Tumor Necrosis Factor-α in Psoriasis and Psoriatic Arthritis: A Clinical, Genetic, and Histopathologic Perspective

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The successful introduction of anti-tumor necrosis factor (TNF) therapies in psoriasis and psoriatic arthritis has sharpened considerable interest in this chronic and frequently disabling disease. Unlike the situation in rheumatoid arthritis, where anti-TNF therapies were introduced after years of painstaking research which confirmed a key proinflammatory role for TNF, the evidence for TNF having a key role in psoriatic arthritis has lagged behind. In this paper, the emerging immunohistochemical, genetic, and clinical literature relating to TNF's role in skin and joint manifestations of this disease is reviewed and areas for future research are suggested.

Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in approximately 5% to 42% of cases of psoriasis, with an estimated prevalence of approximately 0.3% in the general population [1]. PsA ranges in severity, from a mild nondestructive disease to a severe rapidly erosive arthropathy [2]. Initially, PsA was believed to have a good prognosis with only 10% of patients having radiologic damage [3]. Subsequent studies have found that approximately 47% of early PsA patients and approximately 57% of patients with established PsA have erosive arthritis on x-ray evaluation [4] and there is evidence that patients with PsA have a subsequent reduced life expectancy [5]. Disease-modifying antirheumatic drugs, including sulfasalazine, methotrexate, and cyclosporine are used in PsA but evidence of efficacy is limited [6]. The proinflammatory cytokine tumor necrosis factor (TNF)-α has now been characterized in inflamed skin and joint tissues of patients with psoriasis and PsA and specific inhibition of TNF-α produces significant clinical improvement. This paper examines the accumulating scientific and clinical evidence for a central role of TNF-α in the inflammation of psoriasis and PsA.

The Role of Tumor Necrosis Factor-α in Inflammation

Cytokines are small protein mediators that are capable of regulating processes in human tissues such as the process of inflammation in skin and synovium [7]. Cytokines are capable of producing multiple regulatory effects on the inflammatory response through a variety of mechanisms including gene expression, cell migration, cell differentiation and proliferation, and cell survival and apoptosis [7]. Cytokines may be differentiated into proinflammatory (interleukin [IL]-1, TNF-α, IL-6) and antiinflammatory (IL-4, IL-10), or by their ability to influence the functional differentiation of CD4+ T-cells into T helper cell type 1 (Th 1) (IL-2, interferon-γ, TNF-α, IL-12, IL-15, and IL-18) or Th2 (IL-4, IL-5, IL-6, IL-10, and IL-13) [8]. In health, there is a balance between Th1 and Th2 cytokines, but this balance is believed to be altered in favor of Th1 cytokines in autoimmune diseases such as rheumatoid arthritis (RA) [9].

The initial discovery that there were multiple proinflammatory cytokines in RA synovium, including interferons, IL-1, IL-6, and TNF-α, suggested that a strategy of blocking a single cytokine would be ineffective with other cytokines remaining available to drive the inflammatory process. However, in vitro studies demonstrated that the selective blockade of TNF-α was capable of abrogating RA synovial culture production of other proinflammatory cytokines including IL-1, IL-6, IL-8, and granulocyte macrophage colony stimulating factor [10]. This suggests a central role for TNF-α in the regulation of synovial inflammation in RA. Subsequent clinical trials of selective TNF-α inhibition in RA confirmed significant improvement in clinic and radiologic parameters of disease activity [11] and a marked reduction in the synovial inflammatory

infiltrate [12], ushering in the era of targeted therapy in rheumatologic disease.

Tumor necrosis factor-α is a soluble 17 kd protein trimer. In health, TNF-α may play a role in normal tissue homeostasis as low levels of TNF are produced by macrophages under physiologic conditions [13]. In disease, TNF-α is produced in increased amounts by macrophages, T cells, mast cells, neutrophils, dendritic cells, fibroblasts, keratinocytes, and endothelial cells in response to infection, tissue injury, or inflammation [7]. TNF-α is a proinflammatory cytokine which increases the recruitment of leukocytes to the site of inflammation through increased adhesion molecule expression [14], increased vascular permeability and through stimulation of other cytokines [10,15,16] and chemokines.

