

TNF Receptor and Ligand Superfamilies

The TNF receptor superfamily (TNFRSF) consists of a group of glycoproteins characterized by cysteine-rich motifs in the extracellular domain (CRDs). These receptors share about 20-30% overall homology. Most TNFRSF are type I membrane proteins (with an extracellular N-terminus and an intracellular C-terminus). TNFRSF members can be divided into death receptors, decoy receptors, and activating receptors. Most activating receptors mediate intracellular signals through adaptor proteins, i.e., TNF receptor-associated factors (TRAFs), while the death receptors mediate intracellular signals through death domain (DD) associated proteins (FADD, TRADD). Members of the TNFRSF can also be proteolytically cleaved to form soluble receptors that act as “slow release” depots for ligands.

Ligands that bind TNFRSF are members of the TNF superfamily (TNFSF). TNFSF ligands are either soluble or membrane-bound glycoproteins. Soluble TNFSF proteins usually have biological activities similar to other cytokines. Membrane-bound TNFSF ligands are type II transmembrane proteins (extracellular C-terminus) with short cytoplasmic domains and longer extracellular regions. Most TNFSF molecules are homotrimeric and share a common structural motif, the TNF homology domain (THD), which binds to the CRDs of TNFRs.

The interaction of TNFSF ligands with their receptors plays divergent and important roles in the regulation of cell growth, survival, and death. Abnormal expression of some family members results in a variety of pathophysiological states, including immune deficiency, autoimmune diseases, and enhanced tumor growth and metastasis. TNFRSF/TNFSF molecules have proven to be effective clinical therapeutic targets.

Nomenclature of the TNF Superfamily		
TNFSF Nomenclature	Molecular Aliases	Gene
TNFSF1	TNF- β , LT, LT- α	6p21.3
TNFSF2	TNF- α , TNF, cachectin, necrosin, cytotoxin	6p21.3
TNFSF3	LT- β , TNFC, LTB	6p21.3
TNFSF4	OX-40 ligand (OX-40L), gp34, TXGP-1, CD252	1q25
TNFSF5	CD40 ligand (CD40L), CD154, gp39, TRAP	Xq26
TNFSF6	Fas ligand (FasL), CD95L, CD178, ApoL	1q23
TNFSF7	CD70, CD27 ligand (CD27L), Ki-24	19p13
TNFSF8	CD30 ligand (CD30L), CD153	9q33
TNFSF9	4-1BB ligand (4-1BBL), CDw137L	19p13.3
TNFSF10	TRAIL, Apo-2 ligand (Apo-2L), TL2, CD253	3q26
TNFSF11	RANK ligand (RANKL), TRANCE, OPGL, ODF, CD254	13q14
TNFSF12	TWEAK, Apo-3 ligand (Apo3L), CD255	17p13
TNFSF12-13	TWE-PRIL	17p13.1
TNFSF13	APRIL, TALL2, TRDL-1, ZTNF2, TNFSF13A, CD256	17p13.1
TNFSF13B	BAFF, TALL1, zTNF4, THANK, Blys, DTL, CD257	13q32-34
TNFSF14	LIGHT, LTg, TR2, HVEM-L, CD258	19p13.3
TNFSF15	TL1, TL1A, VEGI	9q32
TNFSF18	AITRL, TL6, hGITRL	1q23

