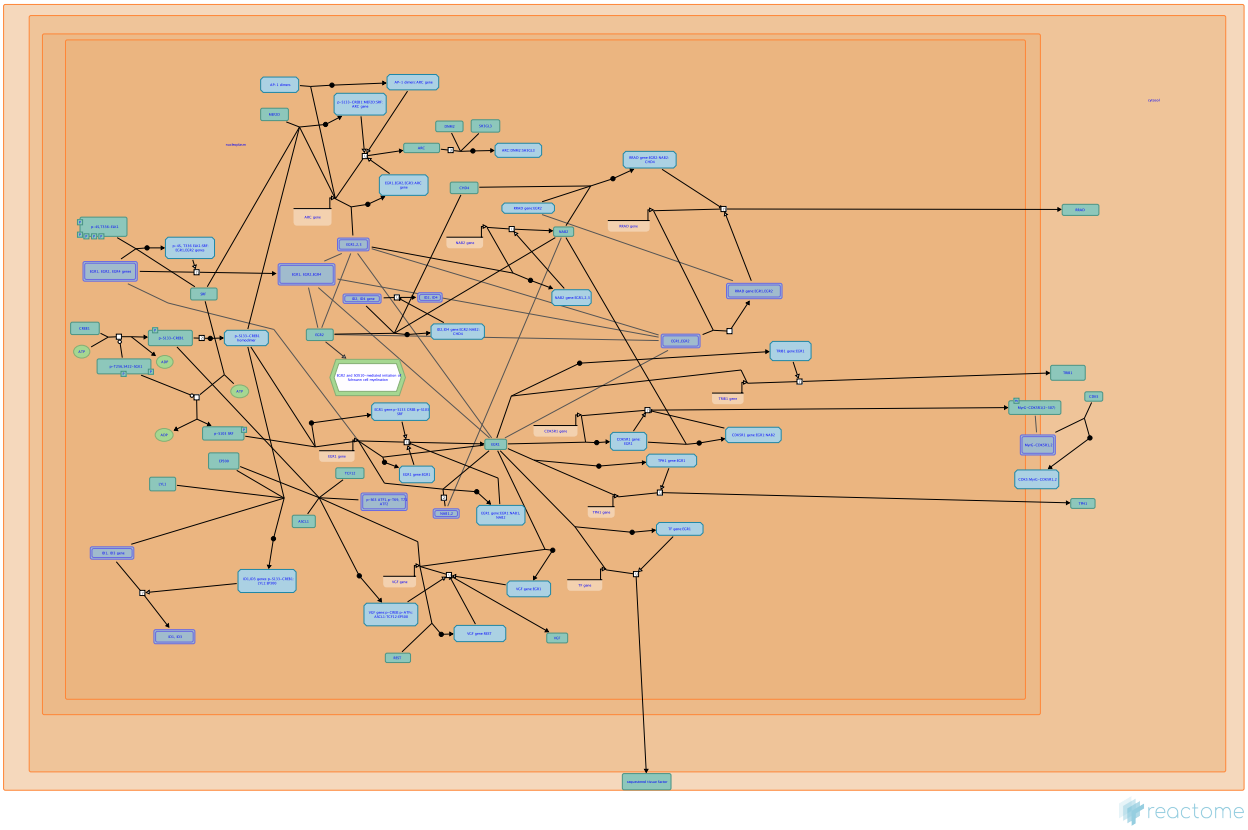
NGF-stimulated transcription



Aletta, J M., Castagnoli, L., Jassal, B., Le Novere, N., Rothfels, K.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

10/09/2021

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. ↗

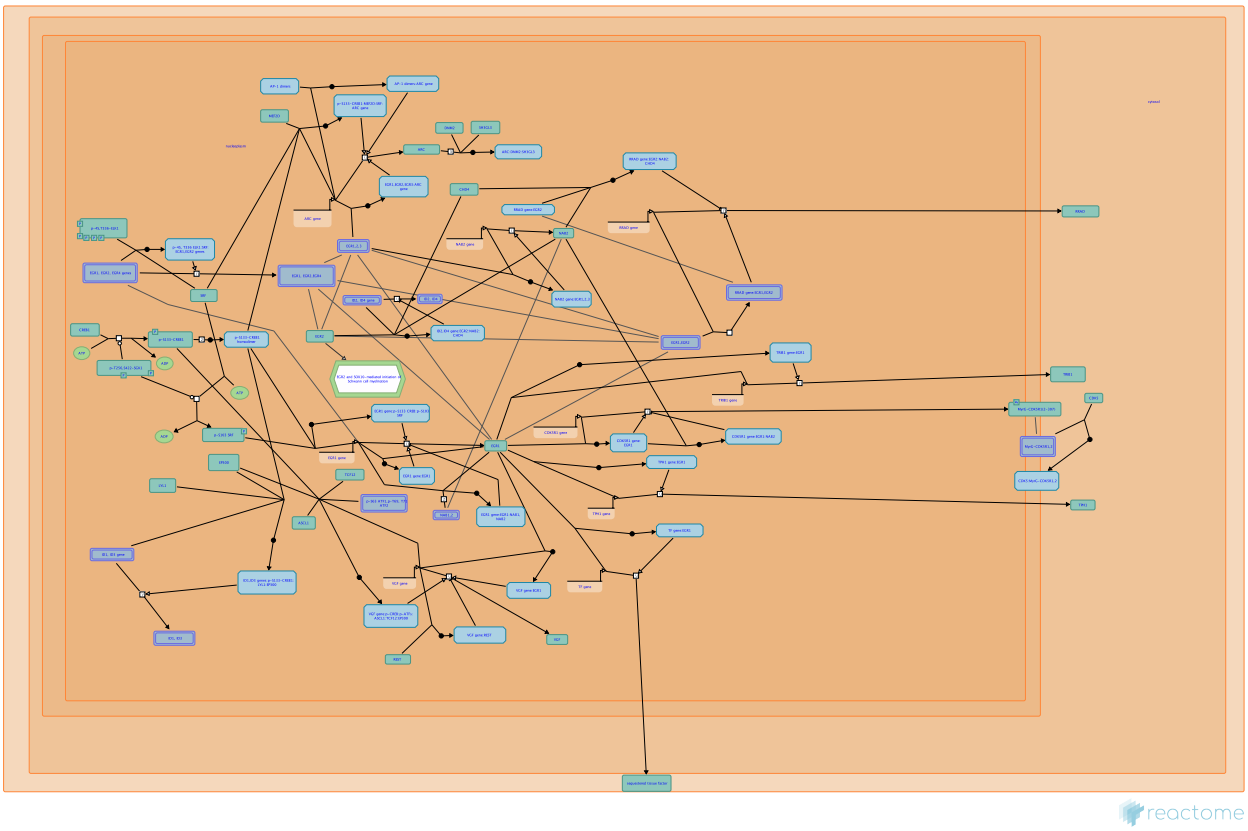
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

NGF-stimulated transcription ↗

Stable identifier: R-HSA-9031628



NGF stimulation induces expression of a wide array of transcriptional targets. In rat PC12 cells, a common model for NGF signaling, stimulation with NGF causes cells to exit the cell cycle and undergo a differentiation program leading to neurite outgrowth. This program is driven by the expression of immediate early genes (IEGs), which frequently encode transcription factors regulating the activity of NGF-specific delayed response genes (reviewed in Sheng and Greenberg, 1990; Flavell and Grennberg, 2008; Santiago and Bashaw, 2014).

Literature references

Santiago, C., Bashaw, GJ. (2014). Transcription factors and effectors that regulate neuronal morphology. *Development , 141*, 4667-80. ↗

Guérin, M., Sheng, ZM., Andrieu, N., Riou, G. (1990). Strong association between c-myb and oestrogen-receptor expression in human breast cancer. *Oncogene, 5*, 131-5. ↗

Flavell, SW., Greenberg, ME. (2008). Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system. *Annu. Rev. Neurosci., 31*, 563-90. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

p-S133 CREB1, MEF2D and SRF bind the ARC gene ↗

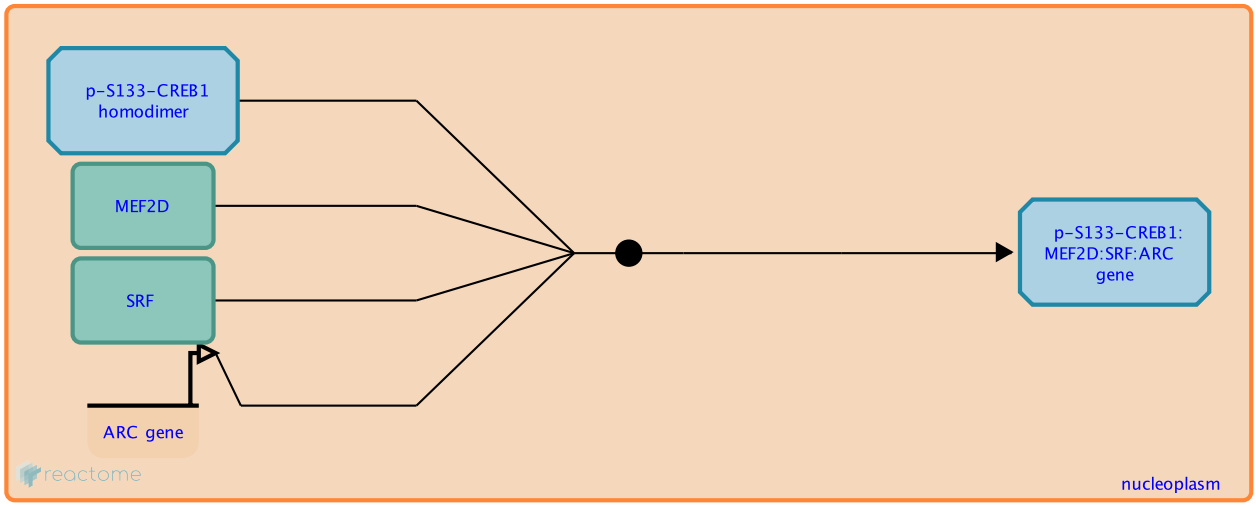
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9031610

Type: binding

Compartments: nucleoplasm

Inferred from: Creb, Srf, and Mef2d bind the ARC gene (Mus musculus)



Activity-responsive transcription of the ARC gene is driven in part by a Synaptic Activity Response Element located ~7kb upstream of the transcription start site. This element is bound by CREB, SRF and MEF2D as assessed by EMSA and ChIP in mouse cells (Kawashima et al, 2009). SARE-driven ARC expression is responsive to stimulation through AMPAR and NMDAR activity, and depends on CaMK and MAPK signaling pathways, consistent with previous studies (Kawashima et al, 2009; Falvell et al, 2006; Ramanan et al, 2005; Bourtchuladze et al, 1994; reviewed in Inoue et al, 2010; Finkbeiner et al, 1997; Epstein and Finkbeiner, 2018). Additional binding sites for SRF, MEF2D and ELK1 were also identified in another study, along with putative binding sites for an as-yet uncharacterized Zeste-like mammalian homologue (Pintchovski et al, 2006).

Followed by: ARC gene expression

Literature references

Kawashima, T., Okuno, H., Nonaka, M., Adachi-Morishima, A., Kyo, N., Okamura, M. et al. (2009). Synaptic activity-responsive element in the Arc/Arg3.1 promoter essential for synapse-to-nucleus signaling in activated neurons. *Proc. Natl. Acad. Sci. U.S.A., 106*, 316-21. ↗

Flavell, SW., Cowan, CW., Kim, TK., Greer, PL., Lin, Y., Paradis, S. et al. (2006). Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number. *Science, 311*, 1008-12. ↗

Ramanan, N., Shen, Y., Sarsfield, S., Lemberger, T., Schütz, G., Linden, DJ. et al. (2005). SRF mediates activity-induced gene expression and synaptic plasticity but not neuronal viability. *Nat. Neurosci., 8*, 759-67. ↗

Bourtchuladze, R., Frenguelli, B., Blendy, J., Cioffi, D., Schütz, G., Silva, AJ. (1994). Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell, 79*, 59-68. ↗

Finkbeiner, S., Tavazoie, SF., Maloratsky, A., Jacobs, KM., Harris, KM., Greenberg, ME. (1997). CREB: a major mediator of neuronal neurotrophin responses. *Neuron, 19*, 1031-47. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

AP-1 binds ARC gene ↗

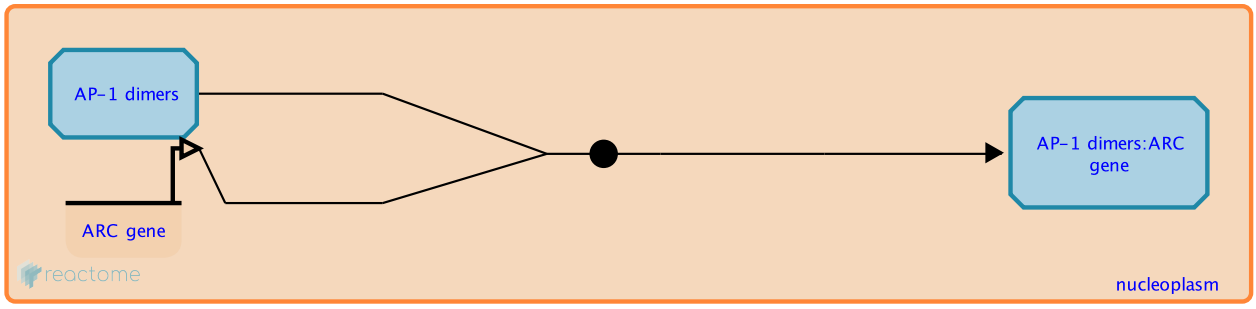
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9031575

Type: binding

Compartments: nucleoplasm

Inferred from: Ap-1 dimers bind Arc gene (Rattus norvegicus)



Based on studies done in rat PC12 cells, AP-1 binding sites were identified upstream of the ARC gene. Recruitment of AP-1 family members FOS, FOSB, FRA1, JUNb and JUND to the ARC gene was stimulated after treatment of cells with NGF as assessed by ChIP (Adams et al, 2011; Mullenbrock et al, 2017).

Followed by: ARC gene expression

Literature references

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

EGR binds ARC gene ↗

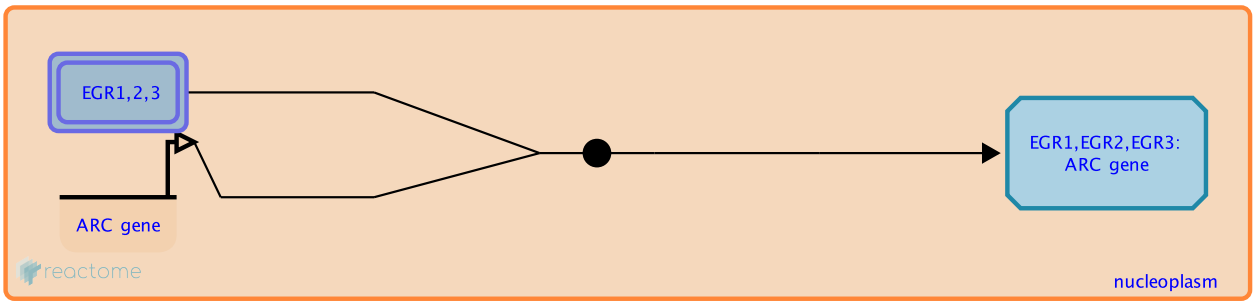
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9031616

Type: binding

Compartments: nucleoplasm

Inferred from: Egr1, Egr3 bind the Arc promoter (Mus musculus), Egr1, Egr2 bind the Arc gene (Rattus norvegicus)



EGR1, 2 and 3 have been shown to bind to cognate response elements in the ARC promoter and upregulate gene expression (Li et al, 2005; Mullenbrock et al, 2011, Adams et al, 2017). EGR1 and 2 protein and transcript levels are upregulated in response to sustained NGF signaling, while EGR3 transcript but not protein levels increase with NGF treatment (Adams et al, 2017). EGR3-dependent ARC expression may contribute to the delayed, protein-synthesis dependent increase in ARC protein levels (Li et al, 2005).

Followed by: ARC gene expression

Literature references

Li, L., Carter, J., Gao, X., Whitehead, J., Tourtellotte, WG. (2005). The neuroplasticity-associated arc gene is a direct transcriptional target of early growth response (Egr) transcription factors. *Mol. Cell. Biol., 25*, 10286-300. ↗

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

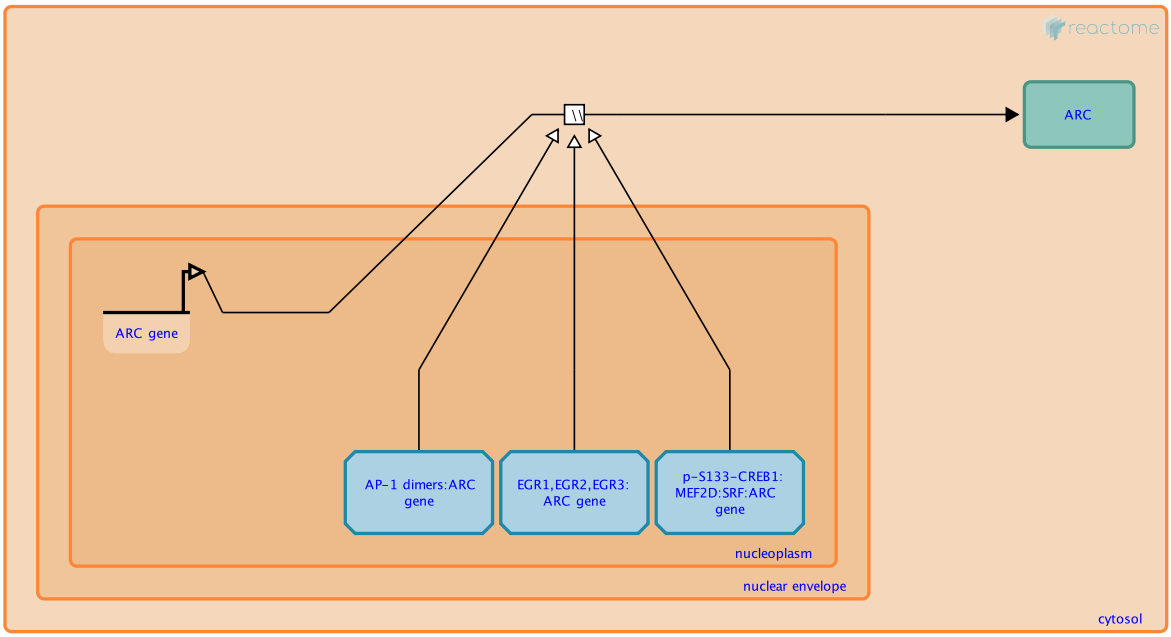
ARC gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9031624

Type: omitted

Compartments: cytosol, nucleoplasm



The neuronal activity regulated cytoskeletal gene (ARC) is an immediate early gene that has roles in memory consolidation and synaptic plasticity, including long-term potentiation and depression (Plath et al, 2006; Mesaoudi et al, 2007; reviewed in Epstein and Finkbeiner, 2018). ARC was identified as a gene induced by seizures in the hippocampus, and is activated downstream of signaling pathways such as muscarinic acetylcholine receptors (mAChR), NTRK and NMDA receptors in response to synaptic activity (Link et al, 1995; Lyford et al, 1995; Steward et al, 2001; Teber et al, 2004; Pintchovski et al, 2009). These receptors initiate signaling through intracellular calcium, cAMP, PKA and MAPK signaling pathways and converge on transcription factors such as CREB, SRF and MEF2, among others, to activate ARC gene expression (reviewed in Epstein and Finkbeiner, 2018).

