Cellular Mechanisms of TNF Function in Models of Inflammation and Autoimmunity

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Abstract

The TNF/TNF receptor (TNFR) system has a prominent role in the pathogenesis of chronic inflammatory and autoimmune disorders. Extensive research in animal models with deregulated TNF expression has documented that TNF may initiate or sustain inflammatory pathology, while at the same time may exert immunomodulatory or disease-suppressive activities. The TNF/TNFR system encompassing both the soluble and the transmembrane form of TNF with differential biological activities, as well as the differential usage of its receptors, mediating distinct functions, appears to confer complexity but also specificity in the action of TNF. The inherent complexity in TNF-mediated pathophysiology highlights the requirement to address the role of TNF taking into account both proinflammatory tissue-damaging and immunomodulatory functions in a cellular and receptor-specific manner. In this review, we discuss our current understanding of the involvement of TNF in chronic inflammation and autoimmunity, focusing on TNF-mediated cellular pathways leading to the pathogenesis or progression of joint and intestinal inflammatory pathology. Knowledge of the mechanisms by which TNF either initiates or contributes to disease pathology is fundamentally required for the design of safe and effective anti-TNF/TNFR therapies for human inflammatory and autoimmune disorders.

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TNF-α is a pleiotropic, proinflammatory mediator whose function is implicated in a wide range of inflammatory, infectious, autoimmune and malignant conditions. TNF is produced in response to infection to confer immunity to the host. While the effect of the TNF in infection is beneficial, tight regulation of TNF production is required to protect the host from the detrimental activities of TNF. Deregulated TNF overexpression can give rise to chronic inflammatory and autoimmune disorders, such as chronic inflammatory arthritis, inflammatory bowel disease (IBD) and multiple sclerosis (MS). Currently, TNF-blocking agents are widely used and have shown encouraging results for the treatment of rheumatoid arthritis (RA) and other inflammatory disorders including Crohn’s disease (CD), ankylosing spondylitis and psoriasis [1–3]. By contrast, anti-TNF therapy in patients with MS led to the adverse outcome
worsening disease symptoms [4, 5]. Thus, blocking the TNF activity is not always beneficial. Moreover, anti-TNF therapy has led to side effects including opportunistic infections, demyelination, systemic lupus erythematosus symptoms and increased risk for lymphoma [6–9].

TNF is produced in response to bacterial, inflammatory and other stimuli primarily by cells of the immune system, such as macrophages and T and B lymphocytes, but also by additional cell types, including endothelial cells, mast cells and neuronal tissues [10]. Although TNF is initially synthesized as a transmembrane molecule [11], upon cleavage by the metalloprotease TNF-a-converting enzyme (TACE or ADAM17), the secreted monomers that are generated form biologically active homotrimers [12]. Both the soluble and transmembrane forms of TNF are biologically active in their trimeric forms [12]. TNF exerts its biological functions following interaction with its cognate membrane receptors (TNFR), p55TNFR (TNFR1) and p75TNFR (TNFR2) [13], which can additionally be released from the cell surface by proteolysis to produce soluble forms suggested to neutralize the action of TNF [14, 15]. Although most cell types appear to express TNFR1, TNFR2 is preferentially expressed in hematopoietic cells and is more efficiently activated by transmembrane as opposed to soluble TNF [16]. Both opposing and overlapping effects are mediated following activation of TNFR1 or TNFR2 by TNF. Signaling through TNFR1 leads to the activation of the transcription factor nuclear factor-κB (NF-κB) and mitogen-activated protein kinase pathways, and has been prominently associated with proinflammatory, cytotoxic and apoptotic responses [17, 18]. In turn, TNFR2 lacks an intracellular death domain, which is present in TNFR1, and appears to mediate signals promoting cellular activation, proliferation and migration [19, 20].

