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Chapter

The Role of TNF in the Pathogenesis of Inflammatory Bowel Disease

Martina Perše and Ana Unkovič

Abstract

Tumor necrosis factor (TNF) is a pleotropic cytokine involved in a wide range of pathological processes, including inflammatory bowel disease (IBD). In the past, TNF was recognized as a pro-inflammatory cytokine with deleterious effects. This has led to the development of anti-TNF drugs, which revolutionized the treatment of inflammatory disorders such as Crohn's disease. However, in the past 20 years, clinical studies have shown that anti-TNF drugs are not always effective. Moreover, in some rare cases, anti-TNF drugs can even cause an aggravation of the disease. Nowadays, there is increasing evidence that TNF is not only detrimental but can also play an important role in health and the maintenance of homeostasis. The aim of this chapter is to briefly summarize the literature demonstrating the complex dichotomous role of TNF in IBD and discuss the role of anti-TNF drugs in the treatment of IBD.

Keywords: tumor necrosis factor, inflammatory bowel disease, side effects, TNF inhibitors, paradoxical side effects, homeostasis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory condition of gastrointestinal tract with high incidence and prevalence in Western countries (North America, Europe, the highest in Scandinavia, and the United Kingdom) [1]. It is estimated that IBD affects 2.5–3 million people in Europe [2].

IBD consist primarily of Crohn's disease (CD) and ulcerative colitis (UC), which are distinguished by the location and the nature of the inflammation [3]. Patients with IBD experience many symptoms, such as abdominal pain, fever, vomiting, diarrhea, rectal bleeding, anemia, and weight loss, which have significant impact on their quality of life. Symptoms vary depending on the location and severity of inflammation and can be very painful and disruptive and in some cases even life-threatening (CD patients have 40% risk of mortality) [3].

IBD affects a young population, in the second and third decades of life or even in late adolescence [4]. The majority of patients with IBD progress to relapsing and chronic disease and need lifelong treatment and care. The health economic burden and permanent work disability in IBD are high in Europe with a total yearly direct healthcare cost of 4.6–5.6 billion Euros [2]. In recent years, the management of IBD has improved, due to the fact that the new treatments with anti-TNF drugs induce

not only clinical remission but also a significant endoscopic improvement or even disappearance of the intestinal lesions [5, 6].

However, in the past two decades, clinical studies have shown that anti-TNF drugs are not always effective. Moreover, in some rare cases, anti-TNF drugs can even cause an aggravation of the disease. Therefore, this chapter aims to briefly summarize the detrimental role of TNF in the pathogenesis of IBD and to highlight the beneficial role of TNF, which is too often overlooked in the health and the disease.

2. Dual identification of TNF (cachectin)

Tumor necrosis factor (TNF, also known as TNFa, cachectin, or cachexin) was identified/named in 1975 by Carswell et al. who demonstrated that the serum of endotoxin-treated mice, rat, and rabbits, previously infected with *Mycobacterium bovis* strain Bacillus Calmette-Guerin caused hemorrhagic necrosis of various tumors in mice. They found that hemorrhagic necrosis of tumors in vivo was caused by so-called tumor necrosis factor (TNF) released from host cells, very likely macrophages, in response to injected endotoxin. They showed that both, a TNF-positive serum and endotoxin, were effective in causing necrosis of similar spectrum of transplanted tumors and at a similar phase of their growth. Moreover, a TNF-positive serum had cytotoxic effects on mouse and human tumor cells in vitro as well [7].

In 1985, human TNF was purified, characterized, and cloned, which enabled production of large quantities of a highly purified TNF protein for extensive investigations [8, 9]. Since recombinant TNF has shown antitumor activity in both transplantable murine tumors and human tumor xenografts, TNF was quickly launched into clinical trials as a potential anticancer agent. Recombinant human TNF has been tested in several phase I and phase II clinical trials in the 1980s and 1990s. However, the initial enthusiasm for the use of TNF as a systemic treatment has waned in the face of significant toxicities and a lack of evidence for therapeutic benefit. Systemic TNF treatment was found to cause dose-dependent toxicities such as fever, hypotension, and tachycardia [10–12].

Independently, other groups of researchers investigated metabolic basis for cachexia and endotoxin-induced septicemia and septic shock syndrome. Hypertriglyceridemia in animals injected with endotoxin was found to result from defective triglyceride clearance due to systemic suppression of the enzyme lipoprotein lipase. Finally, the substance responsible for specific suppression of lipoprotein lipase activity was identified and named cachectin [13, 14]. Interestingly, soon after the characterization of human TNF in 1985, it was recognized that the TNF and cachectin are the same single protein with the complex dual role [8, 9, 15].

