

Pathogenesis of psoriasis and psoriatic arthritis

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Pathophysiology of psoriasis

The pathophysiology of psoriasis is multifaceted and dynamic, involving a complex interplay between constitutive cells of the skin and the innate and adaptive immune systems. Until the early 1980s, psoriasis was considered to be primarily a disease of epidermal keratinocyte proliferation, with the cutaneous inflammatory infiltrate a secondary consequence [1]. However, the effective use of therapies designed to inhibit T-cell activation, such as cyclosporine [2] in the late 1970s, and interleukin (IL)-2 toxin [3] and alefacept [4,5] (lymphocyte function-associated antigen-3-Ig) and IL-17A [6] more latterly, has led to a paradigm shift in psoriasis pathogenesis to an immune cell-mediated inflammatory etiology.

Over the past decade, evidence from mouse models and translational research strongly indicates that psoriatic plaques result from both a primary defect in keratinocytes and an inappropriate innate and adaptive immune response mediated mainly by resident and infiltrating T cells [7–10]. Psoriatic skin lesions are highly infiltrated most notably with CD3⁺ T lymphocytes, CD4⁺ T helper cells and CD11c⁺ myeloid dendritic cells within the dermis [11,12], and CD8⁺ T cells and neutrophils in the epidermis [13]. Complex interactions between these T cells,

dendritic cells, keratinocytes, neutrophils and the proinflammatory cytokines produced by these cells – including tumour necrosis factor alpha (TNF- α), interferon-gamma (IFN- γ), IL-17, IL-22, IL-23, IL-12 and IL-1 β – contribute to the initiation and perpetuation of cutaneous inflammation characteristic of psoriasis [14,15].

Etiology

Population studies clearly signify a genetic association in psoriasis, with the incidence being greater amongst first-degree and second-degree relatives of patients than among the general population [16,17]. Genetic linkage and subsequent genome wide association studies (GWAS) have confirmed associations with numerous polymorphisms within genes involved in: (i) immune regulation such as IL-23 signalling (IL-23A, IL-12B and IL-23R) [18–21] and nuclear factor (NF)- κ B signalling (*REL*, *TNIP1*, *TRAF3IP2*, *TNFAIP3*, *KFKBIA*, *FBXL19*, and *CARD14*) [18,19,22,23]; (ii) barrier function (late cornified envelope (LCE) proteins 3B and 3C) [18]; and (iii) epidermal microbial defence (DEFB4) [24]. These analyses add confirmation to the definition of psoriasis as an immune cell-mediated disease of defective keratinocytes [25], although the precise functional effects of these associated single nucleotide polymorphisms remain to be determined.

The locus with the largest effect identified to date in genetic studies of psoriasis is PSORS1, a major histocompatibility complex (MHC) class I region on chromosome 6p21 [26]. Within PSORS1, the human leukocyte antigen (HLA)-Cw06 allele is pinpointed as the risk variant that confers the strongest susceptibility to psoriasis [27]. However, only 60–65% of patients with psoriasis carry the *HLA-Cw06* gene, compared with 15% of individuals without psoriasis [28]. Furthermore, a low penetrance of approximately 10% points towards other genetic and environmental factors being involved [29].

In individuals with a genetic predisposition, external stimuli such as trauma (Koebner phenomenon), infections, stress, drugs, and alcohol can all trigger an initial episode of psoriasis through activation of the innate immune system. A cascade of immunological events then ensues, leading to a persistent inflammatory state within the skin:

- Following epidermal damage, ‘stressed’ keratinocytes release both LL-37 (cathelicidin) antimicrobial peptide and host DNA/RNA, which together activate plasmacytoid dendritic cells to produce large quantities of interferon (IFN)-alpha [9,30,31].
- IFN-alpha induces the maturation of myeloid (dermal) dendritic cells, which in turn produce cytokines including IL-23 and IL-12 [8].
- IL-23 and IL-12 stimulate the attraction, activation and differentiation of T cells within skin draining lymph nodes, thereby bridging the gap between the innate and adaptive immune systems [32]. Subsequent T-cell expansion and migration into the epidermis (through expression of $\alpha 1\beta 1$ integrin) results in characteristic epidermal remodeling [10].
- Differentiated psoriatic T cells are of two distinctly polarised types [33,34]: IFN-gamma secreting T helper 1 (Th1) cells [35] and Th17 cells, which when influenced by IL-23 [35–37] produce IL-17 and IL-22 [39–41].
- IFN-gamma enhances expression of MHC class I on keratinocytes, which may promote presentation of putative autoantigens to intra-epidermal T cells. In turn, this may lead to further activation of pathogenic autoimmune T cells [42].
- IL-17 and IL-22 are key mediators linking the adaptive immune response and epithelial dysregulation in psoriasis [43,44]:
 - IL-22 causes keratinocyte hyperproliferation (seen histologically as acanthosis). This is enhanced by IFN-alpha which up-regulates IL-22 receptor expression on keratinocytes [45]. IL-22 therefore provides an interface between immune activation and epidermal acanthosis [45,46].
 - Both IL-17 and IL-22 increase production of LL-37 [47–49] leading to sustained production of IFN-alpha and unregulated activation of myeloid dendritic cells, thus fuelling the continued activation of the immune system through a positive feedback loop [50].

In addition to the established role of conventional T cells in the pathogenesis of psoriasis, increasing interest surrounds innate $\gamma\delta$ T cells resident

within the dermis. $\gamma\delta$ T cells constitutively express the IL-23 receptor (IL-23R), and in the presence of IL-23, rapidly produce copious IL-17, thus amplifying Th17 responses [51–53]. Accumulations of $\gamma\delta$ T cells have been found in psoriatic plaques [52], as have V γ 9V δ 2 T cells (a novel proinflammatory subset that seems to mediate an immediate tissue response upon koebnerization) [54], suggesting these innate cells may play some role in psoriasis pathogenesis.