The generation of animal models with engineered defects in TNF or TNFR expression has been pivotal in our current understanding or TNF/TNFR function. Early studies in TNF-deficient mice revealed the physiological role of TNF in secondary lymphoid organ microarchitecture and function, and in the host defense response [21]. These properties have been attributed to TNFR1 [22–24]. With relevance to disease pathogenesis, studies in mice with perturbed TNF expression have advanced our understanding of the detrimental activities of TNF leading to inflammatory pathology, but have additionally revealed a critical immunomodulatory function for TNF in inhibiting autoimmunity. Deregulated TNF overproduction in transgenic mice is sufficient to initiate multi-organ or tissue-specific inflammation, leading to the spontaneous pathology resembling RA [25, 26], IBD [26] or MS [27, 28]. The ensuing pathology that develops appears to be determined by the locality, cellular context, bioactivity, and chronicity of TNF production. In addition to the above models in which pathology develops as a result of TNF overexpression, mice expressing non-sheddable TNFR1 exhibit increased host defense responses but develop spontaneous liver pathology and enhanced susceptibility to inflammation and autoimmunity, indicating that TNFR1 receptor shedding
may regulate TNF activity in vivo by defining thresholds of TNF function [29]. In humans, mutations affecting the shedding of TNFR1 have been associated with the development of TNFR-associated periodic syndrome, characterized by episodes of fever and localized inflammation [30]. It appears therefore that detrimental TNF activities may also arise when mechanisms that aim to control the opposing beneficial and hazardous functions of TNF are eliminated. Still, the paradigm of sustained TNF activity resulting in organ-specific autoimmune or inflammatory pathology is not always followed. In models of systemic autoimmunity or autoimmune diabetes, TNF appears to either promote or inhibit autoimmune pathology depending on factors such as developmental stage, background genetic susceptibility and timing of TNF expression [31–34].

Mechanistically, the contrasting proinflammatory and disease-suppressing activities of TNF may be partly attributed to the diverse functions of its receptors, as well as the differential bioactivities of its soluble and transmembrane forms. Thus transgenic TNF overexpression in the central nervous system results in spontaneous inflammatory demyelinating disease [27, 28], whereas TNF appears to promote the initiation phase in the antigen-induced experimental encephalomyelitis (EAE) model [35], in line with a harmful proinflammatory TNF activity. Most interestingly however, TNF-deficient mice immunized with myelin oligodendrocyte glycoprotein display prolonged self-reactivity to myelin, resulting in exacerbated EAE at a time point when remission would normally take place [36]. In the context of TNFR deficiency, in TNFR1-deficient mice although the initial phase of EAE is suppressed as in TNF-deficient mice, regression to myelin autoreactivity is preserved [36]. By contrast, in double-deficient TNFR1, -2–/– mice, disease is exacerbated in a manner similar to TNF–/– mice, resulting in chronic EAE and late autoimmune reactivity [36]. These data indicate an important role for TNFR1 in mediating the detrimental effects of TNF in the initial stages of the disease, whereas TNFR2 appears sufficient in mediating TNF suppression of autoimmune reactivity. In the same disease setting using the EAE model and mice generated to express an uncleavable mutant TNF protein, we have shown that transmembrane TNF can actively suppress both the inflammatory and autoimmune phase of disease [37]. Furthermore, although transmembrane TNF fails to support splenic structure and function [37, 38], it is capable of supporting host defense responses against *Listeria monocytogenes* [37]. Notably, transmembrane TNF is not adequate to support development of arthritis in the TNF-dependent tristetraprolin (TTP)-deficient model [37]. Therefore, transmembrane TNF may preserve some of the beneficial activities of TNF while lacking detrimental functions.

In view of the above therapeutic approaches, aiming to block TNFR1 or soluble TNF may be preferable to the complete blockade of TNF in the treatment of chronic inflammation and autoimmunity. On this basis, in the following paragraphs we discuss current knowledge derived from animal models on the cellular and receptor-specific functions of TNF in arthritis and IBD.
RA is traditionally described as a pattern of arthropathy involving a prolonged synovitis of multiple diarthodial joints. The synovitis leads to pain, soft tissue swelling and stiffness resulting in loss of joint function. RA is characterized by the presence of inflammatory infiltrate in the synovium, the thin membrane predominated mostly by resident fibroblasts and scarcely detected macrophages located adjacent to and in direct contact with the intra-articular cavity of the joint. During the course of disease, the synovial membrane gradually increases in thickness, transforming itself into an aggressive cellular mass called pannus that invades and destroys articular structures [39]. The disease affects about 1% of the population worldwide, thus creating a substantial personal, social and economical burden [40].

