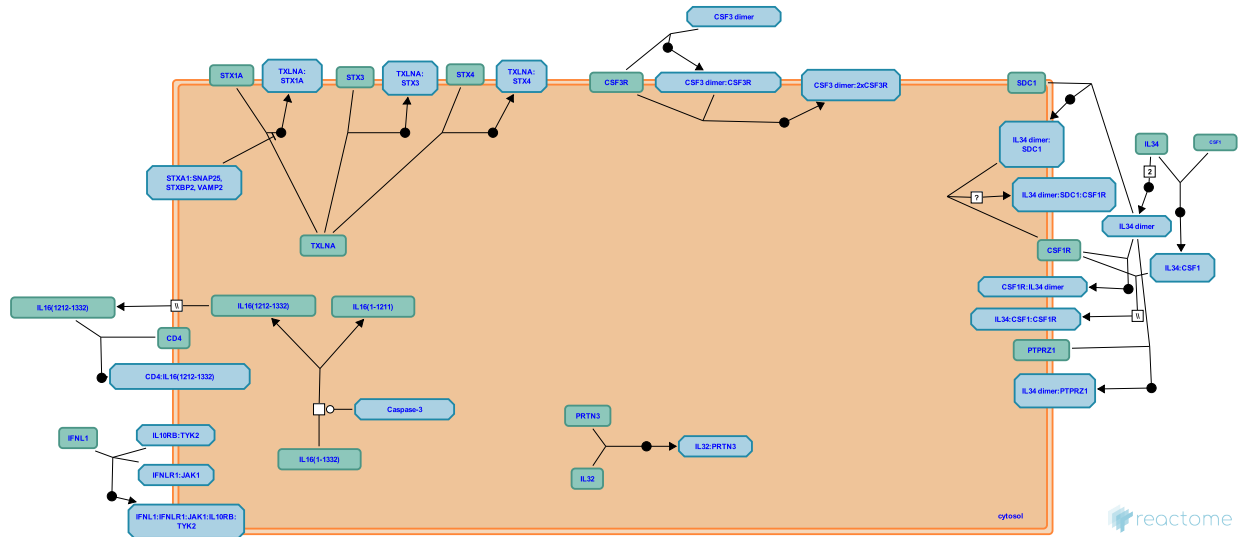


# Other interleukin signaling



Jupe, S., Meldal, BH., Varusai, TM.

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

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## 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

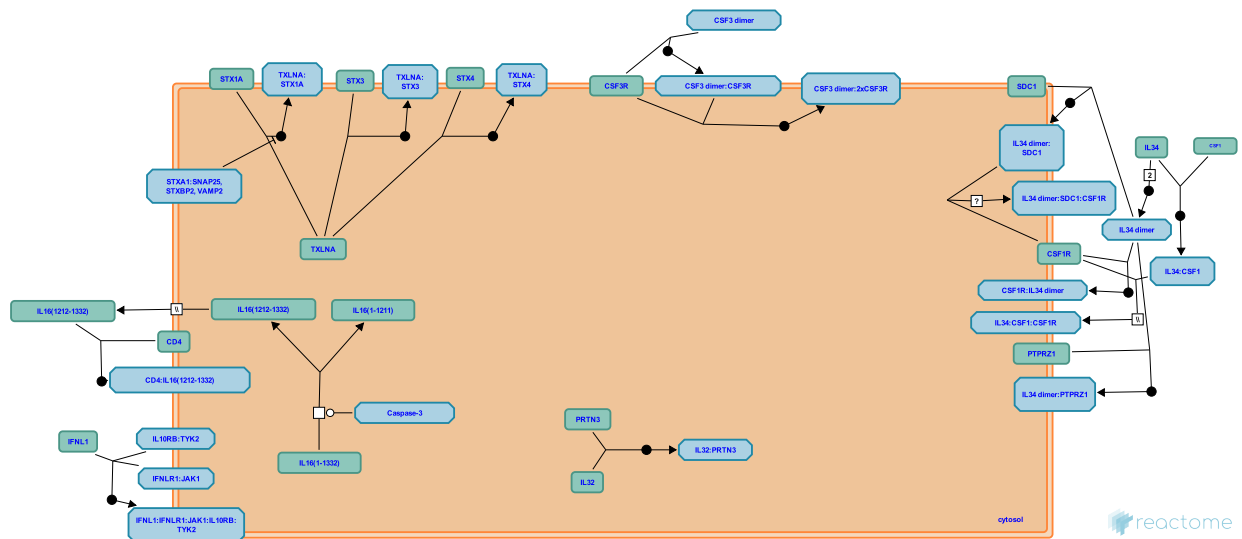
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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
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Reactome database release: 70

This document contains 1 pathway and 17 reactions ([see Table of Contents](#))

## Other interleukin signaling ↗

Stable identifier: R-HSA-449836



Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

## Literature references

Akdis, M., Burgler, S., Cramer, R., Eiwegger, T., Fujita, H., Gomez, E. et al. (2011). Interleukins, from 1 to 37, and interferon- $\gamma$ : receptors, functions, and roles in diseases. *J. Allergy Clin. Immunol.*, 127, 701-21.e1-70. ↗

## Editions

2014-06-04	Authored	Jupe, S.
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2016-01-28	Reviewed	Meldal, BH.

