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Beyond TNF: TNF superfamily cytokines as targets for the treatment of rheumatic diseases

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Abstract

TNF blockers are highly efficacious at dampening inflammation and reducing symptoms in rheumatic diseases such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and also in nonrheumatic syndromes such as inflammatory bowel disease. As TNF belongs to a superfamily of 19 structurally related proteins that have both proinflammatory and anti-inflammatory activity, reagents that disrupt the interaction between proinflammatory TNF family cytokines and their receptors, or agonize the anti-inflammatory receptors, are being considered for the treatment of rheumatic diseases. Biologic agents that block B cell activating factor (BAFF) and receptor activator of nuclear factor-κB ligand (RANKL) have been approved for the treatment of systemic lupus erythematosus and osteoporosis, respectively. In this Review, we focus on additional members of the TNF superfamily that could be relevant for the pathogenesis of rheumatic disease, including those that can strongly promote activity of immune cells or increase activity of tissue cells, as well as those that promote death pathways and might limit inflammation. We examine preclinical mouse and human data linking these molecules to the control of damage in the joints, muscle, bone or other tissues, and discuss their potential as targets for future therapy of rheumatic diseases.

Over 30 years have passed since the molecular identification of TNF as a mediator of fever and cachexia[1], and approximately 20 years since the first introduction of TNF inhibitors into clinical practice for the treatment of rheumatoid arthritis (RA)[2]. During this time, much has been learned about the basic biology of the 19 structurally related cytokines of the TNF superfamily (TNFSF), their receptors (TNF receptor superfamily, TNFRSF), the intracellular signalling pathways activated by these receptors, as well as the unique and overlapping roles of TNFSF cytokines in a number of inflammatory and autoimmune diseases. TNFSF proteins organize lymphoid tissue development, co-stimulate lymphocyte activation and can

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Author contributions

Both authors researched data for the article and made a substantial contribution to discussion of content, writing, reviewing and editing of the manuscript before submission.

Competing interests statement

M.C. has licensed patents on several TNF superfamily molecules. R.S. has issued patents on antibodies against the TNF superfamily molecule TL1A.

either increase lymphocyte survival and function or induce cell death[3–6]. Outside the immune system, TNFSF cytokines can promote the development and survival of osteoclasts, as well as cells in the mammary glands, hair follicles and sweat glands. TNFSF cytokines can also regulate neuronal activity and drive inflammatory responses in a range of tissue structural cells, including epithelial cells and fibroblasts. These insights have led to intensive efforts to treat other inflammatory diseases through TNF neutralization, and multiple TNF-blocking agents (such as adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are now approved for diseases such as juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, spondylarthropathies, inflammatory bowel disease and uveitis[7,8] (TABLE 1). Investigations into the targeting of other TNFSF members have led to a number of clinical trials in different diseases and resulted in the successful development of belimumab, an antibody against B cell activating factor (BAFF, also known as TNFSF13B), and denosumab, an antibody targeting receptor activator of nuclear factor-κB (NF-κB) ligand (RANKL, also known as TNFSF11), for the treatment of systemic lupus erythematosus (SLE) and osteoporosis, respectively[9–11].

Clinical targeting of TNF, BAFF and RANKL has been reviewed elsewhere[7–10,12–17], as has the targeting of all the TNF and TNFRSF members in both immune and nonimmune disorders[11]. In this Review, we focus on TNF family proteins that are produced by the immune system but are not yet targets of approved drugs. These molecules might be crucial to the immune response underlying rheumatic diseases and are promising future targets for intervention and therapy in diseases such as RA and SLE (FIG. 1). Although blocking nerve growth factor binding to its receptor TNFRSF16 (also known as nerve growth factor receptor) is of primary interest for the treatment of pain associated with osteoarthritis, TNFRSF16 is not an immune-system-related molecule and so we do not present a discussion here but refer readers to several other published articles[11,18–21].

TNF superfamily

Multiple functional polymorphisms in the genes encoding TNFSF cytokines, their receptors and their signalling proteins are associated with susceptibility to autoimmune diseases[11,22]. Yet, many functions of TNFSF proteins remain poorly understood. TNFSF and TNFRSF proteins have many structural and biological similarities (FIG. 1). TNFSF molecules are trimeric type II transmembrane proteins characterized by C-terminal TNF homology domains that can be cleaved from cells to form soluble ‘cytokine-like’ molecules[23]. Their receptors are type I transmembrane proteins that have varying numbers of extracellular ligand-binding cysteine-rich domains[23]. The extracellular domains of the TNFRSF can also be cleaved to form soluble molecules, which might be useful as biomarkers for inflammation, although their exact function is not clear. Engagement of receptors by their cognate ligands is thought to primarily lead to trimerization of the receptors, which can further form higher-order oligomers on a cell’s surface. Although overall sequence similarity between TNFRSF molecules is low (20–30%), once engaged by their cognate ligands they can drive common or overlapping signalling pathways[24–26] (FIG. 2). Moreover, membrane-bound TNF family ligands can also signal through themselves when engaged to their cognate receptors (a process known as reverse signalling), which might contribute to their function. When crosslinked on the surface of cells, various consequences of reverse

signalling have been described, such as proinflammatory cytokine production (for example IL-1 and IL-6) and cell maturation, which depend on the cell type that receives the TNFSF ligand signal[27].

The expression of TNF family proteins is quite broad and dynamically regulated (FIG. 1). Many ligand–receptor pairs are constitutive or inducible on lymphocytes, including antigen presenting cells (APCs; such as dendritic cells, macrophages and B cells) and T cells, and normally participate in promoting T and B cell responses, which are central to most autoimmune and rheumatic diseases. Similarly, death-inducing molecules can also be expressed by lymphocytes, and participate in maintaining self-tolerance and limiting adaptive immune responses. Additionally, a number of TNF family ligands and/or receptors are constitutive or inducible in non-lymphoid cells including epithelial cells, fibroblasts, smooth muscle cells, and endothelial cells. These molecules participate in the proinflammatory and anti-inflammatory crosstalk that occurs between tissue structural cells and the immune system, which might either contribute to autoimmune tissue pathology or limit damage.

Below, we discuss the biological activities of TNFSF members and their potential involvement in rheumatic diseases. For simplicity, we have grouped TNFSF proteins, as described above, into immune cell activators, tissue inflammatory proteins and molecules that induce cell death or immune suppression. This classification is not absolute and the reader should be aware that molecules such as TNF, CD40 ligand (CD40L, also known as TNFSF5), LIGHT (also known as TNFSF14), TNF-like ligand 1A (TL1A, also known as TNFSF15), and TNF-related apoptosis inducing ligand (TRAIL, also known as TNFSF10) can exert functions on both immune cells and tissue cells (FIG. 1). Moreover, a number of proteins, including TNF and Fas ligand (FasL, also known as TNFSF6), are able to promote cell death as well as being proinflammatory, depending on the target cell type and the context in which they are active.

Immune cell activation

CD40L

CD40 (also known as TNFRSF5) is a stimulatory receptor expressed on dendritic cells, macrophages and B cells, whose signals drive activation, maturation, survival and inflammatory cytokine production[28,29] (FIG. 3). CD40 is crucial in both inducing IgG autoantibodies and driving immunoglobulin class switching[30,31], and is also a primary driver of T cell immunity. Its ligand, CD40L, is induced in T cells shortly after activation and, via ligation of CD40 on professional APCs, can lead to an increase in antigen presentation and activation of T cells by upregulating MHC molecules and inducing expression of stimulatory ligands such as CD86 and those belonging to the TNF superfamily, which are described below (for example OX40 ligand (OX40L))[32,33].

Studies have long linked the interaction between CD40L and CD40 to rheumatic disease pathogenesis. In the early 1990s, studies of multiple autoimmune models, including collagen-induced arthritis and lupus-like disease in NZB/SWR or NZB/NZW F1 mice[34–36], demonstrated markedly reduced signs of inflammation in mice lacking either CD40 or

CD40L, or in wildtype mice treated with CD40L blocking reagents. Similar to other molecules discussed below, the idea that the CD40L–CD40 axis is also active in human disease largely derives from expression studies in patients. The caveat with expression studies is that detection of the molecules in serum or tissues does not automatically imply they are functional or important, but could simply reflect the presence of activated immune cells. However, such data, particularly for conventional cytokines such as IL-5, IL-13, and IL-17, has aided their clinical targeting and enabled patient stratification into those most likely to respond to biologic agents. Therefore, with TNFSF molecules the expression data are highly useful regardless of the caveats, especially if linked to either other disease markers or the magnitude of clinical symptoms. Soluble CD40L in serum, or CD40L expression in inflamed tissue, epithelial cells, endothelium or T cells, is upregulated in patients with RA, psoriatic arthritis, ankylosing spondylitis, SLE, Sjögren syndrome and systemic sclerosis (Ssc), often correlating with disease severity or levels of autoantibodies[28,29]. Additionally, polymorphisms near the genes encoding CD40L or CD40, which are thought to lead to elevated or prolonged expression, have been associated with susceptibility to SLE, RA and other rheumatic disorders (such as Behçet disease)[37–44].

