Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

The Tumor Necrosis Factor Family: Family Conventions and Private Idiosyncrasies

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The tumor necrosis factor (TNF) cytokine family and the TNF/nerve growth factor (NGF) family of their cognate receptors together control numerous immune functions, as well as tissue-homeostatic and embryonic-development processes. These diverse functions are dictated by both shared and distinct features of family members, and by interactions of some members with nonfamily ligands and coreceptors. The spectra of their activities are further expanded by the occurrence of the ligands and receptors in both membrane-anchored and soluble forms, by "re-anchoring" of soluble forms to extracellular matrix components, and by signaling initiation via intracellular domains (IDs) of both receptors and ligands. Much has been learned about shared features of the receptors as well as of the ligands; however, we still have only limited knowledge of the mechanistic basis for their functional heterogeneity and for the differences between their functions and those of similarly acting cytokines of other families.

The study of protein families and their individual members contribute cooperatively to the assembly of knowledge, providing insights into the features shared by family members as well as their distinctive features. The benefit of such a cooperative endeavor is lavishly demonstrated by the huge advances in understanding the mechanisms of action of the tumor necrosis factor (TNF) ligand and TNF/nerve growth factor receptor (NGFR) families. The founding members of these families—the cytokine TNF and the low-affinity NGFR—were isolated and cloned three decades ago (Old 1985; Johnson et al. 1986; Radeke et al. 1987). In this review, I will present a brief overview of the knowledge of common structural, mechanistic, and functional features of the TNF ligand and TNF/NGFR families. I will also refer to interactions that are known for only a few family members, but whose occurrence raises the possibility that other family members participate in similar associations.

THE WIDE RANGE OF FUNCTIONS OF THE TNF FAMILY

There are 18 known human genes for the TNF ligand family and 29 for the TNF/NGFR family (see genenames.org/genefamilies/TNFSF and genenames.org/genefamilies/TNFRSF; see Table 1 for their major known functions). Practically, all cells in the body express receptors, and many also express some of the ligands of these families. Each receptor–ligand pair controls a wide range of cellular activities. Assessing the impact of functional arrest of specific members of the TNF and TNF/NGF families has revealed some key physiological roles served ex-

Editors: Warren J. Leonard and Robert D. Schreiber
Additional Perspectives on Cytokines available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a028431
Cite this article as *Cold Spring Harb Perspect Biol* 2018;10:a028431

Table 1. Principal known functions of receptors of the tumor necrosis factor (TNF)/nerve growth factor receptor (NGFR) family and ligands of the TNF family

Receptor			Ligand			
Widely used name	Formal name	Other names	Widely used name	Formal name	Other names	Main known functions of the receptor
TNFR1	TNFRSF1A	p55, CD120a	TNF	Tumor necrosis factor		Orchestration of inflammation; cell killing
			LT	Lymphotoxin α		
TNFR2	TNFRSF1A	p75, CD120b	TNF	Tumor necrosis factor		Costimulation of T lymphocytes (information on various other functions is sporadic)
			LT	Lymphotoxin		
Fn14	TNFRSF12A	TweakR	TWEAK	TNFSF12	APO3L	Control of tissue regeneration in response to injury; inflammation
DR3	TNFRSF12	TRAMP, WSL-1, APO-3	TL1	TNFSF15	TL1A, VEGI	Costimulation of T lymphocytes; inflammation
FAS	FAS	APO-1, CD95	Fas ligand	FASL, Fas ligand	CD178	Cell killing; cell growth; inflammation
DcR3	TNFRSF6B	TR6	Fas ligand, LIGHT, TL1			Secreted decoy receptor that blocks the function of the three indicated ligands; seems also capable of triggering signaling through its binding to HSPG
TRAIL-R1	TNFRSF10A	Apo2, DR4	TRAIL	TNFSF10	Apo-2L, CD253	Cell killing
TRAIL-R2	TNFRSF10B	DR5	TRAIL	TNFSF10		Cell killing
DcR1	TNFRSF10C	TRAILR3	TRAIL	TNFSF10		GPI-linked decoy receptor restraining the function of TRAIL
DcR2	TNFRSF10D	TRAILR4	TRAIL	TNFSF10		Transmembrane truncated decoy receptor restraining the function of TRAIL
LTβR	LTβR (lymphotoxin β receptor)		LTα1β2 (lymphotoxin β [LTβ] in complex with lymphotoxin α), LIGHT	LTβ TNFSF14	 CD258	Development and function of lymphoid organs; amplification of antiviral response and various other innate and adaptive immune functions

Continued

Table 1. *Continued*

Receptor			Ligand			
Widely used name	Formal name	Other names	Widely used name	Formal name	Other names	Main known functions of the receptor
HVEM	TNFRSF14	ATAR, CD270	LIGHT LT (weak binding)	TNFSF14		Costimulation in T and B lymphocytes and in NK cells; triggering of immunosuppression through BTLA, and immunosuppression, inflammation, and NK activation through CD160
OX40	TNFRSF4	CD134	OX40 ligand (OX40L)	TNFSF4	CD252	Costimulation of T lymphocytes
CD27	TNFRSF7		CD70	CD70	CD27 ligand	Costimulation of T lymphocytes
CD30	TNFRSF8		CD30 ligand (CD30L)	TNFSF8		Costimulation of T lymphocytes
4-1BB	TNFRSF9	CD137	4-1BB ligand (4-1BBL)	TNFSF9		Costimulation of T lymphocytes
GITR	TNFRSF18	AITR, CD357	GITR ligand (GITRL)	TNFSF18	AITR	Costimulation of T lymphocytes
RELT	RELT		?			Unknown
CD40	TNFRSF5		CD40 ligand (CD40L)	CD40LG	CD154	Wide range of effects contributing to initiation and progression of adaptive immunity
TACI	TNFRSF13B	CD267	BAFF APRIL	TNFSF20 TNFSF13	BLYS, CD257 CD256	B-lymphocyte growth, survival, and differentiation; costimulation of T lymphocytes
BAFFR	TNFRSF13C	CD268	BAFF			B-lymphocyte survival, growth, and differentiation
BCMA	TNFRSF17	CD269	BAFF APRIL			B-lymphocyte survival, growth, and differentiation
RANK	TNFRSF11A		RANK ligand (RANKL)	TNFSF11	RANKL, TRANCE, OPGL, CD254	Osteoclast differentiation and activation; mammary gland development; development of lymph nodes; various immune functions
OPG	TNFRSF11B	OCIF, TR1	RANK ligand TRAIL			Secretory decoy receptor that blocks the functions of RANKL and TRAIL; seems also capable of triggering signaling through its binding to HSPG

Continued

Table 1. *Continued*

Receptor			Ligand			
Widely used name	Formal name	Other names	Widely used name	Formal name	Other names	Main known functions of the receptor
EDAR	EDAR (ectodysplasin A receptor)	EDA1R	EDA	EDA (ectodysplasin A)		Embryonic development of ectodermal appendages
XEDAR	EDA2R (ectodysplasin A2 receptor)		EDA-A2 (a shorter splice variant of the EDA gene)			Unknown
NGFR	Nerve growth factor receptor	p75NTR, CD271	Neurotrophins; myelin-associated inhibitory factors; fragments of β-amyloid precursor protein; prion peptide			Neuronal growth and death; arrest of axonal degeneration; pain sensation
TROY	TNFRSF19	TAJ	Myelin-associated inhibitory factors			Repression of axonal regeneration
DR6	TNFRSF21	CD358	?			Probably contributes to amyloid-β-induced axonal pruning

