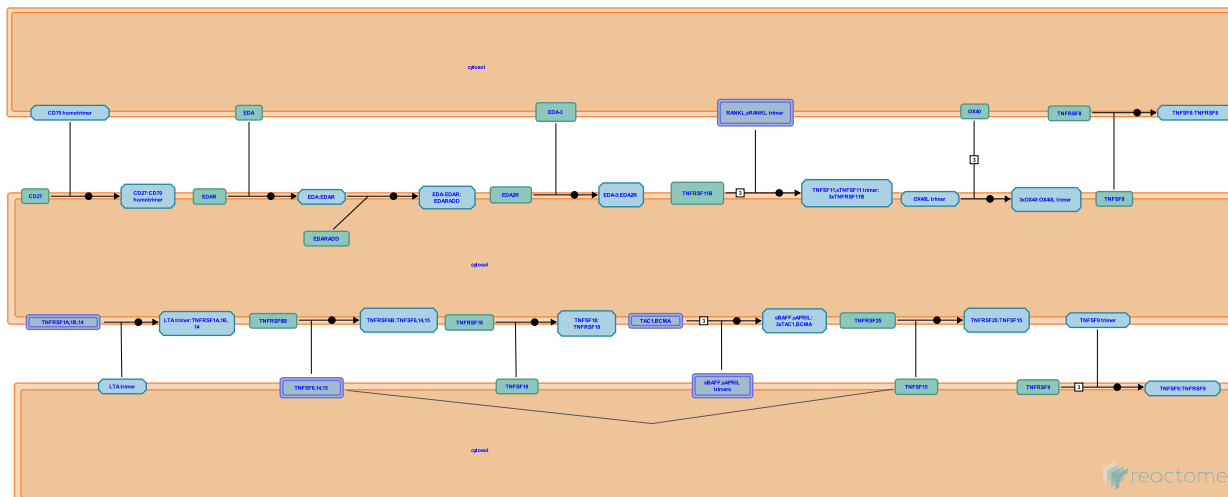


TNFs bind their physiological receptors



Garapati, P V., Jassal, B., Rajput, A., Virgen-Slane, R., Ware, CF.

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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](https://reactome.org/faq-textbook/).

29/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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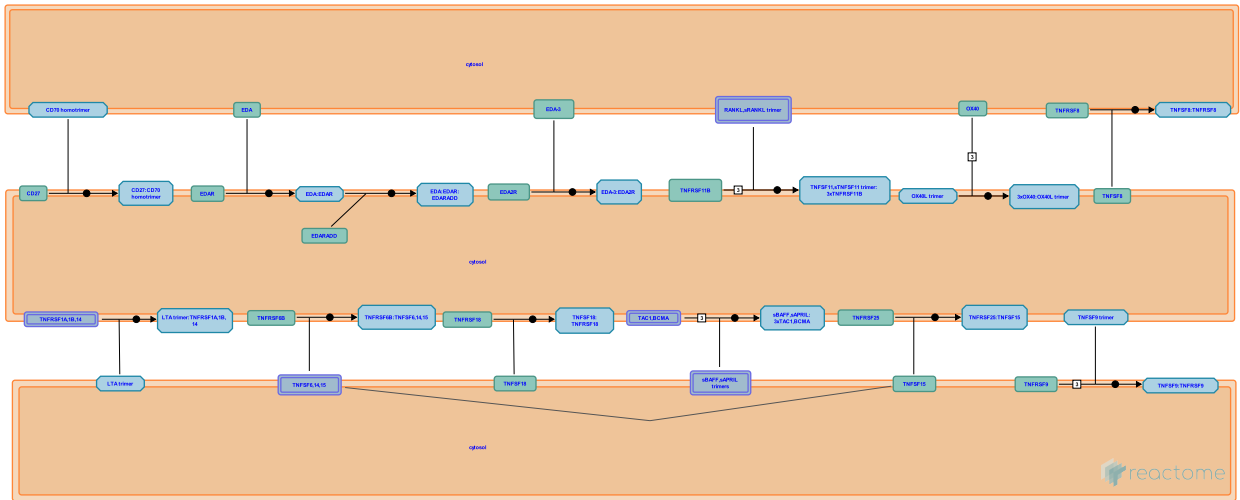
Reactome database release: 88

This document contains 1 pathway and 13 reactions ([see Table of Contents](#))

TNFs bind their physiological receptors

Stable identifier: R-HSA-5669034

Compartments: plasma membrane



Members of the tumour necrosis factor superfamily (TNFSF) and TNF receptor superfamily (TNFRSF) have crucial roles in both innate and adaptive immunity. These members are implicated in various acquired or genetic human diseases, ranging from septic shock to autoimmune disorders, allograft rejection and cancer (So et al. 2006).

Literature references

Lee, SW., So, T., Croft, M. (2006). Tumor necrosis factor/tumor necrosis factor receptor family members that positively regulate immunity. *Int. J. Hematol.*, 83, 1-11.

