Translational Perspectives on Psoriatic Arthritis

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ABSTRACT. The term psoriatic disease encompasses the array of disorders (arthritis, inflammatory bowel disease, uveitis, obesity, metabolic syndrome, type II diabetes, and cardiovascular disease) that are associated with psoriasis. Psoriatic arthritis (PsA) is present in about 25% of patients with psoriasis; in most cases, the psoriasis precedes joint disease by about 10 years. Previous studies revealed that osteoclast precursors (OCP) are elevated in PsA and that the frequency of these circulating cells correlates with bone destruction. More recently OCP were found to be increased also in early rheumatoid arthritis and in 25% of psoriasis patients without arthritis. Bone marrow edema, observed on magnetic resonance imaging, in PsA represents infiltration of underlying marrow with inflammatory cells based on studies in transgenic tumor necrosis factor (TNF) arthritis murine models. Studies in the TNF transgenic mouse model also revealed that changes in lymph node volume precede joint flare. These translational studies point to potential biomarkers of arthritis in psoriasis patients and generate alternative hypotheses to explain the events that lead to arthritic flare. (J Rheumatol 2009;36:30-34; doi:10.3899/jrheum.090219)

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BONE MARROW EDEMA OSTEOCLAST PRECURSORS

Psoriasis, a disease first described in Leviticus, was recognized by Ferdinand von Hebra as a distinct disorder in 1841[1,2]. Over the past century and a half, our knowledge of this relatively common disease has deepened considerably, but recent literature indicates that we still have much to learn. For example, an analysis of the US National Health and Nutrition Examination Survey (NHANES) database revealed that psoriasis prevalence may be 3.4%, and that an additional 0.4% of the population may have undiagnosed psoriasis[3]. These estimates contrast sharply with the prevalence of 2.2%–2.6%, a widely quoted and generally accepted number. Another major advance is the understanding that psoriasis can be associated with an array of comorbidities. In fact, the term psoriatic disease has been applied to encompass the diversity of disorders[4,5] that are associated with psoriasis (Table 1), and many of these extracutaneous disorders are discussed in accompanying articles included in this supplement.

One of the most common manifestations observed in psoriasis patients is psoriatic arthritis (PsA), a condition that can involve not only the peripheral joints but also entheses, tendons, and the axial skeleton. In this review, we highlight how translational research approaches and clinical trials have revealed novel insights into disease pathogenesis. In particular, we will discuss cell populations that link psoriasis and arthritis, review studies that provide a framework to understand the mechanisms responsible for bone marrow edema manifested on magnetic resonance imaging (MRI), and present data that support a new paradigm for joint flare.

Table 1. Disorders associated with psoriasis (reviewed in Ritchlin[5]).

Psoriasis-associated Disorder
Musculoskeletal disease
Peripheral arthritis
Axial disease
Enthesitis
Dactylitis
Uveitis*
Duodenitis*
Inflammatory bowel disease
Obesity
Metabolic syndrome
Type 2 diabetes
Hypertension
Cardiovascular disease

* Associated primarily with psoriatic arthritis.

CELL POPULATIONS THAT LINK PSORIASIS AND INFLAMMATORY ARTHRITIS

Analysis of clinical trial demographics and registry data reveal that psoriasis precedes joint inflammation by about 10 years. One explanation for this observation is that inflammation begins in the skin, and that a second event occurs in a subset of patients (for example an environmental insult in a specific genetic background) that results in arthritis. Many models could be envisioned to

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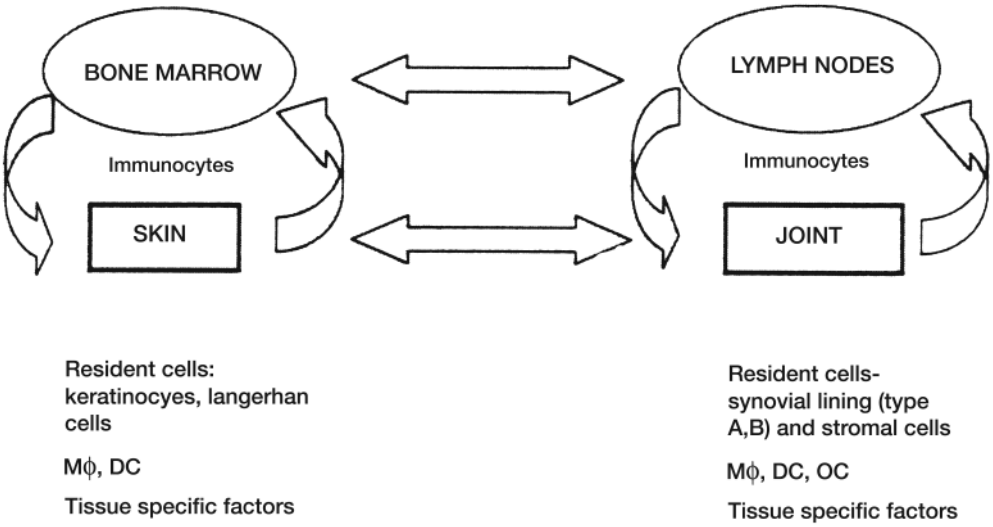

