

Review Article

The Tumor Necrosis Factor Superfamily of Cytokines in the Inflammatory Myopathies: Potential Targets for Therapy

Boel De Paepe, Kim K. Creus, and Jan L. De Bleecker

Laboratory for Myopathology, Department of Neurology and Neuromuscular Reference Center, Ghent University Hospital, 9000 Ghent, Belgium

Correspondence should be addressed to Boel De Paepe, boel.depaepe@ugent.be

Received 27 May 2011; Revised 28 July 2011; Accepted 15 August 2011

Academic Editor: Ludvig A. Munthe

Copyright © 2012 Boel De Paepe et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The idiopathic inflammatory myopathies (IM) represent a heterogeneous group of autoimmune diseases, of which dermatomyositis (DM), polymyositis (PM), and sporadic inclusion body myositis (IBM) are the most common. The crucial role played by tumor necrosis factor alpha (TNF α) in the IM has long been recognized. However, so far, 18 other members of the TNF superfamily have been characterized, and many of these have not yet received the attention they deserve. In this paper, we summarize current findings for all TNF cytokines in IM, pinpointing what we know already and where current knowledge fails. For each TNF family member, possibilities for treating inflammatory diseases in general and the IM in particular are explored.

1. Introduction

The idiopathic inflammatory myopathies (IM) are characterized by distinct immune effector mechanisms. Dermatomyositis (DM) is a complement-mediated endotheliopathy associated with perimysial inflammation and perifascicular muscle fiber atrophy. In polymyositis (PM) and sporadic inclusion body myositis (IBM), muscle fibers are injured by autoaggressive immune cells which predominantly infiltrate the endomysium [1]. Additional degenerative phenomena occur in IBM muscle, such as muscle fiber vacuolation and deposition of β -amyloid and other ectopically localized proteins [2]. Other less well-delineated IM include myositis-associated cancer or connective tissue diseases and immune-mediated necrotizing myopathy. Macrophages, dendritic cells (DCs), and T-cells are prominently present in muscle tissues of the different IM. In DM, large numbers of helper T-cells are found within the perimysial, often perivascular, inflammatory infiltrates. In PM and IBM, activated cytotoxic T-cells surround and invade nonnecrotic muscle fibers, while helper T-cells are found at more distant parts of the infiltrates. B-cell-mediated immunity is an important component of DM/PM pathogenesis, and autoantibodies can be detected in up to 70% of patients [3]. The most common is Jo-1, an antihistidyl-tRNA-synthetase, but more autoantibodies

directed against aminoacyl-tRNA-synthetases or other muscle antigens are continuously being described. Autoantibody profiles are associated with clinical subsets of patients [4]. In IBM on the other hand, humoral autoimmunity is a more controversial subject. However, it has been established that IBM muscle contains large numbers of plasma cells and an environment permissive of ectopic lymphoneogenesis, which suggests the possibility of local maturation of B-cells and autoantibody production. Indeed, a recent report describes IBM-specific autoantibodies directed against a yet unidentified muscle antigen [5].

The important role played by cytokines in the IM has long been recognized [6]. In this respect, a key role for type I interferon (IFN)-mediated innate immunity has been shown in DM and PM [7, 8]. In this paper, the tumor necrosis factor (TNF) family will be systematically overviewed, discussing current knowledge on their involvement in the IM and exploring whether they could represent appropriate targets for future therapeutic intervention. TNF cytokines affect immune cell proliferation, differentiation, and survival. Up till now, 19 members have been identified in man, and they have been assigned systematic names starting from TNFSF1 to TNFSF18 based on the encoding genes. Ectodysplasin A (EDA) 1 and 2 have not been assigned systematic names and will not be discussed in this paper. Most TNF members

are type II transmembrane proteins whose extracellular C-terminal TNF homology domain can be cleaved off by specific metalloproteinases, generating soluble cytokines. The TNF-like receptors (TNFR) are type I transmembrane proteins of which cystein-rich domains are the hallmark structural motif [9].

2. TNFSF2—TNF α

TNF α or cachectin, the prototypic member of the TNF family, is produced mainly by activated macrophages and T-cells. TNF α activates T-cells, B-cells, and macrophages and induces the expression of other cytokines and cell adhesion molecules through interaction with its receptor TNF-R55 (TNFR1). The alternative receptor TNF-R75 (TNFR2) has been shown to chiefly function as a concentrator at cellular surfaces, transferring the cytokine to TNF-R55 [10]. TNF α augments the activity of nuclear factor- κ B (NF- κ B) signaling pathways [11].

In the IM, TNF α is by far the most studied cytokine of its family. The endomysial and perimysial inflammatory cells express varying levels, with macrophages being the primary source of the cytokine. TNF α is also prominently expressed in blood vessel endothelial cells of DM tissues [12–14]. The soluble forms of the receptors TNF-R55 and TNF-R75 are increased in DM/PM sera [15]. TNF-R75 expression is notably increased near inflammatory infiltrates in all IM and on the perimysial and perifascicular blood vessel endothelium in DM even remote from inflammation [12]. Polymorphisms in the gene encoding TNF α have been linked to either an increased risk of, or protection against, the development of juvenile DM [16, 17].

Neutralization of TNF α is efficacious for treating several autoimmune diseases. The important catabolic role of TNF α as a regulator of the chronic inflammation associated with the IM has made it a therapeutic target for these diseases as well. Fortunately, knocking out TNF α appears relatively safe and does not seem to hamper skeletal muscle regeneration [18]. Four agents, that generate excellent results in rheumatoid arthritis (RA) and Crohn's disease, can be considered for IM patients: (1) a mouse/human chimeric anti-TNF α monoclonal antibody termed infliximab (Remicade), (2) a TNF α -neutralizing receptor fusion protein termed etanercept (Enbrel), (3) a humanized anti-TNF α monoclonal antibody termed adalimumab (Humira), and (4) the humanized polyethyleneglycol conjugated Fab' anti-TNF α fragment certolizumab pegol (Cimzia). For the first two compounds, reports so far have revealed variable outcomes in IM patients. Trial results are summarized in Table 1 [19–26]. Several phase II clinical trials have been started up, but, in general, studies suffer from low inclusion rate and notably high drop-out rates mostly due to disease deterioration and adverse events. However, it appears that anti-TNF α treatment could be of benefit to a subset of IM patients. The identification of responsive patients remains difficult, as no specific marker has been identified yet that may predict the therapeutic outcome.

3. Other TNF Members Already Investigated to Some Extent in the IM

3.1. TNFSF1/3—LT α / β . Lymphotoxins (LTs) are versatile cytokines. They are crucial for robust immune responses and are key elements required for lymphoid organogenesis and organization. LT α , also termed TNF β , is secreted as the homotrimer LT α 3, or complexed on the cell surface with LT β , predominantly as LT α 1 β 2 heterotrimers. LT α can bind to the receptor LT β R as well as to the receptors TNFR1 and TNFR2. LT β signals through LT β R ligation only.

