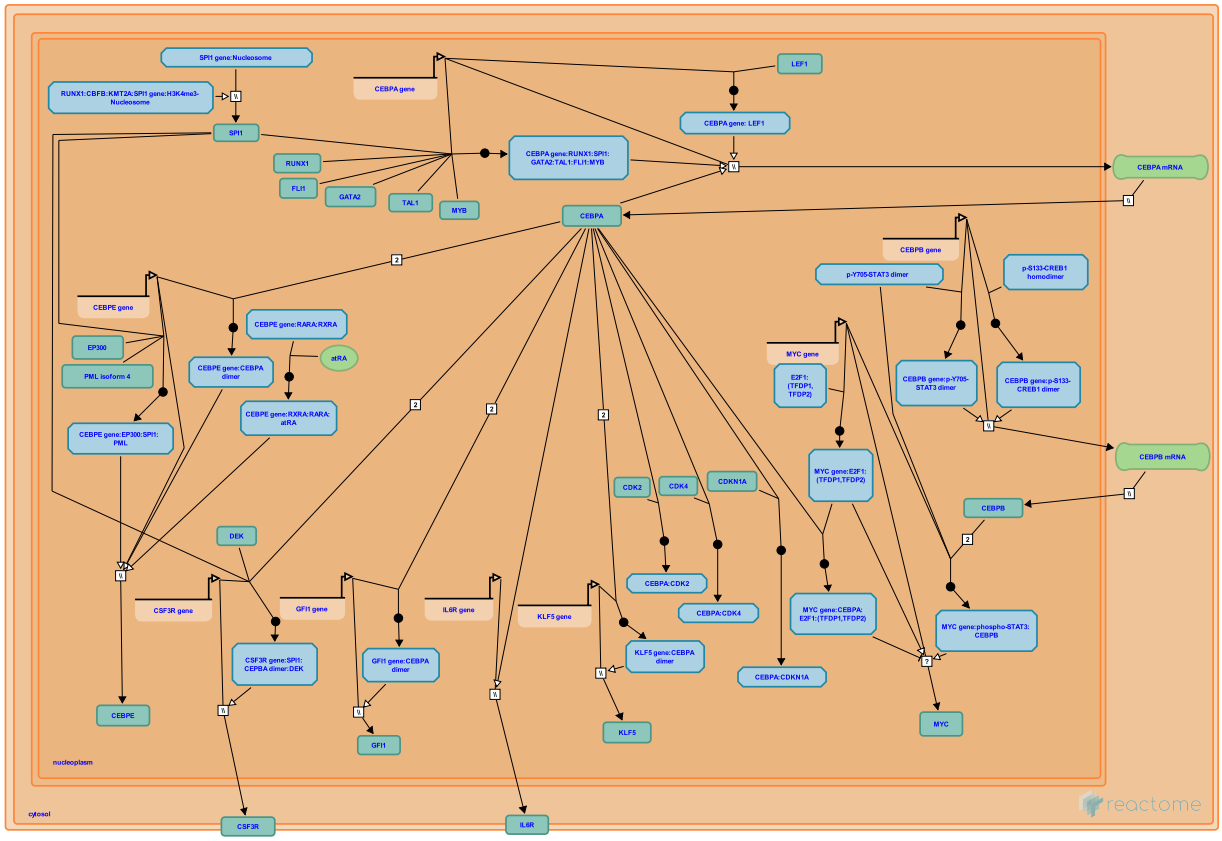
Transcriptional regulation of granulopoiesis



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23/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

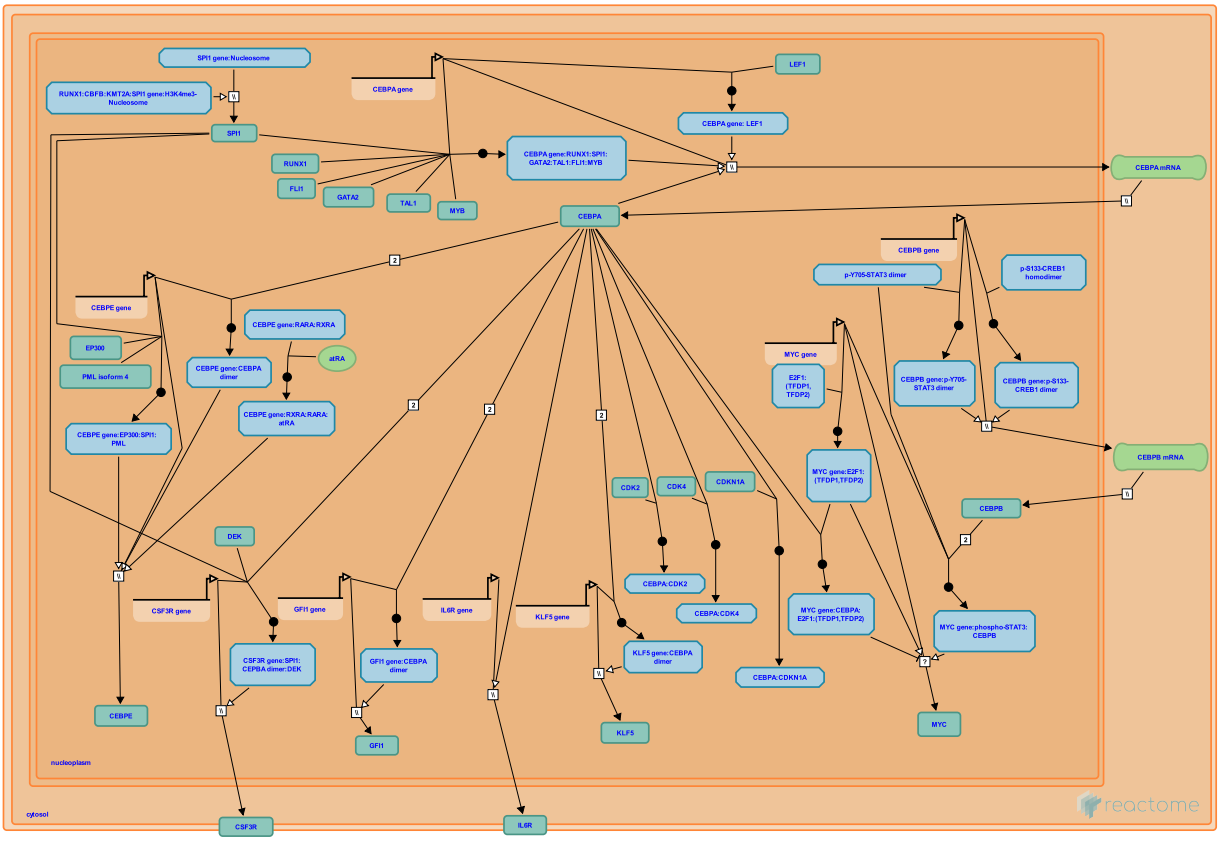
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Transcriptional regulation of granulopoiesis ↗

Stable identifier: 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).

Literature references

Slomiany, BA., D'Arigo, KL., Kurtz, DT., Kelly, MM. (2000). C/EBPalpha inhibits cell growth via direct repression of E2F-DP-mediated transcription. *Mol. Cell. Biol., 20*, 5986-97. ↗

Datta, MW., Zhang, P., Tenen, DG., Darlington, GJ., Iwama, A., Link, DC. (1998). Upregulation of interleukin 6 and granulocyte colony-stimulating factor receptors by transcription factor CCAAT enhancer binding protein alpha (C/EBP alpha) is critical for granulopoiesis. *J. Exp. Med., 188*, 1173-84. ↗

Boettcher, S., Manz, MG. (2014). Emergency granulopoiesis. *Nat. Rev. Immunol., 14*, 302-14. ↗

Watanabe, N., Shibata, F., Nakajima, H., Ikeda, Y., Handa, M., Kitamura, T. (2006). N-terminal region of CCAAT/enhancer-binding protein epsilon is critical for cell cycle arrest, apoptosis, and functional maturation during myeloid differentiation. *J. Biol. Chem., 281*, 14494-502. ↗

Yin, C., Heit, B. (2018). Armed for destruction: formation, function and trafficking of neutrophil granules. *Cell Tissue Res., 371*, 455-471. ↗

Editions

2018-08-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A ↗

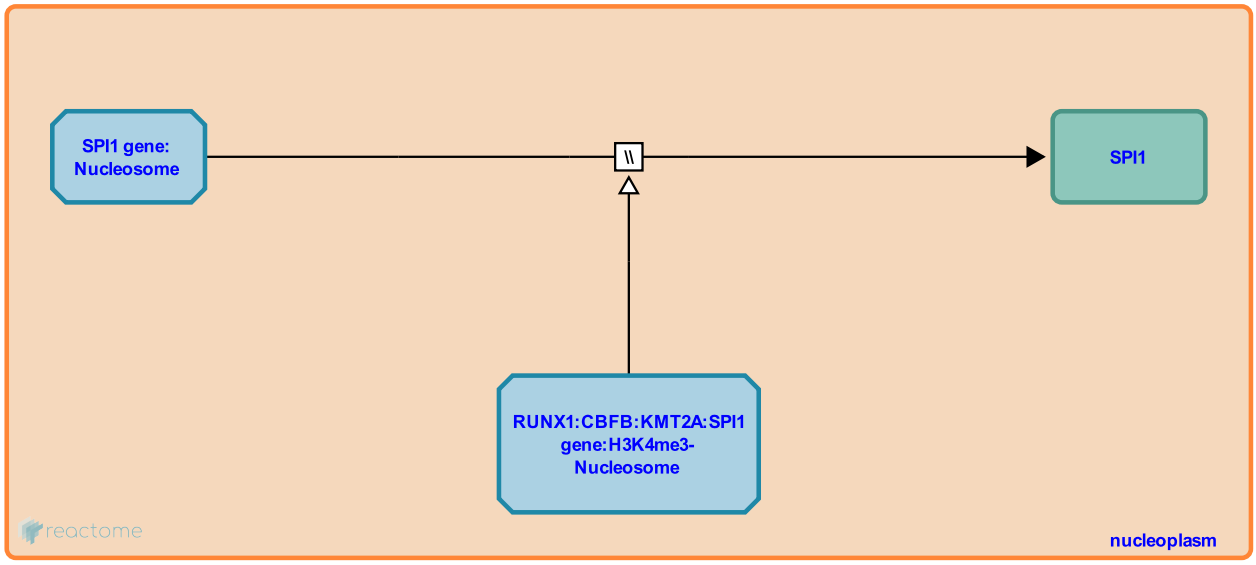
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-8865505

Type: omitted

Compartments: nucleoplasm

Inferred from: Spi1 gene transcription is stimulated by RUNX1:Cbfb:KMT2A (Homo sapiens)



The SPI1 (PU.1) transcription factor represses self renewal and proliferation of HSCs (Fukuchi et al. 2008) and is needed for commitment of HSCs to specific hematopoietic lineages (Imperato et al. 2015), for example differentiation of lymphoid cells. SPI1 gene transcription is directly stimulated by the RUNX1:CBFB transcription factor complex, in the presence of the activating histone methyltransferase KMT2A (MLL) (Huang et al. 2011).

