# From Skin to Bone: Translational Perspectives on Psoriatic Disease

CHRISTOPHER T. RITCHLIN

***ABSTRACT***. In recent years, translational research has provided fresh insights into the mechanisms that underlie both skin and joint inflammation in psoriatic arthritis (PsA). Application of immunological and molecular techniques to the study of involved tissues, combined with magnetic resonance imaging and relevant preclinical models, has unveiled pivotal inflammatory cascades and cytokine networks that lead to sustained inflammation and altered tissue architecture. In this brief overview of a presentation from the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) the key pathophysiologic events associated with inflammation in psoriatic plaques, synovial membranes, and soft tissues (entheses, tendons), and with abnormal bone remodeling are discussed. (J Rheumatol 2008;35:1434–7)

*Key Indexing Terms:*
PSORIATIC ARTHRITIS | PSORIASIS | SYNOVIUM
ENTHESIS | DACTYLITIS | BONE REMODELING

Psoriatic arthritis (PsA), an inflammatory joint disease characterized by diverse phenotypes and a variable disease course, was recognized as a distinct entity about 35 years ago[1]. While initially perceived as a mild form of arthritis with rare extreme phenotypes such as arthritis mutilans, it is now appreciated that the majority of patients can experience progressive joint destruction and new bone formation over a relatively short period of time[2,3]. Moreover, the concept of psoriatic disease emphasizes that patients with psoriasis may have involvement of a number of different tissues including not only musculoskeletal structures but also the eyes, the gut, and the cardiovascular system[4,5].

In recent years, translational research has provided fresh insights into the mechanisms that underlie both skin and joint inflammation in PsA. In this brief overview, the key pathophysiologic events associated with inflammation in psoriatic plaques, synovial membranes, and soft tissues (entheses, tendons), and with abnormal bone remodeling are discussed.

## The Psoriatic Plaque

A central question regarding psoriasis pathogenesis centers on the role of autoimmunity in the formation of psoriatic skin lesions. In a recent study, Lande, *et al* demonstrated that LL37, an endogenous antimicrobial peptide that is overexpressed in psoriatic skin, can form complexes with self-DNA[6]. This complex of LL37 bound to self-DNA is taken up by plasmacytoid dendritic cells where it engages toll receptor 9 in the endocytic compartment and induces interferon-α production. Plasmacytoid dendritic cells were found to infiltrate psoriatic skin and release interferon in a mouse xenograft model, and this provides a mechanism to link cytokine release with T cell activation and keratinocyte proliferation[7]. These studies form the basis for understanding how self-DNA generated by apoptotic keratinocytes can trigger an autoimmune response that results in breakdown of tolerance and activation of cytokine networks.

Recent evidence indicates that interleukin 23 (IL-23) may be a master cytokine in psoriasis. Activation of the Th17 T cell subset by IL-23 can trigger release of IL-17 and IL-22, which promote inflammation and keratinocyte proliferation[8]. In a recent clinical trial, antibody to the p40 subunit, present in both IL-12 and IL-23, was remarkably effective for the treatment of moderate to severe psoriasis[9]. Interestingly, the response was not so impressive in a phase II trial of PsA patients[10]. Studies in murine models have shown that macrophages and most likely dendritic cells are required for psoriatic plaque formation[11]. In another pivotal study, targeted knockout of the transcription factors c Jun and Jun B in murine keratinocytes resulted not only in psoriasiform skin lesions but also in an inflammatory arthritis with features of joint destruction and new bone formation[12]. These studies provide evidence of a dynamic interplay between keratinocytes in the epidermis and immune cells in the dermis; future studies will examine the cellular and cytokine interactions between these populations in greater detail[13]. Events that link skin and joint inflammation are also of great interest.

*From the Clinical Immunology Research Center, University of Rochester Medical Center, Rochester, New York, USA.*

*Supported by an unrestricted financial grant from Abbott, Centocor, Wyeth, Amgen, and UCB Pharma.*

*C.T. Ritchlin, MD, Professor of Medicine, Director.*

*Address reprint requests to Dr. C.T. Ritchlin, Clinical Immunology Research Center, University of Rochester Medical Center, 601 Elmwood Avenue, Box 695, Rochester, NY 14642.*
*E-mail: christopher_ritchlin@urmc.rochester.edu*

## The Synovium

The unusual appearance of the psoriatic joint, namely the absence of periarticular osteopenia, the tendency for a ray distribution in an asymmetric pattern, and the presence of large eccentric erosions, suggests a synovial pathology distinct from rheumatoid arthritis (RA). Detailed analyses of synovial biopsy and surgical specimens have provided intriguing insights into some unique features in psoriatic synovial membranes. One of the most striking is a tortuous macroscopic appearance of synovial blood vessels in psoriatic but not rheumatoid synovium[14]. Similar vascular morphology was also observed in psoriatic skin. *In situ* hybridization studies revealed that psoriatic synovial vasculature expressed higher levels of VEGF and angiopoietin (Ang)2 compared to rheumatoid specimens[15]. VEGF is of particular interest because it can promote osteoclast formation when combined with nuclear factor-κB ligand (RANKL) and paradoxically new bone formation in synergy with transforming growth factor-ß[16,17]. These apparently antagonistic actions may account for the extensive erosions and periostitis observed in some psoriatic joints.

