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Regulation of proliferation, survival and apoptosis by members of the TNF superfamily☆

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Abstract

Tumor necrosis factor (TNF) was first identified in 1984 as a cytokine with anti-tumor effects *in vitro* and *in vivo*. Extensive research since then has shown that there are at least 18 distinct members of the TNF super family and they exhibit 15–25% amino acid sequence homology with each other. These family members bind to distinct receptors, which are homologous in their extracellular domain. These cytokines have been implicated in a wide variety of diseases including tumorigenesis, septic shock, viral replication, bone resorption, rheumatoid arthritis, diabetes, and other inflammatory diseases. TNF blockers have been approved for human use in treating some of these conditions in the United States and other countries. Various members of the TNF super family mediate either proliferation, survival, or apoptosis of cells. Although distinct receptors, all members share a common cell signaling pathway that mediates the activation of nuclear factor-kappaB (NF-κB) and mitogen-activated protein kinases (e.g. c-*jun* N-terminal kinase). Regulation of cell growth and activation of NF-κB and of c-*jun* N-terminal kinase by the TNF super family is mediated through sequential activation/association of a set of cell signaling proteins named TNF receptor-associated factors, Fas-associated death domain and FADD-like ICE, caspases, receptor-interacting protein, NF-κB-inducing kinases, and IκBα kinases. Both apoptotic and antiapoptotic signals are activated simultaneously by the same cytokine in the same cell. Together these cytokines regulate cell growth/survival/apoptosis in a complex dance of changing partners and overlapping steps.

Other index terms: TNFR1 (TNFRSF1A), CD120a, p55; TNFR2 (TNFRSF1B), CD120b, p75; LT-βR (TNFRSF3), TNFR2-RP, TNFR-RP, TNFCR, TNF-R-III; OX-40 (TNFRSF4), ACT35, TXGPIL; CD40 (TNFRSF5), p50, Bp50; Fas (TNFRSF6), CD95, Apo-1, APT1; DcR3 (TNFRSF6B), TR6, M68; CD27 (TNFRSF7), Tp55, S152; CD30 (TNFRSF8), Ki-1, D1S166E; 4-IBB (TNFRSF9), CD137, ILA; DR-4 (TNFRSF10A), Apo-2, TRAILR-1; DR5 (TNFRSF10B), KILLER, TRICK2A, TRAIL-R2, TRICKB; DcR1(TNFRSF10C), TRID, TRAILR3, LIT; DcR2 (TNFRSF10D), TRUNDD, TRAILR4; RANK (TNFRSF11A), TR8; OPG (TNFRSF11B), OCIF, TR1, FDCR-1; DR3 (TNFRSF12), TRAMP, WSL-1, LARD, WSL-LR, DDR3, TR3, Apo-3; TACI (TNFRSF13); BAFF-R (TNFRSF13B); HVEM (TNFRSF14), TR2, ATAR, LIGHTR, HVEA; TR-1 (TNFRSF15); BCMA (TNFRSF17); AITR (TNFRSF18), GITR; TROY (TNFRSF19), TAJ, Apo-4, TRAIN-R, OAF065; DR6 (TNFRSF21), RELT, TANGO129, T129; EDAR, DL; LT (TNFSF1), LTα, TNF-β; TNF (TNFSF2), TNF-α, DIF; LTβ (TNFSF3), TNFC, p33; OX40L (TNFSF4), gp34, TXGP1; CD40L (TNFSF5), hCD40L, TRAP, CD154, gp39, CD40LG, IMD3, HIGM1; FasL (TNFSF6), Apo-1L, APT1LG1; CD27L (TNFSF7), CD70, CD27LG; CD30L (TNFSF8), CD30LG; 4-1BBL (TNFSF9); TRAIL (TNFSF10), Apo-2L, TL2; RANKL (TNFSF11), TRANCE, OPGL, ODF; TWEAK (TNFSF12), DR3LG, Apo-3L; APRIL (TNFSF13),