Editions

2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

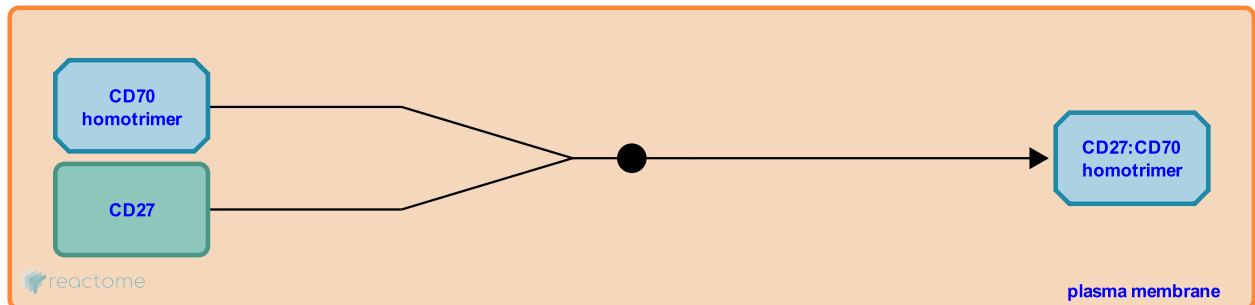
CD70 binds CD27 ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5669024

Type: binding

Compartments: plasma membrane



The CD70 antigen (CD70) is a cytokine that is found on the surface of activated but not resting T and B lymphocytes (Bowman et al. 1994). CD70 can bind to the CD27 antigen receptor (CD27), a dimeric membrane glycoprotein belonging to the tumor necrosis factor receptor family and found on the surface of most T lymphocytes (Camerini et al. 1991). This complex is thought to influence T-, B- and NK-cell functions (Salzer et al. 2013). Defects in CD27 can cause lymphoproliferative syndrome 2 (LPFS2), an autosomal recessive immunodeficiency disorder associated with persistent symptomatic EBV viremia, hypogammaglobulinemia, and impaired T-cell-dependent B-cell responses and T-cell dysfunction (van Montfrans et al. 2012, Salzer et al. 2013).

Literature references

- Boztug, K., Bienemann, K., Daschkey, S., Ginzl, S., Borkhardt, A., Fritsch, G. et al. (2013). Combined immunodeficiency with life-threatening EBV-associated lymphoproliferative disorder in patients lacking functional CD27. *Haematologica*, 98, 473-8. ↗
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- Kelleher, K., Yetz-Aldape, J., Kriz, R., Herrmann, S., Crimmins, MA., Bowman, MR. (1994). The cloning of CD70 and its identification as the ligand for CD27. *J. Immunol.*, 152, 1756-61. ↗

Editions

2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

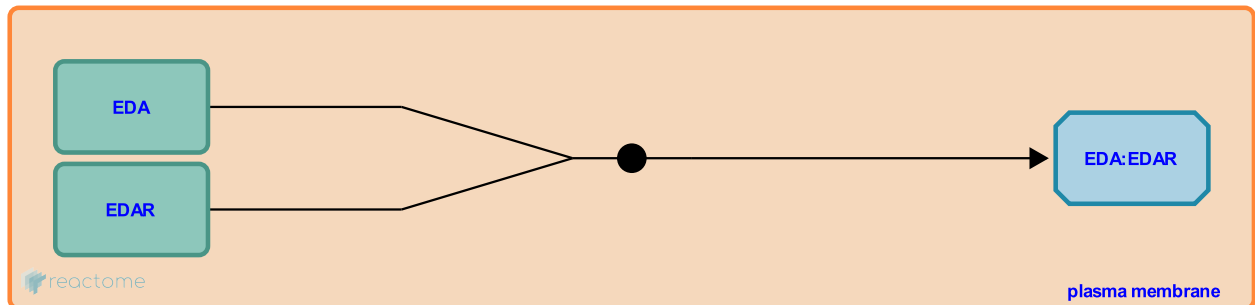
EDA binds EDAR ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5669012

Type: binding

Compartments: plasma membrane



Ectodysplasin-A (EDA) is a trimeric type II membrane protein whose sequence includes an interrupted collagenous domain of 19 Gly-X-Y repeats and a motif conserved in the tumor necrosis factor (TNF)-related ligand family. EDA regulates ectodermal appendage formation by colocalising with cytoskeletal structures on cell surfaces (Ezer et al. 1999). Activation of the NF-kappaB pathway by the tumor necrosis factor receptor superfamily member EDAR (EDAR) and its downstream adaptator EDAR-associated death domain (EDARADD) is essential for the development of hair follicles, teeth, exocrine glands and other ectodermal structures. EDA isoform 1 specifically binds EDAR. Defects in EDA can cause X-linked hypohidrotic ectodermal dysplasia 1 (ECTD1), the most common of many distinct ectodermal dysplasias characterised by sparse hair, abnormal or missing teeth and the inability to sweat (Cluzeau et al. 2011, Sadier et al. 2014).