Nevertheless, direct evidence that cachectin is a mediator of the pathology/septicemia induced by endotoxin was demonstrated by Beutler and colleagues [16, 17]. They showed that passive immunization with rabbit antiserum or purified Ig against murine TNF protected the mice from the lethal effect of the endotoxin lipopolysaccharide [16]. The same group then showed that injection of recombinant human TNF into rats in quantities similar to those produced endogenously in response to endotoxin caused hypotension, metabolic acidosis, hemoconcentration, and death of animals within minutes to hours. Thus, effects similar to those are induced by injection of endotoxin [17]. These observations led to the speculation that neutralization of TNF may be beneficial in life-threatening septicemia. Despite increased interest in the use of anti-TNF drugs for the treatment of sepsis, numerous clinical trials have showed only a small survival benefit (3.6%) [18]. The likely

reason for the failure of anti-TNF drugs in sepsis can be found in the original animal study, where it was clearly demonstrated that neutralization of TNF was efficient in preventing death in mice only when administered before a very short time after the injection of endotoxin [16].

Nevertheless, the effort invested in the development of anti-TNF drugs, originally intended for the treatment of sepsis, enabled the use of anti-TNF therapy in the chronic inflammatory diseases, including IBD. However, the investigations and hopes regarding the use of anti-TNF drugs in sepsis and the use of TNF as an anticancer agent are still in progress [10, 19].

3. A link between TNF and IBD

The first evidence showing a link between TNF and IBD were publications reporting that patients with IBD have increased levels of TNF in serum, stool, or mucosal biopsy specimens [20–23]. However, the initial hopes for the use of TNF as a marker of IBD have waned when it was recognized that TNF can be increased also during infectious colitis [24] or TNF may even not be increased in patients with IBD [25] or TNF can be reduced in response to certain medication such as cyclosporine A [22, 26]. Nevertheless, a published reports about successful treatment of CD patients with TNF chimeric monoclonal antibodies (cA2 or infliximab) [27] established clear association of TNF involvement in the pathogenesis of IBD and caused extensive investigation of TNF role in IBD and production of various genetic models, including transgenic mice with persistent TNF overproduction in various tissues.

It was clearly demonstrated that persistent systemic overproduction of TNF ($TNF^{\Delta ARE/\Delta ARE}$ mice) can cause severe systemic health problems in mice, such as severe chronic polyarthritis, profound inflammatory changes in the terminal ileum and occasionally in the proximal colon, hypoplastic thymus with atrophied and disorganized cortical and medullary areas, and occasional mild inflammation in the liver and lung. These alterations were first detected in homozygous mice between 1 and 4 weeks of their age. Heterozygous mice developed the same health problems but later in their life inflammatory arthritis at 6–8 weeks of age and severe inflammatory bowel disease extending into muscular layers of the bowel wall at 4–7 months of their age. Homozygous mice never exceeded the body weight of 3-week-old mice and died between 5 and 12 weeks of their age [28]. It was also demonstrated that chronic intestinal inflammation can be triggered by persistent local TNF overproduction. Mice homozygous for persistent overproduction of TNF in the intestinal epithelium ($TNF^{i\Delta ARE/i\Delta ARE}$ mice) developed chronic ileitis by the age of 16–20 weeks and had increased mucosal and systemic protein levels of TNF. No inflammation in other tissues was found. No histological signs of joint injury were observed. Heterozygous mice ($TNF^{i\Delta ARE/+}$) develop only mild villous blunting with scarce inflammation (not significant) [29]. In addition, mice with persistent myeloid cell-specific TNF overproduction also developed symptoms of weight loss and ileitis by the age of 5 months (homo and heterozygous) but with more severe symptoms in the homozygous mice. Interestingly, mice with persistent T lymphocyte-specific TNF overproduction developed mild symptoms of IBD but only on homozygous background. On the other hand, mice with persistent B lymphocyte-specific TNF overproduction did not show any signs of IBD by the age of 15 months [30]. Results of numerous animal studies gave tacit confirmation that persistent systemic or local TNF overproduction is detrimental and responsible for intestinal inflammation, serious health problems, and even death [31].