Followed by: SPI1 (PU.1), PML isoform 4, and EP300 bind the promoter of the CEBPE gene, CSF3R gene expression is enhanced by SPI1 (PU.1), CEBPA, and DEK, SPI1 (PU.1), CEBPA and DEK bind the promoter of the CSF3R (G-CSFR) gene, RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, and MYB bind the CEBPA promoter

Literature references

Menendez, S., Zhang, Y., Xu, H., Liu, Y., Tenen, DG., Nimer, SD. et al. (2011). The ability of MLL to bind RUNX1 and methylate H3K4 at PU.1 regulatory regions is impaired by MDS/AML-associated RUNX1/AML1 mutations. *Blood, 118*, 6544-52. ↗

Editions

2016-09-14	Authored	Orlic-Milacic, M.
2016-12-20	Reviewed	Ito, Y., Chuang, LS.
2017-05-09	Edited	Orlic-Milacic, M.
2019-03-10	Reviewed	Skokowa, J.

RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, and MYB bind the CEBPA promoter ↗

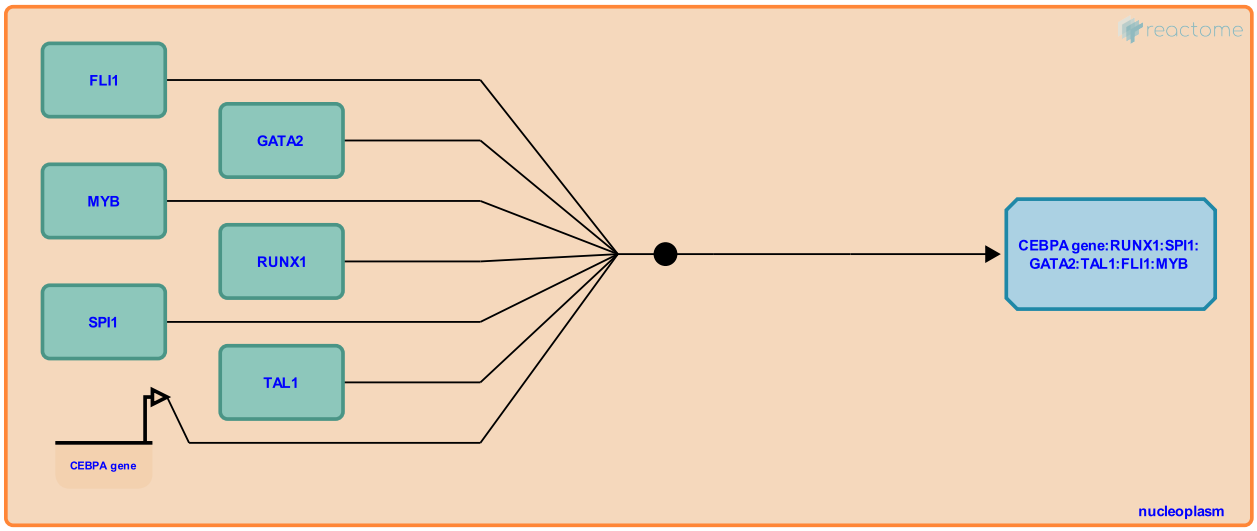
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9616214

Type: binding

Compartments: nucleoplasm

Inferred from: Runx1, Spi1, Gata2, Tal1, Fli1, Myb, and Cebpa bind the promoter of the Cebpa gene (Mus musculus)



The evolutionarily conserved upstream enhancer of the CEBPA gene binds RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, and MYB in hemopoietic progenitor cells and myeloid progenitor cells (inferred from mouse). Unlike the promoter of the mouse Cebpa gene, the human CEBPA promoter does not bind CEBPA and autoregulation of CEBPA occurs indirectly through CEBPA-stimulated binding of USF to the promoter of the CEBPA gene (Timchenko et al. 1995). As inferred from mouse homologs, RUNX1, GATA2, SCL, SPI1, and FLI1 bind concomitantly.

Preceded by: SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A

Followed by: CEBPA gene transcription is enhanced by RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, MYB, LEF1, and CEBPA

Literature references

Taylor, LR., Sawadogo, M., Wilde, M., Timchenko, N., Darlington, GJ., Abdelsayed, S. et al. (1995). Autoregulation of the human C/EBP alpha gene by stimulation of upstream stimulatory factor binding. *Mol. Cell. Biol., 15*, 1192-202. ↗

Editions

2018-08-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

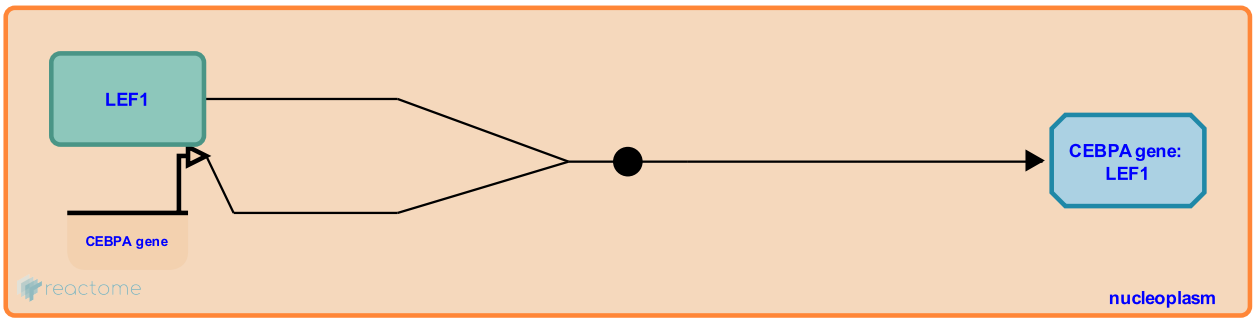
LEF1 binds the promoter of the CEBPA gene ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9622386

Type: binding

Compartments: nucleoplasm



LEF1 binds the CEBPA promoter between 559 bp and 538 bp upstream of the transcription start and directly regulates transcription of CEBPA (Skokowa et al. 2006). LEF1 is most highly expressed in promyelocytes and a reduction of LEF1 expression is associated with neutropenia.
Elevated STAT5A protein binds LEF1, inducing LEF1 degradation and inhibiting LEF1 auto-regulation and activation of LEF1 target genes, MYC, CCND1 (cyclin D1), (BIRC5) Survivin and CEBPA (Gupta et al. 2014).
RUNX1 and LEF1 regulate ELANE (ELA2) mRNA expression in myeloid cells by binding to its promoter (Li et al. 2003).

Literature references

Lehmann, U., Welte, K., Eder, M., Cario, G., Skokowa, J., Grosschedl, R. et al. (2006). LEF-1 is crucial for neutrophil granulocytopoiesis and its expression is severely reduced in congenital neutropenia. *Nat. Med., 12*, 1191-7. ↗

Editions

2018-09-22	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPA gene transcription is enhanced by RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, MYB, LEF1, and CEBPA ↗

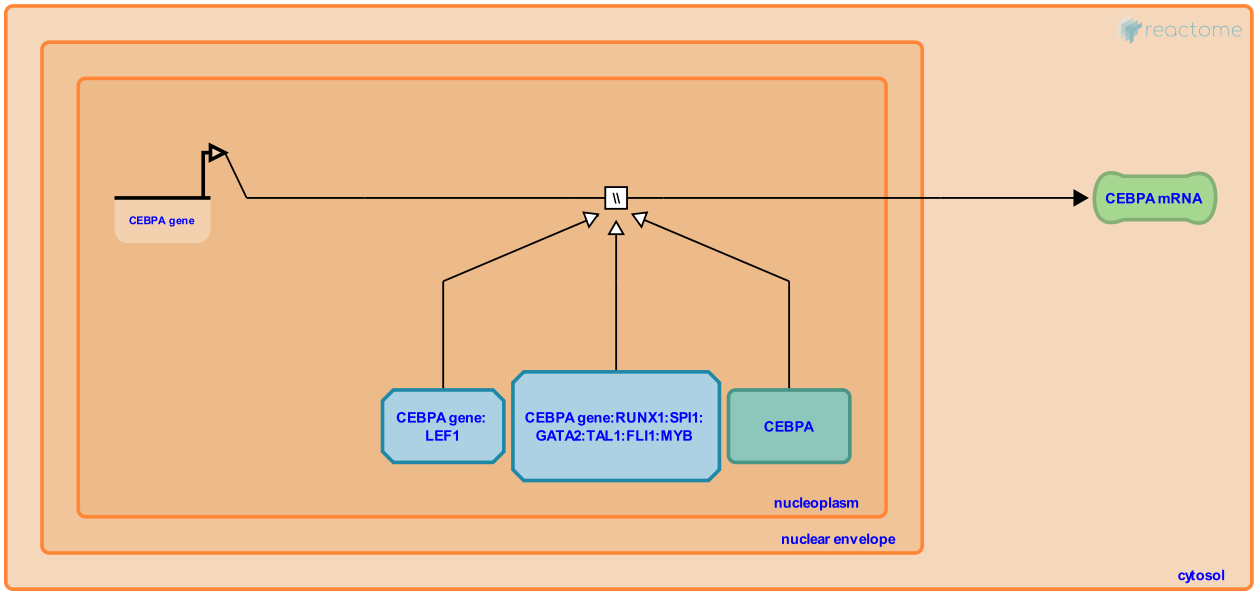
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9616243

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Cebpa transcription is enhanced by Runx1, Spi1 (PU.1), Gata2, Tal1 (Scl), Fli1, Myb, and Cebpa (Mus musculus)



RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), MYB, and CEBPA itself all contribute to the level of transcription of CEBPA in hemopoietic progenitor cells and myeloid progenitor cells (inferred from mouse homologs). High levels of CEBPA appear to favor CEBPA:CEBPA homodimers and lead to granulopoiesis; low levels of CEBPA appear to favor CEBPA:AP-1 heterodimers and lead to monopoiesis. LEF1 also directly activates transcription of CEBPA (Skokowa et al. 2006, Skokowa et al. 2012), but appears to act at the transition of granulocyte-macrophage precursors to promyelocytes, a later stage of granulopoiesis.
The relative levels of SPI1 (PU.1) and CEBPA (SPI1 to CEBPA mRNA expression ratio) in granulocytic–macrophage progenitors have been suggested to regulate monocyte versus neutrophil cell-fate choice (Dahl et al. 2003).