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Abbreviations: APRIL, a proliferation inducing ligand; BAFF, B cell activating factor; BCMA, B cell maturation antigen; Blys, B lymphocyte stimulator; c-FLIP, cellular Flice inhibitory protein; cIAP, cellular inhibitors of apoptosis; COX-2, cycloxygenase-2; DC, dendritic cells; DcR, decoy receptor; DD, death domain; DED, death effector domain; DR, death receptor; EST, expression sequence tag; EDA, ectodermal dysplasin; EDAR, ectodyplasin-A-receptor; FADD, Fas-associated death domain; FLICE, FADD-like ICE; GITR, glucocorticoid-induced tumor necrosis factor receptor family receptor; HVEM, Herpes virus entry mediator; ICE, interleukin-1 converting enzyme; IKK, IκBα kinase; JNK, c-*jun* N-terminal kinase; LIGHT, ligand for HVEM; LT, lymphotoxin; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-kappaB; NIK, NF-κB-inducing kinase; OPG, osteoprotegrin; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; RIP, receptor-interacting protein; RELT, receptor expressed in lymphoid tissues; ROI, reactive oxygen intermediates; SODD, silencer of death domain; TACI, transmembrane activator and cyclophilin ligand interactor; TALL-1, TNF and ApoL related leukocyte expressed ligand; t-BID, truncated form of BID; THANK, TNF homologue that activates apoptosis; TNF, tumor necrosis factor; TNFR2, tumor necrosis factor receptor-2; TRADD, TNF receptor associated death domain; TRAF, TNF receptor-associated factor; TRAIL, TNF-related death inducing ligand; TWEAK, TNF like weak inducer of apoptosis; VEGI, vascular endothelial growth inhibitor; XEDAR, X-linked ectodermal dysplasia receptor; XIAP, X-chromosome linked inhibitor of apoptosis protein.

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TRDL-1; BAFF (TNFSF13B), THANK, Blys, TALL-1, zTNF4; LIGHT (TNFSF14), LTγ, HVEM-L; VEGI (TNFSF15), TL1, TL1A; AITRL (TNFSF18), TL6, hGITRL

Keywords: NF-κB; TNF; Apoptosis; Antiapoptosis; Proliferation; TRAIL

In the past half century it has been a general belief that cytokines/factors/molecules, which can selectively kill tumor cells, have a therapeutic potential in the treatment of cancer. In 1968, Dr. Gale A. Granger from the University of California, Irvine, reported a cytotoxic activity produced by lymphocytes and named it lymphotoxin (LT). Similarly, in 1975 Dr. Lloyd Old from Sloan-Kettering Memorial Cancer Center, New York, reported another cytotoxic activity most likely produced by macrophages, and named it TNF [1,2]. Both activities were described based on their ability to kill murine fibrosarcoma L-929 cells.

Human LT was the first cytotoxic cytokine purified to homogeneity from B lymphoblastoid cell line [3]; its structure was determined by classical protein sequence methods [4]. Neutralization of LT activity by antibodies to LT led to the isolation of a second cytotoxic factor from human myeloid cell line named TNF [5]. The determination of the amino acid sequence of TNF revealed that the two proteins were homologous [5]. The binding of TNF to its receptor and its displacement by LT further confirmed the functional homology between the two proteins [6]. Once most of the protein sequence was identified the cDNAs of LT and of TNF were isolated [7,8]. The structural and functional homology between TNF and LT lead to the renaming of the TNF and LT as TNF-α and TNF-β, respectively. These two cytokines laid the foundation for much larger family of cytokines, now named the TNF superfamily. Expression cloning and expression sequence tags (ESTs), have lead to the identification of 19 different members of this family (see Table 1). Vascular endothelial growth inhibitor (VEGI) and TNF homologue that activates apoptosis (THANK) are the latest members of this family to be identified [9,10]. Individual investigators, have given each member of the TNF superfamily numerous names. For instance, THANK is also called B lymphocyte stimulator (Blys), B cell activating factor (BAFF), and TALL-1. HGNC Gene Family Nomenclature (http://www.gene.ucl.ac.uk/nomenclature/genefamily/tnftop.html) has attempted to streamline the nomenclature of these cytokines in a more systematic manner. New ligands and receptors are numbered consecutively, starting at TNFSF19 or TNFRSF19, unless their symbols are already implied by the scheme, e.g. TNFRSF13, TNFRSF15, TNFSF16, and TNFSF17. The symbols in this table are linked to other databases where further information is available. For more detail, the reader is referred to two recent reviews [11,12].