The introduction of anti-TNF therapies in the 1998 affected the treatment of many chronic inflammatory disorders, including rheumatoid arthritis, ankylosing spondylitis, and IBD. Five therapeutic agents have been licensed in the USA and most other parts of the world. Randomized controlled trials demonstrated the efficacy and safety of induction and maintenance therapy for moderate-to-severe IBD. Subsequent studies have demonstrated that infliximab treatment results in a positive clinical response as well as in a significant endoscopic improvement, confirmed also by histological examination as a complete reduction in the inflammation infiltrate. The breakthrough in the treatment of patients with IBD with anti-TNF therapy has firmly established the dogma that TNF is a major cytokine in this disease [32, 33]. Anti-TNF drugs such as infliximab, adalimumab, and etanercept are nowadays commonly used in the treatment of a variety of inflammatory and autoimmune diseases (IBD, rheumatoid arthritis, psoriasis, psoriasiform arthritis, and ankylosing spondylitis). Nevertheless, with the increasing use and longer follow-up periods, more information about effectiveness and side effects of anti-TNF therapy in IBD has been published.

4. Side effects of anti-TNF drugs

First reported/known adverse events of anti-TNF drugs were mainly immunogenicity leading to acute and delayed infusion reactions and loss of response, infectious complication, and concerns about tumor induction or progression [34, 35].

Today, after two decades of clinical experience with anti-TNF drugs and 2 million treated patients, it is widely known that around 30% of patients do not respond to anti-TNF therapy (primary nonresponders) and almost half of patients with initial response develop secondary loss of response within the first year. Among nonresponders, some may have low serum drug levels which could be explained by under-dosing or high drug clearance. Development of immunogenicity against the anti-TNF drugs is also associated with loss of response. In such cases, consideration of switch in anti-TNF drugs or dose escalation following loss of response may be an effective strategy [32]. However, some patients on anti-TNF drugs experience primary or secondary nonresponse despite adequate serum drug levels and the absence of neutralizing antibodies. Recently, it was proposed that such nonresponders may have upregulated other alternative inflammatory pathways independent of TNF [36]. Nevertheless, despite all complications and high costs of anti-TNF drugs, economic evaluation studies have shown that the benefit of anti-TNF drugs is still higher than the costs [37].

4.1 Anti-TNF drugs and risk of infection and malignancy

Susceptibility to infection and risk of malignancy has been a significant concern from the beginning of anti-TNF drug use. In the past, it was widely reported that anti-TNF therapy was associated with increased susceptibility to infections, particularly tuberculosis and hepatitis B. However, when it was recognized that anti-TNF drugs trigger the reactivation of latent infections [38], screening for tuberculosis and hepatitis B in clinical settings was implemented. Soon, reports about tuberculosis or hepatitis infections associated with anti-TNF therapy diminished [34]. Interestingly, recent publications report that anti-TNF therapy alone does not increase the risk of serious infection in IBD patients [39, 40]. Moreover, a systematic review (5528 patients) reported that the rate of serious infection was significantly lower among pediatric patients with IBD treated with anti-TNF than those treated with steroids or adults with IBD who received anti-TNF therapy [39].

In contrast, increasing number of reports about other untypical opportunistic infectious diseases, such as cytomegalovirus infection, histoplasmosis, aspergillosis appeared [34, 40]. Importantly, recent population-based study (190,694 patients with IBD) found that anti-TNF monotherapy was associated with increased risk of serious infection, mycobacterial infection, and bacterial infection but with decreased risk of opportunistic viral infection when compared with thiopurine monotherapy. However, when anti-TNF drugs are part of combination therapy with other immunosuppressive drugs, particularly thiopurines, the risk of serious infection and opportunistic infection increases [34, 41].

Anti-TNF drugs have been associated with the increased risk for malignancy [34]. In the past, few studies reported T-cell non-Hodgkin's lymphoma or hepatosplenic T-cell lymphoma in IBD patients using anti-TNF drugs [42], while more recent studies found no association between anti-TNF drugs and hematologic malignancies. It was reported that the risk of lymphoma was no greater among children with IBD who received anti-TNF drugs than those treated with other IBD therapies or adults treated with anti-TNF drugs [39]. REFURBISH study found that the risk of T-cell non-Hodgkin's lymphoma in IBD patients is increased with the use of combination anti-TNF and thiopurine therapy but not with the use of anti-TNF monotherapy [43]. However, recent cohort study of 189,289 patients with IBD reported that the use of thiopurine monotherapy or anti-TNF monotherapy in patients with IBD was associated with a small but statistically significant increased risk of lymphoma, and this risk was higher with combination therapy than with each of these treatments used alone [44].