Animal studies have shown that the neutralization of CD40L has a strong suppressive effect on pathogenic T cell development and antibody responses. These results, together with data from human expression and association studies, made CD40L an attractive therapeutic target for rheumatic diseases, particularly SLE and RA. As reviewed elsewhere[11,28,29], phase I–II trials in several patient groups, including patients with lupus nephritis, demonstrated some beneficial activity of antibodies against CD40L (such as ruplizumab, ab1793 and toralizumab)[45–47]. Unfortunately, the thromboembolic activity of these antibodies, linked to crosslinking of CD40L expressed by platelets, led to discontinuation of their further development (TABLE 1). To circumvent the thromboembolic effect, preclinical studies in mice or nonhuman primates are assessing new biologic agents that block CD40L without causing aggregation of the molecule; these biologic agents either lack an Fc region or are mutated to prevent their binding to Fc receptors. Results suggest that they can be as efficacious as the parent (Fc intact) antibody — without the thromboembolic effect — in scenarios such as animal models of lupus[48–50]. However, in certain settings Fc effector function might be necessary for therapeutic activity, as shown by the lack of activity of an aglycosylated anti-CD40L antibody in nonhuman primate transplantation studies[48]. MEDI4920, a Tn3-fusion protein with reactivity to CD40L, is currently in phase I safety trials. Additionally, antagonist and/or depleting antibodies against CD40 have been produced (ch5D12, chi220–BMS-224819, ASKP1240, FFP104, CFZ533), with encouraging preclinical results[51], and some of them are being tested in phase I–II trials in Sjögren syndrome[52], RA[53] and other autoimmune conditions (TABLE 1). If these strategies can overcome the adverse effects associated with agents that block CD40-C40L interactions, such agents are an attractive avenue, and the possibility for clinical benefit in rheumatic diseases is high.

OX40L

OX40L (also known as TNFSF4) is an inducible molecule expressed on several cell types, although arguably most importantly, on APCs. OX40 (also known as TNFRSF4) is largely

found on activated T cells as well as natural killer T cells and innate lymphoid cells such as natural killer cells[5,54] (FIG. 3). OX40L can trigger signalling through its receptor OX40, resulting in a range of activities including expansion and accumulation of effector T cells (such as type 1 T helper cells (T_H1), type 2 T helper cells (T_H2), type 17 T helper cells (T_H17) and cytotoxic T lymphocytes) and their cytokine production[5,6,11,54]. Additionally, reverse signalling through OX40L can promote expression of inflammatory cytokines (such as IL-12 or TNF) in APCs[5,54], although the importance of this activity as compared with that driven by OX40 is not clear at present.

Data from human and mouse studies suggest that the OX40–OX40L axis has an important role in rheumatic diseases. Blockade of OX40L reduces bone and cartilage destruction in mouse models of collagen-induced arthritis[55,56] or autoimmune arthritis[57], with results from the former model being attributed to reduced numbers of collagen-specific T cells. Synovial fluid samples of patients with RA contain elevated numbers OX40-expressing T cells, suggesting OX40 signalling controls T cell numbers in human RA[56,58]. Targeting of OX40 with cytotoxic drugs to deplete T cells has also shown some therapeutic benefit in an animal model of adjuvant arthritis[59]. Surprisingly, signalling via OX40L antagonizes the activity of RANK in promoting osteoclast development from macrophage progenitors. OX40L-deficient mice are accordingly osteopenic[56], although the implication of this finding in the context of therapeutic inhibition of OX40–OX40L interactions in arthritis is not clear.

In patients with SLE who have proliferative glomerulonephritis, OX40L is upregulated in glomeruli, most likely on endothelial cells[60] and/or dendritic cells[61]. Similarly, studies have shown that in peripheral blood and renal biopsy samples from patients with lupus nephritis, OX40 expression by $CD4^+$ T cells correlates with disease activity, urine proteinuria and serum creatinine[62–65]. Furthermore, on the basis of an initial report[66], many studies have confirmed an association between susceptibility to developing SLE and polymorphisms upstream of the *OX40L* gene (also known as *TNFSF4*), which probably leads to its increased expression. The OX40–OX40L axis is also involved in kidney disease, as patients with Henoch–Schönlein purpura with nephritis have elevated levels of serum OX40L and $OX40^+$ T cell numbers compared with patients without nephritis[67]. Surprisingly, no reports have yet demonstrated a functional role for these molecules in mouse models of nephritis, even though human studies imply that OX40–OX40L crosstalk between T cells and endothelial or dendritic cells might contribute to disease.

As well as controlling the accumulation and/or activity of pathogenic effector T cells, OX40–OX40L interactions have been associated with production of pathogenic antibodies. Transgenic mice overexpressing OX40L display elevated levels of anti-DNA antibodies[68]. Furthermore, soluble OX40 and/or OX40L are increased in the plasma of patients with early-stage RA compared with healthy individuals, and correlate with levels of anti-citrullinated protein antibodies and IgM rheumatoid factor[69]. Similarly, an association between OX40L expression on myeloid APCs (dendritic cells and monocytes), SLE disease activity and anti-ribonucleoprotein (RNP) antibodies has been described[61]. As activated B cells express OX40L, this ligand could directly signal and contribute to autoantibody production. However, the primary rationale for the association with anti-RNP antibodies is that OX40L on dendritic cells can signal via OX40 expressed by T cells and might aid

formation of follicular T helper cells that drive B cell differentiation[61]. An association between polymorphisms in the OX40L locus and Sjögren syndrome or SSc has also been confirmed in multiple studies[70,71], with levels of soluble serum OX40 being elevated in patients with early-stage SSc[72]. Lastly, biopsy samples from patients with Wegener granulomatosis, another rheumatic disease that is associated with elevated levels of anti-neutrophil cytoplasmic antibodies (ANCA) and glomerulonephritis[73], contain OX40-expressing T cells[73]. Although clinical grade drugs that neutralize OX40L (such as oxelumab and KY1005) or OX40 (such as KHK4083) exist, at present no trials have attempted to target the OX40–OX40L interaction in rheumatic diseases (TABLE 1). However, such interventions have strong therapeutic potential and might be beneficial, particularly in RA and SLE.

TL1A

Death receptor 3 (DR3, also known as TNFRSF25) is another stimulatory receptor expressed by T cells (FIG. 3) that can regulate effector cell accumulation and/or reactivity regardless of T helper phenotype[74–76]. Its ligand, TNF-like ligand 1A (TL1A, also known as TNFSF15), can be induced in APCs such as dendritic cells and macrophages, as well as in endothelial cells[5,6,11,77,78]. TL1A–DR3 interactions might drive many inflammatory responses, especially mucosal inflammation[77,79], and increasing evidence suggests a role in rheumatic disease.

Levels of TL1A are elevated in the synovial fluid and serum of patients with RA, and are associated with both autoantibody levels and atherosclerotic lesion development[80–86]. Interestingly, human synovial fibroblasts are capable of expressing TL1A after stimulation with TNF or IL-1β, suggesting a potential local source of TL1A in addition to professional APCs[82]. In line with the notion that soluble TL1A could be pathogenic in RA, injection of recombinant TL1A into mice with already-developed collagen-induced or bovine serum albumin (BSA)-induced arthritis leads to an increase in the severity of disease, including increased cartilage damage, bone destruction and increased levels of autoantibodies[82,87]. In these arthritis models, DR3 and TL1A deficiency, or TL1A inhibition in wild-type mice, resulted in reduced swelling and bone erosions, and/or increased kinetics of disease resolution, demonstrating the therapeutic potential of targeting TL1A[87–89]. The reason for reduced disease activity is not clear but could be due to a combination of lower T-cell activity and reduced infiltration of destructive cells such as neutrophils, which is possibly linked to defective chemokine expression. An alternative explanation is that TL1A could have a role in enhancing RANKL-triggered osteoclast differentiation in macrophage precursors that express DR3 (REF. 87). This process could cooperate with the immune-mediated inflammatory effects of TL1A and contribute to bone dysregulation. Although genome-wide association studies have not identified TL1A or DR3 as susceptibility loci for inflammatory arthritides, a duplication in the gene encoding DR3 (*TNFRSF25*) has been linked to RA[90]; in addition, an association study indicated that several SNPs downstream of the gene encoding TL1A (*TNFSF15)* were linked to the development of spondyloarthritis (SpA)[91]. SpA, a disease closely related to RA, can be characterized by gut inflammatory phenotypes and T_H17 cells are thought to be involved in SpA pathogenesis; both of these features are known to be connected with TL1A activity[77–79]. Lastly, DR3 and/or TL1A were

found to be upregulated in lesional skin plaques and serum from patients with psoriasis, another disease with a T_H17 component that can be directly associated with arthritis[92,93]. Although the implications of these observations regarding the pathogenesis of SpA and psoriasis are not clear, these data suggest that DR3 and TL1A are involved in bone and joint disorders and manifestations that arise from these inflammatory diseases.