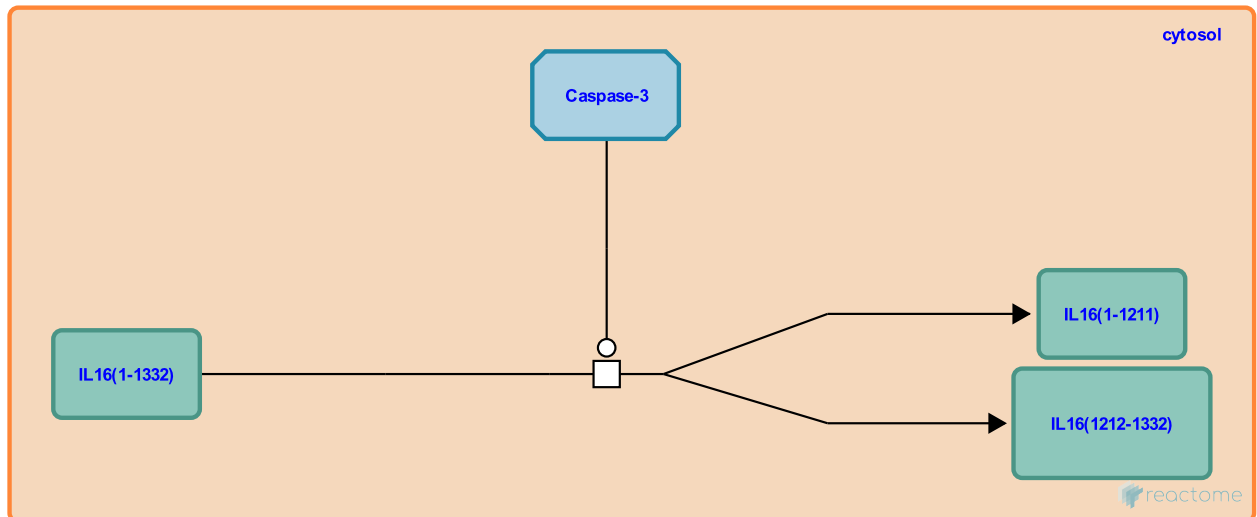
## Caspase-3 cleaves pro-interleukin-16 [↗](#)

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-449073

**Type:** transition

**Compartments:** cytosol



The mature and biologically active secreted interleukin-16 (IL16) is a 13-kDa carboxy terminal peptide derived from a larger intracellular precursor protein. Cleavage of IL16 from the propeptide is mediated by caspase-3. IL16 is a chemoattractant for a variety of cell types that express the cell surface antigen CD4.

**Followed by:** [Interleukin-16 is secreted](#)

### Literature references

Zhang, Y., Center, DM., Wu, DM., Cruikshank, WW., Yuan, J., Andrews, DW. et al. (1998). Processing and activation of pro-interleukin-16 by caspase-3. *J Biol Chem*, 273, 1144-9. [↗](#)

### Editions

2014-06-04	Authored	Jupe, S.
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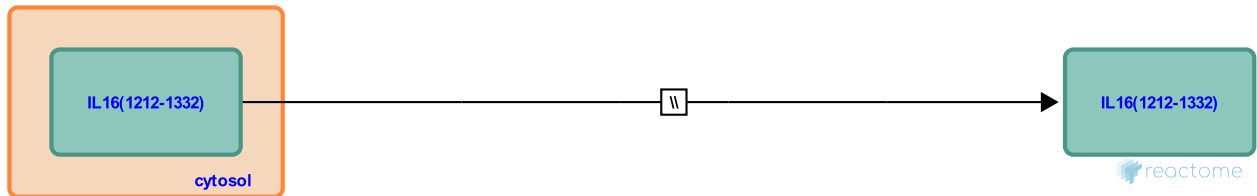
## Interleukin-16 is secreted [↗](#)

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-449077

**Type:** omitted

**Compartments:** extracellular region, cytosol



Interleukin-16 (IL16) does not contain a consensus secretory leader sequence, and the mechanism for its release has not been elucidated. Amino-terminal deletions of IL16 reduce its capacity for secretion (Zhou et al. 1999), but the significance of this is unclear.

**Preceded by:** [Caspase-3 cleaves pro-interleukin-16](#)

### Literature references

Zhou, P., Devadas, K., Tewari, D., Jegorow, A., Notkins, AL. (1999). Processing, secretion, and anti-HIV-1 activity of IL-16 with or without a signal peptide in CD4+ T cells. *J Immunol*, 163, 906-12. [↗](#)

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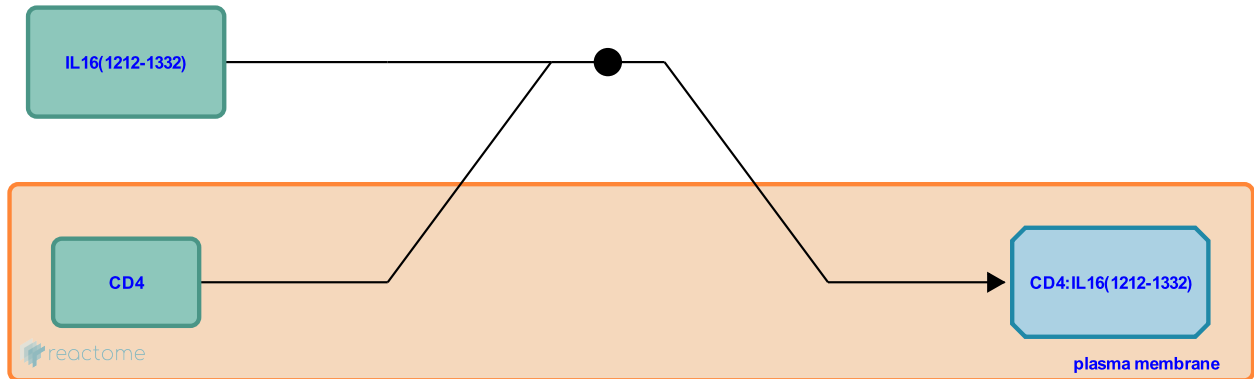
## CD4 binds Interleukin-16 ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-449087

**Type:** binding

**Compartments:** extracellular region, plasma membrane



CD4 is a receptor for Interleukin-16 (IL16), explaining how IL16 acts as a chemoattractant for a variety of CD4+ immune cells (Cruikshank et al. 2000, Cruikshank & Little 2008).

Signaling mediated by CD4 requires the amino acid sequence W345 to S350, located in the proximal end of the D4 domain. CD4 does not appear to require a co-receptor for IL16. Data from CD4 knockout mice suggests that there may be an additional IL16 receptor (Mathy et al. 2000).