Preceded by: RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, and MYB bind the CEBPA promoter

Followed by: GFI1 gene expression is enhanced by CEBPA, CEBPA mRNA is translated to yield CEBPA protein

Literature references

Lehmann, U., Welte, K., Eder, M., Cario, G., Skokowa, J., Grosschedl, R. et al. (2006). LEF-1 is crucial for neutrophil granulocytopoiesis and its expression is severely reduced in congenital neutropenia. *Nat. Med., 12*, 1191-7. ↗

Carrizosa, E., Welte, K., Gupta, K., Hussein, K., Ganser, A., Klimenkova, O. et al. (2012). Interactions among HCLS1, HAX1 and LEF-1 proteins are essential for G-CSF-triggered granulopoiesis. *Nat. Med., 18*, 1550-9. ↗

Editions

2018-08-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPA mRNA is translated to yield CEBPA protein ↗

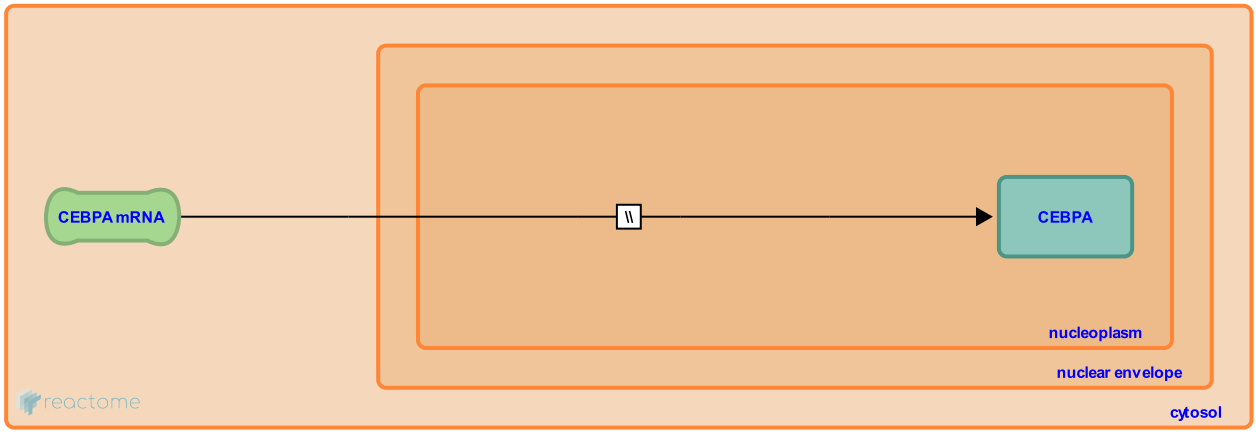
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9622367

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Cebpa mRNA is translated to yield Cebpa protein (Mus musculus)



In the cytosol, 80S ribosomes translate the CEBPA mRNA to yield CEBPA protein (Pabst et al. 2001, Timchenko et al. 2002, Haefliger et al. 2011). Depending on which initiation codon is used, the CEBPA mRNA can be translated to yield a 35.9 kDa protein (p42) or a 25.5 kDa protein (p30). CEBPA protein is then imported into the nucleus. The p30 isoform is not antimitotic (inferred from mouse homologs).

Preceded by: CEBPA gene transcription is enhanced by RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, MYB, LEF1, and CEBPA

Followed by: CSF3R gene expression is enhanced by SPI1 (PU.1), CEBPA, and DEK, IL6R gene expression is enhanced by CEBPA, CEBPA binds the promoter of the GFI1 gene, CEBPA binds CDK2, SPI1 (PU.1), CEBPA and DEK bind the promoter of the CSF3R (G-CSFR) gene, CEBPA binds CDK4, CEBPA binds the promoter of the CEBPE gene, CEBPA binds CDKN1A (p21), CEBPA binds the promoter of the KLF5 gene, CEBPA binds MYC gene:E2F1

Literature references

Timchenko, LT., Cai, ZJ., Timchenko, NA., Iakova, P., Welm, AL. (2002). Calreticulin interacts with C/EBPalpha and C/EBPbeta mRNAs and represses translation of C/EBP proteins. *Mol. Cell. Biol., 22*, 7242-57. ↗

Zhang, P., Behre, G., Narravula, S., Schnittger, S., Mueller, BU., Tenen, DG. et al. (2001). Dominant-negative mutations of CEBPA, encoding CCAAT/enhancer binding protein-alpha (C/EBPalpha), in acute myeloid leukemia. *Nat. Genet., 27*, 263-70. ↗

Haefliger, S., Schaubitzer, K., Klebig, C., Schardt, J., Mueller, BU., Pabst, T. et al. (2011). Protein disulfide isomerase blocks CEBPA translation and is up-regulated during the unfolded protein response in AML. *Blood, 117*, 5931-40. ↗

Editions

2018-09-22	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

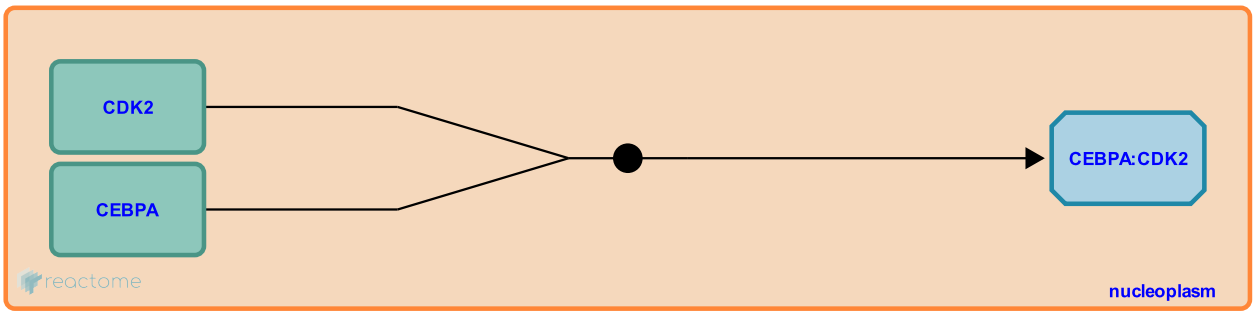
CEBPA binds CDK2 ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9624120

Type: binding

Compartments: nucleoplasm



CEBPA binds CDK2 and disrupts CDK2:cyclin complexes thereby inhibiting kinase activity of CDK2, which may contribute to the inhibition of cellular proliferation observed in response to CEBPA (Wang et al. 2001). CEBPA interacts with the T loop region of CDK2. In mouse liver cells, 35%-50% of Cdk2 is associated with Cebpa (Wang et al. 2001).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Literature references

Welm, A., Iakova, P., Roesler, WJ., Goode, T., Wilde, M., Timchenko, NA. et al. (2001). C/EBPalpha arrests cell proliferation through direct inhibition of Cdk2 and Cdk4. *Mol. Cell, 8*, 817-28. ↗

Nakanishi, M., Albrecht, JH., Harris, TE., Darlington, GJ. (2001). CCAAT/enhancer-binding protein-alpha cooperates with p21 to inhibit cyclin-dependent kinase-2 activity and induces growth arrest independent of DNA binding. *J. Biol. Chem., 276*, 29200-9. ↗

Editions

2018-10-08	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

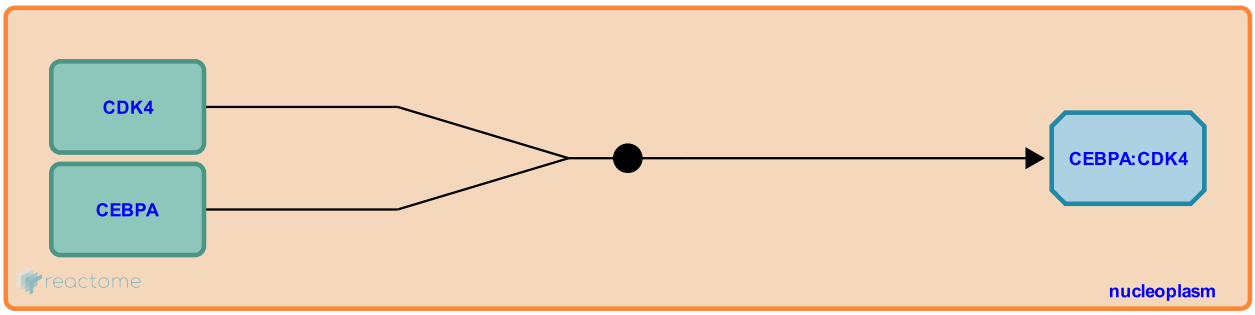
CEBPA binds CDK4 ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9624112

Type: binding

Compartments: nucleoplasm



CEBPA binds CDK4, inhibits the kinase activity of CDK4, and enhances the proteasomal degradation of CDK4 (Wang et al. 2001, Wang et al. 2002). These mechanisms may contribute to the inhibition of cell proliferation observed in response to CEBPA. CEBPA interacts with the T loop region of CDK4. In mouse liver cells, 5%-10% of Cdk4 is associated with Cebpa (Wang et al. 2001).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Literature references

Welm, A., Iakova, P., Roesler, WJ., Goode, T., Wilde, M., Timchenko, NA. et al. (2001). C/EBPalpha arrests cell proliferation through direct inhibition of Cdk2 and Cdk4. *Mol. Cell, 8*, 817-28. ↗

Goode, T., Wang, H., Timchenko, NA., Albrecht, JH., Iakova, P. (2002). C/EBPalpha triggers proteasome-dependent degradation of cdk4 during growth arrest. *EMBO J., 21*, 930-41. ↗

Editions

2018-10-08	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

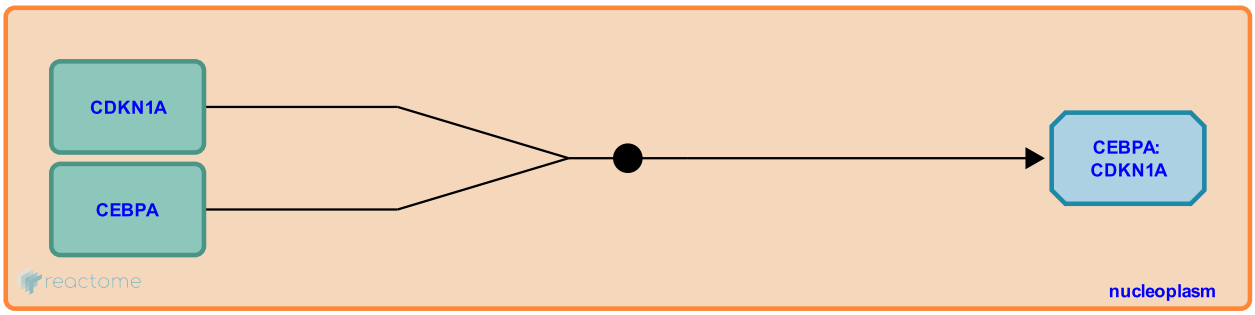
CEBPA binds CDKN1A (p21) ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9624668

Type: binding

Compartments: nucleoplasm



CEBPA interacts with CDKN1A (p21), resulting in a cooperative inhibition of CDK2 and cellular proliferation (Harris et al. 2001). CEBPA also increases the cellular abundance of CDKN1A by stabilizing the CDKN1A protein and activating transcription of the CDKN1A gene (Timchenko et al. 1996, Quintana-Bustamante et al. 2012).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Literature references

Nakanishi, M., Albrecht, JH., Harris, TE., Darlington, GJ. (2001). CCAAT/enhancer-binding protein-alpha cooperates with p21 to inhibit cyclin-dependent kinase-2 activity and induces growth arrest independent of DNA binding. *J. Biol. Chem., 276*, 29200-9. ↗