Data directly implicating TL1A involvement in SLE pathogenesis are currently lacking, except for one report describing a weak correlation between elevated TL1A levels in serum and SLE disease activity[94]. However, during acute kidney allograft rejection, renal tubular epithelial cells express DR3 (REF. 95), and renal vascular endothelial cells express TL1A[96]. DR3 activity might be protective against nephrotoxicity in some settings[96,97], but whether these molecules contribute to nephritis as seen in SLE is an open question. Overall, the data presented above indicate that inhibition of TL1A–DR3 activity might be beneficial for patients with arthritis, and possibly for those with other autoimmune conditions such as SLE.

GITRL

Glucocorticoid-induced TNF receptor-related ligand (GITRL, also known as TNFSF18) is an inducible molecule expressed in professional APCs, and other cell types such as endothelial cells. Its receptor, glucocorticoid-induced TNF receptor-related protein (GITR, also known as TNFRSF18), can stimulate T cell, dendritic cell and B cell activation (FIG. 3). Studies have implicated these molecules in controlling many immune-inflammatory responses, although functional data relating them to rheumatic disease are largely restricted to arthritis at present[6,11,98,99]. GITR-deficient mice display reduced joint inflammation in collagen-induced arthritis compared with wild-type mice, including decreased T-cell reactivity and lower levels of inflammatory mediators such as TNF[100]. Serum from patients with RA have increased levels of GITRL compared with healthy controls, a finding associated with increased IL-17 levels[101]. Furthermore, GITR and GITRL have been detected in synovial tissue sections from patients with RA (primarily in T cells and macrophages); synovial fluid from these patients has also been found to contain both GITR and GITRL as soluble molecules[102,103]. In line with the idea that soluble GITRL is pathogenic, injection of recombinant GITRL into mice with collagen-induced arthritis increases disease kinetics and clinical symptoms[101], as does treatment with an agonistic GITR antibody[104]; this treatment also increases production of the T-cell-derived inflammatory cytokines such as IL-17, TNF and IFNγ[101,104]. Furthermore, stimulation of GITR on synovial fluid macrophages leads to upregulation of several inflammatory proteins including TNF, IL-6 and MMP-9 (REF. 102). Lastly, soluble GITRL and/or GITR might represent useful biomarkers for other rheumatic diseases, as in patients with SLE or Sjögren syndrome the levels of these molecules are increased[105,106]. Given that their expression correlate with disease severity[105,106], GITR–GITRL activity might also contribute to the pathogenesis of these diseases

CD70

CD27 (also known as TNFRSF7) is constitutively expressed on most T cells, and the interaction with its ligand CD70 (also known as TNFSF7) can provide signals to T cells to

control their accumulation and reactivity, similarly to that seen with OX40, GITR and DR3 (REFS 3–5) (FIG. 3). In addition to T cells, CD70 is inducible on dendritic cells and B cells, and can induce reverse signals within these APCs to increase their activation status[27], therefore participating in the crosstalk between T cells and B cells and antibody production. Genetic deletion or neutralization of either CD27 or CD70 in mice has revealed a pathogenic role for the CD27–CD70 axis in many inflammatory settings[4–6,107]. For example, in mice with collagen-induced arthritis, blocking CD27–CD70 interactions with anti-CD70 antibody reduces bone and cartilage erosion and inflammatory infiltrates in the joints, and decreases collagen-specific antibody production, even when the treatment is initiated after disease onset[108]. In the synovial fluid of patients with RA, soluble CD27 levels and $CD27^+$ T cell numbers are elevated and correlates with the levels of rheumatoid factor, supporting a role for CD27 in human RA[109]. Furthermore, in patients with RA, CD70 expression is increased in $CD4^+$ T cells that produce the effector cytokines IFNγ and IL-17 (REFS 110,111). Although the implication of this upregulation is not clear, these $CD4^+$ T cells are probably highly pathogenic, given that ligation of CD27 on B cells by CD70 can promote B cell differentiation. Synovial fluid samples from patients with juvenile idiopathic arthritis are also characterized by increased expression of soluble CD27 (REF. 112).

A correlation between CD27 or CD70 expression and disease activity is also observed in other rheumatic diseases, although functional data are in general lacking at present. Soluble CD27 levels correlate with disease activity in patients with SLE[113,114], and the proportion of plasma cells expressing high levels of CD27 additionally correlates with SLE disease indices[115]. Furthermore, several studies showed that T cells derived from patients with SLE express high levels of CD70 and are capable of driving B cell antibody production via CD27 (REF. 116). Similarly, T cells from MRL/lpr mice with lupus-like disease overexpress CD70 (REF. 117), although no studies to date have shown if CD70 expression is required for disease onset in these mice. Interestingly, plasmacytoid dendritic cells (pDCs), which are thought to be central to SLE pathogenesis via their type I interferon production, can strongly express CD70 (REF. 118). These pDCs can drive antibody secretion by B cells via CD27 without the participation of T cells, implicating pDCs as another important source of CD70. $CD4^+$ T cells from patients with SSc and Sjögren syndrome have also been found to express high levels of CD70 (REFS 119,120). Thus, neutralizing the interaction between CD27 and CD70 could potentially dampen disease activity in RA and/or other diseases such as SLE. A clinical-grade antibody to CD70 (SGN-75) has been developed and conjugated to a toxin for targeting $CD70^+$ B cell cancers[11]. This reagent could be used, with or without toxin, for treatment of rheumatic disease, although no trials have so far been initiated.

4-1BBL

4-1BB (also known as TNFRSF9) is an inducible stimulatory receptor expressed on T cells and innate lymphoid cells that can promote their accumulation and/or activity; expression of its ligand, 4-1BBL (also known as TNFSF9), is also inducible on professional APCs[5,6,121]. 4-1BB is similar to the molecules described above in terms of intrinsic activity (FIG. 3); As with OX40, GITR and CD27, 4-1BB is currently being targeted with receptor agonists to promote antitumour T-cell responses in the context of clinical cancer immunotherapy [122]. However, only a few studies have shown 4-1BB and 4-1BBL involvement in inflammatory

disease pathogenesis[5,6,121]. As such, little data has been generated with regard to rheumatic disease. Serum samples of patients with RA contain elevated levels of soluble 4-1BB and 4-1BBL, which correlate with disease severity[123,124]. Nevertheless, in collagen-induced arthritis in mice, a reagent that blocks the interaction between these two molecules had only a moderate effect in suppressing disease symptoms such as T-cell reactivity and inflammatory cytokines[125]. Although this finding does not exclude a role for 4-1BBL-4-1BB interactions in promoting RA in humans, it is in contrast to the much more robust data obtained when other TNF family molecules (such as OX40L, CD70, GITRL and TL1A) were targeted in the same arthritis model. On the other hand, stimulation of 4-1BB with receptor agonists results in strong suppression of joint inflammation and bone destruction in mouse models of RA[125,126]. This finding is not consistent with the idea that endogenous 4-1BB-4-1BBL interactions promote development or activity of pathogenic T cells in RA. A similar conclusion might be true for SLE; indeed, 4-1BB-deficiency in lupus-prone MRL/lpr mice exacerbates rather than ameliorates disease[127], in line with a regulatory rather than pathogenic role. Similar to mouse models of arthritis, 4-1BB agonists also fully inhibit lupus-like disease in MRL/lpr and NZB/NZW F_1 mice, including reduction of skin lesions, lymphadenopathy, autoantibody production and nephritis[128–130]. These results suggest that the neutralization of 4-1BB or 4-1BBL might have little effect in rheumatic disease, whereas stimulation of 4-1BB could dampen inflammation.

Increasing tissue inflammation

Lymphotoxin and LIGHT

Lymphotoxin and LIGHT (also known as CD258 and TNFSF14, respectively) are TNFSF cytokines with interrelated functions that are similar to those of TNF. They can control T cell and APC responsiveness, and importantly, have marked effects on both development and homeostasis of lymphoid tissue and structural cell responses of non-haematopoietic tissue [131–134] (FIG. 4). Soluble lymphotoxin (also known as LTα or TNFSF1) is a homotrimer that binds TNF receptors (TNFR1 and TNFR2), but might often be redundant with TNF. In RA, anti-TNF antibodies have been found to be as clinically effective as etanercept, a TNFR2-Fc fusion protein that blocks both LTα and TNF[135], and in a clinical trial of RA, pateclizumab, a specific blocker of LTα, showed much reduced efficacy compared with the TNF blocker adalimumab[136]. These findings do not rule out an important role for LTα in some inflammatory diseases, but suggest that its role is secondary to that of TNF when TNF is present in abundance. By contrast, the other version of lymphotoxin, LTαβ might exert distinct and unique functions compared with TNF and LTα. LTαβ is membrane-bound heterotrimer composed of LTα and a distinct β subunit, and exclusively binds to the LTβ receptor (LTβR, also known as TNFRSF3)[137]. LTαβ is constitutively expressed on resting B cells and can also be induced in activated T cells. LTβR is expressed on some haematopoietic cells, such as dendritic cells and macrophages, but importantly, is expressed on tissue stromal cells such as fibroblasts, adipocytes, hepatocytes, endothelial cells, fibroblastic reticular cells, smooth muscle cells and epithelial cells[137]. Studies of gene-knockout mice have shown a non-redundant role for LTαβ–LTβR interactions in controlling the development of lymph nodes and Peyer patch structures, which is due to the absence of LTβ-dependent RANKL production[137]. RANKL acts on stromal cells to induce chemokine

expression, which is critical for recruitment and proper positioning of lymphocytes within these structures[137]. In mature lymphoid tissue, LTαβ signals through LTβR in follicular dendritic cells, controlling the expression of adhesion molecules (vascular cell adhesion protein 1 (VCAM1) and mucosal addressin cell adhesion molecule 1 (MADCAM1)), as well as chemokines, which maintain B cell organization in follicles[137]. These mechanisms have also been implicated in controlling the arrangement of immune cells in tertiary lymphoid structures, which occur in tissues undergoing chronic inflammatory responses[137].