It appears that LTs are important factors orchestrating sustained inflammation in the IM. LT α has been implicated in the cytotoxic response of CD8⁺ T-cells towards nonnecrotic muscle fibers in PM [27]. LT β is increased in muscle tissues of DM patients, where it localizes to blood vessels and intramuscular follicle-like structures. The latter contain large numbers of T-cells, B-cells, and DCs organized in functional compartments [28]. Recent data also show that LT β may well be an early marker for muscle disease [29].

LTs have been pinpointed as important targets for suppressing inflammation in autoimmune diseases. Studies showed that depletory monoclonal anti-LT α and the receptor antagonist LT β R:Ig inhibit disease in murine collagen-induced arthritis [30, 31]. In addition, administering LT β R:Ig inhibited T-cell-driven intestinal inflammation in murine inflammatory bowel disease [32]. In human RA, synovial LT α and LT β expression is elevated [33], but targeting the expression by administering LT β R:Ig failed to meet clinical end points in a phase IIb clinical trial. As TNF α and LT α share the receptors TNFR1 and TNFR2, strategies targeting these receptors influence the activities of both cytokines. Therefore, the therapeutic effects of competitive antagonists of TNFR1 and TNFR2, namely, etanercept and lenercept, are presumed to result from combined inhibition of TNF α and LT α .

3.2. TNFSF4—OX40L. The primary source of the transmembrane glycoprotein OX40L, also termed CD252 or gp34, are antigen presenting cells, and expression is further induced when B-cells, DCs, T-cells, and macrophages become activated. The cytokine promotes clonal expansion of T-cells, leading to long-term T-cell survival and enhanced memory T-cell development. The receptor OX40, also termed CD134, is expressed on activated T-cells, B-cells, and vascular endothelial cells. Proinflammatory cytokines, including TNF α , can further augment the expression of the receptor. The OX40/OX40L interaction provides a costimulatory signal for T-cells and enhances ongoing immune responses driven by either helper T-cell type 1 (Th1), Th2, or Th17 cells [34].

OX40 is present on mononuclear cells in the endomysium and at perivascular sites in PM muscle. OX40 positive cells are mostly CD4⁺ cells, few are CD8⁺ cytotoxic T-cells. Autoaggressive immune cells invading nonnecrotic muscle fibers are invariably OX40 negative [35]. OX40L expression has not yet been described in the IM.

Blocking OX40L has produced strong therapeutic effects in multiple animal models of autoimmune and inflammatory

TABLE 1: Tumor necrosis factor inhibitors for treating inflammatory myopathies: published trial results for infliximab and etanercept.

Compound and treatment regimen	Diagnosis/patients continued to end point	Follow-up time	Clinical outcome at end point	Reference
infliximab 6 mg/kg 4-weekly or more frequent	R-JDM/5	32 to 130 weeks	I (5/5)	[19]
infliximab 10 mg/kg (week 0, 2, 6, 14)	R-DM/1 R-PM/4 R-IBM/4	16 weeks	NC (1/1) I (2/4) W (2/4) I (1/4) NC (3/4)	[20]
infliximab 10 mg/kg (week 0, 2, 4)	R-DM/1 R-PM/1	12 weeks	I (1/1) I (1/1)	[21]
infliximab 10 mg/kg (week 20) infliximab 10 mg/kg (week 14, 18, 22)	R-DM/1 R-PM/1	66 weeks	I (1/1) I (1/1)	[22]
infliximab 10 mg/kg (week 0, 2, 6, 14, 22)	PM/2	26 weeks	I (2/2)	[23]
infliximab 8 mg/kg (week 0, 2, 6)	R-DM/1	6 weeks	I (1/1)	
infliximab 10 mg/kg (week 0, 2, 4, 6, 9)	R-PM/1	69 weeks	I (1/1)	[24]
infliximab 3 mg/kg (week 0, 2, 6, every 8) and etanercept 25 mg twice weekly	R-DM/1 R-PM/2	36 to 96 weeks	PR (1/1) I (2/2)	[25]
etanercept 25 mg twice weekly	R-DM/1	56 weeks	I (1/1)	[26]

Abbreviations: dermatomyositis (DM), improved (I), inclusion body myositis (IBM), juvenile DM (JDM), no change (NC), partial response (PR), polymyositis (PM), refractory DM/PM/IBM (R-DM/PM/IBM), worsened (W).

disease, which include inflammatory bowel disease [36] and arthritis [37]. Neutralizing antibodies to OX40L are currently being tested in phase II clinical trials for treating asthma.

3.3. *TNFSF5—CD40L.* CD40L, also termed CD154 or gp39, is expressed by activated T-cells, mainly on the CD4⁺ subsets. Its receptor CD40 is present on antigen presenting cells and on endothelial cells. CD40L positive T-cells activate monocytes and upregulate adhesion molecules and monocyte chemoattractant protein 1 (CCL2) production by blood vessel endothelial cells [38].

The CD40/CD40L system seems to be involved in the immunopathogenesis of the IM. A subset of inflammatory cells in IM tissues express CD40L, of which the majority are CD4⁺ cells. Also, part of the muscle fibers in PM/DM tissues express CD40. In vitro IFN γ -stimulation of myoblasts induces CD40 expression, leading to increased levels of IL-6, IL-8, IL-15, and CCL2 [39]. The induction of proinflammatory factors through the CD40/CD40L system could contribute to T-cell recruitment and activation found within IM muscle tissues.

CD40L/CD40 interaction engages antigen presenting cells, provokes B-cell responses and enhances the production of proinflammatory cytokines, pinpointing the interaction as an important regulatory mechanism in inflammatory disease. In murine collagen-induced arthritis, for example, an agonistic anti-CD40 antibody exacerbates disease [40], while a blocking anti-CD40L antibody protects against disease [41]. Phase I and II trials in humans have already been initiated, testing the effects of a humanized anti-CD40L antibody in inflammatory bowel disease [42]. However, the development of IDEC-131, another humanized monoclonal

anti-CD40L, is no longer pursued after a placebo-controlled trial demonstrated no clinical activity in systemic lupus erythematosus (SLE) [43].

3.4. *TNFSF6—FASL.* FasL is expressed on activated T-cells and NK-cells. The cytokine comes in a 40 kDa membrane-bound and a 29 kDa-soluble variant. Its receptor Fas, also termed CD95 or apoptosis 1 (Apo1), is constitutively expressed on many cell types. An alternative soluble receptor termed decoy receptor 3 (DCR3) has been described, possibly serving to counteract Fas function. Fas ligation leads to a conformational change, which causes binding of death domain-containing adaptor proteins, subsequently activating caspases and nucleases.

A role for the Fas/FasL system in muscle damage is suspected. Proinflammatory in vitro conditions have been shown to induce apoptosis in muscle cells, a process that can be partially inhibited by an anti-FasL antibody [44]. However, apoptosis is not a prominent feature of IM, and data concerning Fas/FasL expression appear somewhat confusing. FasL was found absent from IM muscle tissue [45] or expressed only by some T-cells [27, 46]. Fas expression has been reported with very different frequencies, but the sarcolemma of regenerating muscle fibers seems to represent the main site of immunoreactivity. Also, some nonnecrotic invaded muscle fibers in PM/IBM and some atrophic perifascicular muscle fibers of DM are Fas positive [45, 47, 48]. Serological studies report unchanged FasL levels, while Fas levels were significantly higher in PM/DM patients compared to normal controls [49]. The peripheral blood of DM patients contains significantly lower percentages of regulatory T-cells, but the

fraction of Fas positive cells is similar, indicating no increased susceptibility of regulatory T-cells to FasL-mediated apoptosis [50].

