

REVIEW

THE ROLE OF TUMOUR NECROSIS FACTOR IN THE PATHOGENESIS OF IMMUNE-MEDIATED DISEASES

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Immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis, psoriatic arthritis, psoriasis, axial spondyloarthropathies, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis, comprise a group of chronic disorders characterized by an immune-mediated pathogenesis. Although at clinical presentation these diseases appear unrelated, they have been recognized to share similar pathogenic mechanisms. Data from epidemiological and genetic studies further support the concept that IMIDs are interrelated, as they can co-occur in the same patient and share a similar genetic susceptibility. The specific aetiologies of IMIDs remain unknown, but all are known to involve dysregulation of the immune system, including an over-expression of the pro-inflammatory cytokine tumour necrosis factor (TNF). The pivotal role played by TNF in the pathogenesis and pathophysiology of IMIDs has been documented by extensive preclinical and clinical investigations, and confirmed by the efficacy of anti-TNF biotechnological drugs, such as etanercept, infliximab and adalimumab, in the therapeutic management of these disorders. In this narrative review, we discuss the available data on the TNF-dependent pathogenesis of IMIDs and associations among the different disorders. Although much remains to be discovered about the pathogenesis and aetiology of IMIDs, their common inflammatory

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pathological features may explain why they can be successfully targeted by anti-TNF drugs. Among these, adalimumab, a fully human monoclonal antibody, has been approved for treatment of nine distinct IMID indications and it is likely to become a valuable therapeutic tool for this complex cluster of chronic inflammatory disorders.

Immune-mediated inflammatory disease (IMID) is a term used to describe a wide array of chronic disorders resulting from an immune-mediated inflammatory pathogenesis (1). Diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis, axial spondyloarthropathies (SpA), including pre-radiographic SpA and ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis (UC), appear, on clinical presentation, to be unrelated, as they display very different signs and symptoms. However, they have been recognized to share common pathogenic mechanisms. The specific aetiologies leading to the onset of each of these diseases remain unknown, and, therefore, it is not clear whether the causative factors are similar among the IMIDs. To date, risk factors for some inflammatory diseases – including genetic and environmental determinants – have been identified, but whether the relationship is causal or not remains to be established. For instance, environmental factors implicated in IBDs include cigarette smoking, appendectomy, urbanization, pollution, diet, antibiotic use, hygiene status, socioeconomic status and microbial exposure (2).

As IMIDs are all inflammatory conditions, it is not unexpected that they share some common pathological pathways, regardless of the specific clinical presentation and underlying risk factors. In particular, all involve dysregulation of the immune system due to an imbalance or inappropriate release of inflammatory cytokines such as interleukin (IL)-12, IL-6 and tumour necrosis factor (TNF) (1, 3, 4). The role of these cytokines has been recognized as being pivotal in the pathogenesis and pathophysiology of IMIDs, particularly TNF (5, 6). This concept has been substantiated by the efficacy of targeted biotechnological drugs – particularly TNF inhibitors, such as etanercept, infliximab and adalimumab, which have been shown to act as modifiers of disease activity in the management of a wide array of apparently clinically distinct

inflammatory disorders (3).

Epidemiological studies have revealed that the overall prevalence of this cluster of inflammatory diseases is approximately 4% of the US population (approximately 12 million people) (7) and 5–7% of Western populations (8), with prevalence rates of individual diseases ranging from 0.04% to 8.5%, depending on geographical and ethnic factors (Table 1; Figure 1). Furthermore, the overall prevalence of IMIDs is expected to increase as the number of diseases classified as IMIDs grows (9). Epidemiological data further support the concept that IMIDs are interrelated and display disease co-occurrence and associations (7). Recently, in addition to the common pathological features, genome-wide association studies have identified genes conferring an increased risk of developing IMIDs, and have highlighted a common background of genetic susceptibility, which lends additional credibility to the reported epidemiological evidence of a co-occurrence ('genetic overlap') of IMIDs (10–13).

Given the prevalence and association of IMIDs, together with the substantial clinical morbidity, disability, reduced quality of life (QoL) and lost work productivity (14, 15), it is not surprising that the socio-economic burden of these disorders is quite high (4, 14–18).