Literature references

- Bayés, M., Elomaa, O., Kere, J., Ezer, S., Schlessinger, D. (1999). Ectodysplasin is a collagenous trimeric type II membrane protein with a tumor necrosis factor-like domain and co-localizes with cytoskeletal structures at lateral and apical surfaces of cells. *Hum. Mol. Genet.*, 8, 2079-86. ↗
- Yan, M., Hymowitz, SG., Compaan, DM., Wallweber, HJ., de Vos, AM., Starovasnik, MA. et al. (2003). The crystal structures of EDA-A1 and EDA-A2: splice variants with distinct receptor specificity. *Structure*, 11, 1513-20. ↗
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- Viriot, L., Pantalacci, S., Laudet, V., Sadier, A. (2014). The ectodysplasin pathway: from diseases to adaptations. *Trends Genet.*, 30, 24-31. ↗

Editions

2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

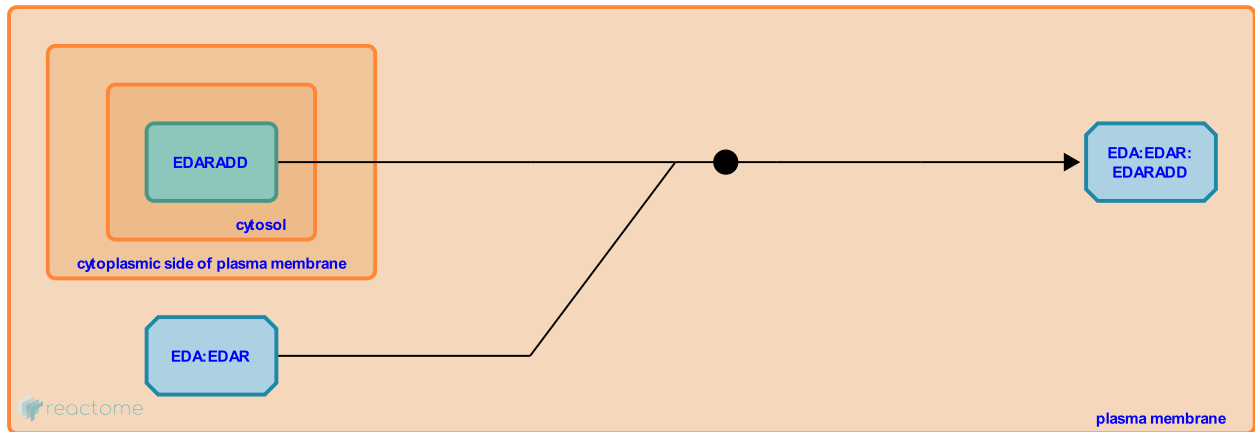
EDA:EDAR binds EDARADD ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5675656

Type: binding

Compartments: plasma membrane, cytosol



Ectodysplasin-A (EDA) is a trimeric type II membrane protein related to the tumor necrosis factor (TNF)-related ligand family. Activation of the NF-kappaB pathway by the tumor necrosis factor receptor superfamily member EDAR (EDAR) and its downstream adaptor EDAR-associated death domain (EDARADD) is essential for the development and regulation of hair follicles, teeth, exocrine glands and other ectodermal structures (Yan et al. 2002). EDA isoform 1 specifically binds EDAR. A small number of hypohidrotic ectodermal dysplasias (HEDs) are caused by mutations in EDARADD (Chassaing et al. 2010).

Literature references

Calvas, P., Chassaing, N., Viot, G., Vincent, MC., Bal, E., Smahi, A. et al. (2010). Mutations in EDARADD account for a small proportion of hypohidrotic ectodermal dysplasia cases. *Br. J. Dermatol.*, 162, 1044-8. ↗

Brady, JR., Yan, M., Fairbrother, WJ., Zhang, Z., Schilbach, S., Dixit, VM. (2002). Identification of a novel death domain-containing adaptor molecule for ectodysplasin-A receptor that is mutated in crinkled mice. *Curr. Biol.*, 12, 409-13. ↗

Editions

2015-02-16	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

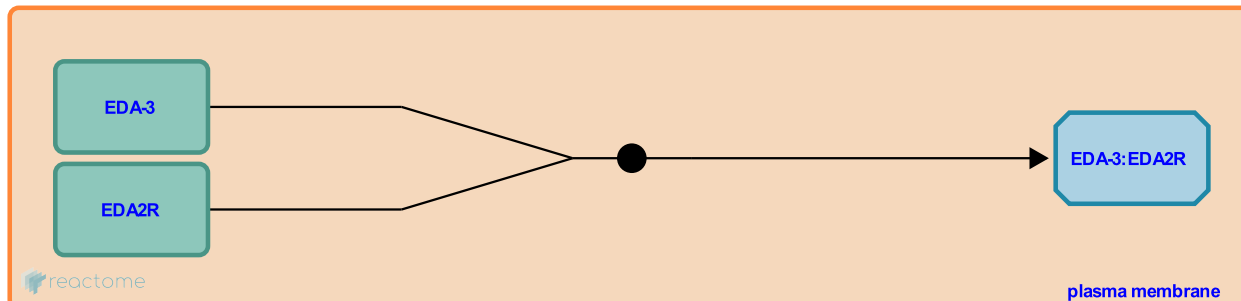
EDA-3 binds EDA2R ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5669013

Type: binding

Compartments: plasma membrane



Ectodysplasin-A (EDA) is a trimeric type II membrane protein whose sequence includes an interrupted collagenous domain of 19 Gly-X-Y repeats and a motif conserved in the tumor necrosis factor (TNF)-related ligand family. EDA regulates ectodermal appendage formation by colocalising with cytoskeletal structures on cell surfaces (Ezer et al. 1999). Activation of the NF-kappaB pathway by the tumor necrosis factor receptor superfamily member EDAR (EDAR) and its downstream adaptator EDAR-associated death domain (EDARADD) is essential for the development of hair follicles, teeth, exocrine glands and other ectodermal structures. EDA isoform 3 specifically binds tumor necrosis factor receptor superfamily member 27 (EDA2R aka XEDAR) whilst EDA isoform 1 specifically binds EDAR (Hymowitz et al. 2003).