4.2 Anti-TNF drugs and paradoxical side effects

Knowledge about immune diseases secondary to TNF target therapy is relatively new. Until 2007, altogether 233 cases of immune diseases secondary to TNF targeted therapy were reported [45]. Nowadays, increasing number of various paradoxical reactions is published such as psoriasiform skin lesions, uveitis, ileitis or colitis, joint manifestations, vasculitis and autoimmune disease (lupus and myositis), and sarcoidosis-like lesions. There are currently no predictors of their occurrence, and the optimal clinical management is still a matter of debate. Mostly paradoxical reactions are poorly described, and their prevalence and pathogenesis are not known. Therefore, it is important to be aware of all possible side effects of TNF therapy to properly inform the patient about potential side effects of anti-TNF therapy before the treatment.

Psoriasis or psoriasiform skin lesions are one of the most frequently reported paradoxical reactions. Until November 2008, altogether 120 cases of psoriasis in patients treated with anti-TNF drugs were published. Among them 18 cases were found in patients with IBD (15%) [46]. Nowadays, increasing number of studies has shown that psoriasis can develop in IBD patients (adults or children) without any history of psoriasis and independent of the type of anti-TNF drugs [46–48]. However, in IBD patients with a history of psoriasis, anti-TNF treatment may trigger reappearance (3/21) [47] or exacerbation of the psoriasis (2/18) [46, 48].

Retrospective cohort (917) reported that 29% patients undergoing anti-TNF therapy (infliximab) developed skin lesions such as psoriasiform eczema, xerosis cutis, palmoplantar pustulosis, and psoriasis. The average time from the start of TNF therapy to the onset of skin lesions varied from 14.3 weeks [46] to 2 years [46–48]. In most patients psoriatic lesions were effectively treated with topical steroids, and in patients with severe psoriasis or patients without response to topical therapy, anti-TNF therapy was discontinued [47]. In another study in almost half of patients changed their initial anti-TNF agent despite conventional skin-directed therapies, and one-third of patients discontinued all anti-TNF therapy [48].

Lichenoid drug reaction in association with anti-TNF therapy was also reported. Until 2015, only seven cases were reported in association with anti-TNF drugs. Oral lichen planus occurred between 8 weeks and 6 months after anti-TNF therapy. Outcome was mainly favorable with improvement or recovery with or without cessation of the TNF blocker. Authors recommend a careful monitoring for oral manifestations in IBD patients treated with TNF inhibitors. OLP is thought to be mediated by dendritic cells and T cells [49].

Patients treated with anti-TNF therapy (i.e., etanercept, adalimumab, and infliximab) can develop sarcoidosis-like lesions. Until 2017, altogether 90 cases were reported, 6 cases in IBD patients. Median duration between initiation of anti-TNF therapy and diagnosis was 22.5 months (range 1–84 months). Most frequently affected organs were lungs, skin, and eyes [50].

Patients with IBD developed new onset arthritis or synovitis after 2.5 ± 1.6 years of successful anti-TNF treatment. The onset of paradoxical arthritis appeared when IBD patients were in clinical and endoscopic remission but with signs of histologically diagnosed subclinical inflammation. The inhibition of inflammatory pathways alternative to TNF (IL12/1L23) may be an effective therapeutic option for severe paradoxical articular manifestations [51].

The lupus-like syndrome can be observed in 0.5–1% of patients treated with anti-TNF drugs and appears independent of the type of anti-TNF drugs. Most patients develop fatigue or fever, musculoskeletal or skin symptoms, or serositis, a rarely major organ disease. The symptoms resolve after discontinuation of TNF therapy [52, 53].

5. The beneficial role of TNF

Soon after the identification of TNF and production of recombinant TNF, it was recognized that the biological effects of TNF may be both injurious and beneficial. TNF can have a direct cytostatic and cytotoxic effect on human tumor cells, as well as a variety of immunomodulatory effects on various immune effector cells, including neutrophils, macrophages, and T cells. It can have a number of anti-infective and metabolic effects [54].

Today, in the era of anti-TNF drugs, the beneficial role of TNF is often in the shadow and is highlighted only after the appearance of a new adverse effect of anti-TNF drugs in clinical use.