Aim and methodology

The aim of this narrative review was to discuss current data on TNF-mediated pathogenesis of IMIDs and associations among the various disorders. Combined literature searches were performed on PubMed using the following search terms: 'immune-mediated inflammatory disease/disorder' AND 'tumour necrosis factor/TNF' AND ['rheumatoid arthritis' OR 'psoriatic arthritis' OR 'psoriasis' OR 'axial spondyloarthropathy' OR 'ankylosing spondylitis' OR 'Crohn's disease' OR 'ulcerative colitis' OR 'juvenile idiopathic arthritis']. Appropriate papers for this review were selected manually from the search results and from the bibliographies of previous review articles.

TNF as a key factor in the pathogenesis of immune-mediated diseases

TNF belongs to a large group of cytokines collectively designated as the 'TNF superfamily', which comprises cytokines that share molecular and functional similarities. Besides TNF, the TNF superfamily includes: lymphotoxins (comprising lymphotoxin- α 3 – previously designated as TNF- β lymphotoxin- α 1 β 2 and lymphotoxin- α 2 β 1); Fas (a pro-apoptotic factor); CD40 (a factor regulating B lymphocytes); receptor activator of nuclear factor kappa-B. These cytokines are involved in the regulation of several steps of the biological processes related to inflammatory and immune responses, through the control of important cellular functions, such as proliferation, differentiation, programmed

cell death (i.e. apoptosis) as well as the biosynthesis and release of a wide array of molecular factors and mediators (19, 20).

TNF is a pleiotropic cytokine deputed to regulate a number of inflammatory reactions and immune functions through the control of various cellular processes, such as proliferation, differentiation, apoptosis, and the release of several molecular factors (21). It is produced by a wide range of cell types, including macrophages, T lymphocytes, mast cells, granulocytes, NK (natural killer) cells, fibroblasts, neurons, keratinocytes and smooth muscle cells (19, 21). Biologically active TNF is a homotrimeric molecular complex consisting of three identical polypeptide subunits. Following biosynthesis, the individual monomers are exposed on the surface of

Table 1. Prevalence of immune-mediated inflammatory diseases

Reference or source	Disorder	Country	Prevalence
Robinson et al. (7)	IMIDs	US	4%
El-Gabalawy et al. (8)	IMIDs	Western society	5–7%
Helmick et al. 2008 (59)	RA	US	1.3 million (0.4%)
Symmons et al. (60)	RA	UK	1.16% in women and 0.44% in men
Myasoedova et al. (61)	RA	US	0.72% in 2005, increased from 0.62% in 1995
Helmick et al. 2008 (59)	JIA	US	294,000 (0.1%)
Helmick et al. 2008 (59)	SpA	US	0.6–2.4 million adults (0.2–0.8%)
http://www.spondylitis.org/about/overview.aspx	Axial spondyloarthritis	US	2.7 million (0.9%)
http://www.patient.co.uk/doctor/ankylosing-spondylitis	AS	Worldwide	0.1–2% (higher in Northern European countries and lowest in people of Afro-Caribbean descent)
http://www.cdfa.org/what-are-crohns-and-colitis/what-is-crohns-disease/	IBD Crohn's disease UC	US	1.4 million (0.4%) 0.7 million (0.2%) 0.7 million (0.2%)
https://www.psoriasis.org/learn_statistics	Psoriasis	US	7.5 million (2.2%)
https://www.psoriasis.org/learn_statistics	Psoriasis	Worldwide	125 million (2–3%)
Parisi et al. (62)	Psoriasis	Worldwide	From 0.91% (US) to 8.5% (Norway)
Gladman et al. (63)	PsA	Worldwide	From 0.04% to 0.1%

AS, ankylosing spondylitis; IMID, immune-mediated inflammatory disease; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; UC, ulcerative colitis.