TWEAK, TNF-related weak inducer of apoptosis; HSPG, heparan sulfate proteoglycan; TRAIL, TNF-related apoptosis-inducing ligand; GPI, glycosylphosphatidylinositol; HVEM, herpesvirus entry mediator; NK, natural killer; BTLA, B- and T-lymphocyte attenuator; GITR, glucocorticoid-induced TNFR-related protein; AITR, activation-inducible TNFR family receptor; RELT, receptor expressed in lymphoid tissue; TACI, transmembrane activator and calcium-modulating cyclophilin ligand interactor; BAFF, B-cell-activating factor of the tumor necrosis factor family; APRIL, a proliferation-inducing ligand; BCMA, B-cell maturation antigen; RANK, receptor activator of nuclear factor κB; OPG, osteoprotegerin; EDA, ectodermal dysplasia.

clusively by them. Listed below and briefly discussed are the functions of family members that have attracted the greatest attention, either because they appear to be unique to the family or because of known pathological consequences of their deficiency or hyperactivity.

Control of Cell Survival

Stimulation of Cell Death

The ability of certain ligands of the TNF family to trigger death of cells independently of protein synthesis was the family's first cellular effect to be described (Granger and Kolb 1968; Ruddle and Waksman 1968), and to this day it remains the only function not known to be shared with other cytokines. Several TNF family receptors (TNFR1, DR3, FAS, TNF-related apoptosis-inducing ligand [TRAIL]-R1, TRAIL-R2) trigger rapid cell death. Others signal for cell death less effectively, either through induction of TNF (Grell et al. 1999; Burkly 2014) or by poorly defined cell-autonomous mechanisms (Force et al. 2000; Georgopoulos et al. 2006; Elmetwali et al. 2010).

The cytotoxic functions of the TNF family contribute to immune-mediated cell killing. They also seem to contribute to the control of expansion and to the duration of activities of immune-cell populations and to the shaping of leukocyte repertoires (Falschlehner et al. 2009; Strasser et al. 2009).

Providing Survival Signaling

One way in which the TNF family members facilitate maintenance and amplification of immune responses is by providing the relevant cells with survival signals. Best documented are the crucial roles of several members of the family in maintaining the survival of B and T lymphocytes (Croft 2014; Figgett et al. 2014). TNF family members are also capable of inducing resistance of cells to the cytotoxic activities that they themselves activate (e.g., Wallach 1984; Hahn et al. 1985; Blomberg et al. 2008; Chen et al. 2010; Jeon et al. 2015).

Orchestration of Inflammation

The best-documented pivotal role of a ligand of the TNF family in pathological disorders is the contribution of TNF to chronic inflammatory diseases. This has been demonstrated by the therapeutic effects of TNF-blocking agents observed in millions of patients, as well as in experimental animal models for both chronic and acute inflammatory diseases (Tracey et al. 1987; Apostolaki et al. 2010; Sfikakis 2010). TNF contributes to the initiation, progression, and termination of inflammation, while displaying antagonistic effects: for example, induction of cell death but also cell growth and resistance to cell death, and obstruction and destruction of capillaries but also stimulation of angiogenesis. TNF is also an important player in systemic manifestations of inflammation, for example, in activating the acute-phase response in the liver (Wallach and Kovalenko 2016).

Also contributing to inflammation, although in more restricted ways, are several TNF family ligands, including TKA1, TNF-related weak inducer of apoptosis (TWEAK), TRAIL, CD40L, LIGHT, and receptor activator of nuclear factor (NF)-κB ligand (RANKL), which are known primarily for other functions.

Tissue Modeling

Tissue Remodeling in Response to Injury

Like TNF, TWEAK exerts a wide range of antagonistic effects on cell functions; it contributes to both inflammation and its arrest, as well as to both destruction and regeneration of tissues. It thus serves important roles in coordinating tissue remodeling in response to injury (Burkly 2014).

Bone Homeostasis

Calcified bone matter undergoes constant turnover as a result of the antagonistic effects of osteoblasts, which construct bones, and osteoclasts, which resorb them. Local inflammation in the bone facilitates bone destruction. RANKL serves a crucial role in maintaining the constitutive activity of the osteoclasts. Its soluble re-

ceptor, osteoprotegerin (OPG), blocks RANKL function by competing for the binding of RANK (Boyce and Xing 2007; Walsh and Choi 2014). CD40L potentiates this inhibition via several effects, including induction of OPG in B lymphocytes (Li et al. 2007). In contrast, TNF enhances bone dissolution. It does this by triggering the egress of osteoclast precursors from the bone marrow as well as by enhancing RANKL generation and triggering osteoclast differentiation and activation synergistically with this ligand as well as with the non-TNF family cytokine interleukin (IL)-1 (Li et al. 2004).

Control of the Development of Ectodermal Tissues

Ectodysplasin (EDA) and its receptor EDAR are the only known ligand–receptor pair within the TNF families that seems to make no contribution to immune regulation. They signal for embryonic development of ectodermal appendages such as the hair, teeth, and sweat glands. This role is evolutionarily conserved in other metazoan phyla in which EDA and its receptor control the development of ectodermal appendages such as feathers, scales, and fins (Lefebvre and Mikkola 2014).

EDA-A2, a slightly shorter splice variant encoded by the *Eda* gene, binds to a distinct receptor of the TNF/NGF family, XEDAR. Although expressed in the developing hair follicle, this receptor does not seem to be required for hair growth. Limited evidence suggests that it might serve to control skeletal muscle homeostasis (Lefebvre and Mikkola 2014). TROY, an orphan receptor of the TNF/NGF family, is also coexpressed with EDAR in hair follicles and in embryonic skin, but its function at these sites is not known (Kojima et al. 2000).

Control of Adaptive Immunity

Elicitation of an adaptive immune response necessitates fine-tuning of the development of lymphocytes and of their interaction with antigen-presenting cells as well as regulation of the development and function of specific organs in which these processes occur. In all of these functions, members of the TNF family play pivotal roles.

Control of the Generation and Maintenance of Lymphoid Organs

Embryonic development of the secondary lymphoid organs crucially depends on signaling by lymphotoxin β receptor (LTβR) and RANK. Both LTβR-triggered and TNF-triggered signaling are required for maintenance of the microarchitecture of the lymphoid organs and their appropriate function in the adult (Ware 2005; McCarthy et al. 2006). Both are also required for the neogenesis of lymphoid assemblages at sites of chronic inflammation (Drayton et al. 2006). A similar "morphogenic" role is served by TNF in dictating the generation of granuloma (Kindler et al. 1989).

