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Immunopathogenesis of psoriatic arthritis: Recent advances

Review Article

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Abstract: Psoriatic Arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. The pathophysiology of PsA includes genetic, environmental and immunologic factors. Recent studies revealed the dynamic role of the immune system in the pathogenesis of the disease. Adhesion molecules, proinflammatory cytokines, angiogenic factors and metalloproteinases appear to orchestrate the inflammatory response in PsA. This article summarizes the current immunologic findings and suggests future therapeutic and researching approaches in the field of PsA.

Keywords: *Psoriatic arthritis • Immunopathogenesis • Cytokines • Adhesion molecules • Bone remodeling*

1. Introduction

Psoriatic Arthritis (PsA), is a chronic systemic inflammatory arthritis of peripheral joints, spine and entheses, is associated with psoriasis and is usually negative for rheumatoid factor [1]. Psoriasis occurs in about 2% of the population [2]. The prevalence of PsA in patients with psoriasis varies widely and ranges from 7-42% [3]. In approximately 70% of patients with PsA, skin involvement precedes the joint disease and in about 15% the two conditions occur within 1 year of each other [4,5]. Almost 15% of patients, develop arthritis one year before the onset of psoriasis [4,5]. The clinical spectrum of PsA is heterogeneous and Moll and Wright have identified five subtypes of PsA according to the pattern of articular involvement: symmetric polyarthritis, asymmetric oligoarthritis, spondylitis, distal interphalangeal arthritis and arthritis mutilans [1]. Moreover, almost half of the patients classified as polyarticular in the early stages have been reclassified as oligoarticular after 2 years [6]. Thus, new criteria for PsA classification has been proposed by the CASPAR Study Group [7].

The exact cause of PsA remains unknown although genetic, environmental and immunologic factors seem to contribute to the pathogenesis of the disease. Almost 40% of patients with PsA, have a first degree family member with either skin or joint disease [4,8]. Many susceptibility genes have been proposed such as MHC I [8,9], and II genes [10] as well as gene polymorphisms of TNF [11-13]. Both viral and bacterial infections have been implicated as causative agents of PsA. Serum from patients with PsA had increased levels of antibody to streptococcal exotoxin [14] and indirect observations of enhanced humoral and cellular immunity, and supported a possible link between bacterial infections and PsA or psoriasis [10]. Similarly, viral infections have also been suggested to induce PsA but this has never been confirmed [15,16]. Physical trauma is another environmental factor that could possibly result in psoriasis [17] and PsA [18]. This article focuses on the role of the immune system and summarizes the recent immunological findings in the field of PsA.

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2. Immunopathology

The psoriatic synovium is characterized by increased vascularity which is considered an early feature of PsA [19,20]. The presence of dilated and tortuous vessels denotes impaired angiogenic mechanisms which are responsible for the construction of this abnormal vascular net. Many angiogenic factors have been involved including vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ) and angiopoietins (Ang1, Ang2). Ang 2 seems to disrupt the in vivo angiogenesis and contribute to the blood vessel remodeling while Ang1 is responsible for the maturation of blood vessels [21]. More specifically, the levels of VEGF and TGFβ have been found elevated in the synovial fluid of patients with PsA [22]. In addition, levels of VEGF, Ang2 and mRNA expression are significantly higher in the synovium of patients with PsA compared with rheumatoid arthritis (RA) patients [23]. On the contrary Ang1 levels and expression of mRNA were considerably decreased compared with those of Ang2. These findings are consistent with the histological blood vessel abnormalities of the psoriatic synovium and might explain the molecular basis of this phenomenon. However, not all studies have confirmed the increased vascularity in PsA compared with RA [24].

