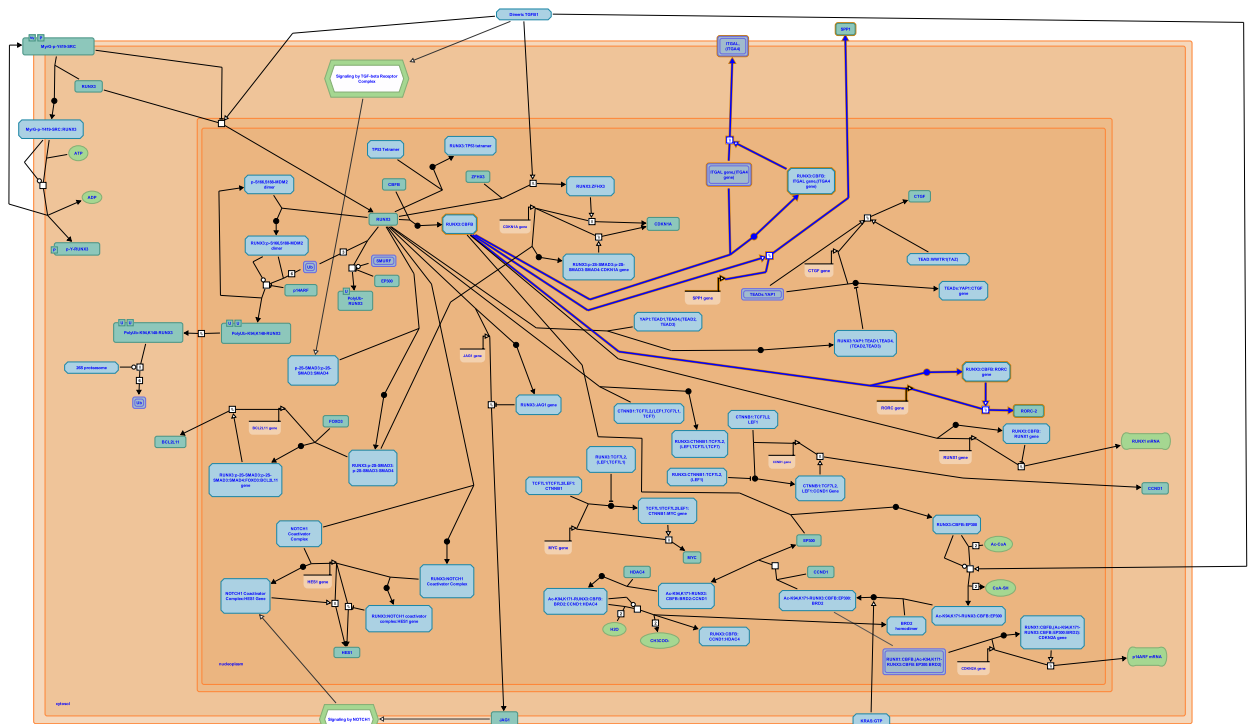


RUNX3 Regulates Immune Response and Cell Migration



Chuang, LS., Ito, Y., Orlic-Milacic, M.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://creativecommons.org/licenses/by/4.0/).