The involvement of Fas/FasL interactions in human inflammatory disease is complex. It has been shown that Fas/FasL deficiencies are associated with the accumulation of lymphocytes and establishment of autoimmune disease. Indeed, a number of inflammatory diseases seem to be associated with decreased serum levels of soluble FasL. Administering DCs overexpressing FasL resulted in protection against murine collagen-induced arthritis [51] possibly through elimination of autoreactive T-cells. Nonetheless, in RA synovial fluid, increased levels of soluble FasL have been found [52]. More research is needed to unravel the precise involvement of the cytokine in human diseases.

3.5. *TNFSF7—CD27L.* CD27L, also termed CD70, is expressed on T-cells, B-cells, and NK-cells. It is a T-cell costimulatory molecule whose expression is upregulated upon activation. CD27L regulates the formation of effector and memory T-cells and induces their secretion of cytokines. In the B-cell compartment, CD27L promotes differentiation into plasma cells and subsequent antibody production, commitment to memory B-cell responses, and the formation of germinal centers. The receptor CD27 is constitutively expressed on resting T-cells and is upregulated upon T-cell activation. In B-cells, CD27 expression is induced by antigen-receptor activation.

Very limited data is currently available on CD27L expression in the IM. We do know that unlike in the series of SLE patients, CD27L is not increased on peripheral CD4⁺ cells of a single DM patient, who was included as a disease control in the study [53].

Under physiological conditions, expression of CD27L is restricted and transient in nature. Thus, CD27L offers a potential mechanism to selectively target only the activated cells of the immune system, B-cells in particular, potentially avoiding generalized immunosuppression and overt toxicity. Anti-CD27L was found to improve disease and reduce autoantibodies in murine collagen-induced arthritis [54].

3.6. *TNFSF10—TRAIL.* TNF-related apoptosis-inducing ligand (TRAIL), also termed Apo2L, can be expressed by various cell types. It binds TRAIL receptors 1 to 4 and osteoprotegerin (OPG), inducing target cell apoptosis.

Only one report is available that describes TRAIL in PM, stating that many inflammatory cells are TRAIL positive [55]. TRAIL is expressed in the endomysial capillaries of healthy skeletal muscle and patients alike.

TRAIL potentially dampens autoimmune responses by silencing autoreactive T-cell populations and, therefore, could be beneficial to patients suffering from inflammatory diseases. A study showed that a blocking anti-TRAIL monoclonal antibody, on the one hand, exacerbates murine experimental autoimmune encephalomyelitis, while recombinant TRAIL, on the other hand, suppressed disease [56]. Thus, strategies delivering a soluble TRAIL equivalent may be effective in suppressing disease episodes. In addition, a hu-

man study identified TRAIL as a prognostic marker for IFN β -response in multiple sclerosis (MS). Upregulated concentrations of TRAIL in response to IFN β distinguished drug responders from nonresponders [57].

3.7. *TNFSF11—RANKL.* Receptor activator of NF- κ B ligand (RANKL), expressed on the membranes of T-cells, is also called TNF-related activation-induced cytokine (TRANCE), OPG ligand (OPGL), or osteoclast differentiation factor (ODF). Two putative receptors for RANKL have been proposed, being RANK and OPG. RANK is a transmembrane receptor present on DCs and T-cells. OPG is a soluble secreted decoy receptor for RANKL. RANKL acts in synergy with TNF α , activating a cascade of intracellular signaling events which lead to osteoclast activation.

In mice, RANKL mRNA is expressed in healthy skeletal muscle [58], which points to a role in normal muscle physiology. A study reported serum RANKL concentrations to be significantly higher and RANK levels to be significantly lower in juvenile DM than in healthy age-matched controls [59].

RANKL/RANK is of major pathophysiological importance in the bone and joint destruction associated with RA [59], where RANK expression appears to be limited to the sites of immune reaction. The development of compounds that mimic OPG action may prevent osteoclast-mediated bone loss in patients [60]. Denosumab (AMG-162), a monoclonal anti-RANKL antibody, is currently being tested for treating RA.

3.8. *TNFSF13—BAFF and APRIL.* B-cell activating factor (BAFF), also termed TNFSF13b or B-lymphocyte stimulator (BLyS), is expressed on the surface of monocytes, DCs, and activated T-cells. BAFF binds three receptors: transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), BAFF receptor (BAFFR), and B-cell maturation antigen (BCMA). BAFF is crucial for B-cell maturation and survival and antibody production by plasma cells. In addition, BAFF regulates T-cell activation and differentiation. A proliferation-inducing ligand (APRIL) or TNFSF13 is homologous to BAFF and exists only as a soluble homotrimer. APRIL binds TACI and BCMA and is important for B-cell development and function [61].

Serological studies have shown that BAFF levels are significantly increased in DM patients [62] but not in PM/IBM [63]. BAFF levels in serum correlated with IL-7, IL-12, and CXCL10 [64] and with Jo-1 expression, supporting a role for BAFF in autoantibody production. In addition, BAFF transcripts were found markedly upregulated in muscle extracts from DM (12-fold), PM (14-fold), and IBM (21-fold) patients [65]. In DM muscle, BAFF localizes to the muscle fibers in perifascicular areas [66]. Interestingly, mononuclear cells infiltrating IM muscle express IFN α [67], a potent BAFF inducer. Serum APRIL levels were found unaltered in IM patients [64].

Blocking BAFF and APRIL potentially diminishes autoreactive B-cells, which would interrupt B-cell differentiation and prevent autoantibody production. Thus, BAFF and APRIL represent appropriate targets for intervention

in autoimmune diseases with an important humoral pathogenic component. B-cells are especially associated with DM infiltrates, where IFN α expression could well be the trigger to activate autoantibody production. In addition, differentiated plasma cells can also be encountered in PM/IBM muscle samples [68].

The anti-BAFF monoclonal antibody belimumab has been tested in two phase III trials for the treatment of SLE. In both trials, belimumab met the primary endpoints, showing significant clinical improvement compared to standard of care alone. LY2127399, another BAFF neutralizing antibody, has entered phase II trials for RA. Atacicept, an Ig fusion protein of the extracellular domain of the TACI receptor that binds BAFF and APRIL, has currently reached phase II/III for treating SLE [69].

4. TNF Members Not Yet Explored in IM

4.1. TNFSF8—CD30L. CD30L is expressed on the membranes of activated T-cells, resting B-cells, and monocytes. Interaction with its receptor CD30, expressed on T-cells, and B-cells, leads to their proliferation and activation. In inflammatory diseases, CD30L/CD30 interactions seem to represent both deleterious and beneficial effects. A blocking monoclonal anti-CD30L antibody aggravates allograft rejection in mice by suppressing regulatory T-cell function [70], while soluble CD30-Ig fusion protein ameliorates murine experimental colitis through inhibition of Th17 responses [71]. Elevated levels of soluble CD30 have been observed in autoimmune diseases such as RA [72] and SLE [73].