Control of the Development and Function of T Lymphocytes

Signaling by several TNF/NGF family receptors, including TNFR1, LTβR, RANK, herpesvirus entry mediator (HVEM), OX40, and CD40, controls the migration, maturation, and activation of dendritic cells (Ware 2005; Summers deLuca and Gommerman 2012; Walsh and Choi 2014). Signaling by receptors of the TNF/NGF family contributes to the selection of lymphocytes in the thymus. TNFR1, TNFR2, DR3, HVEM, OX40, CD27, CD30, 4-1BB, B-cell-activating factor of the tumor necrosis factor family (BAFF), and transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) provide costimulatory signals in antigen-stimulated T lymphocytes. Some of those receptors also initiate stimulatory signals in T lymphocytes whose antigen receptors have not been activated. These stimulatory signals enhance lymphocyte survival, growth, and effector functions. The various costimulatory family members apparently serve distinct roles at different phases of T-lymphocyte response, and the relative contribution of their costimulatory effects to defense varies depending on the nature of the particular pathogenic challenge (Croft 2014; Mbanwi and Watts 2014).

Control of the Development and Function of B Lymphocytes

Activation of the TNF/NGF family receptors BAFFR, B-cell maturation antigen (BCMA), TACI, and CD40 provide B lymphocytes with survival and growth signals at distinct stages of their development. CD40 signaling is crucially required also for antibody isotope switching and for the generation of memory B lymphocytes. Various other TNF/NGF family members also affect B-cell biology (Bishop and Hostager 2003; Dillon et al. 2006; Elgueta et al. 2009; Figgett et al. 2014).

Functions of the TNF Family in the Brain

At times of injury or autoimmune response within the brain, the affected cells display the same modes of TNF family–induced regulation as those observed in such situations elsewhere in the body (Akassoglou et al. 1999; Shohami et al. 1999). Some of these cytokine effects result in tissue damage. However, TNF also provides protective and survival signals in nervous tissue, in part through TNFR2 (Bruce et al. 1996; Fontaine et al. 2002). Effects of TNF on brain functions contribute to several behavioral responses to disease, including enhanced slow-wave sleep (Shoham et al. 1987), fever (Dinarello et al. 1986), anorexia (Cerami et al. 1985; Plata-Salaman et al. 1988), increased pain perception (Hess et al. 2011), and others (Dantzer 2001). Fever induction by TNF, as well as by several other inflammatory cytokines, is triggered indirectly through induction of RANK-mediated signaling in astrocytes (Hanada et al. 2009).

Emerging knowledge indicates that TNF family members also contribute to brain functions unrelated to immune defense. TNF produced by glial cells stabilizes neuronal circuits by dictating homeostatic synaptic scaling (Stellwagen and Malenka 2006). Some evidence indicates that FAS signals for neurogenesis in the adult brain (Corsini et al. 2009). The receptor DR3 is expressed in motor neurons and its tonic signaling seems to be necessary for their survival (Richard et al. 2015).

The function of NGFR, a TNF/NGF family receptor for which no ligand of the TNF family is known, serves cooperatively with several co-receptors to control the growth and survival of neurons in response to simulation by several ligands and also to control pain sensation (Hempstead 2002; Chao 2003; Ibanez and Simi 2012). Limited evidence suggests that TROY and DR6, additional members of the TNF/NGFR family not known to bind any ligand of the TNF family, also serve to signal for neuronal death (Shao et al. 2005; Nikolaev et al. 2009; Olsen et al. 2014).

TRIGGERING OF SIGNALING: INDUCED JUXTAPOSITION

Members of the TNF ligand and TNF/NGFR families share conserved extracellular motifs by which they bind each other. With the exception of lymphotoxin (LT), a secretory protein, all ligands are produced as type II transmembrane (TM) proteins in which the receptor-binding motif, whose structure consists of two packed sheets of eight antiparallel β strands, is located at the carboxyl terminus. Most ligands also occur in soluble forms, generated by proteolytic processing of the TM forms to yield soluble ligand-binding molecules. Both in their membrane-bound and in their soluble forms, the ligand molecules associate constitutively in trimers.

The receptors are produced as type I TM proteins, whose amino-terminal ligand-binding motif consists of a variable number of two conserved modules that together form a 40-amino-acid structure containing several cysteines, the "cysteine-rich domain" (CRD).

Distinct parts of receptors' extracellular domains (EDs) serve opposing roles in controlling signaling. The amino-terminal CRD serves as a "pre-ligand assembly domain" (PLAD), which safeguards against ligand-independent signaling (Chan 2007). In the absence of ligands, the PLADs in the EDs of three or (more likely) two (Naismith et al. 1995) receptor molecules associate in a way that keeps their intracellular domains (IDs) apart. In contrast, ligand binding, which occurs downstream from the PLAD, im-

poses juxtaposition of the receptor IDs. In receptors whose IDs contain a death domain (DD) (see below), such juxtaposition is fostered by the propensity of the DD to self-associate (Boldin et al. 1995). Proline-containing motifs found in the transmembrane domain (TD) in FAS, and apparently also in the other receptors of the family, also tend to self-associate (forming homotrimers), further strengthening the ligand-binding effect (Fu et al. 2016).

Juxtaposition of the IDs of the receptors exposes their binding surfaces to signaling proteins. Their binding to the receptors and consequent juxtaposition triggers their enzymatic activity and/or their association with downstream signaling proteins (Fig. 1A).