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

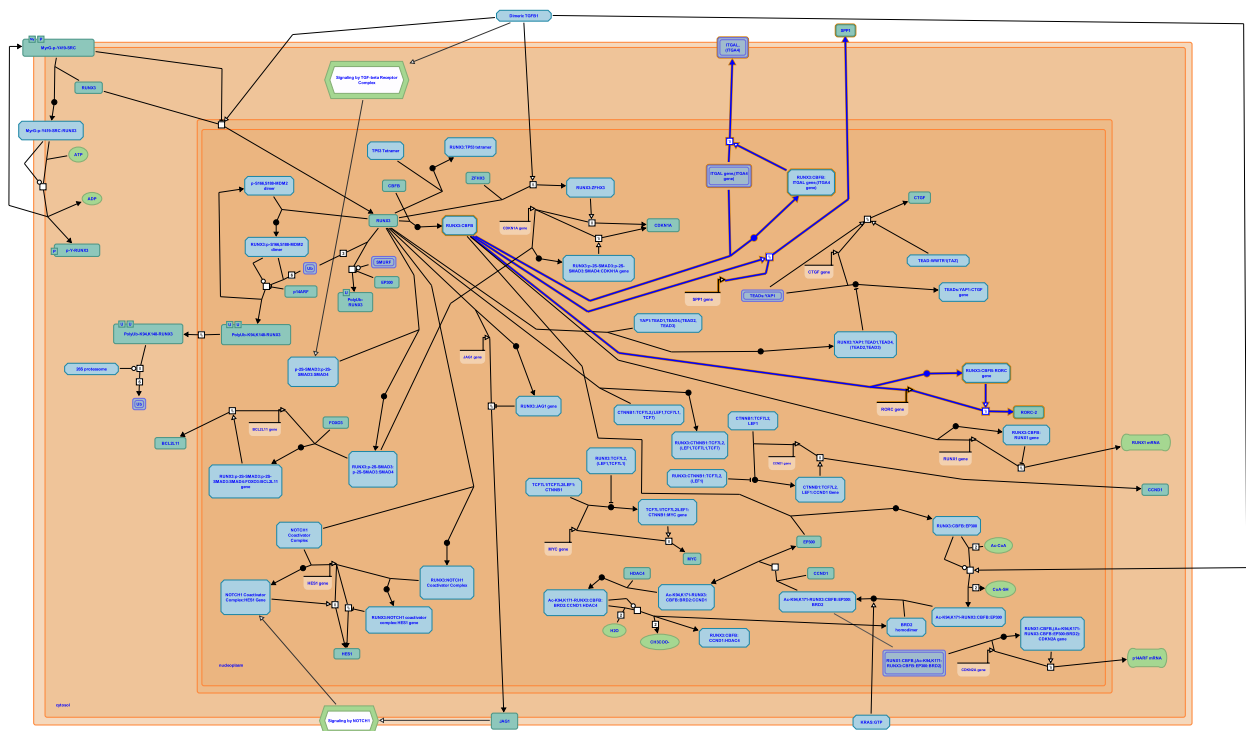
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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. [↗](#)

Reactome database release: 75

This document contains 1 pathway and 5 reactions ([see Table of Contents](#))

RUNX3 Regulates Immune Response and Cell Migration ↗

Stable identifier: R-HSA-8949275



reactome

RUNX3-mediated transcription regulates development of immune system cells. RUNX3 is necessary for the development of innate lymphoid cells (ILCs) of ILC1 and ILC3 lineages, which reside in the mucosa and are involved in response to external pathogens. RUNX3 exerts its role in the development of ILC1 and ILC3 lineages by stimulating expression of the RORC (RORgamma) gene, encoding nuclear retinoid-related orphan receptor-gamma (Ebihara et al. 2015).

RUNX3 regulates transcription of integrin genes ITGA4 (CD49d), involved in transendothelial migration of leukocytes during immune and inflammatory responses as well as co-stimulation of T cells (Domínguez-Soto et al. 2005). The RUNX3 splicing isoform p33 lacks the Runt domain and is unable to transactivate integrin genes. The p33 isoform is induced during maturation of monocyte-derived dendritic cells (MDDC), leading to reduced expression of genes involved in inflammatory responses, such as IL8 (interleukin-8) (Puig-Kröger et al. 2010).

RUNX3 positively regulates transcription of the SPP1 (osteopontin) gene, which contributes to invasiveness of pancreatic cancer cells (Whittle et al. 2015).

Literature references

- Whittle, MC., Izeradjene, K., Rani, PG., Feng, L., Carlson, MA., DelGiorno, KE. et al. (2015). RUNX3 Controls a Metastatic Switch in Pancreatic Ductal Adenocarcinoma. *Cell*, 161, 1345-60. ↗
- Domínguez-Soto, A., Rellosó, M., Vega, MA., Corbí, AL., Puig-Kröger, A. (2005). RUNX3 regulates the activity of the CD11a and CD49d integrin gene promoters. *Immunobiology*, 210, 133-9. ↗
- Puig-Kröger, A., Aguilera-Montilla, N., Martínez-Nuñez, R., Domínguez-Soto, A., Sánchez-Cabo, F., Martín-Gayo, E. et al. (2010). The novel RUNX3/p33 isoform is induced upon monocyte-derived dendritic cell maturation and downregulates IL-8 expression. *Immunobiology*, 215, 812-20. ↗
- Ebihara, T., Song, C., Ryu, SH., Plougastel-Douglas, B., Yang, L., Levanon, D. et al. (2015). Runx3 specifies lineage commitment of innate lymphoid cells. *Nat. Immunol.*, 16, 1124-33. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, L.S.
2017-01-31	Edited	Orlic-Milacic, M.

