Etiology and Pathogenesis of Psoriatic Arthritis

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KEYWORDS

• Psoriatic arthritis • IL-23 • IL-17 • Psoriasis • Spondyloarthropathy • Enthesitis • Inflammatory arthritis • Dactylitis

KEY POINTS

- Psoriatic arthritis appears to be triggered by autoinflammatory cytokine networks responding to microbiome and mechanical stress signals.
- Interleukin (IL)-23, IL-17, and tumor necrosis factor-α are instrumental in pathogenesis and have served as clinically effective therapeutic targets.
- Alterations in bone resorption and formation are due to interplay of several signaling networks, including RANK-L, Wnt, and BMP.

Arthritis associated with psoriasis was first described in 1956 by Wright.[1] It was not until 1973, however, that Moll and Wright[2] defined the various clinical phenotypes, including asymmetric arthritis, enthesitis, dactylitis, and nail disease. The following year, these authors introduced the concept of spondyloarthritis, a cluster of diseases with shared clinical and immunogenetic features.[3] Despite these advances, the immunopathogenesis of psoriatic arthritis (PsA) remained poorly understood, awaiting a more detailed understanding of immune networks and the inflammatory response. In particular, discovery of the interleukin (IL-23)/T helper 17 (Th17) axis transformed the understanding of mechanisms that underlie not only PsA but also the spondyloarthritis family in general. Data derived from animal models, human tissues, and clinical trials underscore the concept that PsA is fundamentally different from rheumatoid arthritis (RA) (**Table 1**). Although RA is considered an autoimmune disorder given the strong association with shared epitopes in the DRβ region of the major histocompatibility complex (MHC) and antibodies against citrullinated peptides, a parallel autoimmune response has not been identified in PsA. Indeed, the data point to an immune response that is largely innate in composition, promoting differentiation of both type 1 and 17 T lymphocytes. Moreover, the link between infections and spondyloarthritis raises the possibility that the composition of the microbiome, in the skin, the gut, or

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Table 1
Psoriatic arthritis versus rheumatoid arthritis

	Psoriatic Arthritis	Rheumatoid Arthritis
Inflammatory arthritis	Yes	Yes
Autoantibodies	No	Anti-cyclic citrullinated peptides
Erosive disease	Yes	Yes
Genetic associations	MHC I	MHC II
Peripheral involvement	Yes	Yes
Axial involvement	Sacroiliac joint, spine	Rarely cervical spine
DIP involvement	Yes	No
Enthesitis	Yes	No
Dactylitis	Yes	No
Skin disease	Yes	No
New bone formation	Yes	No
Symmetry	Often asymmetric	Symmetric
Origin of joint inflammation	Enthesis	Synovium
Responds to rituximab	No	Yes
Responds to abatacept	Arthritis but not psoriasis	Yes
Responds to TNF blockade	Yes	Yes
Responds to IL-17 blockade	Yes	No
Responds to apremilast	Yes	No

both sites, may be important in the cause and persistence of skin and joint inflammation in PsA.

GENETIC FACTORS

PsA is a highly heritable, polygenic disease. The recurrence risk (λ) ratio, defined as the ratio of a disease manifestation in family members to the affected individual compared with the prevalence in the general population, is significantly higher in PsA than RA and psoriasis.[4–6] This high ratio underscores the strong familial component of this disease; the genetic risk factors are discussed in the article in this issue. In contrast to RA, which shows an association with specific MHC class II alleles, psoriasis and PsA are associated with MHC class I alleles. In particular, HLA-C*06 (previously called HLA-Cω06) is the genetic risk factor most strongly linked to psoriasis.[7] Interestingly, this MHC I allele does not track with joint and nail disease.[8] HLA-B*08, B*27, B*38 are found in increased frequency in PsA, and a recent study showed that the presence of glutamine in the HLA-B27 gene at amino acid position 45 significantly increased the risk for PsA, but not psoriasis.[9] Immunochip genotype array case-controlled analysis also identified HLA-C*0602, amino acid position 67 of HLA-B, and HLA-A*0201 as independently associated with PsA in a study that included nearly 2000 PsA patients and 9000 controls.[10] The presence of HLA-B*27 correlates with the severity of axial involvement on MRI studies[11] as well as a shortened interval between the development of skin and joint disease.[12]

ENVIRONMENTAL FACTORS

The concept that psoriatic plaques develop in response to bacterial antigens originated from clinical observations of a close temporal relationship between