4.2. TNFSF9—4-1BBL. 4-1BBL is predominantly expressed on activated antigen presenting cells and interacts with the 4-1BB receptor expressed early and transiently on activated T-cells and on DCs. The 4-1BBL/4-1BB interaction is relevant to the pathogenesis of inflammatory disease. In sera of RA patients, soluble 4-1BB and 4-1BBL levels are increased and correlate with disease severity [74]. Treatment with an antagonistic anti-4-1BB antibody reduces severity of arthritis in animal models, ameliorating inflammation, and the associated B-cell responses [75].

4.3. TNFSF12—TWEAK. The multifunctional cytokine TNF-like weak inducer of apoptosis (TWEAK) triggers multiple and often seemingly conflicting cellular responses, which range from cell proliferation to cell death. Moreover, TWEAK signaling through the FN14 receptor [76] has an impact on normal muscle functioning. In vitro, TWEAK inhibits the differentiation of myoblasts to myotubes [77] and induces the expression of proinflammatory CCL2 [78]. TWEAK knockout mice exhibit augmented muscle tissue regeneration [79], while overexpression results in inhibited myofiber regeneration and increased expression of proinflammatory cytokines including TNF α , IL-1 β , IL-6, and CCL2 [80–83]. The proinflammatory cytokines inducible by TWEAK are important regulators of IM [84], which warrants further exploration. Also, circulating TWEAK levels are significantly increased in other human autoimmune dis-

eases such as MS and SLE [85]. A TWEAK-neutralizing monoclonal antibody ameliorates collagen-induced arthritis in mice, reducing serum and joint CCL2 levels significantly [86].

4.4. TNFSF14—LIGHT. Lymphotoxin-related inducible ligand that competes for glycoprotein D binding to herpes simplex virus entry mediator (HVEM) on T-cells (LIGHT), also termed LT γ , binds the receptors LT β R, HVEM, and the decoy receptor DCR3. LIGHT is expressed by activated T-cells and immature DCs, and is a potent T-cell costimulatory molecule [87] with profound effects on T-cell-mediated disease [88]. LIGHT enhances Th1-mediated immune responses and in vitro strongly induces CXCR3 ligands [89]. The predominance of Th1-mediated immunity and CXCL10 expression have been demonstrated in the IM [90]. In synovial tissues from RA patients, both LIGHT and its receptor HVEM are expressed by CD68+ macrophages, and their interaction induces the proinflammatory cytokines TNF α , IL-6, and IL-8 [91]. Blocking LIGHT activity significantly reduces graft versus host disease [92, 93].

4.5. TNFSF15—TL1. TNF-like 1 (TL1), also termed vascular endothelial growth inhibitor (VEGI), is expressed by macrophages, lymphocytes, and plasma cells. TL1 binding enhances the expression of IFN γ by T-cells [94] and induces apoptosis in endothelial cells. TL1 has been implicated in human inflammatory bowel disease, where it is found to be increased in macrophages, plasma cells and lymphocytes [95], and TL1 gene variants have been linked to disease susceptibility [96, 97].

4.6. TNFSF18—GITRL. Glucocorticoid-induced TNF receptor ligand (GITRL), also termed TNF-like 6 (TL6), is expressed by endothelial cells, DCs, macrophages, and B-cells. Its receptor GTR is present on naive, activated, and regulatory T-cells that, upon ligation, proliferate and produce cytokines. In RA, both GTR and GITRL are expressed in synovial macrophages that, in response to in vitro stimulation with an anti-GTR monoclonal antibody, produce TNF α , IL-6, IL-8, and CCL2 [98]. Agonistic anti-GTR monoclonal antibodies exacerbate joint inflammation and cytokine production [99].

5. Conclusions and Future Prospects

Oral corticosteroids are still standard treatment for DM and PM, but they come with serious side effect and incomplete treatment responses. Patients anxiously await more selective treatment options. Moreover, IBM patients do not respond to the immunosuppressive and immunomodulatory drugs currently available. A better understanding of the deleterious and beneficial effects of the different players that make up the IM muscle microenvironment is necessary to aid the development of novel routes for therapy. In addition, such knowledge could provide markers to distinguish potentially responsive from nonresponsive patients, better predicting the outcome of costly immune interventions.

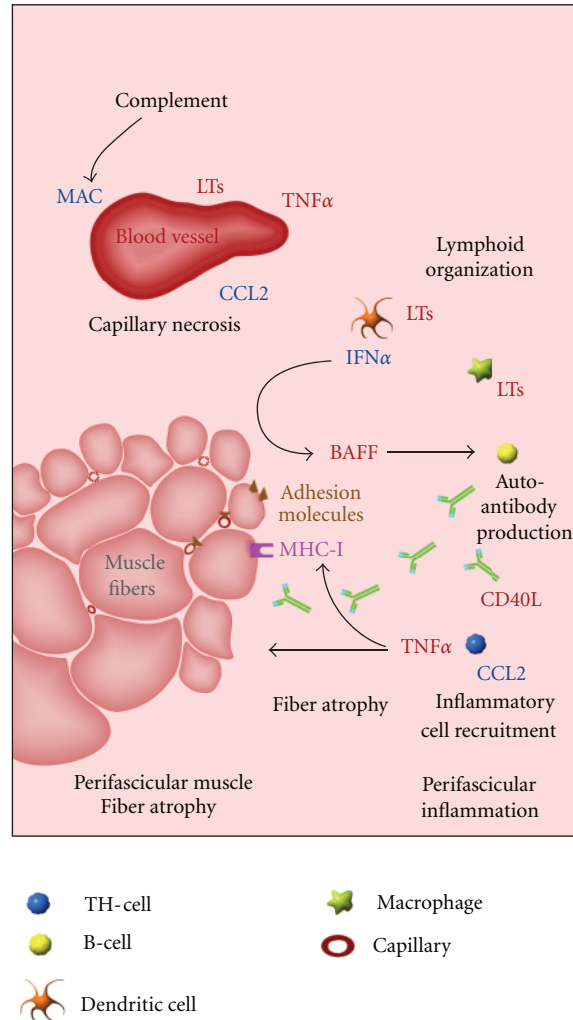


FIGURE 1: Potential roles for tumor necrosis factor cytokines in the muscle damage associated with dermatomyositis. Based on current knowledge, a model is developed describing the possible involvement of tumor necrosis factor (TNF) cytokines in the sustained inflammation in perifascicular regions of muscle. Activation of the complement system leads to membrane attack complex (MAC) deposition on blood vessels and subsequent necrosis. Endothelial monocyte chemoattractant protein-1 (CCL2) recruits inflammatory cells that accumulate and organize in perimysial areas. Lymphocytes organize into functional compartments and produce lymphotoxins (LTs), TNF α and CD40L, which further recruit responsive immune cells from the circulation, leading to the buildup of perimysial inflammation. Dendritic cells (DCs) produce IFN α , which stimulates muscle fibers to secrete B-cell activating factor (BAFF). The latter activates B-cells that, in response, begin to produce autoantibodies. TNF α , mostly produced by Th-cells, provokes muscle fiber atrophy and stimulates major histocompatibility complex I (MHC-I) and expression of adhesion molecules.

