



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 83 on 10/03/2023. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMzAzMTAxMzM0NDZfNDI2NjM%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.

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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:

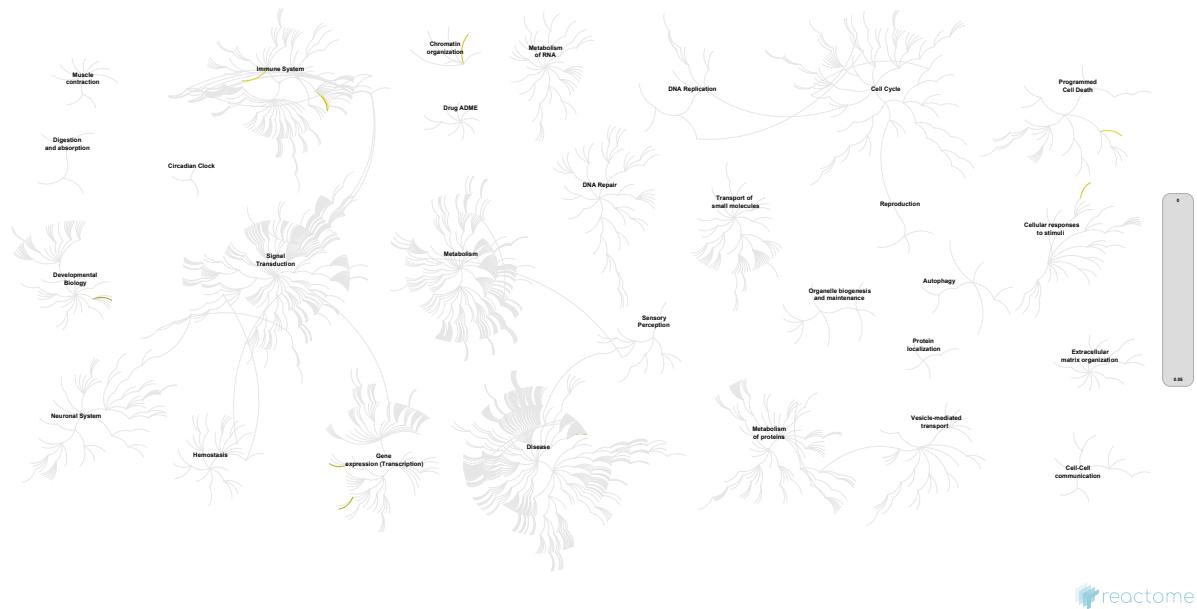
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 54 out of 155 identifiers in the sample were found in Reactome, where 387 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 MjAyMzMzAzMTAxMzM0NDZfNDI2NjM%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
Interleukin-7 signaling	5 / 31	0.002	2.55e-05	0.01	14 / 26	0.002
Butyrophilin (BTN) family interactions	2 / 12	7.87e-04	0.008	0.537	2 / 8	5.65e-04
Apoptosis induced DNA fragmentation	2 / 13	8.53e-04	0.009	0.537	2 / 12	8.48e-04
Formation of Senescence-Associated Heterochromatin Foci (SAHF)	2 / 17	0.001	0.015	0.537	1 / 2	1.41e-04
PKMTs methylate histone lysines	3 / 51	0.003	0.018	0.537	17 / 22	0.002
Other interleukin signaling	2 / 24	0.002	0.028	0.537	2 / 17	0.001
RNA Polymerase I Promoter Escape	3 / 61	0.004	0.029	0.537	2 / 2	1.41e-04
B-WICH complex positively regulates rRNA expression	3 / 62	0.004	0.03	0.537	3 / 3	2.12e-04
Variant SLC6A20 contributes towards hyperglycinuria (HG) and iminoglycinuria (IG)	1 / 3	1.97e-04	0.032	0.537	1 / 1	7.07e-05
Variant SLC6A20 contributes towards hyperglycinuria (HG) and iminoglycinuria (IG)	1 / 3	1.97e-04	0.032	0.537	1 / 1	7.07e-05
Formation of paraxial mesoderm	2 / 28	0.002	0.037	0.537	9 / 12	8.48e-04
RNA Polymerase I Transcription Termination	2 / 33	0.002	0.05	0.537	3 / 4	2.83e-04
RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	3 / 78	0.005	0.054	0.537	20 / 33	0.002
Positive epigenetic regulation of rRNA expression	3 / 80	0.005	0.057	0.537	5 / 7	4.95e-04
NoRC negatively regulates rRNA expression	3 / 80	0.005	0.057	0.537	4 / 7	4.95e-04
Activation of the pre-replicative complex	2 / 36	0.002	0.059	0.537	7 / 9	6.36e-04
RNA Polymerase I Promoter Clearance	3 / 85	0.006	0.066	0.537	6 / 10	7.07e-04
Activation of ATR in response to replication stress	2 / 39	0.003	0.067	0.537	2 / 9	6.36e-04
RNA Polymerase I Transcription	3 / 87	0.006	0.069	0.537	9 / 14	9.89e-04
Negative epigenetic regulation of rRNA expression	3 / 89	0.006	0.073	0.537	7 / 12	8.48e-04
RAS signaling downstream of NF1 loss-of-function variants	1 / 9	5.91e-04	0.093	0.537	1 / 1	7.07e-05

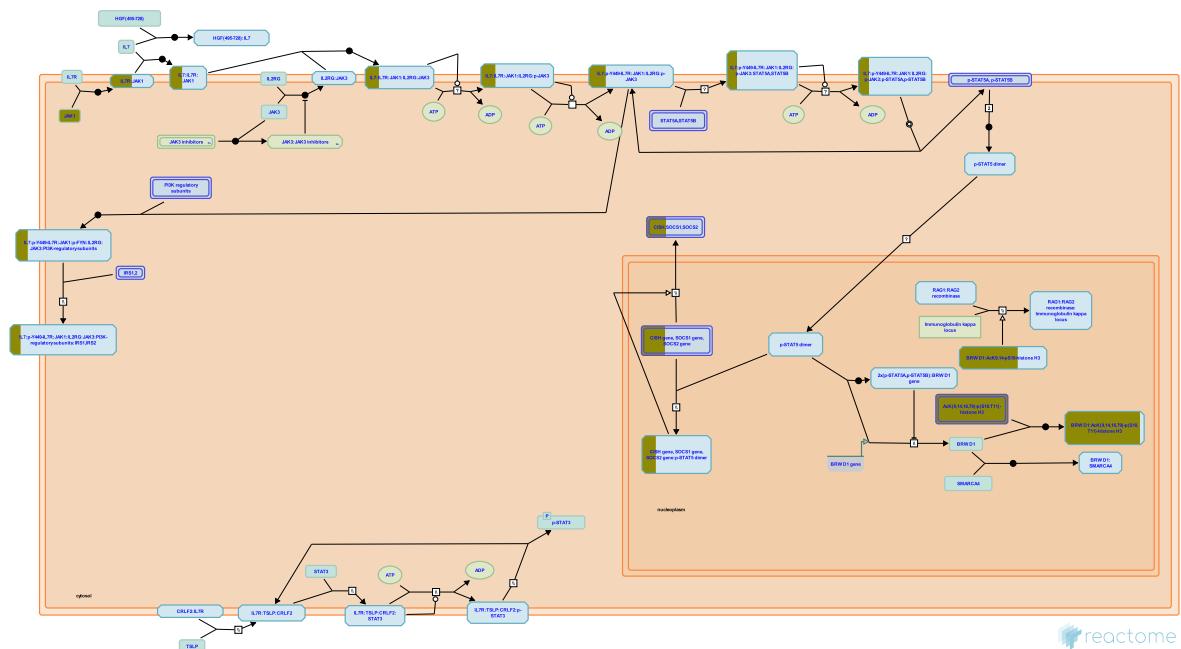
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Disinhibition of SNARE formation	1 / 10	6.56e-04	0.103	0.537	1 / 2	1.41e-04
RNA Polymerase I Transcription Initiation	2 / 50	0.003	0.103	0.537	3 / 6	4.24e-04
TBC/RABGAPs	2 / 51	0.003	0.106	0.537	2 / 14	9.89e-04
Interleukin-9 signaling	1 / 11	7.22e-04	0.112	0.537	7 / 13	9.19e-04

* 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. Interleukin-7 signaling (R-HSA-1266695)



Interleukin-7 (IL7) is produced primarily by T zone fibroblastic reticular cells found in lymphoid organs, and also expressed by non-hematopoietic stromal cells present in other tissues including the skin, intestine and liver. It is an essential survival factor for lymphocytes, playing a key anti-apoptotic role in T-cell development, as well as mediating peripheral T-cell maintenance and proliferation. This dual function is reflected in a dose-response relationship that distinguishes the survival function from the proliferative activity; low doses of IL7 (<1 ng/ml) sustain only survival, higher doses (>1 ng/ml) promote survival and cell cycling (Kittipatarin et al. 2006, Swainson et al. 2007).

The IL7 receptor is a heterodimeric complex of the common cytokine-receptor gamma chain (IL2RG, CD132, or Gc) and the IL7-receptor alpha chain (IL7R, IL7RA, CD127). Both chains are members of the type 1 cytokine family. Neither chain is unique to the IL7 receptor as IL7R is utilized by the receptor for thymic stromal lymphopoietin (TSLP) while IL2RG is shared with the receptors for IL2, IL4, IL9, IL15 and IL21. IL2RG consists of a single transmembrane region and a 240aa extracellular region that includes a fibronectin type III (FNIII) domain thought to be involved in receptor complex formation. It is expressed on most lymphocyte populations. Null mutations of IL2RG in humans cause X-linked severe combined immunodeficiency (X-SCID), which has a phenotype of severely reduced T-cell and natural killer (NK) cell populations, but normal numbers of B cells. In addition to reduced T- and NK-cell numbers, Il2rg knockout mice also have dramatically reduced B-cell populations suggesting that Il2rg is more critical for B-cell development in mice than in humans. Patients with severe combined immunodeficiency (SCID) phenotype due to IL7R mutations (see Puel & Leonard 2000), or a partial deficiency of IL7R (Roifman et al. 2000) have markedly reduced circulating T cells, but normal levels of peripheral blood B cells and NK cells, similar to the phenotype of IL2RG mutations, highlighting a requirement for IL7 in T cell lymphopoiesis. It has been suggested that IL7 is essential for murine, but not human B cell development, but recent studies indicate that IL7 is essential for human B cell production from adult bone marrow and that IL7-induced expansion of the progenitor B cell compartment is increasingly critical for human B cell production during later stages of development (Parrish et al. 2009).

IL7 has been shown to induce rapid and dose-dependent tyrosine phosphorylation of JAKs 1 and 3, and concomitantly tyrosine phosphorylation and DNA-binding activity of STAT5a/b (Foxwell et al. 1995). IL7R was shown to directly induce the activation of JAKs and STATs by van der Plas et al. (1996). Jak1 and Jak3 knockout mice displayed severely impaired thymic development, further supporting their importance in IL7 signaling (Rodig et al. 1998, Nosaka et al. 1995).

The role of STAT5 in IL7 signaling has been studied largely in mouse models. Tyr449 in the cytoplasmic domain of IL7RA is required for T-cell development in vivo and activation of JAK/STAT5 and PI3k/Akt pathways (Jiang et al. 2004, Pallard et al. 1999). T-cells from an IL7R Y449F knock-in mouse did not activate STAT5 (Osbourne et al. 2007), indicating that IL7 regulates STAT5 activity via this key tyrosine residue. STAT5 seems to enhance proliferation of multiple cell lineages in mouse models but it remains unclear whether STAT5 is required solely for survival signaling or also for the induction of proliferative activity (Kittipatarin & Khaled, 2007).

The model for IL7 receptor signaling is believed to resemble that of other Gc family cytokines, based on detailed studies of the IL2 receptor, where IL2RB binds constitutively to JAK1 while JAK3 is pre-associated uniquely with the IL2RG chain. Extending this model to IL7 suggests a similar series of events: IL7R constitutively associated with JAK1 binds IL7, the resulting trimer recruits IL2RG:JAK3, bringing JAK1 and JAK3 into proximity. The association of both chains of the IL7 receptor orients the cytoplasmic domains of the receptor chains so that their associated kinases (Janus and phosphatidylinositol 3-kinases) can phosphorylate sequence elements on the cytoplasmic domains (Jiang et al. 2005). JAKs have low intrinsic enzymatic activity, but after mutual phosphorylation acquire much higher activity, leading to phosphorylation of the critical Y449 site on IL7R. This site binds STAT5 and possibly other signaling adapters, they in turn become phosphorylated by JAK1 and/or JAK3. Phosphorylated STATs translocate to the nucleus and trigger the transcriptional events of their target genes.

The role of the PI3K/AKT pathway in IL7 signaling is controversial. It is a potential T-cell survival pathway because in many cell types PI3K signaling regulates diverse cellular functions such as cell cycle progression, transcription, and metabolism. The ERK/MAPK pathway does not appear to be involved in IL7 signaling (Crawley et al. 1996).