### Literature references

Ryan, TC., Cruikshank, WW., Kornfeld, H., Collins, TL., Center, DM. (1995). The CD4-associated tyrosine kinase p56lck is required for lymphocyte chemoattractant factor-induced T lymphocyte migration. *J Biol Chem*, 270, 17081-6. ↗

Liu, Y., Cruikshank, WW., O'Loughlin, T., O'Reilly, P., Center, DM., Kornfeld, H. (1999). Identification of a CD4 domain required for interleukin-16 binding and lymphocyte activation. *J Biol Chem*, 274, 23387-95. ↗

### Editions

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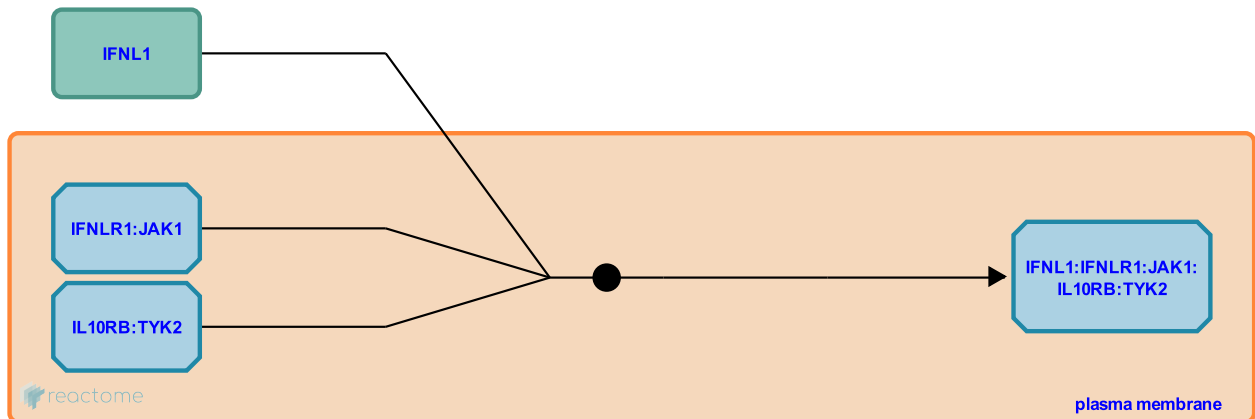
## IFNL1 binds IL10RB:TYK2 and IFNLR1:JAK1 ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-448661

**Type:** binding

**Compartments:** plasma membrane, extracellular region, cytosol



Interferon lambda-1 (IFNL1) binds Interleukin-10 receptor subunit beta (IL10RB), which is associated with Non-receptor tyrosine-protein kinase TYK2 (TYK2), and Interferon lambda receptor-1 (IFNLR1), which is associated with Tyrosine-protein kinase JAK1 (JAK1). Interferon lambda-2 (IFNL2, IL28A), Interleukin-28B (IL28B, Interferon lambda-3) and Interferon lambda-1 (IFNL1, Interleukin-29) are related cytokines, collectively known as the type III interferons. They are distantly related to the type I interferons (IFNs) and are members of the class II cytokine family, which includes type I, II, and III interferons and the Interleukin-10 family (IL10, Interleukin-19 (IL19), Interleukin-20 (IL20), Interleukin-22 (IL22), Interleukin-24 (IL24), and Interleukin-26 (IL26)). They are encoded by genes that form a cluster on 19q13. Expression of all three IFNLs can be induced by viral infection. They share a heterodimeric class II cytokine receptor that consists of IFNLR1 and interleukin-10 receptor beta (IL10RB) (Kotenko et al. 2003, Sheppard et al. 2003). IL10RB is also part of the receptor complexes for IL10, IL22, IL24 and IL26. IFNL1, IFNL2 and IFNL3, like type I IFNs, can signal through ISRE regulatory sites and are likely to provide antiviral activity by the induction of at least a subset of IFN-stimulated genes (Dumoutier et al. 2004, Gad et al 2004, Sheppard et al. 2003).

### Literature references

- Sheppard, P., Kindsvogel, W., Xu, W., Henderson, K., Schlutsmeyer, S., Whitmore, TE. et al. (2003). IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol*, 4, 63-8. ↗
- Vandenbroeck, K., Alvarez, J., Swaminathan, B., Alloza, I., Matesanz, F., Urcelay, E. et al. (2012). A cytokine gene screen uncovers SOCS1 as genetic risk factor for multiple sclerosis. *Genes Immun.*, 13, 21-8. ↗
- Prokunina-Olsson, L., Muchmore, B., Tang, W., Pfeiffer, RM., Park, H., Dickensheets, H. et al. (2013). A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. *Nat. Genet.*, 45, 164-71. ↗

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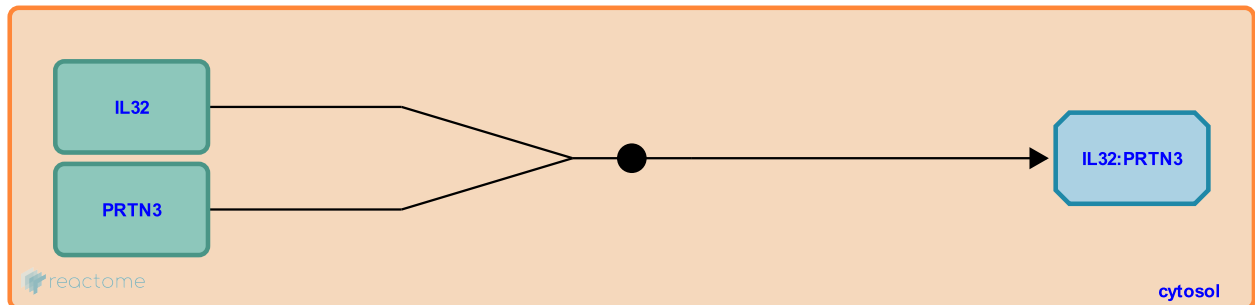
## Interleukin-32 binds proteinase-3 [↗](#)

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-448591

**Type:** binding

**Compartments:** cytosol



IL-32 has properties of a typical pro-inflammatory mediator, stimulating TNF-alpha, IL-1beta and IL-8 production, and activating the NF-kappaB and p38 mitogen-activated protein (MAP) kinase pathways. It is produced mainly by T, natural killer, epithelial and monocyte cells after stimulation by Interleukin-2, Interleukin-18 or IFN-gamma (Kim et al. 2005). IL-32 can bind proteinase 3, a neutrophil-derived serine protease, but its (assumed) receptor is unknown.