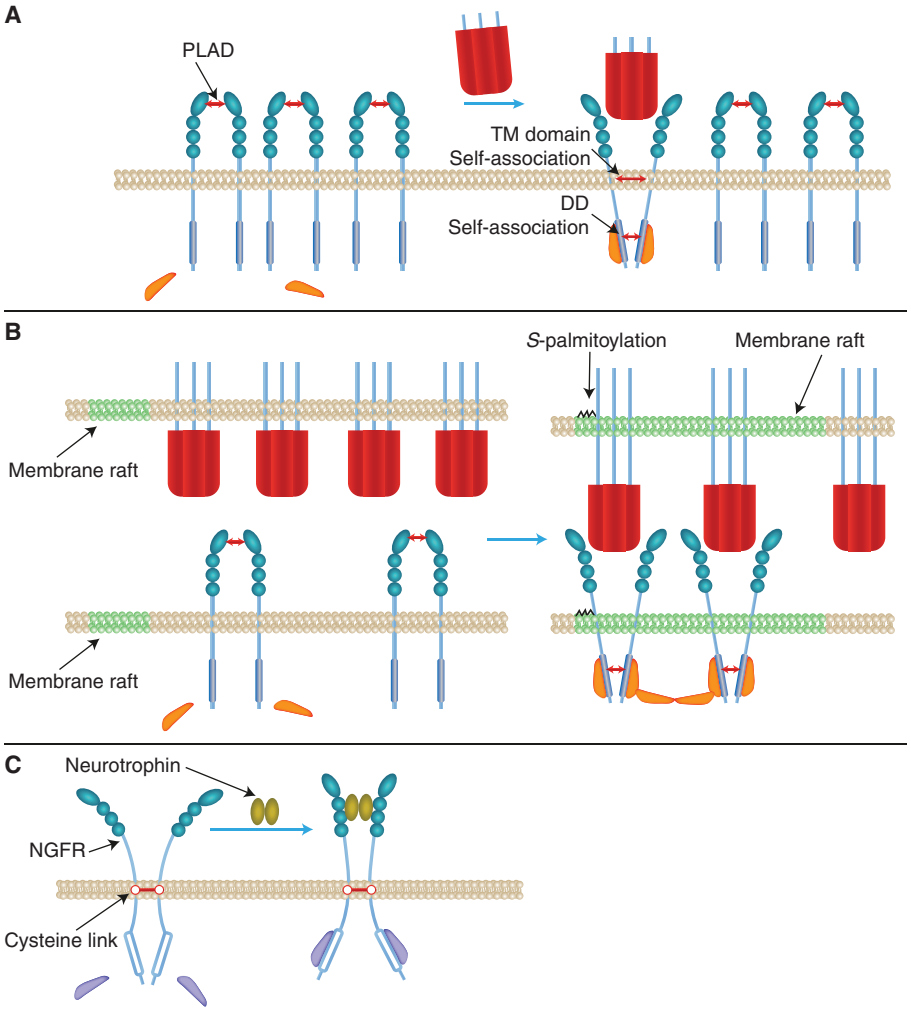

Figure 1. Signaling triggering: proposed mechanisms. (*A*) Triggering by intracellular domain (ID) juxtaposition imposed by tumor necrosis factor (TNF) family ligands, and its restriction by the pre-ligand assembly domain (PLAD). (*B*) Triggering potentiation by anchorage of ligands to membranes. (*C*) Triggering by ID distancing: A fraction of the nerve growth factor receptor (NGFR) molecules occurs as dimers of receptor molecules that are covalently linked through a conserved transmembrane (TM) cysteine residue. In these dimers, the intracellular death domains (DDs) seem to be constitutively associated. Neurotrophin-induced triggering of these dimers to signal for death was suggested to occur by distancing of the IDs, imposed rather like a snail tongue, with the TM cysteine link serving as a fulcrum (Vilar et al. 2009). (See discussion of these findings in the last paragraph of this review.)

The self-association of four of the receptors (CD40, NGFR, CD27, and the soluble receptor OPG) is facilitated by constitutive cysteine links (found in the ID of CD40, in the TD of NGFR, at the carboxyl terminus of OPG, and apparently in the ED of CD27) (Van Lier et al. 1987; Schneeweis et al. 2005; Vilar et al. 2009; Nadiri et al. 2015). Constitutive dimerization of the soluble receptor OPG is also dictated by two DD motifs found at its carboxyl terminus (Schneeweis et al. 2005).

Structural studies of glucocorticoid-induced TNFR-related protein (GITR) suggest that the trimeric ligands of the TNF family may tend to undergo further clustering through noncovalent homotypic self-association (Zhou et al. 2008). However, formation of a soluble supercluster (of 20 trimers) has been documented only in the case of one TNF family member, BAFF (Liu et al. 2002; Cachero et al. 2006). The trimers of EDA are exceptional in that they are constitutively dimerized by homotypic self-association of an amino-terminal collagen-like domain unique to this ligand (Swee et al. 2009).

SIGNALING FACILITATION BY MEMBRANE ANCHORAGE

The ability of membrane-anchored forms of the ligands to induce clustering of the receptors that they bind is greater than that of the soluble forms. This ability is enhanced by positioning of both the membrane-bound ligands and their receptors within membrane rafts (Legler et al. 2003; Muppidi et al. 2004; So and Croft 2013) and by *S*-palmitoylation of the ligands and their receptors (Chakrabandhu et al. 2007; Feig et al. 2007; Rossin et al. 2009; Poggi et al. 2013). Formation of larger aggregates stabilizes binding of the ligands to the receptors. It can also dictate higher-order organization of signaling proteins (Fig. 1B).

The various signaling functions activated by the TNF family differ in the extents of their dependence on such higher-order signaling-protein organization. Accordingly, membrane and soluble forms of the ligands have differential abilities to trigger different cellular responses. For example, although TNFR1 can be activated both by soluble and by membrane-anchored TNF, TNFR2 is activated only by the latter. FAS can be triggered to signal for death by a dimer of FASL trimers, but not by a single trimer. Fn14, when massively aggregated, activates both the canonical and the alternative NF-κB transcription factor pathways, but only the alternative one when mildly aggregated (Grell et al. 1995; Schneider et al. 1998; Muhlenbeck et al. 2000; Bishop and Hostager 2003; Holler et al. 2003; Stone et al. 2006; O'Reilly et al. 2009; Wyzgol et al. 2009; Burkly 2014).

BIDIRECTIONAL SIGNALING: MULTIPLE FORMS AND FUNCTIONS OF SOLUBLE AND MEMBRANE-ANCHORED LIGANDS AND RECEPTORS

Similar to the IDs of TNF/NGF family receptors, the IDs of membrane-anchored TNF family ligands are found to recruit and activate signaling proteins on receptor–ligand interaction. Thus, they trigger "reverse signaling" within the ligand-producing cells (Stuber et al. 1995; Arens et al. 2004; Eissner et al. 2004; Grohmann et al. 2007; Kang et al. 2007; Sun et al. 2007; Juhasz et al. 2013). Various other similarities in action of the TNF and TNF/NGF families further blur the distinction between their identities as ligands and as receptors. As with the ligands, many of the receptors can be proteolytically cleaved, yielding ligand-binding "soluble receptors." Two of these receptors, OPG and DcR3, occur only in soluble forms, while two others, DcR1 and DcR2, despite their anchorage to the membrane, are devoid of the molecular structures within the IDs that are required for signaling.

The various forms of soluble and membrane-anchored ligands and receptors, and the functions served by the transitions in these forms, are shown in Figure 2.

"RE-ANCHORING" OF SOLUBLE FORMS OF LIGANDS AND RECEPTORS VIA THEIR BINDING TO EXTRACELLULAR MATRIX COMPONENTS

Several ligands of the TNF family and the two TNF-family receptors that occur only in soluble form (OPG and DCR3) contain sites