Control of the inflammatory processes induced by TNF-α—allowing resolution of inflammation—is obtained through the counterbalancing effects of antiinflammatory cytokines and by the induction of soluble TNF receptors [z]. Levels of soluble TNF receptors are elevated in disease and they neutralize circulating TNF by binding TNF without inducing a cellular response. Chronic inflammation is a failure of resolution of the acute inflammatory response and the persistent production of TNF is a feature of chronic inflammatory diseases such as psoriasis and PsA. Anti–TNF-α therapies have now been pioneered in PsA subsequent to the successful clinical application of these biologic agents in RA but without the extensive elucidation of the role of TNF-α in psoriasis and PsA. In this article, the available scientific and clinical evidence for a central role of TNF-α in the inflammation of psoriasis and PsA will be reviewed.

Evidence for a Role of Tumor Necrosis Factor-α in Psoriasis

Concepts related to psoriasis pathogenesis have undergone considerable evolution in recent years. Initially considered to be primarily a disorder of keratinocyte proliferation with secondary inflammation, evidence now supports the concept of a primary disorder of inflammatory cells and that the striking proliferation of keratinocytes is a secondary phenomenon [18]. Evidence that T cells play a prominent role in psoriasis is supported by studies which have shown that T cell infiltration in early lesions precedes epidermal changes [19,20]. Reports of patients developing psoriasis or PsA for the first time after syngeneic bone marrow transplantation from psoriasis donors further supports an immune mediated disorder [21]. Perhaps the most compelling evidence for a role for T cells comes from the observations that treatment which specifically target T cells such as DAB389IL-2 [22••] and more recently alefacept [23], can all result in significant clinical benefits in patients with recalcitrant psoriasis.

It is the interaction of T cells with antigen presenting cells such as Langerhans cells which results in T cell activation. While the identity of the antigen presented is not established, the outcome of T cell activation includes the secretion of type 1 cytokines such as interferon-γ, IL-2, and TNF-α. The secretion of these cytokines results in kerotinocyte proliferation and the associated vascular changes [24–26] thus making these cytokines rational therapeutic targets in psoroiasis.

Tumor necrosis factor-α is a key proinflammatory cytokine in psoriasis as suggested by a number of studies. TNF-α protein has been identified in psoriasis lesions as intense and diffuse expression by dermal dendrocytes and focally by keratinocytes and intraepidermal Langerhans cells [27]. In a further study, median TNF-α levels in skin blister fluids were statistically higher in blisters from involved psoriasis skin than uninvolved skin or healthy controls [28]. Furthermore, levels of TNF-α correlated with Psoriasis Area and Severity Index (PASI) scores, in particular erythema scores, suggests a relationship between TNF-α and clinical features [28]. Finally, serum TNF-α levels have been shown to be significantly increased in psoriasis patients compared with controls, with correlations also found between TNF-α levels and PASI scores at baseline and after effective therapy [29].

Once synthesized, released, and bound to its receptor, TNF-α up-regulates the inflammatory response in a number of ways. It induces kerotinocyte and endothelial cell adhesion molecule expression [26] and it upregulates production of chemokines, such as IL-8 [30]. This up-regulation of adhesion molecules and chemokines results in the recruitment of additional inflammatory cells to the plaque, which can produce further cytokines, including TNF-α, therefore amplifying the process.

Psoriatic arthritis/synovium

Synovial inflammation in PsA is characterized by a similar degree of lymphocyte infiltration as is observed in RA, but there is less macrophage infiltration and lining layer (LL) hyperplasia with increased vascularity [31]. Psoriasis precedes the onset of arthritis in PsA in the majority of patients by a mean of 10 years [32••] and there are a number of common histologic features in the skin and joint in PsA including activation and expansion of tissue specific cells (keratinocytes and synoviocytes), infiltration by mononuclear cells, and angiogenesis [33]. Given the roles of cytokines in regulating these cellular events, it is not unexpected that there are a number of similarities in cytokine expression—particularly with respect to TNF—in skin and joint inflammation [34••].