The inflammatory infiltrate of psoriatic synovium follows a perivascular distribution and is mainly localized to the sublining stroma of the joint [25,26]. It consists mainly of activated CD4+ lymphocytes, CD8+ lymphocytes and macrophages. B cells are also present in fewer numbers and form germinal centers but their role in psoriatic arthritis has not yet been elucidated because neither psoriasis nor PsA is associated with high levels of circulating autoantibodies such as RF or anti-CCPs [25,27]. The ratio of CD4+ to CD8+ is 2:1 in the tissues and 1:2 in the synovial fluid [27,28]. It has been suggested that CD8+ lymphocytes play a crucial role in the inflammatory process of psoriatic synovium [29]. Data to support this speculation come from a PsA population study which revealed an increase frequency of HLA-I antigens including HLA-B13, B17, B27, B38, B39 and Cw6 [8]. In another study, Gonzales et al supported the idea that MHC class I chain-related A (MICA) A9 and Cw6, are the strongest genetic susceptibility factors in PsA [9]. In addition, an association between severe PsA and HIV infection has been reported by many investigators [30-32]. Taking into consideration that HIV infection decreases selectively the number of CD4 lymphocytes and that some diseases such as lupus erythematosus (LE) or RA are improved in the presence of HIV infection, it seems possible that CD8 lymphocytes could interact with HLA I molecules and mediate the immunological process observed in PsA [33,34]. Finally, analyses of the TCR repertoire of CD8+ lymphocytes, revealed a specific oligoclonality implying an antigen-driven immunological response [35]. Interestingly, involvement of HLA class II molecules has also been implied in the pathogenesis of PsA [36,37].

On the contrary, the role of macrophages is not clear. In a recent study, it has been shown that synovial biopsies from patients with Spondyloarthropathies (SpA) including psoriatic arthritis, had decreased numbers of macrophages (CD68+) compared with patients with RA [38]. Moreover, these macrophages have been found more potent since they highly express the CD163 scavenger receptor and release increased levels of proinflammatory cytokines such as TNF and IL-1 after stimulation with LPS [39]. Another study supported the idea that the synovial infiltrate of patients with PsA and RA was comparable with regard of fibroblasts-like synoviocytes and macrophages [40]. However, the number of CD4, CD8 and macrophages tended to be lower in patients with PsA although the difference did not reach the statistical significance [40]. Lately, Natural Killer cells have been purposed to have a role in the development of PsA. NK cells express both activating and inhibiting Ig-like receptors and the balance between these signals determines the functional status of the cell. It is well known that HLA-I molecules interact with inhibitory receptors whereas the ligands for activating receptors have not been defined yet.

In a recent study, a genetic association between specific Ig-like receptors expressed by the NK cells and PsA, has been reported [41]. Specific activating Ig-like receptors, if combined with the absence of HLA molecules, enhance the susceptibility to PsA [41]. Similarly, Nelson et al purposed a model to interpret the susceptibility to PsA based on the role of NK cells. They suggested that protective and susceptible phenotypes depend on the balance between activating receptors and inhibitory receptors-HLA interactions [42]. Moreover, Spadaro et al have found reduced numbers of NK cells in the synovial fluid of patients with PsA without investigating the role of NK cells in the inflamed synovial membrane [43].

3. Cytokines and the role of tumor necrosis factor (TNF)

A variety of cytokines have been studied in order to identify their role in the development of PsA. Serum and synovial tissue from patients with PsA have elevated levels of IL-18 [44]. Proinflammatory cytokines including

TNF and IL-1 induce the expression of IL-18 which is produced by macrophages [45] and not promote the Th1 differentiation, stimulate the expression of not chemokine and enhance the recruitment of mononuclear cells. Ritchlin et al have found elevated levels of IL-1β, IL-2, INF-γ, TNF and IL-10 but not IL-4 and IL-5 in supernatants from synovial explant cultures [46]. A similar pattern of gene expression has been detected in the whole synovial tissue [46]. The predominance of Th1 cytokines and the elevated levels of IL-10 in PsA compared to RA, suggests a different underlying mechanism [46]. In addition, it has been shown that the synovial fluid of patients with early PsA, has increased levels of TNF, IL-10 and MMP-1 and-3 [47]. Both MMP-1 and MMP-3 levels correlated with histological infiltration of the synovial membrane but surprisingly TNF and IL-10 levels did not [47]. In another study it has been found that the expression of TNF, IL-1β, IL-6 and IL-18 in PsA was as high as in RA and that the expression of matrix metalloproteinases including MMP-1 and MMP-3 was comparable for PsA and RA [40].

