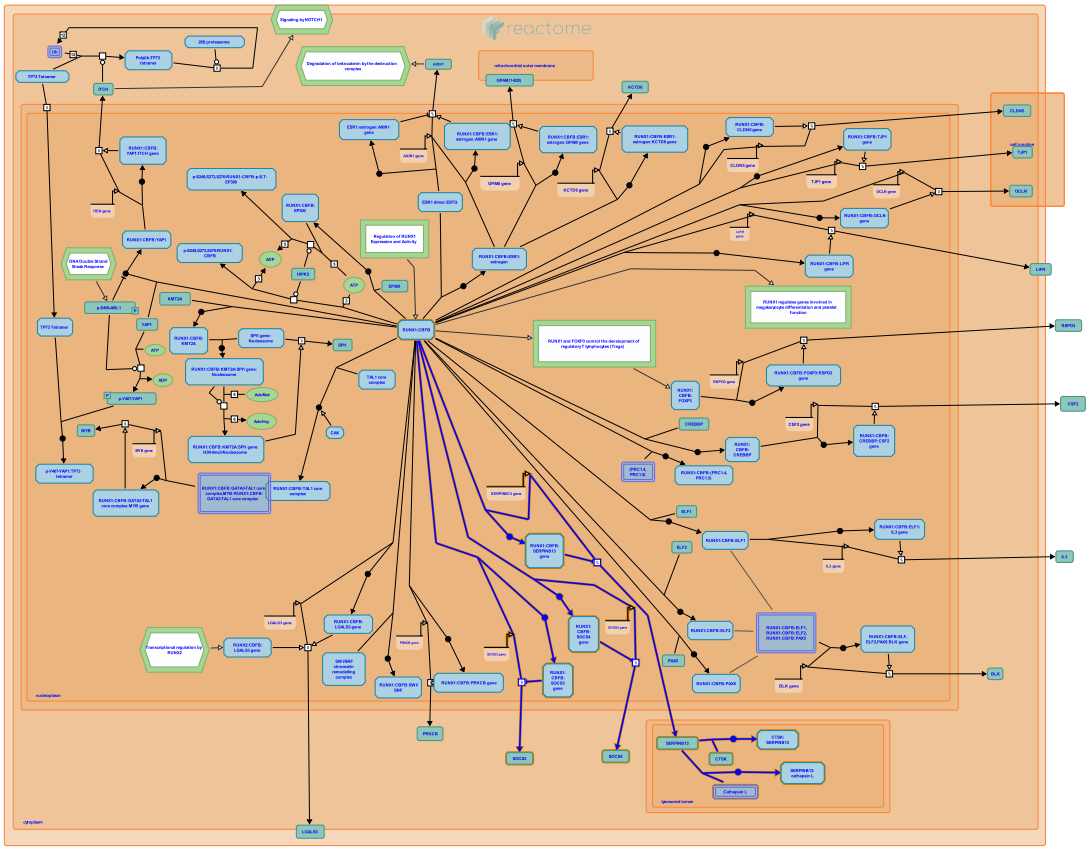
RUNX1 regulates transcription of genes involved in differentiation of keratinocytes



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.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