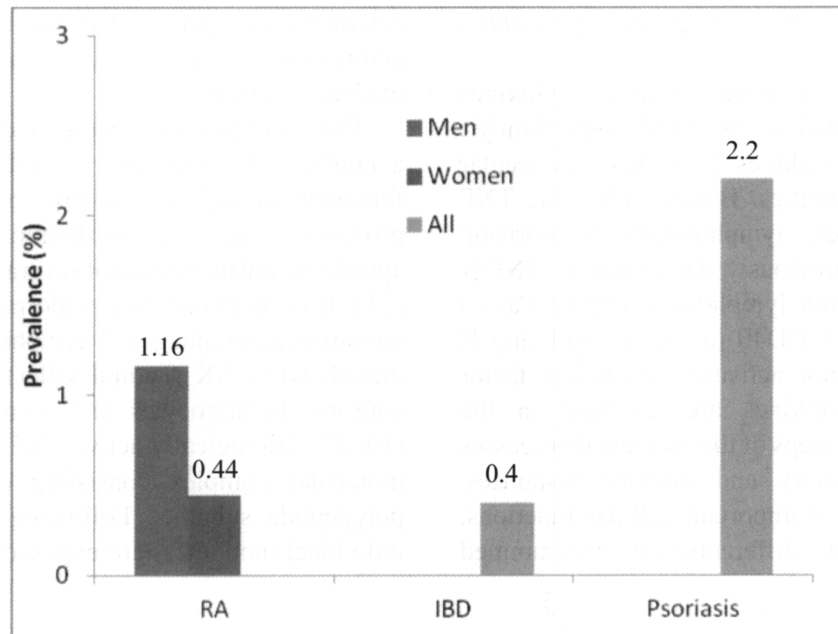


Fig. 1. Prevalence of RA, IBD and psoriasis.

cell membrane, where they are assembled to form the membrane-bound homotrimeric transmembrane TNF (tmTNF). tmTNF can then be cleaved by TNF- α converting enzyme (TACE) to generate the homotrimeric soluble form (sTNF), which is released into the extracellular fluids and thereby into the blood stream. TNF is biologically active in both its trimeric forms – i.e. the membrane bound tmTNF and the circulating sTNF. The monomeric form of sTNF circulates also in the blood and, while it does not appear to exert any biological activity as such, it can assemble with other monomers to generate biologically active trimeric sTNF complexes (21, 22).

TNF carries out its biological actions through interaction with two specific receptors, designated as TNF receptor 1 (TNFR1 [p55, CD120a]) and receptor 2 (TNFR2 [p75, CD120b]). Both receptors are trimeric glycoproteins localized on the cell membrane surface, but they differ in terms of cellular expression, affinity for the different molecular forms of TNF and transduction mechanisms. TNFR1 is constitutively expressed in the majority of cell types, and displays preferential affinity for tmTNF. TNFR2 expression is mainly inducible, particularly

in hematopoietic and endothelial cells, and has a preferential affinity for sTNF (21, 23). tmTNF, owing to its cell membrane location, can interact with target cells equipped with TNF receptors and can exert a dual action: on one hand it can stimulate cell surface receptors on the target cell to elicit a biological response in the target cell through the activation of transduction pathways linked to the membrane receptor (signalling); on the other hand, tmTNF itself can be activated by its binding to the receptors on the target cell (reverse signalling), thus becoming able to mediate anti-inflammatory/immunomodulatory actions, such as inhibition of T cell proliferation, inhibition of pro-inflammatory cytokine release and apoptosis. Of note, the anti-inflammatory responses mediated by reverse signalling can be activated also by binding of tmTNF with the large molecular complexes generated by interaction of sTNF with anti-TNF drugs, such as infliximab and adalimumab (21, 24).

TNF plays a central role in the pathogenesis of most IMIDs (5). Over-expression of TNF has been shown indeed to promote pro-inflammatory conditions. In particular, along with the dysregulation of other cytokines and a variety of cell types, TNF is