Various members of the TNF superfamily have been shown to regulate apoptosis (a mode of cell death identified well after the discovery of TNF), proliferation, survival, and differentiation of cells. How these cytokines regulate these processes is not fully understood. Cellular receptors for 19 members of the TNF superfamily have been identified [11,12] (Table 1). One ligand has been found to bind to as many as five different receptors. For instance TRAIL has

Table 1
Regulation of apoptosis and proliferation of cells by members of the TNF superfamily

Ligand	Receptor	Apoptosis	Proliferation	NF-κB	JNK	p42MAPK	p38MAPK
TNF-α	TNFR1, R2	+	+	+	+	+	+
LTα	TNFR1, R2	+	+	+	+	+	+
FasL	Fas	+	−	+	+	−	−
VEGI	DR3	+	−	+	−	−	−
TRAIL	DR4, DR5	+	−	+	+	−	−
LTβ	LT-βR	+	+	+	−	−	−
CD27L	CD27	+	+	+	+	+	−
CD30L	CD30	+	+	+	+	−	−
4-1BBL	4-1BB	+	−	+	+	−	−
TWEAK	Fn 14	+	+	+	+	−	−
LIGHT	LT-βR, HVEM	+	+	+	−	−	−
CD40L	CD40	−	+	+	+	−	−
OX40L	OX-40	−	+	+	−	−	−
RANKL	RANK	−	+	+	+	+	+
APRIL	TACI	−	+	+	+	−	−
BAFF	TACI, BCMA	−	+	+	+	−	−
GITRL	GITR	−	+	+	−	−	−
EDA-A1	EDAR	+	−	+	+	−	−
EDA-A2	XEDAR	−	−	+	−	−	−
?	TROY	−	+	+	−	−	−
?	DR6	−	−	+	+	−	−
?	RELT	?	+	+	?	?	?

been shown to bind DR4, DR5, DcR1, DcR2 and OPG, whereas receptor activator of NF-κB ligand (RANKL) has been shown to bind receptor activator of NF-κB (RANK) and OPG. Why there are multiple receptors for the same ligand is not fully understood. DcR1, DcR2, DcR3 (binds FasL and LIGHT) and OPG are the decoy receptors (DcRs) which have been shown to dampen the cytokine response. No ligand has yet been identified for DR6, TROY and receptor expressed in lymphoid tissues (RELT).

As many as 30 different members of the TNF receptor superfamily have been identified, and these receptors are of two types; those with the death domain (DD) in the cytoplasmic portion of the receptor and others without a DD. There are six different DD-containing receptors; with FasL binding to DR1, TNF to DR2, VEGI to DR3, and TRAIL to DR4 and DR5. The ligand for DR6 is unknown at present. DD is the domain that recruits other cell-signaling proteins. For instance TNF receptor 1 (also called DR2) sequentially recruits TRADD, Fas-associated death domain (FADD), FADD-like ICE (FLICE), and caspase-3, leading to apoptosis (see Fig. 1). DD in Fas (also called DR1) and TRAIL receptors (DR4 and DR5) directly recruit FADD and FLICE also leading to apoptosis. An alternate pathway for apoptosis has been described which is independent of TRADD, FADD, and FLICE but is dependent on activation of mitochondria leading to sequential caspase-9 and caspase-3 activation. How receptors that lack DD domains (and are thus unable to recruit TRADD-FADD-FLICE) mediate apoptosis remains to be determined. For instance it has been shown that overexpression of TNFR2 which lacks a DD can mediate apoptosis ([13] and references therein).

The cell types that express at their surface or secrete various members of the TNF superfamily are shown in Table 2. Most of these cytokines are produced by the cells of the immune system, indicating their role in immune regulation. Various cell types that express receptors for different members of the TNF superfamily are also indicated in Table 2. Not all the cell types that express receptors respond to the ligands. For instance high-affinity TNFR1 receptors are expressed in all cell types, and yet only very selected cells respond to TNF for growth modulation [14]. Why some cells respond while others do not remains to be understood. Interestingly, however, all cell types respond to TNF for NF-κB activation which mediates antiapoptosis. The precise basis for this differential signaling is not yet known.