Nakanishi, M., Wilde, M., Smith, JR., Timchenko, NA., Darlington, GJ. (1996). CCAAT/enhancer-binding protein alpha (C/EBP alpha) inhibits cell proliferation through the p21 (WAF-1/CIP-1/SDI-1) protein. *Genes Dev., 10*, 804-15. ↗

Lan-Lan Smith, S., Quintana-Bustamante, O., Vargaftig, J., Lister, TA., Bonnet, D., Fitzgibbon, J. et al. (2012). Overexpression of wild-type or mutants forms of CEBPA alter normal human hematopoiesis. *Leukemia, 26*, 1537-46. ↗

Editions

2018-10-13	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPA binds the promoter of the CEBPE gene ↗

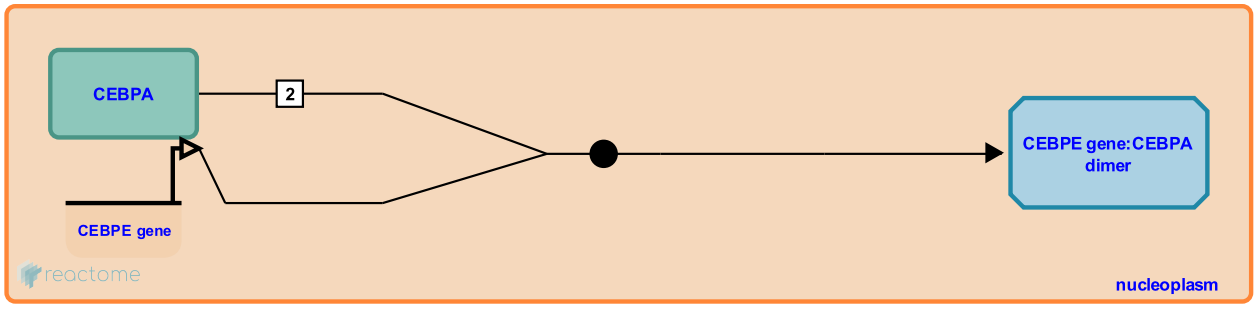
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9616241

Type: binding

Compartments: nucleoplasm

Inferred from: Cebpa binds the promoter of the Cebpe gene (Mus musculus)



CEBPA homodimers bind the promoter of the CEBPE gene (Loke et al. 2018 and inferred from mouse homologs). It is unclear if CEBPA homodimerizes before or during binding to DNA.

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Followed by: CEBPE gene expression is enhanced by CEBPA, SPI1 (PU.1), and retinoic acid

Literature references

Pickin, A., Imperato, MR., Bonifer, C., Ptasinska, A., Cockerill, PN., Loke, J. et al. (2018). C/EBPα overrides epigenetic reprogramming by oncogenic transcription factors in acute myeloid leukemia. *Blood Adv, 2*, 271-284. ↗

Editions

2018-08-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

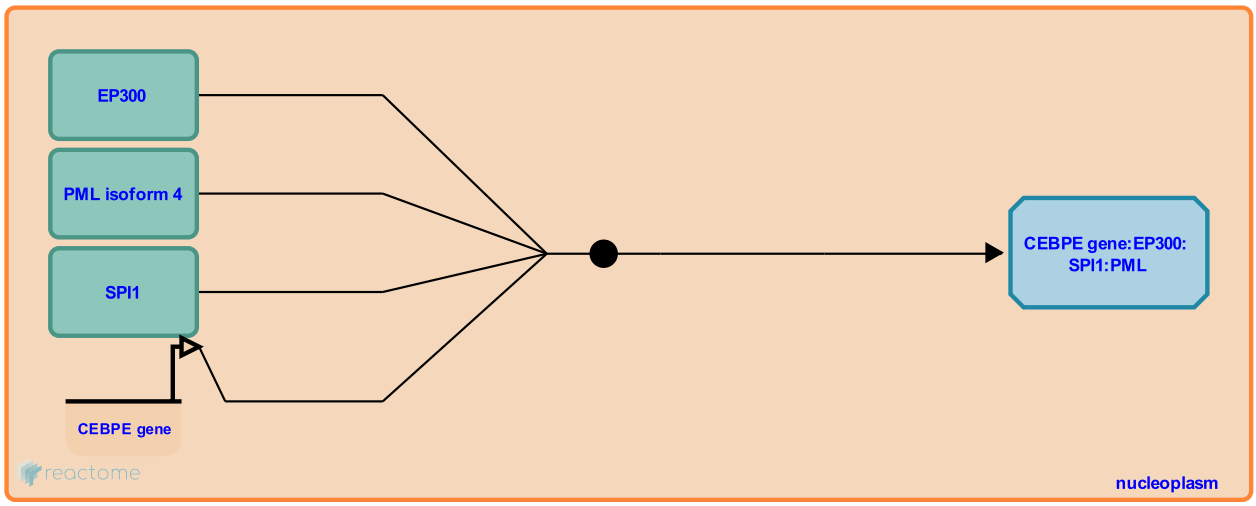
SPI1 (PU.1), PML isoform 4, and EP300 bind the promoter of the CEBPE gene ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617064

Type: binding

Compartments: nucleoplasm



SPI1 (PU.1) binds the promoter of the CEBPE gene. PML (isoform 4) interacts with SPI1 and recruits the coactivator EP300 (p300) to SPI1 (Yoshida et al. 2007). The PML-RARA leukemogenic fusion protein dissociates the SPI1:PML:EP300 complex and inhibits transcription of CEBPE, thereby interfering with granulocyte differentiation (Yoshida et al. 2007).

Preceded by: SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A

Literature references

Pandolfi, PP., Naoe, T., Ichikawa, H., Akao, Y., Yoshida, H., Katsumoto, T. et al. (2007). PML-retinoic acid receptor alpha inhibits PML IV enhancement of PU.1-induced C/EBPepsilon expression in myeloid differentiation. *Mol. Cell. Biol., 27*, 5819-34. ↗

Editions

2018-08-15	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

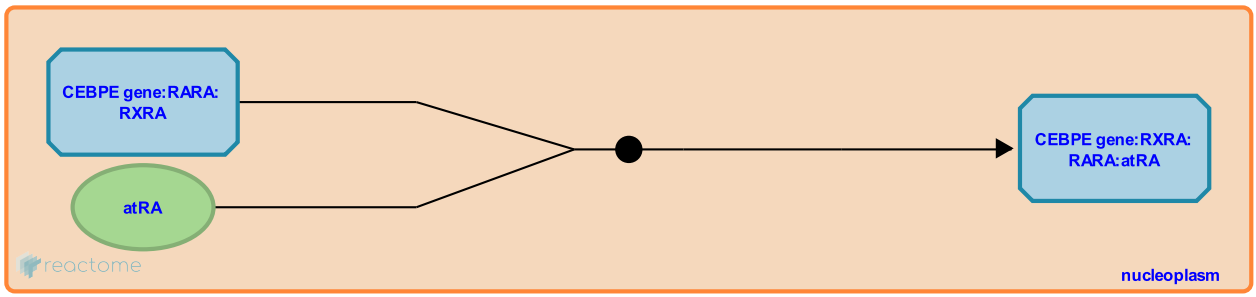
All-trans retinoic acid binds RARA:RXRA at the promoter of the CEBPE gene ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617067

Type: binding

Compartments: nucleoplasm



The RARA:RXR heterodimeric retinoic acid receptor binds a retinoic acid receptor element (RARE) in the promoter of the CEBPE gene (Park et al. 1999). Retinoic acid binds RARA:RXR at the CEBPE gene and activates transcription of CEBPE (Park et al. 1999).

Literature references

Vuong, PT., Park, DJ., Miller, WH., Koeffler, HP., Gombart, AF., Chih, DY. et al. (1999). CCAAT/enhancer binding protein epsilon is a potential retinoid target gene in acute promyelocytic leukemia treatment. *J. Clin. Invest., 103*, 1399-408. ↗

Editions

2018-08-15	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPE gene expression is enhanced by CEBPA, SPI1 (PU.1), and retinoic acid ↗

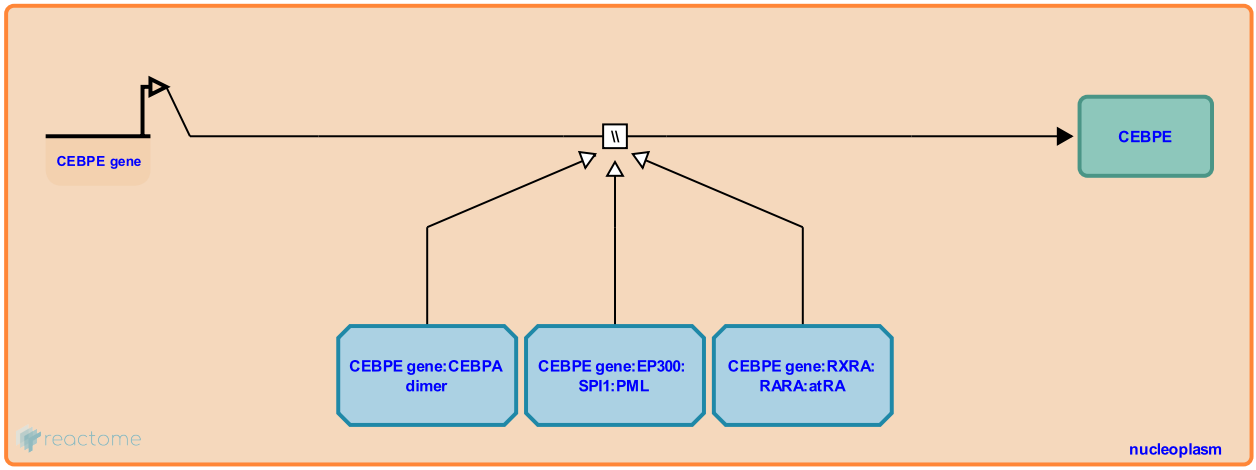
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9634433

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Cebpe gene expression is enhanced by Cebpa (Mus musculus)



CEBPE is expressed exclusively in myeloid progenitor cells and is required for terminal differentiation of granulocyte precursors. Transcription of CEBPE is activated by at least 3 mechanisms:
1) CEBPA dimers bound to the promoter of CEBPE (Yamanaka et al. 1997, Matsushita et al. 2008, Loke et al. 2018, and inferred from mouse homologs),
2) SPI1 (PU.1), PML. and EP300 bound to the promoter of CEBPE (Yoshida et al. 2007), and
3) retinoic acid activation of the RARA:RXR retinoic acid receptor bound to the CEBPE promoter (Park et al. 1999, Verbeek et al. 1999, Cai et al. 2010, Iriyama et al. 2014). Activation of CEBPE by retinoic acid is believed to ameliorate some cases of leukemia (Park et al. 1999).