During synaptic activity, ARC mRNA is rapidly transported to active synapses after transcription and is locally translated (Steward et al, 1998; Giorgi et al, 2007). ARC contributes to synaptic strength by promoting AMPA receptor internalization (Chowdhury et al, 2006).

Preceded by: p-S133 CREB1, MEF2D and SRF bind the ARC gene, EGR binds ARC gene, AP-1 binds ARC gene

Followed by: ARC binds DNM2 and SH3GL3

Literature references

Plath, N., Ohana, O., Dammermann, B., Errington, ML., Schmitz, D., Gross, C. et al. (2006). Arc/Arg3.1 is essential for the consolidation of synaptic plasticity and memories. *Neuron, 52*, 437-44. ↗

Messaoudi, E., Kanhema, T., Soulé, J., Tiron, A., Dagyte, G., da Silva, B. et al. (2007). Sustained Arc/Arg3.1 synthesis controls long-term potentiation consolidation through regulation of local actin polymerization in the dentate gyrus in vivo. *J. Neurosci., 27*, 10445-55. ↗

Epstein, I., Finkbeiner, S. (2018). The Arc of cognition: Signaling cascades regulating Arc and implications for cognitive function and disease. *Semin. Cell Dev. Biol., 77*, 63-72. ↗

Link, W., Konietzko, U., Kauselmann, G., Krug, M., Schwanke, B., Frey, U. et al. (1995). Somatodendritic expression of an immediate early gene is regulated by synaptic activity. *Proc. Natl. Acad. Sci. U.S.A., 92*, 5734-8. ↗

Lyford, GL., Yamagata, K., Kaufmann, WE., Barnes, CA., Sanders, LK., Copeland, NG. et al. (1995). Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. *Neuron, 14*, 433-45. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

ARC binds DNM2 and SH3GL3 ↗

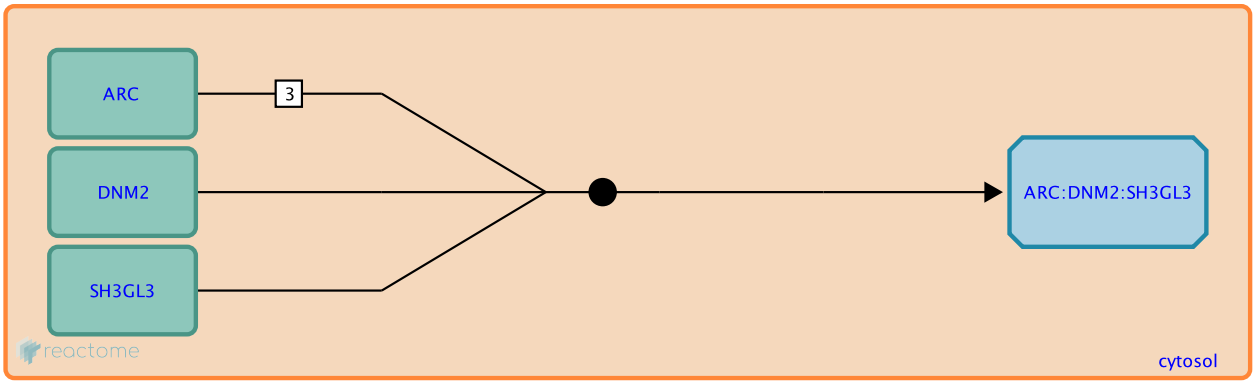
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9619838

Type: binding

Compartments: cytosol

Inferred from: Arc binds Sh3gl3 and Dnm2 (Rattus norvegicus)



ARC mRNA is rapidly transported to active synapses during synaptic activity where it is locally translated (Steward et al, 1998). At the synapse, ARC protein oligomerizes into virion-like capsids and interacts directly with dynamin2 (DYN2) and endophilin (SH3GL3) to promote the internalization of AMPA receptors (Myrum et al, 2015; Chowdhury et al, 2006; Rial Verde et al, 2006). Because AMPA receptors are also known to transcriptionally inhibit ARC gene expression through a Gi-specific G protein mechanism, this establishes a negative feedback loop between ARC gene expression and cell surface localization of AMPA receptors. The details of this relationship remain to be elucidated (Rao et al, 2006; Mokin et al, 2003; reviewed in Epstein and Finkbeiner, 2018).

Preceded by: ARC gene expression

Literature references

Steward, O., Wallace, CS., Lyford, GL., Worley, PF. (1998). Synaptic activation causes the mRNA for the IEG Arc to localize selectively near activated postsynaptic sites on dendrites. *Neuron, 21*, 741-51. ↗

Myrum, C., Baumann, A., Bustad, HJ., Flydal, MI., Mariaule, V., Alvira, S. et al. (2015). Arc is a flexible modular protein capable of reversible self-oligomerization. *Biochem. J., 468*, 145-58. ↗

Chowdhury, S., Shepherd, JD., Okuno, H., Lyford, G., Petralia, RS., Plath, N. et al. (2006). Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. *Neuron, 52*, 445-59. ↗

Rial Verde, EM., Lee-Osbourne, J., Worley, PF., Malinow, R., Cline, HT. (2006). Increased expression of the immediate-early gene arc/arg3.1 reduces AMPA receptor-mediated synaptic transmission. *Neuron, 52*, 461-74. ↗

Rao, VR., Pintchovski, SA., Chin, J., Peebles, CL., Mitra, S., Finkbeiner, S. (2006). AMPA receptors regulate transcription of the plasticity-related immediate-early gene Arc. *Nat. Neurosci., 9*, 887-95. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

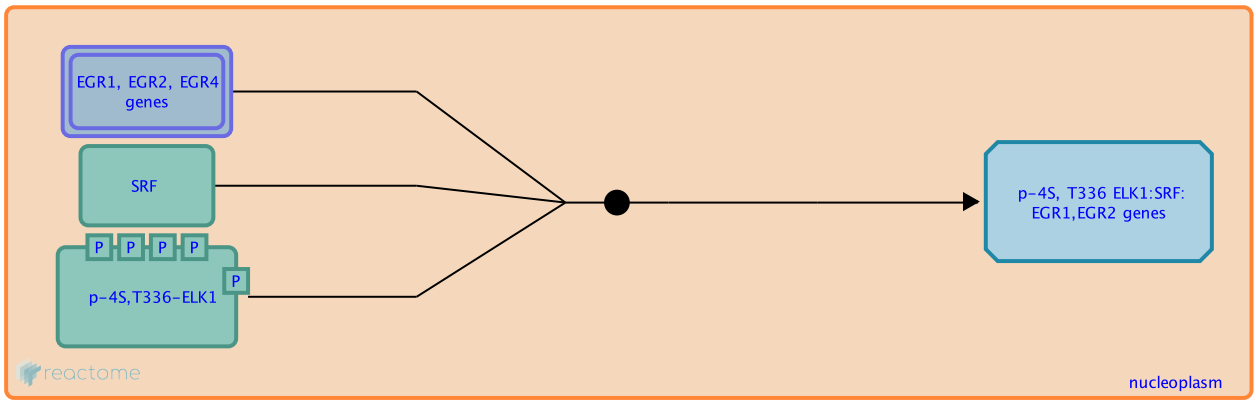
p-4S, T366 ELK1:SRF bind EGR1 and EGR2 gene promoters ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612076

Type: binding

Compartments: nucleoplasm



Expression of Early Growth Response (EGR) genes is dependent in part on the presence of upstream serum response elements (SREs) that bind SRF (serum response factor) and its co-activator ELK1 in response to mutiptle stimuli (Quereshi et al, 1991; Alexandre et al, 1991; de Franco et al, 1993; McMahon and Monroe, 1995;Chen et al, 2004; Vickers et al, 2004; Adams et al, 2017; Esnault et al, 2017; reviewed in O'Donovan et al, 1999; Pérez-Cadahía et al, 2011; Pagel and Deindl, 2011).

Literature references

Qureshi, SA., Cao, XM., Sukhatme, VP., Foster, DA. (1991). v-Src activates mitogen-responsive transcription factor Egr-1 via serum response elements. *J. Biol. Chem., 266*, 10802-6. ↗

Alexandre, C., Charnay, P., Verrier, B. (1991). Transactivation of Krox-20 and Krox-24 promoters by the HTLV-1 Tax protein through common regulatory elements. *Oncogene, 6*, 1851-7. ↗

DeFranco, C., Damon, DH., Endoh, M., Wagner, JA. (1993). Nerve growth factor induces transcription of NGFIA through complex regulatory elements that are also sensitive to serum and phorbol 12-myristate 13-acetate. *Mol. Endocrinol., 7*, 365-79. ↗

McMahon, SB., Monroe, JG. (1995). A ternary complex factor-dependent mechanism mediates induction of egr-1 through selective serum response elements following antigen receptor cross-linking in B lymphocytes. *Mol. Cell. Biol., 15*, 1086-93. ↗

Chen, CC., Lee, WR., Safe, S. (2004). Egr-1 is activated by 17beta-estradiol in MCF-7 cells by mitogen-activated protein kinase-dependent phosphorylation of ELK-1. *J. Cell. Biochem., 93*, 1063-74. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

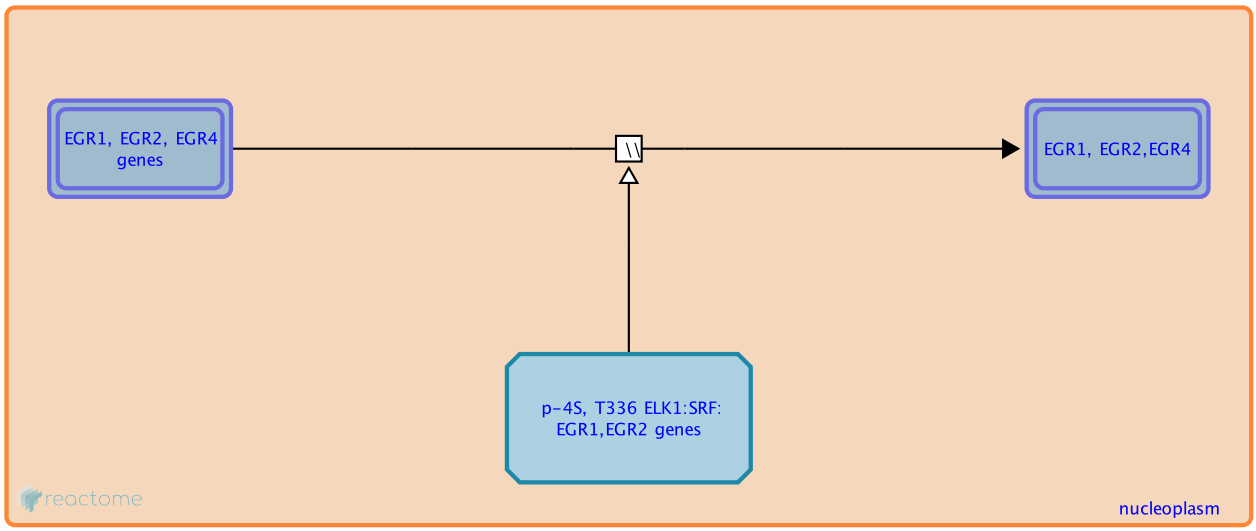
NGF- and MAPK-dependent EGR1, EGR2 and EGR4 expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612073

Type: omitted

Compartments: nucleoplasm



The Early Growth Response (EGR) gene family includes EGR1-4 and WT1. These Cys2-His2 zinc finger transcription factors are immediate early genes (IEG) that are rapidly turned on downstream of a number of stimuli and regulate expression of genes involved in stress response and differentiation (reviewed in Pagel and Deindl, 2001; Bahrami and Drabløs, 2016). Roles for EGR proteins are well established in the nervous system, with EGR target genes contributing to synaptic plasticity, long-term potentiation, peripheral nerve myelination and NGF-induced neurite outgrowth (reviewed in Perez-Cadahia et al, 2011; Herdegen and Leah, 1998; O'Donovan et al, 1999).

Expression of EGR genes depends on binding of phosphorylated ternary complex factor (TCF) protein ELK1 and its transcriptional coactivator SRF (serum response factor) to their cognate DNA binding sequences in the promoters (Hooker et al, 2017; De Franco et al, 1993; Harada et al, 2001; reviewed in Herdegen and Leah, 1998). NGF-stimulated expression of EGR1 and 2 occurs downstream of sustained MAPK signaling (Millbrandt et al, 1987; Sukhatme et al, 1988; de Franco et al, 1998; Mullenbrock et al, 2011; Crosby et al, 1991; Lönn et al, 2005). In addition to SRF and TCF binding sites, the EGR1 promoter also contain consensus binding sequences for AP-1 and CREB, as well as binding sites for EGR1 protein itself (Schwachtgen et al, 2000; Thiel et al, 2000; Svaren et al, 1996; reviewed in Page; and Deindl, 2001). Expression of EGR1 is limited by a negative feedback loop mediated by the binding of a complex of EGR1 with a repressor protein of the NAB family (NGF1A binding protein) to the EGR1 binding site (Cao et al, 1990; Thiel et al, 2000; Svaren et al, 1996).

Literature references

Pagel, JI., Deindl, E. (2011). Early growth response 1--a transcription factor in the crossfire of signal transduction cascades. *Indian J. Biochem. Biophys., 48*, 226-35. ↗

Bahrami, S., Drabløs, F. (2016). Gene regulation in the immediate-early response process. *Adv Biol Regul, 62*, 37-49. ↗

Pérez-Cadahía, B., Drobic, B., Davie, JR. (2011). Activation and function of immediate-early genes in the nervous system. *Biochem. Cell Biol., 89*, 61-73. ↗

Herdegen, T., Leah, JD. (1998). Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. *Brain Res. Brain Res. Rev., 28*, 370-490. ↗

O'Donovan, KJ., Tourtellotte, WG., Millbrandt, J., Baraban, JM. (1999). The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. *Trends Neurosci., 22*, 167-73. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

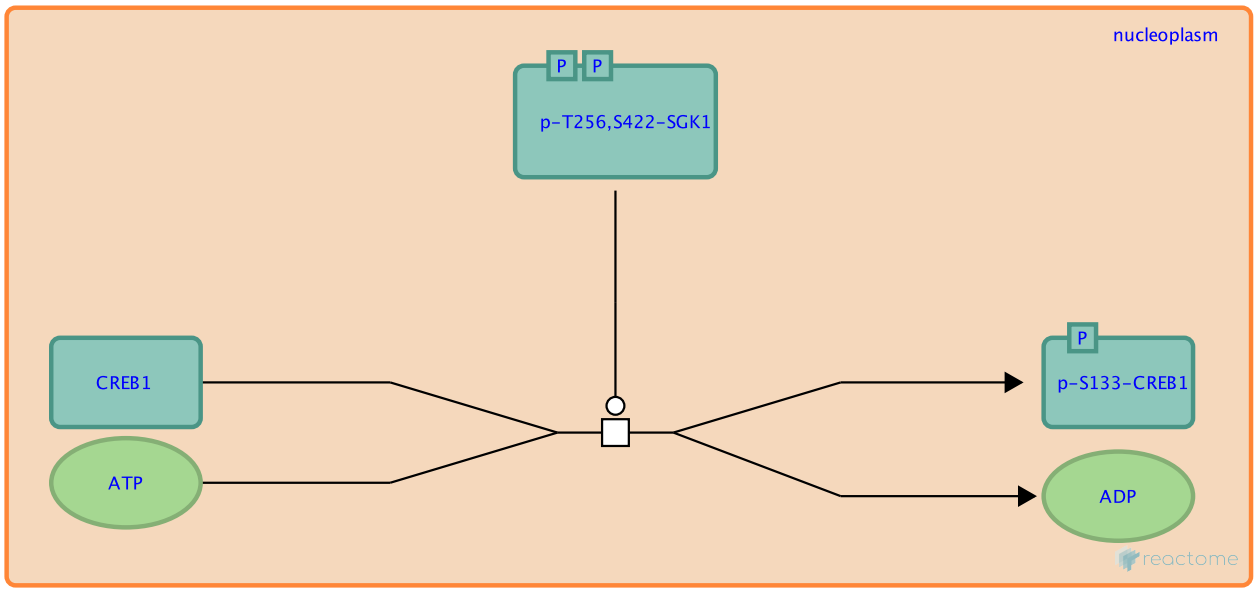
SGK phosphorylates CREB1 ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612501

Type: transition

Compartments: nucleoplasm



Serum/glucocorticoid-induced kinase (SGK) phosphorylates CREB1 at S133 downstream of mutiple cellular stimuli (Lee et al, 1995; David et al, 2005). SGK activity contributes to EGR1 gene expression by promoting the phosphorylation of CREB1 and SRF transcription factor, both of which have binding sites in the EGR1 promoter (Tyan et al, 2008; Sakomoto et al, 1991; Schwachtgen et al, 2000).