### Literature references

Novick, D., Rubinstein, M., Azam, T., Rabinkov, A., Dinarello, CA., Kim, SH. (2006). Proteinase 3 is an IL-32 binding protein. *Proc Natl Acad Sci U S A*, 103, 3316-21. [↗](#)

### Editions

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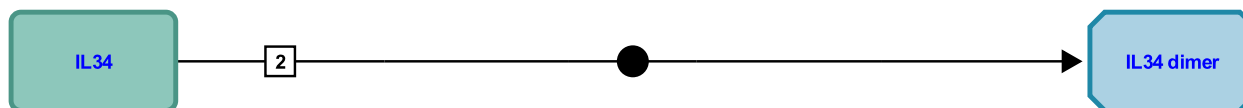
## IL34 dimerizes ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-448632

**Type:** binding

**Compartments:** extracellular region



reactome

interleukin-34 (IL34) was identified as a potent activator of monocytes and macrophages, signaling through Colony-stimulating factor-1 (CSF1) receptor (CSF1R) with a distinct tissue distribution from CSF1 (Lin et al. 2008). IL34 and CSF1 share many functional properties. IL34 has no appreciable sequence similarity with any other protein but shares a four-helix bundle structure seen in CSF1 (Garceau et al. 2010, Liu et al. 2012). IL34 forms a noncovalently linked dimer (Ma et al. 2012) whereas CSF1 contains an inter-subunit disulfide bond. The structure of the IL34:CSF1R complex shows a similar ligand-receptor assembly to that of CSF1:CSF1R.

**Followed by:** [IL34 dimer binds SDC1](#)

## Literature references

Lin, H., Lee, E., Hestir, K., Leo, C., Huang, M., Bosch, E. et al. (2008). Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. *Science*, 320, 807-11. ↗

## Editions

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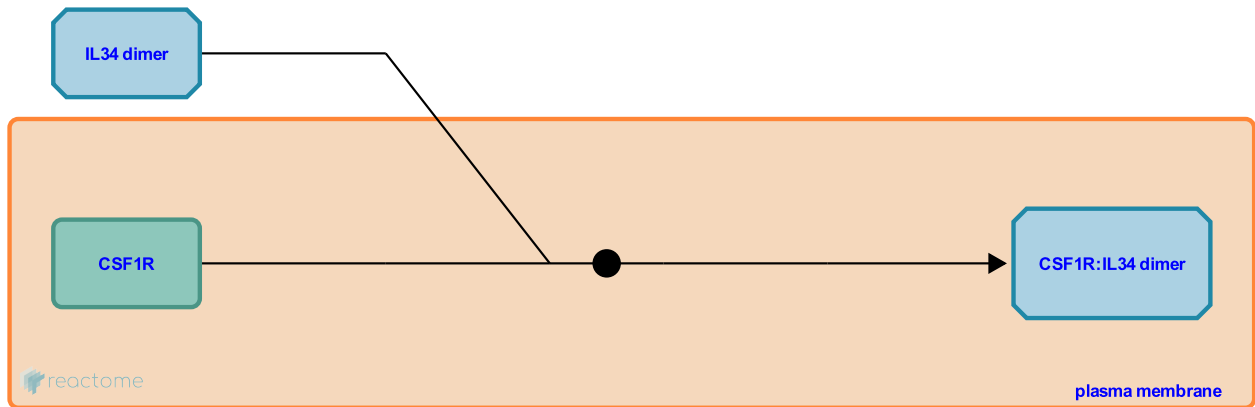
## IL34 dimer binds CSF1R ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-6787820

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The receptor for Interleukin-34 (IL34) is colony stimulating factor 1 receptor (CSF1R), also called macrophage colony stimulating factor receptor (M-CSF-R). Dimeric IL34 and CSF1 bind the same general region of CSF1R, interacting with overlapping but distinct epitopes. Ligand binding leads to receptor dimerisation (Ma et al. 2012, Liu et al. 2012). Like CSF1, IL34 stimulation of CSF1R leads to phosphorylation of extracellular signal-regulated kinase (ERK) 1 and 2 in human monocytes (Lin et al. 2008).

CSF1R activates several signaling pathways including JAK-STAT3, 5A/B, phosphorylation of PIK3R1, PLCG2, GRB2, SLA2 and CBL. PLCG2 phosphorylation leads to increased production of the cellular signaling molecules diacylglycerol (DAG) and inositol 1,4,5 trisphosphate (IP3), which activate protein kinase C family members, especially PRKCD. Phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3 kinase, leads to activation of the AKT1 signaling pathway. Activated CSF1R also mediates activation of MAPK1 (ERK2) or MAPK3 (ERK1) and the SRC family kinases SRC, FYN and YES1. Activated CSF1R binds GRB2 and promotes tyrosine phosphorylation of SHC1 and INPP5D (SHIP1). Signaling is down regulated by protein phosphatases such as INPP5D that can dephosphorylate the receptor and its downstream effectors.

### Literature references

Lin, H., Lee, E., Hestir, K., Leo, C., Huang, M., Bosch, E. et al. (2008). Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. *Science*, 320, 807-11. ↗

### Editions

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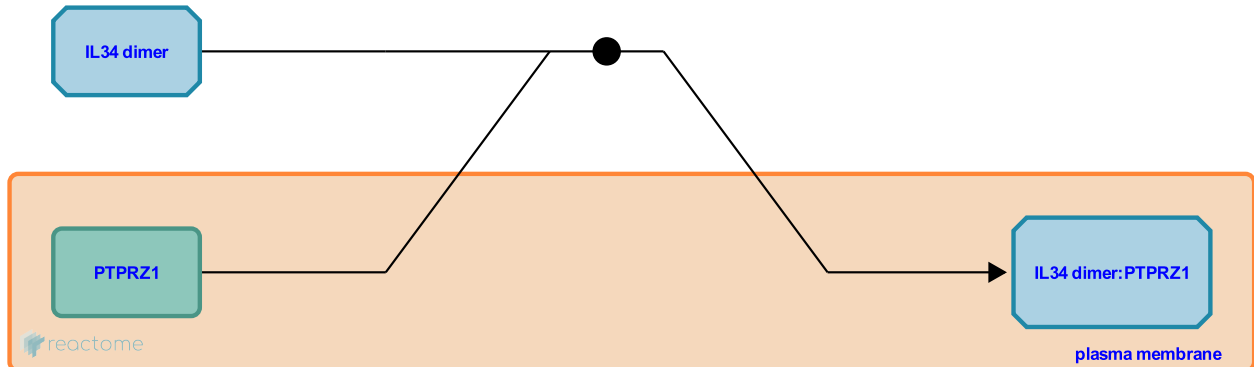
## IL34 dimer binds PTPRZ1 ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-8981657

**Type:** binding

**Compartments:** extracellular region, plasma membrane



Interleukin-34 (IL34) signals via the Colony-stimulating factor-1 receptor (CSF1R). It can also bind Receptor-type protein-tyrosine phosphatase zeta (PTPRZ1), a cell surface chondroitin sulfate (CS) proteoglycan. PTPRZ1 is primarily expressed on neural progenitor and glial cells. IL34 selectively bound PTPRZ1 in CSF1R-deficient U251 human glioblastoma cell lysates, inhibiting proliferation, clonogenicity and motility, and promoting an increase in tyrosine phosphorylation of focal adhesion kinase 1 (PTK2) and paxillin (PXN) (Nandii et al. 2013).