It is not clear how IL7 influences cell proliferation. In the absence of a proliferative signal such as IL7 or IL3, dependent lymphocytes arrest in the G0/G1 phase of the cell cycle. To exit this phase, cells typically activate specific G1 Cyclin-dependent kinases/cyclins and down regulate cell cycle inhibitors such as Cyclin-dependent kinase inhibitor 1B (Cdkn1b or p27kip1). There is indirect evidence suggesting a possible role for IL7 stimulated activation of PI3K/AKT signaling, obtained from transformed cell lines and thymocytes, but not confirmed by observations using primary T-cells (Kittipatarin & Khaled, 2007). IL7 withdrawal results in G1/S cell cycle arrest and is correlated with loss of cdk2 activity (Geiselhart et al. 2001), both events which are known to be regulated by the dephosphorylating activity of Cdc25A. Expression of a p38 MAPK-resistant Cdc25A mutant in an IL-7-dependent T-cell line as well as in peripheral, primary T-cells was sufficient to sustain cell survival and promote cell cycling for several days in the absence of IL7 (Khaled et al. 2005). Cdkn1b is a member of the CIP/KIP family of cyclin-dependent cell cycle inhibitors (CKIs) that negatively regulates the G1/S transition. In IL7 dependent T-cells, the expression of Cdkn1b was sufficient to cause G1 arrest in the presence of IL7. Withdrawal of IL7 induced the upregulation of Cdkn1b and arrested cells in G1 while siRNA knockout of Cdkn1b enhanced cell cycle progression. However, adoptive transfer of Cdkn1b-deficient lymphocytes into IL7 deficient mice indicated that loss of Cdkn1b could only partially compensate for the IL7 signal needed by T-cells to expand in a lymphopenic environment (Li et al. 2006), so though Cdkn1b may be involved in negative regulation of the cell cycle through an effect on cdk2 activity, its absence is not sufficient to fully induce cell cycling under lymphopenic conditions.

References

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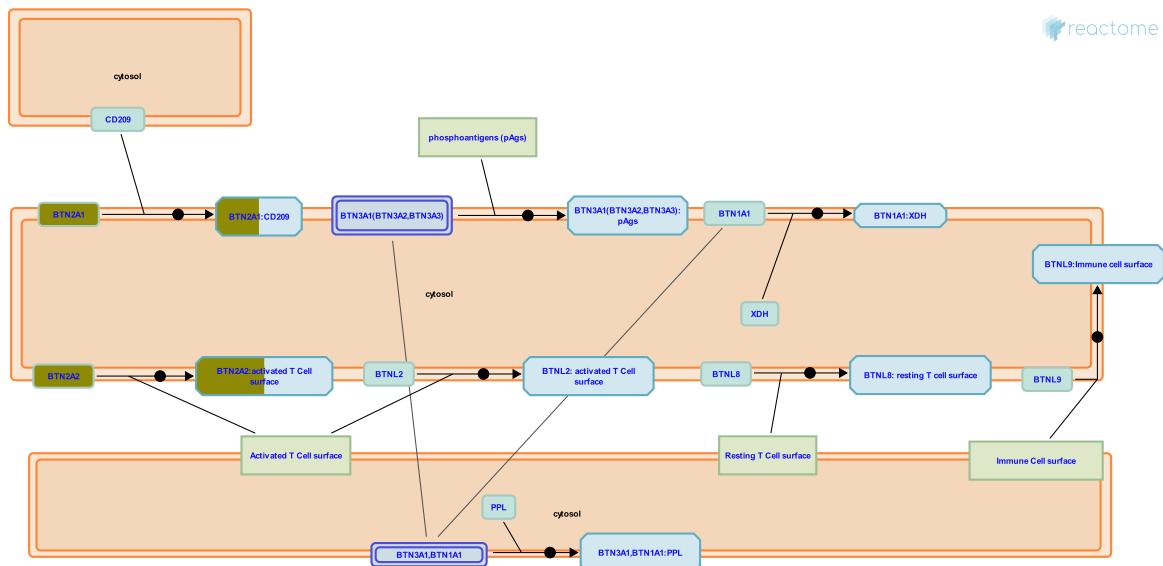
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2011-11-03	Reviewed	Puck J
2016-03-23	Edited	Orlic-Milacic M
2016-05-11	Revised	Mandal M
2017-07-26	Reviewed	Kumar U
2017-08-21	Reviewed	Goronzy JJ
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431, Q71DI3	JAK1	P23458	SOCS2	O14508

Input	Ensembl Id
SOCS2	ENSG00000120833

2. Butyrophilin (BTN) family interactions (R-HSA-8851680)



Butyrophilins (BTNs) and butyrophilin like (BTNL) molecules are regulators of immune responses that belong to the immunoglobulin (Ig) superfamily of transmembrane proteins. They are structurally related to the B7 family of co-stimulatory molecules and have similar immunomodulatory functions (Afrache et al. 2012, Arnett & Viney 2014). BTNs are implicated in T cell development, activation and inhibition, as well as in the modulation of the interactions of T cells with antigen presenting cells and epithelial cells. Certain BTNs are genetically associated with autoimmune and inflammatory diseases (Abeler Domer et al. 2014).

The human butyrophilin family includes seven members that are subdivided into three subfamilies: BTN1, BTN2 and BTN3. The BTN1 subfamily contains only the prototypic single copy BTN1A1 gene, whereas the BTN2 and BTN3 subfamilies each contain three genes BTN2A1, BTN2A2 and BTN2A3, and BTN3A1, BTN3A2 and BTN3A3, respectively (note that BTN2A3 is a pseudogene). BTN1A1 has a crucial function in the secretion of lipids into milk (Ogg et al. 2004) and collectively, BTN2 and BTN3 proteins are cell surface transmembrane glycoproteins, that act as regulators of immune responses. BTNL proteins share considerable homology to the BTN family members. The human genome contains four BTNL genes: BTNL2, 3, 8 and 9 (Abeler Domer et al. 2014).

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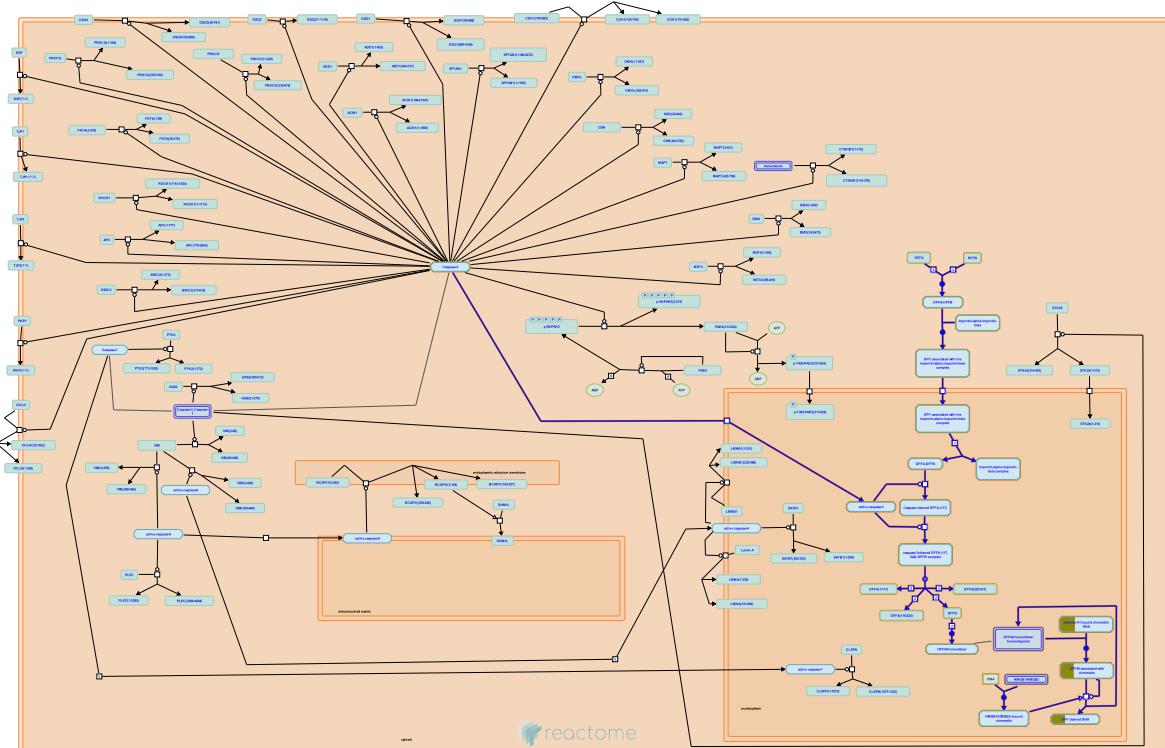
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2016-01-05	Edited	Garapati P V
2016-01-05	Authored	Garapati P V
2016-01-08	Created	Garapati P V
2016-09-09	Reviewed	Reith W
2017-03-01	Reviewed	Rhodes DA
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
BTN2A1	Q7KYR7	BTN2A2	Q8WVV5

3. Apoptosis induced DNA fragmentation (R-HSA-140342)



Cellular compartments: nucleoplasm, cytosol.

DNA fragmentation in response to apoptotic signals is achieved, in part, through the activity of apoptotic nucleases, termed DNA fragmentation factor (DFF) or caspase-activated DNase (CAD) (reviewed in Widlak and Garrard, 2005). In non-apoptotic cells, DFF is a nuclear heterodimer consisting of a 45 kD chaperone and inhibitor subunit (DFF45)/inhibitor of CAD (ICAD-L) and a 40 kD nuclease subunit (DFF40/CAD)(Liu et al. 1997, 1998; Enari et al. 1998). During apoptosis, activated caspase-3 or -7 cleave DFF45/ICAD releasing active DFF40/CAD nuclease. The activity of DFF is tightly controlled at multiple stages. During translation, DFF45/ICAD, Hsp70, and Hsp40 proteins play a role in insuring the appropriate folding of DFF40 during translation(Sakahira and Nagata, 2002). The nuclease activity of DFF40 is enhanced by the chromosomal proteins histone H1, Topoisomerase II and HMGB1/2(Widlak et al., 2000). In addition, the inhibitors (DFF45/35; ICAD-S/L) are produced in stoichiometric excess (Widlak et al., 2003).

References

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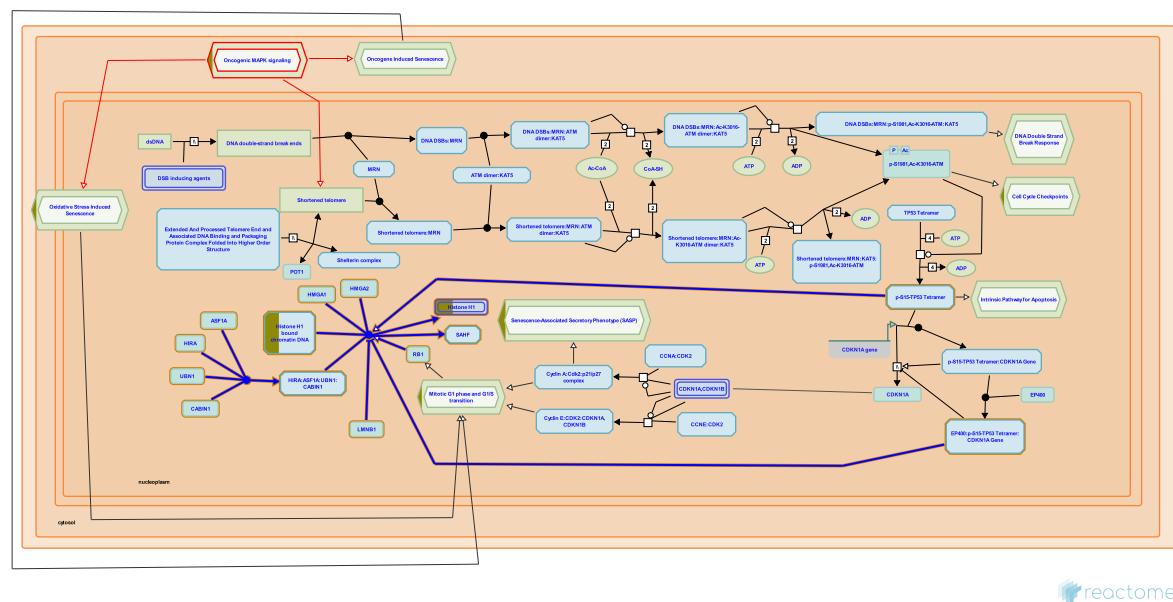
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2004-02-17	Created	Alnemri E
2008-04-25	Reviewed	Widlak P
2008-04-25	Authored	Matthews L
2008-05-18	Revised	Matthews L
2008-05-18	Edited	Matthews L
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
H1-0	P07305	H1-3	P16402

4. Formation of Senescence-Associated Heterochromatin Foci (SAHF) ([R-HSA-2559584](#))



The process of DNA damage/telomere stress induced senescence culminates in the formation of senescence associated heterochromatin foci (SAHF). These foci represent facultative heterochromatin that is formed in senescent cells. They contribute to the repression of proliferation promoting genes and play an important role in the permanent cell cycle exit that characterizes senescence (Narita et al. 2003 and 2006). SAHF appear as compacted, punctate DAPI stained foci of DNA. Each chromosome is condensed into a single SAH focus, with telomeric and centromeric chromatin located predominantly at its periphery (Funayama et al. 2006, Zhang et al. 2007).

An evolutionarily conserved protein complex of HIRA, ASF1A, UBN1 and CABIN1 plays a crucial role in the SAHF formation. As cells approach senescence, HIRA, ASF1A, UBN1 and CABIN1 accumulate at the PML bodies (Zhang et al. 2005, Banumathy et al. 2009, Rai et al. 2011). PML bodies are punctate nuclear structures that contain PML protein and numerous other proteins and are proposed to be the sites of assembly of macromolecular regulatory complexes and protein modification (Fogal et al. 2000, Guo et al. 2000, Pearson et al. 2000). Recruitment of HIRA to PML bodies coincides with altered chromatin structure and deposition of macroH2A histone H2A variant onto chromatin. As cells become senescent, HIRA, ASF1A, UBN1 and CABIN1 relocate from PML bodies to SAHF. HIRA accumulation at PML bodies is RB1 and TP53 independent, but may require phosphorylation of HIRA serine S697 by GSK3B (Ye, Zerlanko, Kennedy et al. 2007). SAHF formation itself, however, requires functional RB1 and TP53 pathways (Ye, Zerlanko, Zhang et al. 2007).

