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TNF superfamily in inflammatory disease: translating basic insights

Michael Croft, Wei Duan, Heonsik Choi, So-Young Eun, Shravan Madireddi, and Amit Mehta

La Jolla Institute for Allergy and Immunology, Division of Immune Regulation, 9420 Athena Circle, La Jolla, CA 92037, USA

Abstract

The tumor necrosis factor (TNF) and TNF receptor superfamilies (TNFSF and TNFRSF) consist of approximately 50 membrane and soluble proteins that can modulate cellular function. Most of these molecules are expressed by or can target cells of the immune system, and they have a wide range of actions including promoting cellular differentiation, survival, and production of inflammatory cytokines and chemokines. Emerging data show that TNFSF ligand–receptor signaling pathways are active in inflammatory and autoimmune disease. Furthermore, several genetic polymorphisms in TNFSF and TNFRSF associate with susceptibility to developing disease. Here, we examine recent data regarding the potential of these molecules as targets for therapy of autoimmune and inflammatory disease.

Tumor necrosis factor (TNF) and TNF receptor superfamily (TNFSF and TNFRSF) members control many inflammatory cells

The TNFSF and TNFRSF molecules are found in all mammals and are highly conserved. There is evidence that many of these molecules evolved with, or closely after, the adaptive immune system 350–450 million years ago, before the divergence of bony fish and tetrapods. Since the discovery in the 1980s of structural similarities between the founding members of the superfamily, TNF and lymphotoxin (LT), many additional members have been described that probably exert similar and overlapping functional activities on diverse cell types. TNF family molecules have canonical TNF homology domains and are thought to be active primarily in trimeric form, either on the cell surface, or soluble after extracellular cleavage. TNFR family molecules contain several cysteine-rich domains in their ligand-binding extracellular regions and again can be cell membrane-expressed or soluble. TNF itself has been known as a proinflammatory molecule for many years, and antibodies or Fc fusion proteins that target TNF (TNF blockers) have been highly successful in subsets of patients for treatment of several immune diseases including rheumatoid arthritis (RA) and Crohn's disease. This has led to great interest in other members of the superfamily as possible alternate or additional therapeutic targets for inflammatory and autoimmune disease.

Proinflammatory members of the TNFSF were initially described to stimulate T and B lymphocytes and antigen-presenting cells, such as dendritic cells (DCs). It is now recognized that many lymphoid and some nonlymphoid cells can be modulated by various

ligand–receptor interactions within the superfamilies (Table 1). Many members of the TNFSF seem to drive cell division or differentiation and promote cell survival. Conversely, several TNFSF molecules (that are not a focus of this review), suppress responses by promoting cell death. The function of individual TNFSF and TNFRSF molecules or groups of molecules, and their role in protection against pathogens and tumor growth, or how they relate to tolerance, inflammation, and autoimmunity has been examined in several reviews [1–4]. However, recent data further define the function of superfamily members other than TNF itself, namely the ligand–receptor pairs shown in Table 1. In this review, we summarize the new data regarding the potential of these molecules to be therapeutic targets for multiple inflammatory and autoimmune diseases, and present an overview of data from animal models linking these molecules to control of immune disease.

OX40 and OX40L

OX40 and its ligand, OX40L, are widely expressed and regulate many cell types including T cells, natural killer (NK) cells, NKT cells, B cells, and DCs (Table 1). These molecules are proinflammatory, and knockout or blocking studies have shown they play a role in development of disease in murine models of colitis, asthma, diabetes, multiple sclerosis (MS), RA, atherosclerosis, and graft-versus-host disease (GVHD) [5] (Figure 1). Antibodies to OX40L are in clinical trials for mild to moderate asthma, and it has recently been reported that OX40 and OX40L are upregulated in the bronchial submucosa in mild asthmatics compared to healthy individuals [6]. These molecules have been linked to sepsis because the presence of OX40L-positive monocytes and neutrophils, and soluble OX40, in the initial phase of sepsis in humans, is correlated with mortality and intensive care unit stay [7]. Furthermore, in a mouse model of polymicrobial sepsis OX40L-deficient mice have improved survival, decreased cytokine production, and reduced organ damage. The majority of studies of OX40 relate to control of T cells, but blocking OX40L in the sepsis model provides a similar level of protection in *Rag*^{−/−} mice, suggesting a T cell-independent activity, although the targets of this activity have not been defined. Blocking OX40L also has inhibited ocular inflammation in a mouse model of experimental autoimmune uveitis, expanding the range of inflammatory disease controlled by OX40 and OX40L [8].