17/05/2024

Introduction

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

Literature references

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

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

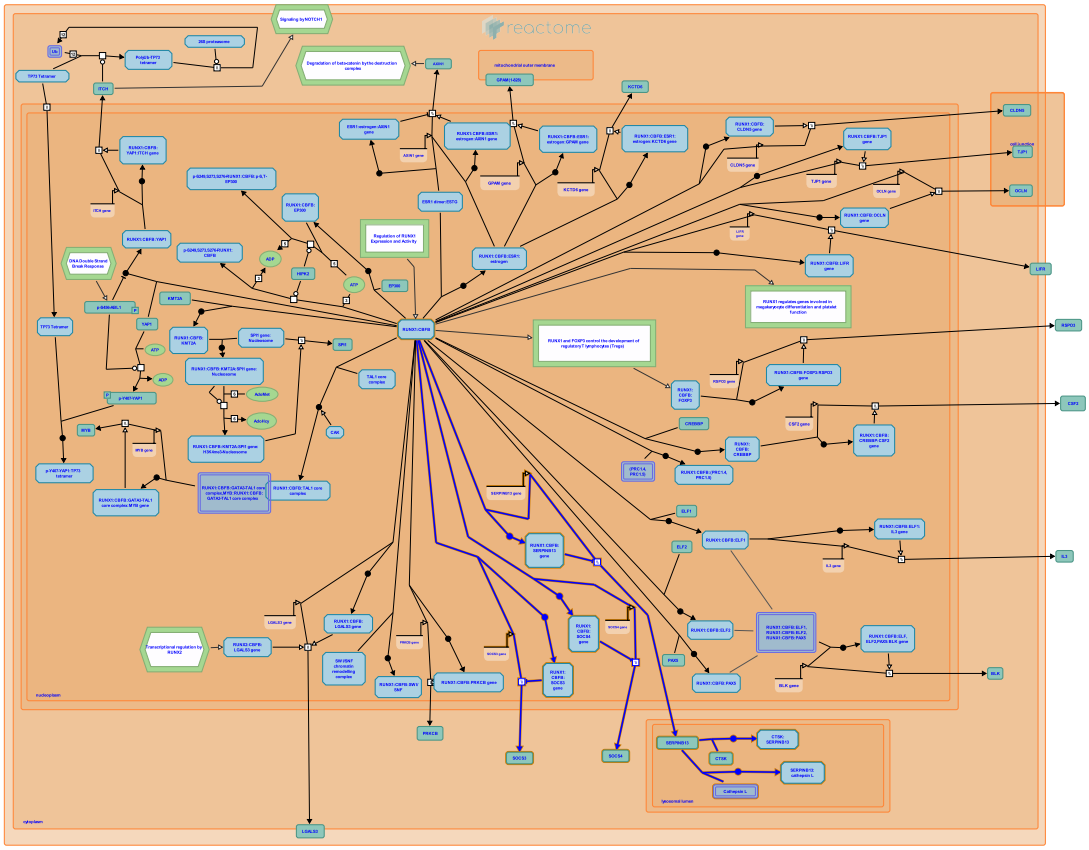
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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

RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

↗

Stable identifier: R-HSA-8939242



The RUNX1:CBFB complex directly inhibits transcription of the SERPINB13 gene (Nomura et al. 2005), a gene involved in keratinocyte differentiation that is frequently down-regulated in head and neck cancers (Boyapati et al. 2011). RUNX1 also inhibits transcription of STAT3 inhibitors SOCS3 and SOCS4, resulting in elevated STAT3 activity. RUNX1-mediated increase in STAT3 activity, first discovered in keratinocytes, is thought to be involved in the maintenance of epithelial stem cells and contributes to development of epithelial cancers, including squamous cell carcinoma (SCC) of the skin (Scheitz et al. 2012).

Literature references

Nomura, T., Katunuma, N. (2005). Involvement of cathepsins in the invasion, metastasis and proliferation of cancer cells. *J. Med. Invest., 52*, 1-9. ↗

Boyapati, A., Ren, B., Zhang, DE. (2011). SERPINB13 is a novel RUNX1 target gene. *Biochem. Biophys. Res. Commun., 411*, 115-20. ↗

Lee, TS., Tumbar, T., McDermitt, DJ., Scheitz, CJ. (2012). Defining a tissue stem cell-driven Runx1/Stat3 signalling axis in epithelial cancer. *EMBO J., 31*, 4124-39. ↗