Figure 1. Pathways that link skin and joint inflammation in PsA. Events that begin in the skin or the bone marrow result in activation of T lymphocytes and monocytes (immunocytes) that circulate to the joint. A second event in the joint (e.g., trauma, activation of Toll receptors by pathogens) triggers synovitis, which is modulated by events in the draining lymph node and the bone marrow. Circulating and resident monocytes undergo differentiation to dendritic cells (DC) and macrophages (Mϕ) in the skin. Similar differentiation programs unfold in the joint but monocytes can also mature into osteoclasts (OC), an event not observed in the skin.

explain the mechanisms that link joint and skin disease in patients with PsA (Figure 1). One approach to understanding the link between skin and joint disease is to examine the cellular populations that have been implicated in inflammation at both sites. The major immune cells that play a central role in psoriasis and PsA are T cells and monocytes, although a prominent mouse model discussed below provided evidence for the potential contribution of keratinocytes.

T lymphocytes. Immunohistochemical studies and clinical trials have underscored a central role for the T lymphocyte in the pathogenesis of psoriasis[6]. It has been known for some time that CD4+ cells infiltrate the dermis and CD8+ cells are found in the epidermis. From a clinical trial perspective, anti–T cell therapies including cyclosporine, alefacept (LFA3–Ig), and efalizumab (anti–CD11a) have been effective in psoriasis although in the case of the latter 2 agents, efficacy is considerably less compared to anti-tumor necrosis factor (TNF) therapies[7]. Initial studies supported a major role for Th1 cells in the pathogenesis of psoriasis, but more recent work has demonstrated a major contribution from Th17 cells[8] (Table 2). Perhaps the most exciting data come from clinical trials with ustekinumab, an antibody to the P40 subunit, present in both interleukin 12 (IL–12) and IL–23, which has demonstrated high efficacy in moderate to severe psoriasis[9].

The importance of Th17 cells in psoriatic joint inflammation has not been formally established. Certainly, this subset is of critical importance in T cell-mediated osteoclastogenesis in animal models of arthritis and in rheumatoid synovium[10], but the direct relevance of this pathway to PsA has not been demonstrated. In phase IIb PsA trials, neither efalizumab nor alefacept was particularly effective for treatment of PsA[11,12]. A phase IIb clinical trial with ustekinumab did show efficacy in PsA, although the American College of Rheumatology response measures were lower than those observed with the anti-TNF agents, and radiographic endpoints were not examined[13]. It will be interesting to compare the efficacy of another anti-T cell agent, abatacept [CTLA4 immunoglobulin (Ig) construct] with ustekinumab when the trial results with this molecule become available.

Monocytes. Monocytes can differentiate into macrophages, osteoclasts, Langerhans cells, or dendritic cells in response to cytokines and/or other signals in the microenvironment[14]. Monocytes were required in 2 distinct animal models of psoriasis, and it is now apparent that a number of monocyte subsets are greatly expanded in psoriatic skin[15]. In pathologic analyses of entheseal tissues, monocytes were the principal cells identified in the fibrocartilage[16]. Monocytes are also present in the synovial lining of psoriatic joints, and they infiltrate the subsynovial lining. An increased frequency of circulating osteoclast precursors (OCP) was identified in the circulation and synovial tissues of patients with PsA[17]. The OCP numbers dropped rapidly after treatment with TNF antagonists[18].

In additional studies, we demonstrated that OCP are also elevated in the circulation of patients with early RA and a subset of psoriasis patients without arthritis, an unanticipated finding[19]. In patients with Crohn's disease,

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Table 2. Evidence for the involvement of the interleukin 23 (IL–23) / T helper 17 (Th17) pathway in psoriasis (reviewed in Fitch, et al[8]).