Older work links OX40 and OX40L with atherosclerosis development [5]. It has been reported more recently, using a model of myocarditis driven by infection with coxsackie virus B3, that blockade of OX40L ameliorated heart inflammation and increased survival [9]. Additionally, a haplotype identified upstream of the OX40L gene, and linked to enhanced protein expression, has been found to correlate with increased risk for systemic lupus erythematosus (SLE) in several cohorts of patients [10]. This has been confirmed in a genome-wide association study (GWAS) as well as several studies in selective patient populations, furthering the conclusion that single nucleotide polymorphisms (SNPs) in or around *TNFSF4* are associated with SLE [11,12]. OX40 expression on kidney-infiltrating Th17 cells has also been associated with lupus nephritis [13]. Lastly, several of the polymorphisms that have been identified around the OX40L gene in the SLE studies are linked to susceptibility of developing systemic sclerosis (SSc), a fibrotic disease, based on a selective analysis of patients in the United States [14]. However, a GWAS of atherosclerosis or SSc, or experimental studies to disrupt OX40–OX40L interactions in murine models of lupus or SSc, have not been performed to support these hypotheses.

CD30 and CD30L

CD30 is best known as a molecule expressed on malignant tumors such as Hodgkin's lymphoma and anaplastic large cell lymphoma, but CD30 can be highly expressed on T cells as well as other cell types (Table 1). Data relating CD30 to inflammatory disease are less

extensive than other members of the superfamily. *Cd30*-deficiency or blocking CD30–CD30L interactions reduces development of disease in the NOD mouse model of diabetes and Th2-driven models of asthma (Figure 1). The latter correlates with publications dating back more than 10 years showing that CD30 is expressed on Th2 cells and also in patients with allergic asthma and atopic dermatitis [15]. These molecules are also implicated in other immune diseases: deficiency in *CD30L* or blocking CD30L interactions suppressed development of dextran sulfate sodium- or trinitrobenzene sulfonic acid (TNBS)-induced colitis [16,17], although it had no effect in a third colitis model using oxazolone [17]. Depending on the experimental protocol, these models are either T cell-independent or driven by Th1 or Th17 cells. These results suggest that neutralizing CD30 or CD30L may be a potential therapy for inflammatory disease controlled by multiple pathogenic T cell subsets or innate cells.

The soluble forms of CD30 or CD30L have been assessed as possible diagnostic tools, and correlations have been reported between disease and high amounts of expression of one or both molecules. For example, serum from patients with SLE, or serum and synovial fluid from patients with RA, has elevated concentrations of soluble CD30 and/or CD30L compared to controls [18,19]. It is unclear if these molecules drive pathogenesis of these diseases. Another study has found an inverse correlation between serum concentration of CD30 and alleviation of disease symptoms in RA patients treated with anti-TNF [20]. Broadly applying to all TNFRSF molecules, this might indicate that soluble variants, as opposed to the more common membrane-bound version, are endogenous inhibitors naturally produced to suppress inflammation in late-stage or chronic disease.

