKN1A transcription (Williams et al. 2009, Scibetta et al. 2010, Wong et al. 2012). Transcription of the TFAP2A gene may be inhibited by CREB and E2F1 (Melnikova et al. 2010).

For review of the AP-2 family of transcription factors, please refer to Eckert et al. 2005.

References

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Edit history

Date	Action	Author
2016-03-14	Edited	Orlic-Milacic M
2016-03-14	Authored	Orlic-Milacic M

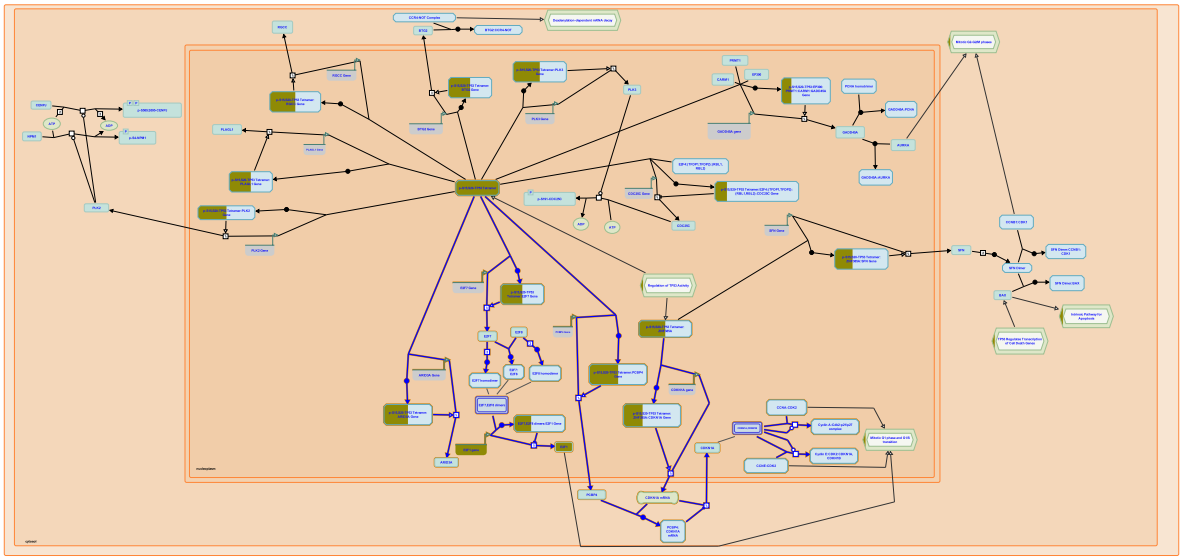
Date	Action	Author
2016-03-14	Created	Orlic-Milacic M
2016-05-04	Reviewed	Dawid IB, Zarelli VE
2016-05-17	Reviewed	Bogachek MV, Weigel RJ
2020-05-29	Modified	Cook J

Entities found in this pathway (3)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ESR1	P03372	MYC	P01106	YY1	P25490

Input	Ensembl Id
ESR1	ENSG00000091831

18. TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest (R-HSA-6804116)



The most prominent TP53 target involved in G1 arrest is the inhibitor of cyclin-dependent kinases CDKN1A (p21). CDKN1A is one of the earliest genes induced by TP53 (El-Deiry et al. 1993). CDKN1A binds and inactivates CDK2 in complex with cyclin A (CCNA) or E (CCNE), thus preventing G1/S transition (Harper et al. 1993). Considering its impact on the cell cycle outcome, CDKN1A expression levels are tightly regulated. For instance, under prolonged stress, TP53 can induce the transcription of an RNA binding protein PCBP4, which can bind and destabilize CDKN1A mRNA, thus alleviating G1 arrest and directing the affected cell towards G2 arrest and, possibly, apoptosis (Zhu and Chen 2000, Scoumanne et al. 2011). Expression of E2F7 is directly induced by TP53. E2F7 contributes to G1 cell cycle arrest by repressing transcription of E2F1, a transcription factor that promotes expression of many genes needed for G1/S transition (Aksoy et al. 2012, Carvajal et al. 2012). ARID3A is a direct transcriptional target of TP53 (Ma et al. 2003) that may promote G1 arrest by cooperating with TP53 in induction of CDKN1A transcription (Lestari et al. 2012). However, ARID3A may also promote G1/S transition by stimulating transcriptional activity of E2F1 (Suzuki et al. 1998, Peeper et al. 2002).

TP53 has co-factors that are key determinants of transcriptional selectivity within the p53 network. For instance, the zinc finger transcription factor ZNF385A (HZF) is a direct transcriptional target of TP53 that can form a complex with TP53 and facilitate TP53-mediated induction of CDKN1A, strongly favouring cell cycle arrest over apoptosis (Das et al. 2007).