Editions

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

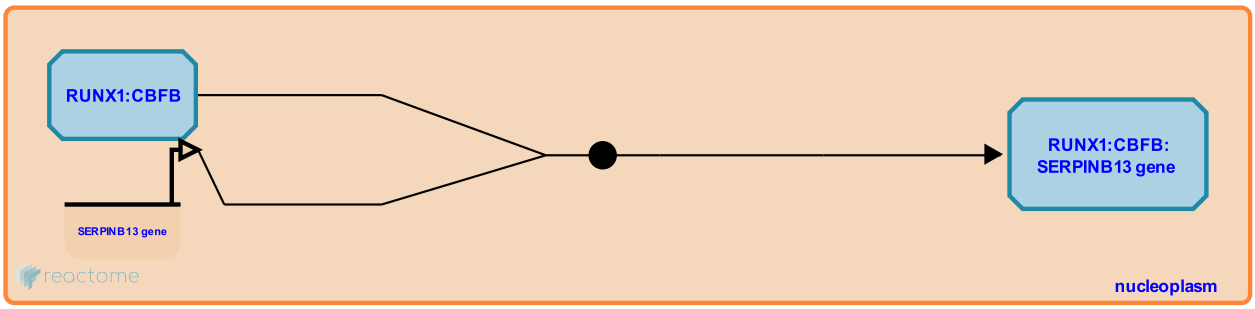
RUNX1:CBFB binds the SERPINB13 gene promoter ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8938053

Type: binding

Compartments: nucleoplasm



The RUNX1:CBFB complex binds the RUNX1 element in the promoter of the SERPINB13 gene (Boyapati et al. 2011).

Followed by: SERPINB13 gene expression is inhibited by RUNX1:CBFB

Literature references

Boyapati, A., Ren, B., Zhang, DE. (2011). SERPINB13 is a novel RUNX1 target gene. *Biochem. Biophys. Res. Commun.*, *411*, 115-20. ↗

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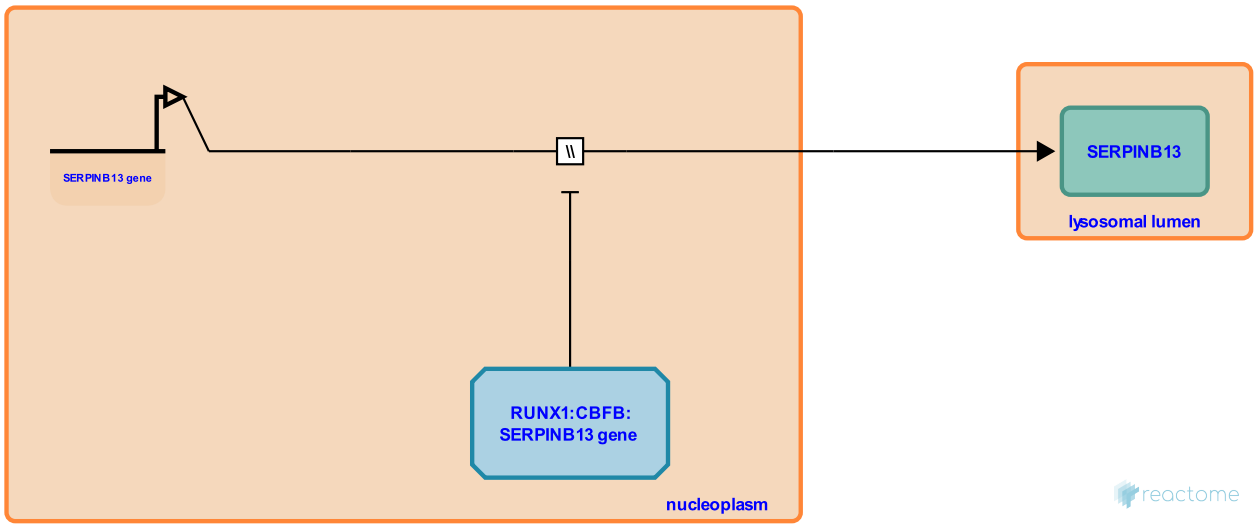
SERPINB13 gene expression is inhibited by RUNX1:CBFB ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8938063

Type: omitted

Compartments: nucleoplasm, lysosomal lumen



Binding of the RUNX1:CBFB complex to the promoter of the SERPINB13 gene inhibits SERPINB13 transcription and results in higher cathepsin K activity in cells, as SERPINB13 is an inhibitor of cathepsin K and L. Cathepsin K and L are associated with proliferation and invasiveness of cancer cells (Nomura and Katunuma 2005). SERPINB13 is frequently downregulated in head and neck cancers (Boyapati et al. 2011).