LIGHT binds to LTβR and also to a receptor termed herpes virus entry mediator (HVEM, also known as TNFRSF14). LIGHT can be expressed by activated T cells and other lymphoid cells, and HVEM is expressed on many haematopoietic cells in addition to the same structural cells that express LTβR (such as fibroblasts, epithelial cells and smooth muscle cells)[132–134]. Whereas LIGHT does not participate in controlling lymphoid organogenesis, growing evidence suggests that its activity in tissue cells, via both LTβR and HVEM, might be a strong component of the remodelling processes characteristic of many chronic inflammatory and autoimmune diseases, including epithelial–mesenchymal transition and myofibroblast differentiation[134] (FIG. 4). The physiological role of LTβR and HVEM might be to protect the epithelium and other tissues against injury or infection[138,139]. However, their reported activities in epithelial cells, fibroblasts, osteoclasts, adipocytes and hepatocytes suggest that if LIGHT or LTαβ are produced in excess these receptors directly or indirectly induce the production of inflammatory cytokines, chemokines, extracellular matrix proteins and proteinases. These effects are similar to that seen with TNF–TNFR1 activity, implying that these molecules cooperate in orchestrating tissue inflammation[134,140–144].

An Fc fusion protein of LTβR, which can neutralize both LTαβ and LIGHT, can block disease symptoms in many mouse models of rheumatic disease, including collagen-induced and adjuvant arthritis, several models of SLE and the Sjögren-syndrome-like salivary gland inflammation of non-obese diabetic mice[131–133,145–148]. Additionally, genetic deletion of LIGHT protects mice from lung and skin inflammation and tissue remodelling in models of SSc[144,149]. Despite these results, targeting the LTαβ–LIGHT axis with baminercept, a soluble LTβR-Fc fusion protein, did not demonstrate clinical efficacy in RA and Sjögren's syndrome (TABLE 1), although some modulation of immune reactivity was noted[150]. A caveat of these trials was the recruitment of difficult-to-treat patient populations that had previously shown inadequate responses to TNF inhibitors or other DMARDs. More specific reagents targeting LIGHT, LTβ or their receptors still have potential for the treatment of rheumatic diseases that involve tissue remodelling and inflammation, although they are more likely to be efficacious in patients who are also responsive to TNF-directed therapy. A fully human LIGHT blocking antibody has been generated and has successfully completed phase I safety trials (TABLE 1); this antibody is currently entering phase II studies of paediatric inflammatory bowel disease but hasn't yet entered any trials for rheumatic disease.

TWEAK

TNF-related weak inducer of apoptosis (TWEAK, also known as TNFSF15) has high degree of homology with TNF and is thought to primarily act on tissue cells[151,152]. TWEAK is

produced by a large range of myeloid and immune cells, but its receptor, fibroblast growth factor-inducible 14 (Fn14, also known as TNFRSF12A), is more highly expressed on non-haematopoietic cells than on lymphoid cells. Fn14 is upregulated by fibroblast-like growth factor[153,154], as well as by other factors associated with injury and inflammation[151]. TWEAK has pleiotropic effects in stromal cell types, including regenerative-like activities in hepatocytes, endothelial cells, myocytes and epithelial cells[152] (FIG. 4). Arguably, the physiological role of the TWEAK–Fn14 axis is to protect against tissue injury, but like the LIGHT–LTαβ axis, if TWEAK or Fn14 are excessively produced they could drive and orchestrate inflammation, fibrosis and tissue remodelling.

TWEAK and Fn14 are elevated in the synovium and serum of patients with RA and/or psoriatic arthritis, with levels correlating with disease severity in some instances, although their levels in joints are not affected by TNF inhibitor treatment[155–158]. In normal fibroblasts or fibroblast-like synoviocytes, TWEAK can induce proliferation and upregulate the production of inflammatory cytokines such as IL-6, chemokines, adhesion molecules and proteinases[159–162]. As such, blocking TWEAK reduces disease severity in collagen-induced arthritis in mice without affecting titres of anti-collagen antibodies[163,164], suggesting that TWEAK largely contributes to inflammation and bone destruction locally in the joint. Osteoclasts express Fn14, and consequently TWEAK can promote osteoclastogenesis, which is relevant to RA pathogenesis[165]. These data suggest that neutralizing TWEAK has the potential to dampen disease activity in RA. Phase I trials of a blocking antibody against TWEAK (BIIB023) have been conducted in patients with RA[166], but further trials in RA have not yet been pursued (TABLE 1).

TWEAK has also been implicated in kidney disease. Fn14 deficiency or TWEAK blockade reduces a variety of renal pathologies in several mouse models of disease, including fibrosis after ureteral obstruction[162], folate-induced interstitial nephritis[167], nephrotoxic serum-induced immune complex glomerulonephritis[168] and nephritis associated with chronic graft-versus-host disease[169]. Additionally, in Fn14-deficient mice, renal, neuropsychiatric and dermatological manifestations were considerably reduced in the MRL/lpr model of spontaneous lupus-like autoimmunity[170–172]. As with collagen-induced arthritis, titres of systemic auto-antibodies were not affected in these studies, further suggesting that Fn14 mediates local effects in target tissues. Which cell types receive Fn14 signals in the context of lupus nephritis or other kidney disease is an unresolved question. However, TWEAK can stimulate inflammatory mediator production (cytokines and/or chemokines) *in vitro* by a variety of different kidney cell types, including renal tubular epithelial cells, podocytes and mesangial cells[167,173,174]. In human SLE, TWEAK can serve as a urinary biomarker for nephritis[175]. Despite these promising results, a trial investigating the efficacy of anti-TWEAK antibodies in SLE was terminated following failure to increase rates of renal remission in patients with nephritis already being treated with mycophenolate[176] (TABLE 1).

Cell death and immunosuppression

FasL and TRAIL

FasL and TRAIL have a potent ability to induce apoptosis. FasL can promote apoptosis in activated primary B cells, T cells and dendritic cells through Fas (also known as TNFRSF6)[174,175], and TRAIL has been shown to induce apoptosis in activated mouse $CD8^+$ T cells via TRAIL receptor 1 (TRAILR1, also known as TNFRSF10A) or TRAILR2 (also known as TNFRSF10B)[177–179]. Defective activity of the FasL–Fas or TRAIL–TRAILR axis might increase the susceptibility to autoimmune disease. Genetic defects in FasL, or more commonly in Fas, result in spontaneous autoimmunity in mice and in auto-immune lymphoproliferative syndrome in humans[180–184]. TRAIL-deficient mice are hypersensitive to diseases such as collagen-induced arthritis[185]. Less is known about the role of TRAIL and its receptors in human cells. Although activated human T cells express TRAILR1 and TRAIL2, unlike FasL, TRAIL does not generally induce apoptosis in these cells[186]. Dendritic cells might be more relevant targets for TRAIL in the human immune system as a deficiency in caspase 10, which is activated by TRAIL, underlies a variant of autoimmune lymphoproliferative syndrome, which is marked by accumulation of these cells[187]. For these reasons, the function of FasL and TRAIL is mainly to restrain persistent immune responses to curb autoimmunity. Fas and TRAILRs can also be expressed outside the immune system; crosslinking of these molecules on cells such as synovial fibroblasts or dermal fibroblasts, which are associated with RA and SSc, respectively, might induce apoptosis[188,189]. However, either an elevated activation state or increased proliferative activity of such cells might make them more resistant to the effects of the naturally produced death-inducing ligands[189,190], which could be another contributing factor to diseases such as RA.

The apoptotic potential of FasL and TRAIL, either to dampen activity of autoreactive T cells or to kill highly proliferative tissue cells, has led to the hypothesis that recombinant FasL or TRAIL, or biologic agents acting as receptor agonists, could be candidate therapeutics for rheumatic diseases[191]. Results from experimental studies on the injection of various forms of FasL or TRAIL into rodents have reinforced this idea[192–196]. However, several factors might hinder this therapeutic strategy. Fas engagement has the potential to cause off-target effects, as exemplified by induction of hepatocyte cell death and acute liver failure in mice injected with Fas agonists[197]. Although all activated T cells express Fas, stimulation with this molecule fails to induce efficient apoptosis of memory T cells or T cells in the early stages of activation, which are the likely T cells that would be active in rheumatic diseases[178,198]. Rather, Fas might stimulate T-cell activation in some scenarios[199–201]. Some data suggest that fibroblast-like synoviocytes can be induced to proliferate when treated with soluble FasL or with low doses of agonist Fas antibody, whereas only oligomeric FasL or high doses of anti-Fas agonists induce apoptosis[202,203]. These factors further complicate the development of biologic agents to stimulate Fas or TRAILRs that might be therapeutically useful in rheumatic diseases.