More specifically, TNF is a potent proinflammatory cytokine which is involved in the pathogenesis of PsA in many ways. TNF activates both endothelial cells and lymphocytes which express a variety of adhesion molecules including ICAM and E-selectins. In addition, TNF is involved in cartilage degradation and bone erosions via the increased production of matrix metalloproteinases. In order to identify the role of TNF, gene polymorphisms have been studied in patients with PsA. In a previous study, it was mentioned that TNF-a promoter polymorphism or a gene in linkage disequilibrium with TNF, may predispose or increase susceptibility to psoriasis and PsA [12]. In another study, although no significant differences in genotype frequencies were observed between PsA patients and normal subjects, the presence of joint erosions was associated with TNFa-308 and TNFβ+252 polymorphisms [11]. These two gene polymorphisms were also associated with age at psoriasis onset and the progression of joint erosions [11]. Finally, a meta-analysis in patients with PsA, revealed that the TNFa-238 variant was a significant risk factor for PsA [13]. The most convincing evidence for the important role of TNF comes from clinical trials using anti-TNF therapies. Turkiewicz *et al.* reviewed recently all the key clinical trials of anti-tumor necrosis factors agents for psoriatic arthritis [48]. All the currently available TNF antagonists have been used clinically including etanercept which was firstly administrated, infliximab, adalimumab and onercept. Anti-TNF treatment resulted in clinical improvement and inhibition of radiographic progression implying a disease-modifying role for anti-TNF agents like in RA. In parallel, etanercept and infliximab have been already approved for the treatment of psoriasis whereas adalimumab is under investigation [49]. The fact that anti-TNF agents affect both psoriasis and PsA suggests that these two entities share common immunological mechanisms and that anti-TNF treatment is a good therapeutic approach for patients who suffer from both psoriasis and PsA.

4. Adhesion molecules and MRPs

Many different studies point out the role of adhesion molecules in PsA. These adhesion molecules are expressed by the activated endothelium and play an important role in T cell adhesion and transmigration through the vessel wall. Blood vessels of psoriatic synovium express a variety of adhesion molecules including ICAM-1, VCAM-1 and E-selectin [25,50]. Carson et al have found increased levels of soluble E-selectin in synovial fluid of patients with PsA and RA compared with patients with osteoarthritis and gout [51]. Immunohistochemical analysis of synovial membrane in patients with PsA and RA revealed no differences between the two groups for the adhesion molecules ICAM-1, VCAM-1 and E-selectin [40]. Furthermore, administration of anti-TNF therapy resulted in a decrease of expression of adhesion molecules in synovium of patients with PsA [52,53]. On the contrary, it has been found that the cutaneous lymphocyte associated antigen (CLA) is upregulated on lymphocytes in psoriatic skin but not in psoriatic synovial membrane [54] suggesting that psoriasis and PsA may share common immunopathogenic mechanisms but are different entities.

Recently, there is evidence of myeloid related proteins (MRPs) involvement in the pathogenesis of PsA. MRP 8 and 14, are calcium-binding proteins which are highly expressed in infiltrating granulocytes and monocytes [55] and have the ability to form the noncovalently associated heterodimer MRP8/MRP14. In activated monocytes, this heterodimer is being translocated from the cytocol to the membrane [56], increasing the migratory capacity of these cells in an adhesion molecule dependent way [57]. MRP 8 and 14 can be secreted in a soluble form and play a role in cell adhesion and in neutrophil and macrophage infiltration and activation at the sites of inflammation [58,59]. The expression of MRP 8 and 14 is minimally expressed in normal tissues. Kane et al have found that MRP levels in serum and synovial fluid are equally increased in PsA and RA and correlate with local and systemic inflammation [60]. On the contrary, MRP8, MRP14 and MRP8/MRP14 expression was increased