Nomenclature of the TNF Receptor Superfamily			
TNFRSF Nomenclature	Molecular Aliases	Signaling Adaptors	Gene
TNFRSF1A	TNFR type I, CD120a, TNFAR, p55TNFR, TNFR60	TRADD	12p13.2-p13.31
TNFRSF1B	TNFR type II, CD120b, TNFR80, p75TNFR, TNFBR	TRAF1,2,5	1p36.3-p36.2
TNFRSF3	TNFR III, LTBR, TNFCR, TNFR-RP, TNFR2-RP, CD18	TRAF3,4,5	12p13
TNFRSF4	OX-40, ACT35, TXGP1L, CD134	TRAF1,2,3,5	1p36
TNFRSF5	CD40, Bp50, p50	TRAF1,2,3,5,6	20q12-q13.2
TNFRSF6	Fas, CD95, APO-1, APT1, TNFRSF6A	FADD	10q24.1
TNFRSF6B	DcR3, TR6, M68	secreted	20q13
TNFRSF7	CD27, S152, Tp55, T14	TRAF2, SIVA	12p13
TNFRSF8	CD30, Ki-1	TRAF1,2,3,5	1p36
TNFRSF9	4-1BB, CDw137, ILA	TRAF1,2,3	1p36
TNFRSF10A	DR4, TRAIL-R1, APO-2, CD261	FADD	8p22
TNFRSF10B	DR5, TRAIL-R2, KILLER, CD262, TRICK2A, TRICKB	FADD	8p22-p21
TNFRSF10C	DcR1, TRAIL-R3, LIT, TRID, CD263		8p22-p21
TNFRSF10D	DcR2, TRAIL-R4, TRUNDD, CD264		8p21
TNFRSF11A	RANK, ODFR, TRANCE-R, CD265	TRAF1,2,3,5,6	18q22.1
TNFRSF11B	OPG, TR1, OCIF	secreted	8q24
TNFRSF12	DR3, TRAMP, APO-3, TRS, WSL-1, LARD, DDR3, WSL-LR	TRADD	1p36.3
TNFRSF12A	TWEAK-R, Fn14, FGF-inducible 14, CD266	TRAF1,2,3,5	16p13.3
TNFRSF12L	DR3L		1p36.2
TNFRSF13B	TACI, CD267	TRAF2,5,6	17p11
TNFRSF13C	BAFF-R, CD268, BR3	TRAF3	22q13.1-q13.31
TNFRSF14	HVEM, TR2, LIGHT-R, ATAR, HVEA	TRAF1,2,3,5	1p36.3-p36.2
TNFRSF16	NGF-R, NTR, p75NGFR, CD271	TRAF2,4,6	17q21-q22
TNFRSF17	BCMA, BCM, TNFRSF13, TNFRSF13a, CD269	TRAF1,2,3,5,6	16p13.1
TNFRSF18	AITR, GITR	TRAF1,2,3	1p36.3
TNFRSF19	TROY, TAJ, TAJ- α , TRADE	TRAF1,2,3,5	13q12.11-q12.3
TNFRSF19L	RELT	TRAF1	11q13.4
TNFRSF21	DR6, Death receptor 6	TRADD	6p21.1-12.2
TNFRSF22	SOBa; Tnfrh2, Tnfrsf1a12, mDcTrail2		
TNFRSF23	mSOB, Tnfrh1, mDcTrail1		

Interaction of TNF Superfamily Members and their Receptors	
Receptor	Ligands
TNFRSF1A	TNFSF1, TNFSF2
TNFRSF1B	TNFSF1, TNFSF2
TNFRSF3	TNFSF3, TNFSF14
TNFRSF4	TNFSF4
TNFRSF5	TNFSF5
TNFRSF6	TNFSF6
TNFRSF6B	TNFSF14, TNFSF15, TNFSF6
TNFRSF7	TNFSF7
TNFRSF8	TNFSF8
TNFRSF9	TNFSF9
TNFRSF10A	TNFSF10
TNFRSF10B	TNFSF10
TNFRSF10C	TNFSF10
TNFRSF10D	TNFSF10
TNFRSF11A	TNFSF11
TNFRSF11B	TNFSF11
TNFRSF12	TNFSF15, TNFSF12?
TNFRSF12A	TNFSF12
TNFRSF12L	
TNFRSF13B	TNFSF13B
TNFRSF13C	TNFSF13B
TNFRSF14	TNFSF14, TNFSF1, BTLA
TNFRSF16	NGF, BDNF, NT-3, NT-4
TNFRSF17	TNFSF13B, TNFSF13
TNFRSF18	TNFSF18
TNFRSF19	
TNFRSF19L	
TNFRSF21	
TNFRSF22	
TNFRSF23	