References

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Edit history

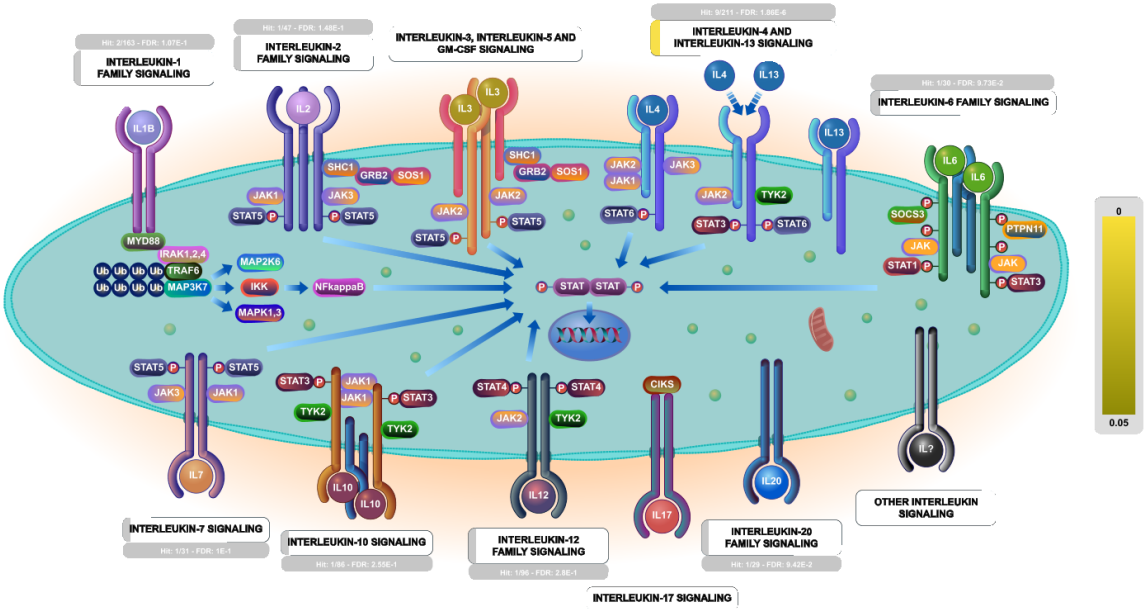
Date	Action	Author
2015-10-08	Created	Orlic-Milacic M
2015-10-14	Edited	Orlic-Milacic M
2015-10-14	Authored	Orlic-Milacic M
2016-02-04	Reviewed	Zaccara S, Inga A
2017-01-03	Revised	Orlic-Milacic M
2020-06-04	Modified	Cook J

Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
E2F1	Q01094	TP53	P04637

Input	Ensembl Id
E2F1	ENSG00000101412

19. Signaling by Interleukins (R-HSA-449147)



Cellular compartments: plasma membrane.

Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

References

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Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, ... Akdis CA (2016). Interleukins (from IL-1 to IL-38), interferons, transforming growth factor , and TNF-: Receptors, functions, and roles in diseases. J. Allergy Clin. Immunol., 138, 984-1010.

Edit history

Date	Action	Author
2009-11-27	Created	Jupe S
2010-05-17	Reviewed	Pinteaux E
2010-05-17	Authored	Ray KP
2010-05-26	Edited	Jupe S
2020-05-29	Modified	Cook J

Entities found in this pathway (6)

Input	UniProt Id
MYC	P01106
SOX2	P48431

Input	UniProt Id
NANOG	Q9H9S0
STAT3	P40763

Input	UniProt Id
RELA	Q04206
TP53	P04637

Input	Ensembl Id
MYC	ENSG00000136997
SOX2	ENSG00000181449

Input	Ensembl Id
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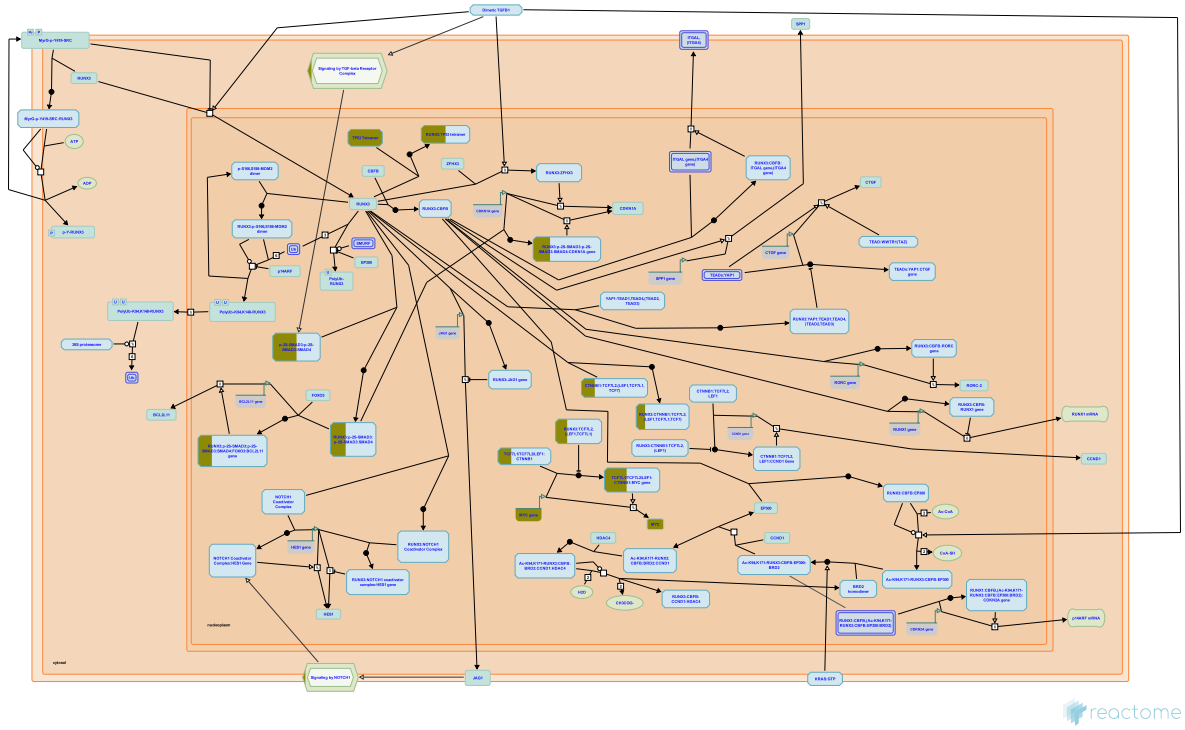
TP53	ENSG00000141510