Preceded by: RUNX1:CBFB binds the SERPINB13 gene promoter

Followed by: SERPINB13 binds cathepsin L, SERPINB13 binds CTSK

Literature references

Boyapati, A., Ren, B., Zhang, DE. (2011). SERPINB13 is a novel RUNX1 target gene. *Biochem. Biophys. Res. Commun., 411*, 115-20. ↗

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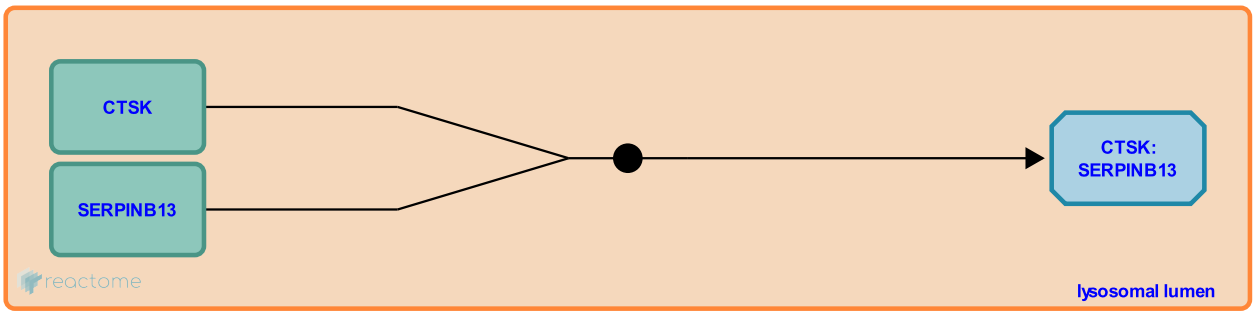
SERPINB13 binds CTSK ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8938121

Type: binding

Compartments: lysosomal lumen



SERPINB13 binds the lysosomal cystein proteinase cathepsin K (CTSK) and ihbits its catalytic activity (Jayakumar et al. 2003).

Preceded by: SERPINB13 gene expression is inhibited by RUNX1:CBFB

Literature references

Brömme, D., Silverman, GA., Jayakumar, A., Clayman, GL., Kang, Y., Pak, SC. et al. (2003). Inhibition of the cysteine proteinases cathepsins K and L by the serpin headpin (SERPINB13): a kinetic analysis. *Arch. Biochem. Biophys., 409*, 367-74. ↗

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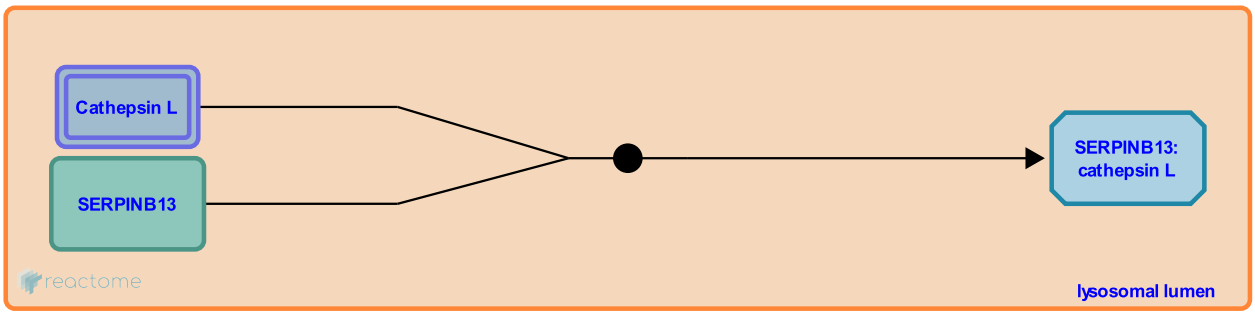
SERPINB13 binds cathepsin L ↗

Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8938108

Type: binding

Compartments: lysosomal lumen



SERPINB13 binds the lysosomal cystein protease cathepsin L and inhibits its catalytic activity (Jayakumar et al. 2003, Welss et al. 2003). It is uncertain whether SERPINB13 functions in the lysosomes or exclusively in the cytosol, where it would inhibit the enzymatic activity of ectopic cathepsin L (Welss et al. 2003).