Other studies have highlighted the presence of CD163-positive macrophages in psoriatic tissue (also identified in the colonic tissue from patients with Crohn's disease) and a relative decline in the number of infiltrating T cells coupled with increased neutrophils in psoriatic compared to rheumatoid synovial membranes[18]. Lastly, ectopic lymphoid neogenesis was also identified in psoriatic membranes despite the absence of antibodies to citrullinated proteins[19,20]. The cytokine profile in psoriatic membranes is characterized by Th1 pattern (interferon-γ and IL-2 but not IL-4, IL-5), and monokines such as tumor necrosis factor-α (TNF-α) and IL-1 have also been identified[21]. A prominent role for IL-17 in the psoriatic joint has been proposed but is not yet proven.

## Enthesitis and Dactylitis

Both enthesitis and dactylitis are cardinal clinical manifestations associated with PsA, and investigators have begun to unravel their pathological and anatomical basis. In magnetic resonance imaging (MRI) studies and analyses of cadaver specimens, McGonagle, *et al* have proposed the concept of the synovio-entheseal complex[22]. In this model, the mechanically stressed enthesis in the proper genetic background liberates danger signals that activate Toll receptors and trigger subsequent inflammatory events. In addition, a functional, anatomic, and physiologic interdependence between the adjacent synovium and enthesis is proposed that may result in more generalized inflammation presumably initiated by a local stress response and microenvironmental responses. Tan, *et al* demonstrated that the extensor tendon in the distal interphalangeal joint can bifurcate to attach on the dorsal surface of the distal phalanx and also ensheath the formative nail plate and nail matrix, which may provide a link between enthesitis, distal joint inflammation, and psoriatic nail disease[23]. The DBA/1 mouse model, which develops ankylosing enthesitis (discussed below), provides evidence for a dominant entheseal response that does not depend on synovitis. Elegant MRI studies of psoriatic hands have demonstrated isolated flexor tenosynovitis of the digits in subjects with dactylitis[24]. Recent MRI studies, however, have shown bone marrow edema and synovitis adjacent to flexor tenosynovitis[25]. McGonagle and Benjamin have proposed a leading role for enthesitis in development of dactylitis, given the multiple attachment sites in the finger[26].

## Bone Remodeling

Any model of PsA must account for excess bone resorption and new bone formation that is often present in radiographs of peripheral joints and the axial skeleton. In normal bone, ongoing bone resorption mediated by osteoclasts is closely linked to new bone formation by osteoblasts[27]. In psoriatic synovium, high expression of RANKL by synovial fibroblastoid cells coupled with diminished expression of osteoprotegerin (OPG), a physiologic antagonist of RANKL, was observed by immunohistochemistry[28]. An elevated RANKL/OPG ratio favors the differentiation of osteoclasts from monocytes and tips the balance towards bone resorption. An increased frequency of circulating osteoclast precursors was also identified in the circulation and synovial tissues of PsA patients. A gradient of increasing numbers of these cells extended from vessels in the subsynovium to the bone pannus junction, where large multinucleated osteoclasts were observed in deep resorption pits. These precursors, derived from circulating CD14+ monocytes, differentiate into osteoclasts after exposure to monocyte colony-stimulating factor and receptor activator of RANKL expressed by synovial lining cells in inflamed psoriatic synovium. The frequency of osteoclast precursors in patients with PsA declined rapidly following treatment with TNF antagonists[23].

Some factors that participate in osteoproliferation and new bone formation have recently been identified. Bone morphogenetic proteins (BMP) are pivotal molecules in bony ankylosis as shown in the DBA/1 mouse model[29]. Aging DBA/1 male mice, when caged together, become extremely aggressive and develop an ankylosing enthesitis, which has features that are similar to the pathology observed in psoriatic joints[30]. The BMP are required for the formation of new bone, as shown by a significant decline in ankylosis following treatment of these mice with the BMP antagonist noggin. Increased expression of BMP signaling molecules was also seen in bone obtained from the calcaneal bone biopsy from a patient with ankylosing spondylitis (AS). Another recently identified molecule, Dickkopf-1 (DKK-1), is induced by TNF, and inhibits osteoblast function. DKK-1 is upregulated in RA, thereby providing a rationale for the impaired bone repair mechanism that occurs in the rheumatoid joint[6]. Interestingly, serum DKK-1 levels were low in

patients with AS, a situation that might contribute to the osteoproliferation characteristic of this disorder; however, the level of DKK-1 in PsA is not known. One might predict that DKK-1 levels would be low in patients with ankylosis or periostitis and elevated in patients with a predominance of erosive disease. Of particular note are studies that documented the inability of TNF inhibitors to arrest bony progression in AS and raise the possibility that bone resorption and pathologic new bone formation are not coupled events[31,32].

