Pathogenetic Overview of Psoriatic Disease

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ABSTRACT. Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease with both autoimmune and autoinflammatory features. Evidence supports the distinct nature of PsA regarding its clinical, genetic, immunohistochemical, and imaging features. Such features can help to distinguish PsA from other common rheumatic diseases. Apart from peripheral joint involvement, the musculoskeletal lesions in PsA include enthesitis and involvement of the distal interphalangeal joint (frequently associated with nail involvement, dactylitis, and axial involvement). The traditional model of pathogenesis in PsA has identified it as an autoimmune disease; however, an alternative model classifies it as having autoinflammatory features. Similarly, there are important new genetic observations focusing on the HLA region, and genome-wide association that confirms the genetic heterogeneity of patients with psoriasis and patients with PsA. Newer imaging techniques have also provided a much more detailed characterization of tissue abnormalities, in particular highlighting the extent of new bone formation, which is quite distinct from rheumatoid arthritis. (J Rheumatol 2012;39 Suppl 89:7–10; doi:10.3899/jrheum.120232)

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Psoriatic arthritis (PsA) is an inflammatory musculoskeletal (MSK) disease with both autoimmune and autoinflammatory features. While there are no agreed diagnostic criteria, PsA is characterized by distinct clinical, genetic, immunohistochemical, and imaging features. We outline here each of these distinct features.

PsA IS CLINICALLY DISTINCT

PsA may be defined as a disorder of the MSK system that occurs in association with the skin condition, psoriasis. Apart from peripheral joint involvement, the MSK lesions in PsA include involvement of the enthesis (enthesitis is inflammation of the entheses, the sites where tendons or ligaments insert into the bone) and of the distal interphalangeal joint, which is frequently associated with nail involvement, dactylitis, or "sausage"-shaped digital swelling and axial involvement. Patients frequently present with more than 1 of these MSK lesions. The lesions may present before the development of psoriasis in 10% of cases; in other words, PsA may be diagnosed in patients without the classic rash by meeting other criteria. It can sometimes prove difficult to assess which MSK or skin lesion predominates. Both dermatologists and rheumatologists must try to assess and quantify all the ways in which PsA may affect an individual. Only then can appropriate therapeutic decisions be made that are tailored to the individual patient's needs. A number of composite disease activity tools[1,2] have been proposed that may well fulfill this clinical need, and these are currently being tested and compared in randomized clinical trials.

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TRADITIONAL MODEL OF PATHOGENESIS OF PsA

The traditional model of pathogenesis is that PsA is predominately an autoimmune disease driven by T cells reacting to as yet unknown skin or synovial antigens presented by macrophages or dendritic cells. This antigen-specific T cell activation in turn leads to an upregulation of proinflammatory cytokines and to the influx of nonspecific T cells and neutrophils into involved tissues. Evidence supports the important role of T cells in PsA[3] (Table 1)[4,5,6,7,8,9,10,11,12].

ALTERNATIVE MODEL OF PATHOGENESIS OF PsA

McGonagle and McDermott have proposed a new classification for immunological diseases with PsA that demonstrates both autoimmune and autoinflammatory features[13]. In autoinflammatory conditions, local factors such as microtrauma at sites predisposed to disease may lead to activation of innate immune cells including macrophages and neutrophils with resultant target tissue damage. It was suggested that this site-specific inflammation might be independent of adaptive immune responses. In further elaboration of this hypothesis, the authors propose that the enthesis is an area of high mechanical stress where, together with the associated bone and adjacent soft tissue, inflammation might be initiated[14]. While an attractive hypothesis, because some patients with PsA show prominent entheseal or capsular involvement, this falls short of explaining all PsA lesions.

On the basis of these pathogenetic models, perhaps a unifying explanation can be put forward in which microtrauma at entheseal sites exposes entheseal antigens that in a genet-

Table 1. Evidence supports the important role of T cells in the pathogenesis of psoriatic arthritis (PsA).

1.	T lymphocytes are present in psoriatic synovial tissue and skin[4].
2.	CD8-positive T cells dominate in PsA synovial fluid with a CD4:CD8 ratio of 0.7:1. This compares with 1.1:1 in rheumatoid arthritis synovial fluid ($p < 0.001$)[5].
3.	Studies have shown that CD8-positive T cells, and to a lesser extent CD4-positive T cells, are clonally expanded in both synovial tissue and fluid suggesting antigen-drive[6].
4.	Both psoriasis and PsA occur more frequently and severely in the setting of HIV infection, revealing independence from participation of CD4+ T cells[7,8].
5.	There are reports of PsA development following allogeneic bone marrow transplantation from a PsA donor[9,10].
6.	There is mounting evidence that both psoriasis and PsA are associated with certain class I HLA antigens, and it is well described that CD8-positive T cells only recognize cell-associated antigens in association with HLA class 1 molecules.
7.	Psoriasis and PsA improve following treatment with antilymphocyte therapies (e.g., cyclosporine)[11].
8.	Change in CD3 infiltration in synovial tissue best correlates with clinical and MRI responses following anti-TNF therapy[12].