In this paper, we summarized current knowledge on the involvement of the TNF superfamily of cytokines in IM, finding ourselves humbled by the lack of data regarding some of them. The TNF cytokines represent plausible therapeutic targets for the IM, as they are regulators of the complex inflammatory cascade that leads to sustained inflammation. For PM and IBM, limited information is available for TNF cytokines other than TNF α . However, for DM, a picture is slowly emerging in which TNF cytokines no doubt play a crucial role. Based on current knowledge, we developed a model describing the TNF-mediated sequence of events that lead to the characteristic muscle damage, being blood vessel loss,

perifascicular muscle fiber atrophy, and inflammation (Figure 1).

Selectively targeting individual TNF members provides new promises and opportunities to develop more efficacious therapies for IM while avoiding the toxicity seen in existing systemic anti-inflammatory therapeutics.

Acknowledgments

This work was supported by a grant from the University Fund for Scientific Research (BOF) and CAF DCF. The authors thank Sophie D'hose for graphics.

References

- [1] M. C. Dalakas and R. Hohlfeld, "Polymyositis and dermatomyositis," *The Lancet*, vol. 362, no. 9388, pp. 971–982, 2003.
- [2] V. Askanas and W. K. Engel, "Inclusion-body myositis: muscle-fiber molecular pathology and possible pathogenic significance of its similarity to Alzheimer's and Parkinson's disease brains," *Acta Neuropathologica*, vol. 116, no. 6, pp. 583–595, 2008.
- [3] A. L. Mammen, "Dermatomyositis and polymyositis: clinical presentation, autoantibodies, and pathogenesis," *Annals of the New York Academy of Sciences*, vol. 1184, pp. 134–153, 2010.
- [4] A. L. Mammen, "Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis," *Nature Reviews Neurology*, vol. 7, no. 6, pp. 343–354, 2011.
- [5] M. Salajegheh, T. Lam, and S. A. Greenberg, "Autoantibodies against a 43 kDa muscle protein in inclusion body myositis," *PLoS ONE*, vol. 6, no. 5, article e20266, 2011.
- [6] I. Lundberg, A. K. Ulfgrén, P. Nyberg, U. Andersson, and L. Klareskog, "Cytokine production in muscle tissue of patients with idiopathic inflammatory myopathies," *Arthritis and Rheumatism*, vol. 40, no. 5, pp. 865–874, 1997.
- [7] S. A. Greenberg, D. Sanoudou, J. N. Haslett et al., "Molecular profiles of inflammatory myopathies," *Neurology*, vol. 59, no. 8, pp. 1170–1182, 2002.
- [8] C. Cappelletti, F. Baggi, F. Zolezzi et al., "Type I interferon and Toll-like receptor expression characterizes inflammatory myopathies," *Neurology*, vol. 76, no. 24, pp. 2079–2088, 2011.
- [9] C. F. Ware, "The TNF superfamily-2008," *Cytokine and Growth Factor Reviews*, vol. 19, no. 3–4, pp. 183–186, 2008.
- [10] L. A. Tartaglia, D. Pennica, and D. V. Goeddel, "Ligand passing: the 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signaling by the 55-kDa TNF receptor," *Journal of Biological Chemistry*, vol. 268, no. 25, pp. 18542–18548, 1993.
- [11] S. Bhatnagar, S. K. Panguluri, S. K. Gupta, S. Dahiya, R. F. Lundy, and A. Kumar, "Tumor necrosis factor- α regulates distinct molecular pathways and gene networks in cultured skeletal muscle cells," *PLoS ONE*, vol. 5, no. 10, article e13262, 2010.
- [12] J. L. De Bleeker, V. I. Meire, W. Declercq, and E. H. Van Aken, "Immunolocalization of tumor necrosis factor-alpha and its receptors in inflammatory myopathies," *Neuromuscular Disorders*, vol. 9, no. 4, pp. 239–246, 1999.
- [13] S. Kuru, A. Inukai, Y. Liang, M. Doyu, A. Takano, and G. Sobue, "Tumor necrosis factor- α expression in muscles of polymyositis and dermatomyositis," *Acta Neuropathologica*, vol. 99, no. 5, pp. 585–588, 2000.
- [14] D. S. Tews and H. H. Goebel, "Cytokine expression profile in idiopathic inflammatory myopathies," *Journal of Neuro pathology and Experimental Neurology*, vol. 55, no. 3, pp. 342–347, 1996.
- [15] C. Gabay, F. Gay-Croisier, P. Roux-Lombard et al., "Elevated serum levels of interleukin-1 receptor antagonist in polymyositis/dermatomyositis: a biologic marker of disease activity with a possible role in the lack of acute-phase protein response," *Arthritis and Rheumatism*, vol. 37, no. 12, pp. 1744–1751, 1994.
- [16] T. O. Fedczyna, J. Lutz, and L. M. Pachman, "Expression of TNFalpha by muscle fibers in biopsies from children with untreated juvenile dermatomyositis: association with the TNFalpha-308A allele," *Clinical Immunology*, vol. 100, no. 2, pp. 236–239, 2001.
- [17] G. Mamyrova, T. P. O'Hanlon, L. Sillers et al., "Cytokine gene polymorphisms as risk and severity factors for juvenile dermatomyositis," *Arthritis and Rheumatism*, vol. 58, no. 12, pp. 3941–3950, 2008.
- [18] R. A. Collins and M. D. Grounds, "The role of tumor necrosis factor-alpha (TNF- α) in skeletal muscle regeneration: studies in TNF- α (-/-) and TNF- α (-/-)/LT- α (-/-) mice," *Journal of Histochemistry and Cytochemistry*, vol. 49, no. 8, pp. 989–1001, 2001.
- [19] P. Riley, L. J. McCann, S. M. Maillard, P. Woo, K. J. Murray, and C. A. Pilkington, "Effectiveness of infliximab in the treatment of refractory juvenile dermatomyositis with calcinosis," *Rheumatology*, vol. 47, no. 6, pp. 877–880, 2008.
- [20] M. Dastmalchi, C. Grundtman, H. Alexanderson et al., "A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies," *Annals of the Rheumatic Diseases*, vol. 67, no. 12, pp. 1670–1677, 2008.
- [21] G. J. D. Hengstman, F. H. J. Van Den Hoogen, P. Barrera et al., "Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminary observations," *European Neurology*, vol. 50, no. 1, pp. 10–15, 2003.
- [22] G. J. D. Hengstman, J. L. De Bleeker, E. Feist et al., "Open-label trial of anti-TNF- α in dermato- and polymyositis treated concomitantly with methotrexate," *European Neurology*, vol. 59, no. 3–4, pp. 159–163, 2008.
- [23] G. J. D. Hengstman, F. H. J. Van Den Hoogen, and B. G. M. Van Engelen, "Treatment of dermatomyositis and polymyositis with anti-tumor necrosis factor- α : long-term follow-up," *European Neurology*, vol. 52, no. 1, pp. 61–63, 2004.
- [24] L. Labioche, E. Liozon, B. Weschler, V. Loustaud-Ratti, P. Soria, and E. Vidal, "Refractory polymyositis responding in infliximab: extended follow-up," *Rheumatology*, vol. 43, no. 4, pp. 531–532, 2004.
- [25] P. Efthimiou, S. Schwartzman, and L. J. Kagen, "Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients," *Annals of the Rheumatic Diseases*, vol. 65, no. 9, pp. 1233–1236, 2006.
- [26] H. Sprott, M. Glatzel, and B. A. Mitchel, "Treatment of myositis with etanercept/Enbrel, a recombinant human soluble fusion protein of TNF- α type II receptor and IgG1," *Rheumatology*, vol. 43, no. 4, pp. 524–526, 2004.
- [27] Y. Liang, A. Inukai, S. Kuru, T. Kato, M. Doyu, and G. Sobue, "The role of lymphotoxin in pathogenesis of polymyositis," *Acta Neuropathologica*, vol. 100, no. 5, pp. 521–527, 2000.
- [28] C. M. L. De Padilla, A. N. Vallejo, D. Lacomis, K. Mcnallan, and A. M. Reed, "Extranodal lymphoid microstructures in inflamed muscle and disease severity of new-onset Juvenile dermatomyositis," *Arthritis and Rheumatism*, vol. 60, no. 4, pp. 1160–1172, 2009.
- [29] K. K. Creus, B. De Paepe, J. Weis, and J. L. De Bleeker, "The multifaceted character of lymphotoxin β in inflammatory myopathies," Submitted.
- [30] E. Y. Chiang, G. A. Kolumam, X. Yu et al., "Targeted depletion of lymphotoxin- α -expressing T H 1 and T H 17 cells inhibits autoimmune disease," *Nature Medicine*, vol. 15, no. 7, pp. 766–773, 2009.
- [31] R. A. Fava, E. Notidis, J. Hunt et al., "A role for the lymphotoxin/LIGHT axis in the pathogenesis of murine collagen-induced arthritis," *Journal of Immunology*, vol. 171, no. 1, pp. 115–126, 2003.
- [32] T. Dohi, P. D. Rennert, K. Fujihashi et al., "Abrogation of lymphotoxin-beta receptor signal pathway inhibits colonic patch genesis and Th2-type colitis," *The FASEB Journal*, vol. 14, no. 6, p. 975, 2000.