SAHF contain H3K9Me mark, characteristic of transcriptionally silent chromatin, and HP1, macroH2A histone H2A variant and HMGA proteins are also components of SAHF (Narita et al. 2006), besides the HIRA:ASF1A:UBN1:CABIN1 complex. A yet unidentified H3K9Me histone methyltransferase may be recruited to SAHF by UBN1 (Banumathy et al. 2009). One of the functions of the HIRA:ASF1A:UBN1:CABIN1 complex is to deposit histone H3.3. variant to chromatin, which influences gene expression (Zhang et al. 2007, Rai et al. 2011).

Further studies are needed to fully elucidate the mechanism of SAHF formation and mechanism by which SAHF promote cell senescence.

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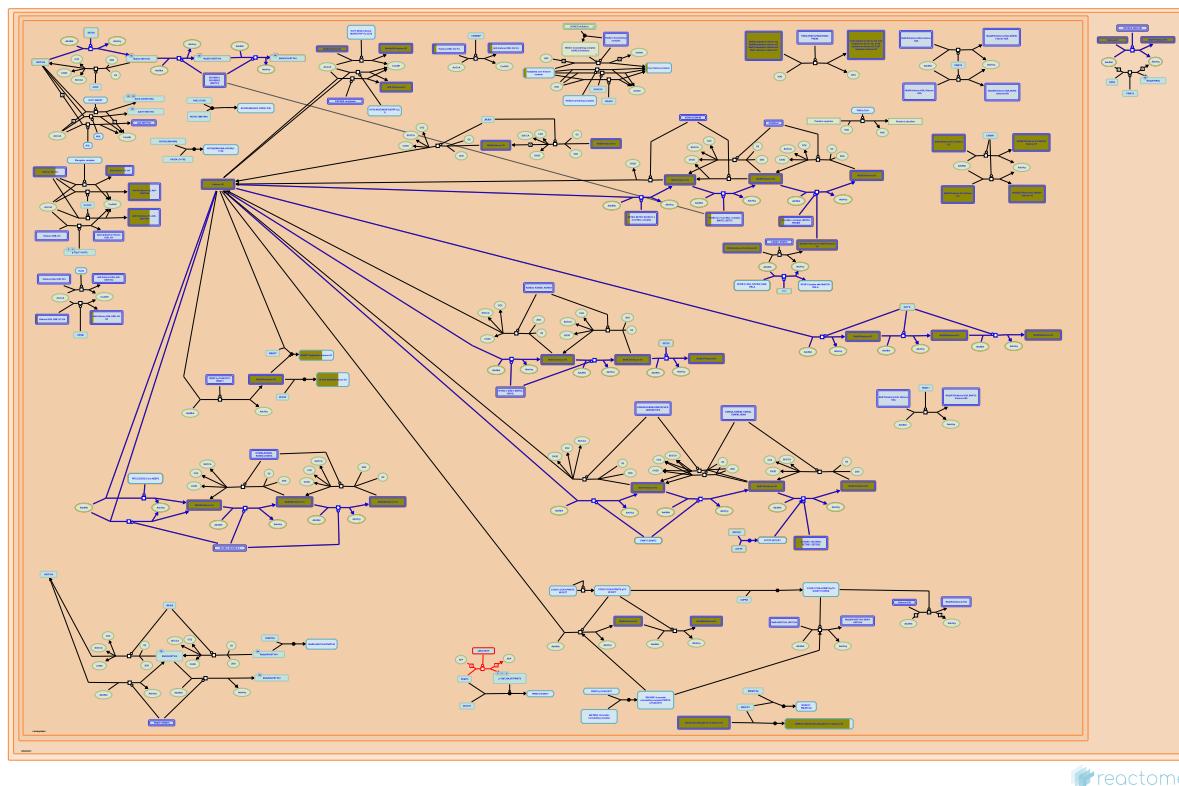
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2013-07-15	Edited	Matthews L, D'Eustachio P
2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
H1-0	P07305	H1-3	P16402

5. PKMTs methylate histone lysines (R-HSA-3214841)



Lysine methyltransferases (KMTs) and arginine methyltransferases (RMTs) have a common mechanism of catalysis. Both families transfer a methyl group from a common donor, S-adenosyl-L-methionine (SAM), to the nitrogen atom on the epsilon-amino group of lysine or arginine (Smith & Denu 2009) using a bimolecular nucleophilic substitution (SN2) methyl transfer mechanism (Smith & Denu 2009, Zhang & Bruice 2008). All human KMTs except DOT1L (KMT4) (Feng et al. 2002, van Leeuwen et al. 2002, Lacoste et al. 2002) have a ~130 amino acid catalytic domain referred to as the SET domain (Del Rizzo & Trievel 2011, Dillon et al. 2005, Herz et al. 2013).

Some KMTs selectively methylate a particular lysine residue on a specific histone type. The extent of this methylation (mono-, di- or tri-methylation) also can be stringent (Herz et al. 2013, Copeland et al. 2009). Many KMTs also have non-histone substrates (Herz et al 2013), which are not discussed in this module.

The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any processing. Histone literature typically refers to specific residues by numbers which are determined after the initiating methionine has been removed. Therefore the coordinates of post-translated residues in the Reactome database and described here are frequently +1 when compared to the histone literature.

SET domain-containing proteins are classified in one of 7 families (Dillon et al. 2005). First to be discovered were the SUV39 family named after founding member SUV39H1 (KMT1A), which selectively methylates lysine-10 of histone H3 (H3K9) (Rea et al. 2000). Family member EHMT2 (KMT1C, G9A) is the predominant H3K9 methyltransferase in mammals (Tachibana et al. 2002). SETDB1 (KMT1E, ESET) also predominantly methylates H3K9, most effectively when complexed with ATF7IP (MCAF, hAM) (Wang et al. 2003).

SETD2 (KMT3A, HYPB), a member of the SET2 family, specifically methylates histone H3 lysine-37 (H3K36) (Sun et al. 2005). WHSC1 (KMT3G, NSD2, MMSET) a member of the same family, targets H3K36 when provided with nucleosome substrates but also can methylate histone H4 lysine-45 when octameric native or recombinant nucleosome substrates are provided (Li et al. 2009); di-methylation of histone H3 at lysine-37 (H3K36me2) is thought to be the principal chromatin-regulatory activity of WHSC1 (Kuo et al. 2011). Relatives NSD1 (KMT3B) and WHSC1L1 (KMT3F, NSD3) also methylate nucleosomal H3K36. NSD1 is active on unmethylated or a mimetic monomethylated H3K36, but not di- or trimethylated H3K36 mimetics (Li et al. 2009). Human SETD7 (KMT7, SET7/9), not classified within the 7 SET-domain containing families, mono-methylates lysine-5 of histone H3 (H3K4) (Xiao et al. 2003).

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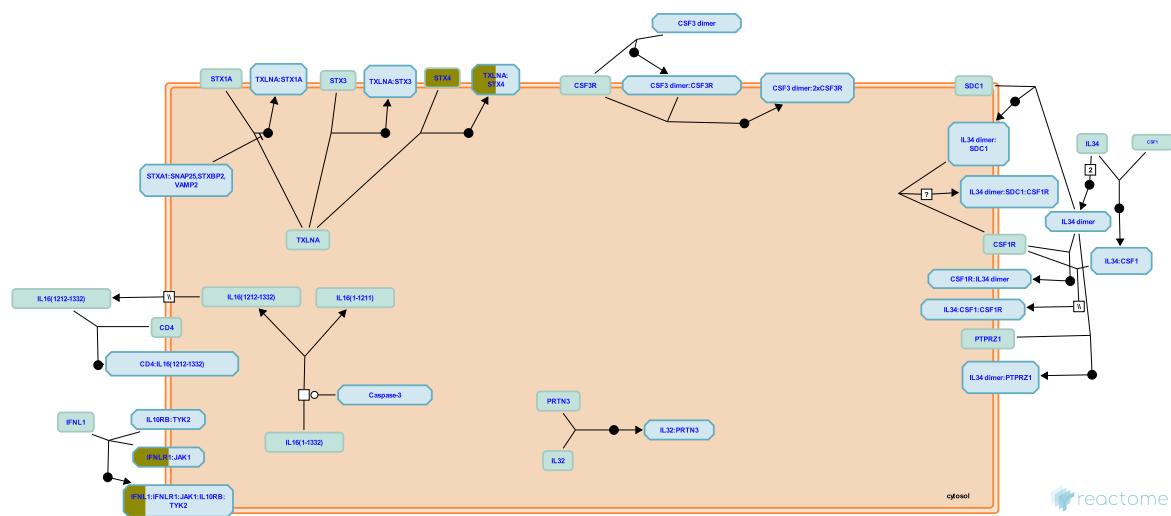
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Date	Action	Author
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2013-03-12	Created	Jupe S
2014-09-10	Edited	Jupe S
2014-11-17	Reviewed	Motamed M
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id
H3C6	P68431	SETD1A	O15047, Q9UPS6

6. Other interleukin signaling (R-HSA-449836)



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.

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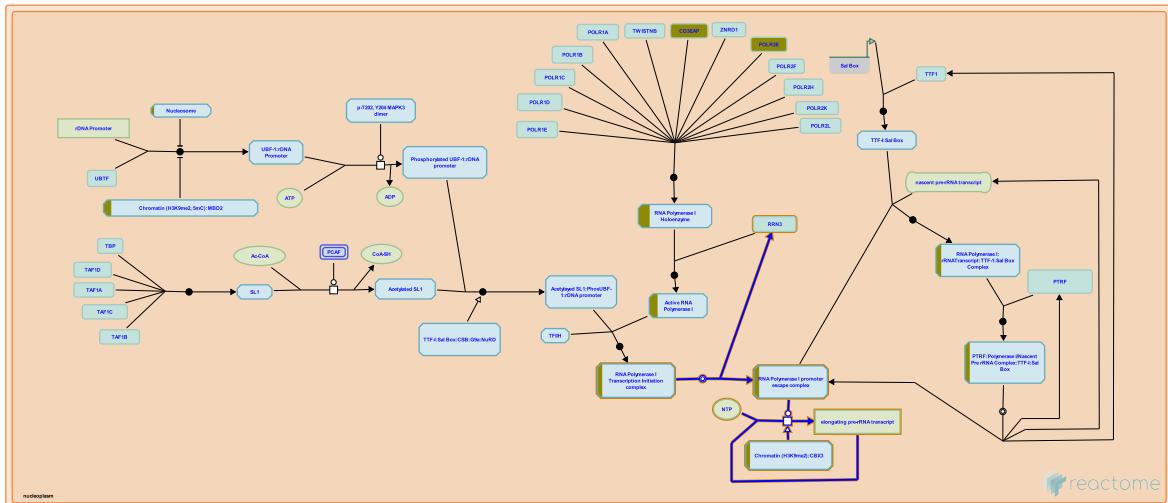
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2014-06-04	Authored	Jupe S
2016-01-28	Edited	Jupe S
2016-01-28	Reviewed	Meldal BH
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
JAK1	P23458	STX4	Q12846

7. RNA Polymerase I Promoter Escape (R-HSA-73772)



Cellular compartments: nucleolus.

As the active RNA Polymerase I complex leaves the promoter Rrn3 dissociates from the complex. RNA polymerase I Promoter Clearance is complete and Chain Elongation begins (Milkereit and Tschochner, 1998).

The assembly of the initiation complex on the promoter and the transition from a closed to an open complex is then followed by promoter clearance and transcription elongation by RNA Pol I. Unlike the RNA polymerase II system, RNA polymerase I transcription does not require a form of energy such as ATP for initiation and elongation. Regulatory mechanisms operating at both the level of transcription initiation and elongation probably concurrently to adjust the level of rRNA synthesis to the need of the cell.

References

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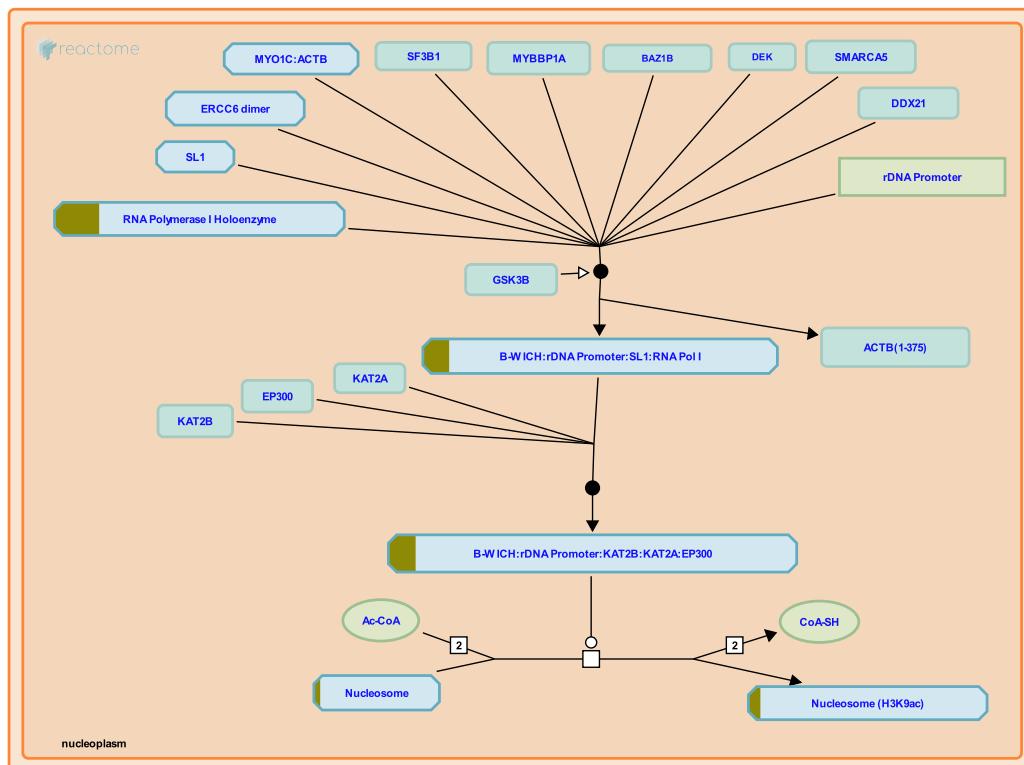
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2022-11-17	Edited	Gillespie ME
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

8. B-WICH complex positively regulates rRNA expression (R-HSA-5250924)



Cellular compartments: nucleoplasm.