Challenges and limitations

Is targeting one TNFSF member enough?

Several potential challenges exist when looking at modulating the activity of TNF family members other than TNF in rheumatic diseases. Blockade of TNF is highly efficacious in treating patients with a wide range of inflammatory arthritides including RA, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis, and also in other inflammatory diseases such as plaque psoriasis, Crohn's disease and ulcerative colitis[11,204]. However, whether neutralizing another TNFSF protein in isolation will produce the same strong and broad benefit is not clear. Blocking TNF might have a potent therapeutic effect for two main reasons. Firstly, TNF is a primary end-stage inflammatory mediator in tissues, as it is produced at high levels by multiple cell types (both immune and non-immune) and induced by many different stimuli. Secondly, TNF has two receptors that are both expressed on immune cells as well as stromal non-haematopoietic cells, broadening its activity from tissues to the immune system. In comparison, the majority of other TNFSF molecules are produced at lower levels, triggered by fewer stimuli, act on a smaller number of cell types and primarily control immune cells and not tissue cells. Hence, a number of TNFSF proteins, particularly the immune modulators, might have a narrower range of action compared with TNF, limiting the therapeutic effects of biologic agents that target them.

A possible example in this regard is BAFF, a molecule that primarily, although not exclusively, controls B cell activity. Preclinical data, particularly in mouse models, suggest that BAFF and B cells are central to lupus-like autoimmunity[10,17]. However, belimumab, a BAFF inhibitor, although approved for SLE treatment and having considerable effects on human B cells, has been found to be only moderately efficacious in a small number of patients with SLE[205,206]. This unexpected outcome could reflect differences between human SLE and the disease that manifests in animal models. As suggested above, the fact that BAFF primarily controls only one immune cell type and does not play an important role within the affected tissues of patients with SLE might also explain this outcome. Belimumab has only a moderate effect in patients with RA, although slightly more promising results have been observed in Sjögren's syndrome[207,208]. Again, suppression of the B cell arm of the immune response might not be sufficient for a notable disease modification, given the activity of other immune cell types in these diseases and the strong tissue component, which is dependent on crosstalk between multiple immune cells and tissue structural cells. Thus, when considering other molecules such as CD40L, OX40L, GITRL, TL1A and CD70, which arguably exert the majority of their activity on T cells, B cells, dendritic cells and macrophages, and are possibly not functional within the affected tissues during the active phase of disease, we have to consider whether neutralizing only one of their interactions will produce a pronounced therapeutic effect.

Another obstacle for successfully targeting TNFSF proteins, particularly those that primarily control immune cell activation, is that an alteration in activity of cells such as T cells and B cells might take a long time to manifest in terms of disease symptoms. As current trials are typically short term and largely designed to compare to an already approved drug (such as a TNF inhibitor) whose target or mechanism of action could be different, future success in this

area might require careful trial designs and end points based around modulation of the perceived primary target cell or cells.

Towards immunological tolerance

Despite the caveats of targeting some TNFSF members discussed above, inhibiting molecules such as CD40L, OX40L, GITRL, CD70 and TL1A, which control the accumulation and activity of pathogenic T cells and B cells, might be a good strategy to re-establish immunological tolerance. Such targeting could prevent the formation of these disease-causing T cell and B cell populations, lead to their deletion and/or reset immune homeostasis in favour of regulatory T cells and B cells; such regulatory cells are now acknowledged to be critical for limiting autoimmunity.

Abatacept (a CTLA4–Ig fusion protein) is a drug already approved for RA therapy and used either as first-line treatment or in patients not responding to conventional therapy. This reagent is primarily thought to act by disrupting CD28 stimulatory signals in T cells. As CD28 can cooperate with TNFRSF proteins in driving T-cell activation[4,209], blocking one or more of these TNF family members might have therapeutic effects similar to those of abatacept in RA and possibly other rheumatic diseases. However, given the apparent overlap in the activities of several TNFRSF molecules on T cells and B cells, and the idea that TNFRSF and CD28 cooperate in driving T cell and B cell responses[4,5,210], we still have to consider that combination therapies that neutralize two or more interactions might be required to see marked and broad-reaching activity in many patients, regardless of the disease. Furthermore, as discussed above, therapeutic effects might take time to manifest in terms of disease control. Mouse transplantation models using fully MHC-mismatched allografts have shown that neutralization of CD40L with OX40L, or CD40L with CD70, with or without concomitant inhibition of CD28, can help to establish immune tolerance in situations where targeting the individual interactions is ineffective[5]. However, the best combined therapy for any given rheumatic disease is not obvious at present. Information regarding the timing of action of TNF family molecules during disease development will also be critical to any therapeutic success. Immune monitoring of levels of TNFSF ligands and receptors in fluids or tissues of patients with rheumatic disease will probably help, although this approach still assumes that their presence signifies their activity. Immune monitoring might also lead to an improved understanding of molecules that can be targeted simultaneously. Furthermore, translational studies in animal models that more realistically mimic the active phases of human rheumatic disease should aid the formulation of effective combination therapies.

Blocking tissue inflammation

Although the TNFSF members that primarily control T cells and APCs (FIG. 3) are probably good targets for restoring tolerance in rheumatic diseases, the molecules that regulate tissue cell responses (FIG. 4) similarly to TNF might be more attractive targets for therapy. For example, several structural cell types express LTβR, HVEM and Fn14. A few reports have shown that molecules such as CD40 and DR3 are expressed and active in mouse and human fibroblasts in disease settings as diverse as RA, SSc and inflammatory bowel disease[211–213]. What is not clear is how much synergy or overlap occurs between

these receptors on structural cells in terms of function, and again whether blocking a single molecule in humans is likely to have a profound effect on any given disease phenotype. The failure of TWEAK–Fn14 blockade to achieve its end point in lupus nephritis might reflect the challenges inherent in nephritis trials[214], and trials in other diseases will be necessary to assess its full potential. However, TWEAK blockade could be an example of where combining treatment with a biologic agent targeting another protein is necessary, as TWEAK has a functional activity similar to that of other TNFSF molecules such as TNF and LIGHT.

Related to this discussion is the observation that anti-TNF treatment is ineffective in about one-third of patients with RA[204]. The reasons for this lack of response are not clear, but an open question is whether some patients do not respond to anti-TNF monotherapy because several other TNFSF molecules, such as TWEAK and LIGHT, are also active. Would these anti-TNF nonresponders (in any rheumatic disease) be the preferred population to treat with biologic agents targeting other tissue-acting TNFSF members? To test this theory, a clinical trial investigated the use of baminercept, which inhibits LIGHT and LTαβ, in patients with RA who were unresponsive to TNF blockers. Although some effect on biological activity was noted[150], this monotherapy was abandoned as it did not achieve the therapeutic end point. However, in this case redundancy or cooperative action between multiple TNFSF members, including LIGHT, TNF and TWEAK, could explain this lack of activity. Combination therapy might then be more efficacious than targeting molecules separately. This might apply to patients that do respond to TNF inhibitors as well as those who do not respond to anti-TNF therapy alone.

Conclusions

At present, our knowledge of the TNF family members is quite advanced and, at least in some cases, has translated well into the clinic. However, there have been notable failures despite preclinical data suggesting important roles for many of these molecules in rheumatic or other inflammatory diseases. As discussed above, the potential overlap in expression and activities of TNFRSF might hinder therapeutic approaches that only neutralize a single interaction. However, these setbacks should not discourage the enthusiasm for attempting to modulate these molecules alone or in combination. Historically, combination treatment of TNF inhibitors with other biological drugs (such as abatacept and anakinra) has not improved efficacy in the treatment of rheumatic disease and only increased adverse events such as infections[215,216]. These findings might be specific to TNF, as the evolutionary role of this cytokine is arguably to limit replication of infectious pathogens. Therefore, neutralizing two TNFSF members other than TNF might not result in a similar increase in such deleterious effects. Regardless, any combination will probably require extensive safety data before being introduced in the clinic. Advances in technology might enable two or more proteins to be targeted with a single biologic agent (such as with a bi-specific antibody), potentially making the path to inhibiting multiple interactions more feasible.