Literature references

Bayés, M., Elomaa, O., Kere, J., Ezer, S., Schlessinger, D. (1999). Ectodysplasin is a collagenous trimeric type II membrane protein with a tumor necrosis factor-like domain and co-localizes with cytoskeletal structures at lateral and apical surfaces of cells. *Hum. Mol. Genet.*, 8, 2079-86. ↗

Yan, M., Hymowitz, SG., Compaan, DM., Wallweber, HJ., de Vos, AM., Starovasnik, MA. et al. (2003). The crystal structures of EDA-A1 and EDA-A2: splice variants with distinct receptor specificity. *Structure*, 11, 1513-20. ↗

Editions

2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

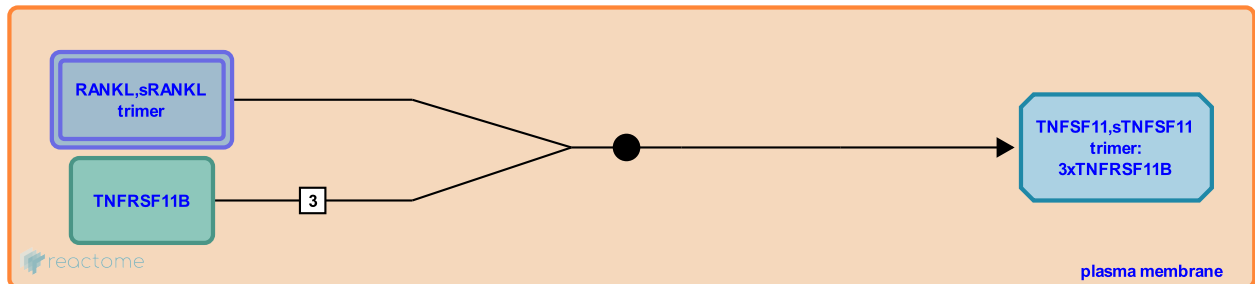
TNFSF11 binds TNFRSF11A, B ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5669035

Type: binding

Compartments: plasma membrane, extracellular region



Tumor necrosis factor ligand superfamily member 11 (TNFSF11 aka osteoclast differentiation factor, ODF) is a cytokine that is involved in the regulation of bone remodeling and playing multiple roles in the immune system. Its effects are mediated by its binding to tumor necrosis factor receptor superfamily members TNFRSF11A (aka RANK) (Nakagawa et al. 1998) and TNFRSF11B (aka OPG) (Luan et al. 2012).

Defects in TNFSF11 can cause autosomal recessive osteopetrosis 2 (OPTB2; MIM:259710), characterised by abnormally dense bone due to defective resorption of immature bone (Sobacchi et al. 2007). Defects in TNFRSF11A and B cause bone remodelling/osteopathy disorders (Hughes et al. 2000, Guerrini et al. 2008, Cundy et al. 2002).

Literature references

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- Anderson, DM., Marken, J., Wallace, RG., Whyte, MP., Nakatsuka, K., Hovy, L. et al. (2000). Mutations in TNFRSF11A, affecting the signal peptide of RANK, cause familial expansile osteolysis. *Nat. Genet.*, 24, 45-8. ↗

Editions

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2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

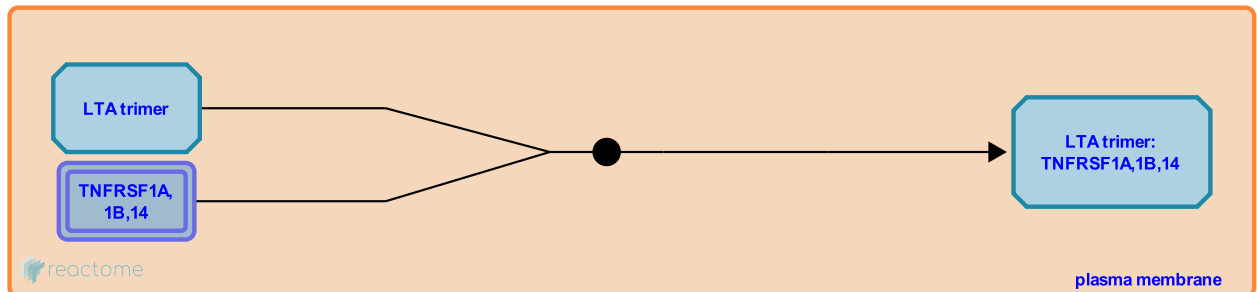
LTA trimer binds TNFRSF1A,1B,14 ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5669097

Type: binding

Compartments: plasma membrane



Lymphotoxin-alpha (LTA) is a cytokine produced by lymphocytes that plays an important role in the inflammatory and immunologic response. LTA is a product of stimulated T cells and can help elicit cytotoxic effects on cancer cells. In its homotrimeric form, LTA binds the tumor necrosis factor receptor superfamily members TNFRSF1A, 1B and 14 (Aggarwal 2003).