HIV: human immunodeficiency virus; MRI: magnetic resonance imaging; TNF: tumor necrosis factor.

ically predisposed individual (i.e., HLA genes) trigger antigen-specific T cell responses.

PsA IS GENETICALLY DISTINCT

Multiple studies have implicated several HLA Class 1 alleles in susceptibility to psoriasis. The principal susceptibility HLA allele is HLA-C*0602 (psors1), which is present in 60% of most series[15]. A group of HLA-B alleles including HLA-B57, HLA-B37, and HLA-B13 are also associated, as they are in linkage disequilibrium with HLA-C*0602[16,17,18]. Other Class 1 alleles implicated in PsA, such as HLA-B27, HLA-B38, or HLA-B39, are not strongly associated with psoriasis.

In relation to PsA, there is little agreement on the actual frequency of HLA alleles. For example, the frequency of HLA-B27 ranges from 17% in Northern Spain to 39% in Taiwan, and the frequency of HLA C*0602 ranges from 29% in Israel to 60% in Northern Spain. There are many factors that can confound identifying susceptibility genes in PsA. Examples are the accuracy of PsA diagnosis, the relationship between psoriasis and PsA, heterogeneity in clinical findings and response to therapy, the difference in the genetic features of PsA, whether the studied cohort is ascertained in a rheumatology clinic or a dermatology clinic, and heterogeneity in the distribution in HLA alleles in different populations.

A recent study has examined the relationship of psoriasis to PsA in the same genetically homogeneous population by comparing ascertainment of a PsA case series with a psoriasis case series, where all individuals with arthritis were specifically excluded following rheumatological assessment[19]. If psoriasis and PsA are indeed homogeneous, one would expect that the frequencies of HLA-C*0602 and HLA-B locus alleles in linkage disequilibrium would be similar in both cohorts. The results of this particular study indicated that in PsA the frequency of HLA-C*0602 was significantly lower at 28.7%, compared to those with psoriasis only at 57.5% ($p = 9.9 \times 10(-12)$). Further, haplotypes containing B-2705 or B-3901 were significantly increased in frequency in PsA but not in the psoriasis cohort. Being HLA-B27-positive was associated with an interval of 0.98 years between onset of skin and MSK disease, compared to 10.14 years if HLA C*0602-positive ($p = 2.5 \times 10(-6)$). These data suggest that the psoriasis phenotype includes those with the classic psoriasis susceptibility gene HLA-C*06 and is characterized by more penetrant skin disease with less penetrant and more time-dependent MSK phenotype development. PsA appears to be mediated by HLA-B alleles, notably –B27 or –B39, which includes temporally more coincident MSK involvement that is nearly equivalent in penetrance to skin disease.

The results of the first genome-wide association study (GWAS) in PsA have been published[20]. Apart from confirming previously described associations with the HLA region and with interleukin 12ß (IL-12ß), the results suggested a significant association with the other arm of the sixth chromosome, where there were 4 mutations in TRAF3IP2. This is a region that codes for Act1, a signaling adapter involved in the regulation of adaptive immunity. Given the lack of an autoantibody signature in PsA, it is of interest that Act1 is a negative regulator of humoral immunity, but on the other hand Act1 concomitantly operates as a positive signaling adapter in IL-17-mediated cellular immune responses[21,22,23]. Early functional studies suggest that the introduction of the risk allele into Act1 results in loss of Act1's ability to interact with TRAF6, a change that may have important effects on IL-17 signaling downstream. An association with TRAF3IP2 was also found in a recent psoriasis GWAS (Wellcome Psoriasis GWAS), but the association was not as strong, and it is possible that some of the association might relate to the inclusion of PsA cases[24]. To date, similar associations have not been described in other autoimmune diseases such as rheumatoid arthritis (RA).