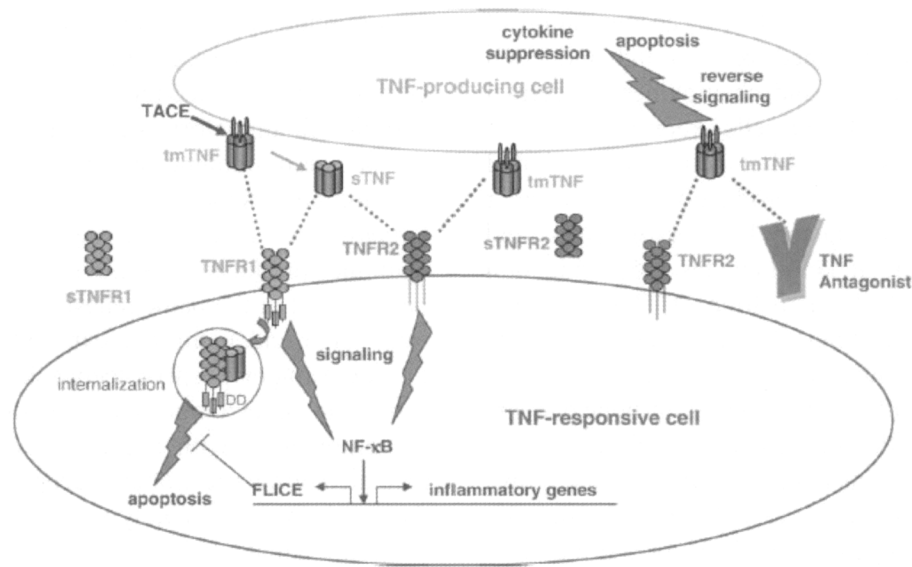


Fig. 2. Schematic diagram showing the involvement of TNF in immune-mediated inflammatory disorders. Reproduced with permission from Tracey D, et al. *Pharmacol Ther* 2008;117:244-79 (21). FLICE, FADD-like IL-1 β -converting enzyme; sTNF, soluble tumour necrosis factor; sTNFR1, soluble TNFR1; sTNFR2, soluble TNFR2; TACE, TNF alpha converting enzyme; tmTNF, trans-membrane tumour necrosis factor; TNF, tumour necrosis factor; TNFR1, TNF receptor 1; TNFR2, TNF receptor 2.

implicated in the pathogenesis of RA, Crohn's disease, psoriasis, PsA, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, asthma, allergy and UC (3) (Figure 2).

Preclinical and clinical studies on RA have paved the way towards our understanding of the pivotal role played by TNF in the pathophysiology of IMIDs and the identification of this inflammatory cytokine as a relevant target for their therapeutic management (21). The main pathologic hallmark of RA is represented by chronic synovial inflammation leading to progressive joint cartilage and bone destruction. Studies aimed at identifying the molecular pathogenesis of these processes highlighted both TNF and IL-1 as key factors promoting inflammation and matrix disruption (25, 26). It was then established that abnormal elevations of TNF concentrations at the sites of inflammation were a primary factor accounting for the disease activity, and these observations generated the hypothesis that the removal of TNF excess from inflamed joints would have conferred therapeutic benefits (27, 28). In support of these concepts, transgenic mice over-expressing TNF were found to spontaneously develop an arthritic pathology which displayed clinical and histological features similar to

RA (29). Furthermore, in an experimental model of collagen-induced arthritis, the blockade of TNF was effective in reducing the disease activity (30, 31).

A number of experimental and clinical studies have provided compelling evidence to support a strong role of TNF in the pathogenesis of IBDs (32, 33). The major findings in this field can be concisely summarized as follows: 1) elevated levels of TNF, along with high concentrations of IL-1, transforming growth factor- α and interferon- γ , are present in the inflamed mucosa of patients with Crohn's disease (32); 2) there is an enhanced expression of TNF in patients with both Crohn's disease and UC (34, 35); 3) studies in animals with experimental bowel inflammation have shown that TNF functions as a driving factor of disease activity (36, 37), and that TNF inhibition or genetic suppression can prevent disease onset and/or reduce disease severity (38).

TNF is involved in a number of mechanisms underlying the pathogenesis of both psoriasis and PsA (39). In the setting of psoriasis, the main TNF-dependent mechanisms include: stimulation of the maturation of Langerhans cells and dendritic cells, with skewing of lymphocyte differentiation (40); promotion of dendritic cell migration from

the skin to lymph nodes (41, 42); accumulation of leukocytes in the inflamed skin through induction of adhesion molecules and chemokines on dermal microvascular endothelial cells, keratinocytes, and dermal fibroblasts (43, 44); induction of dermal vascular changes via production of vascular endothelial growth factor by keratinocytes and hyperproliferation of keratinocytes (45); induction of itching through the activation of TNF receptors on sensory nerve endings (39). With regard for PsA, TNF has been shown to play a primary role in the determinism of inflammation and joint-bone damage by virtue of the following mechanisms: production of lytic enzymes, such as matrix metalloproteases (46); contribution to synovial vascular proliferation by induction of angiogenic growth factors; stimulation of bone resorption, inhibition of bone formation, and inhibition of synthesis of proteoglycans, with subsequent occurrence of bone erosions up to osteolysis, new bone deposition, or both; in particular, based on evidence provided by preclinical investigations, it has been appreciated that TNF can promote osteoclastogenesis either directly, via actions on osteoclast precursors and osteoclasts, or indirectly, via induction of synovial inflammation and various osteoclastogenic factors (39, 47, 48).