The B-WICH complex is a large 3 Mdalton complex containing SMARCA5 (SNF2H), BAZ1B (WSTF), ERCC6 (CSB), MYO1C (Nuclear myosin 1c), SF3B1, DEK, MYBBP1A, and DDX21 (Cavellan et al. 2006, Percipalle et al. 2006, Vintermist et al. 2001, Sarshad et al. 2013, Shen et al. 2013, reviewed in Percipalle and Farrants 2006). B-WICH is found at active rRNA genes as well as at 5S rRNA and 7SL RNA genes. B-WICH appears to remodel chromatin and recruit histone acetyltransferases that modify histones to transcriptionally active states.

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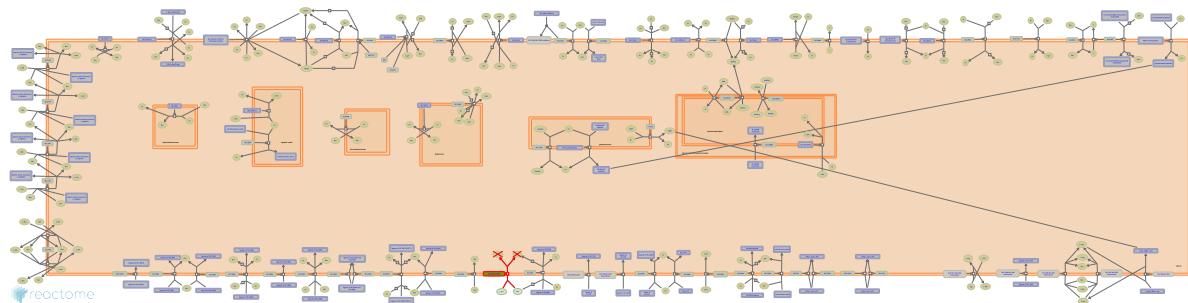
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2014-01-31	Created	May B
2015-11-07	Reviewed	Percipalle P
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

9. Variant SLC6A20 contributes towards hyperglycinuria (HG) and iminoglycinuria (IG) (R-HSA-5660686)



Diseases: amino acid metabolic disorder.

SLC6A20 encodes the sodium- and chloride-dependent transporter SIT1 and mediates the sodium-dependent uptake of imino acids such as L-proline, N-methyl-L-proline and pipecolate as well as N-methylated amino acids and glycine (Broer & Gether 2012, Schweikhard & Ziegler 2012). The human protein is expressed in the intestine and kidney. A common SNP in the SLC6A20 gene, a 596C-T transition that results in a thr199-to-met (T199M) substitution can contribute towards iminoglycinuria (IG; MIM:242600) or hyperglycinuria (HG; MIM:138500) (Broer et al. 2008). Overall, mutations in SLC36A2 together with polymorphisms in the modifiers SLC6A20, SLC6A18, and SLC6A19 constitute the genetic basis for these phenotypes.

References

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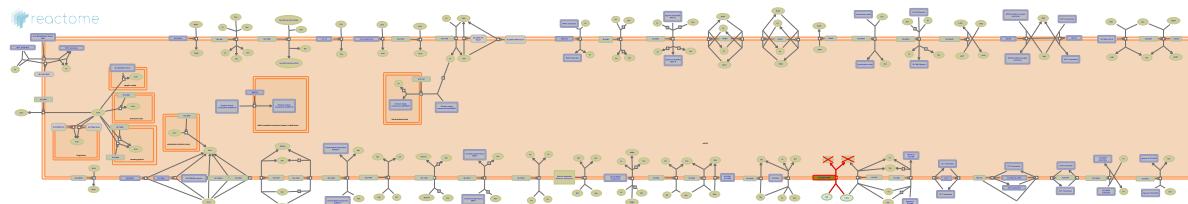
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2015-01-06	Created	Jassal B
2015-08-04	Reviewed	Broer S
2022-11-23	Modified	Wright A

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
SLC6A20	Q9NP91

10. Variant SLC6A20 contributes towards hyperglycinuria (HG) and iminoglycinuria (IG) (R-HSA-5619101)



Diseases: amino acid metabolic disorder.

SLC6A20 encodes the sodium- and chloride-dependent transporter SIT1 and mediates the sodium-dependent uptake of imino acids such as L-proline, N-methyl-L-proline and pipecolate as well as N-methylated amino acids and glycine (Broer & Gether 2012, Schweikhard & Ziegler 2012). The human protein is expressed in the intestine and kidney. A common SNP in the SLC6A20 gene, a 596C-T transition that results in a thr199-to-met (T199M) substitution can contribute towards iminoglycinuria (IG; MIM:242600) or hyperglycinuria (HG; MIM:138500) (Broer et al. 2008). Overall, mutations in SLC36A2 together with polymorphisms in the modifiers SLC6A20, SLC6A18, and SLC6A19 constitute the genetic basis for these phenotypes.

References

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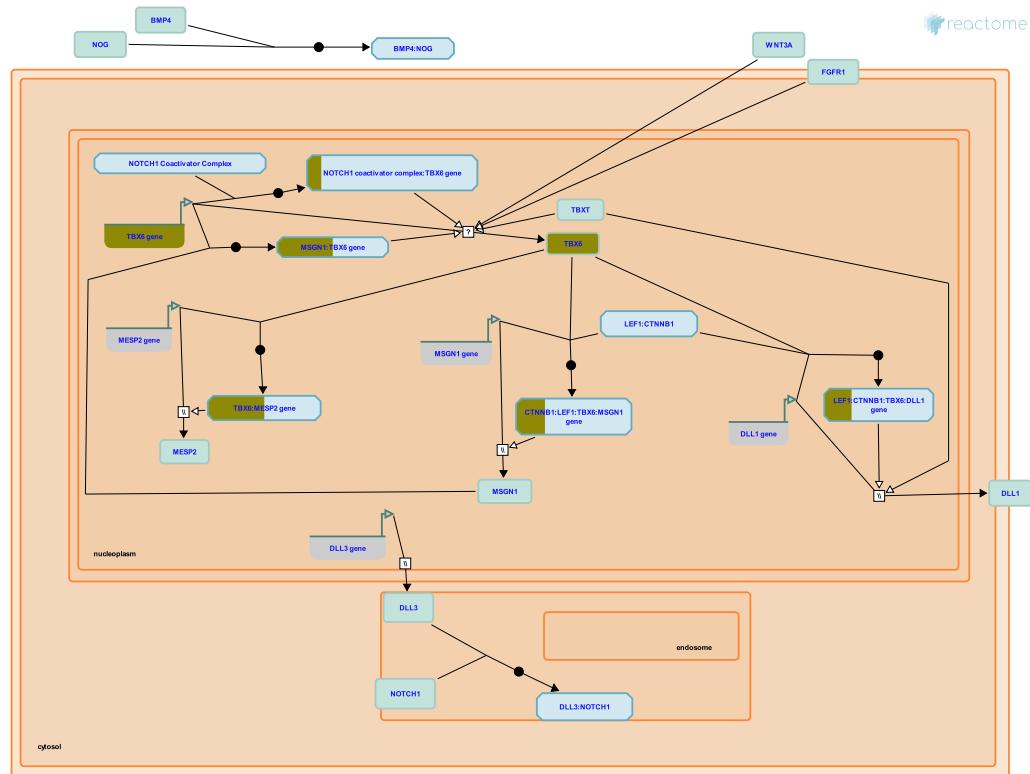
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2015-08-04	Reviewed	Broer S
2022-11-23	Modified	Wright A

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
SLC6A20	Q9NP91

11. Formation of paraxial mesoderm (R-HSA-9793380)



Skeletal tissues originate from paraxial mesoderm, lateral plate mesoderm, and neural crest. Paraxial mesoderm is produced by invagination of cells through the primitive streak and is the precursor of somites, which are spheres of mesenchyme bounded by epithelium that bud at fixed intervals from the anterior paraxial mesoderm (reviewed in Tam and Trainor 1994, Pourquie 2003). Somites give rise to the axial skeleton and skeletal muscles.

Paraxial mesoderm becomes specified at a lower level of BMP signaling (Xi et al. 2017) that results from the interaction of BMP4, produced by the lateral plate mesoderm, with NOGGIN (NOG), a negative regulator of BMP signaling produced by the notochord (reviewed in Tani et al. 2020). WNT signaling by WNT3A that activates beta β catenin (CTNNB1), FGF signaling that acts through FGFR1, and TBXT activate expression of TBX6 and Mesogenin 1 (MSGN1). MSGN1 binds and activates SNAI1 to promote epithelial-mesenchymal transitions (EMT). TBX6 activates MSGN1, and MSGN1 activates TBX6, to establish a positive feedback loop that ensures commitment to the paraxial mesoderm lineage. TBX6 and MSGN1 act with WNT signaling to activate expression of MSGN1, and the NOTCH ligand Delta δ like 1 (DLL1), which enhances NOTCH signaling. MSGN1 binds and activates expression of DLL1, DLL3, NOTCH1, and NOTCH2, and binds to Clock enhancers that regulate periodic expression of LFNG during somitogenesis in the anterior paraxial mesoderm. The counterbalancing DLL3 protein inhibits NOTCH signaling by binding NOTCH1 in endosomes and targeting NOTCH1 for lysosomal degradation.

TBX6 alone is capable of reprogramming pluripotent stem cells to paraxial mesoderm (Sadahiro et al. 2018) and acts in a regulatory loop with MESP2 to create the boundaries of nascent somites (Oginuma et al. 2011): TBX6 activates expression of MESP2 which then represses TBX6 by targeting TBX6 for degradation, leaving MESP2 alone at the segmental boundary.

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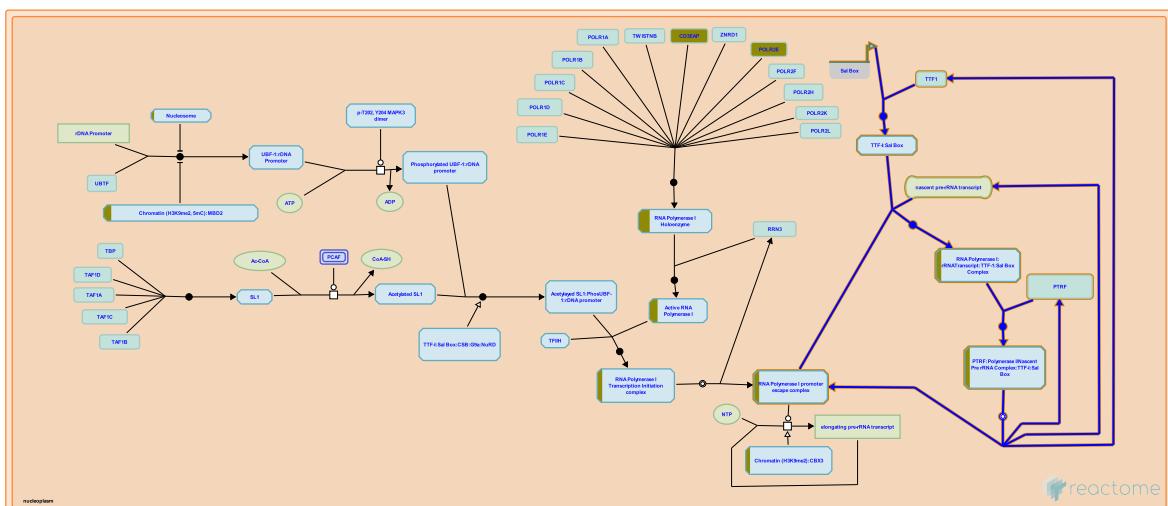
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2022-11-09	Reviewed	Yamaguchi TP, Chalamalasetty RB
2022-11-18	Modified	Wright A

1 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id
TBX6	O95947

Input	Ensembl Id
TBX6	ENSG00000149922

12. RNA Polymerase I Transcription Termination (R-HSA-73863)



Cellular compartments: nucleolus.

Termination of transcription by RNA polymerase I is a 4 step process. Initially TTF-1 binds the template rDNA. This complex pauses polymerase I allowing PTRF to interact with the quaternary complex releasing both pre-rRNA and Pol I from the template and TTF-1.