20. Transcriptional regulation by RUNX3 (R-HSA-8878159)



The transcription factor RUNX3 is a RUNX family member. All RUNX family members, RUNX1, RUNX2 and RUNX3, possess a highly conserved Runt domain, involved in DNA binding. For a more detailed description of the structure of RUNX proteins, please refer to the pathway 'Transcriptional regulation by RUNX1'. Similar to RUNX1 and RUNX2, RUNX3 forms a transcriptionally active heterodimer with CBFB (CBF-beta). Studies in mice have shown that RUNX3 plays a role in neurogenesis and development of T lymphocytes. RUNX3 is implicated as a tumor suppressor gene in various human malignancies.

During nervous system formation, the Cbfb:Runx3 complex is involved in development of mouse proprioceptive dorsal root ganglion neurons by regulating expression of Ntrk3 (Neurotrophic tyrosine kinase receptor type 3) and possibly other genes (Inoue et al. 2002, Kramer et al. 2006, Nakamura et al. 2008, Dykes et al. 2011, Ogihara et al. 2016). It is not yet known whether RUNX3 is involved in human neuronal development and neuronal disorders.

RUNX3 plays a major role in immune response. RUNX3 regulates development of T lymphocytes. In mouse hematopoietic stem cells, expression of Runx3 is regulated by the transcription factor TAL1 (Landry et al. 2008). RUNX3 promotes the CD8+ lineage fate in developing thymocytes. In the CD4+ thymocyte lineage in mice, the transcription factor ThPOK induces transcription of SOCS family members, which repress Runx3 expression (Luckey et al. 2014). RUNX3, along with RUNX1 and ETS1, is implicated in regulation of transcription of the CD6 gene, encoding a lymphocyte surface receptor expressed on developing and mature T cells (Arman et al. 2009). RUNX3 and ThPOK regulate intestinal CD4+ T cell immunity in a TGF-beta and retinoic acid-dependent manner, which is important for cellular defense against intestinal pathogens (Reis et al. 2013). Besides T lymphocytes, RUNX3 is a key transcription factor in the commitment of innate lymphoid cells ILC1 and ILC3 (Ebihara et al. 2015). RUNX3 regulates expression of CD11A and CD49D integrin genes, involved in immune and inflammatory responses (Dominguez-Soto et al. 2005). RUNX3 is involved in mouse TGF-beta-mediated dendritic cell function and its deficiency is linked to airway inflammation (Fainaru et al. 2004).

In addition to its developmental role, RUNX3 is implicated as a tumor suppressor. The loss of RUNX3 expression and function was first causally linked to the genesis and progression of human gastric cancer (Li et al. 2002). Expression of RUNX3 increases in human pancreatic islet of Langerhans cells but not in pancreatic adenocarcinoma cells in response to differentiation stimulus (serum withdrawal) (Levkovitz et al. 2010). Hypermethylation of the RUNX3 gene is associated with an increased risk for progression of Barrett's esophagus to esophageal adenocarcinoma (Schulmann et al. 2005). Hypermethylation-mediated silencing of the RUNX3 gene expression is also frequent in granulosa cell tumors (Dhillon et al. 2004) and has also been reported in colon cancer (Weisenberger et al. 2006), breast cancer (Lau et al. 2006, Huang et al. 2012), bladder cancer (Wolff et al. 2008) and gastric cancer (Li et al. 2002). In colorectal cancer, RUNX3 is one of the five markers in a gene panel used to classify CpG island methylator phenotype (CIMP+) (Weisenberger et al. 2006).