Preceded by: CEBPA binds the promoter of the CEBPE gene

Literature references

Pandolfi, PP., Naoe, T., Ichikawa, H., Akao, Y., Yoshida, H., Katsumoto, T. et al. (2007). PML-retinoic acid receptor alpha inhibits PML IV enhancement of PU.1-induced C/EBPepsilon expression in myeloid differentiation. *Mol. Cell. Biol., 27*, 5819-34. ↗

Asai, S., Hotta, T., Tsukamoto, H., Nakamura, Y., Nosaka, T., Ando, K. et al. (2008). C/EBPalpha and C/EBPvarepsilon induce the monocytic differentiation of myelomonocytic cells with the MLL-chimeric fusion gene. *Oncogene, 27*, 6749-60. ↗

Horikoshi, A., Takagi, N., Yoshino, Y., Toyoda, H., Takeuchi, J., Takei, M. et al. (2014). Enhancement of differentiation induction and upregulation of CCAAT/enhancer-binding proteins and PU.1 in NB4 cells treated with combination of ATRA and valproic acid. *Int. J. Oncol., 44*, 865-73. ↗

Verbeek, W., Müller, C., Friedman, AD., Koeffler, HP., Gombart, AF., Chumakov, AM. (1999). C/EBPepsilon directly interacts with the DNA binding domain of c-myb and cooperatively activates transcription of myeloid promoters. *Blood, 93*, 3327-37. ↗

Antonson, P., Xanthopoulos, KG., Smith, LT., Tenen, DG., Yamanaka, R., Radomska, HS. et al. (1997). CCAAT/enhancer binding protein epsilon is preferentially up-regulated during granulocytic differentiation and its functional versatility is determined by alternative use of promoters and differential splicing. *Proc. Natl. Acad. Sci. U.S.A., 94*, 6462-7. ↗

Editions

2018-08-14	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPA binds the promoter of the GFI1 gene ↗

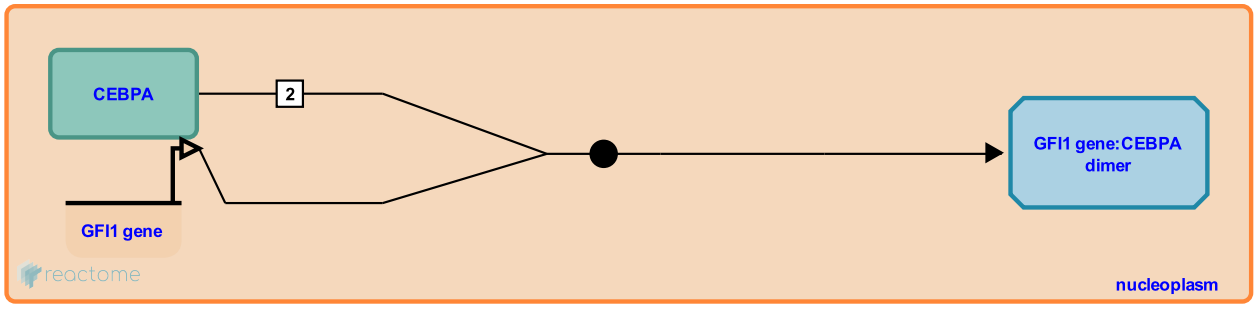
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617087

Type: binding

Compartments: nucleoplasm

Inferred from: Cebpa binds the promoter of the Gfi1 gene (Mus musculus)



CEBPA binds an upstream element in the promoter of the gene encoding the transcriptional repressor GFI1 (inferred from mouse homologs).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Editions

2018-08-15	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

GFI1 gene expression is enhanced by CEBPA ↗

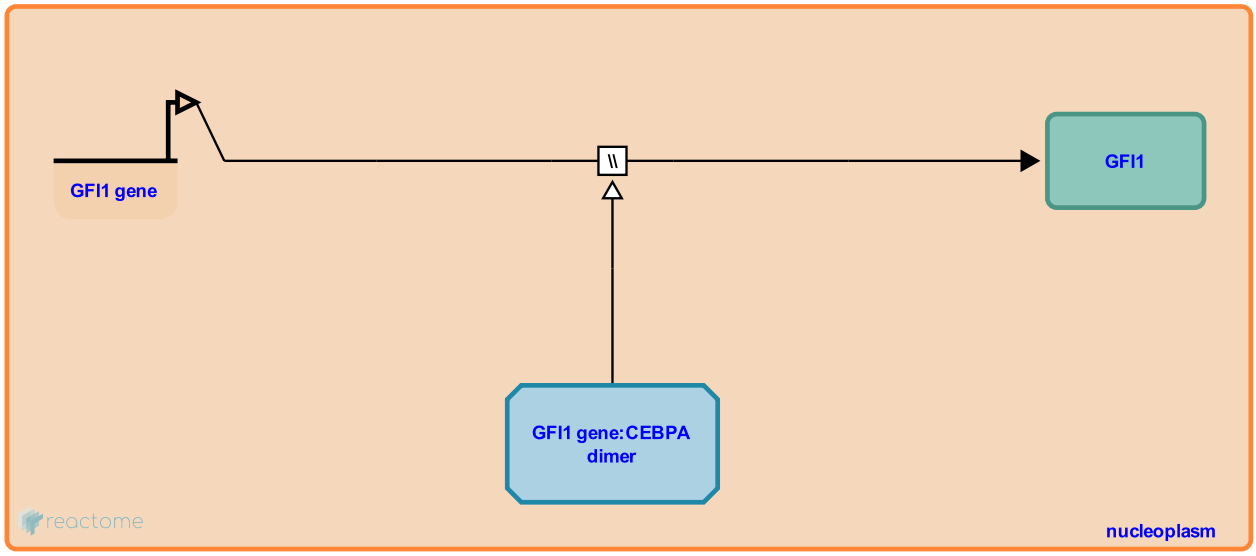
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9634446

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Gfi1 gene expression is enhanced by Cebpa (Mus musculus)



CEBPA bound to the promoter of the GFI1 gene activates transcription of GFI1 approximately 3-fold (inferred from mouse homologs). Activation of the transcription repressor GFI1 by CEBPA is required for the inhibition of cellular proliferation caused by CEBPA (inferred from mouse homologs).

Preceded by: CEBPA gene transcription is enhanced by RUNX1, SPI1 (PU.1), GATA2, TAL1 (SCL), FLI1, MYB, LEF1, and CEBPA

Editions

2018-08-15	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

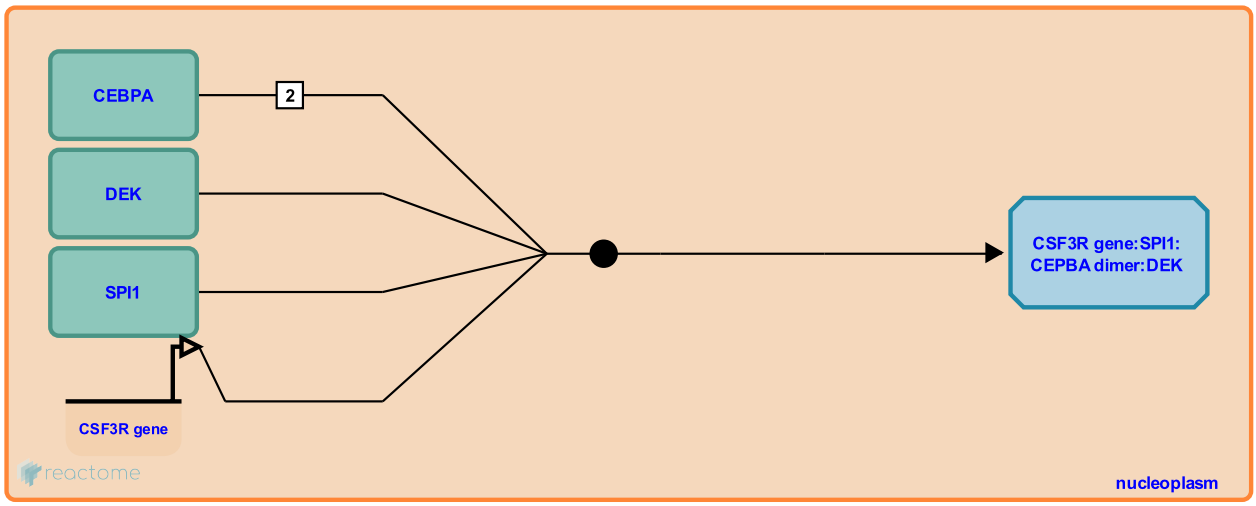
SPI1 (PU.1), CEBPA and DEK bind the promoter of the CSF3R (G-CSFR) gene ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617207

Type: binding

Compartments: nucleoplasm



The promoter of the CSF3R gene contains 2 binding sites for SPI1 (PU.1) in the 5' untranslated region (Smith et al. 1996). The 3' site binds SPI1 less strongly (Smith et al. 1996). SPI1 and CEBPA appear to act synergistically in activating transcription of CSFR3. Chromatin immunoprecipitation indicates CEBPA and DEK1 together bind the CSF3R promoter and depletion of DEK1 reduces activation of transcription by CEBPA (Koleva et al. 2012).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein, SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A

Literature references

Dziennis, SE., Gonzalez, DA., Smith, LT., Tenen, DG., Hohaus, S. (1996). PU.1 (Spi-1) and C/EBP alpha regulate the granulocyte colony-stimulating factor receptor promoter in myeloid cells. *Blood, 88*, 1234-47. ↗

Marto, JA., Webber, JT., Alberta, JA., Carrasco-Alfonso, MJ., Radomska, HS., Marcucci, G. et al. (2012). C/EBPα and DEK coordinately regulate myeloid differentiation. *Blood, 119*, 4878-88. ↗

Editions

2018-08-16	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CSF3R gene expression is enhanced by SPI1 (PU.1), CEBPA, and DEK ↗

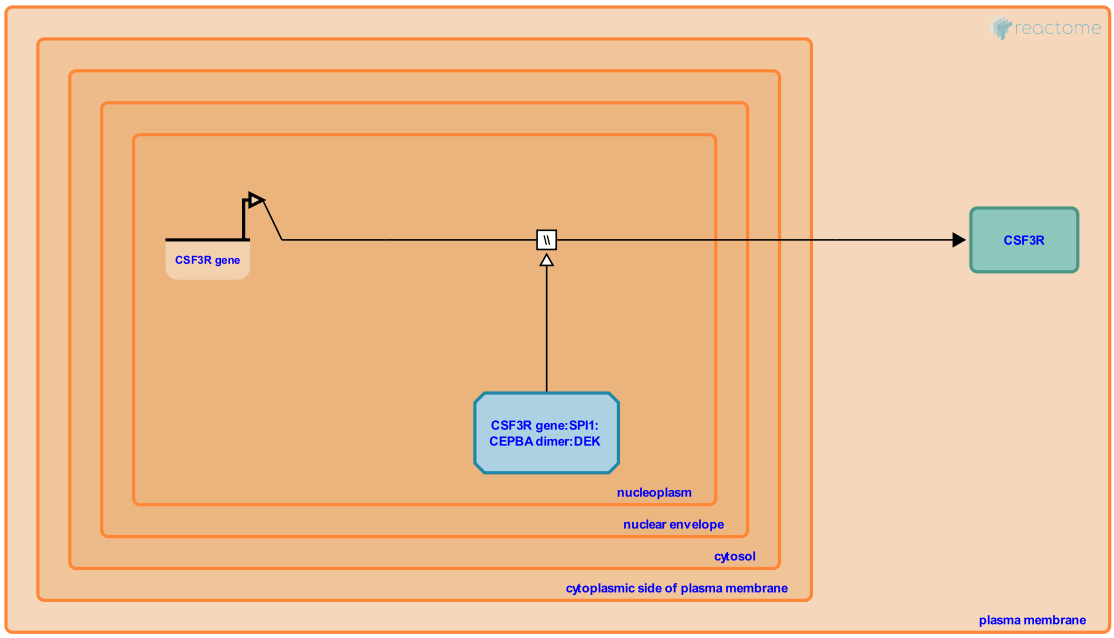
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9634429