- [33] S. Takemura, A. Braun, C. Crowson et al., "Lymphoid neogenesis in rheumatoid synovitis," *Journal of Immunology*, vol. 167, no. 2, pp. 1072–1080, 2001.
- [34] M. Croft, T. So, W. Duan, and P. Soroosh, "The significance of OX40 and OX40L to T-cell biology and immune disease," *Immunological Reviews*, vol. 229, no. 1, pp. 173–191, 2009.
- [35] M. Tateyama, K. Fujihara, N. Ishii, K. Sugamura, Y. Onodera, and Y. Itoyama, "Expression of OX40 in muscles of polymyositis and granulomatous myopathy," *Journal of the Neurological Sciences*, vol. 194, no. 1, pp. 29–34, 2002.
- [36] T. Totsuka, T. Kanai, K. Uraushihara et al., "Therapeutic effect of anti-OX40L and anti-TNF- α MABs in a murine model of chronic colitis," *American Journal of Physiology*, vol. 284, no. 4, pp. G595–G603, 2003.
- [37] T. Yoshioka, A. Nakajima, H. Akiba et al., "Contribution of OX40/OX40 ligand interaction to the pathogenesis of rheumatoid arthritis," *European Journal of Immunology*, vol. 30, no. 10, pp. 2815–2823, 2000.
- [38] V. Henn, J. R. Slupsky, M. Gräfe et al., "CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells," *Nature*, vol. 391, no. 6667, pp. 591–594, 1998.
- [39] T. Sugiura, Y. Kawaguchi, M. Harigai et al., "Increased CD40 expression on muscle cells of polymyositis and dermatomyositis: role of CD40-CD40 ligand interaction in IL-6, IL-8, IL-15, and monocyte chemoattractant protein-1 production," *Journal of Immunology*, vol. 164, no. 12, pp. 6593–6600, 2000.
- [40] A. C. Tellander, E. Michaëlsson, C. Brunmark, and M. Andersson, "Potent adjuvant effect by anti-CD40 in collagen-induced arthritis. Enhanced disease is accompanied by increased production of collagen type-II reactive IgG2a and IFN- γ ," *Journal of Autoimmunity*, vol. 14, no. 4, pp. 295–302, 2000.
- [41] F. H. Durie, R. A. Fava, T. M. Foy, A. Aruffo, J. A. Ledbetter, and R. J. Noelle, "Prevention of collagen-induced arthritis with an antibody to gp39, the ligand for CD40," *Science*, vol. 261, no. 5126, pp. 1328–1330, 1993.
- [42] P. Maerten, K. Geboes, G. D. Hertogh et al., "Functional expression of 4-1BB (CD137) in the inflammatory tissue in Crohn's disease," *Clinical Immunology*, vol. 112, no. 3, pp. 239–246, 2004.
- [43] K. C. Kalunian, J. C. Davis, J. T. Merrill, M. C. Totoritis, and D. Wofsy, "Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial," *Arthritis and Rheumatism*, vol. 46, no. 12, pp. 3251–3258, 2002.
- [44] M. Kondo, Y. Murakawa, N. Harashima, S. Kobayashi, S. Yamaguchi, and M. Harada, "Roles of proinflammatory cytokines and the Fas/Fas ligand interaction in the pathogenesis of inflammatory myopathies," *Immunology*, vol. 128, no. 1, pp. e589–e599, 2009.
- [45] J. L. De Bleecker, V. I. Meire, I. E. Van Walleghem, I. M. Groesens, and J. M. Schröder, "Immunolocalization of Fas and Fas ligand in inflammatory myopathies," *Acta Neuropathologica*, vol. 101, no. 6, pp. 572–578, 2001.
- [46] L. Behrens, A. Bender, M. A. Johnson, and R. Hohlfeld, "Cytotoxic mechanisms in inflammatory myopathies. Coexpression of Fas and protective Bcl-2 in muscle fibres and inflammatory cells," *Brain*, vol. 120, no. 6, pp. 929–938, 1997.
- [47] I. M. Fyhr and A. Oldfors, "Upregulation of Fas/Fas ligand in inclusion body myositis," *Annals of Neurology*, vol. 43, no. 1, pp. 127–130, 1998.
- [48] A. Inukai, Y. Kobayashi, K. Ito et al., "Expression of Fas antigen is not associated with apoptosis in human myopathies," *Muscle and Nerve*, vol. 20, no. 6, pp. 702–709, 1997.
- [49] K. Nozawa, N. Kayagaki, Y. Tokano, H. Yagita, K. Okumura, and H. Hasimoto, "Soluble Fas (APO-1, CD95) and soluble Fas ligand in rheumatic diseases," *Arthritis and Rheumatism*, vol. 40, no. 6, pp. 1126–1129, 1997.
- [50] E. Antiga, C. C. Kretz, R. Klemmt et al., "Characterization of regulatory T cells in patients with dermatomyositis," *Journal of Autoimmunity*, vol. 35, no. 4, pp. 342–350, 2010.
- [51] L. Guéry, F. Batteux, N. Bessis et al., "Expression of Fas ligand improves the effect of IL-4 in collagen-induced arthritis," *European Journal of Immunology*, vol. 30, no. 1, pp. 308–315, 2000.
- [52] H. Hashimoto, M. Tanaka, T. Suda et al., "Soluble fas ligand in the joints of patients with rheumatoid arthritis and osteoarthritis," *Arthritis and Rheumatism*, vol. 41, no. 4, pp. 657–662, 1998.
- [53] K. Oelke, Q. Lu, D. Richardson et al., "Overexpression of CD70 and overstimulation of IgG synthesis by lupus T cells and T cells treated with DNA methylation inhibitors," *Arthritis and Rheumatism*, vol. 50, no. 6, pp. 1850–1860, 2004.
- [54] E. Oflazoglu, T. E. Boursalian, W. Zeng et al., "Blocking of CD27-CD70 pathway by anti-CD70 antibody ameliorates joint disease in murine collagen-induced arthritis," *Journal of Immunology*, vol. 183, no. 6, pp. 3770–3777, 2009.
- [55] O. Danielsson, C. Nilsson, B. Lindvall, and J. Ernerudh, "Expression of apoptosis related proteins in normal and diseased muscle: a possible role for Bcl-2 in protection of striated muscle," *Neuromuscular Disorders*, vol. 19, no. 6, pp. 412–417, 2009.
- [56] E. Cretney, J. L. McQualter, N. Kayagaki et al., "TNF-related apoptosis-inducing ligand (TRAIL)/Apo2L suppresses experimental autoimmune encephalomyelitis in mice," *Immunology and Cell Biology*, vol. 83, no. 5, pp. 511–519, 2005.
- [57] K. P. Wandinger, J. D. Lünemann, O. Wengert et al., "TNF-related apoptosis inducing ligand (TRAIL) as a potential response marker for interferon-beta treatment in multiple sclerosis," *The Lancet*, vol. 361, no. 9374, pp. 2036–2043, 2003.
- [58] V. Kartsogiannis, H. Zhou, N. J. Horwood et al., "Localization of RANKL (receptor activator of NF κ B ligand) mRNA and protein in skeletal and extraskelatal tissues," *Bone*, vol. 25, no. 5, pp. 525–534, 1999.
- [59] G. Page and P. Miossec, "RANK and RANKL expression as markers of dendritic cell-T cell interactions in paired samples of rheumatoid synovium and lymph nodes," *Arthritis and Rheumatism*, vol. 52, no. 8, pp. 2307–2312, 2005.
- [60] P. J. Bekker, D. L. Holloway, A. S. Rasmussen et al., "A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women," *Journal of Bone and Mineral Research*, vol. 20, no. 12, pp. 2275–2282, 2005.
- [61] F. Mackay, P. Schneider, P. Rennert, and J. Browning, "BAFF and APRIL: a tutorial on B cell survival," *Annual Review of Immunology*, vol. 21, pp. 231–264, 2003.
- [62] T. Matsushita, M. Hasegawa, K. Yanaba, M. Kodera, K. Takehara, and S. Sato, "Elevated serum BAFF levels in patients with systemic sclerosis: enhanced BAFF signaling in systemic sclerosis B lymphocytes," *Arthritis and Rheumatism*, vol. 54, no. 1, pp. 192–201, 2006.
- [63] O. Kryštůfková, T. Vallerskog, S. Barbasso Helmers et al., "Increased serum levels of B cell activating factor (BAFF) in subsets of patients with idiopathic inflammatory myopathies," *Annals of the Rheumatic Diseases*, vol. 68, no. 6, pp. 836–843, 2009.
- [64] P. Szodoray, P. Alex, N. Knowlton et al., "Idiopathic inflammatory myopathies, signified by distinctive peripheral cytokines,