References

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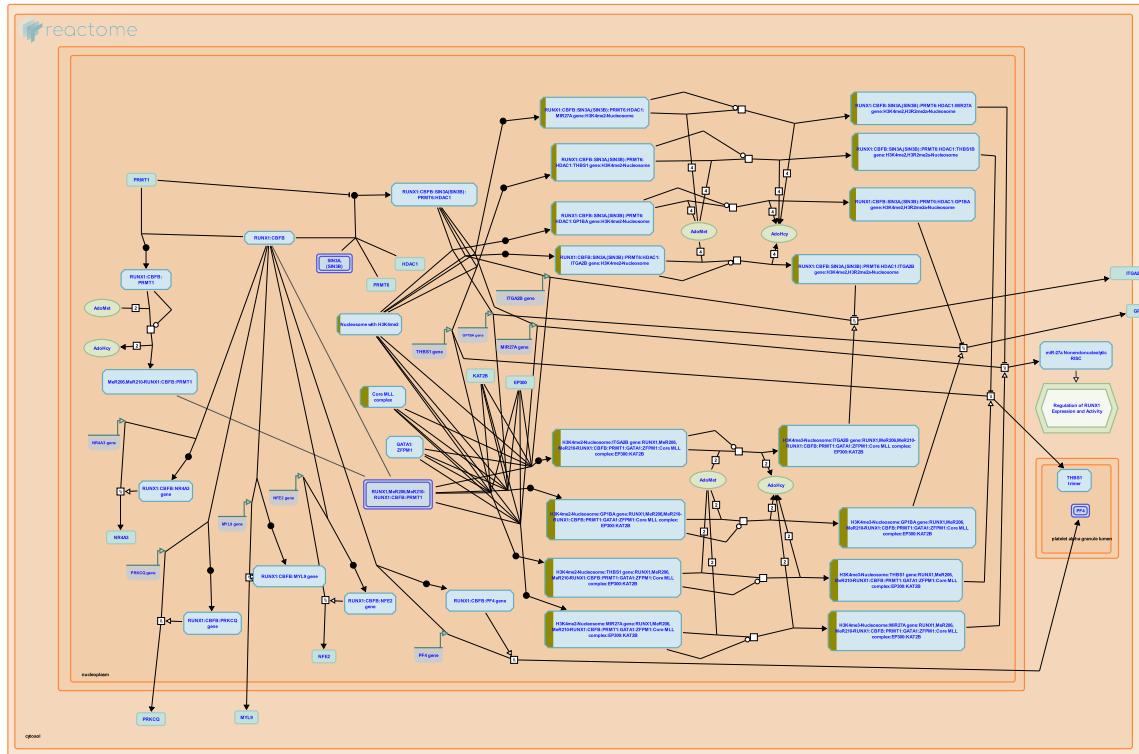
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2022-11-17	Edited	Gillespie ME
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
POLR1G	O15446	POLR2E	P19388

13. RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function (R-HSA-8936459)



In human hematopoietic progenitors, RUNX1 and its partner CBFB are up-regulated at the onset of megakaryocytic differentiation and down-regulated at the onset of erythroid differentiation. The complex of RUNX1 and CBFB cooperates with the transcription factor GATA1 in the transactivation of megakaryocyte-specific genes. In addition, RUNX1 and GATA1 physically interact (Elagib et al. 2003), and this interaction involves the zinc finger domain of GATA1 (Xu et al. 2006). Other components of the RUNX1:CBFB activating complex at megakaryocytic promoters are GATA1 heterodimerization partner, ZFPM1 (FOG1), histone acetyltransferases EP300 (p300) and KAT2B (PCAF), the WDR5-containing histone methyltransferase MLL complex and the arginine methyltransferase PRMT1 (Herglotz et al. 2013). In the absence of PRMT1, the transcriptional repressor complex can form at megakaryocytic promoters, as RUNX1 that is not arginine methylated can bind to SIN3A/SIN3B co-repressors (Zhao et al. 2008). Besides SIN3A/SIN3B, the RUNX1:CBFB repressor complex at megakaryocytic promoters also includes histone deacetylase HDAC1 and histone arginine methyltransferase PRMT6 (Herglotz et al. 2013).

Megakaryocytic promoters regulated by the described RUNX1:CBFB activating and repressing complexes include ITGA2B, GP1BA, THBS1 and MIR27A (Herglotz et al. 2013). ITGA2B is only expressed in maturing megakaryocytes and platelets and is involved in platelet aggregation (Block and Poncz 1995). GP1BA is expressed at the cell surface membrane of maturing megakaryocytes and platelets and participates in formation of platelet plugs (Cauwenberghs et al. 2000, Jilma-Stohlawetz et al. 2003, Debili et al. 1990). THBS1 homotrimers contribute to stabilization of the platelet aggregate (Bonnefoy and Hoylaerts 2008). MIR27A is a negative regulator of RUNX1 mRNA translation and may be involved in erythroid/megakaryocytic lineage determination (Ben-Ami et al. 2009).

The RUNX1:CBFB complex stimulates transcription of the PF4 gene, encoding a component of platelet alpha granules (Aneja et al. 2011), the NR4A3 gene, associated with the familial platelet disorder (FPD) (Bluteau et al. 2011), the PRKCQ gene, associated with inherited thrombocytopenia (Jalagadugula et al. 2011), the MYL9 gene, involved in thrombopoiesis (Jalagadugula et al. 2010), and the NFE2 gene, a regulator of erythroid and megakaryocytic maturation and differentiation (Wang et al. 2010).

References

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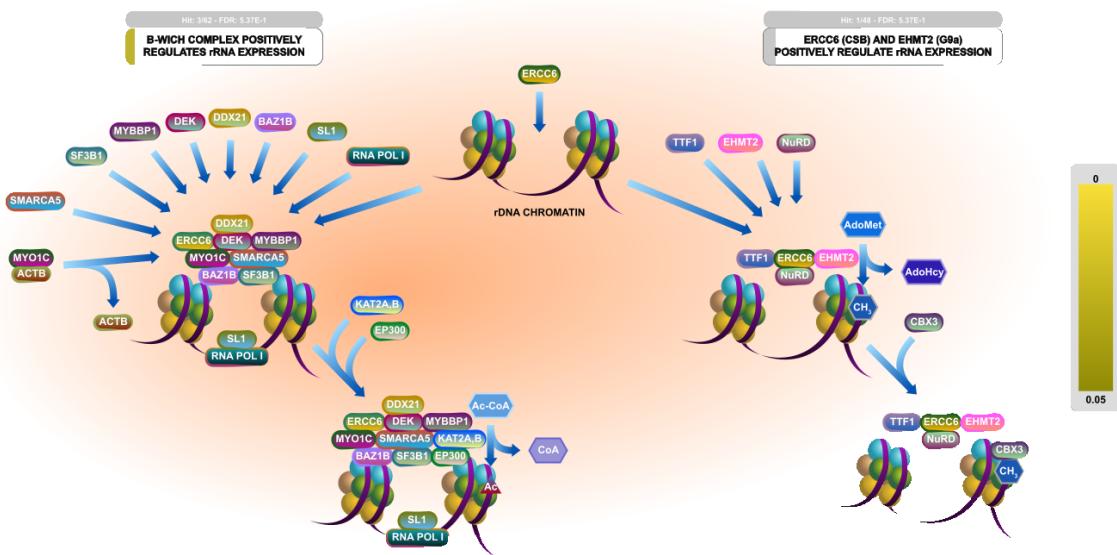
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2016-09-14	Authored	Orlic-Milacic M
2016-12-20	Reviewed	Ito Y, Chuang LS
2017-05-09	Edited	Orlic-Milacic M
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id
H3C6	P68431	SFTD1A	O15047, Q9UPS6

14. Positive epigenetic regulation of rRNA expression (R-HSA-5250913)



Cellular compartments: nucleoplasm.

Transcription of rRNA genes is controlled by epigenetic activation and repression according to the metabolic requirements of the cell (reviewed in Percipalle and Farrants 2006, McStay and Grummt 2008, Goodfellow and Zomerdijk 2012, Grummt and Langst 2013). Depending on the growth state of the cell, about half of the approximately 400 rRNA genes are expressed and these have the modifications characteristic of active chromatin: unmethylated DNA and acetylated histones. Repressed genes generally have methylated DNA and histone H3 methylated at lysine-9. Regulators of activation include ERCC6 (CSB), histone acetylases such as KAT2B (PCAF), and the B-WICH complex. Dysregulation of RNA polymerase I transcription plays a role in disease (reviewed in Hannan et al. 2013).

The B-WICH complex positively regulates rRNA expression by remodeling chromatin and recruiting histone acetyltransferases that modify histones to transcriptionally active states

ERCC6 (CSB) and EHMT2(G9a) positively regulate rRNA expression by ERCC6 recruiting the histone methyltransferase EHMT2 (also known as G9a) which dimethylates histone H3 at lysine-9 within the transcribed regions of rRNA genes.

ERCC6 (CSB) and KAT2B (PCAF) positively regulate rRNA expression by ERCC6 recruiting the histone acetyltransferase KAT2B to the promoter where KAT2B acetylates histone H4 at several lysine residues and histone H3 at lysine-9. The acetylated chromatin facilitates the assembly of RNA polymerase I initiation complex.

References

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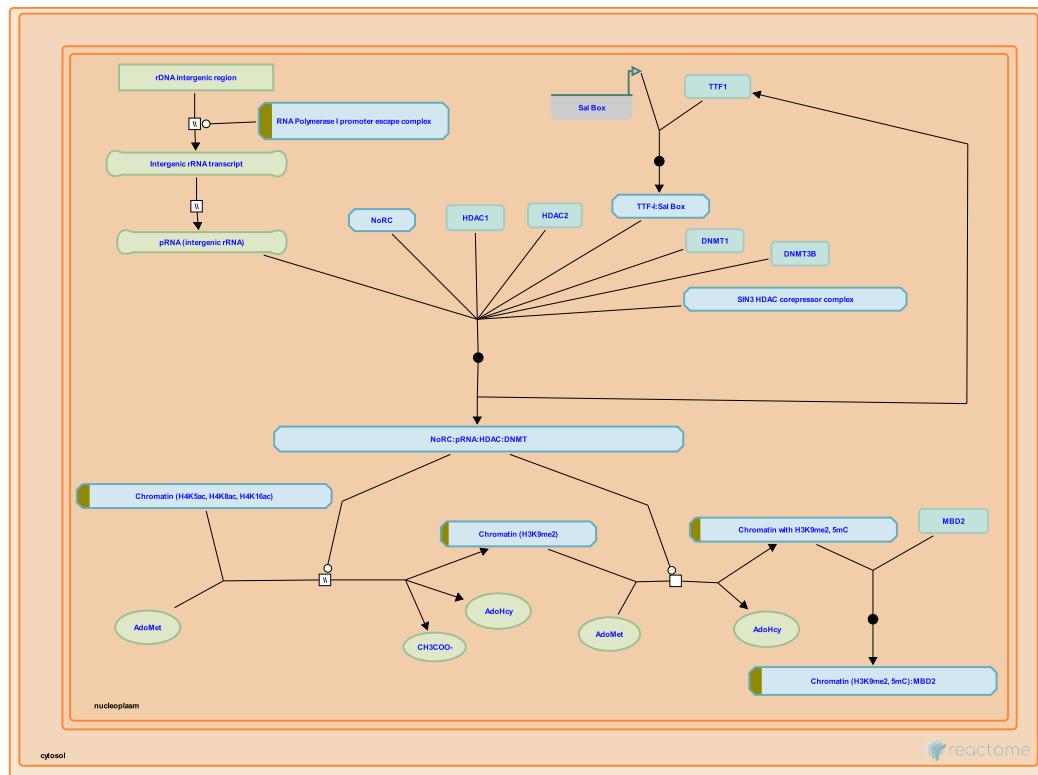
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2015-11-07	Reviewed	Percipalle P
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

15. NoRC negatively regulates rRNA expression (R-HSA-427413)



Cellular compartments: nucleoplasm.

The Nucleolar Remodeling Complex (NoRC) comprising TIP5 (BAZ2A) and the chromatin remodeler SNF2H (SMARCA5) silences rRNA gene (reviewed in Santoro and Grummt 2001, Grummt 2007, Preuss and Pikaard 2007, Birch and Zommerdijk 2008, McStay and Grummt 2008, Grummt and Langst 2013). The TAM domain of TIP5 (BAZ2A) binds promoter-associated RNA (pRNA) transcribed from the intergenic spacer region of rDNA. The pRNA bound by TIP5 is required to direct the complex to the main promoter of the rRNA gene possibly by triple helix formation between pRNA and the rDNA. The PHD domain of TIP5 binds histone H4 acetylated at lysine-16. Transcription Termination Factor-I (TTF-I) binds to a promoter-proximal terminator (T0 site) in the rDNA and interacts with the TIP5 subunit of NoRC. NoRC also interacts with the SIN3-HDAC complex, HDAC1, HDAC2, DNMT1, and DNMT3B. DNMT3B interacts with a triple helix formed by pRNA and the rDNA. HDAC1, DNMT1, and DNMT3B have been shown to be required for proper DNA methylation of silenced rRNA gene copies, although the catalytic activity of DNMT3B was not required.