CD40 and CD40L

CD40L was initially characterized on T cells and CD40 on B cells, and their interaction was shown to be a primary driver of B cell activity and isotype switching. Additional cell types are now known to express these molecules (Table 1), and the interaction of CD40 with CD40L is reported to promote disease in murine models of SLE, MS, RA, Graves' disease, psoriasis, diabetes, asthma, inflammatory bowel disease (IBD), and GVHD [21]. Mutations in the *CD40L* gene lead to X-linked hyper IgM syndrome, and selective association studies and GWAS have linked polymorphisms in or around *CD40* with increased risk of SLE [22]. More recently, a GWAS with RA [23] that was confirmed with a selective association study [24], together with a selective association study of patients with Crohn's disease [23,25], linked polymorphisms in *CD40* with disease risk. Antibodies to CD40L have now been tested in clinical trials for several of the described indications. Although positive effects have been reported, an unexpected complication with some antibody clones that recognize CD40L is prothrombotic activity, which may be mediated by platelets that express this molecule [2,21]. The physiological significance of platelet-expressed CD40L has been unclear, but a possible role in atherosclerosis has recently been reported [26]. Platelets from *CD40L*-deficient mice show markedly reduced adhesion to vascular endothelium *in vivo* and fail to form platelet–leukocyte aggregates that promote atherosclerotic lesions. This suggests that inhibiting CD40–CD40L interactions without aggregating CD40L could be beneficial in this setting, as well as for other inflammatory diseases. Furthering the link to vascular disease, several studies have found that signaling through CD40 expressed on adipocytes could induce proinflammatory cytokine production and increase accumulation of fat droplets [27,28]. The concentration of soluble CD40L in serum is also significantly higher in obese patients compared with nonobese people, and *CD40* mRNA levels are elevated in subcutaneous adipose tissue, implying that CD40–CD40L interactions might participate in inflammation related to obesity.

CD40 interactions have been implicated in Alzheimer's disease based on animal models (Figure 1) and soluble CD40 or CD40L has been studied as a possible diagnostic biomarker. The apolipoprotein E type 4 allele has been the primary marker for Alzheimer's disease, but the increased amount of CD40 and CD40L expression observed in patients with disease suggest that a combined biomarker panel may be more specific for clinical diagnosis [29]. Additionally, a mouse model of amyotrophic lateral sclerosis, driven by transgenic expression of a mutant human superoxide dismutase gene, has shown an association between neurodegenerative disease and expression of molecules controlled by CD40–CD40L interactions [30]. Correspondingly, neutralizing CD40L decreases markers of neuroinflammation, and slows weight loss and paralysis while delaying time to death. Extending the therapeutic potential of targeting CD40–CD40L, tight-skin (TSK/+) mice that spontaneously develop a disease similar to human SSc are substantially protected from developing cutaneous fibrosis and autoantibodies by treatment with anti-CD40L [31].

4-1BB and 4-1BBL

4-1BB was originally described as a stimulatory molecule for activated T cells. Its ligand is expressed on activated DCs, B cells, macrophages and other cell types (Table 1). Agonist antibodies to 4-1BB are in clinical trials for cancer, based on multiple studies showing that they augment cytotoxic T lymphocyte and NK activity in murine tumor models [2,4]. Paradoxically, stimulation of 4-1BB with agonist antibodies also inhibits inflammation in many murine models of autoimmunity, which may be due to augmenting regulatory CD8 T cell activity and/or driving death of pathogenic CD4 T cells [1,4]. Reports of blocking 4-1BB–4-1BBL interactions in autoimmune/inflammatory models are limited, although there is some evidence that these molecules may promote arthritis and GVHD [1].

4-1BB is expressed on T cells and endothelial cells in human atherosclerotic lesions, and treatment with an agonist anti-4-1BB antibody increases the number of atherosclerotic plaques in hypercholesterolemic *Apoe*^{−/−} mice [32]. The latter shows that, in addition to the beneficial effects reported in other disease models, stimulatory antibodies to 4-1BB can have adverse effects on inflammation [1–4]. A deficiency of *41BB* in either atherosclerosis prone *Ldlr*^{−/−} or *Apoe*^{−/−} mice also reduces atherosclerosis, and reduces accumulation of interferon (IFN)- γ -expressing T cells in lesions [33]. Furthermore, in a rat model of experimental autoimmune myocarditis, a blocking 4-1BB-Fc reagent reduces signs of heart inflammation, again probably by lowering of T cell activity [34]. Agonistic anti-4-1BB antibody also reduces high-fat diet-induced obesity in mice, which is associated with improved glucose tolerance, glycolysis, and oxygen consumption [35]. In this case, the mechanism of action is not clear.