- chemokines and the TNF family members B-cell activating factor and a proliferation inducing ligand," *Rheumatology*, vol. 49, no. 10, pp. 1867–1877, 2010.
- [65] M. Salajegheh, J. L. Pinkus, A. A. Amato et al., "Permissive environment for B-cell maturation in myositis muscle in the absence of B-cell follicles," *Muscle and Nerve*, vol. 42, no. 4, pp. 576–583, 2010.
- [66] A. H. Baek, G. I. Suh, J. M. Hong, B. C. Suh, D. S. Shim, and Y. C. Choi, "The increased expression of B cell activating factor (BAFF) in patients with dermatomyositis," *Neuromuscular Disorders*, vol. 20, no. 9–10, p. 634, 2010.
- [67] I. E. Lundberg and S. Barbasso Helmers, "The type I interferon system in idiopathic inflammatory myopathies," *Autoimmunity*, vol. 43, no. 3, pp. 239–243, 2010.
- [68] S. A. Greenberg, E. M. Bradshaw, J. L. Pinkus et al., "Plasma cells in muscle in inclusion body myositis and polymyositis," *Neurology*, vol. 65, no. 11, pp. 1782–1787, 2005.
- [69] D. H. Yoo, "Anticytokine therapy in systemic lupus erythematosus," *Lupus*, vol. 19, no. 12, pp. 1460–1467, 2010.
- [70] Z. Dai, Q. Li, Y. Wang et al., "CD4+CD25+ regulatory T cells suppress allograft rejection mediated by memory CD8+ T cells via a CD30-dependent mechanism," *Journal of Clinical Investigation*, vol. 113, no. 2, pp. 310–317, 2004.
- [71] X. Sun, H. Yamada, K. Shibata et al., "CD30 ligand is a target for a novel biological therapy against colitis associated with Th17 responses," *Journal of Immunology*, vol. 185, no. 12, pp. 7671–7680, 2010.
- [72] R. Gerli, C. Muscat, O. Bistoni et al., "High levels of the soluble form of CD30 molecule in rheumatoid arthritis (RA) are expression of CD30+ T cell involvement in the inflamed joints," *Clinical and Experimental Immunology*, vol. 102, no. 3, pp. 547–550, 1995.
- [73] F. Caligaris-Cappio, M. T. Bertero, M. Converso et al., "Circulating levels of soluble CD30, a marker of cells producing Th2-type cytokines, are increased in patients with systemic lupus erythematosus and correlate with disease activity," *Clinical and Experimental Rheumatology*, vol. 13, no. 3, pp. 339–343, 1995.
- [74] H. W. Jung, S. W. Choi, J. I. L. Choi, and B. S. Kwon, "Serum concentrations of soluble 4-1BB, and 4-1BB ligand correlated with the disease severity in rheumatoid arthritis," *Experimental and Molecular Medicine*, vol. 36, no. 1, pp. 13–22, 2004.
- [75] S. K. Seo, J. H. Choi, Y. H. Kim et al., "4-1BB-mediated immunotherapy of rheumatoid arthritis," *Nature Medicine*, vol. 10, no. 10, pp. 1088–1094, 2004.
- [76] J. A. Winkles, "The TWEAK-Fn14 cytokine-receptor axis: discovery, biology and therapeutic targeting," *Nature Reviews Drug Discovery*, vol. 7, no. 5, pp. 411–425, 2008.
- [77] C. Dogra, H. Changotra, S. Mohan, and A. Kumar, "Tumor necrosis factor-like weak inducer of apoptosis inhibits skeletal myogenesis through sustained activation of nuclear factor- κ B and degradation of MyoD protein," *Journal of Biological Chemistry*, vol. 281, no. 15, pp. 10327–10336, 2006.
- [78] M. Kumar, D. Y. Makonchuk, H. Li, A. Mittal, and A. Kumar, "Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) activates proinflammatory signaling pathways and gene expression through the activation of TGF-beta activated kinase 1," *Journal of Immunology*, vol. 182, no. 4, pp. 2439–2448, 2009.
- [79] A. Mittal, S. Bhatnagar, A. Kumar, P. K. Paul, S. Kuang, and A. Kumar, "Genetic ablation of TWEAK augments regeneration and post-injury growth of skeletal muscle in mice," *American Journal of Pathology*, vol. 177, no. 4, pp. 1732–1742, 2010.
- [80] N. Harada, M. Nakayama, H. Nakano, Y. Fukuchi, H. Yagita, and K. Okumura, "Pro-inflammatory effect of TWEAK/Fn14 interaction on human umbilical vein endothelial cells," *Biochemical and Biophysical Research Communications*, vol. 299, no. 3, pp. 488–493, 2002.
- [81] C. N. Lynch, Y. C. Wang, J. K. Lund, Y. W. Chen, J. A. Leal, and S. R. Wiley, "TWEAK induces angiogenesis and proliferation of endothelial cells," *Journal of Biological Chemistry*, vol. 274, no. 13, pp. 8455–8459, 1999.