Tumor necrosis factor-α was initially noted to be increased in PsA synovial fluid, though levels were found to be higher in RA [35,36]. The TNF receptors—soluble TNF receptor 55 (sTNF-R55) and sTNF-R75—are also increased in PsA as compared with osteoarthritis and healthy volunteers though levels were again less than those observed in RA [37]. Conversely a study of cultured PsA synovial explants (n = 8) noted higher levels of TNF-α production in PsA compared with RA (n = 7) or PsA skin [38].

The most extensive study to date on TNF was performed in synovium from 24 PsA patients and 20 RA patients and in lesional and perilesional skin from 25 PsA patients [34]. Using immunohistochemical techniques, TNF-α was found to be present in PsA and RA synovium with marked expression in the LL and a lesser degree of staining in the subsynovial lining layer (SLL), predominantly around blood vessels. TNF-α expression was greater in RA synovial LL and in sublining synovium than in PsA and this was probably because of the greater degree of macrophage infiltration in RA [34••]. Levels of TNF-α expression in the skin and synovium were comparable but did not correlate in patients with PsA. There was diffuse TNF-α expression in the basal areas of the epidermis and dermis of lesional skin, again primarily around blood vessels. Perilesional skin showed significantly more dermal expression of TNF than lesional skin, which may indicate a role for TNF in the initiation of psoriatic inflammation at the plaque edge.

In 10 PsA patients who were successfully treated with methotrexate, the clinical improvements observed were associated with improvements in histologic synovial inflammation [39]. A marked reduction in TNF gene expression in the synovium was observed after methotrexate treatment, though patients with clinical improvement continued to have low levels of mononuclear cell infiltration and TNF messenger-RNA expression. This may suggest that the immunomodulatory effects of methotrexate are partially mediated by a reduction in TNF and other proinflammatory cytokine expression. The association of functional TNF genes with the development of joint erosions in PsA [40•] explained by the finding that anti-TNF antibodies inhibit osteoclast formation by peripheral blood mononuclear cells (PBMC) in vitro and that anti-TNF treatment reduced circulating osteoclast precursor numbers in PsA [41]. As osteoclasts are implicated in bone resorption, this would provide a rationale for why patients with high TNF levels may be more likely to develop bony erosions.

Genetics

Population studies have determined that first degree relatives of patients with psoriasis and PsA have an increased risk for developing disease, with a multifactorial pattern of inheritance [42,43]. Many researchers initially focused on disease associations with human leukocyte antigen (HLA) class I genes [44] located in the major histocompatibility complex region on chromosome 6p because of their role in cellular immunity. The results of these studies are conflicting in PsA, though there appears to be a consistent association between the HLA Cw*0602 gene and susceptibility to psoriasis [45]. More recently, investigators have proposed that the HLA class I genes associations may be a marker for other closely linked HLA class III genes—such as TNF-α—and that these may have a role as susceptibility genes in psoriasis and PsA [46]. TNF is a particularly strong candidate susceptibility gene because of the evidence of increased TNF production in skin and joint tissues in psoriasis and PsA.

Using microsatellite markers mapping close to the TNF-α gene, a significant HLA class I independent increase of the TNFa6c1d3 haplotype was found in patients with PsA but not in patients with psoriasis [46], suggesting a disease susceptibility role for the TNF-α gene in PsA. TNF-α genes are known to be polymorphic, and the two most common TNF-α promoter polymorphisms are adenosine to guanine substitution at the -308 and -238 positions. Allele adenosine at position -308 is associated with higher levels of TNF-α (constitutive and inducible) while the effect allele adenosine at position -238 has on TNF-α production is incompletely determined [47,48]. The -238 TNF-α promoter polymorphism has been associated with juvenile onset psoriasis and PsA in European patients [46,49,50]. Two other smaller studies in 20 Japanese [51] and 52 Jewish [52] PsA patients and a larger study of 124 English whites with PsA did not reproduce these findings but the -238 adenosine allele was associated with the development of peripheral arthritis rather than spondylitis [49].