Literature references

Aggarwal, BB. (2003). Signalling pathways of the TNF superfamily: a double-edged sword. *Nat. Rev. Immunol.*, 3, 745-56. ↗

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2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

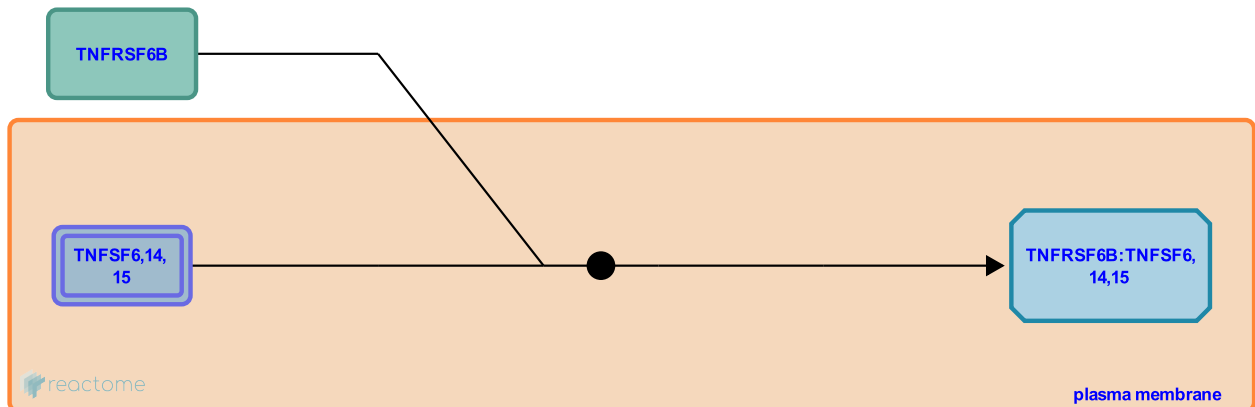
TNFRSF6B binds TNFSF6,14,15 ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5675948

Type: binding

Compartments: plasma membrane, extracellular region



Tumor necrosis factor ligand superfamily member 15 (TNFSF15 aka VEGI) mediates the activation of NF-kappaB and subsequently can inhibit vascular endothelial growth, angiogenesis and promote activation of caspases and apoptosis (Haridas et al. 1999). TNFSF15 can bind the secreted decoy receptor tumor necrosis factor receptor superfamily member 6B (TNFRSF6B aka DcR3). Upon binding, the cytotoxic effects of TNFSF15 are neutralised thereby protecting against apoptosis. TNFRSF6B can also neutralise the cytotoxic ligands TNFSF14 (aka LIGHT) and TNFSF6 (aka FASL) (Zhan et al. 2011).

Literature references

Ramagopal, U., Zhan, C., Yan, Q., Li, Z., Almo, SC., Patskovsky, Y. et al. (2011). Decoy strategies: the structure of TL1A:DcR3 complex. *Structure*, 19, 162-71. ↗

Haridas, V., Yu, GL., Su, J., Liu, D., Aggarwal, BB., Shrivastava, A. et al. (1999). VEGI, a new member of the TNF family activates nuclear factor-kappa B and c-Jun N-terminal kinase and modulates cell growth. *Oncogene*, 18, 6496-504. ↗

Editions

2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

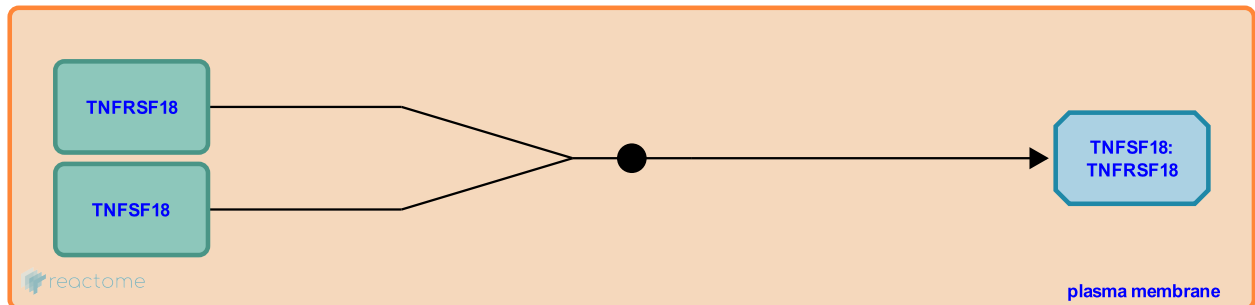
TNFSF18 binds TNFRSF18 [↗](#)

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5675947

Type: binding

Compartments: plasma membrane



Tumor necrosis factor ligand superfamily member 18 (TNFSF18) is a cytokine that regulates T-cell receptor-mediated cell death and promotes leukocyte adhesion to endothelial cells. It binds to tumor necrosis factor receptor superfamily member 18 (TNFRSF18 aka GITR) (Gurney et al. 1999).