4-1BB may also control sepsis and biliary cirrhosis. *41bb*-deficient mice exhibit lower mortality in a model of sepsis driven by cecal ligation and puncture, and similar results are obtained by blocking 4-1BBL in wild-type mice [36]. In patients with primary biliary cirrhosis [37], there is additionally a positive correlation between expression of soluble and membrane 4-1BBL and mRNA for 4-1BBL, with serum levels of disease markers such as bilirubin, γ -glutamyltransferase, and interleukin (IL)-18.

CD27 and CD70

CD27 is constitutively expressed on most T, NK and NKT cells, and expression can be induced on a number of other cells including B cells. Its ligand, CD70, can also be induced on a range of immune and some nonimmune cell types (Table 1). Until recently, data on CD27 and CD70 in autoimmune disease were mostly restricted to EAE mouse models of MS as well as older data associating membrane or soluble CD27 or CD70 expression with SLE disease in humans and murine models [1,38].

In a recent study of the collagen-induced mouse model of RA, treatment with an anti-CD70 blocking antibody markedly reduced disease symptoms [39]. The targets of activity were not investigated. In the T cell transfer and TNBS models of colitis, CD70 blockade prevents induction of disease as well as having therapeutic activity. No effect is seen in a colitis model induced by anti-CD40 in *Rag*^{-/-} animals, suggesting that CD4 T cells are primarily targeted [40]. Furthering conclusions from older data in proteolipid protein-induced EAE, in Theiler's murine encephalomyelitis virus-induced demyelinating disease, anti-CD70 treatment ameliorates the effector but not induction phase of disease [41]. Th1 cells are the suggested target, which correlates with the RA and colitis studies. This may indicate some preferential activity of CD70 on T cell subsets, and although CD27 is ubiquitously expressed on T cells, Th1 cell-specific CD70 expression has been reported [42]. In line with this, either CD27 deficiency, or CD70 blockade, inhibits Th1-driven delayed-type hypersensitivity (DTH) and contact hypersensitivity reactions, but has no effect on the extent of inflammation in Th2-driven models of asthma [42,43] and does not inhibit development of experimental allergic conjunctivitis, another Th2-type model [44].

Herpesvirus entry mediator (HVEM) and LT β receptor and their ligands LIGHT and LT $\alpha\beta$

LIGHT (homologous to LT, shows inducible expression, competes with HSV glycoprotein D for HVEM, a receptor expressed by T lymphocytes) is a TNFSF molecule expressed on activated lymphocytes. LIGHT binds HVEM and LT β receptor, molecules that are widely expressed on many hematopoietic cells as well as some structural cells (Table 1). The LIGHT–HVEM pathway is an important co-signaling pathway in T cells, whereas LIGHT–LT β receptor can regulate DC and macrophage activity. LT β receptor can also interact with the ligand, LT $\alpha\beta$, an interaction that promotes lymph node organogenesis and maintenance of secondary lymphoid organs. An LT β receptor–Fc fusion protein reduces disease in models of arthritis, IBD, MS and lupus among others, and this reagent is now being pursued clinically, particularly in patients with RA that do not respond to anti-TNF therapy ([45] and Figure 1). In addition to blocking LIGHT, some of the beneficial results of LT β receptor–Fc are probably due to blocking LT $\alpha\beta$ and lymphoid tissue organization, which in humans may not be an ideal therapeutic strategy because the integrity of secondary lymphoid structures is required for many immune responses, including those against infectious pathogens. Membrane LT $\alpha\beta$ is expressed on a number of cells, particularly resting B cells, but is also inducible on subsets of T cells including Th1 and Th17. Targeted depletion of LT $\alpha\beta$ -expressing Th1 and Th17 cells with a monoclonal antibody to LT α inhibits autoimmune disease in mouse models of DTH, EAE, and collagen-induced arthritis [46]. This is without disturbing LT $\alpha\beta$ interaction with LT β receptor, preserving lymphoid tissue structure and thus presenting an alternate therapeutic targeting strategy.