in perivascular synovial membrane and endothelium of patients with PsA compared with RA patients [60]. These data suggest a possible role for MRP proteins in transendothelial migration of leukocytes in PsA. The elevated levels of MRPs, despite the decreased number of macrophages in psoriatic synovium, could be attributed according to the investigators to other causes such as binding of MRP antigens to endothelium, secretion of MRP antigens during the migration phase of the source cells or increased neutrophil infiltration of the synovial sublining layer.

5. Bone remodeling and metalloproteinases

Bone erosions and cartilage degradation in inflammatory arthritides, are believed to involve the actions of cytokines and metalloproteinases. The signaling pathway RANK-RANKL seems to mediate the formation and activation of osteoclasts [61]. RANK belongs to the TNF-receptor family and is expressed mainly on the surface of osteoclast precursors and osteoclasts while RANKL is the associated ligand and is expressed by osteoblasts and synoviocytes in the inflamed joints. The interaction between RANK-RANKL induces osteoclastogenesis and activation of osteoclasts leading to abnormal bone remodeling and bone resorption. In contrast, OPG or osteoprotogerin is a decoy receptor which can bind RANKL and blockade the actions of the RANK-RANKL pathway. Thus, OPG is considered a regulatory molecule which assures the balance between osteosynthesis and osteolysis.

Ritchlin et al have described the presence of osteoclasts in deep resorption pits at the synovium-bone interface [62]. In the same study it was found that RANKL was expressed by synovial lining cells while RANK bearing cells showed an increasing gradient number from blood vessels to synovium-bone interface. On the contrary, OPG was restricted to the endothelium. Finally, it was demonstrated that TNF and RANKL mediated osteoclastogenesis and bone resorption in PsA [62].

Metalloproteinases also contribute to the abnormal bone remodeling in PsA. As it has been mentioned above, both MMP-1 and MMP-3 levels correlated with histological infiltration of the synovial membrane [47] and their expression was comparable for PsA and RA [40]. In another study, staining for MMPs showed a cellular and interstitial pattern in the synovial lining layers that was similar between patients with RA and Spondyloarthropathies (SpA) including PsA [63]. It was also found that serum levels of MMP-3 and MMP-9 were significantly higher in patients with RA and SpA as compared to healthy controls and MMP-3 levels in the serum reflected the presence of peripheral synovitis but not systemic inflammation [63]. Finally, administration of anti-TNF treatment with infliximab, resulted in down regulation of all MMPs in the synovium as well as in a rapid decrease of serum MMP-3, confirming the important role of TNF [63].

