

Cytokine Receptors (Tumor Necrosis Factor Superfamily)

Key References

- Benedict, C.A., et al., Death and survival: viral regulation of TNF signaling pathways., *Curr. Opin. Immunol.*, **15**, 59-65 (2003).
- Bodmer, J.L., et al., The molecular architecture of the TNF superfamily., *Trends Biochem. Sci.*, **27**, 19-26 (2002).
- Croft, M., Co-stimulatory members of the TNFR family: keys to effective T-cell immunity?, *Nat. Rev. Immunol.*, **3**, 609-620 (2003).
- Kishore, U., et al., C1q and tumor necrosis factor superfamily: modularity and versatility., *Trends Immunol.*, **25**, 551-561 (2004).
- Locksley, R.M., et al., The TNF and TNF receptor superfamilies: integrating mammalian biology., *Cell*, **104**, 487-501 (2001).
- Mackay, F., et al., The TNF family members BAFF and APRIL: the growing complexity., *Cytokine Growth Factor Rev.*, **14**, 311-324 (2003).
- Mikkola, M.L., et al., Ectodysplasin signaling in development., *Cytokine Growth Factor Rev.*, **14**, 211-224 (2003).
- Pomerantz, J.L., et al., Two pathways to NF-kappaB., *Mol. Cell*, **10**, 693-695 (2002).
- Schneider, K., et al., Lymphotoxin and LIGHT signaling pathways and target genes., *Immunol. Rev.*, **202**, 49-66 (2004).
- Sedy, J.R., et al., B and T lymphocyte attenuator regulates T cell activation through interaction with herpesvirus entry mediator., *Nat. Immunol.*, **6**, 90-98 (2005).
- Sfikakis, P.P., et al., Tumor necrosis factor biology in experimental and clinical arthritis., *Curr. Opin. Rheumatol.*, **15**, 380-386 (2003).
- Ware, C.F., The TNF Superfamily., *Cytokine Growth Factor Rev.*, **14**, 181-184 (2003).

Overview

The cytokines and receptors of the Tumor Necrosis Factor (TNF) superfamily serve as an intercellular communication network integrating cellular responses in vertebrates. TNF receptors activate signaling pathways for cell survival, death, and differentiation orchestrating the development, organization and homeostasis of lymphoid, mammary, neuronal and ectodermal tissues. Members of the TNF receptor superfamily (TNFRSF) may pair off with one or more specific ligands, which form a corresponding superfamily of ligands (TNFSF). Each ligand-receptor pair is considered a "system", with more than 40 distinct systems currently recognized (see Table). The significant shared use of ligands or receptors observed in the different systems indicates the signaling pathways are highly integrative with unique functions derived in part from distinct signaling pathways activated by these cytokine systems. A standardized nomenclature for the TNF/TNFR superfamily was adopted aiding accessibility of the genomic databases (<http://www.gene.ucl.ac.uk/nomenclature/>), although the original acronyms remain in common use.

TNFR are type 1 membrane glycoproteins structurally defined by a cysteine-rich motif forming a molecule with an elongated extracellular domain containing the binding site for its specific ligand. The TNF related ligands are also membrane-anchored (type II) glycoproteins assembling into compact trimers that induce oligomerization of their specific receptors, which in turn activate signaling within the cell. From their membrane-anchored position, cell-to-cell contact is required to initiate signaling, except for those ligands that are shed from their membrane position diffusing to cellular receptors at distant sites. Soluble receptors formed by shedding and others that lack

an encoded membrane domain function as decoys (antagonists). Some TNFR, like Fas, TRAIL-R1 and 2, and TNFR1 activate cell death by recruiting specific adaptor molecules, like FADD and caspase 8, which lead to apoptosis. Other TNFR, like the LT β R, CD40 and RANK activate transcription factors like NF κ B and AP1 that regulate expression of genes protecting cells from apoptosis. Activating both cell death and survival pathways is the signaling paradox of this cytokine family.