Followed by: p-S133 CREB and p-S103 SRF bind the EGR1 promoter, Dimerization of p-S133-CREB1

Literature references

Lee, HJ., Mignacca, RC., Sakamoto, KM. (1995). Transcriptional activation of egr-1 by granulocyte-macrophage colony-stimulating factor but not interleukin 3 requires phosphorylation of cAMP response element-binding protein (CREB) on serine 133. *J. Biol. Chem., 270*, 15979-83. ↗

David, S., Kalb, RG. (2005). Serum/glucocorticoid-inducible kinase can phosphorylate the cyclic AMP response element binding protein, CREB. *FEBS Lett., 579*, 1534-8. ↗

Tyan, SW., Tsai, MC., Lin, CL., Ma, YL., Lee, EH. (2008). Serum- and glucocorticoid-inducible kinase 1 enhances zif268 expression through the mediation of SRF and CREB1 associated with spatial memory formation. *J. Neurochem., 105*, 820-32. ↗

Sakamoto, KM., Bardeleben, C., Yates, KE., Raines, MA., Golde, DW., Gasson, JC. (1991). 5' upstream sequence and genomic structure of the human primary response gene, EGR-1/TIS8. *Oncogene, 6*, 867-71. ↗

Schwachtgen, JL., Campbell, CJ., Braddock, M. (2000). Full promoter sequence of human early growth response factor-1 (Egr-1): demonstration of a fifth functional serum response element. *DNA Seq., 10*, 429-32. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

Dimerization of p-S133-CREB1 ↗

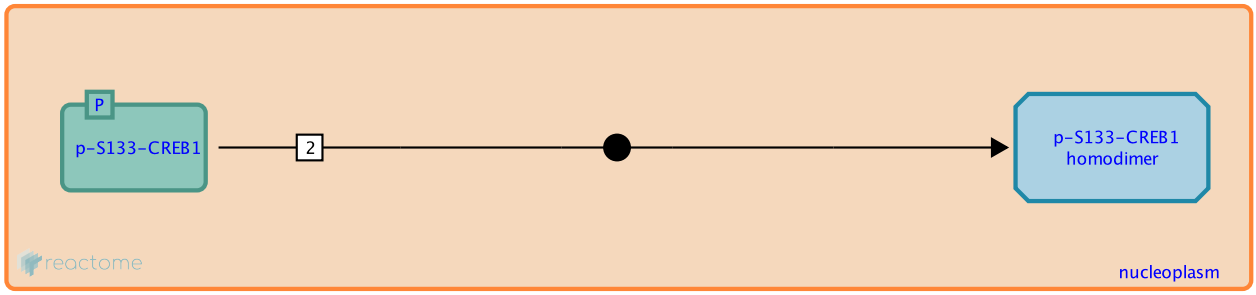
Location: NGF-stimulated transcription

Stable identifier: R-HSA-111916

Type: binding

Compartments: nucleoplasm

Inferred from: Dimerization of p-S133-Creb1 (Rattus norvegicus)



Based on studies in rat cells, activation of CREB1 by phosphorylation at serine residue S133 induces formation of CREB1 homodimers which are able to bind DNA (Yamamoto et al. 1988). The DNA binding and dimerization domains reside in the C-terminal region of CREB1 (Yun et al. 1990).

Preceded by: SGK phosphorylates CREB1

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.

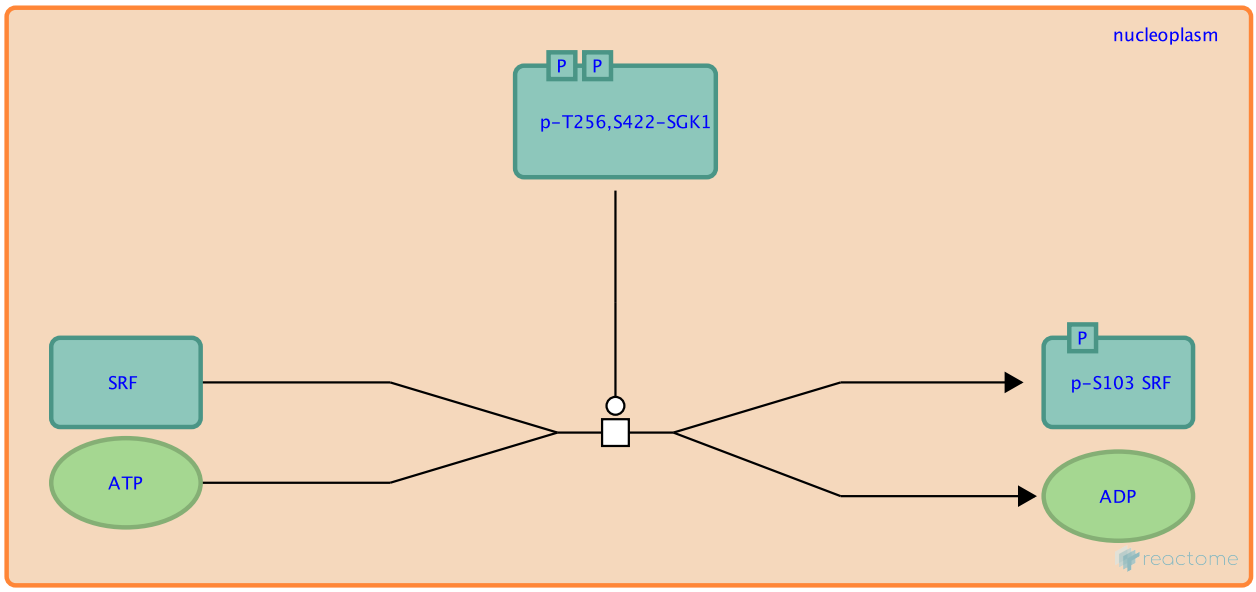
SGK phosphorylates SRF ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612509

Type: transition

Compartments: nucleoplasm



Serum/glucticocorticoid kinase (SGK) phosphorylates SRF at serine residue 103 in response to multiple upstream stimuli (Tyan et al, 2008). Phosphorylation of SRF and CREB1 by SGK contributes to the SGK-dependent expression of EGR1, an immediate early gene with roles in neuronal development, (David et al, 2005; Tyan et al, 2008; reviewed in Pagel and Deindl, 2011).

Followed by: p-S133 CREB and p-S103 SRF bind the EGR1 promoter

Literature references

Tyan, SW., Tsai, MC., Lin, CL., Ma, YL., Lee, EH. (2008). Serum- and glucocorticoid-inducible kinase 1 enhances zif268 expression through the mediation of SRF and CREB1 associated with spatial memory formation. *J. Neurochem., 105*, 820-32. ↗

David, S., Kalb, RG. (2005). Serum/glucocorticoid-inducible kinase can phosphorylate the cyclic AMP response element binding protein, CREB. *FEBS Lett., 579*, 1534-8. ↗

Pagel, JI., Deindl, E. (2011). Early growth response 1--a transcription factor in the crossfire of signal transduction cascades. *Indian J. Biochem. Biophys., 48*, 226-35. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

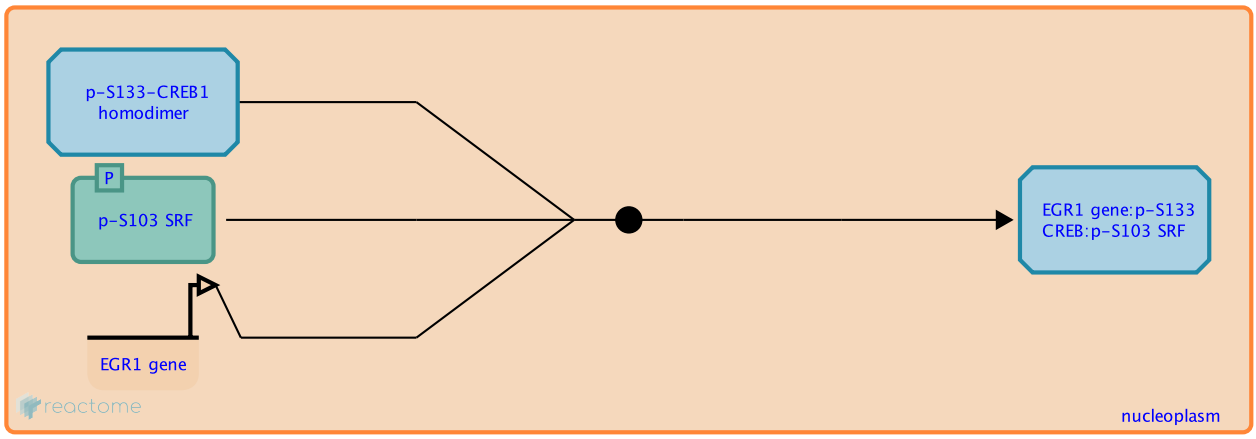
p-S133 CREB and p-S103 SRF bind the EGR1 promoter ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612514

Type: binding

Compartments: nucleoplasm



Expression of EGR1 depends in part on the binding of phosphorylated CREB and SRF factors to their cognate sites in the promoter (Quereshi et al, 1991; Alexandre et al, 1991; McMahon et al, 1995; Chen et al, 2004; Vickers et al, 2004; Tyan et al, 2008; David et al, 2005; Esnault et al, 2017). Phosphorylation of CREB can be mediated by RSK proteins, MAPKAPK2 or by SGK (de Cesare et al, 1998; Bonni et al, 1995; David et al, 2005; Tyan et al, 2008). SGK-mediated phosphorylation of SRF has also been implicated in the activation of EGR1 gene expression (Tyan et al, 2008).

Preceded by: SGK phosphorylates CREB1, SGK phosphorylates SRF

Followed by: EGR1 gene expression

Literature references

Qureshi, SA., Cao, XM., Sukhatme, VP., Foster, DA. (1991). v-Src activates mitogen-responsive transcription factor Egr-1 via serum response elements. *J. Biol. Chem., 266*, 10802-6. ↗

Alexandre, C., Charnay, P., Verrier, B. (1991). Transactivation of Krox-20 and Krox-24 promoters by the HTLV-1 Tax protein through common regulatory elements. *Oncogene, 6*, 1851-7. ↗

McMahon, SB., Monroe, JG. (1995). A ternary complex factor-dependent mechanism mediates induction of egr-1 through selective serum response elements following antigen receptor cross-linking in B lymphocytes. *Mol. Cell. Biol., 15*, 1086-93. ↗

Chen, CC., Lee, WR., Safe, S. (2004). Egr-1 is activated by 17beta-estradiol in MCF-7 cells by mitogen-activated protein kinase-dependent phosphorylation of ELK-1. *J. Cell. Biochem., 93*, 1063-74. ↗

Vickers, ER., Kasza, A., Kurnaz, IA., Seifert, A., Zeef, LA., O'Donnell, A. et al. (2004). Ternary complex factor-serum response factor complex-regulated gene activity is required for cellular proliferation and inhibition of apoptotic cell death. *Mol. Cell. Biol., 24*, 10340-51. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

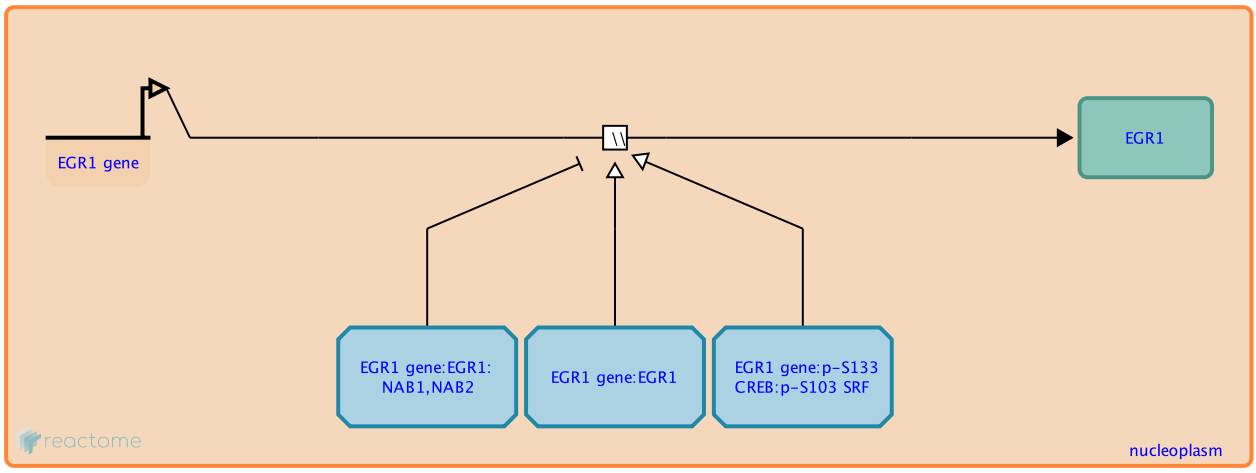
EGR1 gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612516

Type: omitted

Compartments: nucleoplasm



Early Growth Response 1 (EGR) is an immediate early gene that is rapidly expressed downstream of a number of stimuli. It encodes a Cys2-His2 zinc finger transcription factor that regulates expression of genes involved in stress response, differentiation and neuronal development (reviewed in Pagel and Deindl, 2001; Bahrami and Drabløs, 2016; Perez-Cadahia et al, 2011; Herdegen and Leah, 1998; O'Donovan et al, 1999).

Expression of EGR1 depends on binding of phosphorylated TCF protein ELK1 and its transcriptional co-activator SRF (serum response factor) to their cognate DNA binding sequences in the promoters (Hooker et al, 2017; De Franco et al, 1993; Harada et al, 2001; reviewed in Herdegen and Leah, 1998). In addition to SRF and TCF binding sites, the EGR1 promoter also contain consensus binding sequences for AP-1 and CREB, as well as binding sites for EGR1 protein itself (Schwachtgen et al, 2000; Thiel et al, 2000; Svaren et al, 1996; David et al, 2005; Tyan et al, 2008; reviewed in Page; and Deindl, 2001). Expression of EGR1 is limited by a negative feedback loop mediated by the binding of a complex of EGR1 protein with a repressor protein of the NAB family (NGF1A binding protein) to the EGR1 binding site (Cao et al, 1990; Thiel et al, 2000; Svaren et al, 1996).

Preceded by: p-S133 CREB and p-S103 SRF bind the EGR1 promoter

Followed by: EGR1, EGR2 bind the RRAD promoter

Literature references

Pagel, JI., Deindl, E. (2011). Early growth response 1--a transcription factor in the crossfire of signal transduction cascades. *Indian J. Biochem. Biophys., 48*, 226-35. ↗

Bahrami, S., Drabløs, F. (2016). Gene regulation in the immediate-early response process. *Adv Biol Regul, 62*, 37-49. ↗

Pérez-Cadahía, B., Drobic, B., Davie, JR. (2011). Activation and function of immediate-early genes in the nervous system. *Biochem. Cell Biol., 89*, 61-73. ↗

Herdegen, T., Leah, JD. (1998). Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. *Brain Res. Brain Res. Rev., 28*, 370-490. ↗

O'Donovan, KJ., Tourtellotte, WG., Millbrandt, J., Baraban, JM. (1999). The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. *Trends Neurosci., 22*, 167-73. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

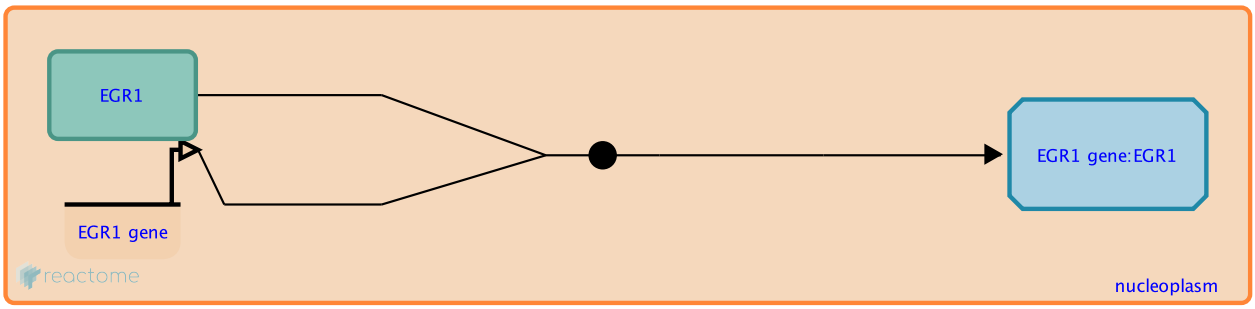
EGR1 binds to the EGR1 promoter ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613207

Type: binding

Compartments: nucleoplasm



EGR1 protein binds to three sites in its own promoter, upregulating its own expression (Cao et al, 1990)

Literature references

Cao, XM., Koski, RA., Gashler, A., McKiernan, M., Morris, CF., Gaffney, R. et al. (1990). Identification and characterization of the Egr-1 gene product, a DNA-binding zinc finger protein induced by differentiation and growth signals. *Mol. Cell. Biol., 10*, 1931-9. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

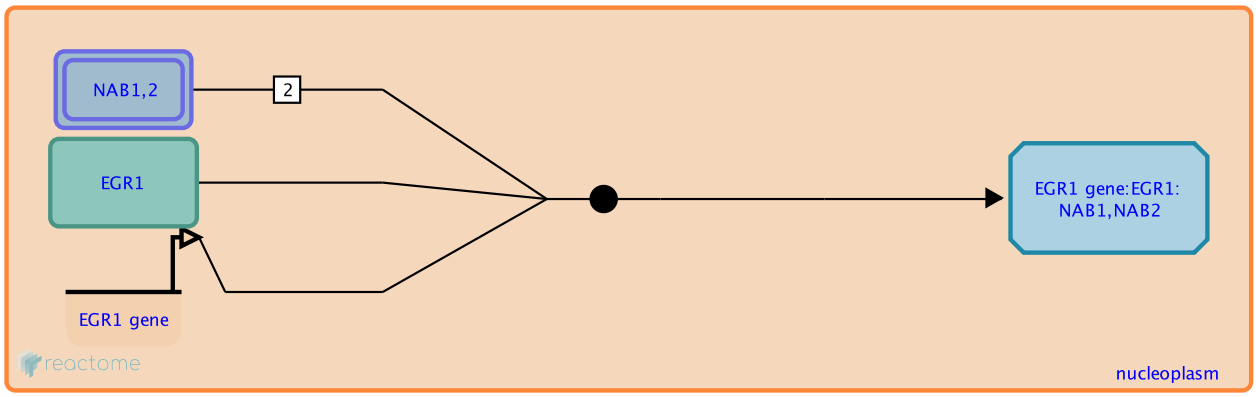
EGR1 and NAB co-repressors bind EGR1 gene ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613202

Type: binding

Compartments: nucleoplasm



EGR1 expression is repressed by the recruitment of NAB proteins (NGFI-A binding protein) 1 and 2 through an interaction with EGR1 at its cognate promoter site, establishing a negative feedback loop (Russo et al, 1993; Russo et al, 1995; Svaren et al, 1996; Kumbrick et al, 2005; Kumbrick et al, 2010). NAB proteins interact with the EGR R1 domain through a conserved NCD1 domain (NAB conserved domain 1) and this interaction is abrogated by mutation of EGR residue I293 (Svaren et al, 1996; Russo, 1993). NCD1 is also required for multimerization of the NAB proteins (Savern et al, 1996; Svaren et al, 1998). Two other conserved regions of NAB proteins (NCD2 and CID, for CHD4-interacting domain) are required for the repression function of the proteins (Svaren et al, 1996; Srinivasan et al, 2006). In some contexts, NAB proteins have also been shown to activate EGR-mediated transcription, and EGR- and NAB-dependent transcription is required for peripheral nervous system myelination (Sevetson et al, 2000; Le et al, 2005).