RUNX3:CBFB binds the RORC gene promoter [↗](#)

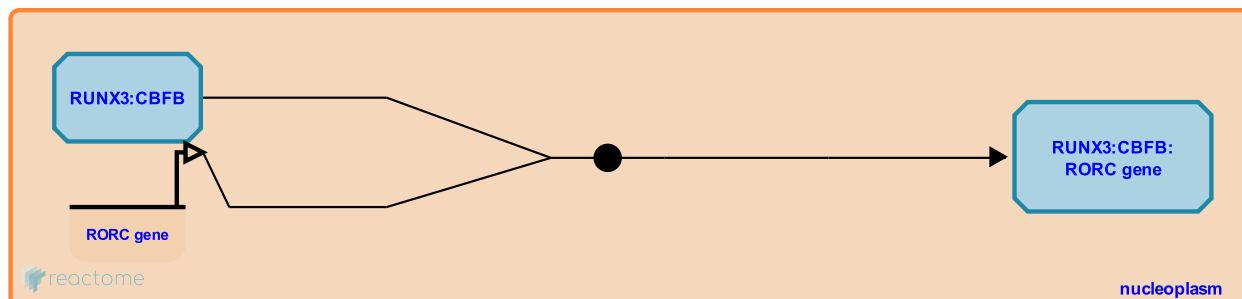
Location: [RUNX3 Regulates Immune Response and Cell Migration](#)

Stable identifier: R-HSA-8949276

Type: binding

Compartments: nucleoplasm

Inferred from: [Runx3:Cbfb binds the Rorc gene promoter \(Mus musculus\)](#)



Based on studies in mice, the complex of RUNX3 and CBFB binds the promoter of the RORC (RO-Rgamma) gene, encoding nuclear retinoid-related orphan receptor-gamma. The RUNX binding site TGT-GGT is conserved between mouse and human RORC promoters. Mouse Runx3 is expressed in innate lymphoid cell lineages ILC1 and ILC3, but not ILC2 (Ebihara et al. 2015).

Followed by: [RORC gene expression is stimulated by RUNX3:CBFB](#)

Literature references

Ebihara, T., Song, C., Ryu, SH., Plougastel-Douglas, B., Yang, L., Levanon, D. et al. (2015). Runx3 specifies lineage commitment of innate lymphoid cells. *Nat. Immunol.*, 16, 1124-33. [↗](#)

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

RORC gene expression is stimulated by RUNX3:CBFB ↗

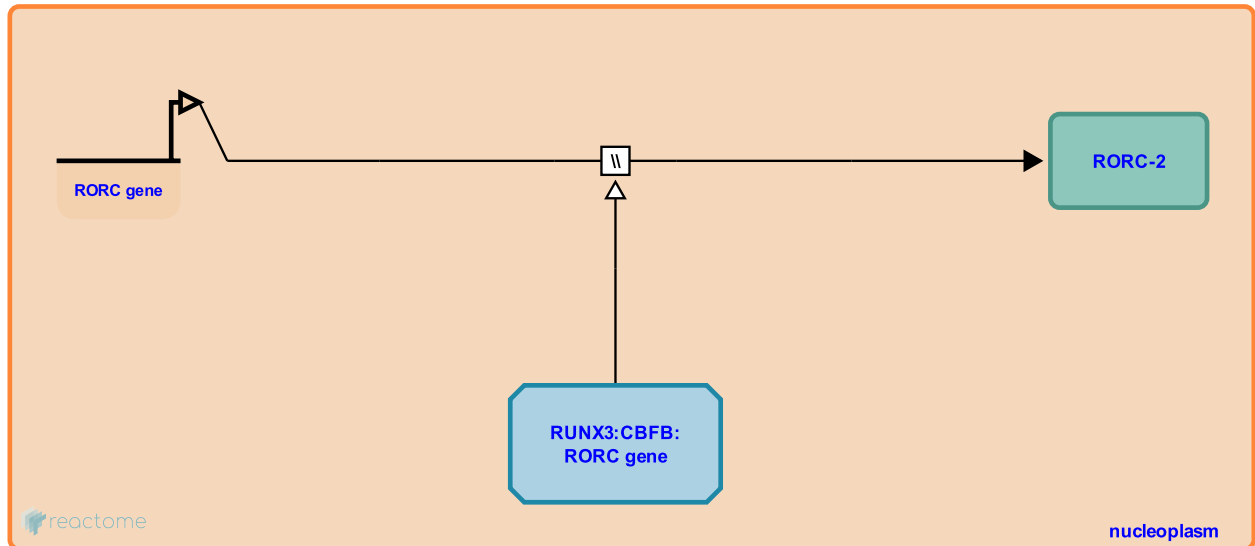
Location: [RUNX3 Regulates Immune Response and Cell Migration](#)