- [82] S. H. Kim, Y. J. Kang, W. J. Kim et al., "TWEAK can induce pro-inflammatory cytokines and matrix metalloproteinase-9 in macrophages," *Circulation Journal*, vol. 68, no. 4, pp. 396–399, 2004.
- [83] C. Dogra, H. Changotra, N. Wedhas, X. Qin, J. E. Wergedal, and A. Kumar, "TNF-related weak inducer of apoptosis (TWEAK) is a potent skeletal muscle-wasting cytokine," *FASEB Journal*, vol. 21, no. 8, pp. 1857–1869, 2007.
- [84] J. L. De Bleeker, B. De Paepe, I. E. Vanwalleghem, and J. M. Schröder, "Differential expression of chemokines in inflammatory myopathies," *Neurology*, vol. 58, no. 12, pp. 1779–1785, 2002.
- [85] L. C. Burkly, J. S. Michaelson, K. Hahm, A. Jakubowski, and T. S. Zheng, "TWEAKing tissue remodeling by a multifunctional cytokine: role of TWEAK/Fn14 pathway in health and disease," *Cytokine*, vol. 40, no. 1, pp. 1–16, 2007.
- [86] K. Kamata, S. Kamijo, A. Nakajima et al., "Involvement of TNF-like weak inducer of apoptosis in the pathogenesis of collagen-induced arthritis," *Journal of Immunology*, vol. 177, no. 9, pp. 6433–6439, 2006.
- [87] K. Tamada, K. Shimozaki, A. I. Chapoval et al., "LIGHT, a TNF-like molecule, costimulates T cell proliferation and is required for dendritic cell-mediated allogeneic T cell response," *Journal of Immunology*, vol. 164, no. 8, pp. 4105–4110, 2000.
- [88] K. Schneider, K. G. Potter, and C. F. Ware, "Lymphotoxin and LIGHT signaling pathways and target genes," *Immunological Reviews*, vol. 202, pp. 49–66, 2004.
- [89] Y. Hosokawa, I. Hosokawa, K. Ozaki, H. Nakae, and T. Matsuo, "TNFSF14 coordinately enhances CXCL10 and CXCL11 productions from IFN- γ -stimulated human gingival fibroblasts," *Molecular Immunology*, vol. 47, no. 4, pp. 666–670, 2010.
- [90] B. De Paepe, K. De Keyser, J. J. Martin, and J. L. De Bleeker, "Alpha-chemokine receptors CXCR1-3 and their ligands in idiopathic inflammatory myopathies," *Acta Neuropathologica*, vol. 109, no. 6, pp. 576–582, 2005.
- [91] W. J. Kim, Y. J. Kang, E. M. Koh, K. S. Ahn, H. S. Cha, and W. H. Lee, "LIGHT is involved in the pathogenesis of rheumatoid arthritis by inducing the expression of pro-inflammatory cytokines and MMP-9 in macrophages," *Immunology*, vol. 114, no. 2, pp. 272–279, 2005.
- [92] K. Tamada, H. Tamura, D. Flies et al., "Blockade of LIGHT/IT β and CD40 signaling induces allospecific T cell anergy, preventing graft-versus-host disease," *Journal of Clinical Investigation*, vol. 109, no. 4, pp. 549–557, 2002.
- [93] Q. Wu, Y. X. Fu, and R. D. Sontheimer, "Blockade of lymphotoxin signaling inhibits the clinical expression of murine graft-versus-host skin disease," *Journal of Immunology*, vol. 172, no. 3, pp. 1630–1636, 2004.
- [94] K. A. Papadakis, D. Zhu, J. L. Prehn et al., "Dominant role for TL1A/DR3 pathway in IL-12 plus IL-18-induced IFN- γ production by peripheral blood and mucosal CCR9+ T lymphocytes," *Journal of Immunology*, vol. 174, no. 8, pp. 4985–4990, 2005.
- [95] G. Bamias, C. Martin, M. Marini et al., "Expression, localization, and functional activity of TL1A, a novel Th1-polarizing cytokine in inflammatory bowel Disease," *Journal of Immunology*, vol. 171, no. 9, pp. 4868–4874, 2003.

- [96] K. Yamazaki, A. Takahashi, M. Takazoe et al., "Positive association of genetic variants in the upstream region of NKX2-3 with Crohn's disease in Japanese patients," *Gut*, vol. 58, no. 2, pp. 228–232, 2009.
- [97] M. Tremelling, C. Berzuini, D. Massey et al., "Contribution of TNFSF15 gene variants to Crohn's disease susceptibility confirmed in UK population," *Inflammatory Bowel Diseases*, vol. 14, no. 6, pp. 733–737, 2008.
- [98] E. Bae, W. J. Kim, Y. M. Kang et al., "Glucocorticoid-induced tumour necrosis factor receptor-related protein-mediated macrophage stimulation may induce cellular adhesion and cytokine expression in rheumatoid arthritis," *Clinical and Experimental Immunology*, vol. 148, no. 3, pp. 410–418, 2007.
- [99] M. Patel, D. Xu, P. Kewin et al., "Glucocorticoid-induced TNFR family-related protein (GITR) activation exacerbates murine asthma and collagen-induced arthritis," *European Journal of Immunology*, vol. 35, no. 12, pp. 3581–3590, 2005.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