Another characteristic feature of all members of the TNF superfamily is that they all activate NF-κB (see Table 1), a transcription factor that has been implicated in suppression of apoptosis, cell survival, proliferation, viral replication, inflammation, bone resorption, tumorigenesis, and metastasis (for references see [15]). The activation of NF-κB by TNF and other members of the TNF family is mediated through recruitment of TNF receptor-associated factors (TRAFs). Six different TRAFs have been identified. Different TRAFs are recruited by different TNF receptors to activate NF-κB. For instance TRAF2 is recruited by TNFR1 to activate NF-κB by TNF; whereas TRAF2, TRAF5, and TRAF6 are recruited by RANK to activate

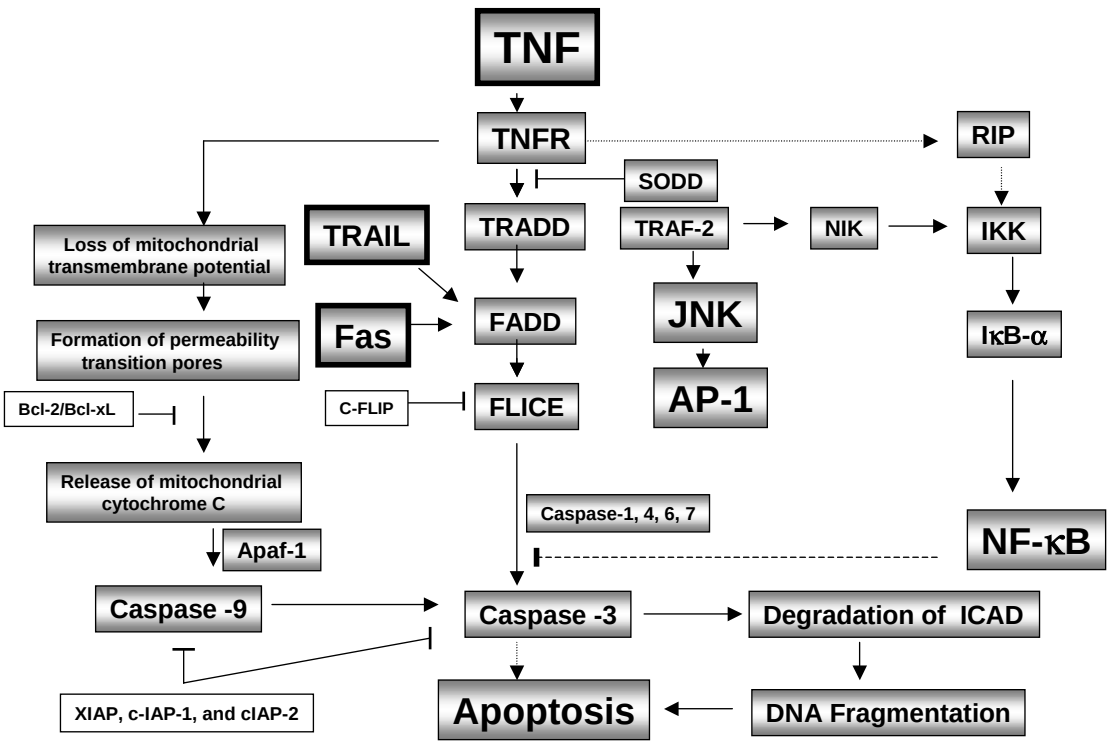

Fig. 1. TNF cell signaling pathway leading to apoptosis, survival and proliferation. XIAP, c-IAP-1, and cIAP-2 have been shown to inhibit caspase-3, -7 and -9. Survivin binds an IAP-inhibiting protein, Smac/DIABLO, thus releasing IAP to suppresses caspases.

Table 2
Cellular expression of ligands and receptors of the members of the TNF superfamily