Pathophysiology of psoriatic arthritis

Psoriatic arthritis (PsA) was not recognized as a disease separate from RA until the 1950s, but since then our understanding of where PsA fits within a spectrum of spondyloarthritides alongside cutaneous psoriasis has clarified considerably. As in psoriasis, PsA seems to be associated with changes in both the innate immune system and also in the adaptive immune system with the involvement of T cells.

Etiology

Genetic factors

As with many other inflammatory arthritides, PsA was recognized to be highly heritable from early family studies. Interestingly the heritability of PsA (recurrence risk or γ S estimated at 27 [55]) seems to be much greater than that of psoriasis (γ S between 4 and 11) [56]. A study in Iceland confirmed the significantly increased risk ratios for development of PsA in first- to fourth-degree relatives of those with PsA (39, 12, 3.6, and 2.3, respectively, $p < 0.0001$ [17]. On review of GWAS studies, it is clear that the majority of the genetic associations found in PsA are the same as those seen in cutaneous psoriasis, with a much smaller overlap seen with RA [57]. There are also shared genetic susceptibilities with ankylosing spondylitis (AS), including HLA-B27, IL-23R, and IL-12B [58], particularly in those with axial involvement. It has been recognized that psoriatic patients are at high risk of developing systemic co-morbidities and have an association with the metabolic syndrome. The relationship between skin disease and a co-morbid condition has recently been reviewed [59].

Environmental factors

As in cutaneous psoriasis, there is some evidence in PsA that environmental factors can trigger the disease in genetically susceptible individuals. The most reported trigger of PsA is trauma, suggested as a ‘deep Koebner phenomenon’ with multiple studies showing an association with acute physical trauma [60,61] or psychological trauma (eg, moving house) [62]. Infection may also be a significant trigger for PsA. Clear associations between human immunodeficiency virus (HIV) infection and psoriasis and PsA have been reported [63], and an increased prevalence of hepatitis C viral infection has been observed in patients with PsA as compared with psoriasis, RA and general population controls [64]. Despite strong links to streptococcal infections in psoriasis, particularly guttate psoriasis, there is no evidence of a relationship between such infections and the development of PsA.

Inflammatory pathways in psoriatic arthritis

Investigating inflammatory pathways in PsA is complex given the heterogeneity of the condition. PsA can result in inflammation within the synovium, entheses and spine, affecting both soft tissue and bone. Within the synovium, significant morphological changes are seen in the vasculature similar to that seen in psoriatic skin plaques and this angiogenesis has been related to functional changes in infiltrating immune cells [65]. Raised levels of proinflammatory cytokines have also been identified within the joint including p40 (a common subunit of IL-12 and IL-23), TNF- α , IL-1, IL-6, IL-8, and IL-10 with some relationships noted between cytokine levels and clinical arthritis severity [66]. There is some evidence of a relationship between synovitis and subsequent bone erosion in PsA [67] and destructive matrix metalloproteinases identified in the synovium. Severe osteolysis can also be seen in subtypes of PsA such as arthritis mutilans and there is an implication of increased osteoclastic activity in PsA. In the joint, increased receptor activator of nuclear factor kappa-B ligand (RANKL) expression is associated with activation of osteoclasts. Increased levels of osteoclast precursors have been identified in the peripheral blood of patients with PsA, which decreased after administration of anti-TNF therapies [68].

Investigation of the immunopathogenesis of enthesitis has been limited by the difficulty in obtaining appropriate material for study given the inability to biopsy entheses. Imaging studies have suggested increased vascularity at the tendon insertions as well as extracapsular inflammation seen adjacent to synovial joints and soft tissue inflammation in subcutaneous tissues in dactylitis. This led to the theory of differentiation in pathogenesis in PsA. Jevtic et al [69] first described the extensive extra-capsular inflammation seen on magnetic resonance imaging (MRI), with half of their cases showing predominantly synovial inflammation whereas other cases showed neighboring inflammation in thickened collateral ligaments and periarticular soft tissue, particularly in dactylitic joints. This research suggested that there may be heterogeneity in PsA where some patients have a predominantly synovial disease, as in RA, and some show a predominantly enthesal-driven disease, as in spondyloarthritis. After similar imaging results, McGonagle et al went on to hypothesize the primary role of enthesitis in PsA with a secondary spread of inflammation to the synovium [70].

Among the sites affected by PsA, axial involvement is perhaps the least understood. Although there are some similarities with other spondyloarthritides such as AS, different morphological patterns of spinal involvement are seen in PsA and some important genetic associations seen in AS do not apply to all patients with PsA. Radiological changes in the cervical spine occur in up to 70–75% of patients with PsA [71,72], much more common than observed in patients with sacroiliitis. Disease seen in the cervical spine is particularly interesting as it seems that two distinct pathological types occur. In 1964, Kaplan et al observed that radiological changes in the cervical spine in PsA and skin psoriasis bore a closer resemblance to AS than to RA [73]. Blau and Kaufman went on to describe two separate patterns of cervical spine disease: primarily ankylosing in nature or a rheumatoid-like form of inflammatory cervical involvement [71]. Despite the strikingly different radiological features, there seems to be no difference between the two groups in terms of clinical symptoms, however rheumatoid-like disease is associated with B39 and DR4 antigens with evidence of radiocarpal erosions [72].

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