Stable identifier: R-HSA-8949301

Type: omitted

Compartments: nucleoplasm

Inferred from: [Rorc gene expression is stimulated by Runx3:Cbfb \(Mus musculus\)](#)



Based on mouse studies, binding of the RUNX3:CBFB heterodimer to the RUNX binding motif TGTGGT conserved between the mouse and human promoters of the RORC (RORgamma) gene, stimulates transcription of the RORC transcript variant 2 (RORC-2), also known as RORgT (RORgamma-t). In the ILC3 lineage of innate lymphoid cells in mice, expression of the Ahr transcription factor is positively indirectly regulated by Runx3, most likely through RORgT (Ebihara et al. 2015).

Preceded by: [RUNX3:CBFB binds the RORC gene promoter](#)

Literature references

Ebihara, T., Song, C., Ryu, SH., Plougastel-Douglas, B., Yang, L., Levanon, D. et al. (2015). Runx3 specifies lineage commitment of innate lymphoid cells. *Nat. Immunol.*, 16, 1124-33. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

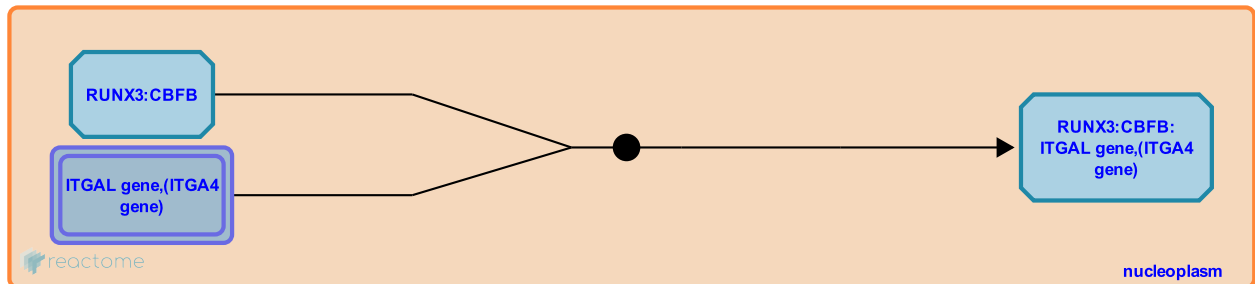
RUNX3:CBFB binds the ITGAL gene,(ITGA4 gene) promoter ↗

Location: [RUNX3 Regulates Immune Response and Cell Migration](#)

Stable identifier: R-HSA-8949335

Type: binding

Compartments: nucleoplasm



RUNX3, presumably in complex with CBFB, binds the RUNX response element in the promoter of the ITGAL (CD11a) gene, encoding leukocyte integrin involved in transendothelial migration of leukocytes during immune and inflammatory responses as well as co-stimulation of T cells (Puig-Kroger et al. 2003, Dominguez-Soto et al. 2005). RUNX3, as well as RUNX1, may also be involved in regulation of integrin alpha 4 (ITGA4, also known as CD49d) expression. A RUNX binding site exists in the ITGA4 promoter, but the direct binding of RUNX transcription factors has not been demonstrated (Dominguez-Soto et al. 2005).