Animal models

- Overexpression of p40, a subunit present in IL-12 and IL-23, in basal keratinocytes induces inflammatory skin disease
- Injection of recombinant IL-23 into normal skin resulted in a psoriasiform phenotype
- IL-17A levels are elevated in psoriasiform skin compared to nonlesional skin
- IL-22, induced by IL-17, promotes keratinocyte hyperproliferation and is overexpressed in psoriatic skin
- IL-22 knockout mice do not develop keratinocyte hyperproliferation

Psoriasis in humans

- IL-23 is highly expressed by dendritic cells in psoriatic plaques but not normal skin
- Increased Th17 cytokine mRNA levels for IL-23 subunits, IL-12/23p40 and IL-23p19, are present in psoriasis
- Cells producing IL-17 are present in psoriatic plaques
- Antibody to the p40 subunit is a highly effective treatment for psoriasis

ankylosing spondylitis and in healthy controls dendritic cell precursors but not OCP were increased in the circulation. These findings support the concept that monocyte effector cells differ among the various immune-mediated disorders, and this heterogeneity may partly explain the diverse phenotypes of these diseases despite the fact that they are all associated with increased production of TNF.

Keratinocytes. The role of keratinocytes in psoriasis is currently a matter of debate. Recent emphasis has centered on the Th17 immune response orchestrated by T cell cytokines, particularly IL–22, which stimulates keratinocyte proliferation. It is well known, however, that keratinocytes can release an array of cytokines that exert effects on neighboring cell populations[20]. The recent demonstration that LL37, an antimicrobial peptide overexpressed in psoriasis[21], exerts anti-apoptotic effects on keratinocytes may provide an additional mechanism responsible for the hyperproliferation phenotype.

One of the most intriguing findings in regards to a pathway linking skin and joint inflammation was the demonstration that a targeted deletion of keratinocyte *Junb* and *c-jun*, components of the activator protein (AP) 1 transcription factor, resulted in a psoriasiform phenotype followed by an erosive inflammatory arthritis and periostitis in all the animals[22]. The mechanistic connection between the altered keratinocyte phenotype and murine arthritis with many features of human PsA remains a puzzle, but hopefully additional studies in this model will provide insights into the mechanisms that result in joint inflammation after the development of psoriasis.

BONE MARROW EDEMA

A striking feature reported in PsA hand and knee joints is diffuse bone marrow edema (BME)[23]. In RA, BME is usually not as extensive, but it has been recognized as a pre erosive lesion[24]. Moreover, studies of rheumatoid metacarpophalangeal joints and zygapophyseal and sacroiliac joints from patients with ankylosing spondylitis revealed a correlation between histopathologic findings and MRI scans of bone marrow edema lesions[25,26]. The BME does improve considerably after treatment with an anti TNF agent, although the rapidity of this response is highly variable[18].

To clarify the etiology of BME, we imaged the arthritic joints of TNF transgenic mice with gadolinium MRI[27]. These mice develop a destructive inflammatory arthritis at about week 6 to 8. The mice with knee inflammation demonstrated prominent BME with contrast enhancement, and this finding was noted in bone adjacent to both involved and uninvolved joints (Figure 2). In contrast, BME was not noted in the nonarthritic littermates without the transgene. Histopathologic analysis of the marrow showed a transition from a normocellular yellow to a hypercellular red marrow that was packed with CD11b+ monocytes, a finding not detected in the littermates without the transgene. The BME lessened significantly following treatment with an anti-TNF agent and the marrow changed from a cellular laden red marrow to a yellow marrow as seen in the controls. Thus, our data suggest that BME reflects expansion of monocytes in the marrow, where they can differentiate into dendritic cells, osteoclasts, or macrophages depending on the signals that are present in the surrounding environment.

RELATIONSHIP BETWEEN JOINT FLARE AND DRAINING LYMPH NODE

A consistent finding on the gadolinium MRI studies of the TNF transgenic mice described above was the presence of enlarged popliteal lymph nodes draining joints with inflammatory synovitis[28]. In parallel studies, these mice produce high levels of vascular endothelial growth factor-C, a factor that can induce lymphangiogenesis[29]. Interestingly, the popliteal lymph nodes increased in size after 2.5 months of age, a time when TNF serum levels increase and alteration in peripheral blood mononuclear cell populations takes place. The increased lymph node