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Csf3r gene expression is enhanced by Cebpa (Mus musculus)



SPI1 (PU.1) and CEBPA bind the promoter of the CSF3R (G-CSFR) gene and synergistically activate transcription of CSF3R (Smith et al. 1996, Tavor et al. 2003). Absence of CEBPA binding reduces transcription by about 60% and absence of SPI1 binding reduces transcription by about 75% (Smith et al. 1996). DEK interacts with CEBPA at the CSF3R promoter and enhances transcription (Koleva et al. 2012). DEK is required for CSF3 (G-CSF) mediated granulocyte differentiation (Koleva et al. 2012).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein, SPI1 (PU.1) gene transcription is stimulated by RUNX1:CBFB:KMT2A

Literature references

Vuong, PT., Gery, S., Park, DJ., Gombart, AF., Koeffler, HP., Tavor, S. (2003). Restoration of C/EBPalpha expression in a BCR-ABL+ cell line induces terminal granulocytic differentiation. *J. Biol. Chem., 278*, 52651-9. ↗

Dziennis, SE., Gonzalez, DA., Smith, LT., Tenen, DG., Hohaus, S. (1996). PU.1 (Spi-1) and C/EBP alpha regulate the granulocyte colony-stimulating factor receptor promoter in myeloid cells. *Blood, 88*, 1234-47. ↗

Marto, JA., Webber, JT., Alberta, JA., Carrasco-Alfonso, MJ., Radomska, HS., Marcucci, G. et al. (2012). C/EBPα and DEK coordinately regulate myeloid differentiation. *Blood, 119*, 4878-88. ↗

Editions

2018-08-16	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

IL6R gene expression is enhanced by CEBPA ↗

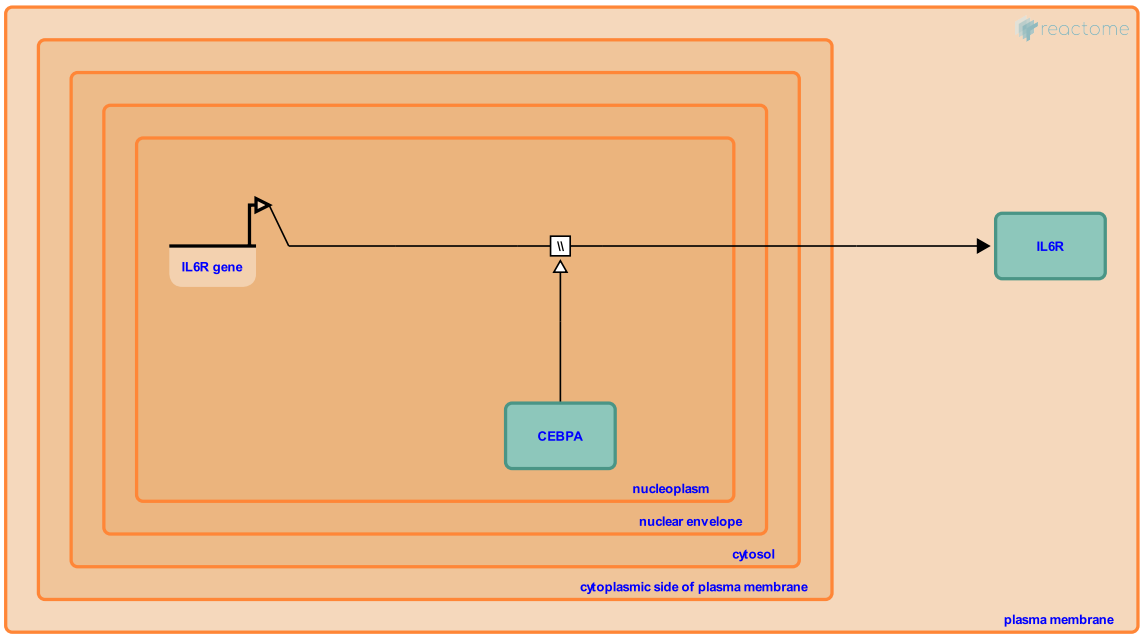
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9634430

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Il6ra gene expression is enhanced by Cebpa (Mus musculus)



CEBPA activates transcription of the IL6R gene, which encodes the receptor for IL6 (interleukin-6, IL-6) (inferred from mouse homologs). Based on inferences from gene knockouts in mice, CEBPA activates both IL6R and CSF3R and is required for granulopoiesis. In mice, the defect in granulopoiesis caused by loss of Cebpa can be rescued by addition of soluble Il6ra plus Il6 or by addition of Csf3r.

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Editions

2018-09-22	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

Phospho-STAT3 binds the promoter of the CEBPB gene ↗

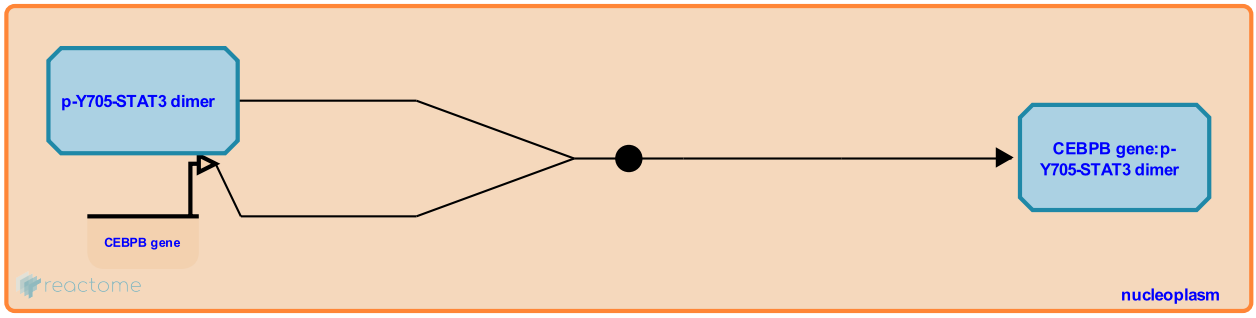
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617194

Type: binding

Compartments: nucleoplasm

Inferred from: Phospho-Stat3 binds the promoter of the Cebpb gene (Mus musculus)



STAT3 that is phosphorylated in response to CSF3 (G-CSF) binds an IL-6 RE II site in the promoter of the CEBPB gene (inferred from mouse homologs). Transcription of CEBPB is activated during "emergency granulopoiesis" by cytokines produced in response to bacterial infection.

Followed by: CEBPB gene transcription is enhanced by phospho-CREB1 and phospho-STAT3

Editions

2018-08-16	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

Phospho-CREB1 binds the promoter of the CEBPB gene ↗

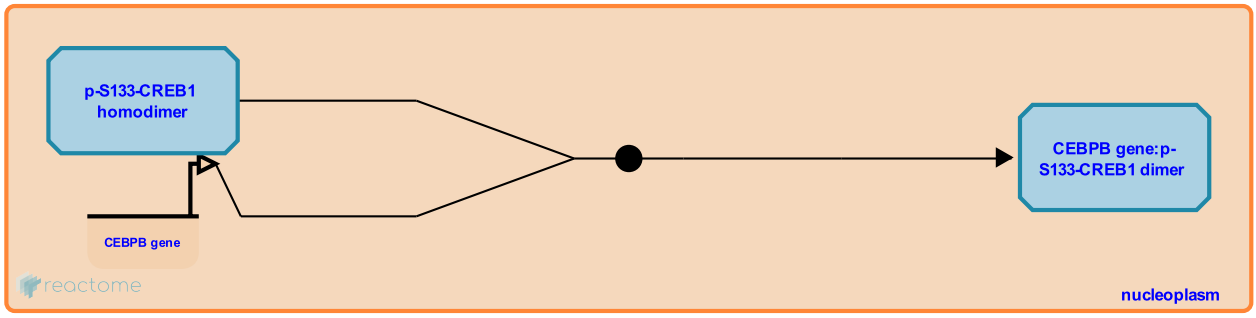
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617217

Type: binding

Compartments: nucleoplasm

Inferred from: Phospho-Creb1 binds the promoter of the Cebpb gene (Mus musculus)



CREB1 that is phosphorylated in response to CSF2 (GM-CSF) binds cyclic AMP responsive elements (CREs) in the promoter of the CEBPB gene (inferred from mouse homologs). Transcription of CEBPB is activated during "emergency granulopoiesis" by cytokines produced in response to bacterial infection.

Followed by: CEBPB gene transcription is enhanced by phospho-CREB1 and phospho-STAT3

Editions

2018-08-16	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPB gene transcription is enhanced by phospho-CREB1 and phospho-STAT3 ↗

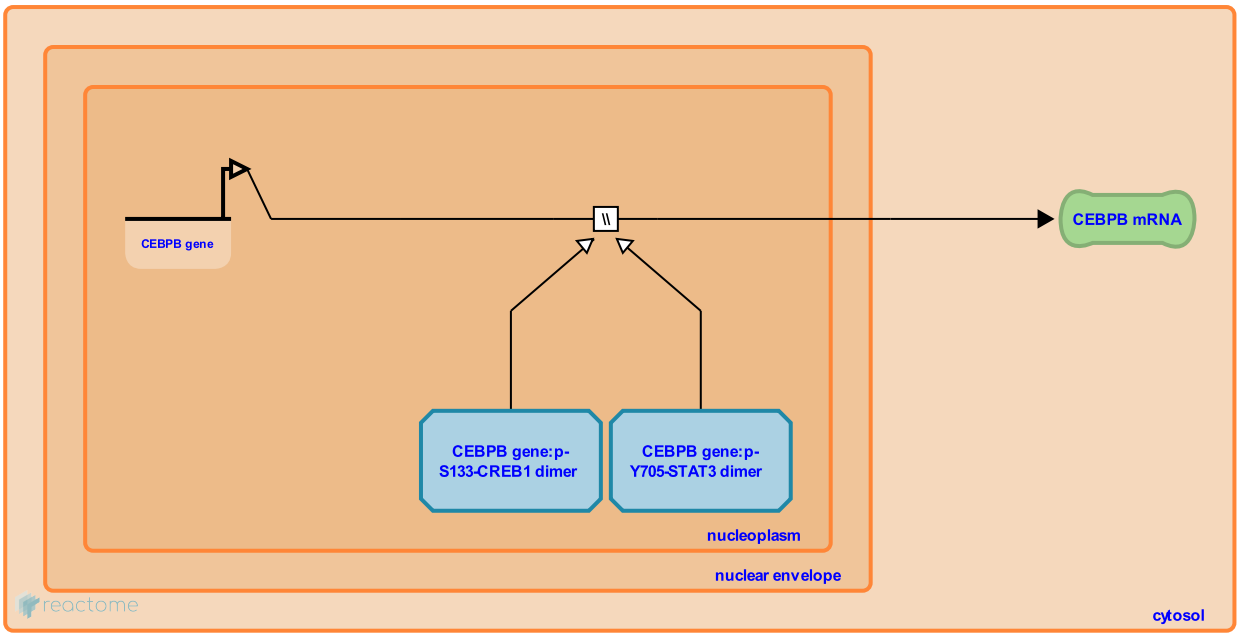
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9617209