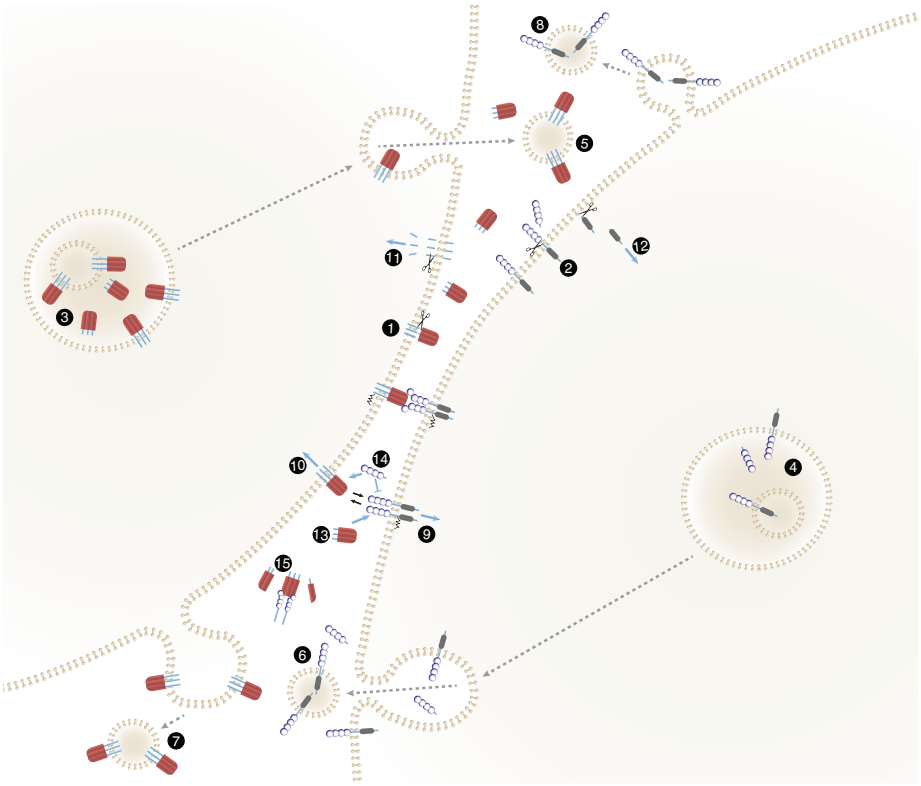

Figure 2. Membrane-anchored and soluble forms of ligands and receptors of the tumor necrosis factor (TNF) families, and their functional roles. The figure shows an intriguing symmetry of the spectra of soluble and membrane-anchored forms attained by TNF family ligands and TNF/nerve growth factor (NGF) family receptors, and of the functions of these forms. Both ligands (*1*) and receptors (*2*) are proteolytically cleaved to yield soluble forms (Kriegler et al. 1988; Engelmann et al. 1990; Nophar et al. 1990; Black et al. 1997; Moss et al. 1997). The cleavage occurs constitutively or inducibly, either on the cell surface as illustrated (Black et al. 1997; Moss et al. 1997; Becker-Pauly and Rose-John 2013) or within the cell (Lopez-Fraga et al. 2001). (*3*,*4*) Some of the ligands (Gordon and Galli 1990; Bossi and Griffiths 1999; Koguchi et al. 2007) and receptors (Wang et al. 2003) accumulate within intracellular vesicles from which they are secreted in response to specific stimuli, thus supplementing either the cell-surface-expressed or the soluble pools. Some are released while anchored to membranes that might correspond either to exosomes that have accumulated in intracellular multivesicular bodies (*5*,*6*) or to microvesicles exfoliating from the cell surface (*7*,*8*) (Albanese et al. 1998; Martinez-Lorenzo et al. 1999; Islam et al. 2007). Binding of membrane-anchored ligands of the TNF family to their receptors, besides triggering receptor signaling (*9*), also triggers "reverse signaling" by the ligand molecules (*10*) (Stuber et al. 1995; Arens et al. 2004; Eissner et al. 2004; Grohmann et al. 2007; Kang et al. 2007; Sun et al. 2007; Juhasz et al. 2013). One mechanism contributing to this reverse signaling is intramembrane proteolytic cleavage, yielding ligand intracellular domain (ID) fragments that apparently mediate signaling following their translocation to the nucleus (Domonkos et al. 2001; Fluhrer et al. 2006; Friedmann et al. 2006; Kirkin et al. 2007) (*11*). Intramembrane cleavage that apparently contributes to signaling has also been reported for two receptors of the TNF/NGF family, nerve growth factor receptor (NGFR) and TNFR1 (Kanning et al. 2003; Kenchappa et al. 2006; Chhibber-Goel et al. 2016) (*12*). Accumulation of the soluble forms of both receptors and ligands interferes with the binding of membrane-bound forms to the ligands and the receptors, respectively, and can thus block signaling (*13*,*14*). To the extent that the soluble forms are incapable of triggering signaling, they may also interfere with signaling activation by their membrane-bound forms. However, the association of soluble receptors with soluble ligands also stabilizes the trimeric structures of the soluble ligands, so that they function not as mere inhibitors but rather as buffering agents. While decreasing the intensity of signaling activation, they also extend its duration (*15*) (Aderka et al. 1992; Eliaz et al. 1996).

that bind extracellular matrix components such as heparan sulfate proteoglycans (HSPGs) and fibronectin. Their associations with these extracellular compounds have several functional consequences. (The numbering that follows corresponds to that shown in Fig. 3.) (1) Binding of TNF (Alon et al. 1994) and of FASL (Aoki et al. 2001; Zanin-Zhorov et al. 2003) to extracellular matrix proteins such as fibronectin, and of APRIL to HSPGs (Ingold et al. 2005; Kimberley et al. 2009), facilitate signaling activation by these ligands, apparently by imposing an oligomeric state on them. Such binding can also impose local restrictions. The anchorage of APRIL to HSPGs in mucosal lymphoid tissues not only augments its function but also restricts this ligand to target cells at this site (Huard et al. 2008), while the binding of EDA to proteoglycan interferes with EDA function by preventing its access to EDAR. (2) Binding of OPG to HSPGs blocks the function of OPG by also causing its uptake into the cell and its subsequent degradation (Standal et al. 2002). (3) Binding of OPG, APRIL, or DcR3 to HSPG appears to also trigger signaling by cell-surface molecules such as syndecans, which are linked to HSPG moieties, or by cell-surface molecules with which these moieties associate noncovalently (Couchman 2003; Mosheimer et al. 2005; Chang et al. 2006; Dillon et al. 2006; You et al. 2008). (4) Conversely, binding of cell-associated HSPG to TACI triggers TACI signaling, apparently independently of any ligand of the TNF family (Bischof et al. 2006). Because both APRIL and its receptor TACI bind HSPG, they probably form tripartite complexes in which the three pro-

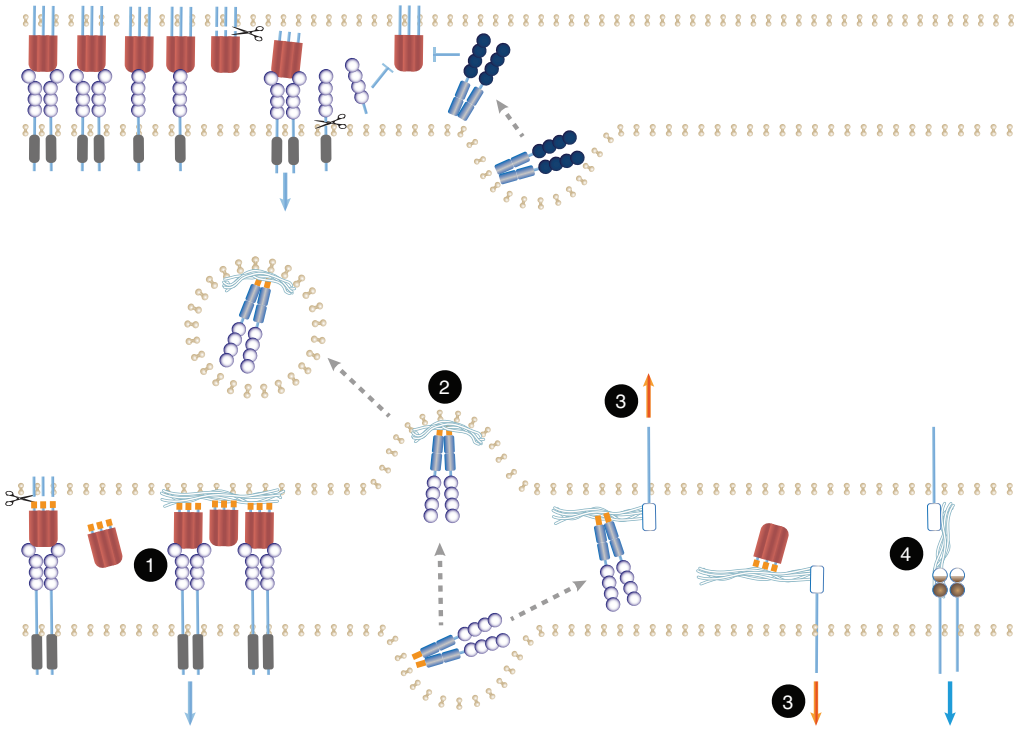

Figure 3. "Re-anchoring" of soluble forms of ligands and receptors by their binding to extracellular matrix components. Various reported effects of extracellular matrix components on the functions of soluble ligands and receptors, shown in the *lower* part of the figure, are compared with the functions of soluble ligands and receptors in the absence of such components, as shown in the *upper* part. See text for details and for numbering of the illustrated effects. Undulating lines correspond to extracellular matrix components. Orange forms correspond to structural motifs that dictate binding to such components.

teins modulate one another's function (Moreaux et al. 2009).