Literature references

Russo, MW., Matheny, C., Milbrandt, J. (1993). Transcriptional activity of the zinc finger protein NGFI-A is influenced by its interaction with a cellular factor. *Mol. Cell. Biol., 13*, 6858-65. ↗

Russo, MW., Sevetson, BR., Milbrandt, J. (1995). Identification of NAB1, a repressor of NGFI-A- and Krox20-mediated transcription. *Proc. Natl. Acad. Sci. U.S.A., 92*, 6873-7. ↗

Svaren, J., Sevetson, BR., Apel, ED., Zimonjic, DB., Popescu, NC., Milbrandt, J. (1996). NAB2, a corepressor of NGFI-A (Egr-1) and Krox20, is induced by proliferative and differentiative stimuli. *Mol. Cell. Biol., 16*, 3545-53. ↗

Kumbrink, J., Gerlinger, M., Johnson, JP. (2005). Egr-1 induces the expression of its corepressor nab2 by activation of the nab2 promoter thereby establishing a negative feedback loop. *J. Biol. Chem., 280*, 42785-93. ↗

Kumbrink, J., Kirsch, KH., Johnson, JP. (2010). EGR1, EGR2, and EGR3 activate the expression of their coregulator NAB2 establishing a negative feedback loop in cells of neuroectodermal and epithelial origin. *J. Cell. Biochem., 111*, 207-17. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

EGR1 binds CDK5R1 gene ↗

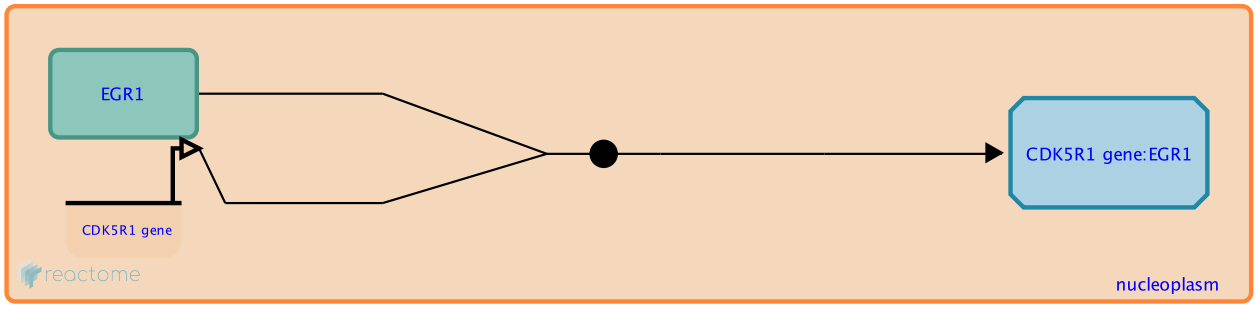
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9616105

Type: binding

Compartments: nucleoplasm

Inferred from: Egr1 binds Cdk5r1 gene (Rattus norvegicus)



EGR1 binds to its cognate site in the promoter element of the CDK5R1 gene in response to sustained stimulation with NGF. Expression of CDK5R1 (also known as p35) depends on activation of the ERK signaling pathway downstream of NGF stimulation, and is required to promote neurite outgrowth (Harada et al, 2001). CDK5R1 is a neuron-specific activator of CDK5, and the CDK5:CDK5R1 complex is required for neuronal differentiation (Tsai et al, 1994; Lew et al, 1994; Nikolic et al, 1996; Xiong et al, 1997; Paglini et al, 1998).

Followed by: NAB2 binds EGR1 to repress CDK5R1 gene expression, EGR1-dependent CDK5R1 gene expression

Literature references

Harada, T., Morooka, T., Ogawa, S., Nishida, E. (2001). ERK induces p35, a neuron-specific activator of Cdk5, through induction of Egr1. *Nat. Cell Biol., 3*, 453-9. ↗

Tsai, LH., Delalle, I., Caviness, VS., Chae, T., Harlow, E. (1994). p35 is a neural-specific regulatory subunit of cyclin-dependent kinase 5. *Nature, 371*, 419-23. ↗

Lew, J., Huang, QQ., Qi, Z., Winkfein, RJ., Aebersold, R., Hunt, T. et al. (1994). A brain-specific activator of cyclin-dependent kinase 5. *Nature, 371*, 423-6. ↗

Nikolic, M., Dudek, H., Kwon, YT., Ramos, YF., Tsai, LH. (1996). The cdk5/p35 kinase is essential for neurite outgrowth during neuronal differentiation. *Genes Dev., 10*, 816-25. ↗

Xiong, W., Pestell, R., Rosner, MR. (1997). Role of cyclins in neuronal differentiation of immortalized hippocampal cells. *Mol. Cell. Biol., 17*, 6585-97. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

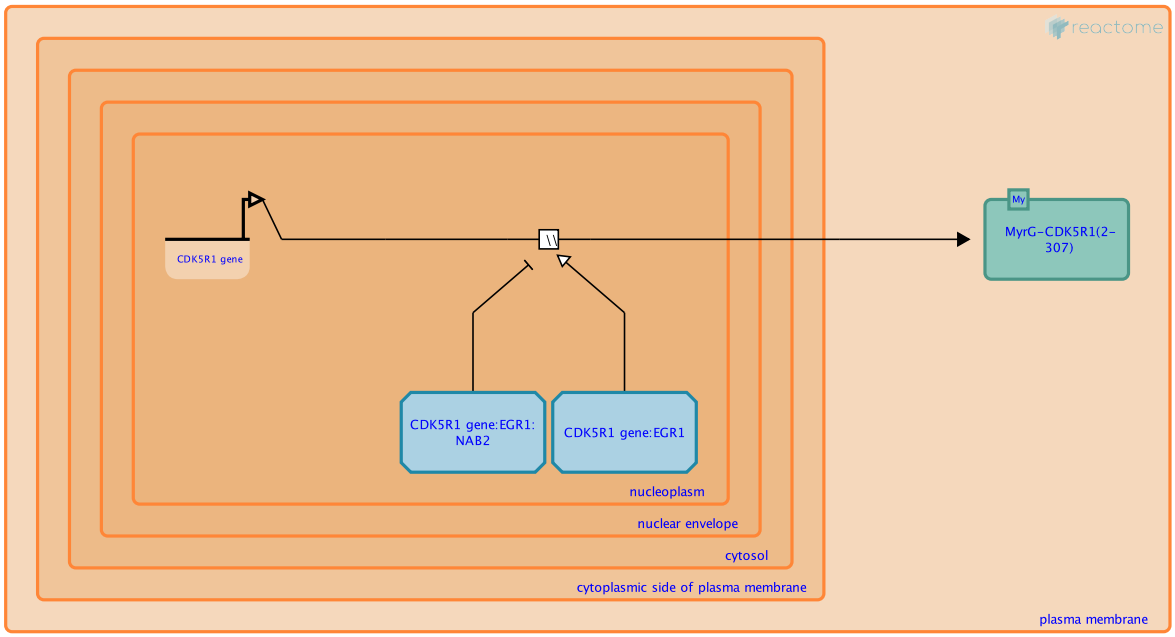
EGR1-dependent CDK5R1 gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9616110

Type: omitted

Compartments: nucleoplasm, plasma membrane



CDK5R1 (also known as p35) is a neuron-specific regulator of CDK5 that activates CDK5 kinase. The complex of CDK5:CDK5R1 is required for neurite outgrowth (Tsai et al, 1994; Lew et al, 1994; Nikolic et al, 1996; Xiong et al, 1997; Paglini et al, 1998). CDK5R1 expression is regulated in part by the binding of EGR1 to its cognate binding sites in the CDK5R1 promoter. EGR1 binding is stimulated by sustained NGF signaling and depends on activation of the ERK signaling pathway (Harada et al, 2001).

Preceded by: EGR1 binds CDK5R1 gene

Followed by: MyrG-CDK5R1,2 bind CDK5

Literature references

Tsai, LH., Delalle, I., Caviness, VS., Chae, T., Harlow, E. (1994). p35 is a neural-specific regulatory subunit of cyclin-dependent kinase 5. *Nature, 371*, 419-23. ↗

Lew, J., Huang, QQ., Qi, Z., Winkfein, RJ., Aebersold, R., Hunt, T. et al. (1994). A brain-specific activator of cyclin-dependent kinase 5. *Nature, 371*, 423-6. ↗

Nikolic, M., Dudek, H., Kwon, YT., Ramos, YF., Tsai, LH. (1996). The cdk5/p35 kinase is essential for neurite outgrowth during neuronal differentiation. *Genes Dev., 10*, 816-25. ↗

Xiong, W., Pestell, R., Rosner, MR. (1997). Role of cyclins in neuronal differentiation of immortalized hippocampal cells. *Mol. Cell. Biol., 17*, 6585-97. ↗

Paglini, G., Pigino, G., Kunda, P., Morfini, G., Maccioni, R., Quiroga, S. et al. (1998). Evidence for the participation of the neuron-specific CDK5 activator P35 during laminin-enhanced axonal growth. *J. Neurosci., 18*, 9858-69. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

NAB2 binds EGR1 to repress CDK5R1 gene expression ↗

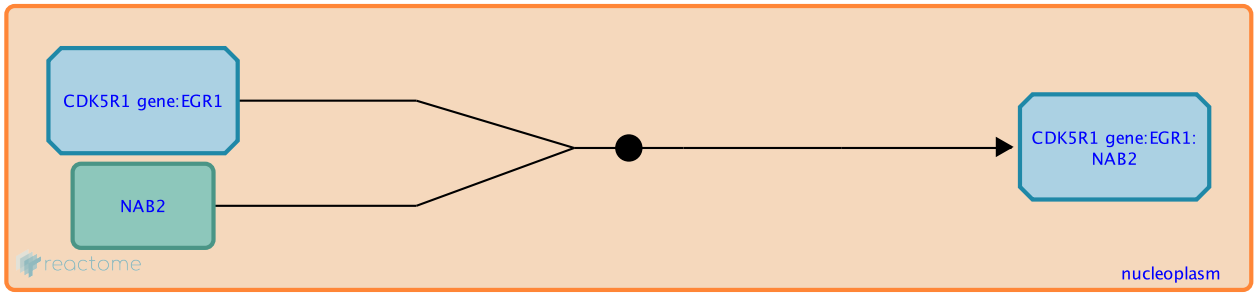
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9616367

Type: binding

Compartments: nucleoplasm

Inferred from: NAB2 binds Egr1 at the Cdk5r1 promoter (Homo sapiens)



ERK- and EGR1-dependent expression of CDK5R1 is inhibited by the EGR1-interacting protein NAB2 (Harada et al, 2001).

Preceded by: EGR1 binds CDK5R1 gene

Literature references

Harada, T., Morooka, T., Ogawa, S., Nishida, E. (2001). ERK induces p35, a neuron-specific activator of Cdk5, through induction of Egr1. *Nat. Cell Biol., 3*, 453-9. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

MyrG-CDK5R1,2 bind CDK5 ↗

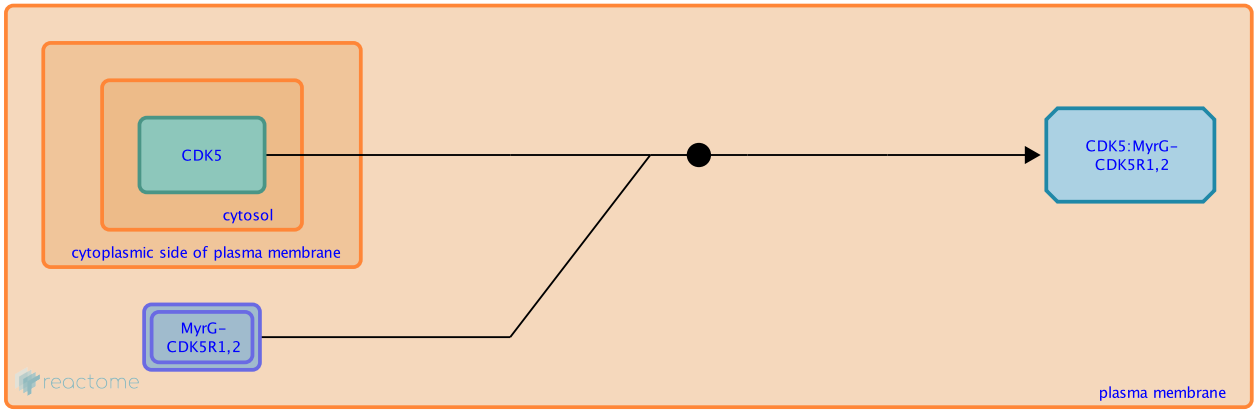
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9616368

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: MyrG-Cdk5r1(2-307) binds Cdk5 (Rattus norvegicus)



CDK5R1 is a neuron-specific regulatory subunit of CDK5 that activates CDK5 kinase activity in a cyclin-type manner and CDK5R1 and CDK5 co-precipitate from rat PC12 cells and from bovine brain (Tsai et al, 1994; Lew et al, 1994; Harada et al, 2001). CDK5 activity is required for neurite outgrowth and disruption of CDK5 or CDK5R1 leads to defects in neuronal migration in mice (Nikolic et al, 1996; Xiong et al, 1997; Paglini et al, 1998). A second CDK5 regulatory protein, CDK5R2 (also known as p39) is required for CDK5-dependent neurite outgrowth in response to bFGF (Tang et al, 1995; Xiong et al, 1997).

Preceded by: EGR1-dependent CDK5R1 gene expression

Literature references

Tsai, LH., Delalle, I., Caviness, VS., Chae, T., Harlow, E. (1994). p35 is a neural-specific regulatory subunit of cyclin-dependent kinase 5. *Nature, 371*, 419-23. ↗

Lew, J., Huang, QQ., Qi, Z., Winkfein, RJ., Aebersold, R., Hunt, T. et al. (1994). A brain-specific activator of cyclin-dependent kinase 5. *Nature, 371*, 423-6. ↗

Harada, T., Morooka, T., Ogawa, S., Nishida, E. (2001). ERK induces p35, a neuron-specific activator of Cdk5, through induction of Egr1. *Nat. Cell Biol., 3*, 453-9. ↗

Nikolic, M., Dudek, H., Kwon, YT., Ramos, YF., Tsai, LH. (1996). The cdk5/p35 kinase is essential for neurite outgrowth during neuronal differentiation. *Genes Dev., 10*, 816-25. ↗

Xiong, W., Pestell, R., Rosner, MR. (1997). Role of cyclins in neuronal differentiation of immortalized hippocampal cells. *Mol. Cell. Biol., 17*, 6585-97. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

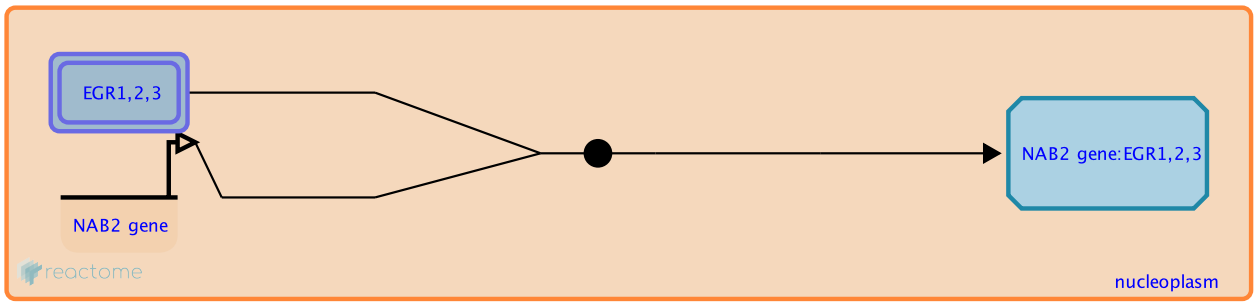
EGR1,2,3 bind the NAB2 promoter ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612483

Type: binding

Compartments: nucleoplasm



NAB1 and 2 (NGFI-A binding protein) are transcriptional co-repressors that interact with EGR1, 2 and 3 and repress transcription of EGR target genes (Swirnoff et al, 1998; Svaren et al, 1996; Russo et al, 1995; Sevetson et al, 2000; Abdulkadir et al, 2001). NAB proteins may contribute to transcriptional repression through the recruitment of CHD4 (Srinivasan et al, 2006).