References

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Längst G & Grummt I (2013). Epigenetic control of RNA polymerase I transcription in mammalian cells. *Biochim. Biophys. Acta*, 1829, 393-404. [🔗](#)

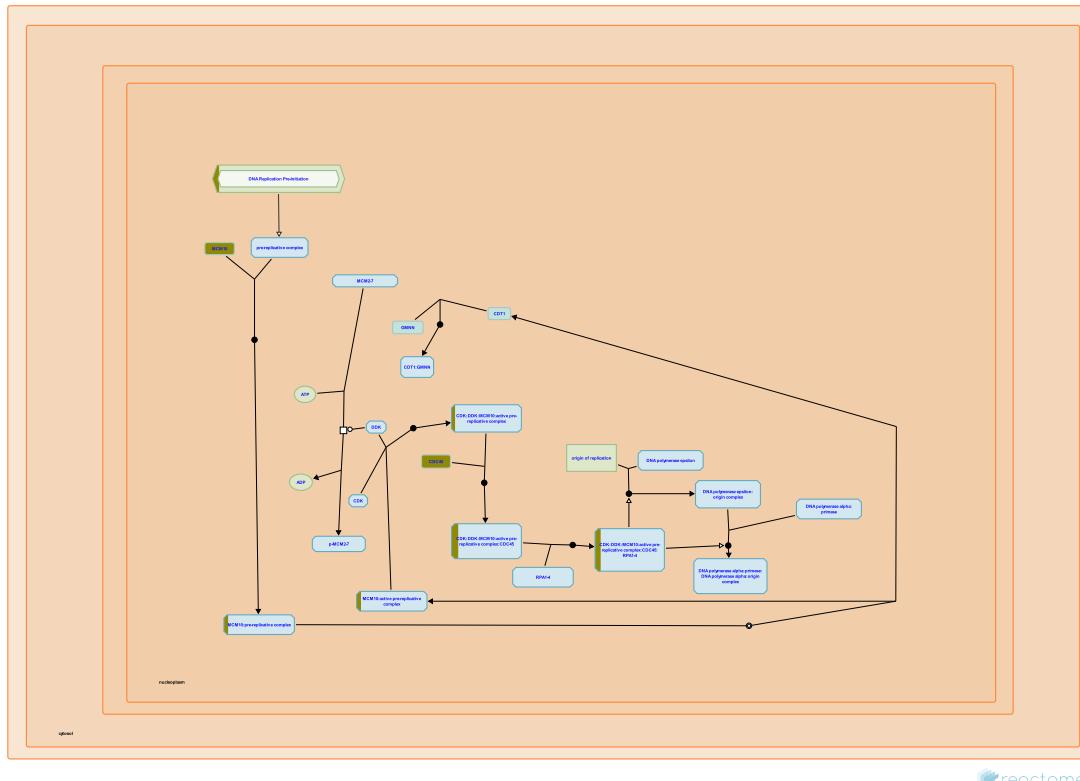
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2009-06-20	Created	May B
2010-04-06	Edited	May B
2014-02-18	Reviewed	Shiao YH
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

16. Activation of the pre-replicative complex (R-HSA-68962)



Cellular compartments: nucleoplasm.

In *S. cerevisiae*, two ORC subunits, Orc1 and Orc5, both bind ATP, and Orc1 in addition has ATPase activity. Both ATP binding and ATP hydrolysis appear to be essential functions in vivo. ATP binding by Orc1 is unaffected by the association of ORC with origin DNA (ARS) sequences, but ATP hydrolysis is ARS-dependent, being suppressed by associated double-stranded DNA and stimulated by associated single-stranded DNA. These data are consistent with the hypothesis that ORC functions as an ATPase switch, hydrolyzing bound ATP and changing state as DNA unwinds at the origin immediately before replication. It is attractive to speculate that ORC likewise functions as a switch as human pre-replicative complexes are activated, but human Orc proteins are not well enough characterized to allow the model to be critically tested. mRNAs encoding human orthologs of all six Orc proteins have been cloned, and ATP-binding amino acid sequence motifs have been identified in Orc1, Orc4, and Orc5. Interactions among proteins expressed from the cloned genes have been characterized, but the ATP-binding and hydrolyzing properties of these proteins and complexes of them have not been determined.

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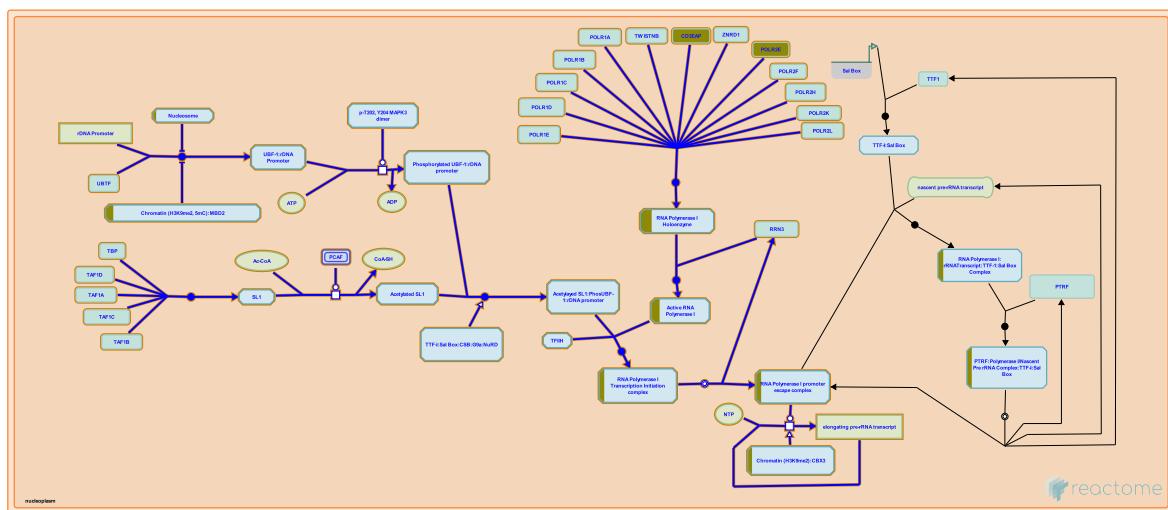
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Date	Action	Author
2003-06-05	Created	Davey MJ, O'Donnell M
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
FOSB	O75419	MCM10	Q7L590

17. RNA Polymerase I Promoter Clearance (R-HSA-73854)



Cellular compartments: nucleolus.

Promoter clearance is one of the rate-limiting steps in Polymerase I transcription. This step is composed of three phases, promoter opening, transcription initiation and promoter escape.

References

Comai L (2004). Mechanism of RNA polymerase I transcription. *Adv. Protein Chem.*, 67, 123-55. 

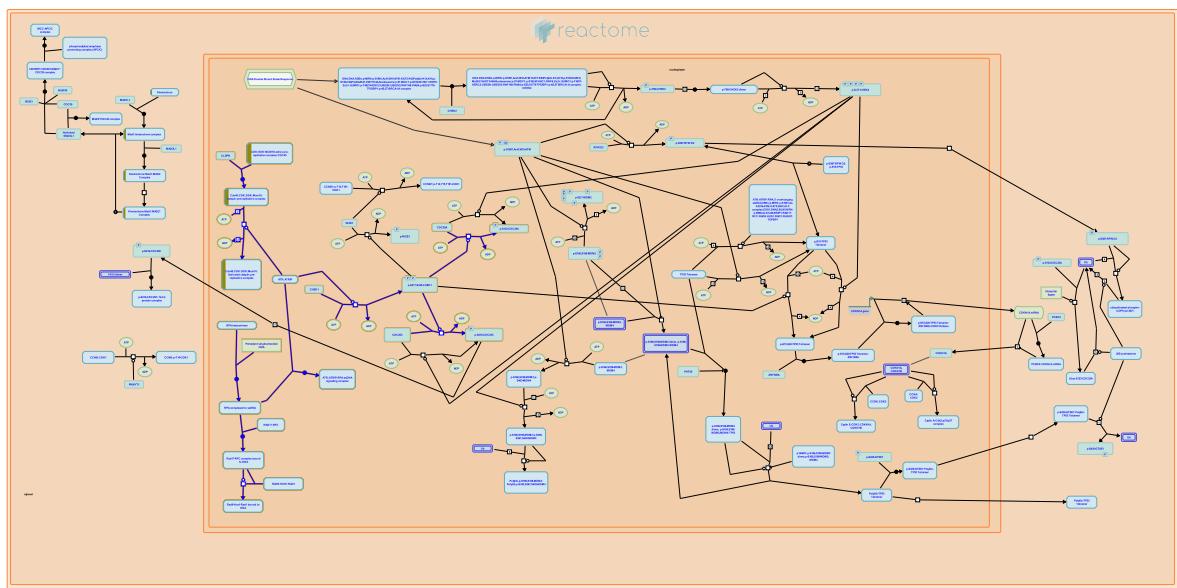
Edit history

Date	Action	Author
2003-07-03	Authored	Comai L
2003-07-03	Created	Comai L
2022-11-17	Edited	Gillespie ME
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

18. Activation of ATR in response to replication stress (R-HSA-176187)



Cellular compartments: nucleoplasm.

Genotoxic stress caused by DNA damage or stalled replication forks can lead to genomic instability. To guard against such instability, genotoxically-stressed cells activate checkpoint factors that halt or slow cell cycle progression. Among the pathways affected are DNA replication by reduction of replication origin firing, and mitosis by inhibiting activation of cyclin-dependent kinases (Cdks). A key factor involved in the response to stalled replication forks is the ATM- and rad3-related (ATR) kinase, a member of the phosphoinositide-3-kinase-related kinase (PIKK) family. Rather than responding to particular lesions in DNA, ATR and its binding partner ATRIP (ATR-interacting protein) sense replication fork stalling indirectly by associating with persistent ssDNA bound by RPA. These structures would be formed, for example, by dissociation of the replicative helicase from the leading or lagging strand DNA polymerase when the polymerase encounters a DNA lesion that blocks DNA synthesis. Along with phosphorylating the downstream transducer kinase Chk1 and the tumor suppressor p53, activated ATR modifies numerous factors that regulate cell cycle progression or the repair of DNA damage. The persistent ssDNA also stimulates recruitment of the RFC-like Rad17-Rfc2-5 alternative clamp-loading complex, which subsequently loads the Rad9-Hus1-Rad1 complex onto the DNA. The latter '9-1-1' complex serves to facilitate Chk1 binding to the stalled replication fork, where Chk1 is phosphorylated by ATR and thereby activated. Upon activation, Chk1 can phosphorylate additional substrates including the Cdc25 family of phosphatases (Cdc25A, Cdc25B, and Cdc25C). These enzymes catalyze the removal of inhibitory phosphate residues from cyclin-dependent kinases (Cdks), allowing their activation. In particular, Cdc25A primarily functions at the G1/S transition to dephosphorylate Cdk2 at Thr 14 and Tyr 15, thus positively regulating the Cdk2-cyclin E complex for S-phase entry. Cdc25A also has mitotic functions. Phosphorylation of Cdc25A at Ser125 by Chk1 leads to Cdc25A ubiquitination and degradation, thus inhibiting DNA replication origin firing. In contrast, Cdc25B and Cdc25C regulate the onset of mitosis through dephosphorylation and activation of Cdk1-cyclin B complexes. In response to replication stress, Chk1 phosphorylates Cdc25B and Cdc25C leading to Cdc25B/C complex formation with 14-3-3 proteins. As these complexes are sequestered in the cytoplasm, they are unable to activate the nuclear Cdk1-cyclin B complex for mitotic entry.

These events are outlined in the figure. Persistent single-stranded DNA associated with RPA binds claspin (A) and ATR:ATRIP (B), leading to claspin phosphorylation (C). In parallel, the same single-stranded DNA:RPA complex binds RAD17:RFC (D), enabling the loading of RAD9:HUS1:RAD1 (9-1-1) complex onto the DNA (E). The resulting complex of proteins can then repeatedly bind (F) and phosphorylate (G) CHK1, activating multiple copies of CHK1.

References

Zou L & Elledge SJ (2003). Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science*, 300, 1542-8. 

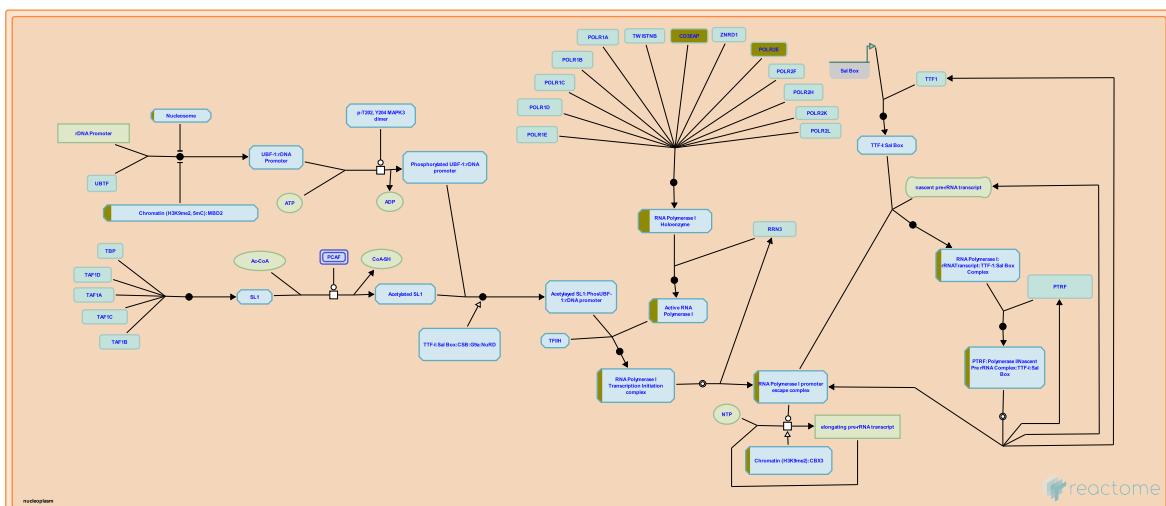
Edit history

Date	Action	Author
2006-02-25	Edited	D'Eustachio P
2006-02-25	Authored	Borowiec JA
2006-03-03	Created	D'Eustachio P
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
FOSB	O75419	MCM10	Q7L590

19. RNA Polymerase I Transcription (R-HSA-73864)



Cellular compartments: nucleolus.