Research in the last decades has focused on unraveling the pathogenesis of RA either by applying molecular techniques and genetic analysis on human tissue or by generating animal models of RA for identifying and analyzing the pathogenic pathways that lead to all aspects of disease: inflammation, cartilage breakdown and bone erosion. Considerable genetic knowledge suggests that the genetic susceptibility and linkage for RA is rather complicated, as several genes and loci are acknowledged to be linked with disease in population studies [41–43]. Interestingly, due to the genetic association of HLA-DR genes with RA [44], a significant role for T cell-dependent mechanisms had also been proposed. However, the lack of abundant detection of T cell-derived products in RA synovium and synovial fluid [45] and the low clinical efficacy of a nondepleting anti-CD4 antibody (keliximab) [46] challenged the notion of a primarily pathogenic role for T cells in RA. Early theories on etiopathogenesis also focused on analyzing clinical findings, such as deregulated autoantibodies and immune complexes, and these observations led to the conclusion that RA is an autoimmune disease. The detection of rheumatoid factor [47], although not a very specific finding for RA, as well as high titers of other autoantibodies signified the role of B cells in RA pathology, and this is further emphasized by clinical improvement in patients receiving rituximab, an anti-CD20 antibody [48]. In the 1990s, Firestein and Zvaifler [49] and Firestein [50] reviewing the current RA literature, disputed the acquired immunity-based orchestration of the inflammatory response in RA and suggested that, most probably, innate signals govern and perpetuate the disease manifestations. This was in line with the detection of innate cytokine networks in joint tissue cultures from RA patients [51]. The experimental paradigm on the role of TNF in arthritic pathology became apparent by the generation of human TNF transgenic mice (hTNF-Tg or Tg197); hTNF-Tg mice express high levels of human TNF transgene due to genetic modification of the 3’ prime UTR of human TNF gene. The mice develop inflammatory polyarthritis with all characteristics of RA, and disease is abrogated by the anti-human TNF regime [25]. The clinical efficacy of anti-TNF therapy in patients with RA indeed showed significant results in dampening disease activity [1], emphasizing the importance of TNF in human disease.
Based on the possible role of 3’UTR in the translational repression of TNF mRNA, a targeted mutant lacking endogenous 3’UTR ARE elements of murine TNF mRNA (TNFΔARE mice) develops arthritis and Crohn’s-like IBD, further confirming TNF-mediated mechanisms in orchestrating the arthritogenic response in mice [26]. In both animal models, the arthritogenic potential of TNF is mediated through TNFR1 [25, 26]. The role of TNFR2 could only be demonstrated for TNFΔARE mice, since human TNF does not signal through murine TNFR2 [52]. Thus, genetic deficiency of TNFR2 in TNFΔARE results in a more aggressive form of arthritis, implying that TNFR2 may act to counterbalance the pathogenic TNF signals [26]. The negative control of TNFR2-mediated signaling in modifying disease phenotype could perhaps be associated with the immunoregulatory function of this receptor. Therefore, the TNFΔARE and hTNF-Tg mice appear to be most informative animal models as to the TNF-mediated mechanisms operating in arthritis.

Importantly, the beneficial effect of TNF neutralization and the key role of this cytokine in arthritic disease have been further demonstrated in animal models other than the hTNF-Tg mice. The widely used collagen-induced arthritis model (CIA), generated by heterologous CII immunization in animals, may be treated effectively with anti-TNF antibody or other TNF inhibitors administered prior to disease onset [53, 54]. In addition, anti-TNF monoclonal antibody treatment was used successfully after disease onset in CIA and resulted in reduced inflammation [55]. Experiments with TNF-deficient animals showed that TNF is crucial but not dominant in the CIA model, as pathology develops with delayed onset and milder symptoms [56]. Similarly, TNFR1 deficiency delays the onset but does not ameliorate the clinical signs of disease in this model [57]. The SKG strain carries a natural point mutation affecting the gene encoding an SH2 domain of ZAP-70, a key signal transduction molecule in T cells, and spontaneously develops arthropathy [58]. TNF deficiency retarded the onset and substantially reduced disease incidence and severity in this model [59]. As other proinflammatory cytokines are implicated in arthritis, such as interleukin (IL)-1 which stands in a leading position at the cytokine cascade of RA, it is worth mentioning that arthropathy developing in IL-1 receptor antagonist-deficient mice due to uncontrolled IL-1 signaling [60] could be rescued in a TNF null background [61]. Even though TTP-deficient animals do not carry any mutations in cytokine-related genes, they develop a systemic inflammatory syndrome with severe polyarticular arthritis and autoimmunity, as well as medullary and extramedullary myeloid hyperplasia [62]. TTP is a zinc finger protein involved in ARE-containing mRNA degradation; in TTP deficiency, ARE-containing TNF mRNA cannot be degraded. Apparently, the phenotype of TTP-deficient mice is TNF/TNFR1 dependent [62, 63]. A recently developed animal model provided evidence that defective apoptosis in macrophages via inducible ablation of DNase II leads to the development of a severe inflammatory polyarthropathy [64]. Pathology is abrogated by anti-TNF administration, implying that the synovial tissue is extremely susceptible to aberrant innate TNF signaling events.
It is therefore evident that TNF/TNFR1 signaling interferes actively with the arthritogenic process at multiple levels regulating immune reactivity and cellular fate, independently of the animal model employed.