Cytokine	Cells	Receptor	Cells
LTα	NK, T, and B cells	TNFR1	All cells
		TNFR2	Endothelial cells, immune cells
TNF-α	NK, T, and B cells	TNFR1, TNFR2	See above
LTβ	T cells, B cells, NK cells, DC, macrophages	LT-βR	NK, $CD4^+$ $CD8^+$ T cells
FasL	Activated T cells and non-T cells	Fas	Nucleated cells
		DcR3	Lung and colon cells
TRAIL	Lymphocytes, DC cells	DR4, DR5, DcR1, DcR2	Most cells
TWEAK	Monocytes	Fn 14	Endothelial cells, fibroblasts
4-IBBL	B cells, dendritic cells, macrophages	4-IBB	Activated T cells, monocytes and NK cells
OX40L	T and B cells	OX-40	T cells
CD40L	T and B cells	CD40	Reed-Sternberg cells
CD27L	NK, B, and T cells	CD27	$CD4^+$ $CD8^+$ T cells
CD30L	T cells, monocytes	CD30	Reed-Sternberg cells
APRIL	Secondary lymphoid organs	BCMA, TACI	B and T cells
Blys	T cells, DC cells	TACI, BCMA	See above
	Monocytes, macrophages	BAFF-R	B cells
LIGHT[a]	T cells, granulocytes, monocytes, DC cells	HVEM	T lymphoid cells
		LT-βR	Nonlymphoid hematopoietic cells, and stromal cells
VEGI[a]	Endothelial cells	DR3	Activated T cells
GITRL		GITR	$CD25^+$ $CD4^+$ T cells
RANKL	Activated T cells, osteoblasts	RANK	Osteoclast precursors
		OPG	Osteoclast precursors, endothelial cells, others
EDA-1	Skin	EDAR	Ectodermal derivative
EDA-2	Skin	XEDAR	Ectodermal derivative
?		DR6	Resting T cells
?		RELT	Lymphoid tissues
?		TROY	Embryo skin, epithelium, hair follicles and brain

[a] Binds to DcR3/TR6; both TNF-α and LTα binds to TNFR1 and TNFR2; THANK (also called TALL-1, BAFF, Blys, zTNF4); VEGI is also called TL1 and TL-1a is a longer variant of TL-1; TROY is also called TAJ.

NF-κB by RANKL [16,17]. Just how TRAFs mediate NF-κB activation has not been established. TRAF2 has been shown to interact with NIK ([18]; see Fig. 1). Both NIK and IκBα kinase (IKK) have been implicated in NF-κB activation by TNF and other family members. Gene deletion studies, however, indicated that NIK is not required for NF-κB activation by TNF but is required for NF-κB activation by LTβ, RANKL, and CD40L [19,20].

Genes that are regulated by NF-κB have been shown to suppress apoptosis. Thus cytokines such as TNF activate both apoptosis and antiapoptosis pathways (see Fig. 2). NF-κB activation usually precedes the apoptotic effects of

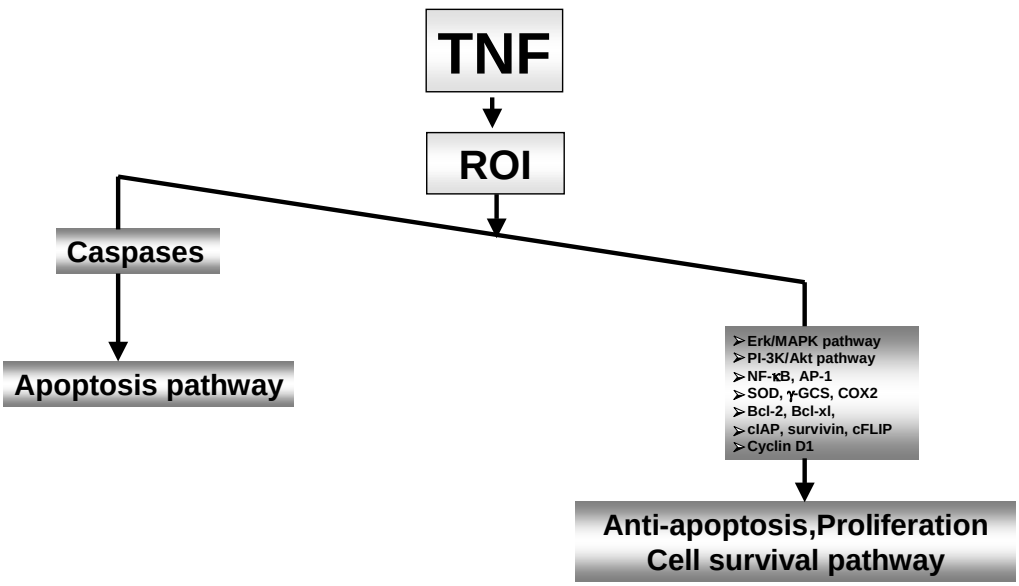

Fig. 2. Members of the TNF superfamily can activate apoptosis and survival signals.