TNF and Lymphotoxin- α (LT α), the prototypic members of the family, function in inflammatory and immune reactions through two shared receptors TNFR1 and TNFR2, having proinflammatory and anti-inflammatory effects. LT α β -LT β R system is necessary for the genesis of secondary lymphoid organs as well as organizing microenvironments for lymphocytes during chronic inflammation. TNF's role in inflammation leads to development of specific inhibitors fashioned from soluble TNFR (Enbrel), which has proved highly effective in the treatment of autoimmune diseases such as rheumatoid arthritis. The related receptors Ox40, 41BB, HVEM, and CD27 for example mediate signals involved in fine tuning T cell responses, promoting differentiation of effector and memory T cells. HVEM binds and regulates signaling through the inhibitory cosignaling regulator BTLA, an Ig superfamily member with an ITIM motif. The BAFF/APRIL and CD40 systems provide critical signals for antibody production by B lymphocytes. Thus, it is not surprising given the important roles played by members of the TNF superfamily in host defense that several different viral pathogens, including pox, herpes and retroviruses encode orthologs (virokines) that mimic or antagonize these cytokine systems.

The several other systems function as mediators of organ development and homeostasis. For example, EDA controls ectoderm and RANK controls bone homeostasis by regulating the differentiation of osteoblasts. Nerve growth factor receptor (p75) and Taj/TROY bind ligands unrelated to TNF demarcating a major branch point in the TNFR family. Rather NGFR and Taj bind neurotrophins and Nogo-66 complex involved in regulating the regeneration of axons. The TNF homology domain (jellyroll β sandwich) is also observed in several proteins related to complement protein C1q. The diversification of the TNF superfamily into so many biological contexts reflects the versatility of the TNF and TNFR binding domains. As additional knowledge accumulates therapeutic manipulation of the TNF superfamily may have significant impact on human disease.

Cytokine Receptors (Tumor Necrosis Factor Superfamily)

STANDARDIZED NAME^a	TNFRSF1A	TNFRSF1B	TNFRSF3	TNFRSF4	TNFRSF5	TNFRSF6	TNFRSF6B	TNFRSF7
ALTERNATIVE NAMES	CD18, p55TNFR, TNFRI	TNFRII, p75TNFR	LTβR	OX40, CD134	CD40	Fas, APO-1, CD95	DcR3, M86, TR6	CD27, Tp55
CHROMOSOME POSITION	12p13.2	1p36-p32	12p13	1p36	20q12-q13.2	10q24.1	20q13.3	12p13
AGONISTS/LIGANDS^c	TNF (T0157, T6674), LTα (T7799)	TNF (T0157, T6674), LTα (T7799)	LIGHT (L0414), LT-αβ2 (L5162)	OX40L	CD40L (L6362)	FasL (F4027, F4428)	FasL, (F4027), TL1A, LIGHT (L0414)	CD27L
ANTAGONISTS	Enbrel™, Remicade™	Enbrel™, Remicade™	LTβR-Fc (L2885)	Ox40-Fc	Not known	Fas-Fc (F8674), DcR3-Fc (D2441)	Not known	CD27-Fc
SIGNAL TRANSDUCTION MECHANISMS	TRAFs, SAPKs, NFκB, Caspases	TRAFs, SAPKs, NFκB	TRAFs, SAPKs, NFκB	TRAFs, SAPKs, NFκB	TRAFs, SAPKs, NFκB	SAPKs, NFκB, Caspases	No signal, NFκB	TRAFs, SAPKs
PHYSIOLOGICAL FUNCTION	Inflammation/host defense	Activated T cell population contraction	Lymphoid organogenesis and homeostasis	Enhances T cell activation and responses	Ig class-switching, germinal center formation	Activated T cell population contraction	Soluble decoy receptor	Germinal center formation
DISEASE RELEVANCE	Autoinflammatory diseases, autoimmunity	Susceptibility to bacterial infections, autoimmunity	Autoimmunity, inflammatory bowel disease (IBD)	Defective T cell recall responses	Immunodeficiency	Autoimmunity (like ALPS) ^d	Tumor evasion	Defective T cell responses, autoimmunity