MECHANISMS OF SIGNALING ACTIVATION BY THE TNF FAMILY

The cellular responses initiated by the TNF family reflect a gamut of molecular changes, including altered expression of many proteins, and extensive changes in their patterns of phosphorylation, ubiquitination, association, localization, and rates of turnover, as well as alterations in the expression of various lipid metabolites. Because neither the IDs of TNF/NGF family receptors nor those of TNF family ligands possess enzymatic activity, they need to bind to signaling proteins that do express such activities, which are stimulated as a consequence of ligand–receptor association.

Protein-Binding Motifs in the Receptors and Ligands

The receptors of the TNF family can be subclassified into two groups with distinct binding motifs in their IDs. The IDs of TNFR1, DR3, FAS, TRAIL-R1, TRAIL-R2, NGFR, and EDAR each contain a DD motif of about 80 amino acids that bind adapter proteins containing the same motif. All other receptors contain short (five to eight amino acid residues) motifs of binding to adapter proteins of the TNF receptor–associated factors (TRAFs) family. NGFR is the only receptor that contains both an (atypical) DD and a TRAF-binding motif. The TRAF-binding receptors are incapable of triggering signaling pathways activated by the DD adapter proteins. In contrast, because two of the DD-containing adapter proteins—TNF receptor-associated death domain (TRADD) and EDAR-associated death domain (EDARADD)—also contain a TRAF-binding motif, the DD-containing receptors are capable of triggering at least part of the signaling pathways activated by the TRAF-binding receptors.

Binding of both DD-containing adapter proteins and the TRAFs to their receptors dictates the formation of large complexes containing several receptor molecules and multiple adapter molecules. As to the associations of the receptors with TRAFs (associations whose structural basis has so far been explored only for TRAF2 and TRAF6), assembly of the signaling complexes is fostered by constitutive trimeric oligomerization of the carboxyl-terminal leucine zipper TRAF motifs and by induced dimeric association of the TRAFs' amino-terminal regions (McWhirter et al. 1999; Park et al. 1999; Yin et al. 2009a). In the initiation of signaling through DD association, an event so far explored only for FAS association with the adapter protein FADD/MORT1, oligomerization is fostered by homotypic associations of the DDs of both FAS and FADD/MORT1 as well as by their heterotypic associations (Scott et al. 2009; Wang et al. 2010; Kersse et al. 2011; Li et al. 2013).

These associations between receptors and their adapter proteins initiate signaling by exposing, within the adapter proteins, binding surfaces for signaling proteins. With the exception of TRAF1, and—as was recently indicated, probably also with the exception of TRAF2 (Yin et al. 2009b)—members of the TRAF adapter protein family possess ubiquitin ligase activity, which is triggered by their induced associations with receptors.

Some adapter proteins initiate the above associations and activities while still bound to receptors expressed on the cell surface. Others do so only after uptake of the receptors into the cells (Schutze et al. 2008; Ganeff et al. 2011). Some of the signaling complexes that they generate remain associated with the receptors. Others dissociate from the receptors and generate signaling complexes in the cytoplasm (Sessler et al. 2013).

Sporadic evidence indicates that various other evolutionarily conserved amino acid residues within the IDs of receptors and of ligands serve—either without modification or after undergoing phosphorylation or ubiquitination—as binding sites for additional cytoplasmic proteins. In so doing, they contribute to the initiation of additional signaling pathways and to the control of trafficking of the receptors and ligands (e.g., Pocsik et al. 1995; Adam Klages et al. 1996; Watts et al. 1999; Eissner et al. 2004; Kimura et al. 2004; Sun et al. 2007; Juhasz et al. 2013; Ma et al. 2013; Fritsch et al. 2014; Chakrabandhu et al. 2016).

In addition to their ligand–receptor interaction motifs, the EDs of both the ligands and the receptors contain, in closer proximity to their TDs, specific sequences that determine their mode of shedding. Several ligands, including EDA, BAFF, and APRIL, contain consensus sequences for furin cleavage and are constitutively shed by intracellularly located furin. Other ligands as well as several receptors, including TNF and its receptors, are shed inducibly after they reach the cell membrane, mainly via the effects of metalloproteinases such as TACE/ADAM17. Little is known of the sequence determinants that dictate this selective shedding (Brakebusch et al. 1994; Thomas 2002; Hayashida et al. 2010).

Signaling Pathways

Studies of the mechanisms of signaling for apoptotic and for necrotic cell death as well as for activation of NF-κB transcription factors by TNF family members provided the foundation for exploring the regulation of these functions by external inducers. These activities of the TNF family are the most extensively studied to date. However, several others are known, including signaling for activation of the extracellular signal-regulated kinase (ERK), c-Jun amino terminal kinase (JNK), and p38 mitogen-activated protein (MAP) kinase cascades, other serine/threonine kinases, the phosphoinositide 3-kinase (PI3K)/Akt pathway, superoxide generation, soluble Src-family tyrosine kinases, the neutral and acidic sphingomyelinases, and phospholipase C. Space constraints preclude further attention in this review to these signaling mechanisms, which have been extensively reviewed elsewhere (Eissner et al. 2004; Hayden and Ghosh 2012; Juhasz et al. 2013; Li et al. 2013; Sessler et al. 2013; So and Croft 2013; Sabio and Davis 2014; Wallach 2016b).

FOREIGN ENCOUNTERS: NONCANONICAL CORECEPTORS AND LIGANDS

The information presented above delineates a shared set of mechanistic principles by which the different members of the TNF ligand and receptor families associate. However, several members of the families can also participate in unique interactions with coreceptors and ligands, including some that do not belong to the TNF ligand and TNF/NGFR families. Examples of these noncanonical associations, some extensively documented and others for which the evidence is limited and requires confirmation, are presented in Figure 4. Although such interactions have been noticed for only a few members of the TNF ligand and receptor families up to now, they might be found to occur with other members as well.

HOW IS REGULATION BY THE TNF FAMILY REGULATED?