RNA polymerase (Pol) I (one of three eukaryotic nuclear RNA polymerases) is devoted to the transcription of the ribosomal DNA genes, which are found in multiple arrayed copies in every eukaryotic cell. These genes encode for the large ribosomal RNA precursor, which is then processed into the three largest subunits of the ribosomal RNA, the 18S, 28S, and 5.8S RNAs. In human cells the rDNA gene clusters are localized on the short arm of the five pairs of the acrocentric chromosomes. The rRNA promoter has two essential and specially spaced sequences: a CORE element and an upstream control element (UCE, also called UPE). The CORE element of the human promoter overlaps with the transcription start site, extending from 20 to 45, and is required for specific initiation of transcription.

The polymerase is a multisubunit complex, composed of two large subunits (the most conserved portions include the catalytic site that shares similarity with other eukaryotic and bacterial multisubunit RNA polymerases) and a number of smaller subunits. Under a number of experimental conditions the core is competent to mediate ribonucleic acid synthesis, in vivo however, it requires additional factors to select the appropriate template. In humans the RNA transcript (45S) is approximately 13,000 nucleotides long. Before leaving the nucleus as assembled ribosomal particles, the 45S rRNA is cleaved to give one copy each of the 28S rRNA, the 18S rRNA, and the 5.8S rRNA. Equal quantities of the three rRNAs are produced by initially transcribing them as one transcript.

References

Comai L (2004). Mechanism of RNA polymerase I transcription. Adv. Protein Chem., 67, 123-55. [View](#)

Edit history

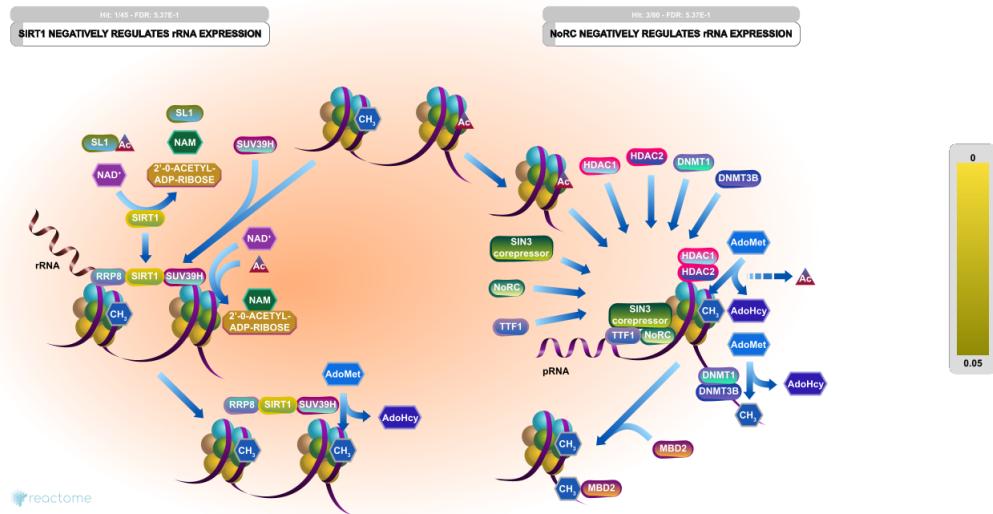
Date	Action	Author
2003-07-03	Authored	Comai L
2003-07-03	Created	Comai L
2022-11-17	Edited	Gillespie ME
2022-11-17	Reviewed	Paule M, Zhao X

Date	Action	Author
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

20. Negative epigenetic regulation of rRNA expression (R-HSA-5250941)



Cellular compartments: nucleoplasm.

Transcription of rRNA genes is controlled by epigenetic activation and repression (reviewed in McStay and Grummt 2008, Goodfellow and Zomerdijk 2012, Grummt and Langst 2013). About half of the roughly 400 rRNA genes are expressed and these have the modifications of active chromatin: unmethylated DNA and acetylated histones. Repressed genes generally have methylated DNA and histone H3 methylated at lysine-9. Regulators of repression include the eNoSC complex, SIRT1, and the NoRC complex.

SIRT1 negatively regulates rRNA expression as a subunit of the eNoSC complex, which deacetylates histone H3 and dimethylates lysine-9 of histone H3 (H3K9me2).

NoRC negatively regulates rRNA expression by shifting a nucleosome near the start of rRNA transcription into a more repressive location and recruiting Histone Deacetylase 1 and 2 (HDAC1, HDAC2) and DNA Methyltransferase 1 and 3b (DNMT1, DNMT3b).

References

- Zomerdijk JC & Goodfellow SJ (2012). Basic mechanisms in RNA polymerase I transcription of the ribosomal RNA genes. *Subcell. Biochem.*, 61, 211-36. [🔗](#)
- Grummt I & McStay B (2008). The epigenetics of rRNA genes: from molecular to chromosome biology. *Annu Rev Cell Dev Biol*, 24, 131-57. [🔗](#)
- Längst G & Grummt I (2013). Epigenetic control of RNA polymerase I transcription in mammalian cells. *Biochim. Biophys. Acta*, 1829, 393-404. [🔗](#)

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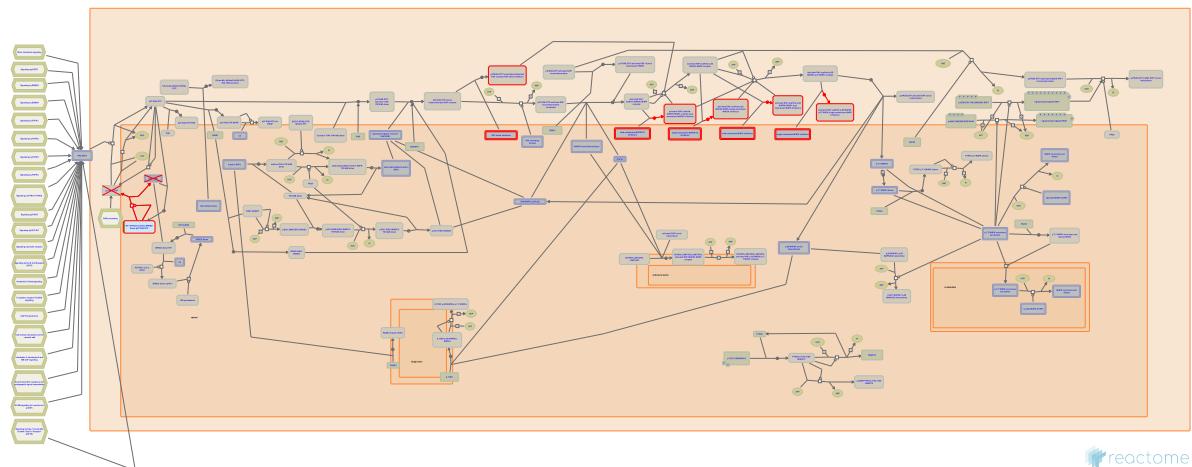
Date	Action	Author
2014-01-29	Edited	May B
2014-01-29	Authored	May B
2014-01-31	Reviewed	May B

Date	Action	Author
2014-01-31	Created	May B
2022-11-19	Modified	Wright A

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
H3C6	P68431	POLR1G	O15446	POLR2E	P19388

21. RAS signaling downstream of NF1 loss-of-function variants (R-HSA-6802953)



Diseases: neurofibromatosis, cancer.

NF1 is a RAS GAP that stimulates the intrinsic RAS GTPase activity, thereby shifting the RAS pathway towards the inactive state (reviewed in King et al, 2013). Loss-of-function mutations in NF1 have been identified both in germline diseases like neurofibromatosis 1 and in a range of sporadically occurring cancers. These mutations, which range from complete gene deletions to missense or frameshift mutations, generally decrease NF1 protein levels and abrogate RAS GAP activity in the cells, resulting in constitutive RAS pathway activation (reviewed in Maertens and Cichowski, 2014; Tidyman and Rauen, 2009; Ratner and Miller, 2015).

References

- Tidyman WE & Rauen KA (2009). The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. *Curr. Opin. Genet. Dev.*, 19, 230-6. [🔗](#)
- Lapinski PE, Lubeck BA & King PD (2013). Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. *Sci Signal*, 6, re1. [🔗](#)
- Cichowski K & Maertens O (2014). An expanding role for RAS GTPase activating proteins (RAS GAPs) in cancer. *Adv Biol Regul*, 55, 1-14. [🔗](#)
- Miller SJ & Ratner N (2015). A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. *Nat. Rev. Cancer*, 15, 290-301. [🔗](#)

Edit history

Date	Action	Author
2015-08-10	Edited	Rothfels K
2015-08-10	Authored	Rothfels K
2015-10-02	Created	Rothfels K
2016-08-05	Modified	Rothfels K
2016-08-05	Reviewed	Stephens RM

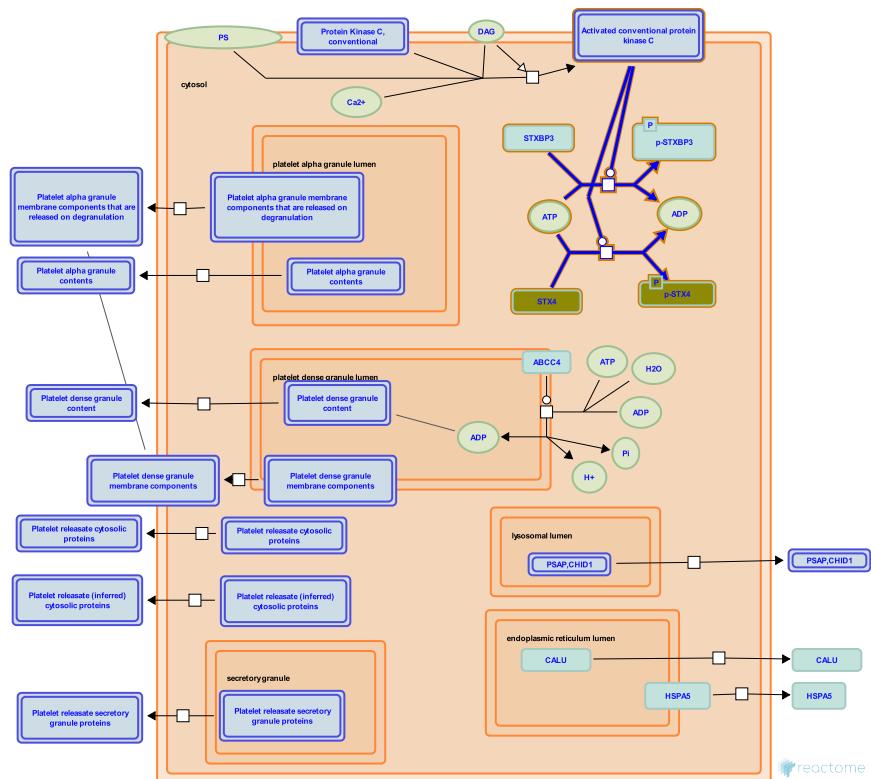
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
VASP	Q2MJR0

Input

UniProt Id

22. Disinhibition of SNARE formation (R-HSA-114516)



The SNARE (SNAP REceptor) family of proteins are critical components of the machinery required for membrane fusion (Söllner et al. 1993, Wu et al. 2017). SNAREs can be grouped into three broad subfamilies: synaptosomal-associated proteins (SNAPS), vesicle-associated membrane proteins (VAMPs) and syntaxins. SNAPS contain two SNARE motifs and lack transmembrane domains, instead they are anchored to the membrane by thioester-linked acyl groups (Hong 2005). VAMPS or R-SNAREs have two subfamilies: short VAMPs or brevins and long VAMPs or longins. Syntaxins are evolutionarily less-well conserved, but except STX11 are transmembrane proteins (Hong 2005). Several SNARE proteins including Syntaxin-2 (STX2), STX4, STX11 and Vesicle-associated membrane protein 8 (VAMP8) are thought to be involved in platelet granule secretion (Golebiewska et al. 2013).

References

Karatekin E, Thiagarajan S, Wu Z & O'Shaughnessy B (2017). Regulation of Exocytotic Fusion Pores by SNARE Protein Transmembrane Domains. *Front Mol Neurosci*, 10, 315. [🔗](#)

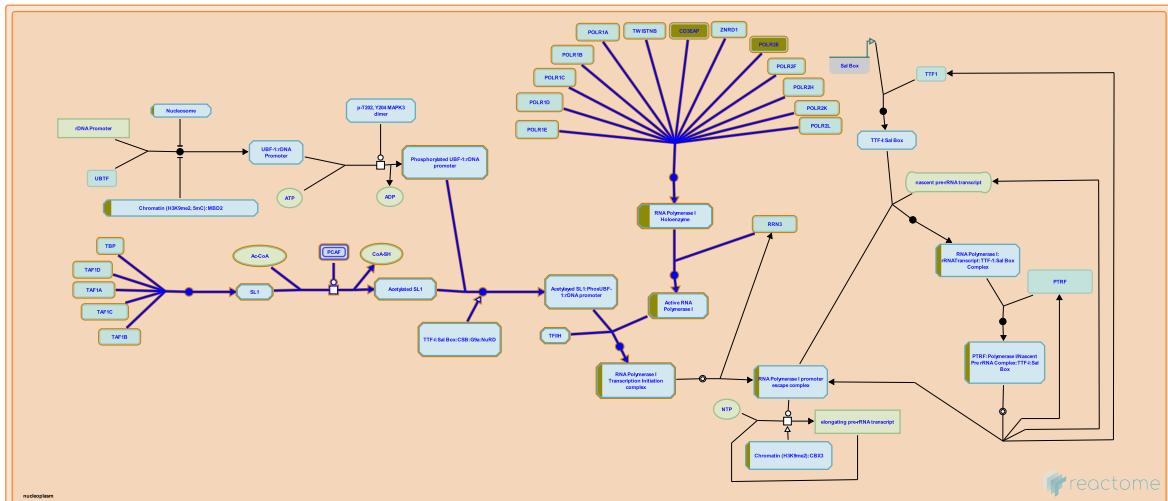
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Date	Action	Author
2004-09-25	Created	Farndale R, Pace NP, de Bono B
2022-11-23	Modified	Wright A

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
STX4	Q12846

23. RNA Polymerase I Transcription Initiation (R-HSA-73762)



Cellular compartments: nucleolus.