Cytokine Receptors (Tumor Necrosis Factor Superfamily) (continued)

STANDARDIZED NAME	TNFRSF8	TNFRSF9	TNFRSF10A	TNFRSF10B	TNFRSF10C	TNFRSF10D	TNFRSF11A	TNFRSF11B
ALTERNATIVE NAMES	CD30	4-1BB	TRAILR1, Apo-2, DR4	TRAILR2, Trick2A, DR5	DcR1, TRAILR3, TRID	DcR2, TRAILR4, TRUND	RANK, TRANCE-R	OPG, OCIF, TR1
CHROMOSOME POSITION	1p36	1p36	8p21	8p22-p21	8p22-p21	8p21	18q22.1	8q24
AGONISTS/LIGANDS^c	CD30L (C6112 (h), C6237 (m))	4-1BBL	TRAIL (T5694, K4761)	TRAIL (T5694, K4761)	TRAIL (T5694, K4761)	TRAIL (T5694, K4761)	RANKL (T3573)	RANKL (T3573)
ANTAGONISTS	Not known	4-1BB-Fc	Not known	Not known	Not known	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	TRAFs, SAPKs, NFκB	NFκB	NFκB caspases	NFκB caspases	No signal	No signal	TRAFs, NFκB	No signal
PHYSIOLOGICAL FUNCTION	Regulates memory T cell responses	T cell costimulation	Lymphocyte and tumor cell apoptosis	Same as TNFRSF10A	Inhibits TRAIL	Same as TNFRSF10C	Bone homeostasis, mammary gland and Peyer's patch development	Bone formation/homeostasis
DISEASE RELEVANCE	Disease marker in Hodgkin's disease, T cell lymphomas	Graft-versus-host disease, cancer immunotherapy	Cancer immunotherapy	Cancer immunotherapy	Not known	Not known	Osteoporosis	Osteoporosis, arterial calcification

Cytokine Receptors (Tumor Necrosis Factor Superfamily)

Cytokine Receptors (Tumor Necrosis Factor Superfamily) (continued)

STANDARDIZED NAME	TNFRSF12A	TNFRSF13B	TNFRSF13C	TNFRSF14	TNFRSF16	TNFRSF17	TNFRSF18	TNFRSF19L
ALTERNATIVE NAMES	FN14, TWEAKR	TACI	BAFFR	HVEM, HveA, TR2, LIGHTR, ATAR	NGFR, p75NTR	BCMA	AITR, GITR, TL6	RELT
CHROMOSOME POSITION	16p13.3	17p11.2	22q13.1-q13.31	1p36.3-p36.2	17q12-q22	16p13.1	1p36.3	11q13.2
AGONISTS/LIGANDS^c	TWEAK	APRIL (A1354), BAFF	BAFF	LIGHT (L0414), LT α (T7799), BTLA	NGF (N1408), BDNF (B3795)	APRIL (A1354) BAFF	AITRL	Not known
ANTAGONISTS^c	Not known	TACI-Fc	BAFFR-Fc (B4060)	HVEM-Fc (H9785)	Not known	Not known	Endokine™	Not known
SIGNAL TRANSDUCTION MECHANISMS	NF κ B	TRAFs	NF κ B	TRAFs	Not known	Not known	Not known	TRAFs NF κ B
PHYSIOLOGICAL FUNCTION	Regulates cell survival/apoptosis, angiogenesis	Enhances B cell survival	Costimulates T, cell proliferation, B cell survival	HSV entry receptor, T cell costimulation	Angiogenesis, cutaneous neuron development	Enhances B cell survival, Ig class switching	Inhibits T cell receptor-dependent apoptosis	Not known
DISEASE RELEVANCE	Skin disorders, CNS inflammation (like EAE) ^e	Autoimmunity	Autoimmunity	Autoimmunity	Defective neuron innervation	Autoimmunity	Autoimmunity	Not known

Cytokine Receptors (Tumor Necrosis Factor Superfamily) (continued)