Expression of NAB2 is regulated in part by the binding of EGR proteins to the cognate site in the NAB2 promoter (Kumbrink et al, 2005; Kumbrink et al, 2010).

Followed by: EGR-dependent NAB2 gene expression

Literature references

Swirnoff, AH., Apel, ED., Svaren, J., Sevetson, BR., Zimonjic, DB., Popescu, NC. et al. (1998). Nab1, a corepressor of NGFI-A (Egr-1), contains an active transcriptional repression domain. *Mol. Cell. Biol., 18*, 512-24. ↗

Svaren, J., Sevetson, BR., Apel, ED., Zimonjic, DB., Popescu, NC., Milbrandt, J. (1996). NAB2, a corepressor of NGFI-A (Egr-1) and Krox20, is induced by proliferative and differentiative stimuli. *Mol. Cell. Biol., 16*, 3545-53. ↗

Russo, MW., Sevetson, BR., Milbrandt, J. (1995). Identification of NAB1, a repressor of NGFI-A- and Krox20-mediated transcription. *Proc. Natl. Acad. Sci. U.S.A., 92*, 6873-7. ↗

Svaren, J., Sevetson, BR., Golda, T., Stanton, JJ., Swirnoff, AH., Milbrandt, J. (1998). Novel mutants of NAB corepressors enhance activation by Egr transactivators. *EMBO J., 17*, 6010-9. ↗

Sevetson, BR., Svaren, J., Milbrandt, J. (2000). A novel activation function for NAB proteins in EGR-dependent transcription of the luteinizing hormone beta gene. *J. Biol. Chem., 275*, 9749-57. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

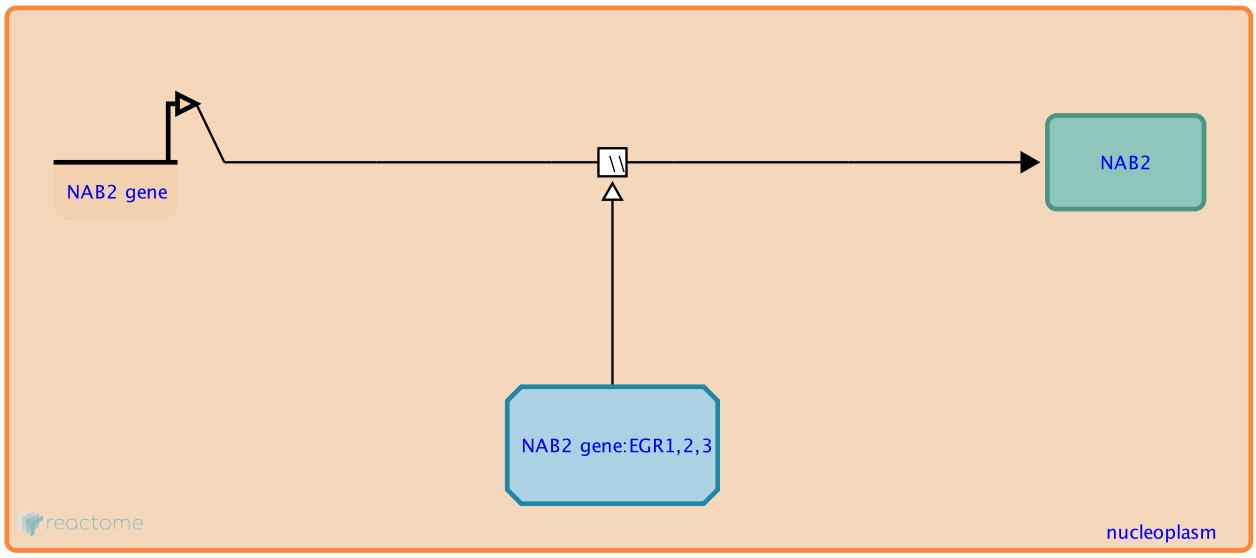
EGR-dependent NAB2 gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612493

Type: omitted

Compartments: nucleoplasm



NAB1 and 2 (NGFI-A binding protein) are transcriptional co-factors that interact with EGR1, 2 and 3 and repress or activate transcription of EGR target genes in a context dependent fashion (Swirnoff et al, 1998; Svaren et al, 1996; Svaren et al, 1998; Russo et al, 1995; Sevetson et al, 2000; Abdulkadir et al, 2001; Le et al, 2005). NAB proteins may contribute to transcriptional repression through the recruitment of CHD4 (Srinivasan et al, 2006).

NAB2 is a delayed immediate early gene that is expressed in response to many of the same stimuli as EGR (Qu et al, 1998). Expression of NAB2 is regulated in part by the binding of EGR proteins to the cognate site in the NAB2 promoter (Kumbrink et al, 2005; Kumbrink et al, 2010). NAB2 expression is in frequently lost in prostate carcinomas and EGR1 is frequently overexpressed (Abdulkadir et al, 2001; Eid et al, 1998; Thigpen et al, 1996).

Preceded by: EGR1,2,3 bind the NAB2 promoter

Literature references

Swirnoff, AH., Apel, ED., Svaren, J., Sevetson, BR., Zimonjic, DB., Popescu, NC. et al. (1998). Nab1, a corepressor of NGFI-A (Egr-1), contains an active transcriptional repression domain. *Mol. Cell. Biol., 18*, 512-24. ↗

Svaren, J., Sevetson, BR., Apel, ED., Zimonjic, DB., Popescu, NC., Milbrandt, J. (1996). NAB2, a corepressor of NGFI-A (Egr-1) and Krox20, is induced by proliferative and differentiative stimuli. *Mol. Cell. Biol., 16*, 3545-53. ↗

Russo, MW., Sevetson, BR., Milbrandt, J. (1995). Identification of NAB1, a repressor of NGFI-A- and Krox20-mediated transcription. *Proc. Natl. Acad. Sci. U.S.A., 92*, 6873-7. ↗

Abdulkadir, SA., Carbone, JM., Naughton, CK., Humphrey, PA., Catalona, WJ., Milbrandt, J. (2001). Frequent and early loss of the EGR1 corepressor NAB2 in human prostate carcinoma. *Hum. Pathol., 32*, 935-9. ↗

Srinivasan, R., Mager, GM., Ward, RM., Mayer, J., Svaren, J. (2006). NAB2 represses transcription by interacting with the CHD4 subunit of the nucleosome remodeling and deacetylase (NuRD) complex. *J. Biol. Chem., 281*, 15129-37. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

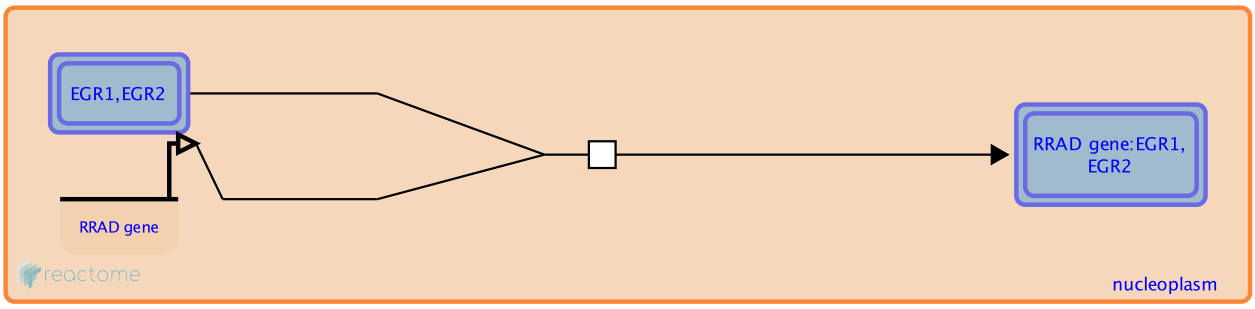
EGR1, EGR2 bind the RRAD promoter ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613210

Type: transition

Compartments: nucleoplasm



EGR1 and EGR2 are required for the activation of RRAD gene expression (Mager et al, 2008; Svaren et al, 2000). RRAD protein plays a role in serum-stimulated DNA synthesis in melanoma cells and contributes to electrical conductance in the heart (Zhu et al, 1999; Wang et al, 2010; Chang et al, 2007).

Preceded by: EGR1 gene expression

Followed by: NAB2 and CHD4 bind and repress EGR-mediated RRAD gene expression

Literature references

Mager, GM., Ward, RM., Srinivasan, R., Jang, SW., Wrabetz, L., Svaren, J. (2008). Active gene repression by the Egr2.NAB complex during peripheral nerve myelination. *J. Biol. Chem., 283*, 18187-97. ↗

Svaren, J., Ehrig, T., Abdulkadir, SA., Ehrengruber, MU., Watson, MA., Milbrandt, J. (2000). EGR1 target genes in prostate carcinoma cells identified by microarray analysis. *J. Biol. Chem., 275*, 38524-31. ↗

Zhu, J., Tseng, YH., Kantor, JD., Rhodes, CJ., Zetter, BR., Moyers, JS. et al. (1999). Interaction of the Ras-related protein associated with diabetes rad and the putative tumor metastasis suppressor NM23 provides a novel mechanism of GTPase regulation. *Proc. Natl. Acad. Sci. U.S.A., 96*, 14911-8. ↗

Chang, L., Zhang, J., Tseng, YH., Xie, CQ., Ilany, J., Brüning, JC. et al. (2007). Rad GTPase deficiency leads to cardiac hypertrophy. *Circulation, 116*, 2976-2983. ↗

Wang, G., Zhu, X., Xie, W., Han, P., Li, K., Sun, Z. et al. (2010). Rad as a novel regulator of excitation-contraction coupling and beta-adrenergic signaling in heart. *Circ. Res., 106*, 317-27. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

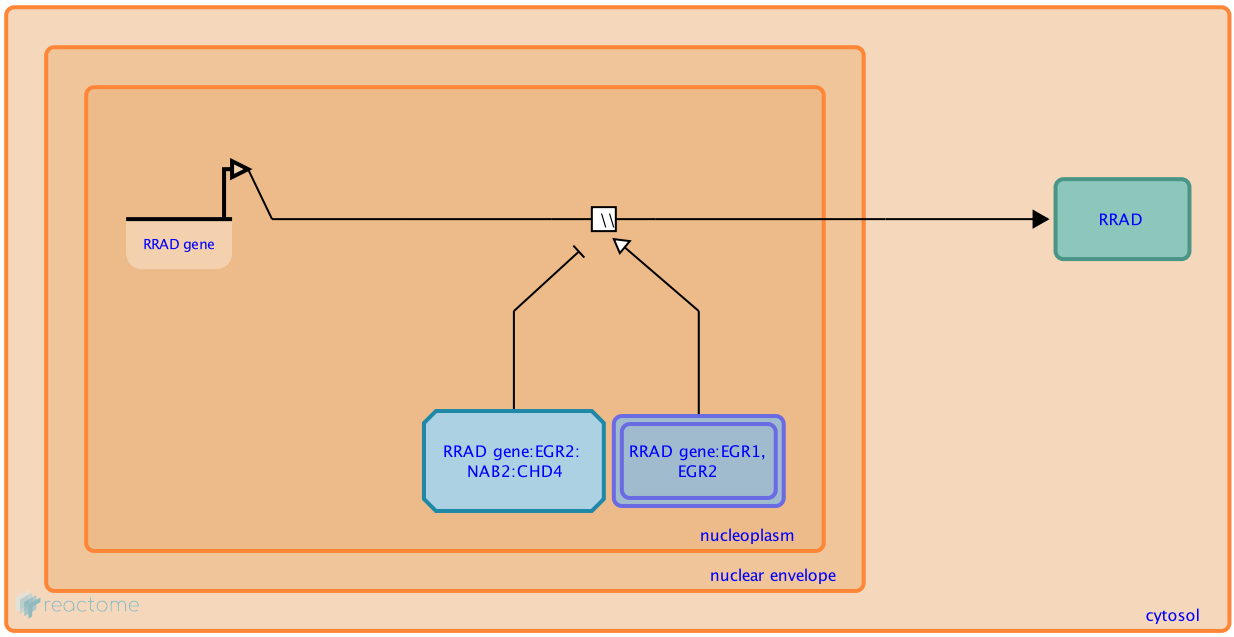
RRAD gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613219

Type: omitted

Compartments: nucleoplasm, cytosol



RRAD (Ras associated with diabetes) is a small GTP-binding member of the RAS superfaily that was originally as being overexpressed in skeletal muscle of people with type II diabetes (Reynet and Kahn, 1993; Zhu et al, 1995). RRAD has roles in cardiac regulation, and contributes to glucose metabolism and tumor metastasis through interaction with NME1 (nucleoside diphosphate kinase A) (Chang et al, 2007; Wang et al, 2010; Zhu et al, 1999; Tseng et al, 2001). In addition, RRAD contributes to Schwann cell development and myelination by modulating the RHO ROCK pathway (Ward et al, 2002; Yamauchi et al, 2004; Melendez-Vasquez et al, 2004). RRAD gene expression is positively regulated upon binding of EGR1 or EGR2 to their cognate sites in the promoter, while EGR-dependent recruitment of NAB proteins leads to EGR-mediated repression through the recruitment of chromatin remodellers and histone deacetylase complexes (Svaren et al, 2000; Mager et al, 2008). RRAD expression is repressed in Schwann cells during myelination and is upregulated in NAB knockout mice, implicating NAB proteins as negative regulators of RRAD expression (Verheijen et al, 2003; Mager et al, 2008; Desmazières et al, 2008). It is worth noting, however, that a number of genes required for Schwann cell differentiation and myelination are activated by EGR:NAB complexes at their promoters (Le et al, 2005).

Literature references

Reynet, C., Kahn, CR. (1993). Rad: a member of the Ras family overexpressed in muscle of type II diabetic humans. *Science, 262*, 1441-4. ↗

Zhu, J., Reynet, C., Caldwell, JS., Kahn, CR. (1995). Characterization of Rad, a new member of Ras/GTPase superfamily, and its regulation by a unique GTPase-activating protein (GAP)-like activity. *J. Biol. Chem., 270*, 4805-12. ↗

Chang, L., Zhang, J., Tseng, YH., Xie, CQ., Ilany, J., Brüning, JC. et al. (2007). Rad GTPase deficiency leads to cardiac hypertrophy. *Circulation, 116*, 2976-2983. ↗

Wang, G., Zhu, X., Xie, W., Han, P., Li, K., Sun, Z. et al. (2010). Rad as a novel regulator of excitation-contraction coupling and beta-adrenergic signaling in heart. *Circ. Res., 106*, 317-27. ↗

Zhu, J., Tseng, YH., Kantor, JD., Rhodes, CJ., Zetter, BR., Moyers, JS. et al. (1999). Interaction of the Ras-related protein associated with diabetes rad and the putative tumor metastasis suppressor NM23 provides a novel mechanism of GTPase regulation. *Proc. Natl. Acad. Sci. U.S.A., 96*, 14911-8. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

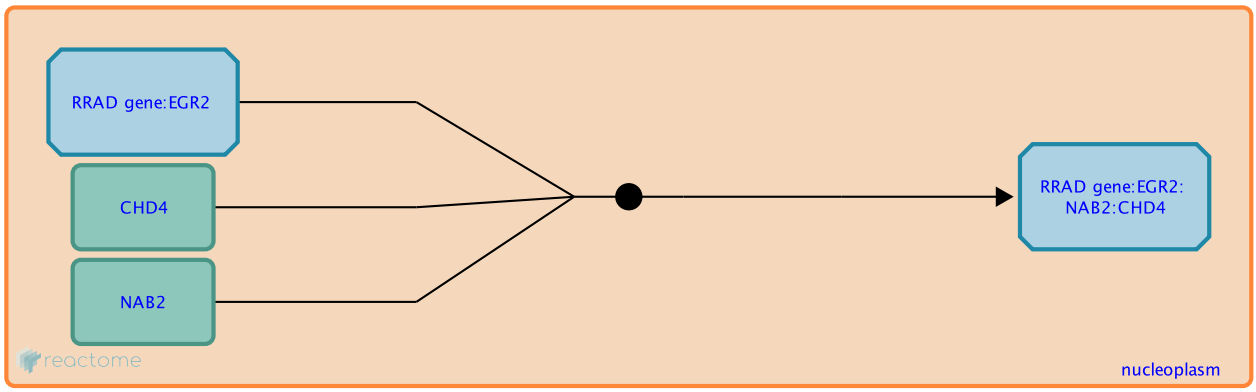
NAB2 and CHD4 bind and repress EGR-mediated RRAD gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613213

Type: binding

Compartments: nucleoplasm



NAB2 is recruited to EGR2 to the RRAD promoter through interaction with the NCD1 (NAB conserved domain 1) (Svaren et al, 1996; Svaren et al, 1998). NAB2 in turn recruits the CHD4 subunit of the NURD chromatin remodelling complex through its CID (CHD4-interacting domain) and in this manner, represses transcription from the RRAD promoter (Srinivasan et al, 2006; Mager et al, 2008). In addition to roles in cellular proliferation and cardiac function, RRAD protein is known to contribute to RHO signaling, which promotes Schwann cell migration and myelination (Zhu et al, 1999; Wang et al, 2010; Chang et al, 2007, Ward et al, 2002; Yamauchi et al, 2004; Melendez-Vasquez et al, 2004).