An alternative therapeutic strategy is to stimulate the death receptors Fas and TRAILR1/2, and attempt to induce apoptosis of immune or structural cells that contribute to disease pathology. The difficulty in this approach is being able to effectively induce death in the

relevant cell types without having off-target effects; given the broad expression of death receptors, more direct approaches (such as bi-specific molecules) that focus the activity of an agonist reagent on individual cell types are probably needed. Another strategy might be to activate stimulatory receptors. In SLE (and multiple sclerosis), TNF inhibitors have not performed well[217,218], and in some cases promote lupus-like disease[219]. Although the reason for this outcome is unclear, studies suggest that inhibition of TNF binding to TNFR2 can impair the expansion of suppressive $CD4^+$ $Foxp3^+$ T_{reg} cells, which maintain immune tolerance in some settings[220–222]. In this regard, similar functional observations have also been drawn for OX40, 4-1BB, CD27, DR3 and GITR. In particular, studies in mouse models of RA and SLE, as well as asthma, graft-versus-host disease and multiple sclerosis, have revealed that 4-1BB agonists are strongly suppressive, as they selectively expand both $CD8^+$ T_{reg} cells that can inhibit effector CD4 T cells and/or $CD4^+$ $Foxp3^+$ T_{reg} cells[5,125,223]. Similarly, stimulation of DR3, GITR or OX40 in some settings can expand T_{reg} cells, and in several mouse models results in suppression of asthma symptoms, allograft rejection, diabetes and multiple sclerosis-like disease[224–230]. However, owing to the possibility of expanding pathogenic self-reactive T cells, agonist targeting might not be a first-line strategy; neutralization of these molecules is instead the logical choice for therapy. If clinical trials reveal contraindications for certain inhibitory reagents, drugs that stimulate TNFSF receptors might represent an alternative treatment option. Agonist antibodies to 4-1BB, OX40, CD27 and GITR are currently in clinical trials for the treatment of cancer to expand tumour-reactive T cells[11], and apart from some hepatotoxicity observed with anti-4-1BB at high doses, they have shown a relatively good safety profile, and could be tested in patients with rheumatic disease.

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Key points

- TNF inhibitors are among the most effective protein-based drugs for reducing inflammation associated with several rheumatic diseases
- In addition to TNF, the TNF superfamily (TNFSF) comprises other ligand–receptor combinations that might participate in the pathogenesis of rheumatic disease
- TNFSF members initiate several processes, including immune activation, tissue inflammatory responses and cell death or suppression
- Many TNFSF proteins other than TNF are being evaluated in preclinical mouse or human studies as possible therapeutic targets in rheumatic diseases
- TNFSF members can be targeted to either restore tolerance in rheumatic diseases or to regulate tissue cell responses

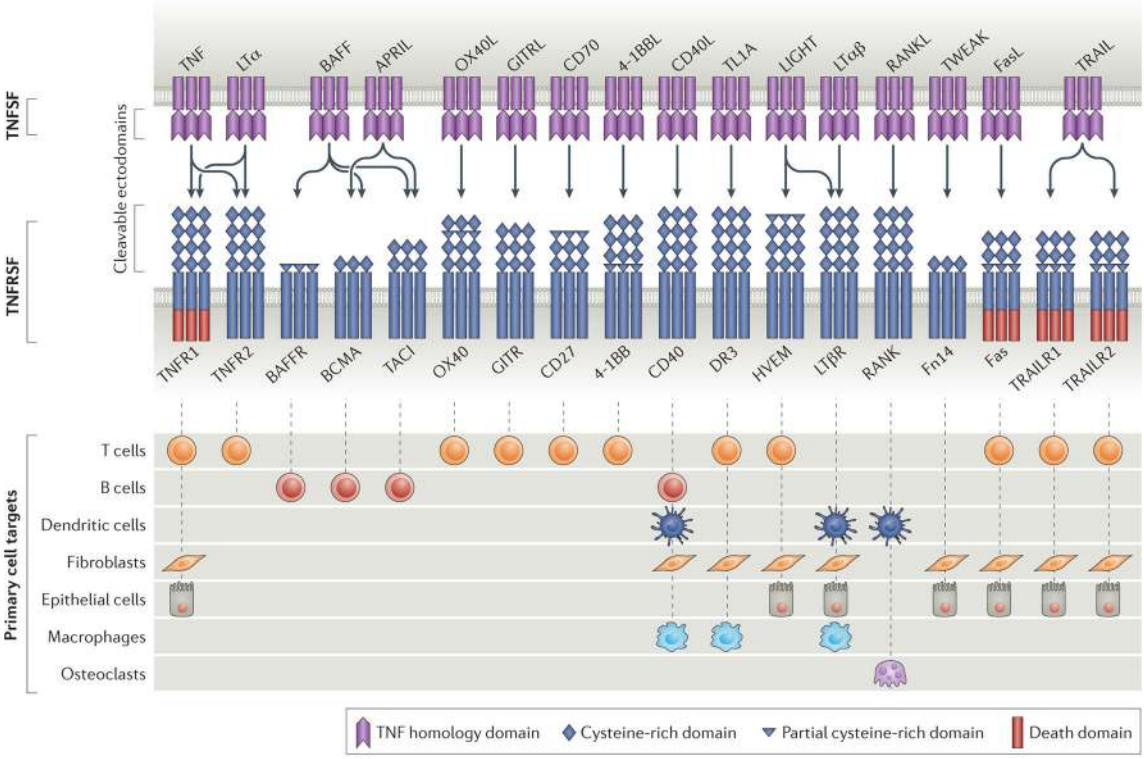

Figure 1. Select members of the TNF and TNFR superfamily implicated in rheumatic diseases

TNF superfamily ligands (TNFSF; top) are active primarily as non-covalently associated homotrimers and can be soluble or membrane-expressed. TNF superfamily receptors (TNFRSF; bottom) contain variable numbers of cysteine-rich domains in their ligand-binding extracellular regions. TNFRSF are mainly membrane-expressed, but can form soluble receptors via enzymatic cleavage of the ectodomains. Also depicted are the primary cell targets that respond to TNFSF through TNFRSF signalling, although this list is not comprehensive in terms of the expression characteristics of each molecule. TNFRSF molecules whose main function is to promote apoptotic cell death (TNFR1, Fas, TNF-related apoptosis-inducing ligands 1 (TRAIL1) and TRAIL2) can recruit a death-inducing signalling complex to their cytoplasmic domains via a death domain. 4-1BBL, 4-1BB ligand; APRIL, a proliferation-inducing ligand; BAFF, B-cell-activating factor; BAFFR, BAFF receptor; BCMA, B-cell maturation antigen; CD40L, CD40 Ligand; DR3, death receptor 3; FasL, Fas ligand; Fn14, fibroblast growth factor-inducible immediate-early response protein 14; GITRL, glucocorticoid-induced TNF receptor-related (GITR) ligand; HVEM, herpes virus entry mediator; LT, lymphotoxin; OX40L, OX40 ligand; RANKL, receptor activator of nuclear factor-κB (RANK) ligand; TACI, transmembrane activator and CAML interactor; TL1A, TNF-like ligand 1; TWEAK, TNF-related weak inducer of apoptosis.