Preceded by: SERPINB13 gene expression is inhibited by RUNX1:CBFB

Literature references

Ruzicka, T., von Mikecz, A., Abts, HF., Irving, JA., Smith, AI., Blum, R. et al. (2003). Hurpin is a selective inhibitor of lysosomal cathepsin L and protects keratinocytes from ultraviolet-induced apoptosis. *Biochemistry, 42*, 7381-9. ↗

Brömme, D., Silverman, GA., Jayakumar, A., Clayman, GL., Kang, Y., Pak, SC. et al. (2003). Inhibition of the cysteine proteinases cathepsins K and L by the serpin headpin (SERPINB13): a kinetic analysis. *Arch. Biochem. Biophys., 409*, 367-74. ↗

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RUNX1 binds the SOCS3 gene ↗

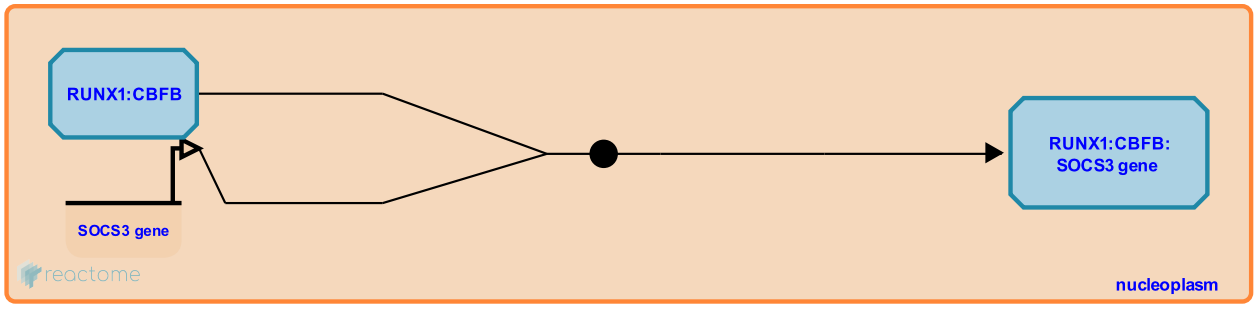
Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8955748

Type: binding

Compartments: nucleoplasm

Inferred from: Runx1 binds the Socs3 gene (Mus musculus)



Based on studies in mouse keratinocytes, RUNX1, presumably in complex with CBFB, binds the SOCS3 gene (Scheitz et al. 2012). By sequence similarity, at least one Runx binding element is conserved between human and mouse SOCS3 gene loci.

Followed by: SOCS3 gene expression is inhibited by RUNX1

Literature references

Lee, TS., Tumbar, T., McDermitt, DJ., Scheitz, CJ. (2012). Defining a tissue stem cell-driven Runx1/Stat3 signalling axis in epithelial cancer. *EMBO J., 31*, 4124-39. ↗

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RUNX1 binds the SOCS4 gene ↗

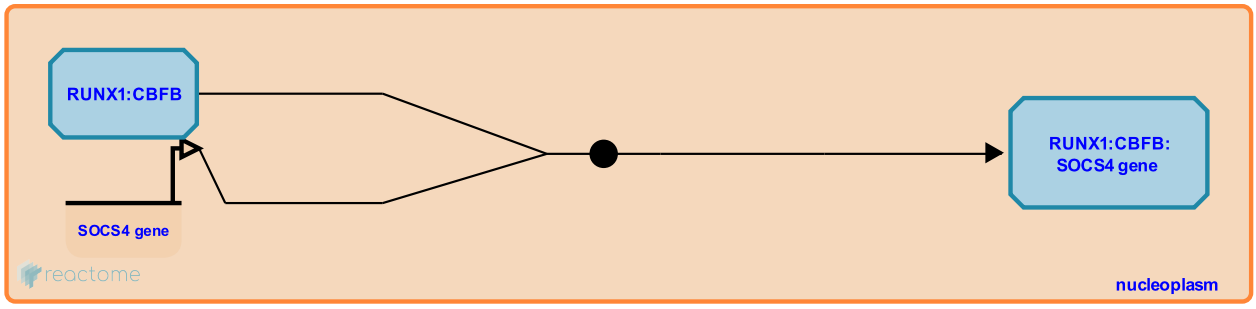
Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8955822