Preceded by: EGR1, EGR2 bind the RRAD promoter

Literature references

Svaren, J., Sevetson, BR., Apel, ED., Zimonjic, DB., Popescu, NC., Milbrandt, J. (1996). NAB2, a corepressor of NGFI-A (Egr-1) and Krox20, is induced by proliferative and differentiative stimuli. *Mol. Cell. Biol., 16*, 3545-53. ↗

Swirnoff, AH., Apel, ED., Svaren, J., Sevetson, BR., Zimonjic, DB., Popescu, NC. et al. (1998). Nab1, a corepressor of NGFI-A (Egr-1), contains an active transcriptional repression domain. *Mol. Cell. Biol., 18*, 512-24. ↗

Srinivasan, R., Mager, GM., Ward, RM., Mayer, J., Svaren, J. (2006). NAB2 represses transcription by interacting with the CHD4 subunit of the nucleosome remodeling and deacetylase (NuRD) complex. *J. Biol. Chem., 281*, 15129-37. ↗

Mager, GM., Ward, RM., Srinivasan, R., Jang, SW., Wrabetz, L., Svaren, J. (2008). Active gene repression by the Egr2.NAB complex during peripheral nerve myelination. *J. Biol. Chem., 283*, 18187-97. ↗

Zhu, J., Tseng, YH., Kantor, JD., Rhodes, CJ., Zetter, BR., Moyers, JS. et al. (1999). Interaction of the Ras-related protein associated with diabetes rad and the putative tumor metastasis suppressor NM23 provides a novel mechanism of GTPase regulation. *Proc. Natl. Acad. Sci. U.S.A., 96*, 14911-8. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

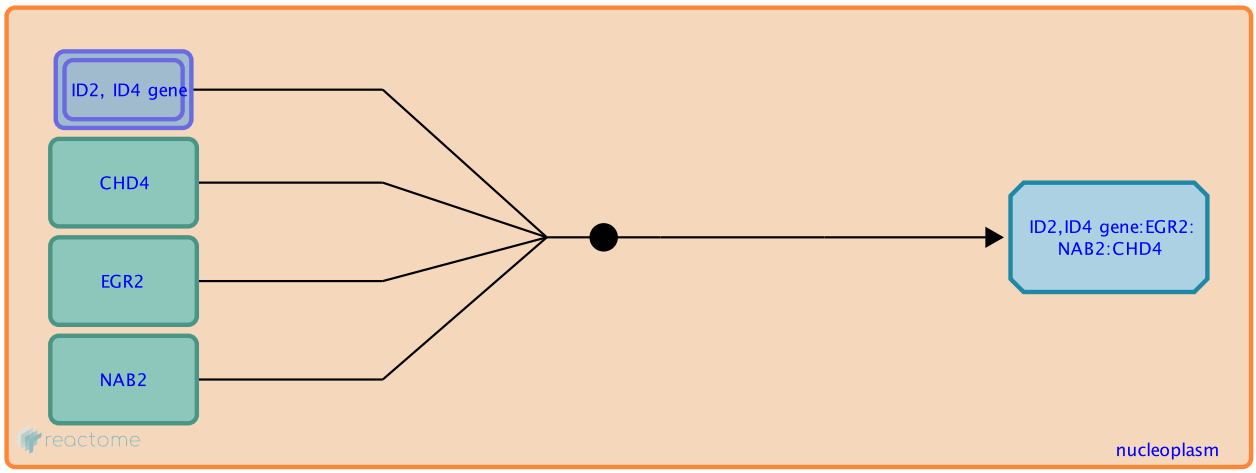
EGR2:NAB2 and CHD4 bind the ID2 and ID4 promoter regions ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613476

Type: binding

Compartments: nucleoplasm



EGR2 is required for peripheral nerve cell myelination in Schwann cells where it activates some target genes and represses others (Topilko et al, 1999; Zorick et al, 1996; Le et al, 2005; Le Blanc et al, 2005). ID2 and ID4 were identified as targets of EGR2-mediated repression during peripheral nerve myelination (Mager et al, 2008). EGR2 represses ID2 and ID4 gene expression by recruiting NAB2 and the NURD chromatin remodelling complex (Mager et al, 2008, Srinivasan et al, 2006).

Followed by: Expression of ID2 and ID4 is repressed by EGR2:NAB

Literature references

Thatikunta, P., Qin, W., Christy, BA., Tennekoon, GI., Rutkowski, JL. (1999). Reciprocal Id expression and myelin gene regulation in Schwann cells. *Mol. Cell. Neurosci., 14*, 519-28. ↗

Zorick, TS., Syroid, DE., Arroyo, E., Scherer, SS., Lemke, G. (1996). The transcription factors SCIP and Krox-20 mark distinct stages and cell fates in Schwann cell differentiation. *Mol. Cell. Neurosci., 8*, 129-45. ↗

Le, N., Nagarajan, R., Wang, JY., Svaren, J., LaPash, C., Araki, T. et al. (2005). Nab proteins are essential for peripheral nervous system myelination. *Nat. Neurosci., 8*, 932-40. ↗

Leblanc, SE., Srinivasan, R., Ferri, C., Mager, GM., Gillian-Daniel, AL., Wrabetz, L. et al. (2005). Regulation of cholesterol/lipid biosynthetic genes by Egr2/Krox20 during peripheral nerve myelination. *J. Neurochem., 93*, 737-48. ↗

Mager, GM., Ward, RM., Srinivasan, R., Jang, SW., Wrabetz, L., Svaren, J. (2008). Active gene repression by the Egr2.NAB complex during peripheral nerve myelination. *J. Biol. Chem., 283*, 18187-97. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

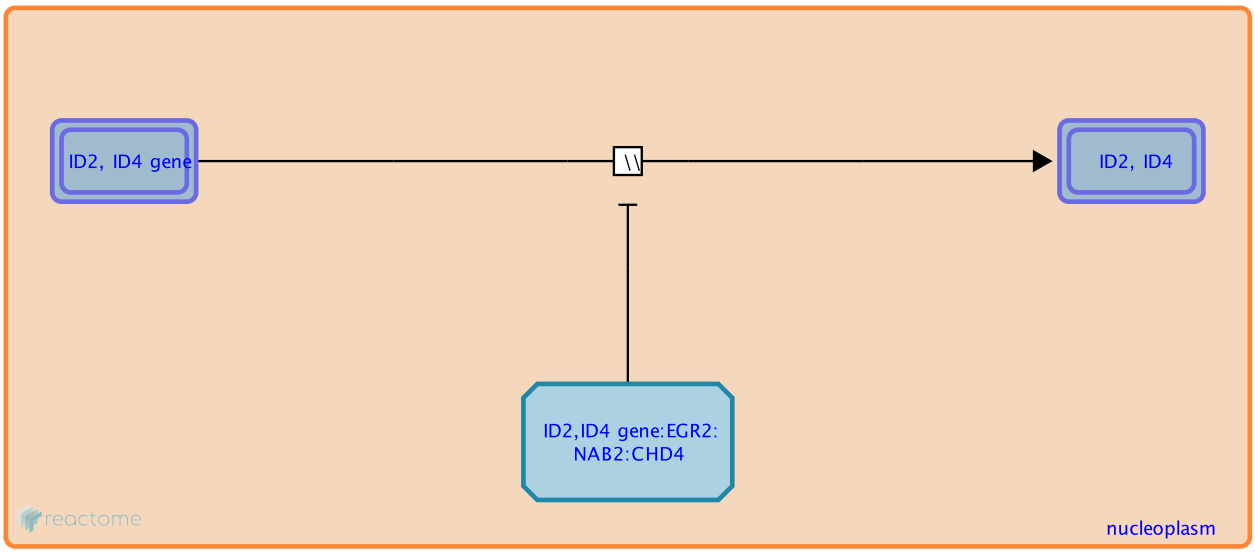
Expression of ID2 and ID4 is repressed by EGR2:NAB ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9612534

Type: omitted

Compartments: nucleoplasm



ID1-4 (Inhibitor of DNA-binding) are members of the helix-loop-helix family of proteins that lack the basic amino acids responsible for DNA binding in basic HLH proteins. HLH domain-mediated heterodimerization of an ID protein with a basic HLH protein therefore acts as a natural dominant negative inhibitor of bHLH function by preventing DNA binding (Massari and Murre, 2000). ID proteins primarily interact with members of the E family of proteins, including E12, E47, HEB and E2-2, but also interact with other bHLH proteins. ID proteins promote cell cycle progression and cell migration, and restrict cellular senescence and the differentiation of a number of progenitor cell types, including oligodendrocytes (reviewed in Perk et al, 2005; Ling et al, 2014).

Expression of ID2 and ID4 is negatively regulated by an EGR2:NAB2 complex that is recruited to the EGR binding sites in the promoter. Repression of ID2 and ID4 during development is associated with increased promoter occupancy of the EGR2:NAB2 complex and may be effected through the recruitment of the NURD chromatin remodelling complex and histone deacetylases. NAB2 has been shown to interact with the CHD4 and CHD3 subunits of the NURD complex through its conserved CHD4-interacting domain (CID) (Mager et al, 2008; Srinivasan et al, 2006; Hung et al, 2012).

Preceded by: EGR2:NAB2 and CHD4 bind the ID2 and ID4 promoter regions

Literature references

Massari, ME., Murre, C. (2000). Helix-loop-helix proteins: regulators of transcription in eucaryotic organisms. *Mol. Cell. Biol., 20*, 429-40. ↗

Perk, J., Iavarone, A., Benezra, R. (2005). Id family of helix-loop-helix proteins in cancer. *Nat. Rev. Cancer, 5*, 603-14. ↗

Ling, F., Kang, B., Sun, XH. (2014). Id proteins: small molecules, mighty regulators. *Curr. Top. Dev. Biol., 110*, 189-216 . ↗

Mager, GM., Ward, RM., Srinivasan, R., Jang, SW., Wrabetz, L., Svaren, J. (2008). Active gene repression by the Egr2.NAB complex during peripheral nerve myelination. *J. Biol. Chem., 283*, 18187-97. ↗

Srinivasan, R., Mager, GM., Ward, RM., Mayer, J., Svaren, J. (2006). NAB2 represses transcription by interacting with the CHD4 subunit of the nucleosome remodeling and deacetylase (NuRD) complex. *J. Biol. Chem., 281*, 15129-37. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

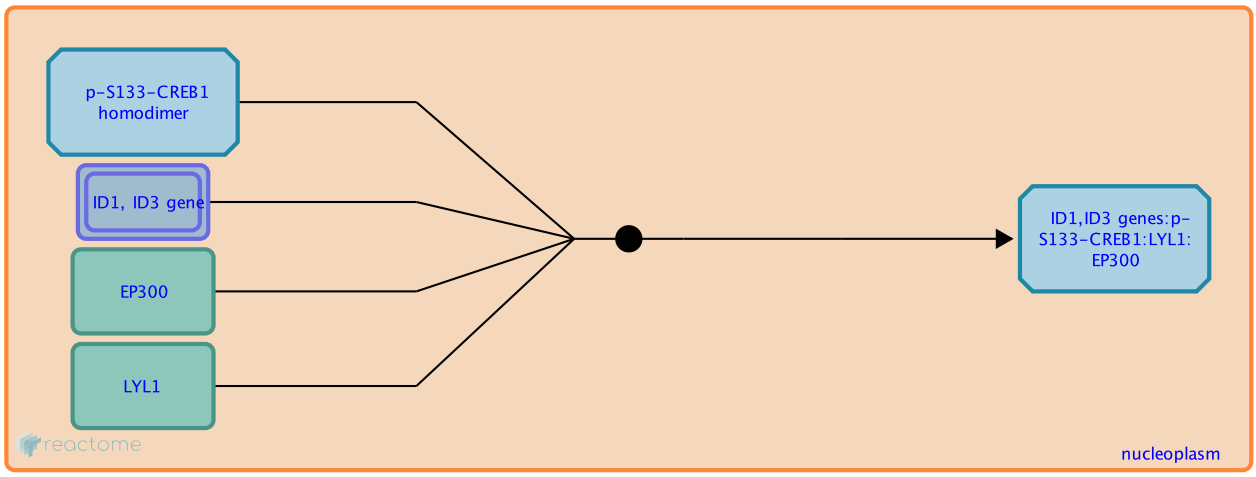
p-S133 CREB1, LYL1 and EP300 bind the ID1 and ID3 genes ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613451

Type: binding

Compartments: nucleoplasm



CREB1, EP300 and LYL1 are required for the activation of the ID1 and ID3 genes, which contribute to cellular proliferation and differentiation (Impey et al, 2004; San Marina et al, 2008; Rivera and Murre, 2001; Hong et al, 2011; Zhao et al, 2016). CREB1 binds to the CRE elements in the ID gene promoters and recruits EP300 in a CREB1 S133 phosphorylation dependent manner. S133 phosphorylation is dispensable for recruitment of LYL1, which instead depends on an interaction between the LYL1 N-terminal domain and the Q2 and KID domains of CREB1 (San Marina et al, 2008).

Followed by: ID1 and ID3 gene expression

Literature references

Impey, S., McCorkle, SR., Cha-Molstad, H., Dwyer, JM., Yochum, GS., Boss, JM. et al. (2004). Defining the CREB regulon: a genome-wide analysis of transcription factor regulatory regions. *Cell, 119*, 1041-54. ↗

San-Marina, S., Han, Y., Suarez Saiz, F., Trus, MR., Minden, MD. (2008). Lyl1 interacts with CREB1 and alters expression of CREB1 target genes. *Biochim. Biophys. Acta, 1783*, 503-17. ↗

Rivera, R., Murre, C. (2001). The regulation and function of the Id proteins in lymphocyte development. *Oncogene, 20* , 8308-16. ↗

Hong, SH., Lee, JH., Lee, JB., Ji, J., Bhatia, M. (2011). ID1 and ID3 represent conserved negative regulators of human embryonic and induced pluripotent stem cell hematopoiesis. *J. Cell. Sci., 124*, 1445-52. ↗

Zhao, Q., Chang, C., Gonzalez, JP., Alzahrani, K., Button, JL., Fraidenraich, D. (2016). Combined Id1 and Id3 Deletion Leads to Severe Erythropoietic Disturbances. *PLoS ONE, 11*, e0154480. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

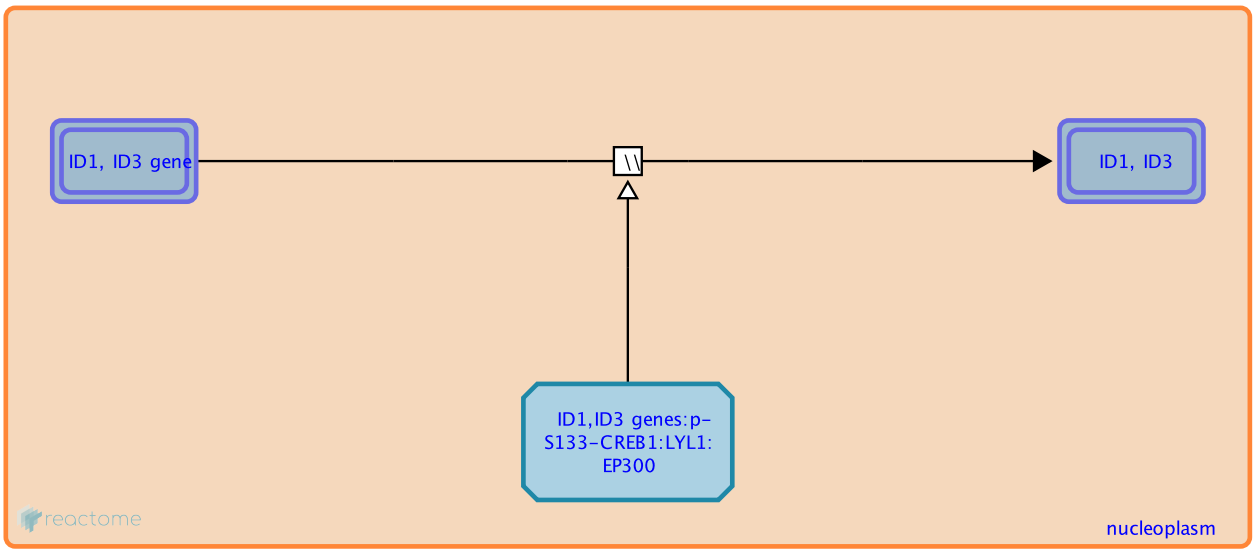
ID1 and ID3 gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9613460

Type: omitted

Compartments: nucleoplasm



ID1-4 (Inhibitor of DNA-binding) are members of the helix-loop-helix family of proteins that lack the basic amino acids responsible for DNA binding in basic HLH proteins. HLH domain-mediated heterodimerization of an ID protein with a basic HLH protein therefore acts as a natural dominant negative inhibitor of bHLH function by preventing DNA binding (Massari and Murre, 2000). ID proteins primarily interact with members of the E family of proteins, including E12, E47, HEB and E2-2, but also interact with other bHLH proteins. ID proteins promote cell cycle progression and cell migration, and restrict cellular senescence and the differentiation of a number of progenitor cell types, including oligodendrocytes (reviewed in Perk et al, 2005; Ling et al, 2014). ID1 and ID3 proteins also have established roles in hematopoiesis (Nogueira et al, 2000; Rivera and Murre, 2001; Hong et al, 2011; Zhao et al, 2016).

ID1 and ID3 gene expression is activated by the binding of CREB1 to CRE sites in the promoter. CREB recruits transcriptional co-activators p300 and CBP in a CREB S133 phosphorylation-dependent manner (reviewed in Shaywitz and Greenberg, 1999). ID1 and ID3 gene activation also depends on the CREB1-dependent recruitment of LYL1, a basic helix-loop-helix transcription factor with roles in cell proliferation and differentiation. The N-terminal domain of LYL1 interacts with the Q2 and KID domains of CREB1 in a manner that does not require CREB1 S133 phosphorylation (San Marina et al, 2008).