RUNX3 and CBFB are frequently downregulated in gastric cancer. RUNX3 cooperates with TGF-beta to maintain homeostasis in the stomach and is involved in TGF-beta-induced cell cycle arrest of stomach epithelial cells. Runx3 knockout mice exhibit decreased sensitivity to TGF-beta and develop gastric epithelial hyperplasia (Li et al. 2002, Chi et al. 2005). RUNX3-mediated inhibition of binding of TEADs:YAP1 complexes to target promoters is also implicated in gastric cancer suppression (Qiao et al. 2016).

RUNX3 is a negative regulator of NOTCH signaling and RUNX3-mediated inhibition of NOTCH activity may play a tumor suppressor role in hepatocellular carcinoma (Gao et al. 2010, Nishina et al. 2011).

In addition to RUNX3 silencing through promoter hypermethylation in breast cancer (Lau et al. 2006), Runx3+/- mice are predisposed to breast cancer development. RUNX3 downregulates estrogen receptor alpha (ESR1) protein levels in a proteasome-dependent manner (Huang et al. 2012).

Besides its tumor suppressor role, mainly manifested through its negative effect on cell proliferation, RUNX3 can promote cancer cell invasion by stimulating expression of genes involved in metastasis, such as osteopontin (SPP1) (Whittle et al. 2015).

References

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Dykes IM, Tempest L, Lee SI & Turner EE (2011). Brn3a and Islet1 act epistatically to regulate the gene expression program of sensory differentiation. J. Neurosci., 31, 9789-99.

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Edit history

Date	Action	Author
2016-06-30	Created	Orlic-Milacic M
2016-12-13	Authored	Orlic-Milacic M
2017-01-31	Edited	Orlic-Milacic M
2017-01-31	Reviewed	Ito Y, Chuang LS
2020-05-29	Modified	Cook J

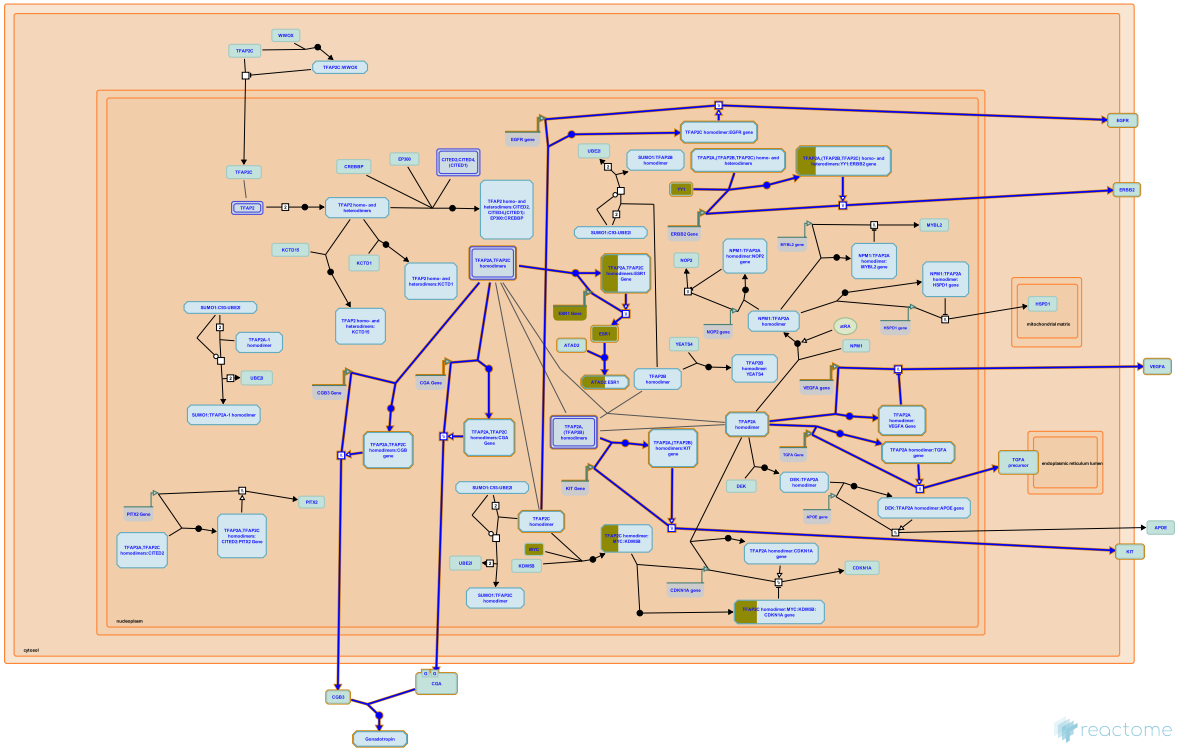
Entities found in this pathway (4)

