Basic Synovial Biology and Immunopathology in Psoriatic Arthritis

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ABSTRACT. Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy with a well recognized propensity for aggressive bone erosions. In some individuals, however, periarticular bone mineralization is maintained, and there is often associated new bone formation with periostitis and frank ankylosis; thus PsA manifests, in different individuals, reciprocal patterns of joint pathology suggesting a disorder of bone remodeling. Recent key scientific advances will be briefly reviewed including T cell, B cell, human leukocyte antigen associations; and the importance of neoangiogenesis, vascularity, and adhesion molecules in conjunction with inflammatory infiltrates and cytokine expression. Finally, the mechanisms of abnormal bone remodeling are discussed, including mediators of osteoclastogenesis such as RANK ligand and molecular signaling pathways including Dickkop-1 and bone morphogenetic proteins. Although much has been learned about the pathogenesis of PsA, much remains to be defined regarding the mechanisms linking synovial biology and immunopathology to different disease outcomes. Identifying key differentiating factors between the diverse PsA phenotypes, correlating findings with the rapidly advancing field of ultrasound image acquisition, and delineating the cellular and molecular mechanisms of abnormal bone remodeling in combination should enable the development of improved prognostic algorithms. This in turn should facilitate the targeting of expensive (about £10k/patient/year) and potentially toxic yet effective biologics to patients most in need. (J Rheumatol 2009;36 Suppl 83:14-16; doi:10.3899/jrheum.090212)

Key Indexing Terms:
PSORIATIC ARTHRITIS | BONE REMODELING | RANK LIGAND
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Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy affecting the peripheral joints, axial skeleton, and entheses; it represents a significant disease burden for the National Health Service and society. There is a well recognized propensity for aggressive bone erosions in PsA, with up to 60% of patients manifesting an erosive and deforming phenotype and 30% evidence of radiographic joint damage within the first 2 years of disease onset[1]. In some individuals, periarticular bone mineralization is maintained and there is often associated new bone formation with periostitis and frank ankylosis. Thus PsA manifests reciprocal patterns of joint pathology suggesting a disorder of bone remodeling within the psoriatic joint. It has also been observed that the pattern and extent of articular bone damage is highly variable despite similar levels of inflammation within affected joints, suggesting a differential coupling of inflammation and erosive joint destruction[1,2]. Understanding of synovial biology and immunology responsible for the distinct phenotypes of psoriatic arthritis lags behind that of rheumatoid arthritis (RA). Recent key scientific advances will be briefly reviewed below.

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T CELL, B CELL, AND HLA ASSOCIATIONS

Memory CD4+ and CD8+ T cells have been identified in inflamed PsA synovium, and clinical trials have demonstrated the efficacy of T cell targeted therapies (cyclosporin A, alefacept, and anti CD3)[3,4]. CD8+ T cells are more common in the synovial fluid compartment and at the enthesis[5,6], and PsA has been associated with HLA class I. Important animal studies conducted by Zenz, *et al*[7] in Jun–/– mice modeled to develop both psoriasis-like skin lesions and an erosive arthropathy have demonstrated the potential for T cell and/or B cell dependence of the arthritis. Synovial inflammation was substantially reduced and bone destruction absent when the JunB/C–Jun deletion was performed in animals that were not able to produce T and B cells.

NEOANGIOGENSIS, VASCULARITY, AND ADHESION MOLECULES

Dysregulated angiogenesis with the presence of immature, tortuous, and elongated vessels has been reported as a prominent early event in PsA[8] with increased vascularity seen in PsA synovial membrane histology[9], and arthroscopic assessment of synovial vascular changes revealing a