Preceded by: p-S133 CREB1, LYL1 and EP300 bind the ID1 and ID3 genes

Literature references

Nogueira, MM., Mitjavila-Garcia, MT., Le Pesteur, F., Filippi, MD., Vainchenker, W., Dubart Kupperschmitt, A. et al. (2000). Regulation of Id gene expression during embryonic stem cell-derived hematopoietic differentiation. *Biochem. Biophys. Res. Commun., 276*, 803-12. ↗

Rivera, R., Murre, C. (2001). The regulation and function of the Id proteins in lymphocyte development. *Oncogene, 20* , 8308-16. ↗

Hong, SH., Lee, JH., Lee, JB., Ji, J., Bhatia, M. (2011). ID1 and ID3 represent conserved negative regulators of human embryonic and induced pluripotent stem cell hematopoiesis. *J. Cell. Sci., 124*, 1445-52. ↗

Zhao, Q., Chang, C., Gonzalez, JP., Alzahrani, K., Button, JL., Fraidenraich, D. (2016). Combined Id1 and Id3 Deletion Leads to Severe Erythropoietic Disturbances. *PLoS ONE, 11*, e0154480. ↗

Shaywitz, AJ., Greenberg, ME. (1999). CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. *Annu. Rev. Biochem., 68*, 821-61. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

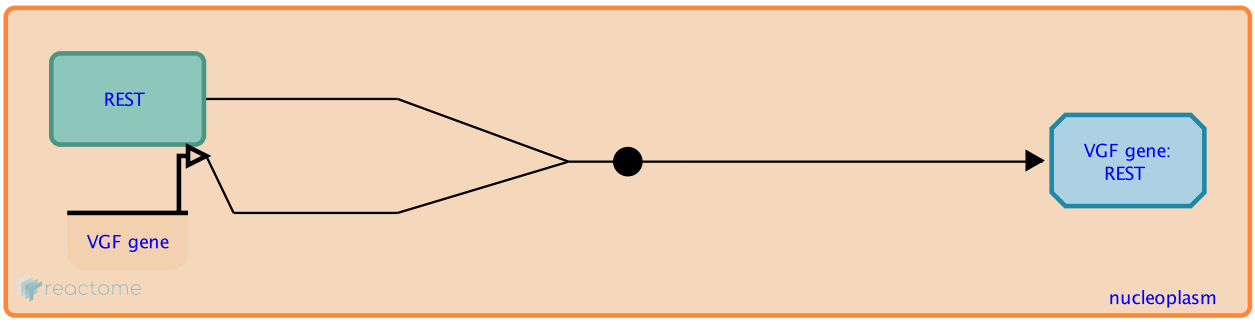
REST binds the VGF promoter ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621054

Type: binding

Compartments: nucleoplasm



RE1-silencing transcription factor (REST, also known as Neuron-restrictive silencer factor or NRSF) is a transcriptional repressor that binds to neuron-restrictive silencer elements (NRSEs) to inhibit transcription in non-neuronal cells and to temporally regulate expression in neuronal cells. REST interacts with 2 corepressor complexes, mSIN3 and CoREST, which recruit histone deacetylases to promoter regions (Schoenherr et al, 1995; Lunyak et al, 2002; Mulligan et al, 2008).

Promoter analysis of the VGF gene identified a functional NRSE element spanning the transcriptional start site, and this element is bound by NRSF as assessed by ChIP. Mutations in the NRSE relieve transcriptional repression and overexpression of NRSF in rat PC12 cells suppresses VGF transcription (Moon et al, 2015).

Literature references

Schoenherr, CJ., Anderson, DJ. (1995). The neuron-restrictive silencer factor (NRSF): a coordinate repressor of multiple neuron-specific genes. *Science, 267*, 1360-3. ↗

Lunyak, VV., Burgess, R., Prefontaine, GG., Nelson, C., Sze, SH., Chenoweth, J. et al. (2002). Corepressor-dependent silencing of chromosomal regions encoding neuronal genes. *Science, 298*, 1747-52. ↗

Mulligan, P., Westbrook, TF., Ottinger, M., Pavlova, N., Chang, B., Macia, E. et al. (2008). CDYL bridges REST and histone methyltransferases for gene repression and suppression of cellular transformation. *Mol. Cell, 32*, 718-26. ↗

Moon, SM., Kim, JS., Park, BR., Kim, DK., Kim, SG., Kim, HJ. et al. (2015). Transcriptional regulation of the neuropeptide VGF by the neuron-restrictive silencer factor/neuron-restrictive silencer element. *Neuroreport, 26*, 144-51. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

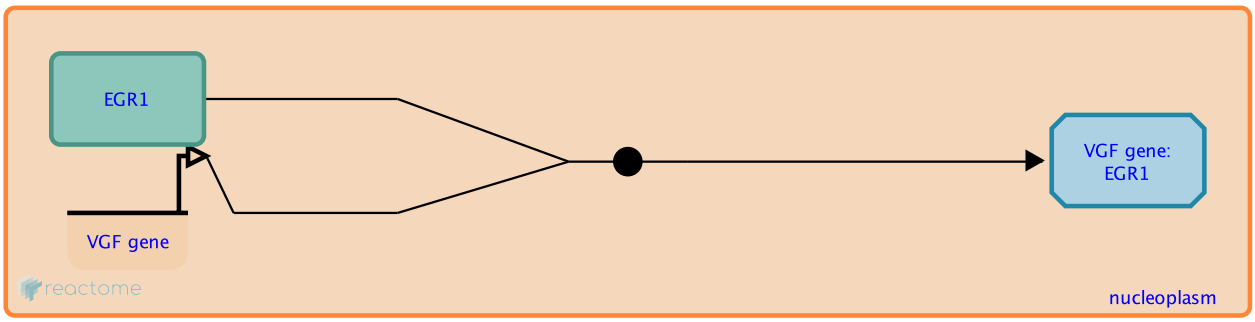
EGR1 binds the VGF gene ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9620663

Type: binding

Compartments: nucleoplasm



In neuronal cells, the VGF gene is induced by sustained NGF signaling, as well as by cyclic AMP and other agents, although to a lower degree (Salton et al, 1991a; Salton et al, 1991b; Mullenbrock et al, 2011). Promoter analysis of the VGF gene identified a proximal promoter element spanning nucleotides -180 to -70 with a number of consensus binding sequences for transcriptional regulators (Canu et al, 1997; Possenti et al, 1992; Di Rocco et al, 1997; D'Arcangelo et al, 1996). This promoter is under negative regulation in non-neuronal cells. Among the promoter elements identified is a G(S)G motif between the TATA box and the transcriptional start site that is bound by EGR1 in an NGF-inducible mannner (D'Arcangelo et al, 1996; Mullenbrock et al, 2011; Adams et al, 2017).

Followed by: VGF gene expression

Literature references

Salton, SR. (1991). Nucleotide sequence and regulatory studies of VGF, a nervous system-specific mRNA that is rapidly and relatively selectively induced by nerve growth factor. *J. Neurochem., 57*, 991-6. ↗

Salton, SR., Fischberg, DJ., Dong, KW. (1991). Structure of the gene encoding VGF, a nervous system-specific mRNA that is rapidly and selectively induced by nerve growth factor in PC12 cells. *Mol. Cell. Biol., 11*, 2335-49. ↗

Canu, N., Possenti, R., Rinaldi, AM., Trani, E., Levi, A. (1997). Molecular cloning and characterization of the human VGF promoter region. *J. Neurochem., 68*, 1390-9. ↗

Possenti, R., Di Rocco, G., Nasi, S., Levi, A. (1992). Regulatory elements in the promoter region of vgf, a nerve growth factor-inducible gene. *Proc. Natl. Acad. Sci. U.S.A., 89*, 3815-9. ↗

Di Rocco, G., Pennuto, M., Illi, B., Canu, N., Filocamo, G., Trani, E. et al. (1997). Interplay of the E box, the cyclic AMP response element, and HTF4/HEB in transcriptional regulation of the neurospecific, neurotrophin-inducible vgf gene. *Mol. Cell. Biol., 17*, 1244-53. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

p-CREB, ASCL1, TCF12, ATFs and p300 bind the VGF promoter ↗

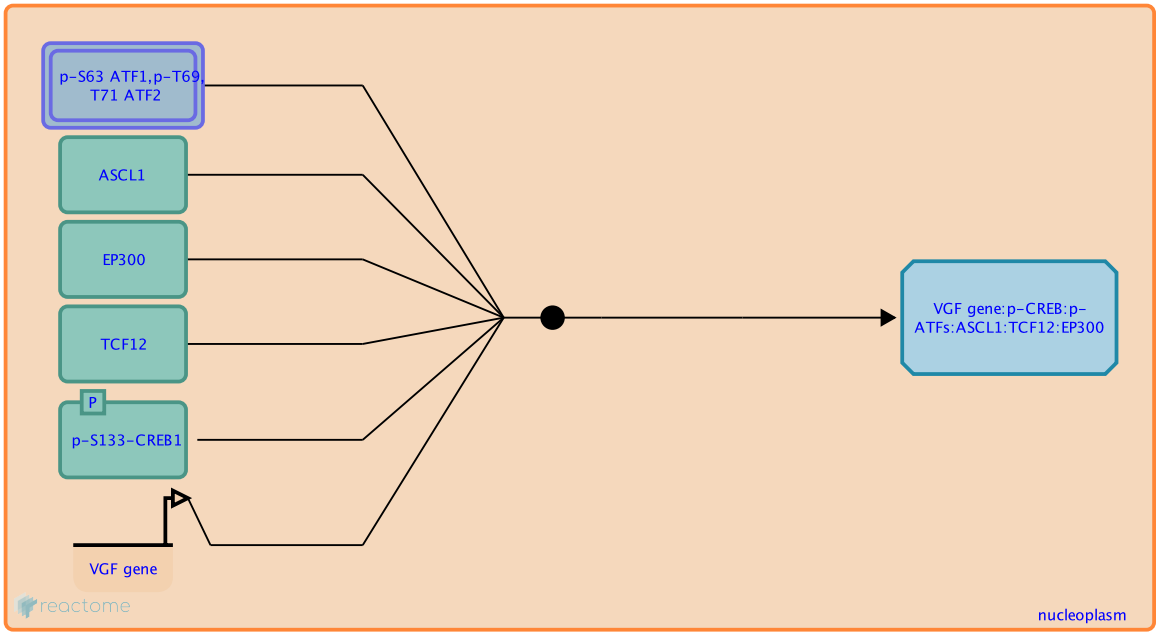
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9620717

Type: binding

Compartments: nucleoplasm

Inferred from: p-Creb, Ascl1, Tcf12, p300 bind the vgf promoter (Rattus norvegicus)



Studies of the VGF promoter have identified a number of consensus sites in a minimal 110 bp promoter spanning -180 to -70 upstream of the transcriptional start site (D'Arcangelo et al, 1996; Possenti et al, 1992; Mandolesi et al, 2002). These sites, which include an E-box, a CCAAT site, a CRE element and a G(S)G site, are required for NGF-responsive transcription in neuronal cells (Possenti et al, 1992; D'Arcangelo et al, 1996; Mandolesi et al, 2002). The E box and CCAAT elements are bound by TCF12 (also known as HEB) and ASCL1 (also known as MASH1) to weakly stimulate trancriptional activity (Di Rocco et al, 1997; Mandolesi et al, 2002). The CRE is bound by phosphorylated CREB and by members of the ATF family . CRE binding is facilitated through protein-protein interactions with an unidentified CCAAT-binding factor (Di Rocco et al, 1997; D'Arcangelo et al, 1996; Mandolesi et al, 2002). The CREB:ASCL1 complex also includes the histone acetyltransferase p300 (Mandolesi et al, 2002; Adams et al, 2017).

Followed by: VGF gene expression

Literature references

Mandolesi, G., Gargano, S., Pennuto, M., Illi, B., Molfetta, R., Soucek, L. et al. (2002). NGF-dependent and tissue-specific transcription of vgf is regulated by a CREB-p300 and bHLH factor interaction. *FEBS Lett., 510*, 50-6. ↗

Possenti, R., Di Rocco, G., Nasi, S., Levi, A. (1992). Regulatory elements in the promoter region of vgf, a nerve growth factor-inducible gene. *Proc. Natl. Acad. Sci. U.S.A., 89*, 3815-9. ↗

D'Arcangelo, G., Habas, R., Wang, S., Halegoua, S., Salton, SR. (1996). Activation of codependent transcription factors is required for transcriptional induction of the vgf gene by nerve growth factor and Ras. *Mol. Cell. Biol., 16* , 4621-31. ↗

Di Rocco, G., Pennuto, M., Illi, B., Canu, N., Filocamo, G., Trani, E. et al. (1997). Interplay of the E box, the cyclic AMP response element, and HTF4/HEB in transcriptional regulation of the neurospecific, neurotrophin-inducible vgf gene. *Mol. Cell. Biol., 17*, 1244-53. ↗

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

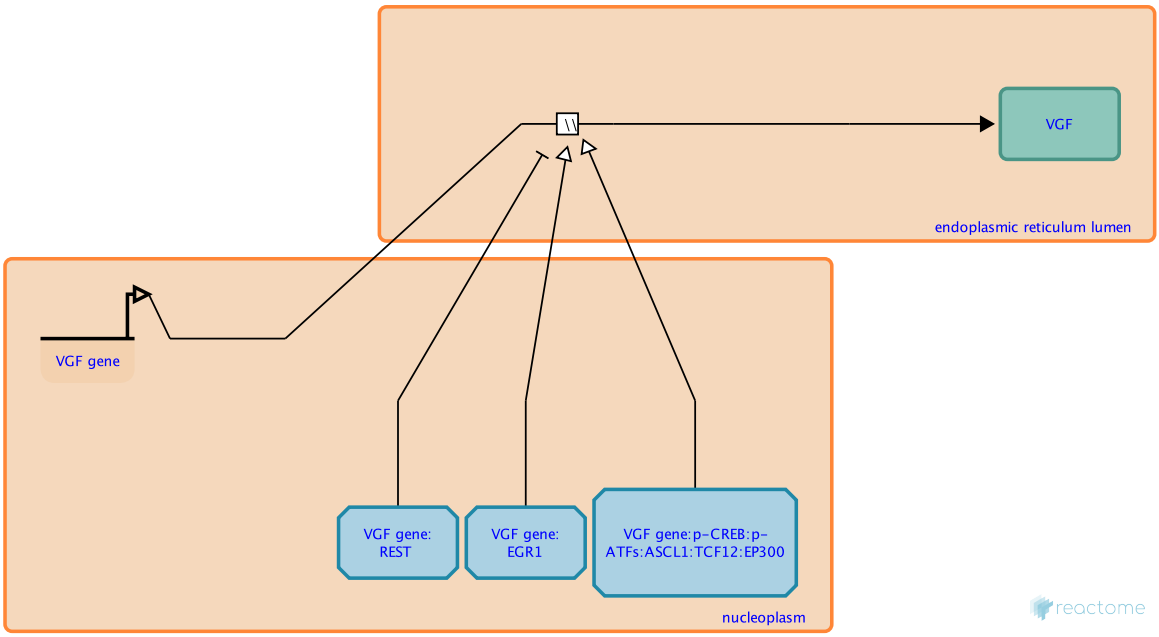
VGF gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9620723

Type: omitted

Compartments: endoplasmic reticulum lumen, nucleoplasm



VGF is a neurosecretory protein that is expressed in neuronal cells in response to NGF signaling as well as other stimuli including cAMP (Salton et al, 1991a; Salton et al, 1991b; Hawley et al, 1992; Nagasaki et al, 1999; reviewed in Salton et al, 2000). VGF traffics through the secretory sytem where it is subject to endoproteolytic cleavage, generating small neuroactive peptides that are released upon depolarization (Possenti et al, 1989; Trani et al, 1995; Garcia et al, 2005; reviewed in Toshinai and Nakazato, 2009; Ferri et al, 2011). VGF peptides play roles in energy and water balance, depression, sensory nerves and pain perception, reproduction and neuronal apoptosis, among others (reviwed in Ferri et al, 2011).

NGF-dependent expression of VGF in neuronal cells is controlled by numerous binding sites in the promixal promoter (Canu et al, 1997; Possenti et al, 1992; Di Rocco et al, 1997; D'Arcangelo et al, 1996; Mullenbrock et al, 2011). Identified DNA-binding positive regulators of NGF-dependent VGF expression include EGR1, AP-1, SP-1, CREB family members, ASCL1 and TCF12, among others (Possenti et al, 2002; Di Rocco et al, 1997; D'Arcangelo et al, 1996; Mullenbrock et al, 2011; Adams et al, 2017; Mandolesi et al, 2002).

Preceded by: p-CREB, ASCL1, TCF12, ATFs and p300 bind the VGF promoter, EGR1 binds the VGF gene

Literature references

Salton, SR. (1991). Nucleotide sequence and regulatory studies of VGF, a nervous system-specific mRNA that is rapidly and relatively selectively induced by nerve growth factor. *J. Neurochem., 57*, 991-6. ↗

Salton, SR., Fischberg, DJ., Dong, KW. (1991). Structure of the gene encoding VGF, a nervous system-specific mRNA that is rapidly and selectively induced by nerve growth factor in PC12 cells. *Mol. Cell. Biol., 11*, 2335-49. ↗

Hawley, RJ., Scheibe, RJ., Wagner, JA. (1992). NGF induces the expression of the VGF gene through a cAMP response element. *J. Neurosci., 12*, 2573-81. ↗

Nagasaki, K., Sasaki, K., Maass, N., Tsukada, T., Hanzawa, H., Yamaguchi, K. (1999). Staurosporine enhances cAMP-induced expression of neural-specific gene VGF and tyrosine hydroxylase. *Neurosci. Lett., 267*, 177-80. ↗

Salton, SR., Ferri, GL., Hahm, S., Snyder, SE., Wilson, AJ., Possenti, R. et al. (2000). VGF: a novel role for this neuronal and neuroendocrine polypeptide in the regulation of energy balance. *Front Neuroendocrinol, 21*, 199-219. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

EGR1 binds the TPH1 promoter ↗

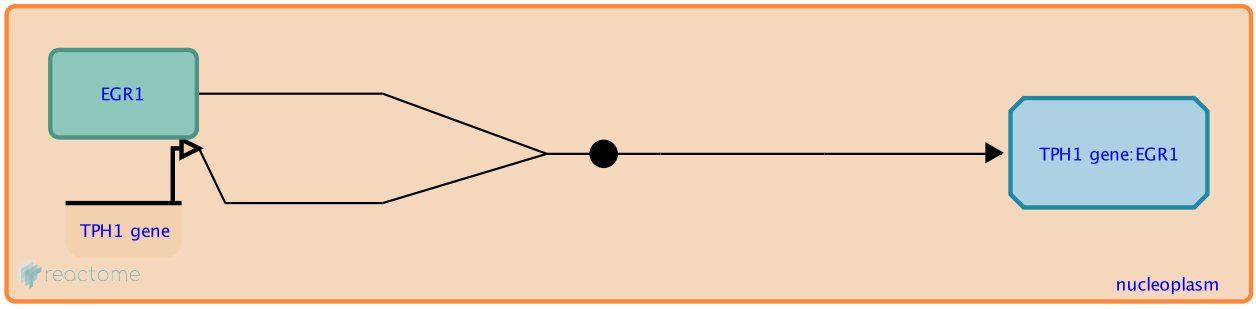
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621032

Type: binding

Compartments: nucleoplasm

Inferred from: Egr1 binds the Tph1 promoter (Rattus norvegicus)



EGR1 binds to the TPH1 promoter as assessed by ChIP and electrophoretic mobility shift assay (EMSA) (Adams et al, 2017; Grasberger et al, 2013). EGR1 binding stimulates NGF-dependent signaling (Mullenbrock et al, 2011; Adams et al, 2017).