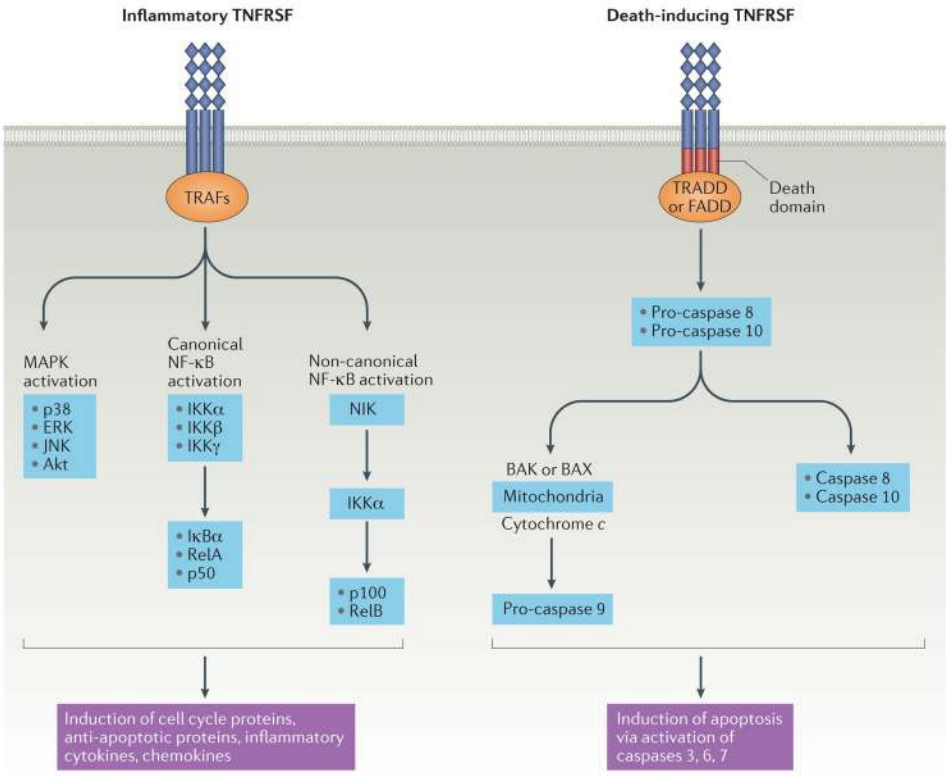

Figure 2. General TNFSF receptor signalling

TNF receptor superfamily (TNFRSF) proteins recruit one or several adaptor proteins (TNFR associated factors 1 to 6 (TRAFs), TNFR associated death domain protein (TRADD) and Fas associated death domain protein (FADD)) after ligand binding. As a generalization, TNFRSF proteins that utilize TRAFs (left) can be regarded as proinflammatory and induce proliferation (cell cycle proteins), survival (anti-apoptotic proteins), differentiation and production of inflammatory mediators such as cytokines and chemokines, according to the responding cell type. These processes can be induced via activation of one or both nuclear factor κB (NF-κB) signalling pathways (canonical and non-canonical) as well as via MAP kinase cascades. The canonical NF-κB signalling pathway is IKKβ-dependent and involves phosphorylation of inhibitor of κB (IkBα) and nuclear translocation of NF-κB subunit p50 and transcription factor p65 (RelA); the non-canonical NF-κB signalling pathway is IKKα-dependent and involves activation of NF-κB-inducing kinase (NIK), processing of p100 to p52, and nuclear translocation of p52 and RelB. The MAP kinase cascades involve c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38 or other kinases such as serine/threonine-protein kinase (AKT). TNFRSF members that contain a ‘death domain’ (right) and recruit the death domain-containing adaptor protein FAS-associated death domain protein (FADD), such as Fas, TNF-related apoptosis-inducing ligands 1 (TRAIL1) and TRAIL2, are often regarded as anti-inflammatory as they generally lead to cell death (apoptosis or necroptosis) through activation of cysteine-aspartic proteases (caspases) and receptor-interacting serine/threonine-protein (RIP) kinases (not shown). TNFR1 and death receptor 3 (DR3), the receptors that recruit the TRADD adaptor proteins, can activate inflammatory responses as TRADD can recruit TRAF proteins, but additionally

activate death pathways through secondary complexes containing TRADD, FAS-associated death domain protein (FADD) and caspase 8. Adapted from *Nat. Rev. Drug Discov.* **12**, 147–68 (2013) © Macmillan Publishers Limited[11].

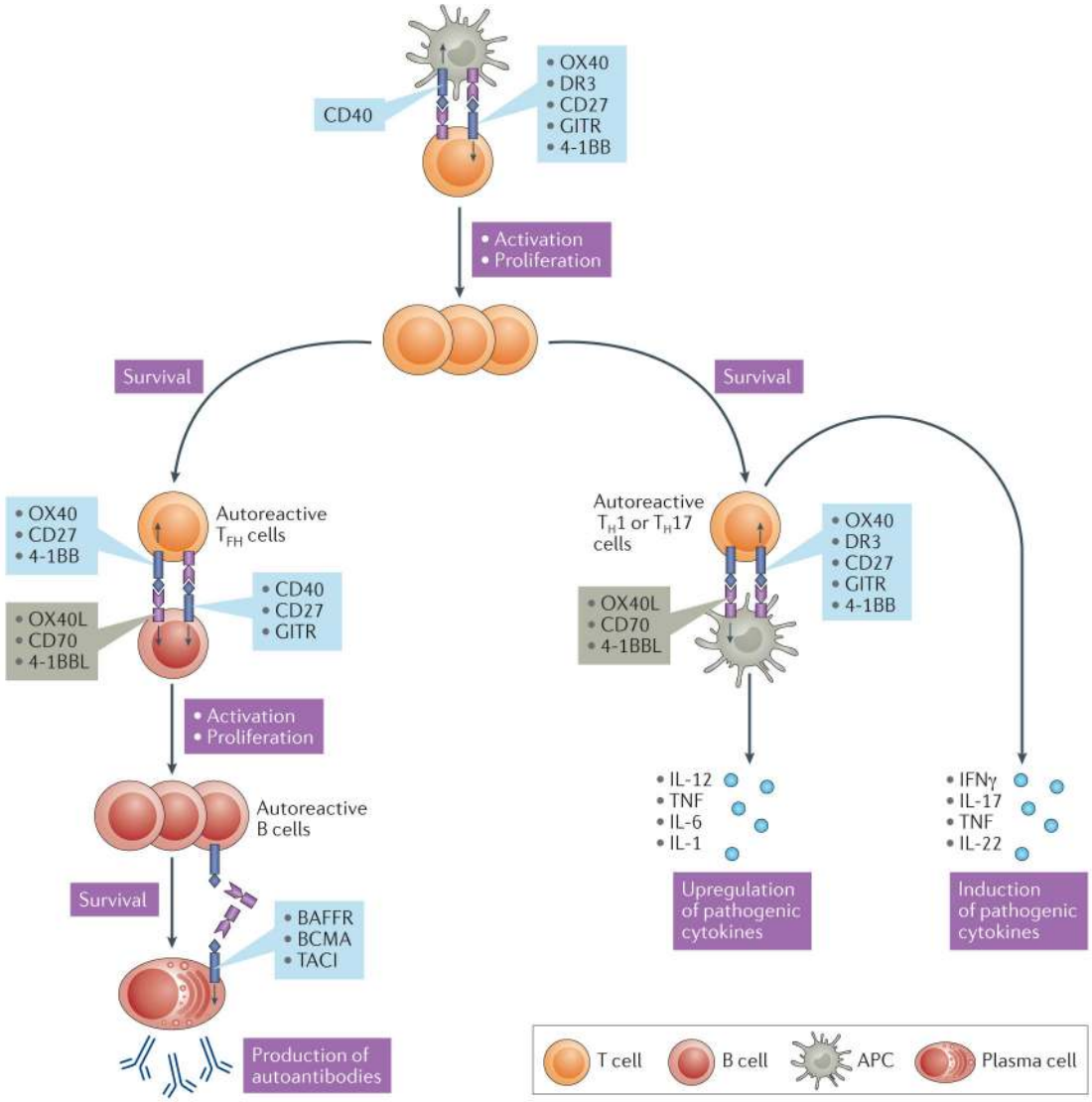

Figure 3. TNFSF activities enhancing immune cell activation

The simplified diagram highlights the possible interactions between TNF superfamily (TNFSF) ligands and TNF receptor superfamily (TNFRSF) proteins expressed on several cells in the immune system (antigen-presenting cells (APCs), B cells, and T cells). Driven by the appropriate antigen, T cells can receive TNFRSF signals through OX40, glucocorticoid-induced TNF receptor-related protein (GITR), death receptor 3 (DR3), CD27, and 4-1BB. These signals enhance their activation, promote division and survival to augment the size of the autoreactive pool, induce differentiation of follicular helper T (T_{FH}) cells that control antibody responses and induce the expression of cytokines that drive tissue pathology. APCs (dendritic cells and macrophages), via CD40, can upregulate MHC molecules, co-stimulatory ligands (including TNFSF molecules) and inflammatory cytokines, which aid the T-cell response. B cells can receive signals from CD40, CD27, GITR, B-cell-activating factor (BAFF) receptor (BAFFR), B-cell maturation antigen (BCMA) and transmembrane activator and CAML interactor (TACI). These signals drive

activation, division and survival, class switching, and plasma cell differentiation, resulting in production of pathogenic autoantibodies. Reverse signalling through membrane-expressed TNFSF ligands such as OX40 ligand (OX40L), CD70 and 4-1BBL, expressed on dendritic cells, macrophages and B cells, can also augment production of inflammatory cytokines and help B cell differentiation. Other reported activities of TNFRSF signalling on immune cells such as mast cells, eosinophils, neutrophils, basophils, Natural killer T cells and innate lymphoid cells are not shown, but these can further result in production of inflammatory mediators that contribute to tissue pathology and amplify the T-cell and B-cell response.