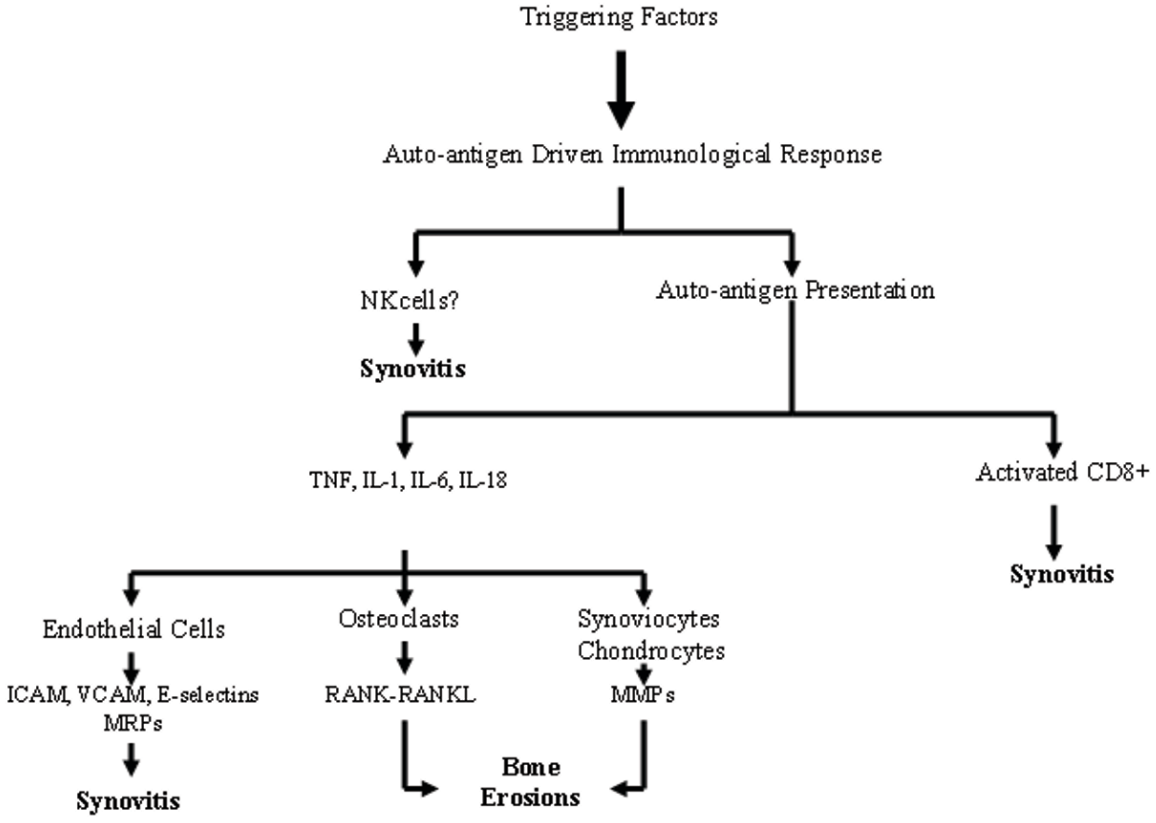
Furthermore, Fraser et al studied the damage and changes in turnover of articular cartilage and proteoglycan aggrecan in patients with early RA, established RA, PsA and osteoarthritis by determining the levels of C2C neopeptide which reflects collagenase cleavage of collagen type II and the levels of C-propeptide of procollagen type II used as a biosynthesis marker [47]. No significant changes in extracellular matrix turnover of aggrecan or collagen type II have been observed in the early stages of inflammatory arthritides but there was a direct correlation between the increased levels of TNF and MMP-1 in synovial fluid and collagen degradation. These findings connect the activities of TNF and MMP-1 with collagenase cleavage of cartilage collagen in PsA [47]. Finally, another study suggested that serum amyloid A is highly expressed by the inflamed human synovial tissue and could bind to formyl peptide receptor-like 1 amplifying the inflammatory response in the synovium [64]. It was also demonstrated that besides proinflammatory cytokines, serum amyloid A, could independently stimulate the release of MMP-1 and MMP-3 from endothelial and fibroblast-like synoviocytes isolated from patients with PsA [64].

6. Overview and Conclusion

The effect of an environmental factor on a genetic susceptible individual could be responsible for the initiation of the inflammatory response in the synovial membrane. Microbial or related antigens could induce the initial inflammatory response of the immune system, leading to T cell proliferation of specific clones although such proof is difficult [10,14]. Similarly, minor recurrent trauma can lead to activation of stress genes and upregulation of adhesion molecules [17,18]. Both microbes and trauma can stimulate the overproduction of proinflammatory cytokines and can lead the normal repair procedures to chronic inflammation.