Input	UniProt Id
MYC	P01106
TCF3	Q9HCS4

Input	UniProt Id
SMAD4	Q13485
TP53	P04637

Input	Ensembl Id
MYC	ENSG00000136997

21. TFAP2 (AP-2) family regulates transcription of growth factors and their receptors (R-HSA-8866910)



TFAP2A and TFAP2C directly stimulate transcription of the estrogen receptor ESR1 gene (McPherson and Weigel 1999). TFAP2A expression correlates with ESR1 expression in breast cancer, and TFAP2C is frequently overexpressed in estrogen-positive breast cancer and endometrial cancer (deConinck et al. 1995, Turner et al. 1998). TFAP2A, TFAP2C, as well as TFAP2B can directly stimulate the expression of ERBB2, another important breast cancer gene (Bosher et al. 1996). Association of TFAP2A with the YY1 transcription factor significantly increases the ERBB2 transcription rate (Begon et al. 2005). In addition to ERBB2, the expression of another receptor tyrosine kinase, KIT, is also stimulated by TFAP2A and TFAP2B (Huang et al. 1998), while the expression of the VEGF receptor tyrosine kinase ligand VEGFA is repressed by TFAP2A (Ruiz et al. 2004, Li et al. 2012). TFAP2A stimulates transcription of the transforming growth factor alpha (TGFA) gene (Wang et al. 1997). TFAP2C regulates EGFR expression in luminal breast cancer (De Andrade et al. 2016). In placenta, TFAP2A and TFAP2C directly stimulate transcription of both subunits of the human chorionic gonadotropin, CGA and CGB (Johnson et al. 1997, LiCalsi et al. 2000).

References

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Johnson W, Albanese C, Handwerger S, Williams T, Pestell RG & Jameson JL (1997). Regulation of the human chorionic gonadotropin alpha- and beta-subunit promoters by AP-2. J. Biol. Chem., 272, 15405-12.

LiCalsi C, Christophe S, Steger DJ, Buescher M, Fischer W & Mellon PL (2000). AP-2 family members regulate basal and cAMP-induced expression of human chorionic gonadotropin. Nucleic Acids Res., 28, 1036-43.

Edit history

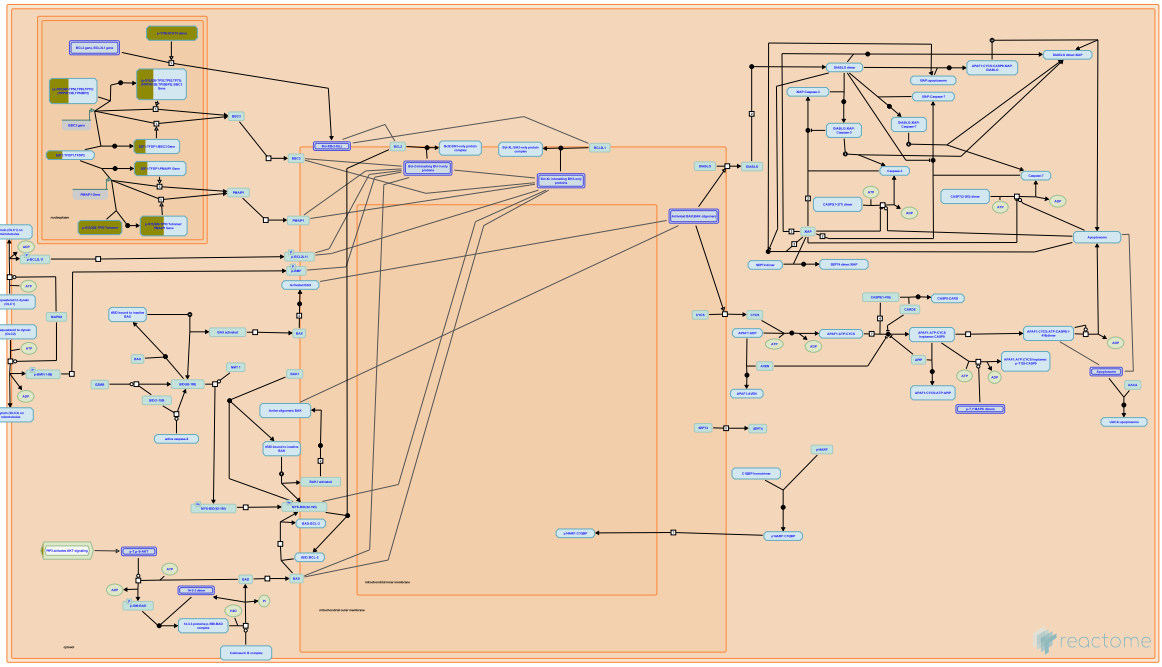
Date	Action	Author
2016-03-14	Edited	Orlic-Milacic M
2016-03-14	Authored	Orlic-Milacic M
2016-04-04	Created	Orlic-Milacic M
2016-05-04	Reviewed	Dawid IB, Zarelli VE
2016-05-17	Reviewed	Bogachek MV, Weigel RJ
2020-05-29	Modified	Cook J

Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
ESR1	P03372	YY1	P25490

Input	Ensembl Id
ESR1	ENSG00000091831

22. Intrinsic Pathway for Apoptosis (R-HSA-109606)



The intrinsic (Bcl-2 inhibitable or mitochondrial) pathway of apoptosis functions in response to various types of intracellular stress including growth factor withdrawal, DNA damage, unfolding stresses in the endoplasmic reticulum and death receptor stimulation. Following the reception of stress signals, proapoptotic BCL-2 family proteins are activated and subsequently interact with and inactivate antiapoptotic BCL-2 proteins. This interaction leads to the destabilization of the mitochondrial membrane and release of apoptotic factors. These factors induce the caspase proteolytic cascade, chromatin condensation, and DNA fragmentation, ultimately leading to cell death. The key players in the Intrinsic pathway are the Bcl-2 family of proteins that are critical death regulators residing immediately upstream of mitochondria. The Bcl-2 family consists of both anti- and proapoptotic members that possess conserved alpha-helices with sequence conservation clustered in BCL-2 Homology (BH) domains. Proapoptotic members are organized as follows:

1. "Multidomain" BAX family proteins such as BAX, BAK etc. that display sequence conservation in their BH1-3 regions. These proteins act downstream in mitochondrial disruption.

2. "BH3-only" proteins such as BID,BAD, NOXA, PUMA,BIM, and BMF have only the short BH3 motif. These act upstream in the pathway, detecting developmental death cues or intracellular damage. Anti-apoptotic members like Bcl-2, Bcl-XL and their relatives exhibit homology in all segments BH1-4. One of the critical functions of BCL-2/BCL-XL proteins is to maintain the integrity of the mitochondrial outer membrane.

References

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Edit history

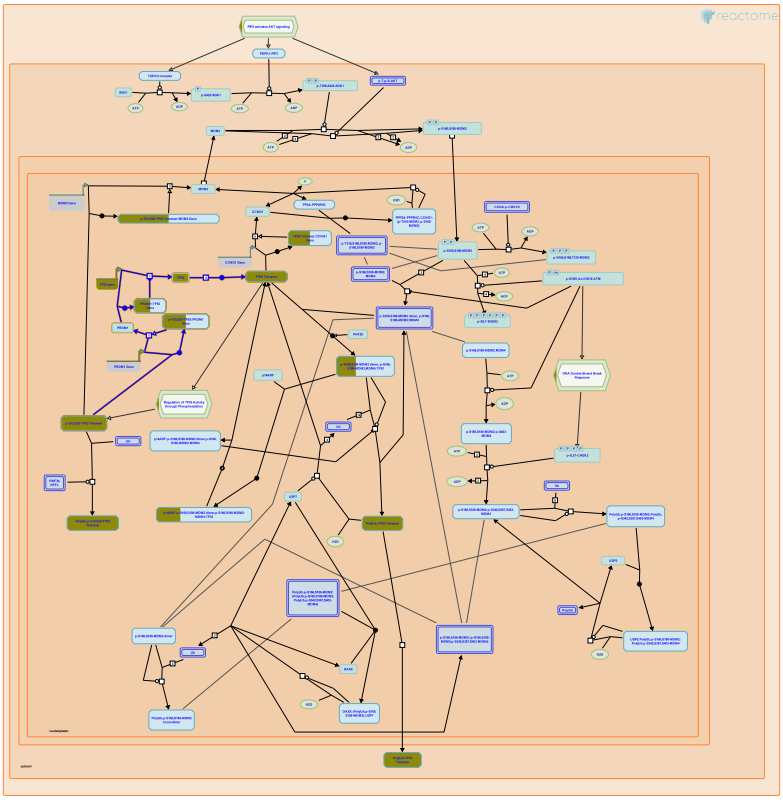
Date	Action	Author
2004-02-17	Created	Alnemri E
2004-08-06	Authored	Matthews L
2020-05-29	Modified	Cook J

Entities found in this pathway (4)

Input	UniProt Id
E2F1	Q01094
TP53	P04637

Input	UniProt Id
STAT3	P40763
TP63	Q9H3D4

23. Regulation of TP53 Expression (R-HSA-6804754)



Transcription of the TP53 (p53) gene is negatively regulated by the TP53 transcriptional target PRDM1 (BLIMP1), which binds to the promoter region of TP53 and probably induces repressive methylation (Yan et al. 2007).

TP53 functions as a homotetramer (Jeffrey et al. 1995, Waterman et al. 1995).

References

Yan J, Jiang J, Lim CA, Wu Q, Ng HH & Chin KC (2007). BLIMP1 regulates cell growth through repression of p53 transcription. Proc. Natl. Acad. Sci. U.S.A., 104, 1841-6.

Jeffrey PD, Gorina S & Pavletich NP (1995). Crystal structure of the tetramerization domain of the p53 tumor suppressor at 1.7 angstroms. Science, 267, 1498-502.

Waterman JL, Shenk JL & Halazonetis TD (1995). The dihedral symmetry of the p53 tetramerization domain mandates a conformational switch upon DNA binding. EMBO J., 14, 512-9.