### Literature references

Nandi, S., Cioce, M., Yeung, YG., Nieves, E., Tesfa, L., Lin, H. et al. (2013). Receptor-type protein-tyrosine phosphatase  $\zeta$  is a functional receptor for interleukin-34. *J. Biol. Chem.*, 288, 21972-86. ↗

### Editions

2017-03-13	Authored	Jupe, S.
2017-11-03	Edited	Jupe, S.
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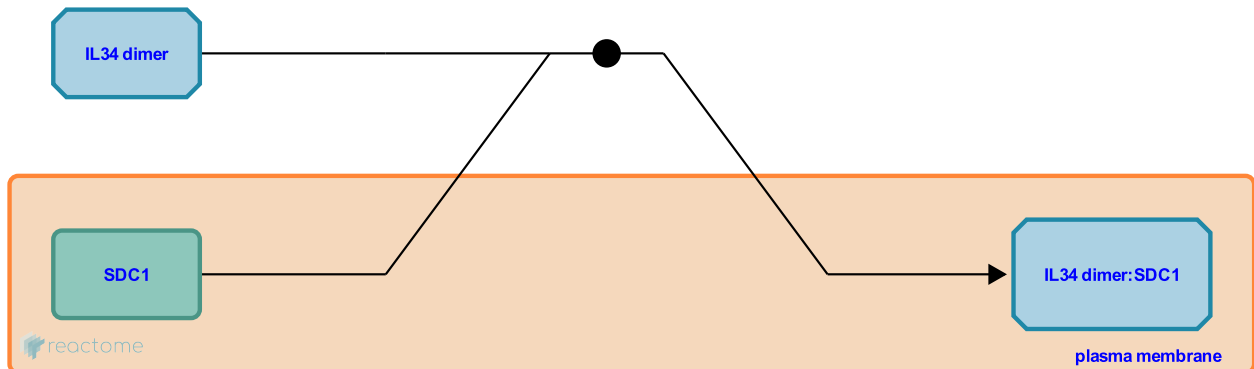
## IL34 dimer binds SDC1 [↗](#)

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-9009558

**Type:** binding

**Compartments:** extracellular region, plasma membrane



Interleukin-34 (IL34) is involved in the survival, proliferation and differentiation of monocytes and macrophages. Syndecan-1 (SDC1) is a cell surface proteoglycan that contains the chondroitin sulphate and primarily functions to link the cytoskeleton to the interstitial matrix. IL34 dimers can bind to the chondroitin sulphate of SDC1. Subsequently, SDC1 modulates IL34-induced CSF1R signaling pathways (Ségaliny et al. 2015). Ultimately, these events lead to the release of pro-inflammatory chemokines regulating the innate immunity and inflammation.

**Preceded by:** [IL34 dimerizes](#)

**Followed by:** [IL34 dimer:SDC1 binds CSF1R](#)

### Literature references

Ségaliny, AI., Brion, R., Mortier, E., Maillason, M., Cherel, M., Jacques, Y. et al. (2015). Syndecan-1 regulates the biological activities of interleukin-34. *Biochim. Biophys. Acta*, 1853, 1010-21. [↗](#)

### Editions

2017-06-20	Authored	Varusai, TM.
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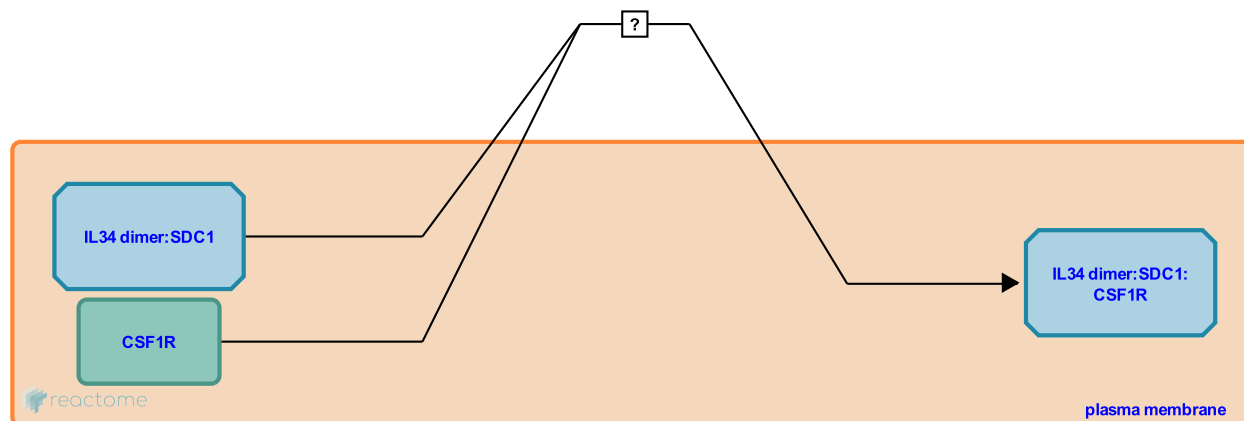
## IL34 dimer:SDC1 binds CSF1R ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-9009554

**Type:** uncertain

**Compartments:** extracellular region, plasma membrane



Interleukin-34 (IL34) can bind Syndecan-1 (SDC1), a cell surface proteoglycan. Low levels of SDC1 may sequester IL34 at the cell surface and prevent it from binding Macrophage colony-stimulating factor 1 receptor (CSF1R), while high SDC1 levels may facilitate IL34-CSF1R signaling (Segaliny et al. 2015). Ultimately, these events lead to the release of pro-inflammatory chemokines regulating the innate immunity and inflammation. The precise interaction between IL34:SDC1 and CSF1R is unknown. Hence, this interaction is represented as an uncertain black box event.