Followed by: [ITGAL gene,\(ITGA4 gene\) expression is stimulated by RUNX3:CBFB](#)

Literature references

Puig-Kröger, A., Sanchez-Elsner, T., Ruiz, N., Andreu, EJ., Prosper, F., Jensen, UB. et al. (2003). RUNX/AML and C/EBP factors regulate CD11a integrin expression in myeloid cells through overlapping regulatory elements. *Blood*, 102, 3252-61. ↗

Domínguez-Soto, A., Relloso, M., Vega, MA., Corbí, AL., Puig-Kröger, A. (2005). RUNX3 regulates the activity of the CD11a and CD49d integrin gene promoters. *Immunobiology*, 210, 133-9. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

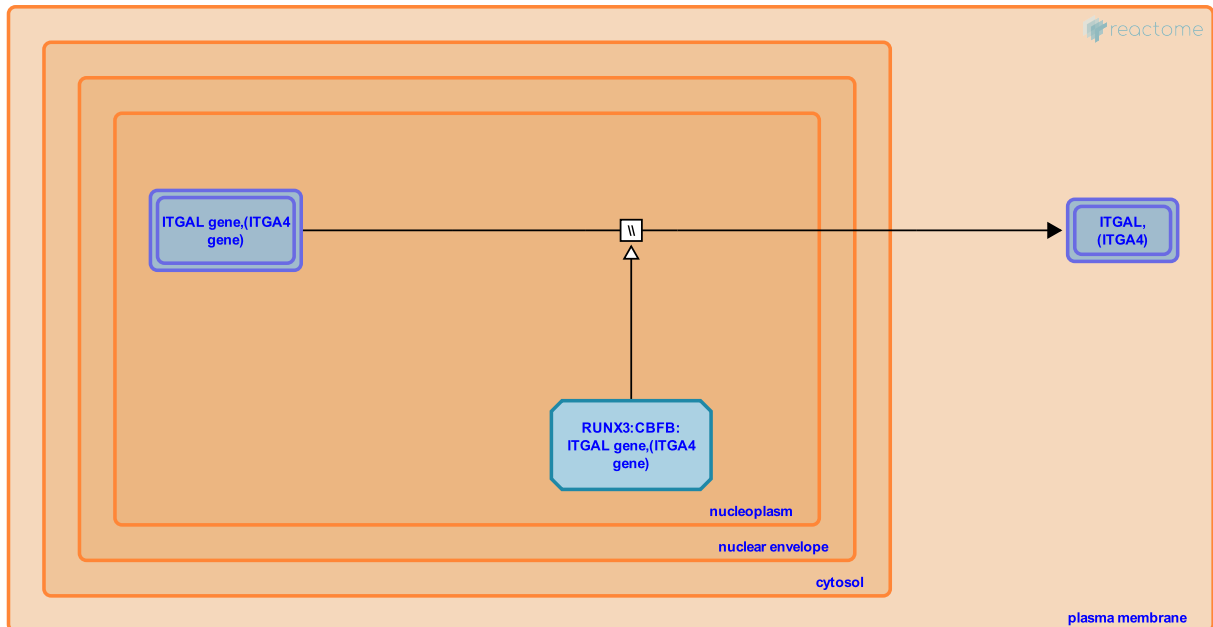
ITGAL gene,(ITGA4 gene) expression is stimulated by RUNX3:CBFB ↗

Location: [RUNX3 Regulates Immune Response and Cell Migration](#)

Stable identifier: R-HSA-8949343

Type: omitted

Compartments: nucleoplasm, plasma membrane



Transcription of the ITGAL (CD11a) gene, is stimulated by binding of RUNX3, presumably in complex with CBFB, to the ITGAL promoter. ITGAL is a leukocyte integrin involved in transendothelial migration of leukocytes during immune and inflammatory responses as well as co-stimulation of T cells. RUNX3, as well as RUNX1, positively regulate integrin alpha 4 (ITGA4, also known as CD49d) expression. A RUNX binding site exists in the ITGA4 promoter, but the direct regulation by RUNX transcription factors has not been demonstrated (Domínguez-Soto et al. 2005).