Edit history

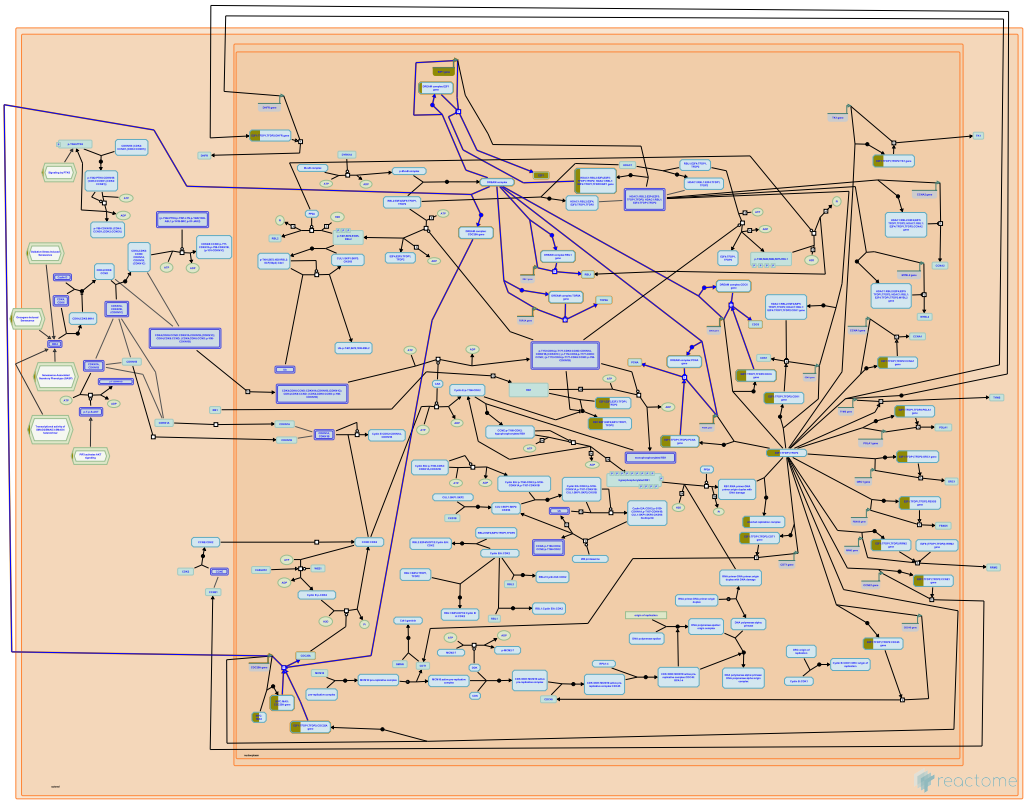
Date	Action	Author
2015-10-14	Edited	Orlic-Milacic M
2015-10-14	Authored	Orlic-Milacic M
2015-10-14	Created	Orlic-Milacic M
2016-02-04	Reviewed	Zaccara S, Inga A
2020-06-04	Modified	Cook J

Entities found in this pathway (1)

Input	UniProt Id
TP53	P04637

Input	Ensembl Id
TP53	ENSG00000141510

24. Transcription of E2F targets under negative control by DREAM complex (R-HSA-1362277)



Cellular compartments: nucleoplasm.

DREAM complex is evolutionarily conserved and is reponsible for transcriptional repressession of cell cycle-regulated genes in G0 and early G1.

References

Litovchick L, Sadasivam S, Florens LA, Zhu X, Swanson SK, Velmurugan S, ... DeCaprio JA (2007). Evolutionarily conserved multisubunit RBL2/p130 and E2F4 protein complex represses human cell cycle-dependent genes in quiescence. Mol Cell, 26, 539-51.

Edit history

Date	Action	Author
2011-06-08	Created	Orlic-Milacic M
2011-06-14	Authored	Orlic-Milacic M
2011-08-25	Reviewed	MacPherson D
2017-02-17	Modified	Orlic-Milacic M