Blocking LIGHT interactions also holds promise therapeutically. Older studies of *Light* transgenic mice together with LIGHT blocking studies suggest that this molecule drives IBD through binding both LT β receptor and HVEM [47]. More recently, using the T cell transfer model of colitis, accelerated pathology has been reported in *Hvem*-deficient hosts. This may be explained by HVEM also being a partner of the inhibitory immunoglobulin superfamily molecule B and T lymphocyte attenuator (BTLA) [48]; an interaction previously described to result in a range of suppressive activities [49]. This highlights the potential complexity of targeting molecules with multiple binding partners; a concept further illustrated in a report using an HVEM–Fc fusion protein that blocks LIGHT interactions but may also block suppressive mechanisms through BTLA. In that study [50], HVEM–Fc had an adverse effect on collagen-induced arthritis, resulting in aggravation of disease, contrasting with an earlier report [45] that an LT β receptor–Fc fusion protein prevented collagen-induced arthritis.

LIGHT has also been suggested to play a broader role in mucosal and systemic immunity. Increased serum LIGHT concentrations are detected in patients with pulmonary arterial hypertension, and LIGHT is produced by platelets, alveolar macrophages, vascular smooth muscle cells, and endothelial cells, suggesting a role in pathogenesis of vascular inflammation [51]. In patients with severe asthma, higher sputum LIGHT concentrations correlate with the most impaired lung function [52], and in mouse models of airway remodeling, LIGHT has been shown to be crucial for pulmonary fibrosis and hyperplasia of lung smooth muscle [53]. LT β receptor–Fc suppresses features of severe asthma in mice, which is caused by altered LIGHT activity because *Light*-deficient mice also show reduced remodeling, and mice given exogenous LIGHT develop lung fibrosis and increased lung smooth muscle mass. This is an effect of LIGHT acting via LT β receptor and HVEM on lung macrophages and eosinophils, and perhaps also effects on epithelial and fibroblast cells. LIGHT–HVEM interactions have additionally been reported to promote long-term survival of memory Th2 and Th1 cells [54], which could be significant for disruption of asthmatic/allergic type responses, as well as reiterating the possibility of targeting LIGHT in Th1- and Th17-driven autoimmune disease.

HVEM might also be involved in the progression of inflammation associated with obesity. Obese subjects have significantly higher subcutaneous *HVEM* gene expression in adipose tissue compared to lean subjects. *HVEM* gene polymorphisms additionally have shown an association with obesity measurements in a selective group of subjects, correlating with high levels of C-reactive protein, IL-18, and soluble LIGHT [55]. Furthermore, *HVEM*-deficient mice on a high-fat diet have fewer macrophages and T cells infiltrating adipose tissue, and display less glucose intolerance and better insulin sensitivity [56].

Death receptor 3 (DR3) and TNF-like factor 1A (TL1A)

DR3 and TL1A interactions have primarily been associated with co-stimulation of Th1 cells, and not cell death, with DR3 expressed on activated T cells and TL1A being an inducible molecule on antigen-presenting cells such as DCs (Table 1). These molecules have been implicated in the pathogenesis of gut inflammation [1], with polymorphisms of *TL1A* linked with IBD, ulcerative colitis, and Crohn's disease, from GWAS and selective association studies [57–59]. In line with this, more recent data have found that transgenic mice that constitutively express TL1A develop T cell-dependent inflammatory small bowel pathology [60,61].

The activity of TL1A has also been expanded to other inflammatory situations. DR3 is expressed on Th17 cells, and in murine EAE models, mice deficient in *DR3* or *TL1A* have significantly reduced numbers of autoreactive CD4 T cells and are impaired in displaying clinical disease symptoms [62,63]. A positive role for the TL1A–DR3 pathway in arthritis development has also been demonstrated in either *DR3*-deficient mice or by treating wild-type mice with blocking anti-TL1A [64]. Furthermore, recombinant TL1A injection exacerbates murine arthritis, correlating with elevated expression of TL1A observed in human RA synovial fluid and on human chondrocytes and synovial fibroblasts [65]. The activity of TL1A in this case may result from modulating T cells that contribute to disease as well as osteoclasts that are responsive to TL1A stimulation.