STANDARDIZED NAME	TNFRSF19	TNFRSF21	TNFRSF25 ^f	EDAR	XEDAR
ALTERNATIVE NAMES	TROY, TAJ TRADE	DR6	WSL-1, TRAMP, AIR, APO-3, DDR3, DR3, LARD, TR3, WSLLR	ED1R, ED5, EDA3	EDA2R
CHROMOSOME POSITION	13q12.11-q12.3	6P12.2-21.1	1p36.3	2q11-q13	Xq11.1
AGONISTS/LIGANDS	NgR1/LINGO1	Not known	TL1A	EDA1	EDA2
ANTAGONISTS	Not known	Not known	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	RhoA c-Jun	NF κ B Caspases	NF κ B Caspases	NF κ B Caspases	TRAFs
PHYSIOLOGICAL FUNCTION	Inhibits neurite outgrowth	Attenuates lymphoproliferation	Enhances NK cell and monocyte cytotoxicity	Hair/sweat gland formation and development	Hair/sweat gland formation and development
DISEASE RELEVANCE	Axonal regeneration	Not known	Not known	Hypohydrotic ectodermal dysplasia	Hypohydrotic ectodermal dysplasia

Cytokine Receptors (Tumor Necrosis Factor Superfamily)

Abbreviations

AIR: Apoptosis-inducing receptor

AITR: Activation-inducible TNF-related member

AP1: Activator protein 1

APO: Apoptosis antigen

APRIL: A proliferation-inducing ligand

ATAR: Another TRAF-associated receptor

BAFF: B cell-activating factor

BCMA: B cell maturation antigen

BDNF: Brain-derived neurotrophic factor

BTLA: B and T lymphocyte attenuator

DcR: Decoy receptor

DDR3: Death-domain-containing receptor

DR: Death receptor

EDA: Ectodysplasin-A

FADD: FAS-associated death domain-containing protein

GITR: Glucocorticoid-induced TNF-related member

HVEM: Herpes virus entry mediator

ITIM: Immunoreceptor tyrosine-based inhibitory motif

LARD: Lymphocyte-associated receptor of death

LIGHT: Lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D (gD) for HVEM, a receptor expressed by T cells

LT: Lymphotoxin

NFκB: Nuclear factor kappa B

NGF: Nerve growth factor

NgR1: Nogo-66 receptor 1

OCIF: Osteoclastogenesis inhibitory factor

OPG: Osteoprotegerin

RANK: Receptor activator of NFκB

RELT: Receptor expressed in lymphoid tissues

SAPK: Stress-activated protein kinases

TACI: Transmembrane activator and CAML interactor

Taj: Toxicity and JNK inducer

TL: TNF-like

TNF: Tumor necrosis factor

TNFR: Tumor necrosis factor receptor

TNFSF: Tumor necrosis factor superfamily

TNFRSF: Tumor necrosis factor receptor superfamily

TR: TNF receptor-like

TRAF: TNF receptor-associated factor

TRAIL: Tumor necrosis factor related apoptosis inducing ligand

TRAMP: TNF-receptor-related apoptosis-mediated protein

TRANCE: TNF-related activation-induced cytokine

TROY: TNFRSF expressed on the mouse embryo

Trick: TRAIL receptor inducer of cell killing

TRID: TRAIL receptor without an intracellular domain

TRUND: TRAIL receptor with a truncated death domain

TWEAK: TNF-like weak inducer of apoptosis

XEDAR: X-linked ectodysplasin-A2 receptor

FOOTNOTES

a Standardized gene symbols were acquired from: <http://www.gene.ucl.ac.uk/nomenclature/>; includes further details, such as linked human genomic and tissue expression databases, etc.

b All accession numbers are for human mRNA.

c Product numbers refer to human proteins. For further species, visit our website at www.sigma-aldrich.com and use our Product Search.

d Autoimmune lymphoproliferative syndrome is typified by defective lymphocyte apoptosis; usually leads to autoimmunity.

e Experimental autoimmune encephalomyelitis.

f Previous