Combined analysis of the patients from two studies found a significant association of the TNF-α -308 guanine allele with PsA [46], though it should be noted that up to 25% of these patients had a predominant spondylitis pattern. The authors also reported the TNF-α -308 guanine allele association in a group of patients with PsA in whom they noted lower TNF-α secretion from PBMCs when compared with patients with psoriasis only. The authors hypothesised that genetically determined low TNF-α production may be related to the development of PsA. Two other studies of 124 English whites with PsA and 147 Irish whites with PsA did not find any difference in the frequencies of -308 alleles in PsA patients and normal healthy controls [40•,49]. It is of interest that a protective effect of the TNF-α -308 adenosine allele on the development of spondylitis was observed in German patients. Thus the increase in the frequency of the guanine allele may reflect the number of patients with spondylitis.

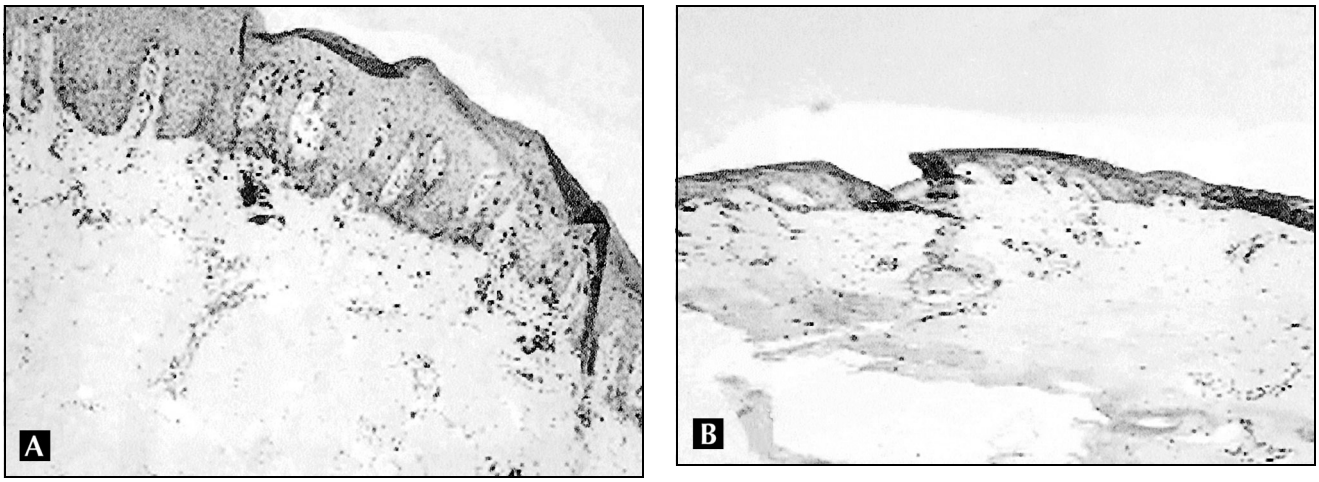

Figure 1. Immunohistochemical staining for CD3 at week 0 (**A**) prior to infliximab treatment and (**B**) at week 12.