The action of TL1A–DR3 is not restricted to Th1- or Th17-regulated diseases. *Tnfrsf25* (encoding DR3)-deficient mice, or wild-type mice injected with anti-TL1A, display reduced airway inflammation and mucus production in Th2-driven models of asthma. This is associated with impaired expression of Th2 cytokines, and reduced accumulation of CD4 T cells and invariant natural killer T cells [62,66].

Glucocorticoid-induced TNF receptor-related protein (GITR) and its ligand

GITR and its ligand (GITRL) exhibit expression patterns and activities similar to a number of the molecules described above (Table 1 and Figure 1; [67]). In particular, ligating GITR can also be stimulatory for both CD4 and CD8 T cells. Early work has suggested that signaling through GITR on T regulatory cells abrogates their suppressive function. Consequently, injection of agonist antibodies to GITR results in spontaneous autoimmunity or enhanced disease in murine models of arthritis, asthma, and colitis. Correspondingly, *Tnfrsf18* (encoding GITR)-deficient mice have reduced inflammatory symptoms in models of gut and lung inflammation [67].

The GITR–GITRL pathway has recently been found to be active in type 1 diabetes and pancreatitis. NOD mice treated with an agonist anti-GITR antibody have a higher incidence and accelerated diabetes, whereas mice treated with a neutralizing antibody against GITRL are substantially protected [68]. These actions are primarily explained by modulating the proliferation and migration of effector T cells into pancreatic lymph nodes or the pancreas. Furthermore, *GITR*-deficient mice, or wild-type mice receiving a blocking GITR-Fc, were protected against acute pancreatitis induced by cerulein, a decapeptide that damages acinar cells [69]. The target in this study was not clear, but decreased neutrophilia was found, along with reduced expression of TNF, IL-1, and inducible NO synthase, suggesting possible T-cell-independent activity. A genetic deficiency in *GITR*, or blocking GITR activity with an Fc fusion protein, additionally reduced inflammation and enhanced motor function in a murine model of spinal cord injury, with data suggesting this was caused by decreased T cell activity, in this case in the CNS [70]. Lastly, two SNPs in the gene encoding GITR have been found to be more frequent in patient cohorts with mild Hashimoto's disease/ autoimmune thyroiditis than those with severe disease, suggesting a possible role in progression of this syndrome [71].

TACI, BAFF-R and BCMA and their ligands APRIL and BAFF

A proliferation-inducing ligand (APRIL) and B-cell-activating factor (BAFF) play a crucial role in the survival and differentiation of B cells [72]. APRIL and BAFF both bind to two receptors expressed at different stages of B cell development, transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B cell maturation protein (BCMA). BAFF can additionally activate BAFF receptor, an alternate receptor expressed on immature B cells. Mice lacking BAFF have reduced numbers of mature B cells, and transgenic mice overexpressing BAFF develop autoimmune-type symptoms reminiscent of SLE and Sjogren's disease. Elevated levels of BAFF and APRIL have been observed at inflammatory sites and in several autoimmune diseases associated with excessive B cell activity, such as SLE, RA, MS, and Sjogren's disease, leading to these molecules being targeted for therapy. Polymorphisms in either the genes encoding APRIL or BAFF have been described to associate with risk of SLE or RA in some selective patient cohorts, although this association has not always been replicated. Belimumab, an antibody specific for BAFF, was approved in 2011 for the clinical treatment of SLE, and atacicept, a TACI-Fc fusion protein that blocks both BAFF and APRIL is also being assessed in the clinic for SLE and RA.

Other activities of BAFF or APRIL that may or may not be explained by modulating B cells have been described more recently. In the murine collagen-induced RA model, a genetic lack of *Tnfsf13* (encoding APRIL) led to decreased incidence of arthritis and IL-17 production [73], and genetic silencing of BAFF with shRNA injected into arthritic joints reduced pathology and again the Th17 and IL-17-associated phenotype [74]. These data may reflect a direct action on T cells given that TACI has been reported on subpopulations of

these cells (Table 1). Another study has found increased plasma levels of BAFF in patients with immune thrombocytopenia, an autoimmune disorder directed towards platelet autoantigens. This correlates with *in vitro* activity of recombinant BAFF in promoting platelet apoptosis, CD8 T cell survival, and IFN- γ secretion [75]. Suggesting these possibly divergent activities are not confined to Th1 and Th17-mediated inflammation, administration of TACI-Fc resulted in reduced Th2 responses and lung inflammation in a murine model of antigen-induced asthma [76].