PsA SYNOVIAL TISSUE IS DISTINCT

In comparison to the synovial immunohistological features of RA, a significant reduction in the number of macrophages, a reduction in lining layer depth, and an increase in synovial vascularity has been observed in PsA; however, the number of T cells, T cell subsets, and B cells were similar in both cohorts[25]. Neovascularization is a hallmark of synovitis, and arthroscopic studies have shown distinct vascular patterns of synovium. For example, patients with PsA have predominantly tortuous, bushy vessels, whereas predominantly straight, branching vessels are seen in patients with

RA[26]. Kruithof and colleagues showed an increase in vascularity in PsA as compared to RA in a large series, where they also highlighted an increase in neutrophil infiltration in PsA[27]. While these changes are potentially of pathogenetic significance, none are specific enough yet to be of diagnostic utility.

PsA IS DISTINCT ON IMAGING

There are a number of plain radiographic features that help distinguish PsA from RA. While there are fewer erosions present in PsA compared to RA, PsA is associated with additional features such as new bone formation, bony resorption, pencil-in-cup type deformity, and asymmetrical spinal involvement. Bony changes develop more slowly in PsA, where 47% of patients have demonstrated erosive change and 29% will demonstrate features of new bone formation within 2 years of disease onset[28]. Bone edema on magnetic resonance imaging (MRI) scans has been described as the strongest predictor of subsequent radiographic progression, and one study found this present in 50% of patients with PsA at baseline; the situation improved or resolved in all cases following infliximab therapy[29]. In a study of swollen metacarpophalangeal (MCP) joints in patients with PsA or RA, MRI was not able to differentiate between the 2 diseases on the basis of the entheseal-related disease. However, a subgroup of patients with PsA had diffuse extracapsular enhancement (30%) or diffuse bone marrow edema (20%), suggesting dominant entheseal-related disease[30]. The RA group had a greater degree of MCP joint synovitis and tenosynovitis than the PsA group. There was no significant difference in either the total number of erosions or the presence of periarticular bone edema between the groups. The authors concluded that enthesitis-associated pathology is not sufficiently common to be of diagnostic utility in PsA.

A recent study using microcomputed tomography has also compared MCP joints in patients with PsA or RA. This study found that both cohorts had the same number of bone erosions, but the erosions in PsA were smaller in size and in depth, and more Ω-shaped and tubule-shaped, whereas U-shaped lesions were mostly typical for RA[31]. Interestingly, new bone formation was increased in PsA, often affecting the entire circumference of the bone, and forming a "bony corona" or crown. That study strongly suggests that the mechanisms of bone repair may be more active in PsA. Consistent with this observation, a study has shown a consistent increase in levels of the bone isoenzyme of alkaline phosphatase, reflecting new bone formation, in PsA as compared with RA[32].

CONCLUSION

Based on the above clinical, genetic, immunohistochemical, and imaging evidence, PsA appears to be a distinct, inflammatory MSK disease with both autoimmune and autoinflammatory features. Further research focusing on genotype:phenotype correlations, the role of the IL-17 pathway, and mechanisms of new bone formation are likely to further inform our emerging concepts of disease pathogenesis.