Type: binding

Compartments: nucleoplasm

Inferred from: Runx1 binds the Socs4 gene (Mus musculus)



Based on studies in mouse keratinocytes, RUNX1, presumably in complex with CBFB, binds the SOCS4 gene (Scheitz et al. 2012). Runx binding elements are found in the promoter region and enhancer elements downstream of the mouse Socs4 gen. In the human SOCS4 gene, Runx binding elements can be found in the first intron and downstream of the SOCS4 gene.

Followed by: SOCS4 gene expression is inhibited by RUNX1

Literature references

Lee, TS., Tumbar, T., McDermitt, DJ., Scheitz, CJ. (2012). Defining a tissue stem cell-driven Runx1/Stat3 signalling axis in epithelial cancer. *EMBO J., 31*, 4124-39. ↗

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SOCS3 gene expression is inhibited by RUNX1 ↗

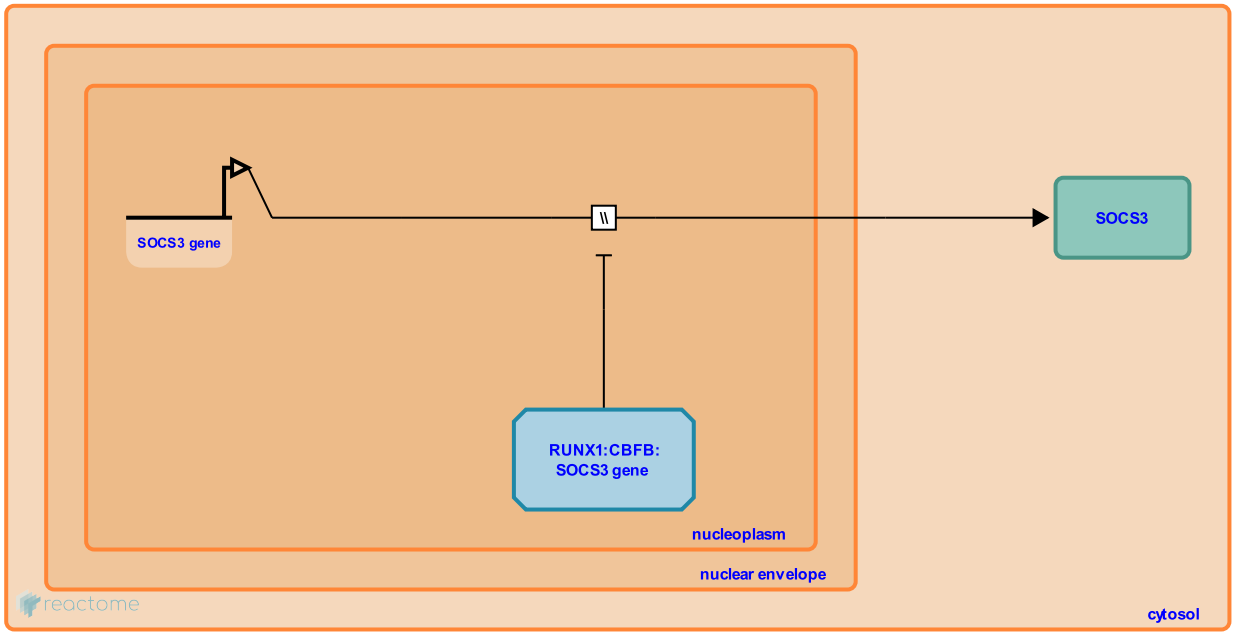
Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8955885

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Socs3 gene expression is inhibited by Runx1 (Mus musculus)



RUNX1, presumably in complex with CBFB, inhibits transcription of the SOCS3 gene. As SOCS3 is an inhibitor of STAT3, RUNX1-mediated repression of SOCS3 increases STAT3 activity, which is implicated in development of epithelial cancers (Scheitz et al. 2012).