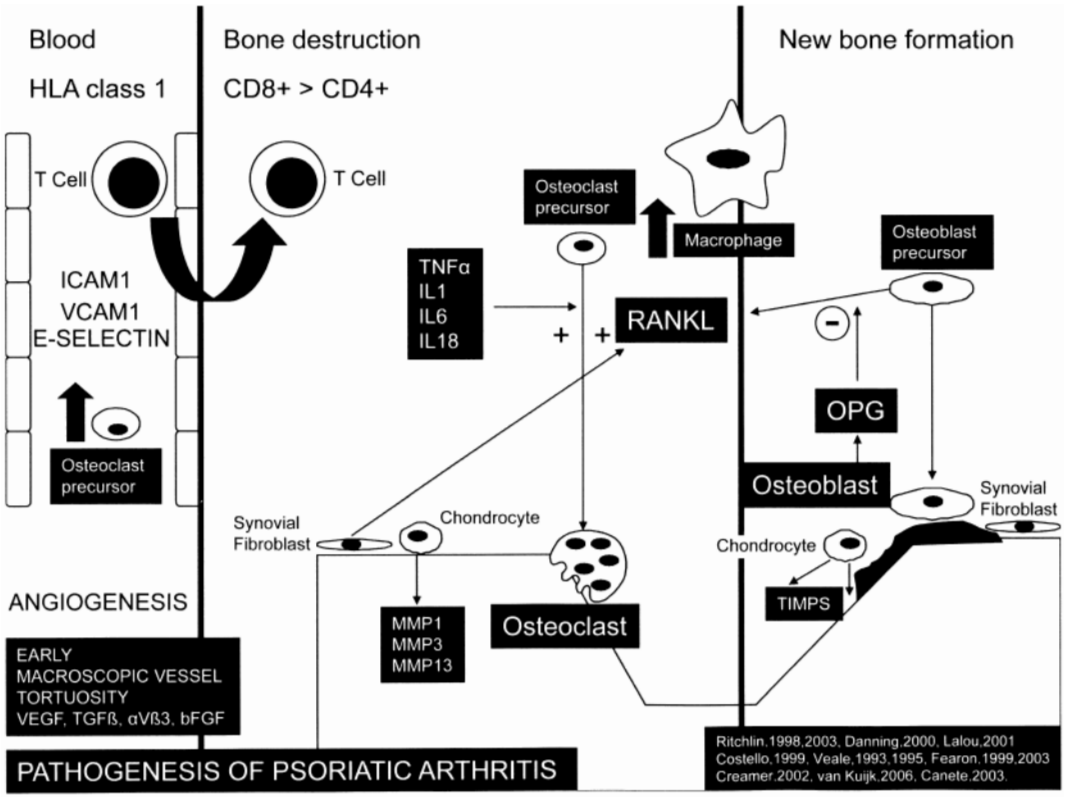

Figure 1. Factors influencing the pathogenesis of psoriatic arthritis (PsA).

tortuous pattern[10]. Angiogenic factors vascular endothelial growth factor (VEGF) and transforming growth factor–β are elevated in the synovial fluid of patients with early PsA, and the vascular markers VEGF, von Willebrand factor, integrin avb3, and basic fibroblast growth factor have been demonstrated in immunohistochemical analyses of PsA synovium[11]. Pronounced upregulation of both intercellular adhesion molecule-1 and vascular adhesion molecule-1 in the synovial membrane has been reported. Interestingly, E-selectin appears to be upregulated in the skin more than in the PsA synovial membrane, and cutaneous lymphocyte associated antigen (CLA) is preferentially expressed on leukocyte "homing" to lesional psoriatic skin but not to the PsA synovial membrane[12].

INFLAMMATORY INFILTRATE AND CYTOKINE EXPRESSION

It has been suggested that the synovium in PsA is characterized by less pronounced lining layer hyperplasia and fewer monocytes/macrophages compared to RA, but more recent reports challenge this finding[11]. The most striking feature in PsA is the abundant overexpression of proinflammatory cytokines, especially tumor necrosis factor–α (TNF–α), interleukin 1β (IL–1β), IL–6, and IL–13[13]. Th17 derived cytokines, in particular the IL–23/IL–17 axis, can be hypothesized to play a role in the pathogenesis of PsA, drawing evidence from studies in mice[14], patients with RA[15], and those with psoriasis[16]. Novel, exciting proof of concept therapeutic studies targeting the IL–23/IL–17 group are currently in progress, and data are eagerly awaited to establish the real therapeutic value in patients with PsA.

ABNORMAL BONE REMODELING

Key molecules that regulate osteoclast differentiation, such as receptor of activated nuclear factor κB ligand (RANKL), are induced in the context of inflammatory arthritis and mediate osteoclast driven destruction of the joint architecture[17]. Relative expression of RANKL and its natural antagonist osteoprotegerin controls osteoclastogenesis, while prevention of osteoclast activation has been shown to abolish arthritic bone erosion and preserve joint architecture[18]. Blood samples from PsA patients exhibit a marked increase in osteoclast precursors, compared to healthy controls, that declines with anti-TNF therapy, while immunohistochemical analysis of the synovium in the same patients reveals dramatic upregulation of RANKL expression[19]. TNF–α levels are elevated in both the synovium and joint fluid of PsA patients[20], with further evidence of a key contribution of this cytokine to the pathology of the disease highlighted by responsiveness of PsA to TNF-blocking therapies[21]. Less is known about the reciprocal process of pathological new bone formation typical of certain PsA phenotypes. Naturally

occurring inhibitors of key signaling pathways involved in the differentiation and function of bone forming osteoblasts such as Dickkopf-1 have been identified as playing a potentially vital role in the regulation of pathological bone remodeling in inflammatory arthritides[22]. It has also been suggested that the reactivation of molecular signaling pathways critical for both developmental tissue formation and growth, including the bone morphogenetic pathways (BMP), may play an important role in the pathogenesis of arthritis[23]. Studies in mouse models of PsA (the aging male DBA/1 mouse) have demonstrated that enthesial new bone formation, a finding typical of spondyloarthropathies (SpA), is associated with the presence of BMP2, BMP6, and BMP7, while activation of the BMP signaling pathways has been demonstrated in human SpA enthesial lesions[24]. Further work in this area, particularly aiming at modulating these pathways in vivo in patients, would provide valuable information on their therapeutic potential.

CONCLUSION

Although much has been learned about the pathogenesis of PsA (as represented in Figure 1), much remains to be defined regarding the mechanisms linking synovial biology and immunopathology to different disease outcomes. The rapid advances in 3-4D ultrasound power Doppler (US/PDU) technology[25], through minimally invasive biopsy, has enabled the collection of synovial tissue from the majority of arthritis patients[26], making pathobiological profiling a realistic prospect at the individual patient level. Identifying key differentiating factors between the diverse PsA phenotypes, correlating findings with ultrasound images, and delineating the cellular and molecular mechanisms of abnormal bone remodeling in combination should enable the development of improved prognostic algorithms. This in turn should facilitate the targeting of expensive (about £10k/patient/year) and potentially toxic yet effective biologics to patients most in need.

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