REFERENCES

1. Mumtaz A, Gallagher P, Kirby B, Waxman R, Coates LC, Veale JD, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis 2011;70:272-7. Erratum in: Ann Rheum Dis 2011;70:716.
2. Helliwell PS, FitzGerald O, Strand CV, Mease PJ. Composite measures in psoriatic arthritis: a report from the GRAPPA 2009 annual meeting. J Rheumatol 2011;38:540-5.
3. Veale D, FitzGerald O. Psoriatic arthritis. Best Pract Res Clin Rheumatol 2002;16:523-35.
4. van Kuijk AW, Reinders-Blankert P, Smeets TJ, Dijkmans BA, Tak PP. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment. Ann Rheum Dis 2006;65:1551-7.
5. Costello P, Bresnihan B, O'Farrelly C, FitzGerald O. Predominance of CD8+ T lymphocytes in psoriatic arthritis. J Rheumatol 1999;26:1117-24.
6. Curran SA, FitzGerald OM, Costello PJ, Selby JM, Kane DJ, Bresnihan B, et al. Nucleotide sequencing of psoriatic arthritis tissue before and during methotrexate administration reveals a complex inflammatory T cell infiltrate with very few clones exhibiting features that suggest they drive the inflammatory process by recognizing autoantigens. J Immunol 2004;172:1935-44.
7. Duvic M, Johnson TM, Rapini RP, Freese T, Brewton G, Rios A. Acquired immunodeficiency syndrome-associated psoriasis and Reiter's syndrome. Arch Dermatol 1987;123:1622-32.
8. Winchester R, Bernstein DH, Fischer HD, Enlow R, Solomon G. The co-occurrence of Reiter's syndrome and acquired immunodeficiency. Ann Intern Med 1987;106:19-26.
9. Daikeler T, Gunaydin I, Einsele H, Kanz L, Kotter I. Transmission of psoriatic arthritis by allogeneic bone marrow transplantation for chronic myelogenous leukaemia from an HLA-identical donor. Rheumatology 1999;38:89-90.
10. Snowden JA, Heaton DC. Development of psoriasis after syngeneic bone marrow transplant from psoriatic donor: further evidence for adoptive autoimmunity. Br J Dermatol 1997;137:130-2.
11. Spadaro A, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. Clin Exp Rheumatol 1995;13:589-93.
12. Pontifex EK, Gerlag DM, Gogarty M, Vinkenoog M, Gibbs A, Burgman I, et al. Change in CD3 positive T-cell expression in psoriatic arthritis synovium correlates with change in DAS28 and magnetic resonance imaging synovitis scores following initiation of biologic therapy — a single centre, open-label study. Arthritis Res Ther 2011;13(1):R7.
13. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3(8):e297.
14. McGonagle D, Lories RJ, Tan AL, Benjamin M. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum 2007;56:2482-91.
15. Winchester R. Genetics of psoriasis and psoriatic arthritis. In: Ritchlin CT, FitzGerald O, eds. Psoriatic and reactive arthritis — a companion to rheumatology. Amsterdam: Elsevier; 2007.
16. Tiilikainen A, Lassus A, Karvonen J, Vartiainen P, Julin M. Psoriasis and HLA-Cw6. Br J Dermatol 1980;102:179-84.
17. Mallon E, Bunce M, Wojnarowska F, Welsh K. HLA-CW*0602 is a susceptibility factor in type I psoriasis, and evidence Ala-73 is

increased in male type I psoriatics. J Invest Dermatol 1997;109:183-6.
18. Leder RO, Mansbridge JN, Hallmayer J, Hodge SE. Familial psoriasis and HLA-B: unambiguous support for linkage in 97 published families. Hum Hered 1998;48:198-211.
19. Winchester R, Minevich G, Steshenko V, Kirby B, Kane D, Greenberg DA, et al. HLA associations reveal genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. Arthritis Rheum 2011;Oct 17 (E-pub ahead of print).
20. Hüffmeier U, Uebe S, Ekici AB, Bowes J, Giardina E, Korendowych E, et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet 2010;42:996-9.
21. Qian Y, Liu C, Hartupee J, Altuntas CZ, Gulen MF, Jane-Wit D, et al. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. Nat Immunol 2007;8:247-56.
22. Hunter CA. Act1-ivating IL-17 inflammation. Nat Immunol 2007;8:232-4.
23. Tesmer LA, Lundy SK, Sarkar S, Fox DA. Th17 cells in human disease. Immunol Rev 2008;223:87-113.
24. Ellinghaus E, Ellinghaus D, Stuart PE, Nair RP, Debrus S, Raelson JV, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet 2010;42:991–5.
25. Veale D, Yanni G, Rogers S, Barnes L, Bresnihan B, Fitzgerald O. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. Arthritis Rheum 1993; 36:893-900.
26. Reece RJ, Canete JD, Parsons WJ, Emery P, Veale DJ. Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis. Arthritis Rheum 1999;42:1481-4.
27. Kruithof E, Baeten D, De Rycke L, Vandooren B, Foell D, Roth J, et al. Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. Arthritis Res Ther 2005;7:R569-80.
28. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology 2003;42:1460-8.
29. Marzo-Ortega H, McGonagle D, Rhodes LA, Tan AL, Conaghan PG, O'Connor P, et al. Efficacy of infliximab on MRI-determined bone oedema in psoriatic arthritis. Ann Rheum Dis 2007;66:778-81.
30. Marzo-Ortega H, Tanner SF, Rhodes LA, Tan AL, Conaghan PG, Hensor EM, et al. Magnetic resonance imaging in the assessment of metacarpophalangeal joint disease in early psoriatic and rheumatoid arthritis. Scand J Rheumatol 2009;38:79-83.
31. Finzel S, Englbrecht M, Engelke K, Stach C, Schett G. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. Ann Rheum Dis 2011;70:122-7.
32. Szentpetery A, Ng CT, Murray BF, Brady JJ, Gallagher P, Van der Kamp S, et al. Markers of bone formation are increased in psoriatic arthritis compared to rheumatoid arthritis at baseline and increase further after 3 years of anti-TNF-therapy [abstract]. Arthritis Rheum 2009;60 Suppl:1783.