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Cebpb gene transcription is enhanced by phospho-Creb1 and phospho-Stat3 (Mus musculus)



During emergency granulopoiesis triggered by bacterial infection, transcription of CEBPB is activated by the cytokines CSF2 (GM-CSF) and CSF3 (G-CSF): CSF2 acts via CSF2R and causes phosphorylation of CREB1, which then binds the promoter of the CEBPB gene (inferred from mouse homologs) while CSF3 acts via CSF3R and causes phosphorylation of STAT3, which also binds the promoter of the CEBPB gene (inferred from mouse homologs). Both phospho-CREB1 and phospho-STAT3 activate transcription of CEBPB (inferred from mouse homologs).

Preceded by: Phospho-STAT3 binds the promoter of the CEBPB gene, Phospho-CREB1 binds the promoter of the CEBPB gene

Followed by: CEBPB mRNA is translated to yield CEBPB protein

Editions

2018-08-16	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPB mRNA is translated to yield CEBPB protein ↗

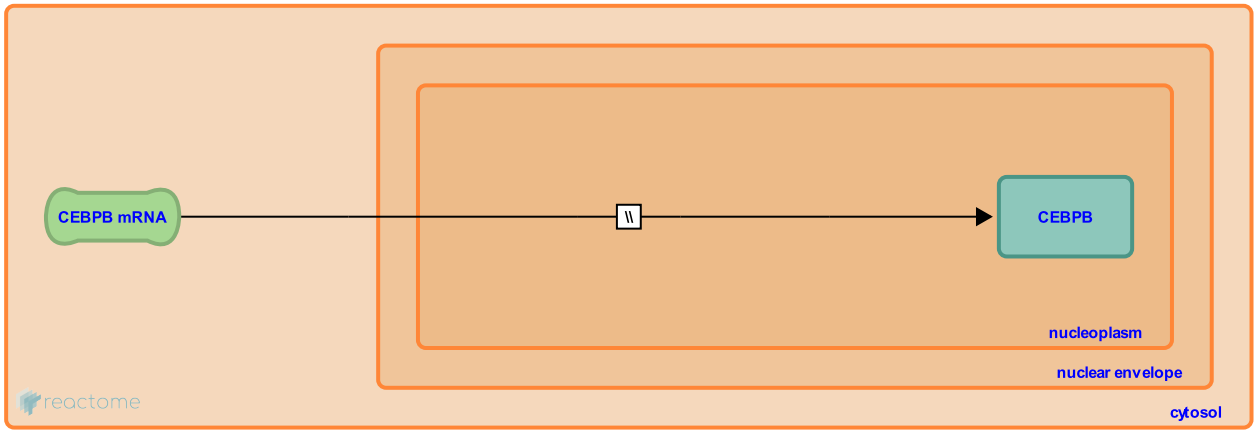
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9622377

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Cebpb mRNA is translated to yield Cebpb protein (Mus musculus)



Cytosolic ribosomes translate the CEBPB mRNA to yield CEBPB protein (Zhang et al. 2015, and inferred from mouse homologs), which is then imported into the nucleus. Translation initiation at 3 different methionine codons produces 3 different isoforms: CEBPB-FL, CEBPB-LAP, and CEBPB-LIP (inferred from mouse homologs).

Preceded by: CEBPB gene transcription is enhanced by phospho-CREB1 and phospho-STAT3

Followed by: CEBPB and phospho-STAT3 bind the promoter of the MYC gene

Literature references

Chen, K., Zhang, XF., Tu, RF., Zhang, JB., Li, KK., Gao, L. et al. (2015). miR-191 promotes tumorigenesis of human colorectal cancer through targeting C/EBPβ. *Oncotarget, 6*, 4144-58. ↗

Editions

2018-09-22	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

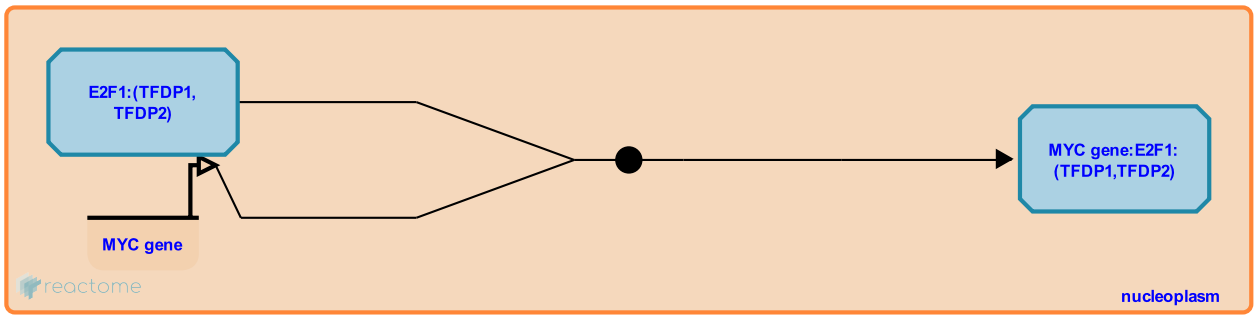
E2F1 binds the promoter of the MYC gene ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9618586

Type: binding

Compartments: nucleoplasm



The transcription factor E2F1 in a complex with TFDP1 or TFDP2 binds two elements in the P2 promoter of the MYC gene and activates transcription (Hiebert et al. 1989, Thalmeier et al. 1989, Weinmann et al. 2001). An intact E2F1 binding site is required for activation of MYC by adenoviral E1a proteins (Hiebert et al. 1989, Thalmeier et al. 1989).

Followed by: MYC gene expression is enhanced by E2F1, STAT3, and CEBPB and repressed by CEBPA, CEBPA binds MYC gene:E2F1

Literature references

Nevins, JR., Lipp, M., Hiebert, SW. (1989). E1A-dependent trans-activation of the human MYC promoter is mediated by the E2F factor. *Proc. Natl. Acad. Sci. U.S.A., 86*, 3594-8. ↗

Bartley, SM., Weinmann, AS., Farnham, PJ., Zhang, T., Zhang, MQ. (2001). Use of chromatin immunoprecipitation to clone novel E2F target promoters. *Mol. Cell. Biol., 21*, 6820-32. ↗

Lipp, M., Mertz, R., Synovzik, H., Thalmeier, K., Winnacker, EL. (1989). Nuclear factor E2F mediates basic transcription and trans-activation by E1a of the human MYC promoter. *Genes Dev., 3*, 527-36. ↗

Editions

2018-09-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPA binds MYC gene:E2F1 ↗

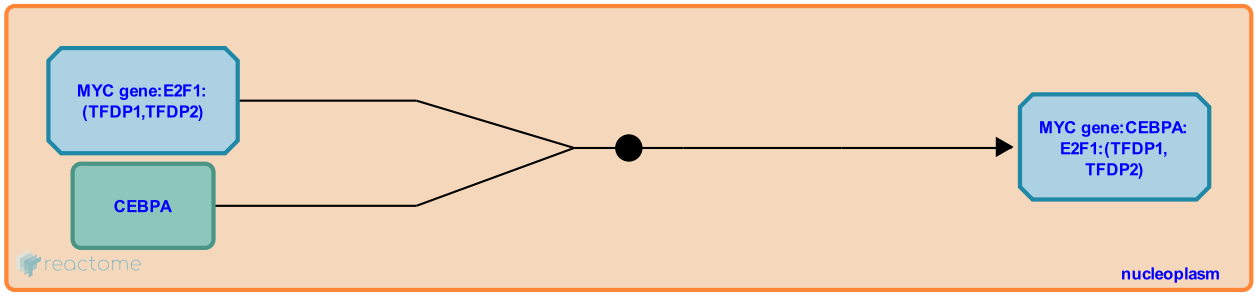
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9618582

Type: binding

Compartments: nucleoplasm

Inferred from: Cebpa binds Myc gene:E2f1 (Mus musculus)



CEBPA interacts with E2F1 (Keeshan et al. 2003) bound to the promoter of the MYC gene (Johansen et al. 2001, D'Alo' et al.2003, also inferred from mouse homologs). CEBPA inhibits the transcriptional activation activity of E2F1 and inhibits transcription of MYC. By inhibiting MYC, CEBPA inhibits cell proliferation and promotes differentiation (Johansen et al. 2001, D'Alo' et al. 2003). The N terminus of the p42 isoform of CEBPA is required for interaction with E2F factors (inferred from mouse homologs) and therefore the p30 isoform, which lacks the N terminus, has a reduced ability to inhibit proliferation.