Followed by: TPH1 gene expression

Literature references

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Grasberger, H., Chang, L., Shih, W., Presson, AP., Sayuk, GS., Newberry, RD. et al. (2013). Identification of a functional TPH1 polymorphism associated with irritable bowel syndrome bowel habit subtypes. *Am. J. Gastroenterol., 108*, 1766-74. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

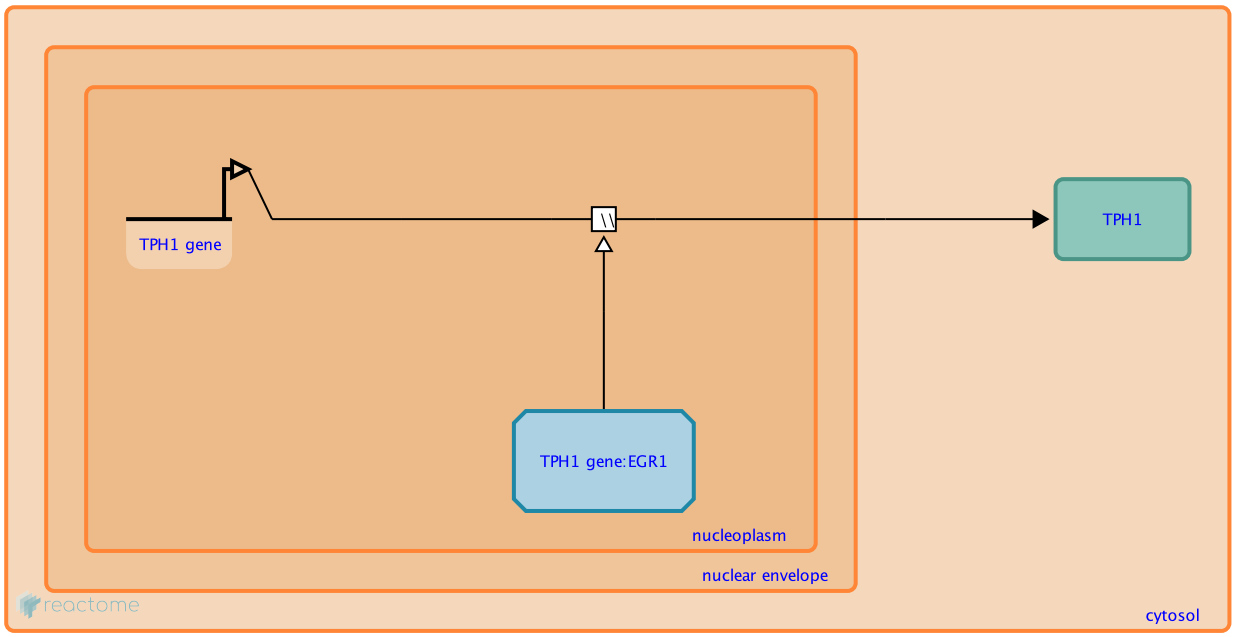
TPH1 gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621048

Type: omitted

Compartments: nucleoplasm, cytosol



TPH1 (Tryptophan hydroxylase 1) is one of two tryptophan hydroxlyase enzymes that catalyze the rate-limiting step in the synthesis of 5-HT (5-hydroxytryptamine or serotonin). TPH1 is expressed in the gut, the periphery and in the pineal gland and additionally has roles during neuronal development. In contrast, TPH2 is expressed at high levels in the brain and the gut (Walther et al, 2003; Côté et al, 2003; Nakamura et al, 2006).

TPH1 has been shown to be a transcriptional target of EGR1 and is transcriptionally activated downstream of sustained NGF signaling (Grasberer et al, 2013; Mullenbrock et al, 2011; Adams et al, 2017).

Preceded by: EGR1 binds the TPH1 promoter

Literature references

Walther, DJ., Peter, JU., Bashammakh, S., Hörtnagl, H., Voits, M., Fink, H. et al. (2003). Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science, 299*, 76. ↗

Côté, F., Thévenot, E., Fligny, C., Fromes, Y., Darmon, M., Ripoche, MA. et al. (2003). Disruption of the nonneuronal tph1 gene demonstrates the importance of peripheral serotonin in cardiac function. *Proc. Natl. Acad. Sci. U.S.A., 100*, 13525-30. ↗

Nakamura, K., Sugawara, Y., Sawabe, K., Ohashi, A., Tsurui, H., Xiu, Y. et al. (2006). Late developmental stage-specific role of tryptophan hydroxylase 1 in brain serotonin levels. *J. Neurosci., 26*, 530-4. ↗

Grasberger, H., Chang, L., Shih, W., Presson, AP., Sayuk, GS., Newberry, RD. et al. (2013). Identification of a functional TPH1 polymorphism associated with irritable bowel syndrome bowel habit subtypes. *Am. J. Gastroenterol., 108*, 1766-74. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

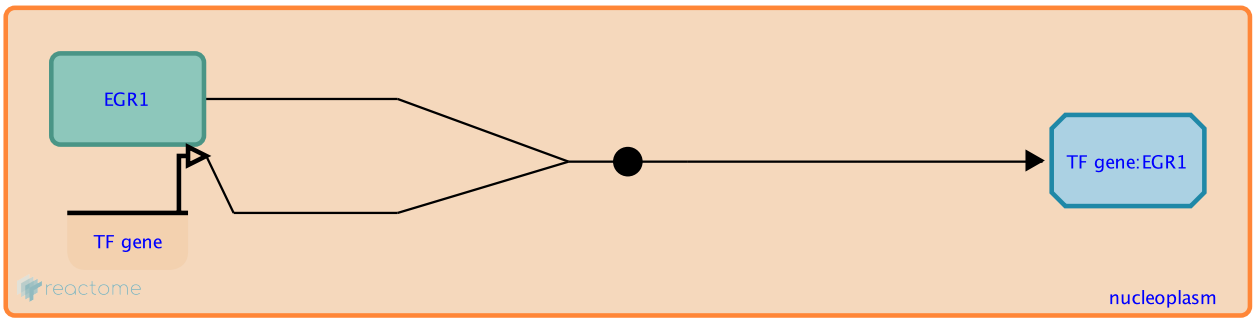
EGR1 binds the TF gene ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621035

Type: binding

Compartments: nucleoplasm



EGR1 binds to the promoter of the TF gene to induce transcription downstream of NGF, serum and PMA (Cui et al, 1996; Mullenbrock et al, 2011; Adams et al, 2017). TF encodes Tissue Factor F3, a key initiator of blood clotting (reviewed in Smith et al, 2015).

Followed by: TF gene expression

Literature references

Cui, MZ., Parry, GC., Oeth, P., Larson, H., Smith, M., Huang, RP. et al. (1996). Transcriptional regulation of the tissue factor gene in human epithelial cells is mediated by Sp1 and EGR-1. *J. Biol. Chem., 271*, 2731-9. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Smith, SA., Travers, RJ., Morrissey, JH. (2015). How it all starts: Initiation of the clotting cascade. *Crit. Rev. Biochem. Mol. Biol., 50*, 326-36. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

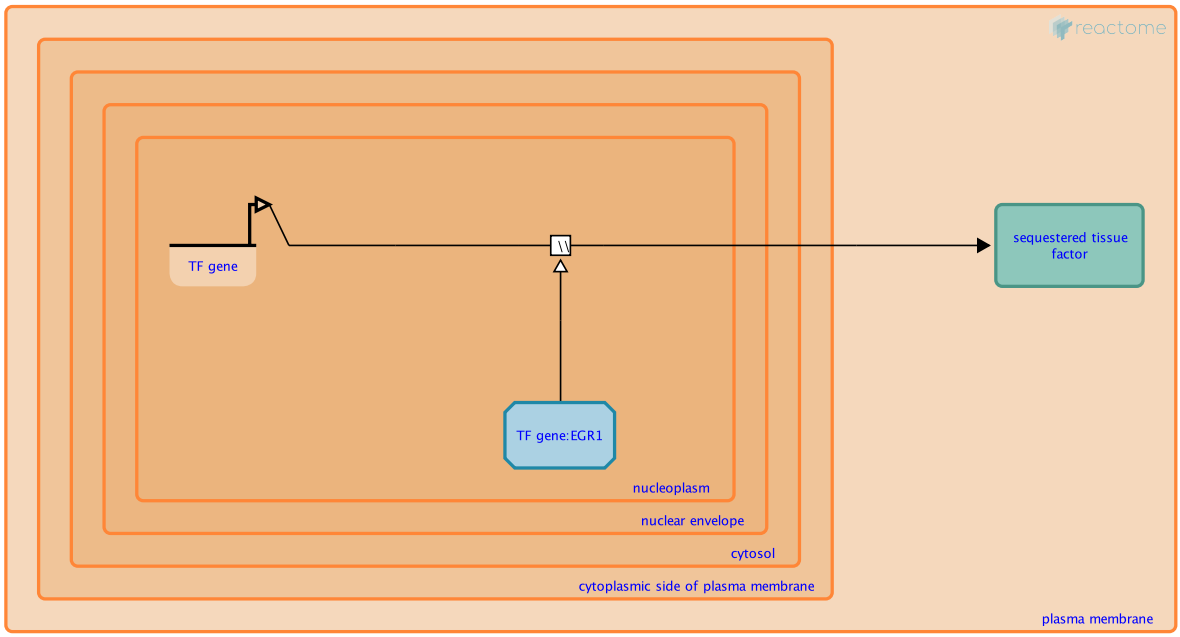
TF gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621042

Type: omitted

Compartments: nucleoplasm, plasma membrane



Tissue Factor F3 (TF) is an intrinsic plasma membrane protein that initiates blood clotting upon injury to the blood vessel (reviewed in Smith et al, 2015). TF is highly expressed in the brain and other tissues where the consequences of unchecked bleeding are high (Fleck et al, 1990). TF expression is regulated in part by binding of EGR1 to cognate sites in the promoter, and EGR1-dependent transcription has been observed downstream of sustained NGF signaling as well as after treatment wtith phorbol 12-myristate 13-acetate (PMA) or serum (Mullenbrock et al, 2011; Adams et al, 2017; Cui et al, 1996).

Preceded by: EGR1 binds the TF gene

Literature references

Smith, SA., Travers, RJ., Morrissey, JH. (2015). How it all starts: Initiation of the clotting cascade. *Crit. Rev. Biochem. Mol. Biol., 50*, 326-36. ↗

Fleck, RA., Rao, LV., Rapaport, SI., Varki, N. (1990). Localization of human tissue factor antigen by immunostaining with monospecific, polyclonal anti-human tissue factor antibody. *Thromb. Res., 59*, 421-37. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Cui, MZ., Parry, GC., Oeth, P., Larson, H., Smith, M., Huang, RP. et al. (1996). Transcriptional regulation of the tissue factor gene in human epithelial cells is mediated by Sp1 and EGR-1. *J. Biol. Chem., 271*, 2731-9. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

EGR1 binds TRIB1 gene ↗

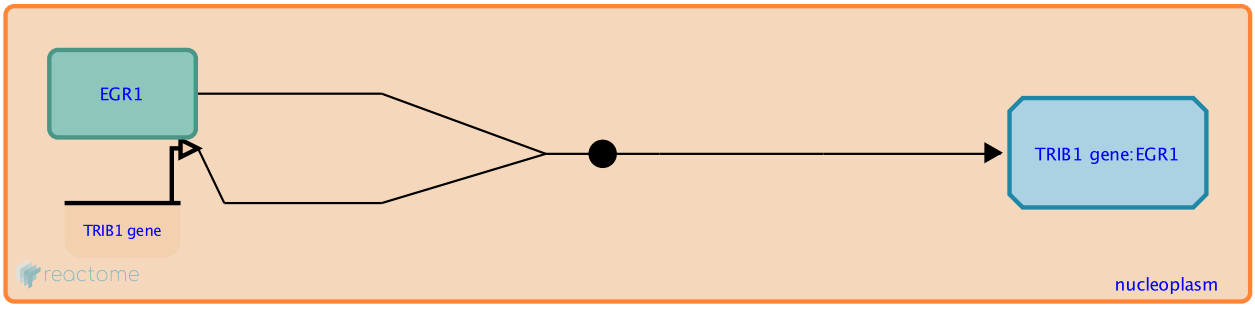
Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621385

Type: binding

Compartments: nucleoplasm

Inferred from: Egr1 binds the Trib1 gene (Rattus norvegicus)



Based on ChIP studies done in rat PC12 cells, EGR1 binds to promoter elements updstream of the TRIB1 gene to regulate NGF-dependent signaling (Mullenbrock et al, 2011; Adams et al, 2017).

Followed by: TRIB1 gene expression

Literature references

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

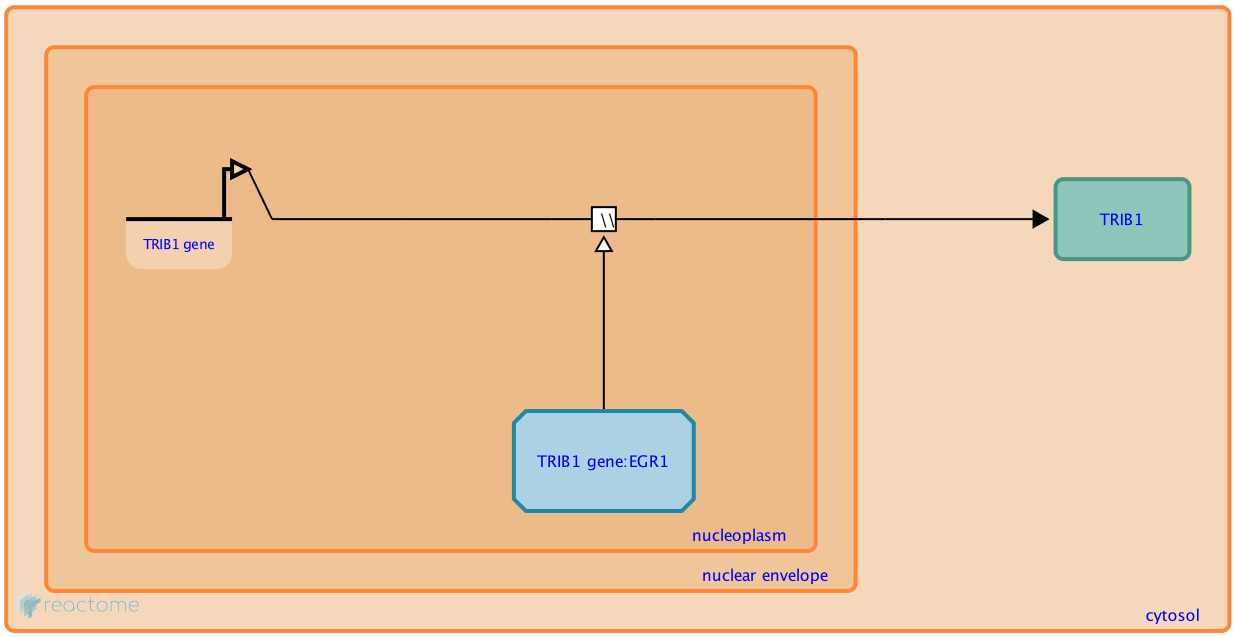
TRIB1 gene expression ↗

Location: NGF-stimulated transcription

Stable identifier: R-HSA-9621386

Type: omitted

Compartments: nucleoplasm, cytosol



TRIB1 is an adapter protein that interacts with COP1 ubiquitin ligase to regulate protein degradation (Uljon et al, 2016). Studies in rat PC12 cells identified TRIB1 as a target gene of EGR1 in response to sustained NGF signaling, and EGR1 was shown to bind to cognate sites in the promoter as assessed by ChIP (Mullenbrock et al, 2011; Adams et al, 2017).

Preceded by: EGR1 binds TRIB1 gene

Literature references

Uljon, S., Xu, X., Durzynska, I., Stein, S., Adelmant, G., Marto, JA. et al. (2016). Structural Basis for Substrate Selectivity of the E3 Ligase COP1. *Structure, 24*, 687-696. ↗

Adams, KW., Kletsov, S., Lamm, RJ., Elman, JS., Mullenbrock, S., Cooper, GM. (2017). Role for Egr1 in the Transcriptional Program Associated with Neuronal Differentiation of PC12 Cells. *PLoS ONE, 12*, e0170076. ↗

Mullenbrock, S., Shah, J., Cooper, GM. (2011). Global expression analysis identified a preferentially nerve growth factor-induced transcriptional program regulated by sustained mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and AP-1 protein activation during PC12 cell differentiation. *J. Biol. Chem., 286*, 45131-45. ↗

Editions

2019-08-16	Authored	Rothfels, K.
2020-01-17	Reviewed	Aletta, J M.
2020-02-24	Edited	Rothfels, K.

Table of Contents