**Preceded by:** [IL34 dimer binds SDC1](#)

### Literature references

Ségaliny, AI., Brion, R., Mortier, E., Maillason, M., Cherel, M., Jacques, Y. et al. (2015). Syndecan-1 regulates the biological activities of interleukin-34. *Biochim. Biophys. Acta*, 1853, 1010-21. ↗

### Editions

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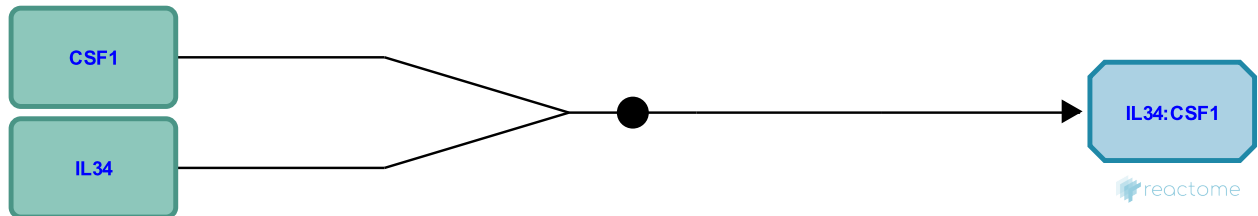
## IL34 binds CSF1 [↗](#)

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-9009488

**Type:** binding

**Compartments:** extracellular region



Interleukin-34 (IL34) can bind Macrophage colony-stimulating factor 1 (CSF1) to form a heteromer, which subsequently binds CSF1R (Segaliny et al. 2015).

**Followed by:** [IL34:CSF1 binds CSF1R](#)

### Literature references

Ségaly, AI., Brion, R., Brulin, B., Maillason, M., Charrier, C., Téletchéa, S. et al. (2015). IL-34 and M-CSF form a novel heteromeric cytokine and regulate the M-CSF receptor activation and localization. *Cytokine*, 76, 170-81. [↗](#)

### Editions

2017-06-19	Authored	Varusai, TM.
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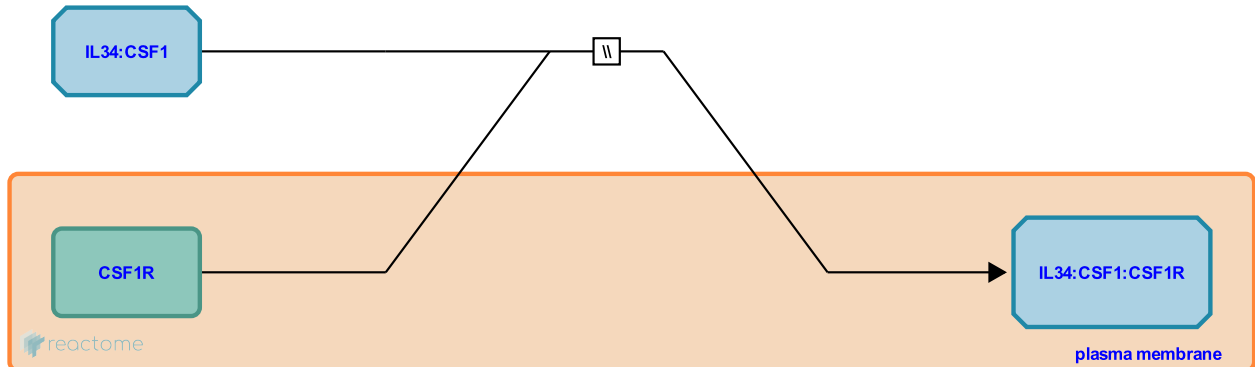
## IL34:CSF1 binds CSF1R ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-9009485

**Type:** omitted

**Compartments:** extracellular region, plasma membrane



Interleukin-34 (IL34) can bind Macrophage colony-stimulating factor 1 (CSF1). The IL34:CSF1 heteromer may bind Macrophage colony-stimulating factor 1 receptor (CSF1R) facilitating receptor maturation and cellular trafficking. Consequently, downstream signaling pathways are activated (Segaliny et al. 2015). Ultimately, these events lead to the release of pro-inflammatory chemokines regulating the innate immunity and inflammation. The exact binding mechanism of IL34:CSF1 to CSF1R is unclear. Hence, this interaction is represented as a black box event.

**Preceded by:** [IL34 binds CSF1](#)

## Literature references

Ségaliny, AI., Brion, R., Brulin, B., Maillason, M., Charrier, C., Téletchéa, S. et al. (2015). IL-34 and M-CSF form a novel heteromeric cytokine and regulate the M-CSF receptor activation and localization. *Cytokine*, 76, 170-81. ↗

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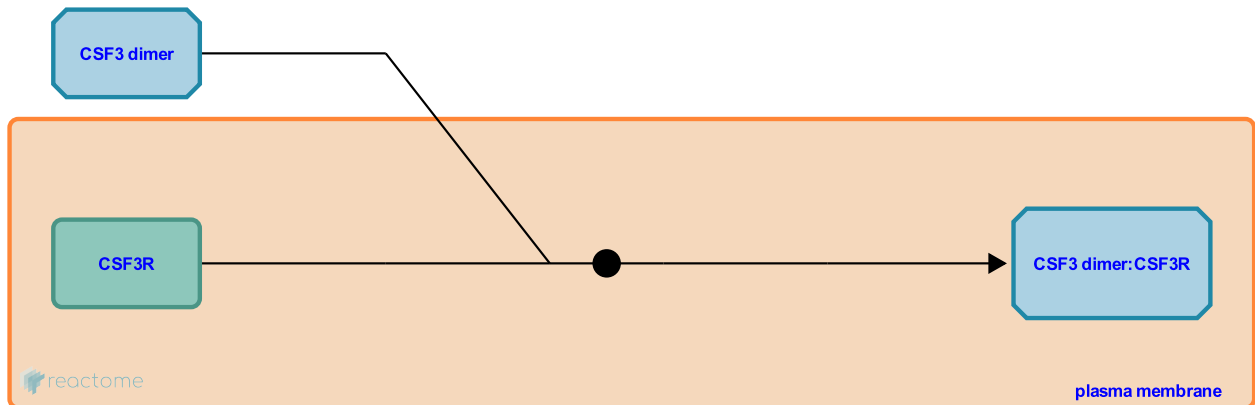
## CSF3R binds CSF3 dimer ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-6787737

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The granulocyte colony-stimulating factor receptor (CSF3R, GCSFR, CD114) is a cell-surface receptor for the granulocyte colony-stimulating factor (CSF3, GCSF) (Larsen et al. 1990, Panopoulos & Watowich 2008). It is present on precursor cells in the bone marrow. CSF3 initiates cell proliferation and differentiation into mature neutrophilic granulocytes and macrophages.