Mesenchymal Cell-Specific Role of TNFR1 in the Pathogenesis of TNF-Driven Inflammatory Arthritis

Despite the debates on the autoimmune or autoinflammatory nature of RA, and the plethora of described mechanisms leading to pathogenic cytokine disbalances in RA, experimental evidence indicates that chronic innate immune activation of the synovial fibroblast (SF) could be a dominant pathogenic event in RA. SFs are resident mesenchymal cells of the synovial membrane and their origin is still debatable; they represent a heterogeneous population of cells in terms of tissue localization, physiology (intimal and subintimal) and derivation (nonepithelial, mesenchymal cells) and display differential activation and differentiation properties [65]. The primary physiological role of the SF is to provide a nourishing environment for the cartilage and to lubricate the articular surfaces through production of hyalorunan, lubricin, and collagens. They lack expression of MHC class II antigens, CD68 and do not present any phagocytic activity. Notably, intimal SFs express CD55, ICAM-1, and increased VCAM-1 levels, as compared to subintimal SFs and other types of fibroblasts [66], enabling them to interact with other cell types, such as mononuclear lymphocytes, T and B cells, and to modulate leukocyte trafficking.

Several lines of evidence have indicated the autonomous arthritogenic function of SFs both in vitro and in vivo. Cultured RA-SFs can proliferate in an anchorage-independent manner, escape contact inhibition growth arrest, and express a variety of transcription factors and matrix metalloproteinases (MMPs) [67], while they exhibit deregulated expression of Wnt-related molecules potentially indicating that they may have reacquired the primordial phenotype, accounting for their hyperproliferation and aggressive invasiveness, properties usually detected in tumors [68]. Notwithstanding the notion that cytokines like TNF can trigger SF activation and proliferation [69, 70], it seems that SFs can maintain their activation status without the need for continuous stimulation from the proinflammatory microenvironment. The most convincing evidence on the autonomous nature of the RA-SFs has been provided by Muller-Ladner et al. [71] in an elegant study showing RA-SFs cotransplanted with human cartilage into immunodeficient mice to grow invasively into adjacent cartilage even in the absence of other cells of the human immune system. The arthritogenicity of murine SFs derived from hTNF-Tg mice was also exhibited when intraarticularly injected in immunodeficient mice [72]. The innate activation of SFs may be explained either by continuous stimulation from paracrine proinflammatory mediators (e.g. TNF), or by chronic innate signals through pattern recognition receptors on their surface [73]. Proinflammatory cytokine and chemokine production, as
well as upregulated expression of adhesion molecules by the activated SF, may in turn promote the recruitment and retention of immune cells in the synovium [74].