Literature references

Mark, DT., Brush, AD., Heldens, AD., Godowski, PJ., Dowd, AD., Gurney, AL. et al. (1999). Identification of a new member of the tumor necrosis factor family and its receptor, a human ortholog of mouse GITR. *Curr. Biol.*, 9, 215-8. [↗](#)

Editions

2015-01-30	Authored, Edited	Jassal, B.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

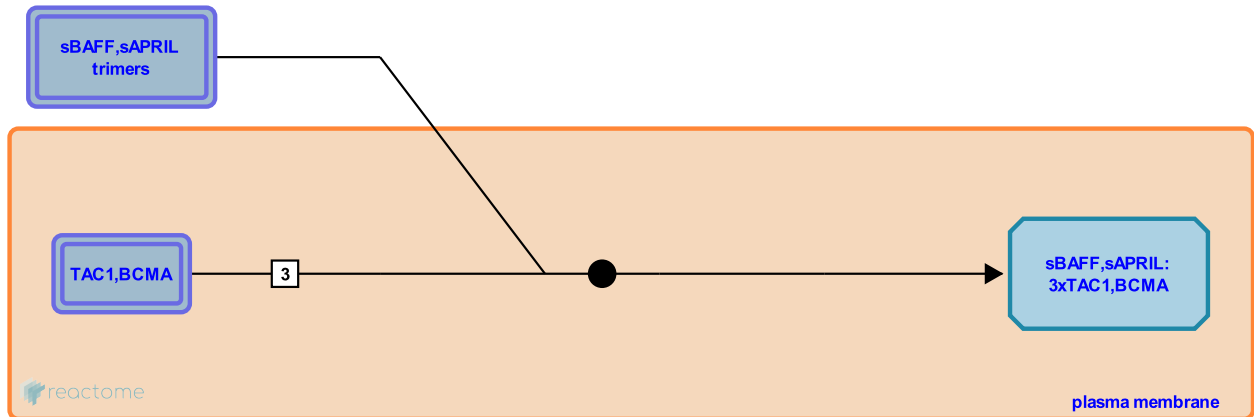
sBAFF,sAPRIL binds TACI,BCMA ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5676607

Type: binding

Compartments: plasma membrane, extracellular region



B cell activating factor (BAFF also known as TNFSF13B) and a proliferation inducing ligand (APRIL also known as TNFSF13) are two related members of the tumour necrosis factor ligand super family (TNFSF) that promote B-cell proliferation. BAFF binds to three receptors B-cell activating factor belonging to the TNF family receptor (BAFFR also known as TNFRSF13C), B-cell maturation antigen (BCMA also known as TNFRSF17) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI also known as TNFRSF13B), whereas APRIL interacts with TACI and BCMA. BAFF and APRIL exhibit structural similarity and overlapping yet distinct receptor binding specificity. Both BAFF and APRIL bind BCMA, but the APRIL:BCMA interaction is of higher affinity. TACI binds to both BAFF and APRIL with similar affinity (Day et al. 2005, Marsters et al. 2000, Gross et al. 2000, Rickert et al. 2011). BAFF or APRIL binding to BCMA or TACI promotes B cell development, proliferation, activation, and survival (Moore et al. 1999, Schneider et al. 1999). BAFF and APRIL are secreted as trimers, but BAFF trimers can be ordered into 60-mer arrays (Liu et al. 2003, Lopez-Fraga et al. 2001).

Literature references

Hofmann, K., Acha-Orbea, H., Lawton, P., Bixler, S., Tschopp, J., Browning, JL. et al. (1999). BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. *J. Exp. Med.*, 189, 1747-56. ↗

Giri, J., Sosnovtseva, S., Orr, A., Moore, PA., Roschke, V., Feng, P. et al. (1999). BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science*, 285, 260-3. ↗

Hahne, M., Albar, JP., López-Fraga, M., Fernandez, R. (2001). Biologically active APRIL is secreted following intracellular processing in the Golgi apparatus by furin convertase. *EMBO Rep.*, 2, 945-51. ↗

Editions

2015-01-26	Authored, Edited	Garapati, P V.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

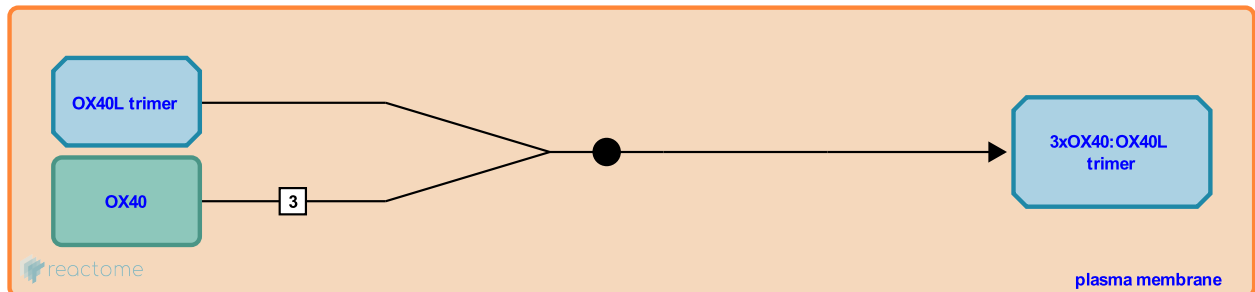
OX40L binds OX40 ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5692315