During initiation the double-stranded DNA must be melted and transcription begins. SL1 forms and interacts with UBF-1 and the rDNA promoter. It is this platform that will recruit active RNA polymerase I to the SL1:phosphorlated UBF-1:rDNA promoter complex.

Mammalian rRNA genes are preceded by a terminator element that is recognized by the SL1 complex. This SL1 modulated acetylation of the basal Pol I transcription machinery has functional consequences suggesting that the reversible acetylation may be one way to regulate rDNA transcription.

References

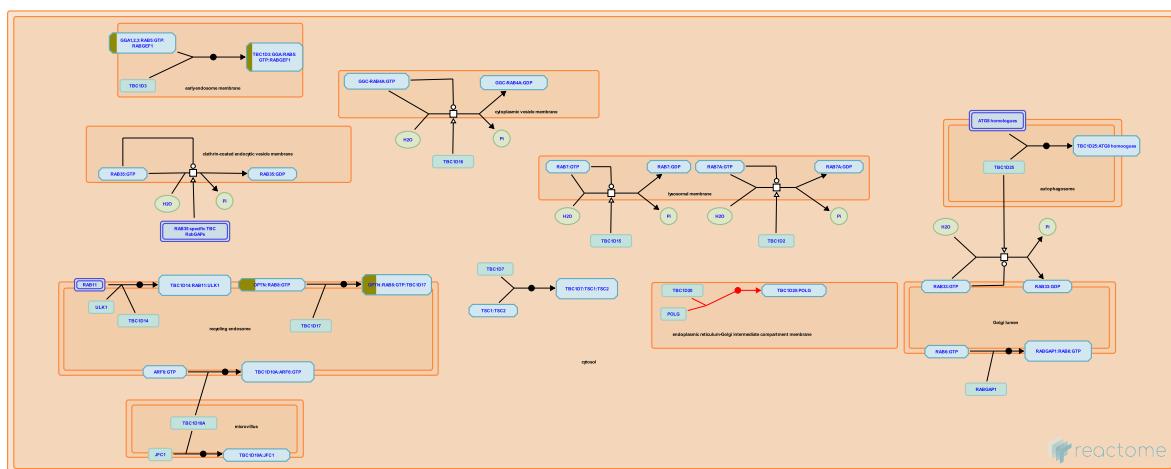
Edit history

Date	Action	Author
2003-07-03	Authored	Comai L
2003-07-03	Created	Comai L
2022-11-17	Edited	Gillespie ME
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
POLR1G	O15446	POLR2E	P19388

24. TBC/RABGAPs (R-HSA-8854214)



Rab GTPases are peripheral membrane proteins involved in membrane trafficking. Often through their indirect interactions with coat components, motors, tethering factors and SNAREs, the Rab GTPases serve as multifaceted organizers of almost all membrane trafficking processes in eukaryotic cells. To perform these diverse processes, Rab GTPases interconvert between an active GTP-bound form and an inactive, GDP-bound form. The GTP-bound activated form mediates membrane transport through specific interaction with multiple effector molecules (Zerial & McBride 2001, Stenmark 2009, Zhen & Stenmark 2015, Cherfils & Zeghouf 2013). Conversion from the GTP- to the GDP-bound form occurs through GTP hydrolysis, which is not only driven by the intrinsic GTPase activity of the Rab protein but is also catalysed by GTPase-activating proteins (GAPs). GAPs not only increase the rate of GTP hydrolysis, but they are also involved in the inactivation of RABs, making sure they are inactivated at the correct membrane. Human cells contain as many as 70 Rabs and at least 51 putative Rab GAPs (Pfeffer 2005). Only a few of these GAPs have been matched to a specific Rab substrate. The Tre-2/Bub2/Cdc16 (TBC) domain-containing RAB-specific GAPs (TBC/RABGAPs) are a key family of RAB regulators, where the TBC domain facilitates the inactivation of RABs by facilitating activation of GTPase activity of the RAB (Pan et al. 2006, Frasa et al. 2012, Stenmark 2009). Studies suggest that TBC/RABGAPs are more than just negative regulators of RABs and can integrate signalling between RABs and other small GTPases, thereby regulating numerous cellular processes like intracellular trafficking (Frasa et al. 2012).

References

- Lambright DG, Pan X, Munson M & Eathiraj S (2006). TBC-domain GAPs for Rab GTPases accelerate GTP hydrolysis by a dual-finger mechanism. *Nature*, 442, 303-6. [\[link\]](#)
- Frasa MA, Braga VM, Ahmadian MR & Koessmeier KT (2012). Illuminating the functional and structural repertoire of human TBC/RABGAPs. *Nat. Rev. Mol. Cell Biol.*, 13, 67-73. [\[link\]](#)

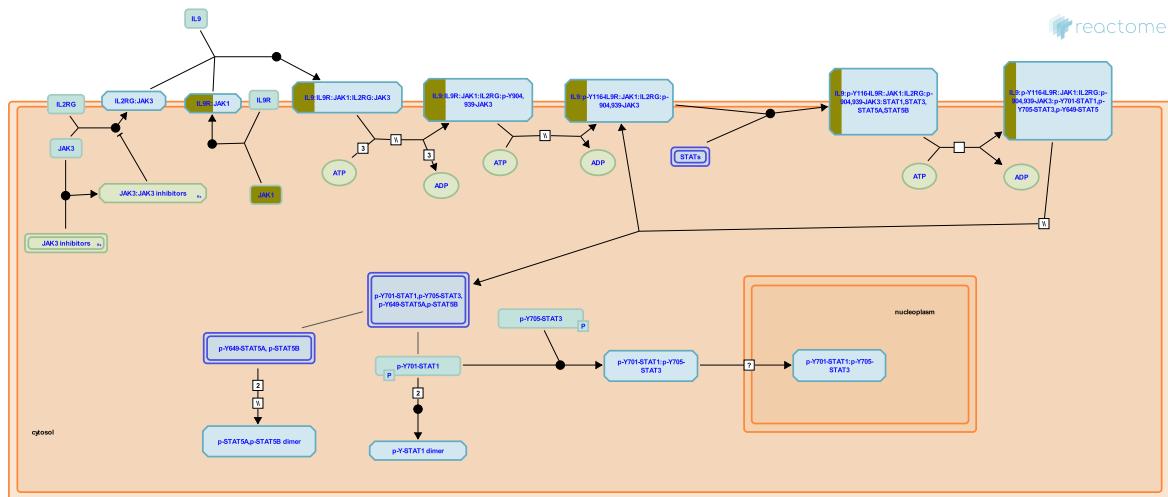
Edit history

Date	Action	Author
2016-01-27	Edited	Garapati P V
2016-01-27	Authored	Garapati P V
2016-01-27	Created	Garapati P V
2022-11-19	Modified	Wright A

2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
GGA1	Q9UJY5	OPTN	Q96CV9

25. Interleukin-9 signaling (R-HSA-8985947)



Interleukin 9 (IL9) binds interleukin 9 receptor α chain (IL9R) and the interleukin 2 receptor common gamma chain (IL2RG) to initiate IL9 signaling downstream cascade. IL9R colocalize with Interleukin 2 receptor β chain and MHC molecules in lipid rafts of human T lymphoma cells (Nizsalóczki et al. 2014). IL2RG is essential for IL9 dependent growth signal transduction (Kimura et al. 1995). IL9R (glycoprotein of 64 kDa) has saturable and specific binding sites with a Kd of 100 pM (Renauld et al. 1992). The activated IL9R complex recruits tyrosine kinase proteins from the Janus kinase (JAK) family: JAK1 (JAK1) and JAK3 (JAK3) for subsequent activation of the Signal transducer and activator of transcription (STAT) factors STAT1, STAT3 and STAT5. The activated STATs form STAT5 dimers and STAT1:STAT3 heterodimers (Neurath & Finotto 2016, Li & Rostami 2010).

References

- Li H & Rostami A (2010). IL-9: basic biology, signaling pathways in CD4+ T cells and implications for autoimmunity. *J Neuroimmune Pharmacol*, 5, 198-209. [🔗](#)
- Nizsalóczki E, Nagy P, Csomós I, Waldmann TA, Goldman CK, Fazekas Z, ... Damjanovich S (2014). Distinct spatial relationship of the interleukin-9 receptor with interleukin-2 receptor and major histocompatibility complex glycoproteins in human T lymphoma cells. *Chemphyschem*, 15, 3969-78. [🔗](#)
- Finotto S & Neurath MF (2016). IL-9 signaling as key driver of chronic inflammation in mucosal immunity. *Cytokine Growth Factor Rev.*, 29, 93-9. [🔗](#)

Edit history

Date	Action	Author
2014-06-04	Authored	Jupe S
2016-01-28	Reviewed	Meldal BH
2017-04-21	Created	Duenas C
2017-05-11	Edited	Jupe S
2018-04-27	Edited	Jassal B
2018-04-27	Reviewed	Limon PL
2022-11-23	Modified	Wright A

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
JAK1	P23458

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.

54 of the submitted entities were found, mapping to 64 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ABCA7	Q8IZY2	ADAMTSL1	Q8N6G6	AK4	P27144
ARHGAP45	Q92619	BTN2A1	Q7KYR7	BTN2A2	Q8WVV5
CCR9	P51686	CD200	P41217	CDC42EP1	Q00587, Q6NZY7
CRADD	P78560	CSNK1E	P49674	DDX17	Q92841
EIF3L	Q9Y262	ERCC1	P07992	ESRRG	P62508
FOSB	O75419	GCAT	O75600	GDPD3	Q7L5L3
GGA1	Q9UJY5	H1-0	P07305	H1-3	P16402
H3C6	P68431, Q71DI3	HSD3B7	Q9H2F3	IFT27	Q9BW83
INO80E	Q8NBZ0	JAK1	P23458	LEPR	P48357-1
LZTFL1	Q9NQ48	MCM10	Q7L590	MVP	Q14764
MYH10	P35580	NDEL1	Q9GZM8	OPTN	Q96CV9
PLXNC1	O60486	POLR1G	O15446	POLR2E	P19388
PPP1R13L	Q8WUF5	RNF40	O75150	SACM1L	Q9NTJ5
SETD1A	O15047, Q9UPS6	SLC14A2	Q15849	SLC6A20	Q9NP91
SLC9C1	Q4G0N8	SLX1A	Q9BQ83	SOCS2	O14508
STX4	Q12846	SULT1A4	P0DMN0	TBX6	O95947
TRIOBP	Q9H2D6-4, Q9H2D6-5	VASP	Q2MJR0	WDR18	Q9BV38
ZNF764	Q96H86	ZNF771	Q7L3S4	ZNF785	A8K8V0

Input	Ensembl Id	Input	Ensembl Id
SOCS2	ENSG00000120833	TBX6	ENSG00000149922

7. Identifiers not found

These 101 identifiers were not found neither mapped to any entity in Reactome.

5MWI_A-078	ABT1	ANKRD54	BCL7C	BTN2A3P	C3orf52	CCDC3	CM03495
CM034966-176	ENSG00000237852	ENSG00000260911	ENSG00000288804	ENSG00000289266	FBRS	FYCO1	GCSA1
H2AC10P	H2AC9P	HCG11	HMGN4	HSALNG0010544	HSALNG0028025	HSALNG0028027	HSALNG0006
HSALNG0070244	HSALNG0070247	HSALNG0093148	HSALNG0093149-001	HSALNG0093149-002	HSALNG0114439	HSALNG0122970	HSALNG01
HSALNG0122974	HSALNG0122975	HSALNG0135322	HSALNG0135324	HSALNG0142416	HSALNG0142718	KRBA2	LEPRC
LGALS2	LINC02980	LOC105369912	LOC107985596	LOC124909374	MIR101-1	MIR567	NPIPBB
NPIPBB13	ORAI3	PPM1N	PRR14	PRRT2	PSMC3P1	RAVER2	RF00017-
RF00017-7032	RNF222	RNU6-1176P	RNU7-43P	RTN2	SAXO1	SETBP1	SMG11
SMG1P5	SPDYE4	SRCAP	TBILA	TPTEP2	USH2A	YPEL3	YPEL3-
ZNF629	ZNF646	ZNF747-DT	Inc-AK4-1	Inc-AK4-2	Inc-CCDC3-1	Inc-CCDC3-2	Inc-CEP
Inc-EPG5-10	Inc-ERCC1-1	Inc-FOSB-1	Inc-FYCO1-4	Inc-FYCO1-5	Inc-GPATCH2-5	Inc-GPATCH2-6	Inc-JAK
Inc-LGALS2-2	Inc-LGALS2-4	Inc-PPP4C-2	Inc-RTN2-1	Inc-TBX6-1	Inc-USH2A-3	piR-30488	piR-394
piR-40203	piR-47028	piR-53168	piR-55598	piR-61753			