More recent concepts suggest the cytoskeletal control machinery as a target of TNF in partly regulating the inflammatory and apoptotic phenomena [75]. In agreement with this concept, TNF-induced activation of NF-κB and cytokine secretion in human cultured RA-SFs is dependent on the activation of RhoA, a GTPase which promotes actin polymerization (F-actin formation), through p65/RelA NF-κB subunit binding to newly formed F-actin, suggesting a central role of this GTPase in the arthritic inflammatory response [76, 77]. Interestingly, stress fiber formation in SFs from the hTNF-Tg mice is significantly more intense [78], and hTNF-Tg SFs show increased proliferative, migratory and adherence capacity compared to WT cells [79]. This phenotype of the hTNF-Tg SF is not reversed by short-term anti-TNF treatment hinting an imprinted phenotype of the murine cells derived from an overexpressing human TNF environment [79], as suggested for RA-SFs [67]. Additionally, it was recently shown that a number of deregulated genes, known to be involved in actin filament and cytoskeleton organization, such as gsn, aqp1, cdc42hom, eef1a1, tuba1, rab14, lsp1, lst1, mylc2b, pitpnm and pstpip1, were strongly deregulated in the hTNF-Tg animal model [78]. Importantly, the genetic ablation of gelsolin, encoded by gsn, a gene found downregulated in hTNF-Tg SFs, resulted in exacerbation of the arthritic disease in hTNF-Tg mice [78], validating the functional significance of the actin cytoskeleton rearrangements in the pathophysiology of the disease. More recently, cadherin-11, a junction molecule ubiquitous to many tissues, was shown to function as a major mediator of synovial architecture by organizing SFs via formation of cell-to-cell adherent junctions [80] and remodeling of the actin cytoskeleton [81]. The stromal cell signature of cadherin-11 in arthritis was confirmed when the passive K/BxN model was applied to cadherin-11-deficient recipients, resulting in suppression of autoimmune arthritis pathology [82]. Interestingly, TNF has been reported to drive cell-cell adhesion molecule cadherin-11 expression in the rheumatic synovium [83] and to promote the invasive behavior of RA-SFs [84]. In view of the above, these data provide further evidence to support the concept that TNF may promote structural changes in the synovial lining leading to the activation and pathogenic function of the SF through direct or indirect modulation of actin cytoskeleton dynamics.

TNF-modeled arthritis offers an adequate system to decipher the cellular requirements for the induction of TNF-mediated arthritic pathology and to explore the potential of cell-specific therapeutic approaches. Remarkably, we have previously shown that, in both the hTNF-Tg and TNFΔARE models, inflammatory arthritis develops in the absence of the adaptive immune response (RAG1 deficiency), implying that either innate immunity or other immune or nonimmune mechanisms could be responsible for initiation and perpetuation of disease [26, 85]. In these models, we have used reciprocal bone marrow transplantation experiments in TNF-overexpressing mice (TNFΔARE or hTNF-Tg mice) and TNFR-deficient mice to decipher the cellular sources and targets of pathogenic TNF. With this approach, we have shown that in
TNFΔARE mice the pathogenic TNF source is located in the radiosensitive bone marrow compartment, whereas in the hTNF-Tg mice, pathogenic human TNF derives from radioresistant-stromal cells [Armaka, unpubl. obs.]. While the TNFΔARE and hTNF-Tg mice do not share the same arthritogenic TNF pool, the bone marrow engraftment experiments indicated that the cellular target of pathogenic TNF is a shared hallmark; arthritic pathology develops exclusively by TNFR1-mediated signaling in radioresistant stromal cells in both models [86]. Furthermore, early activation of the SF, evidenced by the misbalanced production of MMPs and their inhibitors TIMPs (tissue inhibitor of MMPs) prior to the appearance of inflammatory infiltrate in joint area, indicated the early proinflammatory triggering of the SF in TNF-driven arthritis. In this context, the in vivo validation of the SF as the mesenchymal component sufficient to elicit TNF/TNFR1-mediated disease was confirmed by the selective mesenchymal expression of the TNFR1 allele in both TNF-overexpressing murine models using Cre/LoxP technology; the mice develop full-blown arthritis under the restricted SF expression of TNFR1 [86]. These data clearly establish the importance of the SF not only as primary target but also as coordinator of all aspects of the arthritic phenotype in mice. Accordingly, it would be extremely interesting to investigate whether TNFR1 signaling in the SF is an absolute requirement for the induction of disease and further analyze in a cell-specific manner the molecular pathways implicated and their contribution to the course of disease.

In light of the evidence discussed so far, SFs can initiate the pathogenic cascade through sensing of pathogenic triggers such as TNF, promote the disease through tissue destruction and recruitment of inflammatory cells, and thus amplify and sustain the immune response constituting a key cell type in disease pathogenesis and perpetuation (fig. 1).