CSF3 exists as a dimer and higher order oligomeric structures; only the dimer exhibits high affinity binding (Hiraoka & Anaguchi et al. 1994). CSF3R ligand-binding is associated with dimerization of the receptor (Aritomi et al. 1999, Tamada et al. 2006, Layton & Hall 2006) and signal transduction through Jak/STAT, Lyn and Erk1/2. Mutations in CSF3R are a cause of Kostmann syndrome, also known as severe congenital neutropenia (Zeidler & Welte 2002, Vandenberghe & Beel 2011).

### Literature references

Larsen, A., Davis, T., Curtis, BM., Gimpel, S., Sims, JE., Cosman, D. et al. (1990). Expression cloning of a human granulocyte colony-stimulating factor receptor: a structural mosaic of hematopoietin receptor, immunoglobulin, and fibronectin domains. *J. Exp. Med.*, 172, 1559-70. ↗

Hiraoka, O., Anaguchi, H., Ota, Y. (1994). Evidence for the ligand-induced conversion from a dimer to a tetramer of the granulocyte colony-stimulating factor receptor. *FEBS Lett.*, 356, 255-60. ↗

### Editions

2014-06-04	Authored	Jupe, S.
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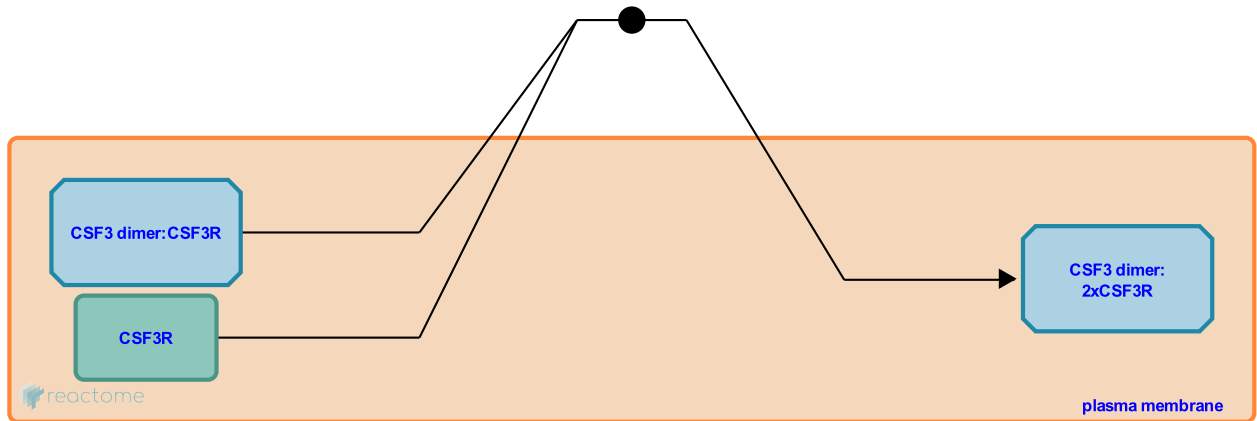
## CSF3 dimer:CSFR binds CSFR ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-8854738

**Type:** binding

**Compartments:** extracellular region, plasma membrane



CSF3R ligand-binding is associated with dimerization of the receptor (Aritomi et al. 1999, Tamada et al. 2006, Layton & Hall 2006) and signal transduction through Jak/STAT, Lyn and Erk1/2.

### Literature references

Tamada, T., Honjo, E., Maeda, Y., Okamoto, T., Ishibashi, M., Tokunaga, M. et al. (2006). Homodimeric cross-over structure of the human granulocyte colony-stimulating factor (GCSF) receptor signaling complex. *Proc. Natl. Acad. Sci. U.S.A.*, 103, 3135-40. ↗

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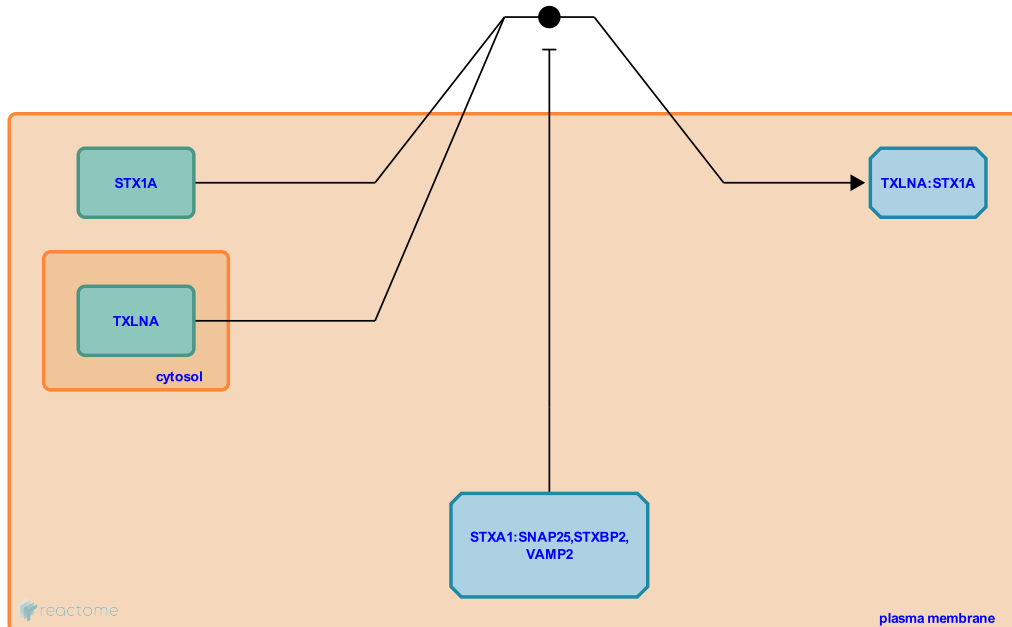
## TXLNA (IL14) binds syntaxin1A ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-449117

**Type:** binding

**Compartments:** extracellular region, plasma membrane



Interleukin-14, renamed alpha-taxilin (TXLNA) was originally described as High molecular weight B-cell growth factor (Ambrus et al. 1994). TXLNA binds several forms of syntaxin (Nogami et al. 2003), but not when they are complexed with SNAP25, VAMP2 or STXBP1, suggesting that TXLNA interacts with syntaxins outside the SNARE complex. This observation and a predicted role in intracellular vesicle trafficking led to renaming of the gene. Txlna transgenic mice show a phenotype similar to systemic lupus erythematosus and Sjogren's syndrome (Shen et al. 2006).