TNF. While TNF activates NF-κB in all cell types, it very rarely induces apoptosis. This may be related to the ability of NF-κB to suppress apoptosis and may also explain why the presence of protein synthesis inhibitors such as cycloheximide can sensitize the cells to TNF-induced apoptosis [3–8]. It may also explain why some members of the TNF superfamily induce apoptosis, whereas others act as survival factors or induce cell proliferation.

Several mechanisms by which TNF superfamily members suppress apoptosis have been described (Table 3). These include DcRs, activation of transcription factors, cellular inhibitors of apoptosis (cIAP) (which inhibit caspases), bcl-2 family members (which inhibit cytochrome c release), cellular Flice inhibitory protein (c-FLIP, which binds to FLICE), and activation of antioxidant enzymes and of other alternate cell survival pathways. Interestingly, however, both apoptotic and antiapoptotic effects of TNF are mediated through the generation of reactive oxygen intermediates (ROI), since transfection of cells with either superoxide dismutase or γ-glutamylcystinyl synthase suppresses activation of both apoptosis and NF-κB activation [21,22].

Table 3
Potential mechanisms of suppression of apoptosis induced by members of the TNF superfamily

Binding	Binding partner/affector/product
Decoy receptors	
DcR1	TRAIL
DcR2	TRAIL
DcR3	FasL, LIGHT, LTβ, VEGI
OPG	TRAIL, RANKL
Transcription factors	
NF-κB	XIAP, cIAP, survivin, cFLIP, Bcl-xl, COX-2
AP-1	COX-2
Inhibitors of caspase activation	
XIAP	Caspase-9, caspase-3, caspase-7
cIAP-1	Caspase-9, caspase-3, caspase-7; TRAF-1
cIAP-2	Caspase-9, caspase-3, caspase-7; TRAF-1
Survivin	Caspase-9, caspase-3, caspase-7
Smac/DIABLO	IAP
Inhibitors of mitochondrial cytochrome *c* release	
Bcl-2, Bcl-xL	t-BID
Inhibitor of caspase-8	
cFLIP	Caspase-8 (FLICE)
Antioxidant enzymes	
MnSOD	$^1O_2$
γ-GCS	GSH
Thioredoxin	
COX-2	PGE_2
Others	
Phosphatidyl inositol-3/AkT pathway	
Mitogen-activated protein kinase pathway	

DcR3 is also called TR6; DcR3 and OPG are homologous; Smac, second mitochondria-derived activator of caspase; DIABLO, direct IAP-binding protein with low pI; Apaf-1, apoptotic protease activating factor-1; Bcl-2, B cell leukemia/lymphoma-2.

Table 4
Gaps in the understanding of TNF cell signaling

TNF and its family members activate both apoptosis and antiapoptosis pathways simultaneously
Transfection with TRAF2 activates NF-κB, DN-TRAF2 inhibits TNF-induced NF-κB activation but TRAF2-deleted cells are normal for TNF-induced NF-κB activation. Fas and TRAIL can activate NF-κB without recruitment of TRAFs
NIK transfection activates NF-κB, DN-NIK inhibits TNF-induced NF-κB activation but NIK-deleted cells are normal for TNF-induced NF-κB activation
Apoptosis can be mediated by receptors of the TNF superfamily which lack death domain responsible for recruiting TRADD-FADD-FLICE
Almost all members of the TNF family induce apoptosis of some cells and proliferation of others

While much has been learned about the mechanism by which various members of the TNF superfamily signal for apoptosis, proliferation and survival, much remains unknown (see Table 4). For instance, it is not clear why some cells undergo apoptosis in response to TNF and not others. While TRAF2 and NIK overexpression activate NF-κB, their dominant negative form inhibits TNF-induced NF-κB activation, and these proteins interact with the TNF receptors, yet cells with genetic deletion of either NIK or TRAF2 respond to TNF for NF-κB activation. Similarly, it is not known why FasL and TRAIL activate NF-κB only in some cells but not others. How receptors that lack DD mediate either NF-κB activation or growth modulation is also unclear. Recent evidence from our laboratory indicates that both TNF receptors are required for optimum signaling by TNF [23]. This suggests a synergy between various receptors.

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