## Conclusion

Over a span of 10 years, translational research has greatly increased our understanding of the pathophysiology of PsA. Studies of human tissues and animal models have disclosed a dynamic interplay between cells of innate immunity such as monocytes, dendritic cells, and neutrophils, and those of the acquired immune response, primarily T lymphocytes with a dominant role proposed for the TH17 subset in the skin. The pivotal cytokines TNF and IL-23 are at the apex of the inflammatory response and thus are particularly effective therapeutic targets, although the importance of IL-23 in the joint has not been established. The enthesis may be the anatomic link between local biomechanical events and systemic inflammation that ultimately results in altered skeletal remodeling. The unusual bone phenotypes arise from enhanced activity in the RANKL signaling pathway, and both BMP and DKK-1 likely contribute to pathologic new bone formation, although the details of these pathways have not been fully elucidated. Collectively, the studies described here provide a tantalizing glimpse of the molecular and cellular pathways that lead to the varied clinical features of PsA. Additional translational approaches, combined with newly available sophisticated genetic analytic techniques, will dramatically deepen and expand our knowledge of disease mechanisms in psoriatic skin and bone over the next decade.

## REFERENCES


1. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
2. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology Oxford 2003;42:1460-8.
3. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. Rheumatology Oxford 2003;42:778-3.
4. Scarpa R, Ayala F, Caporaso N, Olivieri I. Psoriasis, psoriatic arthritis, or psoriatic disease? J Rheumatol 2006;33:210-2.
5. Ritchlin C. Psoriatic disease — from skin to bone. Nat Clin Pract Rheumatol 2007;3:698-706.
6. Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling [see comment]. Nat Med 2007;13:156-63.
7. Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med 2005;202:135-43.
8. Fitch E, Harper E, Skorcheva I, Kurtz SE, Blauvelt A. Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. Curr Rheumatol Rep 2007;9:461-7.
9. Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007;356:580-92.
10. Gottlieb A. Phase II, randomized, placebo-controlled study of CNTO 1275, a human interleukin-12/23 monoclonal antibody, in psoriatic arthritis, arthritis, and rheumatism. Arthritis Rheum 2008;54 (in press).
11. Clark RA, Kupper TS. Misbehaving macrophages in the pathogenesis of psoriasis [see comment]. J Clin Invest 2006;116:2084-7.
12. Zenz R, Eferl R, Kenner L, et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. Nature 2005;437:369-75.
13. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007;445:866-73.
14. 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.
15. Fearon U, Griosios K, Fraser A, et al. Angiopoietins, growth factors, and vascular morphology in early arthritis. J Rheumatol 2003;30:260-8.
16. Peng H, Usas A, Olshanski A, et al. VEGF improves, whereas sFlt1 inhibits, BMP2-induced bone formation and bone healing through modulation of angiogenesis. J Bone Miner Res 2005;20:2017-27.
17. Aldridge SE, Lennard TW, Williams JR, Birch MA. Vascular endothelial growth factor receptors in osteoclast differentiation and function. Biochem Biophys Res Commun 2005;335:793-8.
18. Kruithof E, Baeten D, De Rycke L, 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.
19. Canete JD, Santiago B, Cantaert T, et al. Ectopic lymphoid neogenesis in psoriatic arthritis. Ann Rheum Dis 2007;66:720-6.
20. 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.
21. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland CK, Looney RJ. Patterns of cytokine production in psoriatic synovium. J Rheumatol 1998;25:1544-52.
22. Benjamin M, McGonagle D. Histopathologic changes at "synovio-entheseal complexes" suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. Arthritis Rheum 2007;56:3601-9.
23. Anandarajah AP, Schwarz EM, Totterman S, et al. The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow edema in patients with psoriatic arthritis. Ann Rheum Dis 2008;67:296-301. Epub 2007 Oct 29
24. Olivieri I, Salvarani C, Cantini F, et al. Fast spin echo-T2-weighted sequences with fat saturation in dactylitis of spondylarthritis. No evidence of entheseal involvement of the flexor digitorum tendons. Arthritis Rheum 2002;46:2964-7.
25. Healy PJ, Groves C, Chandramohan M, Helliwell PS. MRI changes in psoriatic dactylitis — extent of pathology, relationship to tenderness and correlation with clinical indices. Rheumatology Oxford 2008;47:92-5.
26. McGonagle D, Tan AL, Benjamin M. The biomechanical link between skin and joint disease in psoriasis and psoriatic arthritis: what every dermatologist needs to know. Ann Rheum Dis 2008;67:1-4.

27. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423:337-42.
28. Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. J Clin Invest 2003;111:821-31.
29. Lories RJ, Derese I, Luyten FP. Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. J Clin Invest 2005;115:1571-9.
30. Lories RJ, Matthys P, de Vlam K, Derese I, Luyten FP. Ankylosing enthesitis, dactylitis, and onychoperiostitis in male DBA/1 mice: a model of psoriatic arthritis. Ann Rheum Dis 2004;63:595-8.
31. van der Heide D, Landewe RDM, Ory P, et al. Two-year etanercept therapy does not inhibit radiographic progression in patients with ankylosing spondylitis [abstract]. Ann Rheum Dis 2006;65:81.
32. van der Heide D, Landewe R, Deodar A, et al. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment not inhibited with infliximab [abstract]. Ann Rheum Dis 2007;66:85.