Cellular Mechanisms of TNF Function in Models of Inflammatory Bowel Disease

IBD is a chronic inflammatory disorder of unknown etiology that affects the gastrointestinal tract. The prevailing concept regarding the etiopathogenesis of both subtypes of IBD, CD and ulcerative colitis (UC), is that disease pathogenesis involves dysregulated immune responses against antigens of the intestinal flora influenced by genetic and environmental factors [87]. Although this concept applies to both subtypes of IBD, these are characterized by distinct localization and histopathological features. In CD, inflammation is primarily manifested in the terminal ileum, but can affect any region of the gastrointestinal tract, whereas in UC inflammation is restricted to the colon. In addition, the presence of transmural inflammation often associated with granulomas is characteristic of CD, whereas in UC inflammation is typically restricted to the superficial mucosal and submucosal layers. Despite these distinct features, both CD and UC are considered predominantly T cell-mediated processes. Recent genome-wide association studies have identified genetic variation in the
innate immune system gene NOD2, and the autophagy genes ATG16L1 and IRGM to be associated with CD, whereas genetic variation in the gene for the IL-23 receptor (IL-23R), or in the gene regions of the common IL-12/23 cytokine subunit p40 (IL-12/23 p40), the cytokine TNFSF15, and the NKX2–3 gene involved in mucosal tissue architecture were associated with both CD and UC [88–91]. These associations provide further support to the hypothesis that innate and adaptive immune responses to intestinal microbiota are involved in IBD pathogenesis and play an emerging role in the autophagy pathway in CD.

A wide collection of animal models generated over the years, either inducible or following genetic gene targeting resulting in spontaneous phenotypes, have proven essential in our current understanding of IBD pathogenesis [92]. TNF has a prominent role in many of these models. Importantly, antibodies against TNF have proven to be effective in the treatment of CD [2], but also more recently in the treatment of UC [93]. The dominant role of TNF as an initiating factor of intestinal inflammation, and CD in particular, was exemplified by the generation of the TNFΔARE mice carrying a genetic deletion in the ARE elements of the TNF mRNA, resulting
to chronic TNF overproduction and the spontaneous development of Crohn’s-like IBD pathology and inflammatory arthritis [26]. Remarkably, intestinal pathology in these mice develops primarily in the terminal ileum and only occasionally in the proximal colon. Histological features include intestinal villous blunting and broadening, transmural inflammation, and the formation of granulomas, which in addition to the ileal localization highlight the unique resemblance of intestinal pathology in the TNFΔARE model to human CD. Intestinal pathology develops in the TNFΔARE mice as a result of spontaneous TNF overproduction from multiple sources including myeloid and lymphoid cells, but also stromal cells, such as fibroblasts [26]. Restricting TNF overproduction in myeloid cells or T lymphocytes is sufficient to drive intestinal inflammation, indicating that chronic TNF overproduction from either innate or adaptive immune effectors can support the development of pathology in this model [94]. TNFR1 appears dominant in mediating TNF pathogenic signals, as IBD pathology fails to develop in TNFR1-deficient TNFΔARE mice. By contrast, TNFΔARE mice genetically deficient for TNFR2 display attenuated but not neutralized inflammation, suggesting that TNFR2 contributes but is clearly less important than TNFR1 in TNF-driven intestinal pathology [26]. Therefore, TNF appears to act as an initiating factor that orchestrates the inflammatory response leading to intestinal inflammation in the ileum.

A key role for TNF has been established in several IBD models, in which regardless of the underlying pathogenic mechanisms, approaches such as TNF/TNFR1-genetic inactivation or the administration of anti-TNF antibodies reduce or ameliorate inflammation [95–99]. Importantly, TNF may be involved in various aspects of the disease process. Evidence on this can be provided in mice with intestinal epithelial cell-specific inhibition of NF-κB, which develop colon inflammation [99]. In this model, compromised epithelial integrity occurs due to increased TNF-mediated apoptosis in epithelial cells with impaired NF-κB signaling. Bacterial translocation in the mucosa as a result of the barrier defect induces proinflammatory TNF and IL-1β overexpression, promoting immune cell activation and recruitment. Pathology was ameliorated in TNFR1-deficient mice [99]. Thus, TNF appears to both induce epithelial apoptosis and amplify the subsequent inflammatory response. However, in contrast to the above, TNF may additionally mediate processes that oppose mucosal inflammation, as evidenced in dextran sodium sulfate-induced colitis, which is aggravated in TNF-deficient mice [100]. TNFR1 signaling in myeloid cells has been reported to contribute to suppression of pathology through the control of epithelial cell apoptosis in this model [101]. TNFR2, however, contributes to exacerbation of colitis through the innate response [101]. A similar contribution for TNFR2 through the adaptive system has been described, as more severe colitis was induced by the reconstitution of severe combined immunodeficient mice with TNFR2-overexpressing CD4+CD62L+ T cells [102]. Therefore, when trying to understand the mode of action of TNF in IBD pathogenesis we should aim to identify the cell- and receptor-specific mechanisms by which TNF contributes to both the initiation and/or progression of disease. These