Preceded by: RUNX1 binds the SOCS3 gene

Literature references

Lee, TS., Tumbar, T., McDermitt, DJ., Scheitz, CJ. (2012). Defining a tissue stem cell-driven Runx1/Stat3 signalling axis in epithelial cancer. *EMBO J., 31*, 4124-39. ↗

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2016-09-14	Authored	Orlic-Milacic, M.
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2017-05-09	Edited	Orlic-Milacic, M.

SOCS4 gene expression is inhibited by RUNX1 ↗

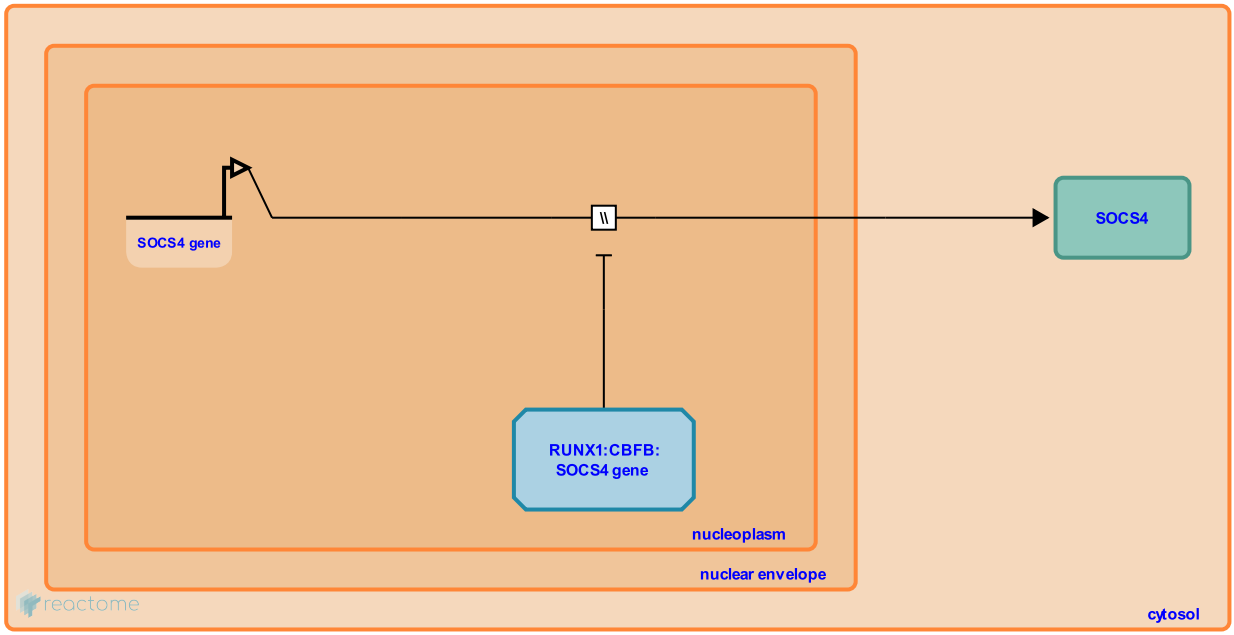
Location: RUNX1 regulates transcription of genes involved in differentiation of keratinocytes

Stable identifier: R-HSA-8955893

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Socs4 gene expression is inhibited by Runx1 (Mus musculus)



RUNX1, presumably in complex with CBFB, inhibits transcription of the SOCS4 gene. As SOCS4 is an inhibitor of STAT3, RUNX1-mediated repression of SOCS4 increases STAT3 activity, which is implicated in development of epithelial cancers (Scheitz et al. 2012).

Preceded by: RUNX1 binds the SOCS4 gene

Literature references

Lee, TS., Tumbar, T., McDermitt, DJ., Scheitz, CJ. (2012). Defining a tissue stem cell-driven Runx1/Stat3 signalling axis in epithelial cancer. *EMBO J., 31*, 4124-39. ↗

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Table of Contents