In 147 Irish PsA patients the presence of joint erosions was significantly associated with the TNF-α -308 adenosine ($P \leq 0.0001$) and TNFB1 ($P = 0.0009$) alleles [40•]. The TNF-α -308 adenosine ($P = 0.01$) and TNFB1 ($P = 0.04$) alleles were also significantly increased in a progressor group (19 out of 52 early PsA patients in whom the number of joint erosions in the hands and feet increased over a median interval of 24 months) as compared with the nonprogressor group. Taken in combination with the other studies this may suggest that high TNF production is associated with the development of peripheral arthritis and with the progression of peripheral arthritis in PsA while low TNF production is associated with the development of spondylitis. The potential use of TNF genes as prognostic or classification markers in PsA requires further evaluation. No susceptibility association in psoriasis or PsA has been reported for the TNF-α +488 polymorphism or for the TNF receptor II polymorphisms at exon 10 (in the 3′ untranslated region), +1663 (adenosine or guanine), +1668 (thymine or guanine), or +1690 (cytosine or thymine) [49].

Tumor Necrosis Factor-α Blockade in Psoriasis and Psoriatic Arthritis

Perhaps the most compelling evidence for an important role for TNF-α in psoriasis and PsA pathogenesis comes from clinical trials of TNF-α blockade. To date, published experience is confined to the use of infliximab, a chimeric monoclonal antibody, and etanercept, a fusion protein compiling the P75 TNF-α receptor and an immunoglobulin G (IgG) construct. With infliximab therapy, case reports [53,54], small series [55], and a small controlled trial [56] have all demonstrated rapid onset and sustained [57] clinical benefit in patients with moderate-to-severe psoriasis. In PsA, case reports [58], a small open-label study incorporating magnetic resonance imaging-assessed synovitis [59] and a double-blind trial of 40 patients with active spondyloarthropathy, including 18 patients with PsA, have also shown infliximab to be effective and safe in short-term studies. A more large-scale double-blind trial is ongoing.

Studies with etanercept have been more conclusive with a license for use in PsA being approved by the US Food and Drug Administration in 2001. This came after an uncontrolled study in six psoriasis patients, three of whom also had PsA [60] and a randomized, double-blind, placebo-controlled trial in 60 PsA patients [61••]. In this latter study, 87% of etanercept-treated compared with 23% of placebo-treated patients met the PsA response criteria [62] with improvement sustained in a 6 month open-label extension study [63]. A phase 3 clinical trial of 205 patients, published in abstract form, has confirmed the efficacy and safety of etanercept at 24 weeks [64].

Studies in PsA have also shown that etanercept is effective therapy for the psoriatic skin lesions [52,64] with a median PASI improvement of 46% versus 9% in placebo-treated patients. A more recent 24-week, double-blind, dose-ranging study in 652 patients also demonstrated considerable dose-dependent improvements [65]. At week 12, an improvement in PASI of 75% or more was seen in 4% of placebo-treated patients as compared with 14% of patients receiving etanercept 25 mg once weekly, 34% of those receiving 25 mg twice weekly, and 49% of those receiving 50 mg twice weekly. Data regarding long-term safety are awaited.

While these clinical studies have demonstrated that anti-TNF treatments are effective, there is little or no information available on the changes induced locally in the skin or joint. In one study, immunohistochemical analysis of serial samples of involved psoriasis skin showed a rapid decrease in epidermal inflammation and

normalization of keratinocyte differentiation after 12 weeks of infliximab treatment [66••]. Studies from our own department have also examined the changes induced in the skin by infliximab in psoriasis patients [67]. To establish the clinical and immunohistochemical effects of TNF-α blockade we examined the expression of cell specific markers for T cells, macrophages, and endothelial cells, in patients receiving infliximab infusions. Thirteen patients (10 males, three females), median age 44 years (ranging from 22–56 years of age), with a mean duration of psoriasis of 25 years were recruited. After 12 weeks of treatment, infliximab produced a dramatic clinical response, paralleled by a reduction in the inflammatory cell infiltrate (Fig. 1) and in angiogenic growth factor expression.

Conclusions

Studies to date have pointed towards a key pathogenic role for TNF-α in skin and joint disease in PsA. Further information is required on the role of TNF-α in driving the inflammatory response, its interactions with other cytokines, and the mechanism by which TNF-inhibition achieves its effect. Careful studies of skin and joint material obtained from patients undergoing treatment may help identify additional and rational therapeutic targets.

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