As in the case of other cytokines, signaling by members of the TNF family is triggered when ligand and receptor molecules are brought close enough to allow their binding to each other. This approximation was found to be dictated at multiple mechanistic levels. In most cases, it occurs by induced up-regulation of the ligand molecules, allowing them to bind to receptor molecules that are constitutively expressed. Such is the case with TNF, whose induction mostly occurs in a transient manner, although TNFR1 to which it binds is widely expressed constitutively. However, the inverse type of modulation is also observed. TWEAK, for example, is a ligand that is constitutively expressed in macrophages, whereas the expression of its receptor Fn14 is induced in injured tissues. Up-regulation of the expression of both ligands and receptors is induced by specific signaling pathways that are activated in response to insults or developmental cues. The best-documented mode of up-regulation is by enhanced transcription. However, it also occurs on other mechanistic levels, including splicing, RNA transport, and altered messenger RNA (mRNA) stability and mRNA translation rates. Also contributing to this regulation are associations of proteins, microRNAs and long noncoding RNAs with transcripts (Wallach 2016a; Wallach and Kovalenko 2016). Once synthesized, the ligands and receptors can be subjected to further regulation by mechanisms controlling their translocation to the cell surface (Bossi and Grif-

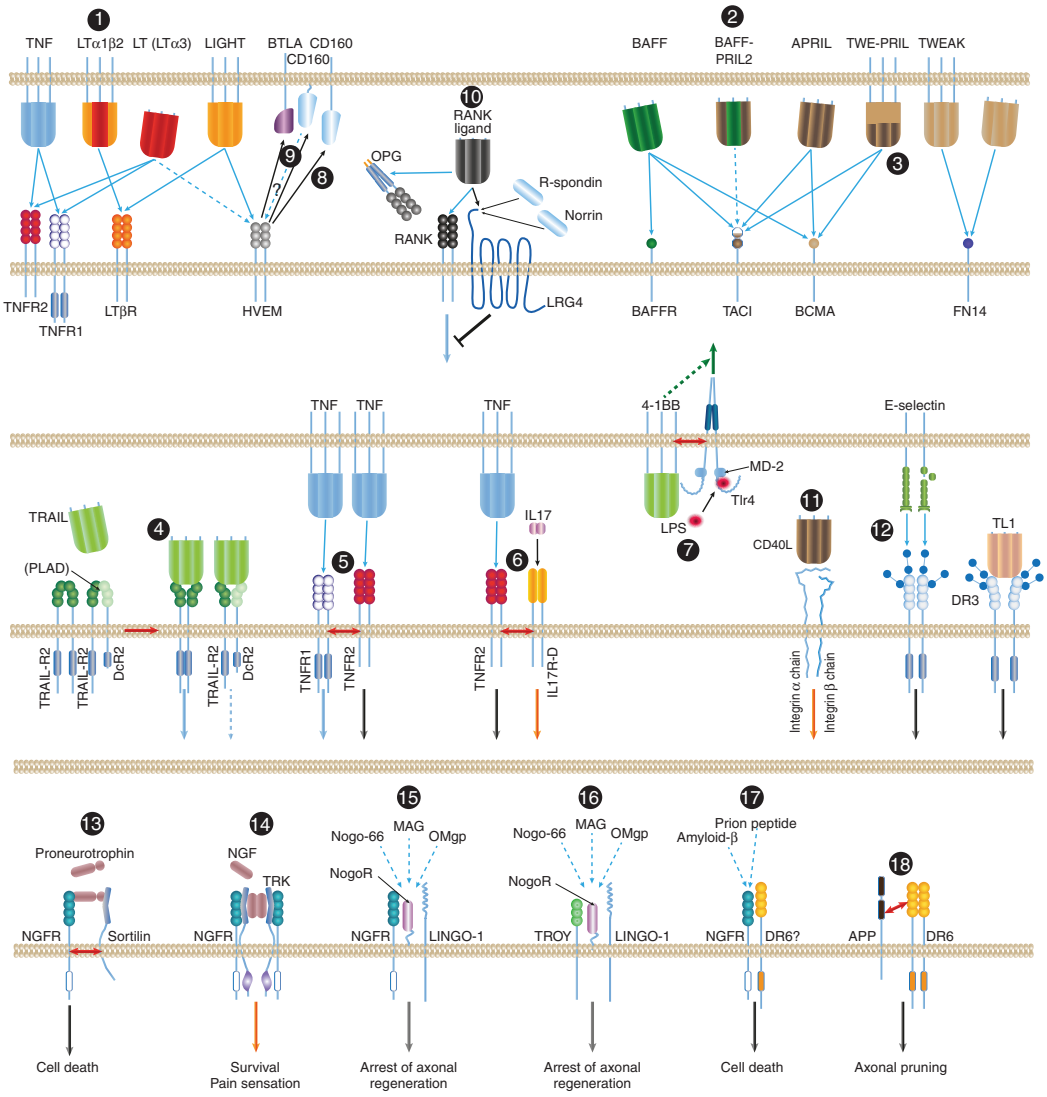

Figure 4. Noncanonical associations of the tumor necrosis factor (TNF) ligand and the TNF/ nerve growth factor receptor (NGFR) families. Most of the interactions of ligands and receptors of the TNF ligand and TNF/NGFR families are known to occur between homotrimeric molecules of a particular ligand and molecules of a particular receptor. A few exceptions, however, are known: (*1*) Lymphotoxin β (LTβ) functions only within heterotrimers that it forms with lymphotoxin α (LTα). Whereas homotrimers of LT bind to the TNF receptors, the LTα1β2 heterotrimer binds to the LTβ receptor (LTβR) (Ware 2005). (*2*) B-cell-activating factor of the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) also form heterotrimers (so far discerned only in patients with autoimmune diseases), and these heterotrimers apparently activate only transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) (Roschke et al. 2002; Dillon et al. 2006; Schuepbach-Mallepell et al. 2015). (*3*) Although APRIL is constitutively shed and its trimers therefore occur only in soluble form, its gene also yields a fused joint splice variant with the neighboring *TWEAK* gene. The protein encoded by this transcript—TWE-PRIL—is anchored to the cell membrane (Pradet-Balade et al. 2002). (*4*) Association of molecules of TRAIL-R2 and the membrane-anchored truncated receptor DcR2 through their preligand assembly domain (PLAD) dictate association of TRAIL with the two receptors in mixed complexes wherein TRAIL-R2 signaling is suppressed by DcR2 (Clancy et al. 2005). (*Legend continues on following page.*)

fiths 1999) and, in the case of their soluble forms, by the proteolytic activity through which these forms are generated. For some family members, this proteolytic activity is exerted constitutively (Lopez-Fraga et al. 2001), whereas for others it is activated by specific signals (Black et al. 1997; Moss et al. 1997; Becker-Pauly and Rose-John 2013). Approximation of receptors to membrane-bound ligands can also be dictated merely by induced juxtapositioning of the cells that express the receptors and ligands.

Some of the ligands accumulate within intracellular reservoirs. Signaling initiation by these ligands is thus dictated by their exocytotic secretion (Gordon and Galli 1990; Bossi and Griffiths 1999; Koguchi et al. 2007).