One potential complication in modulating the BAFF–APRIL pathways derives from data revealing an apparent regulatory role of these molecules. A deficiency of *BCMA* on a lupus-prone mouse background leads to B cell and plasma cell hyperproliferation, rapid autoantibody production, and lethality [77]. A similar regulatory activity has been observed in an EAE model in which deficiency of *BAFF-R* led to increased onset and severity of disease [78], possibly correlating with the enhanced inflammatory activity seen in MS patients treated with atacicept, the TACI-Fc clinical reagent [79]. The explanation for these phenotypes is not clear. It may relate to unknown activities of BAFF or APRIL. Alternatively, BAFF may control the survival or activity of regulatory B cells that make IL-10 and can participate in dampening inflammation.

Concluding remarks

The range of activities of TNFSF members continues to increase, extending the possible therapeutic indications for reagents that target these proteins. The data discussed here, together with prior data from animal models of disease (summarily depicted in Figure 1), suggest possible coordinate and/or temporal activities of many of the TNFSF receptor–ligand interactions in the pathogenesis of most inflammatory and autoimmune syndromes. Signaling studies of each individual receptor have shown a great deal of overlap in intracellular pathways targeted, with activation of both classical and nonclassical nuclear factor- κ B central to most TNFSF, as well as other commonalities [1]. Thus, the location of the receptors and their ligands (tissue and cell type), and the timing of their expression, may be most important in dictating which interaction is dominant at a specific stage of disease, and which interaction is an appropriate target for therapy. Given this issue of overlap in TNFSF activity, understanding which molecular interaction is the better target for a given inflammatory disease requires a more direct comparison of studies in both murine systems, as well as in trials with human patients. In clinical trials with anti-TNF, as well as with antibodies that block cytokines such as IL-5 and IL-13, often efficacy is observed only in a subset of patients. Understanding the expression patterns of TNFSF and TNFRSF molecules throughout the course of human disease may be important for understanding these clinical trial data, and may be essential for true translation of the research findings. The potential for real therapeutic benefit, however, is great and research in this area will no doubt continue to yield important insights in the future.

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Figure 1.

TNF family molecules implicated in driving inflammatory and autoimmune disease. The figure depicts the TNFSF and TNFRSF molecules that control disease in experimental models in the mouse. The figure is compiled using data reporting either a substantial or a partial block in symptoms in mice deficient in either the TNF family ligand or the TNFR family receptor, and/or in wild-type mice treated with neutralizing antibodies to the ligand or receptor.

Table 1

Expression characteristics of TNF family members.