### Literature references

Nogami, S., Satoh, S., Nakano, M., Shimizu, H., Fukushima, H., Maruyama, A. et al. (2003). Taxilin; a novel syntaxin-binding protein that is involved in Ca<sup>2+</sup>-dependent exocytosis in neuroendocrine cells. *Genes Cells*, 8, 17-28. ↗

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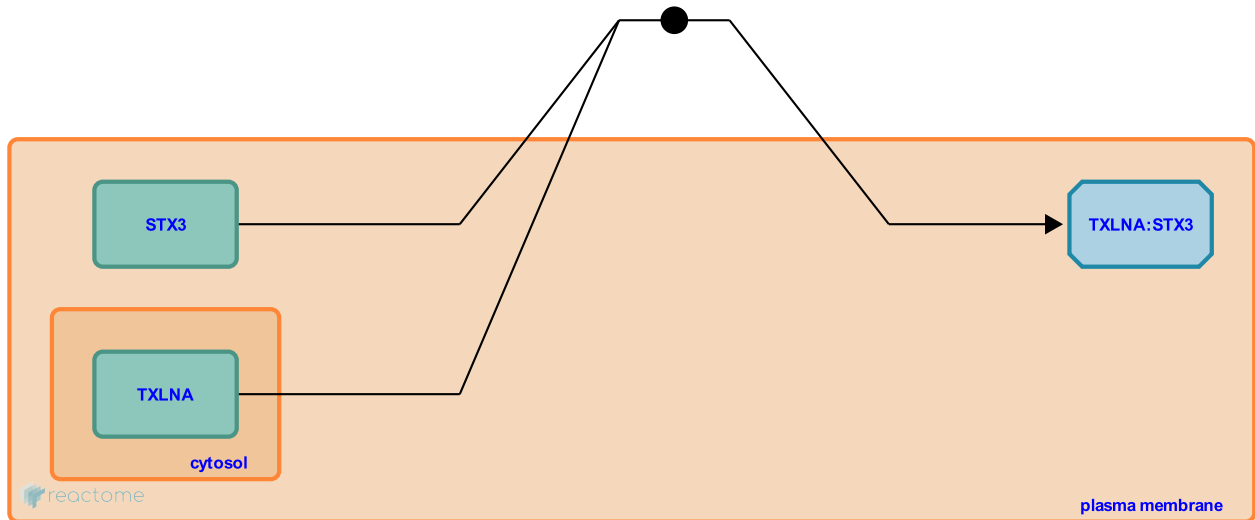
## TXLNA (IL14) binds syntaxin3 ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-9014052

**Type:** binding

**Compartments:** extracellular region, plasma membrane



Interleukin-14, renamed alpha-taxilin (TXLNA) was originally described as High molecular weight B-cell growth factor (Ambrus et al. 1994). TXLNA binds several forms of syntaxin (Nogami et al. 2003), but not when they are complexed with SNAP25, VAMP2 or STXBP1, suggesting that TXLNA interacts with syntaxins outside the SNARE complex. This observation and a predicted role in intracellular vesicle trafficking led to renaming of the gene. Txlna transgenic mice show a phenotype similar to systemic lupus erythematosus and Sjogren's syndrome (Shen et al. 2006).

### Literature references

Nogami, S., Satoh, S., Nakano, M., Shimizu, H., Fukushima, H., Maruyama, A. et al. (2003). Taxilin; a novel syntaxin-binding protein that is involved in Ca<sup>2+</sup>-dependent exocytosis in neuroendocrine cells. *Genes Cells*, 8, 17-28. ↗

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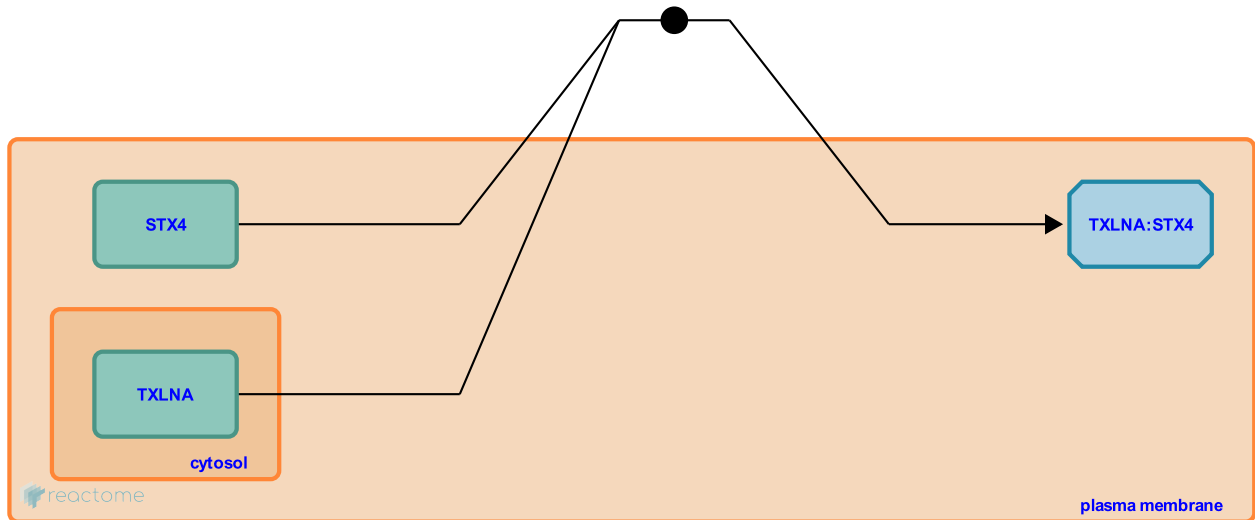
## TXLNA (IL14) binds syntaxin4 ↗

**Location:** [Other interleukin signaling](#)

**Stable identifier:** R-HSA-9014074

**Type:** binding

**Compartments:** extracellular region, plasma membrane



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### Literature references

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