Preceded by: CEBPA mRNA is translated to yield CEBPA protein, E2F1 binds the promoter of the MYC gene

Followed by: MYC gene expression is enhanced by E2F1, STAT3, and CEBPB and repressed by CEBPA

Literature references

Calabretta, B., Keeshan, K., Santilli, G., Perrotti, D., Corradini, F. (2003). Transcription activation function of C/EBPalpha is required for induction of granulocytic differentiation. *Blood, 102*, 1267-75. ↗

Felsher, DW., Tenen, DG., Lodie, TA., Johansen, LM., Sasaki, K., Iwama, A. et al. (2001). c-Myc is a critical target for c/EBPalpha in granulopoiesis. *Mol. Cell. Biol., 21*, 3789-806. ↗

Evans, EK., Nerlov, C., Radomska, HS., Nelson, EA., Johansen, LM., Zhang, P. et al. (2003). The amino terminal and E2F interaction domains are critical for C/EBP alpha-mediated induction of granulopoietic development of hematopoietic cells. *Blood, 102*, 3163-71. ↗

Editions

2018-09-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

CEBPB and phospho-STAT3 bind the promoter of the MYC gene ↗

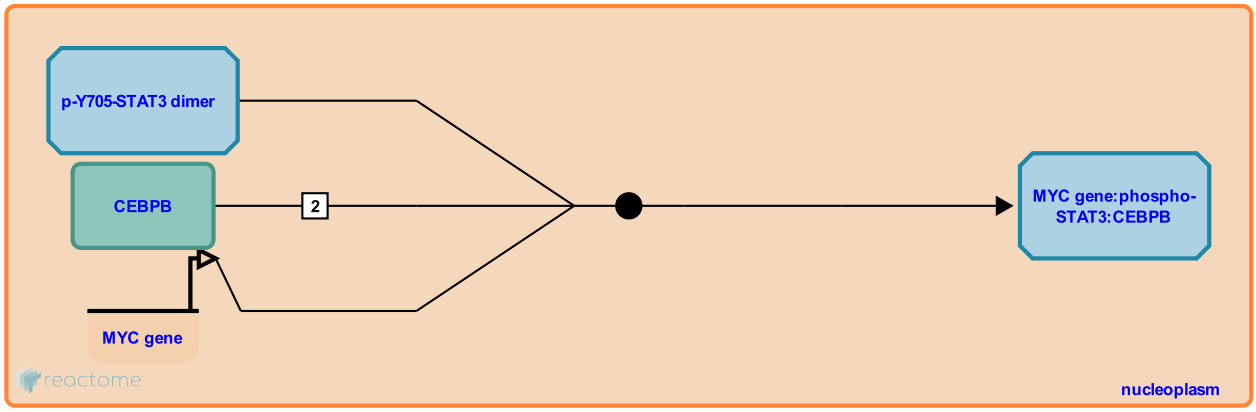
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9618584

Type: binding

Compartments: nucleoplasm

Inferred from: Cebpb and phospho-Stat3 bind the promoter of the Myc gene (Mus musculus)



Activated (phosphorylated) STAT3 activates transcription of CEBPB and both phospho-STAT3 and CEBPB bind the promoter of the MYC gene (inferred from mouse homologs). The expression of MYC enhances proliferation of myeloid progenitors during emergency granulopoiesis in response to bacterial infection.

Preceded by: CEBPB mRNA is translated to yield CEBPB protein

Followed by: MYC gene expression is enhanced by E2F1, STAT3, and CEBPB and repressed by CEBPA

Editions

2018-09-10	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

MYC gene expression is enhanced by E2F1, STAT3, and CEBPB and repressed by CEBPA ↗

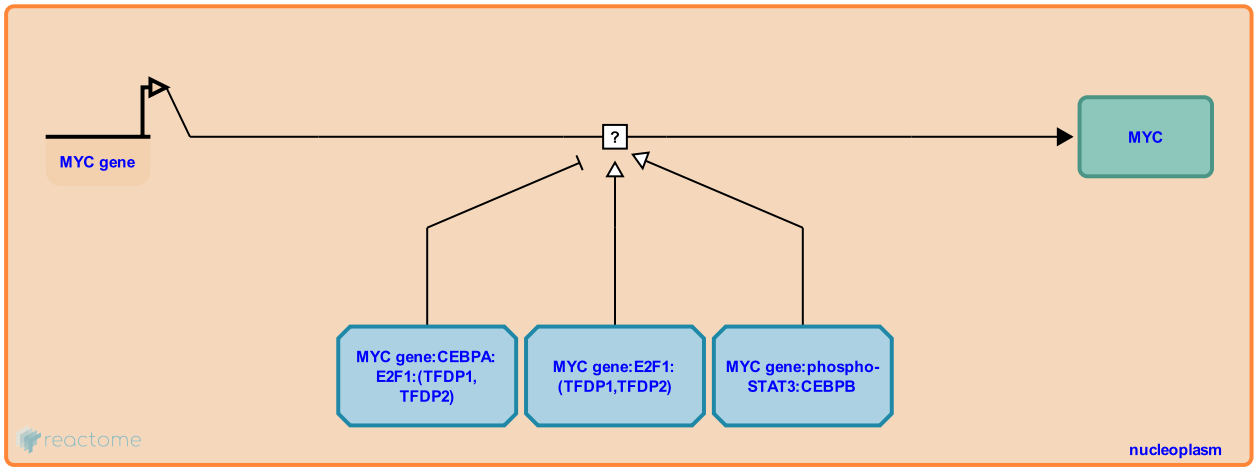
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9634445

Type: uncertain

Compartments: nucleoplasm, cytosol

Inferred from: Myc gene expression is enhanced by E2f1, phospho-Stat3, and Cebpb and repressed by Cebpa (Mus musculus)



E2F1, phospho-STAT3, and CEBPB bind the promoter of the MYC gene and enhance transcription while CEBPA interacts with E2F1 at the MYC promoter and inhibits transcription (D'Alo' et al. 2003, Tavor et al. 2003, Hirai et al. 2006, and inferred from mouse homologs). CEBPB reduces the residency of CEBPA at the MYC promoter (inferred from mouse homologs). CEBPB appears to inhibit expression of MYC less than CEBPA does (Hirai et al. 2006), thus the ratio of CEBPB and CEBPA is believed to determine the proliferation (promoted by CEBPB) and differentiation (promoted by CEBPA) of neutrophil progenitors.

Preceded by: CEBPB and phospho-STAT3 bind the promoter of the MYC gene, E2F1 binds the promoter of the MYC gene, CEBPA binds MYC gene:E2F1

Literature references

Vuong, PT., Gery, S., Park, DJ., Gombart, AF., Koeffler, HP., Tavor, S. (2003). Restoration of C/EBPalpha expression in a BCR-ABL+ cell line induces terminal granulocytic differentiation. *J. Biol. Chem., 278*, 52651-9. ↗

Hirai, H., Dayaram, T., Hetherington, CJ., Imanishi, J., Zhang, P., Tenen, DG. et al. (2006). C/EBPbeta is required for 'emergency' granulopoiesis. *Nat. Immunol., 7*, 732-9. ↗

Evans, EK., Nerlov, C., Radomska, HS., Nelson, EA., Johansen, LM., Zhang, P. et al. (2003). The amino terminal and E2F interaction domains are critical for C/EBP alpha-mediated induction of granulopoietic development of hematopoietic cells. *Blood, 102*, 3163-71. ↗

Editions

2018-08-30	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

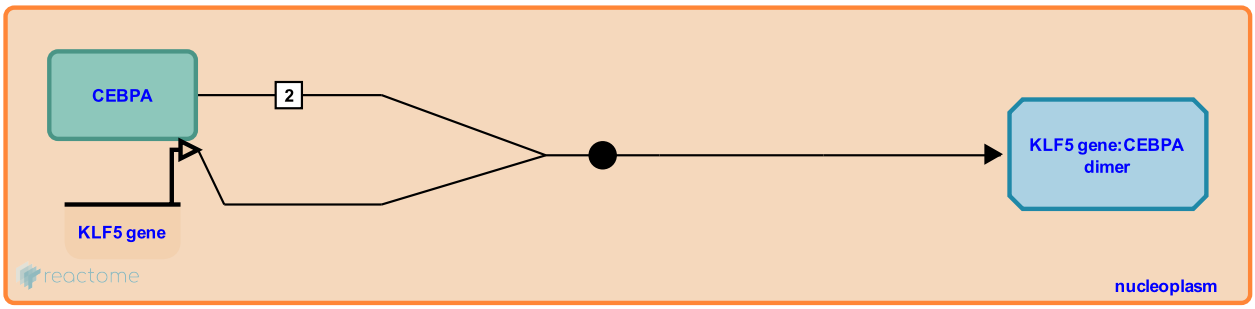
CEBPA binds the promoter of the KLF5 gene ↗

Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9622363

Type: binding

Compartments: nucleoplasm



CEBPA binds sites located 385 bp and 1576 bp upstream of the transcription start site in the promoter of the KLF5 gene (Federzoni et al. 2014).

Preceded by: CEBPA mRNA is translated to yield CEBPA protein

Followed by: KLF5 gene expression is enhanced by CEBPA

Literature references

Tschan, MP., Humbert, M., Fey, MF., Federzoni, EA., Behre, G., Torbett, BE. (2014). CEBPA-dependent HK3 and KLF5 expression in primary AML and during AML differentiation. *Sci Rep, 4*, 4261. ↗

Editions

2018-09-22	Authored, Edited	May, B.
2019-03-10	Reviewed	Skokowa, J.

KLF5 gene expression is enhanced by CEBPA ↗

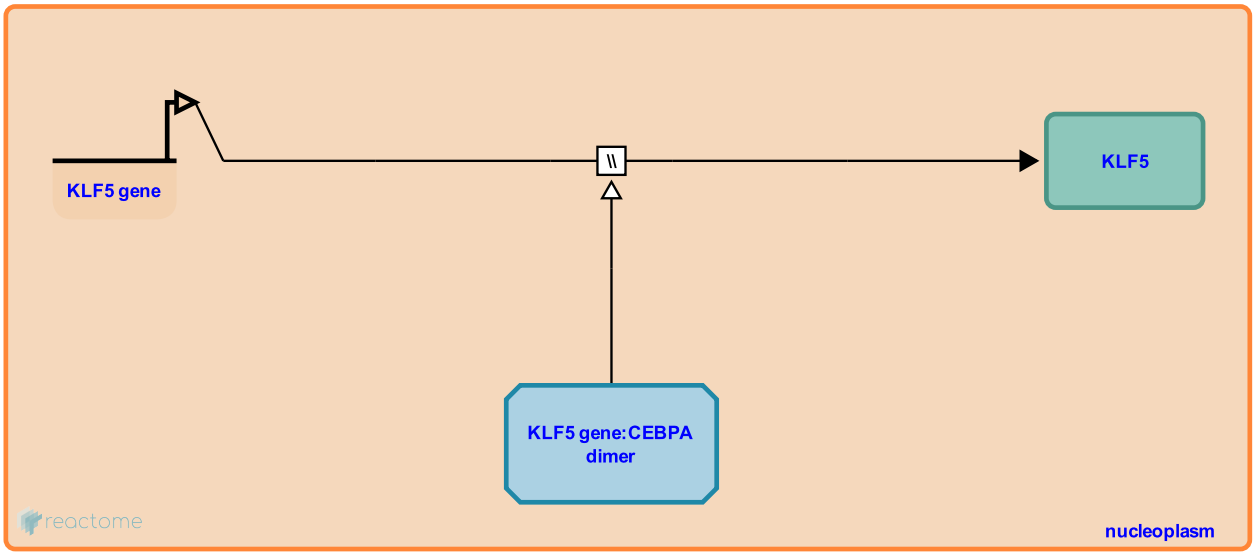
Location: Transcriptional regulation of granulopoiesis

Stable identifier: R-HSA-9634442

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Klf5 gene expression is enhanced by Cebpa (Mus musculus)



CEBPA binds two sites in the promoter of the KLF5 gene and activates transcription (Federzoni et al. 2014, and inferred from mouse homologs). An indirect mechanism of activation may exist, as mutation of the CEBPA binding sites does not impair activation of KLF5 by CEBPA (Federzoni et al. 2014). In mouse 32D cells, KLF5 is required for granulocyte differentiation and in some cases of human acute myelogenous leukemia (AML), KLF5 is silenced by hypermethylation (Diakiw et al. 2012).

Preceded by: CEBPA binds the promoter of the KLF5 gene

Literature references

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Editions

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