Molecule (alternative names indicated)	Expressed by	Expression	Molecule (alternative names indicated)	Expressed by	Expression
CD27 (TNFRSF7)	CD4 ⁺ and CD8 ⁺ T cells B cells (subset) NK cells (subset) FOXP3 ⁺ Treg cells NKT cells Hematopoietic progenitors	Constitutive Inducible Constitutive Constitutive/inducible Constitutive Constitutive	CD70 (TNFSF7)	APCs (DCs and B cells) CD4 ⁺ and CD8 ⁺ T cells Mast cells NK cells Smooth muscle Thymic epithelium	Inducible Inducible Inducible Inducible Inducible Constitutive
DR3 (TNFRSF25)	CD4 ⁺ and CD8 ⁺ T cells NK cells NKT cells FOXP3 ⁺ Treg cells LTi cells	Constitutive/inducible Inducible Constitutive Constitutive/inducible Constitutive	TL1A (TNFSF15)	APCs (DCs, B cells, macrophages) CD4 ⁺ and CD8 ⁺ T cells Endothelial cells	Inducible Inducible Inducible
OX40 (CD134 and TNFRSF4)	CD4 ⁺ and CD8 ⁺ T cells NK cells NKT cells FOXP3 ⁺ Treg cells Neutrophils	Inducible Inducible Inducible Constitutive/inducible Inducible	OX40L (CD252 and TNFSF4)	APCs (DCs, B cells, macrophages) CD4 ⁺ and CD8 ⁺ T cells LTi cells NK cells Mast cells Endothelial cells Smooth muscle	Inducible Inducible Inducible Inducible Inducible Inducible Inducible
4-1BB (CD137 and TNFRSF9)	CD4 ⁺ and CD8 ⁺ T cells NK cells NKT cells Mast cells Neutrophils FOXP3 ⁺ Treg cells DCs Endothelial cells Eosinophils Osteoclast precursors	Inducible Inducible Inducible Inducible Inducible Constitutive/inducible Inducible Inducible Inducible Inducible	4-1BBL (TNFSF9)	APCs (DCs, B cells, macrophages) CD4 ⁺ and CD8 ⁺ T cells Mast cells NK cells Smooth muscle Hematopoietic progenitors Osteoclast precursors	Inducible Inducible Inducible Inducible Inducible Constitutive Inducible
CD30 (TNFRSF8)	CD4 ⁺ and CD8 ⁺ T cells B cells NK cells Macrophages Eosinophils	Inducible (constitutive in transformed cells) Inducible (constitutive in transformed cells) Inducible Inducible	CD30L (CD153 and TNFSF8)	T cells B cells Mast cells Monocytes Neutrophils Eosinophils	Inducible Inducible Inducible Inducible Constitutive Inducible

Molecule (alternative names indicated)	Expressed by	Expression	Molecule (alternative names indicated)	Expressed by	Expression
CD40 (TNFRSF5)	Basophils APCs (DCs, B cells, Macrophages) Epithelial cells Endothelial cells Smooth muscle cells Fibroblasts	Constitutive Constitutive Inducible Constitutive Inducible Inducible	CD40L (CD154 and TNFSF5)	CD4 ⁺ and CD8 ⁺ T cells B cells Eosinophils Mast cells Monocytes Macrophages NK cells Endothelial cells Smooth muscle cells Epithelial cells	Inducible Inducible Inducible Inducible Inducible Inducible Inducible Inducible Inducible
HVEM (CD270 and TNFRSF14)	CD4 ⁺ and CD8 ⁺ T cells APCs (DCs, B cells, Macrophages) NK cells Neutrophils Mucosal epithelium FOXP3 ⁺ Treg cells	Constitutive Constitutive/inducible Constitutive Constitutive Constitutive Constitutive/inducible	LIGHT (CD258 and TNFSF14)	CD4 ⁺ and CD8 ⁺ T cells B cells DCs NK cells Granulocytes and monocytes	Inducible Inducible Inducible Inducible Inducible
L1βR (TNFRSF3)	Stromal cells Epithelial cells DCs and macrophages Fibroblasts	Constitutive Constitutive Constitutive Constitutive	L1α1β2	T cells B cells NK cells	Inducible Constitutive Constitutive
GITR (CD357 and TNFRSF18)	CD4 ⁺ and CD8 ⁺ T cells NK cells NKT cells B cells FOXP3 ⁺ Treg cells Macrophages DCs	Constitutive/inducible Inducible Constitutive/inducible Constitutive/inducible Constitutive Constitutive/inducible Inducible	GITRL (TNFSF18)	APCs (DCs, B cells, macrophages) CD4 ⁺ and CD8 ⁺ T cells Endothelial cells	Constitutive Inducible Constitutive
TAC1 (CD267 and TNFRSF13B) BAFF-R (CD268 and TNFRSF13C) and BCMA (CD269 and TNFRSF17)	B cells CD4 ⁺ T cells (BAFF-R) FOXP3 ⁺ Treg cells (BAFF-R)	Constitutive/inducible Inducible Constitutive	BAFF (CD257 and TNFSF13B) and APRIL (CD256 and TNFSF13)	Neutrophils Basophils APCs (DCs, B cells, macrophages) T cells	Inducible Inducible Inducible Inducible