Type: binding

Compartments: plasma membrane



T-cell activation is mediated not only by antigen stimulation through T-cell receptors but also by costimulatory signals through costimulatory molecules. Among several costimulatory molecules, the tumor necrosis factor (TNF) receptor family member OX40 (also known as TNFRSF4 or CD134) plays a key role in the survival and homeostasis of effector and memory T cells (Godfrey et al. 1994, Kashiwakura et al. 2004, Zingoni et al. 2004). OX40 mediates this costimulation by binding to its partner OX40L (also known as TNFSF4 or CD252). OX40 is a type I transmembrane protein expressed predominantly on T-lymphocytes early after antigen activation. It binds with OX40L trimer expressed on activated antigen presenting cells and endothelial cells within acute inflammatory environments. OX40 mediates signalling independently and also can augment antigen-driven TCR signalling. OX40 signalling leads to the activation of NFκB1 (p50-RELA) to stimulate survival signals to T cells in the absence of antigen recognition. It can also activate hence to activation of noncanonical NF-İB2 (p52-RELB) through NIK which might also be necessary for transmitting survival signals (Kawamata et al. 1998, Arch et al. 1998). OX40 can also enhance TCR-induced calcium influx, leading to strong nuclear accumulation of NFATc1 and NFATc2 that likely regulate production of cytokines (So et al. 2006, Croft 2010).

Literature references

- Zingoni, A., Sornasse, T., Santoni, A., Tanaka, Y., Lanier, LL., Cocks, BG. (2004). Cross-talk between activated human NK cells and CD4+ T cells via OX40-OX40 ligand interactions. *J. Immunol.*, 173, 3716-24. ↗
- Soroosh, P., Takahashi, T., Ishii, N., Sugamura, K. (2010). OX40-OX40 ligand interaction in T-cell-mediated immunity and immunopathology. *Adv. Immunol.*, 105, 63-98. ↗
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- Song, J., So, T., Altman, A., Sugie, K., Croft, M. (2006). Signals from OX40 regulate nuclear factor of activated T cells c1 and T cell helper 2 lineage commitment. *Proc. Natl. Acad. Sci. U.S.A.*, 103, 3740-5. ↗
- Harara, MA., Engleman, EG., Godfrey, WR., Fagnoni, FF., Buck, D. (1994). Identification of a human OX-40 ligand, a costimulator of CD4+ T cells with homology to tumor necrosis factor. *J. Exp. Med.*, 180, 757-62. ↗

Editions

2015-01-26	Authored, Edited	Garapati, P V.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

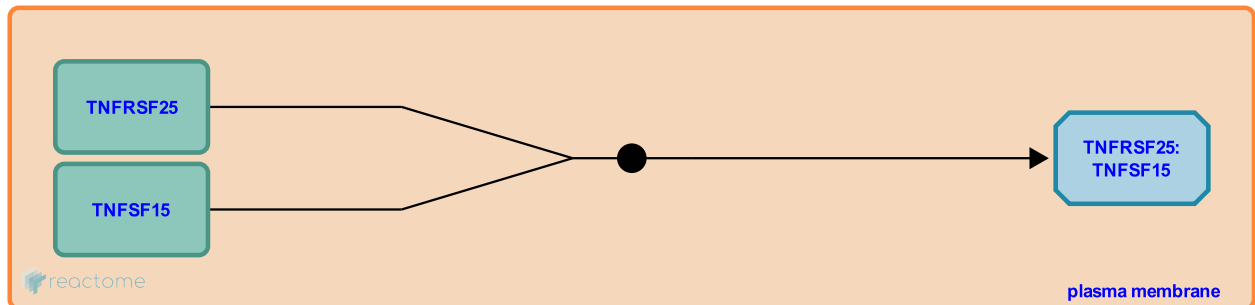
TNFSF15 binds TNFRSF25 [↗](#)

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-5693012

Type: binding

Compartments: plasma membrane



TNFRSF25 (also referred as DR3/TRAMP/LARD/WSL1) is a death-domain-containing tumor necrosis factor (TNF)-family receptor primarily expressed on T cells. It binds with TNFSF15 (TL1A), the TNF family ligand and induces T cell costimulation (Meylan et al. 2008).

Literature references

Olsen, HS., Moore, PA., Cho, YH., Perry, JW., Liu, D., Gentz, R. et al. (2002). TL1A is a TNF-like ligand for DR3 and TR6/DcR3 and functions as a T cell costimulator. *Immunity*, 16, 479-92. [↗](#)

Acharya, K., Keane-Myers, A., Bundoc, V., Wang, EC., Meylan, F., Kinder, M. et al. (2008). The TNF-family receptor DR3 is essential for diverse T cell-mediated inflammatory diseases. *Immunity*, 29, 79-89. [↗](#)

Editions

2015-01-26	Authored, Edited	Garapati, P V.
2015-05-12	Reviewed	Ware, CF., Rajput, A., Virgen-Slane, R.