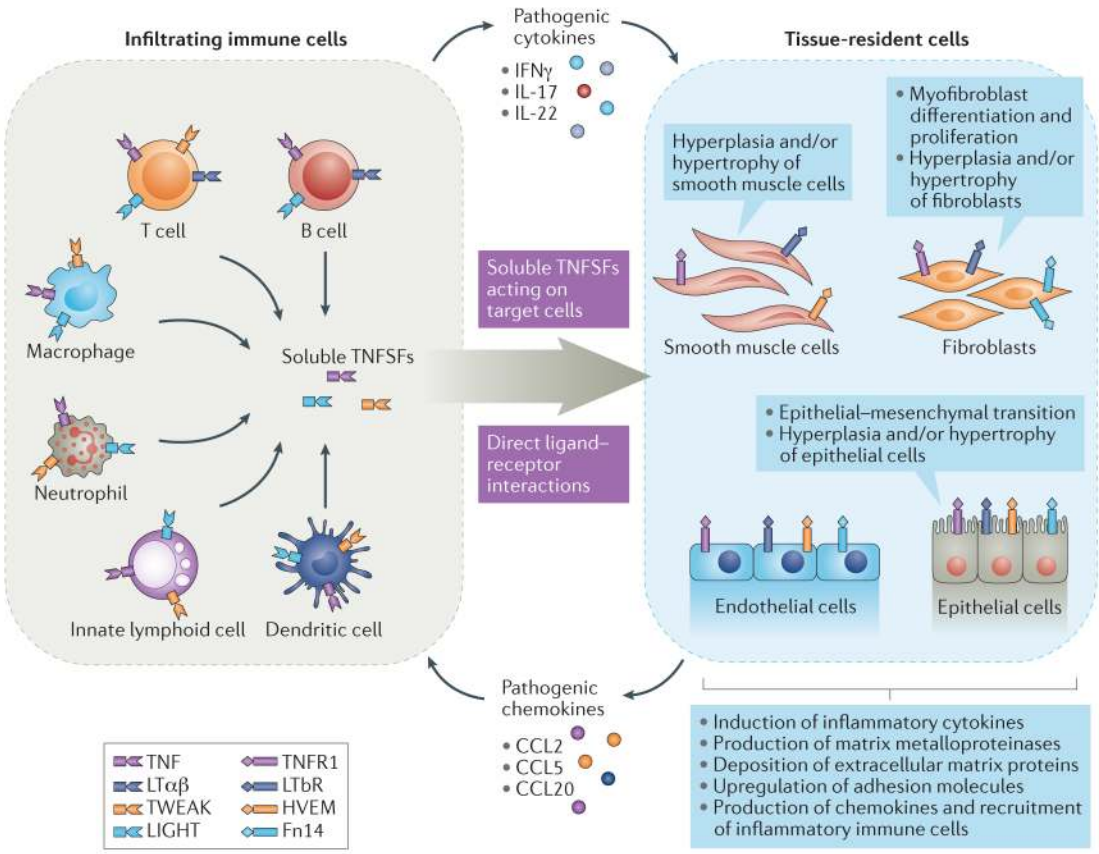

Figure 4. TNFSF inflammatory activities in tissue cells

The simplified diagram shows the possible interactions between TNF superfamily (TNFSF) ligands and their receptors expressed on tissue cells (epithelium, endothelium, fibroblasts and smooth muscle cells) that can affect tissue homeostasis and inflammatory activity. The TNFSF molecules lymphotoxin (LT) αβ, LIGHT and TNF-related weak inducer of apoptosis (TWEAK), together with TNF, are likely to be produced primarily by cells of the immune system, including T cells, B cells, dendritic cells, macrophages, as well as neutrophils, mast cells and innate lymphoid cells. Amplification loops from tissue structural cells, including endothelial and epithelial cells, might further induce production of these molecules. Signals from TNFR1, lymphotoxin-β receptor (LTβR), herpes virus entry mediator (HVEM) and fibroblast growth factor-inducible protein 14 (Fn14) can directly promote tissue pathology through multiple processes, including differentiation events such as epithelial mesenchymal transition and myofibroblast transformation, hyperplasia and hypertrophy of epithelial cells, fibroblasts, and smooth muscle cells, expression of extracellular matrix proteins and proteinases that contribute to tissue remodelling, production of chemokines and adhesion molecules that attract and maintain inflammatory immune cells within the inflamed tissue. CD40 and death receptor 3 (DR3) are also expressed on some tissue cells such as fibroblasts and could further amplify their inflammatory activity (not shown). Furthermore, receptor activator of nuclear factor-κB ligand (RANKL) and TWEAK are regulators of osteoclast activation and differentiation (also not shown). TNFSF might additionally synergize with proinflammatory T-cell-derived

cytokines such as IFNγ, IL-17 and IL-22, which also have receptors on tissue structural cells.

Table 1

Clinical trials of TNF and TNF receptor superfamilies

TNF family ligand	TNF family receptor	Biologic agent targeting receptor or ligand	Name of biologic agent	Stage of drug development for targeted disease(s)
TNF	TNFR1, TNFR2	Chimeric anti-TNF mAb	Infliximab	Approved: AS, CD, PsA, psoriasis, RA, UC
		Human TNFR2-Fc fusion protein	Etanercept	Approved: AS, JIA, PsA, psoriasis, RA
		Human anti-TNF mAb	Adalimumab	• Approved: AS, Crohn disease, JIA, PsA, psoriasis, RA, UV • Phase III (recruiting): UC • Phase III (recruiting): Behcet disease
		Human PEGylated Fab anti-TNF mAb	Certolizumab pegol	• Approved: CD, RA • Phase III (completed): AS, PsA • Phase III (ongoing): psoriasis • Phase II (recruiting): UC
		Human anti-TNF mAb	Golimumab	• Approved: AS, PsA, RA • Phase IV: UC • Phase II (completed): asthma
		Recombinant human TNF conjujugated to KLH	TNF-Kinoid	Phase II (completed): CD, RA
LTα3	TNFR1, TNFR2	Human TNFR2-Fc fusion protein	Etanercept	Approved: AS, JIA, PsA, psoriasis, RA
		Human anti-LTα mAb	Pateclizumab (MLTA3698A)	Phase II (completed): RA
LTα1β2	LTβR	Human LTβR-Ig fusion protein	Baminercept (BG9924)	Phase II (terminated due to lack of activity): RA, Sjögren syndrome
OX40 ligand	OX40	Human anti-OX40L mAb	Oxelumab	Phase II (discontinued owing to lack of activity): asthma
		Human anti-OX40 mAb‡	KHK4083	Phase II (recruiting): UC
		Human anti-OX40 mAb	GBR830	Phase II, (recruiting): AD
CD40L	CD40	Humanized anti-CD40L mAb	Ruplizumab (BG9588)	Phase II (discontinued owing to safety issues): lupus nephritis

TNF family ligand	TNF family receptor	Biologic agent targeting receptor or ligand	Name of biologic agent	Stage of drug development for targeted disease(s)
		Humanized anti-CD40L mAb	Toralizumab (IDEC-131)	Phase II (discontinued owing to safety issues): CD, MS
		Anti-CD40L-Tn3 fusion protein	MEDI4920	Phase I (recruiting): RA
		Chimeric anti-CD40 mAb	FFP104 (PG102)	Phase I (recruiting): CD, primary biliary cirrhosis
		Human anti-CD40 Fc-silent mAb	CFZ533	Phase I–II (recruiting): Grave disease, MG, RA, SS, transplantation
		Human anti-CD40 mAb	ASKP1240 (4D11)	• Phase II (completed): psoriasis • Phase II (ongoing): transplantation
RANKL	RANK	Human anti-RANKL mAb	Denosumab	• Approved: osteoporosis • Phase III (ongoing): RA • Phase II (recruiting): OA • Phase I–II (recruiting): CD
TWEAK	Fn14	Humanized anti-TWEAK mAab	BIIB023	• Phase II (terminated due to lack of activity): lupus nephritis • Phase I (completed): RA
APRIL	TACI, BCMA	Human TACI-Ig fusion protein	Atacicept	• Phase II (completed): RA • Phase II (ongoing): SLE • Phase II (terminated due to safety issues): lupus nephritis • Phase II (terminated due to increased disease): MS
BAFF	BAFFR, BCMA, TACI	Human anti-BAFF mAb	Belimumab	• Approved: SLE • Phase II (completed): MG, RA, Sjogren syndrome

TNF family ligand	TNF family receptor	Biologic agent targeting receptor or ligand	Name of biologic agent	Stage of drug development for targeted disease(s)
				• Phase II (ongoing): SSc
		Human anti-BAFF mAb	Tabalumab (LY2127399)	• Phase III (completed): RA, SLE • Phase II (completed): MS
		Human TACI-Ig fusion protein	Atacicept	• Phase II (completed): RA • Phase II (ongoing): SLE • Phase II (terminated due to safety issues): lupus nephritis • Phase II (terminated due to increased disease): MS
		Human BAFF-binding peptibody	Blisibimod (AMG623)	Phase III (ongoing or recruiting): SLE
LIGHT	HVEM, LTβR	Human LTβR-Ig fusion protein	Baminercept (BG9924)	• Phase II (completed and terminated due to lack of activity): RA • Phase II (terminated due to unavailability of biologic): Sjögren syndrome
		Human anti-LIGHT mAb	KHK252067	Phase I (completed): CD, UC
NGF*	NGFR	Humanized anti-NGF mAb	Tanezumab (RN624)	Phase III (recruiting): chronic back pain, osteoarthritis
		Human anti-NGF mAb	Fulranumab (AMG-403)	Phase III (ongoing): osteoarthritis
		Human anti-NGF mAb	Fasinumab (REGN475)	Phase III (ongoing): osteoarthritis Phase III (recruiting): chronic back pain

AD, atopic dermatitis; APRIL, A proliferation-inducing ligand; AS, ankylosing spondylitis; BAFF, B-cell-activating factor; BAFFR, BAFF receptor; BCMA, B-cell maturation antigen; CD, Crohn's disease; Fn14, Fibroblast growth factor-inducible protein 14; HVEM, Herpes virus entry mediator; JIA, juvenile idiopathic arthritis; LT, lymphotoxin; LTβR, LTβ receptor; NGF, nerve growth factor; NGFR, NGF receptor; mAb, monoclonal antibody; MG, myasthenia gravis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RANK, receptor activator of nuclear factor kappa-

B (NF-κB); RANKL, RANK ligand; SSc, systemic sclerosis; TACI, transmembrane activator and CAML interactor; TNFR, TNF receptor; TWEAK, TNF-related weak inducer of apoptosis; UC, ulcerative colitis.

*NGF is not a canonical TNF family ligand on the basis of structure, although NGFR is part of the TNFR superfamily.

‡Depleting and/or antagonist biologics (all other biologic agents displayed are antagonists).