Figure 4. (*Continued*) (*5*) Molecules of the two receptors for TNF (TNFR1 and TNFR2) reportedly also associate on their binding to ligand. However, this association does not occur through binding of the two receptors to the same ligand molecule. In fact, the two receptor species are incapable of binding simultaneously to the same TNF molecule; molecules of the two receptors rather associate only after binding independently to distinct TNF molecules (Pinckard et al. 1997). (*6*) Molecules of TNFR2 reportedly also associate with molecules of IL-17 receptor D, a member of an unrelated cytokine-receptor family. This association, which occurs on triggering by the ligands of the two receptors, imposes assembly of aggregates of the two receptors and functional cooperation between them (Yang et al. 2015). (*7*) Another example of functional interaction with a structurally unrelated receptor is the association of the ligand for 4-1BB with a coexpressed TLR4–MD2 complex. This apparently occurs through the TMs of 4-1BBL and Tlr4 and the consequent potentiation of lipopolysaccharide (LPS)-induced Tlr4 signaling in a way that depends on the function of the intracellular domain (ID) of 4-1BBL but independently of the association of 4-1BBL with 4-1BB (Kang et al. 2007; Ma et al. 2013). (*8*) A different kind of noncanonical association is observed in the function of herpesvirus entry mediator (HVEM), a receptor of the TNF family. Besides its association with two TNF family ligands (with LIGHT, and [weakly] with LT homotrimers) it also binds to B- and T-lymphocyte attenuator (BTLA) and CD160, two cell-surface proteins of the immunoglobulin superfamily, thereby triggering inhibitory signaling by those two proteins (Shui et al. 2011). (*9*) Whether this association also triggers signaling by the ID of HVEM is not known. (*10*) RANKL, besides binding to RANK and to the soluble receptor osteoprotegerin (OPG), also binds to the seven-transmembrane (TM), leucine-rich repeat containing G protein-coupled receptor 4 (LGR4), which also serves as receptor for R-spondins and for Norrin. It thus triggers signaling antagonistic to that initiated by RANK (Luo et al. 2016). (*11*) Binding of soluble CD40L to integrin αIIbβ3 and to integrin α5β1 triggers signaling by those two membrane–protein complexes (Andre et al. 2002; Leveille et al. 2007). (*12*) Binding of the cell-adhesion lectin, E-selectin, to DR3-linked sialic-acid-linked sugar chains triggers signaling by DR3 (Porquet et al. 2011). Juxtaposition and activation of the two TRAIL receptors, DR4 and DR4, by TRAIL also depends, for a reason not yet clear, on glycosylation of these receptors (Wagner et al. 2007). The most elaborate known set of noncanonical associations is observed in the function of the NGFR, a receptor of the TNF/NGF family for which no ligand of the TNF family is known. NGFR contributes to signaling for different effects in response to different inducers through association with a series of different coreceptors. (*13*) It contributes to signaling for death in response to proneurotrophins, to which it binds in association with a sortilin family receptor. (*14*) When associating with a Trk tyrosine kinase receptor, apparently through the TMs and IDs of both receptors (Esposito et al. 2001), NGFR contributes to high-affinity binding of NGF, and signals for cell survival and for pain sensation. (*15*) NGFR is also found to form, through extracellular domain (ED) associations, a ternary complex with the glycosylphosphatidylinositol (GPI)-linked Nogo-66 receptor (NogoR) and the TM receptor LINGO-1. In response to myelin-associated inhibitory factors (a 66-amino-acid fragment of the oligodendrocyte-derived growth inhibitory protein Nogo, the oligodendrocyte myelin glycoprotein [OMgp] or the myelin-associated glycoprotein [MAG]), this complex signals for arrest of axonal regeneration following injury (Hempstead 2002; Chao 2003; Ibanez and Simi 2012). (*16*) In that complex, NGFR can be replaced by the orphan TNF family receptor TROY (Shao et al. 2005). (*17*) Finally, direct binding of amyloid-β to NGFR (Hempstead 2002; Chao 2003; Ibanez and Simi 2012), and probably also to a complex of NGFR and another orphan receptor of the TNF/NGF family, DR6 (Hu et al. 2013), reportedly triggers signaling for neuronal death. (*18*) DR6 was found to bind to a carboxyl-terminal region in the ED of the amyloid precursor protein (APP). APP and DR6 cooperate in the induction of axonal pruning. The mechanism underlying this cooperation is not clear, nor is it known whether the cooperation occurs between proteins expressed in the same cell, as illustrated in the figure, or in distinct cells (Olsen et al. 2014). BCMA, B-cell maturation antigen.

Increased expression of the receptors or ligands, either artificially (Boldin et al. 1995) or in response to natural stimuli (Lu et al. 2014), is in some situations sufficient to allow the IDs of these molecules to encounter one another and hence to trigger signaling independently of ligand–receptor association.

CONCLUDING THEOLOGICAL REMARKS

Members of the TNF cytokine family and of the TNF/NGFR family are used by almost all metazoan phyla. Some of their activities have been well preserved over more than 500 million years of evolution (Igaki and Miura 2014; Quistad et al. 2014). Their major proximal signaling enzymes originated even earlier (Uren et al. 2000; Zapata et al. 2007; Yuan et al. 2009; Zmasek and Godzik 2013; Sakamaki et al. 2014). Nature, it would seem, had good reason to preserve this cytokine family so well and for so long. At face value, however, the known activities of this family do not seem to be sufficiently unique to warrant such preservation. Other than in the case of the cytotoxic activity of a few family members, the various individual cellular effects of the TNF family and the signaling mechanisms that account for them do not seem to differ radically from those of various other cytokines. The pattern of cellular effects of IL-1 in inflammation, for example, as well as the signaling mechanisms that it activates, greatly resemble those of TNF. Why would nature preserve two cytokines that seem to serve the same set of functions, and why would it choose to use them differentially in different situations?

Also puzzling is the remarkable similarity among the ranges of signaling activities triggered by the various family members. How can the heterogeneous and distinct biological activity patterns of the different family members be explained in terms of a set of mechanisms so limited and so invariant? These enigmas suggest that the mechanisms of action of the TNF families possess a greater degree of sophistication than has so far met the eye.

An example of the insight gained in attempting to deepen our perception of this area was the discovery that, although all TNF family members signal for activation of NF-κB, some are able to do so via a distinct route, the so-called "alternative pathway," which yields molecular targets and functional consequences that differ from those of the more widely used "canonical pathways" (Hayden and Ghosh 2012). The alternative pathway, and the protein kinase NF-κB-inducing kinase (NIK) that initiates it, appear to have evolved relatively late in the history of the TNF family, contemporaneously with emergence of the vertebrates and of their adaptive immunity that this pathway regulates. Other signaling pathways shared by different TNF family members may likewise be found to have evolved into several different forms that are affected differentially by these different members and serve distinct functions.

The various "noncanonical" interactions of the TNF and TNF/NGF families (Fig. 4) doubtless also endow individual members of the family with unique mechanisms of action. An example of a unique mechanism that might depend on such noncanonical interactions is presented in Figure 1C. As opposed to the usual mode of signaling initiation by the TNF/NGF family (by induced juxtaposition), NGFR—which participates in several such noncanonical associations—was suggested rather to trigger signaling by imposing separation of the receptor IDs. This mechanism is dictated by covalent linkage of a conserved cysteine in the TM of NGFR. Conserved cysteines also occur in the TDs of several other TNF/NGF family members. It was therefore suggested that portions of these other receptors also occur as covalently linked dimers and serve similarly to mediate unique functions, which likewise may depend on some noncanonical associations (Vilar et al. 2009).

We have come a long way in clarifying some general mechanisms of action of the various families of cytokines, including the TNF family. It is now time to focus on clarifying the mechanisms that endow each family, and each family member, with uniqueness. Progress in this regard will undoubtedly increase our ability to design selective therapeutic modulation of specific functions of these fascinating molecules.

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