Independently of the triggering factor, it seems that the interaction of antigen presenting cells and T lymphocytes plays a crucial role in the pathogenesis of both psoriasis and PsA. Psoriasis has been considered a T cell driven disease and specific costimulatory blockade strategies have been applied as therapeutic interventions

Figure 1. Current immunological concepts in the pathogenesis of Psoriatic Arthritis.



including alefacept (a fusion LFA3/IgG1 protein that binds to CD2 receptor on T cells) and efalizumab (a monoclonal antibody that binds to the adhesion molecule LFA-1 on T ells) [65-67]. These biological agents have proven efficacious for the treatment of psoriasis and are now tested in phase II clinical trials of patients with PsA, implying that the two conditions share common pathophysiological mechanisms [68,69]. The importance of T cells in the pathogenesis of PsA is also supported by the fact that the inflammatory infiltrate of the psoriatic synovium is dominated by CD4 and CD8 lymphocytes. Macrophages although reduced in number compared to RA, appear particularly potent expressing the CD163 scavenger receptor, a finding which also underlines the importance of the antigen presentation process [39].

The reversed ratio of CD4:CD8 in the synovial fluid of patients with PsA denotes that CD8 lymphocytes might mediate the immune response of the disease [27-29]. Analysis of TCR receptors of CD8 lymphocytes revealed that T-clones expand in a selective autoantigen driven manner [35]. In addition, the association of PsA with HIV infection suggests a crucial role for CD8 lymphocytes [30-32]. Furthermore, recent studies support a possible involvement of NK cells [41]. Although a reduced number has been found in the synovial fluid, their presence in the synovial membrane has not been investigated. The interplay of activating and inhibitory Ig-like receptors could cause an alteration of the functional status of NK cells which subsequently could augment the inflammatory response. Another early histological feature of psoriatic synovium is the increased vascularity and the presence of tortuous and dilated vessels [19,20]. This abnormal vascular net is probably attributed to impaired angiogenic underlying mechanisms which involve many angiogenic factors such as vascular endothelial growth factor (VEGF), transforming growth factor (TGFβ) and angiopoietins. This specific vascular pattern in combination with the overproduction of angiogenic factors might promote functional alterations of endothelium and thus enhance recruitment of leukocytes and initiation of inflammation.

Proinflammatory cytokines appear to play an important role in perpetuating and maintenance of inflammation. Levels of TNF and IL-1 have been found elevated in the synovial membrane of patients with PsA [46]. Other cytokines are also elevated including IL-2, IL-18, IL-10 and INF-γ while synovial fluid contains also high concentrations of TNF [46]. These data suggest a predominance of Th1 cytokines although IL-10, a Th2 cytokine with anti-inflammatory properties, is

also elevated. The presence of IL-10 implies different mechanisms compared to RA which is characterized by the total absence of Th2 cytokines. Proinflammatory cytokines and especially TNF, possess pleiotropic actions and participate in many stages of the inflammatory response including upregulation of adhesion molecules, activation of RANK-RANKL pathway and release of metalloproteinases [62]. The fact that TNF has a central role in the pathogenesis of PsA is also supported by the clinical efficacy of anti-TNF therapies applied to both psoriasis and PsA [48]. Today, all the TNF antagonists including infliximab, etanercept and adalimumab, are approved by the FDA for the treatment of PsA.

Consistent with the previous mentioned, are findings from recent studies that demonstrated increased expression of adhesion molecules by the blood vessels of psoriatic synovium such as ICAM, VCAM and E-selectins [40]. In addition, MRPs have been found to be elevated in perivascular synovial membrane and endothelium of patients with PsA [60]. Both adhesion molecules and MRPs regulate the leukocyte recruitment and migration through the blood vessels and therefore contribute to the maintenance of the effector phase of the immune system. TNF and proinflammatory cytokines seem to activate the RANK-RANKL and stimulate the production of metalloproteinases, resulting in cartilage degradation and bone erosions [62]. The current immunological concepts in the pathogenesis of PsA are summarized in Figure 1. These recent findings provide new insights into the underlying immunologic mechanisms of PsA and imply molecular-oriented therapeutic strategies targeting a variety of potent molecules and cytokines. In addition, genetic polymorphisms and correlations appear promising candidates for the diagnosis and classification of the subtypes of the disease. Further studies with large and well characterized patients are necessary to confirm and validate these findings as well as their clinical efficacy.

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