Experimental studies have shown that TNF has important role in maintaining intestinal integrity [55]. If infection or injury occurs, TNF is rapidly released to promote the acute-phase inflammatory response (i.e., IL1, IL6-production of pro-inflammatory cytokine cascade) and to trigger the localized accumulation of leukocytes. Endothelial cells respond to TNF by releasing chemokines (IL-8, MCP-1, IP-10) and adhesion molecules (E-selectin, ICAM-1, VCAM-1). Collectively, these solubles and cell surface molecules lead to the recruitment of distinct populations of leukocytes to sites of infection/injury to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and initiate tissue repair. Indirectly, TNF also contribute to increased local blood flow and vascular permeability and regulation of coagulation. TNF increases mediators such as prostaglandins and platelet-activating factor [56].

However, in case of chronic TNF deprivation, intestinal barrier is more sensitive to infection and injury. Mice with TNF deprivation (caused by anti-TNF drugs or target mutations) failed to resist *L. monocytogenes* infections and died few days after the infection [57]. Mice deficient in TNF or TNFR1 are highly susceptible to *Mycobacterium* and *Staphylococcus* infection as well [54, 59]. It was found that TNF

deprivation caused delayed elimination of bacterium from the spleens and livers. However the effect was dose and time dependent. The worst results were observed when anti-TNF drug was given between days 0 and 2 of infection [57].

TNF has also important role in maintaining and protecting epithelial cells from toxic injury. For instance, DSS, a toxic agent that damages the intestinal epithelia, induce development of an acute inflammation in mice, which usually resolves in a few weeks. However, when mice have blocked production of TNF (induced by deletion of TNF gene or anti-TNF drugs), the inflammation in the intestine becomes devastating and life-threatening [58].

All these studies demonstrate that homeostatic concentrations of TNF have important protective role against intestinal injury. However, homeostatic concentrations of TNF are also important for effective innate and adaptive immune responses. It was found that mice genetically deficient in TNF completely lack splenic primary B-cell follicles and cannot form organized follicular dendritic cell networks and germinal centers [59]. Thus, chronic TNF deprivation may cause disturbances in innate and adaptive immunity. TNF is an important regulator of macrophage function required to control infection and can also contribute to containment of the disease by promoting migration of immune cells and granuloma formation at sites of infection. In case of tuberculosis, an intracellular pathogen, formation of granulomas and walling off the bacteria by macrophages and T cell (central memory T cells ($CCR7^+CD27^+$) and effector memory T cells ($CCR7^-CD27^-$)), is thus one of the protective mechanisms to control tuberculosis infection. In latency, infection is contained in a nondividing state within macrophages. However, anti-TNF therapy disturbs the physiological TNF-mediated immunoinflammatory responses and causes disease reactivation or dissemination seen in patients receiving TNF blockade [38].

It is interesting that increased susceptibility to infection and a slightly increased risk for malignancy have been expected side effects of anti-TNF drugs and have been confirmed in clinical practice. However, the observation that anti-TNF drug could lead to aggravation of preexisiting autoimmune diseases or onset of a new inflammatory diseases was not expected. Although numerous experimental studies have shown complex role of TNF in the innate and adaptive immunity [60], only paradoxical side effects of anti-TNF drugs clearly demonstrated that the maintenance of homeostatic TNF concentrations is important for normal function of organism. Recently, it was confirmed that paradoxical psoriasis is caused due to the TNF deprivation. Namely, in normal condition a production of type I IFN by plasmacytoid dendritic cells (pDC) is downregulated by TNF. In case of TNF deprivation (caused by anti-TNF drugs), production of IFN by pDC is not regulated anymore. The resulting type I interferon overexpression is responsible for the skin phenotype of paradoxical psoriasis, which, unlike classical psoriasis, is independent of T cells [61].

6. Conclusions

Although our understanding of TNF has increased considerably over the past two decades, novel finding is well in line with what had been predicted from previous mouse studies. However, the observation that anti-TNF drugs could lead to aggravation of preexisiting diseases or onset of a new inflammatory diseases was not expected. Nevertheless, paradoxical reaction appears independently of the underlying disease or the type of anti-TNF drugs used and regresses upon discontinuation of therapy, which suggests that paradoxical reactions really are a side effect of TNF blockade and not de novo disease. Thus, paradoxical reactions can

once again remind us that TNF physiologically possess various beneficial roles, and thus the maintenance of homeostatic TNF concentrations is important for normal function of an organism.

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Conflict of interest

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