Inflammatory and autoimmune pathology

It is worth noting that several IMIDs also harbour an autoimmune component. Indeed both autoimmune diseases and IMIDs arise when adaptive and innate immune system responses are impaired. An autoimmune disease occurs when the organism fails to recognize its own molecular components as self constituents, thereby leading to an adaptive immune response against its own cells and tissues. On the other hand, an IMID results from a dysregulation of the normal body's innate immune functions. An inability to regulate the magnitude and duration of the immune (or autoimmune) response leads to the onset of an inflammatory state or a condition of overreaction of the immune system. Subsequent downstream signalling by proinflammatory mediators, such as TNF, interleukins, interferons, etc., gives rise, eventually, to the occurrence of symptoms and end-organ damage. For instance, the complex pathogenesis of IBDs, although not yet completely elucidated, is known to involve both

auto-immune and immune-mediated mechanisms, with a serious dysregulation of the innate immune system, due to infection or trauma, leading to a chronic inflammatory state and abnormalities of the acquired immune system, which result in an autoimmune response (49). In RA, besides the direct targeting of synovial tissues by autoantibodies, cytokines produced by synovial cells are thought to be involved in the pathogenesis of the disease in its early stage, and, in this context, TNF has been shown to play a major positive feedback role through the activation of cytokine and chemokine expression, in combination with a plethora of other actions, mediated by a variety of cell receptors and molecular factors, leading ultimately to RA clinical symptoms and joint damage (50).

In diseases that appear to result from a combination of both autoimmune and inflammatory pathogenic mechanisms, it still remains unknown how the two components interact or whether one can trigger and maintain the other. Several autoimmune diseases do not appear to be preceded by inflammation, although some do, and many although not all autoimmune diseases cause inflammation. Even though the same mediators, including TNF, are often involved in the pathogenesis of inflammation and autoimmune responses, the relationship between these two processes is far from clear. Indeed, autoimmunity can, and often does occur in the absence of overt inflammation, and vice versa, chronic inflammation can exist in the absence of autoimmunity. The picture is further complicated by the involvement of other factors, such as environmental triggers, genetic predisposition and comorbidities.

Associations of immune-mediated inflammatory diseases

The contention of a common pathophysiology of IMIDs is corroborated by the clinical evidence that, often, two or more IMIDs co-exist in the same patient (7). Certain diseases are more likely than others to present in the same patient: these combinations are designated as 'disease associations' – also termed 'immune-mediated inflammatory syndromes' or 'clustering' (3, 51, 52).

A large US-based epidemiological study has lent support to the concept that IMIDs are interrelated and has shown that a common pathogenic

background translates into similar patterns of disease co-occurrence, with patients affected by at least one IMID having a higher risk of developing another IMID (7). In addition, genome-wide association studies have identified genes conferring an increased risk of developing an IMID and have revealed a common genetic susceptibility among IMIDs (10-13).

Among the currently available TNF antagonists – etanercept, infliximab, adalimumab, certolizumab pegol and golimumab – adalimumab has been approved for use in nine distinct IMID indications (namely RA, PsA, SpA/AS, Crohn's disease, paediatric Crohn's, UC, JIA, psoriasis and Behcet's disease). Within these indications, the IMIDs that have been found to occur in the same patient include: RA + UC (53, 54); AS + Crohn's disease or UC (55); PsA + psoriasis, Crohn's disease or UC (56); Crohn's disease + psoriasis (56, 57); UC + psoriasis (58). In these settings, the use of a multi-indication drug, such as adalimumab, to treat two or more IMIDs in the same patient, decreases the drug burden, thus considerably making this TNF inhibitor a very useful tool for the treatment of co-occurring IMIDs.

At present, the reasons for the occurrence of some disease combinations and not others are not clear. In addition, due to the above-mentioned genetic susceptibility, IMIDs are also more likely to occur in relatives of patients affected by an IMID (3).

CONCLUSIONS

Although much remains to be discovered about the pathogenesis and aetiology of IMIDs, there is presently clear evidence that these diseases share similar pathological inflammatory pathways, and that TNF represents one of the immune mediators known to play a key role in their pathophysiology. The common pathological background of IMIDs, supported by their association in the same patient, have been noted in clinical practice and confirmed by epidemiological studies. Along the same lines, genetic studies have also revealed common patterns of genetic susceptibility. TNF is involved in a wide array of biological activities including a number of stimulating and inhibitory actions on several cellular components within and outside the immune system, resulting from molecular signalling and reverse

signalling mechanisms. The advances made in understanding the role of TNF in the pathophysiology of chronic inflammatory disorders have led to the development of biotechnological drugs acting as TNF inhibitors, most of which are currently employed for the therapeutic management of one or more IMIDs. Among these, adalimumab has been approved for the treatment of nine distinct IMID indications and it is therefore expected to become a valuable therapeutic tool across this complex cluster of inflammatory disorders.

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