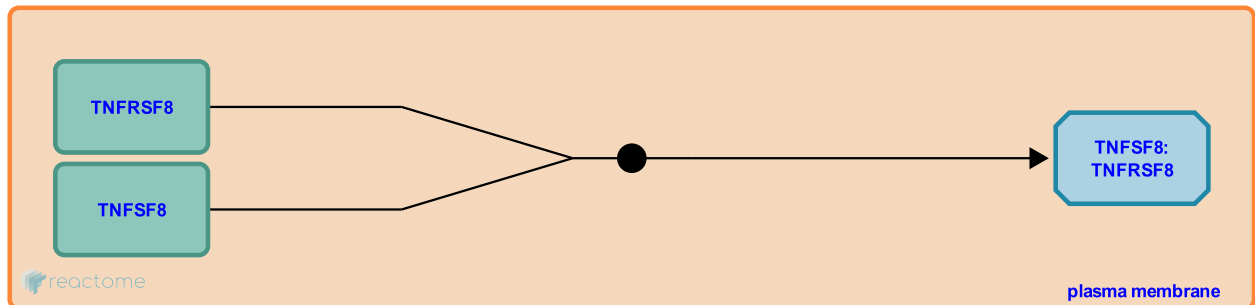
TNFSF8 binds TNFRSF8 [↗](#)

Location: [TNFs bind their physiological receptors](#)

Stable identifier: R-HSA-8856189

Type: binding

Compartments: plasma membrane



Tumor necrosis factor receptor superfamily 8 (TNFRSF8, CD30) and its ligand TNFSF8 (CD30 ligand, CD30L, CD153) are interacting cell-surface glycoproteins. TNFRSF8 is expressed on activated CD4 and CD8 T cells and B cells. It is a marker for Hodgkin's syndrome. TNFRSF8 signaling regulates lymphocyte survival (Blazar et al. 2004) and peripheral T cell responses, controlling T cell survival and down-regulating cytolytic capacity (Duckett et al. 1997, Kurts et al. 1999, Telford et al. 1997).

Literature references

Goodwin, RG., Wiley, SR., Smith, CA. (1996). Reverse signaling via CD30 ligand. *J. Immunol.*, 157, 3635-9. [↗](#)

Editions

2015-05-12	Reviewed	Ware, CF., Virgen-Slane, R.
2016-05-19	Authored, Edited	Garapati, P V.

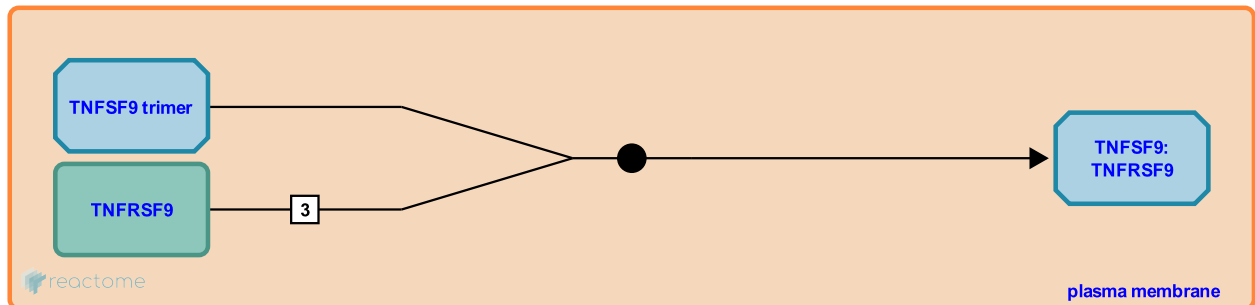
TNFSF9 binds TNFRSF9 ↗

Location: TNFs bind their physiological receptors

Stable identifier: R-HSA-8858475

Type: binding

Compartments: plasma membrane



TNFRSF9 (Tumor necrosis factor receptor superfamily member 9/4-1BB/CD137) is induced when T cells receive antigen-specific stimuli. Its ligand is TNFSF9 (Tumor necrosis factor ligand superfamily member 9/ 4-1BBL/CD137L) and is induced on antigen-presenting cells, such as dendritic cells, macrophages, and B cells. TNFSF9 forms homotrimers like rest of the TNF ligands and it may interact with three TNFRSF9 receptors. Structure of TNFSF9/TNFRSF9 is not available but model has been proposed where one receptor interacts predominantly with just one ligand from the trimer and only slightly with the C-terminal tail of the adjacent subunit (Won et al. 2009). TNFRSF9/TNFSF9 pathway co-stimulates T cells to carry out effector functions such as eradication of established tumors (Halstead et al. 2002, Bertram et al. 2002) and the broadening of primary and memory CD8⁺ T cell responses (Won et al. 2010, Vinay et al. 2006).

Literature references

Rice, AJ., Won, EY., Byun, JS., Kwon, BS., Ahn, B., Cha, K. et al. (2010). The structure of the trimer of human 4-1BB ligand is unique among members of the tumor necrosis factor superfamily. *J. Biol. Chem.*, 285, 9202-10. ↗

Editions

2015-05-12	Reviewed	Ware, CF., Virgen-Slane, R.
2016-05-19	Authored, Edited	Garapati, P V.

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