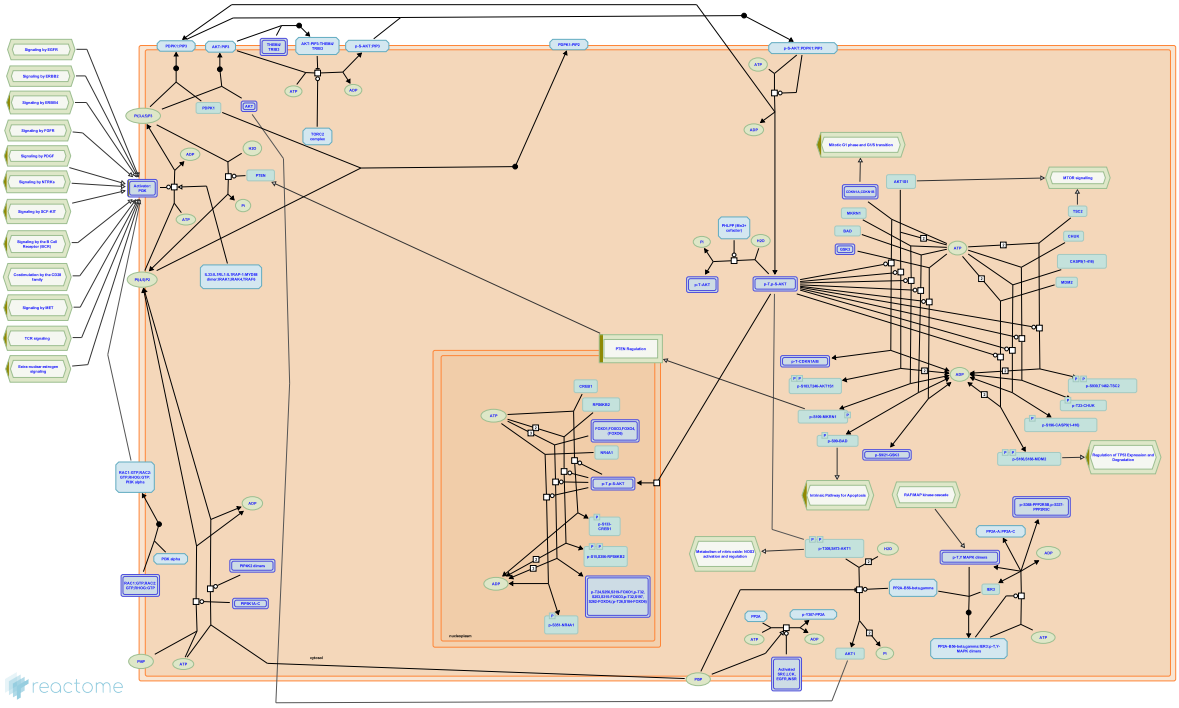
Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
E2F1	Q01094	MYC	P01106

Input	Ensembl Id
E2F1	ENSG00000101412

Input	Ensembl Id

25. PIP3 activates AKT signaling (R-HSA-1257604)



Signaling by AKT is one of the key outcomes of receptor tyrosine kinase (RTK) activation. AKT is activated by the cellular second messenger PIP3, a phospholipid that is generated by PI3K. In ustimulated cells, PI3K class IA enzymes reside in the cytosol as inactive heterodimers composed of p85 regulatory subunit and p110 catalytic subunit. In this complex, p85 stabilizes p110 while inhibiting its catalytic activity. Upon binding of extracellular ligands to RTKs, receptors dimerize and undergo autophosphorylation. The regulatory subunit of PI3K, p85, is recruited to phosphorylated cytosolic RTK domains either directly or indirectly, through adaptor proteins, leading to a conformational change in the PI3K IA heterodimer that relieves inhibition of the p110 catalytic subunit. Activated PI3K IA phosphorylates PIP2, converting it to PIP3; this reaction is negatively regulated by PTEN phosphatase. PIP3 recruits AKT to the plasma membrane, allowing TORC2 to phosphorylate a conserved serine residue of AKT. Phosphorylation of this serine induces a conformation change in AKT, exposing a conserved threonine residue that is then phosphorylated by PDPK1 (PDK1). Phosphorylation of both the threonine and the serine residue is required to fully activate AKT. The active AKT then dissociates from PIP3 and phosphorylates a number of cytosolic and nuclear proteins that play important roles in cell survival and metabolism. For a recent review of AKT signaling, please refer to Manning and Cantley, 2007.

References

Edit history

Date	Action	Author
2007-11-08	Reviewed	Greene LA
2011-05-02	Created	Orlic-Milacic M
2012-06-21	Revised	Orlic-Milacic M
2012-08-13	Reviewed	Yuzugullu H, Thorpe L, Zhao JJ
2020-05-29	Modified	Cook J

Entities found in this pathway (5)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ESR1	P03372, P03372-3, P03372-4	PPARG	P37231	RCOR1	Q9UKL0
SALL4	Q9UJQ4	TP53	P04637		

6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

Entities (24)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AR	P10275	CHD1	O14646	CTCF	P49711
E2F1	Q01094	ESR1	P03372	GATA2	P23769
KLF4	O43474	MYC	P01106	NANOG	Q9H9S0
POU5F1	Q01860	PPARG	P37231	RCOR1	Q9UKL0
RELA	Q04206	SALL4	Q9UJQ4	SMAD4	Q13485
SOX2	P48431	STAT3	P40763	TAF1	P21675, Q8IZX4
TCF3	P15923	TP53	P04637	TP63	Q9H3D4
UBTF	P17480	YY1	P25490	ZNF384	Q8TAQ5

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CHD1	ENSG00000153922, ENST00000284049.7	E2F1	ENSG00000101412	ESR1	ENSG00000091831
KLF4	ENSG00000136826	MYC	ENSG00000136997	NANOG	ENSG00000111704
POU5F1	ENSG00000204531, ENST00000259915	PPARG	ENSG00000132170	SALL4	ENSG00000101115
SOX2	ENSG00000181449	STAT3	ENSG00000168610	TP53	ENSG00000141510

7. Identifiers not found

These 3 identifiers were not found neither mapped to any entity in Reactome.

NFE2L2 PBX3 ZBTB7A