Preceded by: [RUNX3:CBFB binds the ITGAL gene,\(ITGA4 gene\) promoter](#)

Literature references

Puig-Kröger, A., Sanchez-Elsner, T., Ruiz, N., Andreu, EJ., Prosper, F., Jensen, UB. et al. (2003). RUNX/AML and C/EBP factors regulate CD11a integrin expression in myeloid cells through overlapping regulatory elements. *Blood*, 102, 3252-61. ↗

Domínguez-Soto, A., Relloso, M., Vega, MA., Corbí, AL., Puig-Kröger, A. (2005). RUNX3 regulates the activity of the CD11a and CD49d integrin gene promoters. *Immunobiology*, 210, 133-9. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

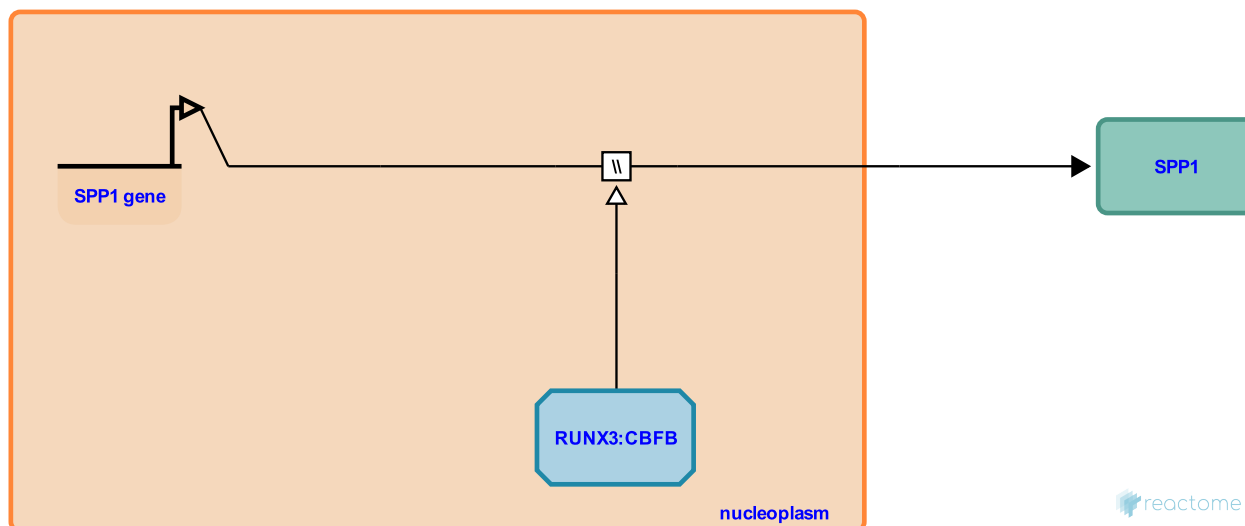
SPP1 gene expression is stimulated by RUNX3 ↗

Location: [RUNX3 Regulates Immune Response and Cell Migration](#)

Stable identifier: R-HSA-8952442

Type: omitted

Compartments: nucleoplasm, extracellular region



Both human and mouse SPP1 (osteopontin) gene promoters contain Runx and SMAD response elements. Transcription of SPP1 increases in response to increased RUNX3 levels, which contributes to invasiveness of pancreatic cancer cells. Direct binding of RUNX3 to the SPP1 promoter has not been examined (Whittle et al. 2015).

Literature references

Whittle, MC., Izeradjene, K., Rani, PG., Feng, L., Carlson, MA., DelGiorno, KE. et al. (2015). RUNX3 Controls a Metastatic Switch in Pancreatic Ductal Adenocarcinoma. *Cell*, 161, 1345-60. ↗

Editions

2016-12-13	Authored	Orlic-Milacic, M.
2017-01-31	Reviewed	Ito, Y., Chuang, LS.
2017-01-31	Edited	Orlic-Milacic, M.

Table of Contents

Introduction	1
❏ RUNX3 Regulates Immune Response and Cell Migration	2
➤ RUNX3:CBFB binds the RORC gene promoter	4
➤ RORC gene expression is stimulated by RUNX3:CBFB	5
➤ RUNX3:CBFB binds the ITGAL gene,(ITGA4 gene) promoter	6
➤ ITGAL gene,(ITGA4 gene) expression is stimulated by RUNX3:CBFB	7
➤ SPP1 gene expression is stimulated by RUNX3	8
Table of Contents	9