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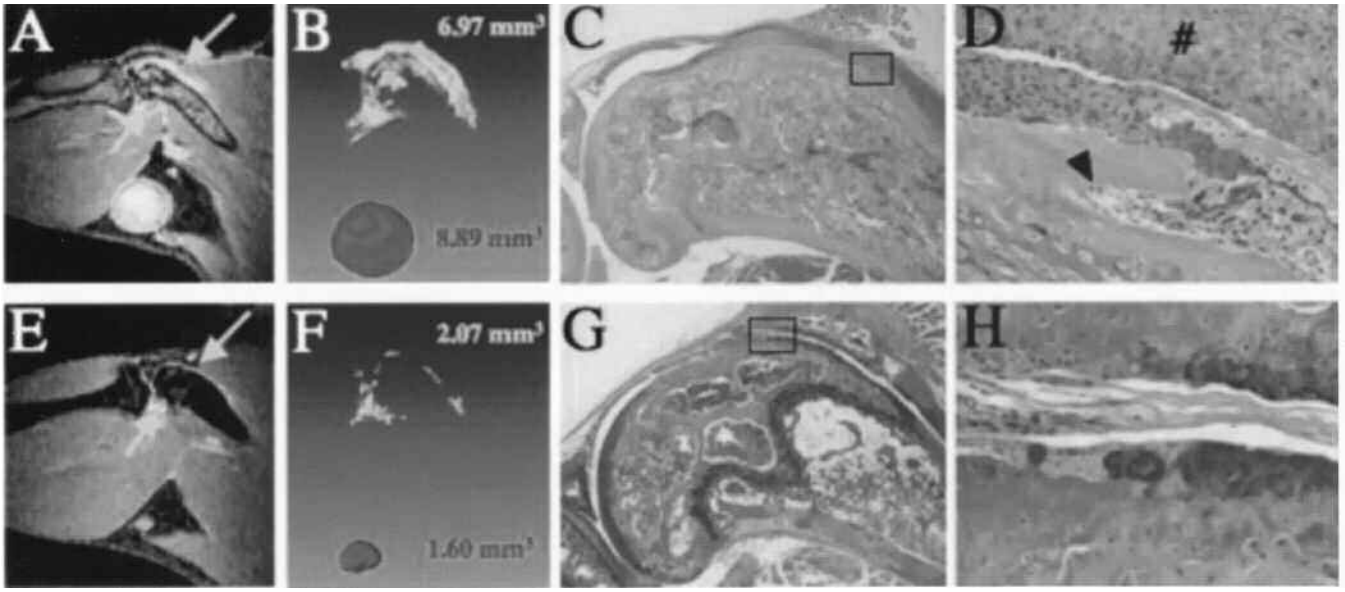

Figure 2. Lymph node dynamics and joint inflammation. Radiology and histology of a knee joint from a representative 5-month-old tumor necrosis factor–transgenic (TNF–Tg) mouse (panels ABD) and its wild type (WT) littermate (panels EBH). Post contrast magnetic resonance images show enhancing synovium (arrows). Bone marrow edema is present in the TNF–Tg mouse, as indicated by the high signal intensity in the bone marrow space (panel A), but is absent in the WT mouse (panel E). Corresponding 3 dimensional reconstructions and calculated synovial (white) and popliteal lymph node (black) volumes (panels B and F) are also shown. Differences in these quantitative imaging biomarkers are validated in the corresponding orange GBAlcian blue–stained histology sections (4× original magnification; panels C and G); boxed areas of C and G are shown at 200× original magnification (D and H, respectively). The TNF –Tg mouse displays thickened synovial lining (#) and infiltration into subchondral bone (arrowhead). Panels I and J: disease progression in TNF–Tg and WT mice as a function of synovial volume (I) and lymph node volume (J). From Proulx ST, et al. Arthritis Rheum 2008;58:2019-29; with permission.

volume was associated with pronounced synovitis (Figure 2) and both of these variables decreased following anti-TNF therapy.

In mice with established arthritis, we noted that just prior to the onset of joint inflammation, the lymph node collapses and demonstrates increased contrast enhancement. Current studies are under way to examine the mechanisms that lead to the collapse of the node and the subsequent synovitis. One potential explanation is that cells, chemokines, and cytokines that sustain joint inflammation cannot exit from the joint, resulting in persistent synovial inflammation. Additional studies are under way to better understand the relationship between synovitis and the draining node. Together, these data suggest that joint flare is precipitated by altered lymphatic flow in murine arthritis. We are now analyzing the relationship between lymph node volume and synovitis in PsA and RA using Doppler ultrasound and MRI. These studies raise the possibility that imaging biomarkers have the potential to anticipate joint flare in inflammatory arthritis.

CONCLUSION

The studies outlined above demonstrate that the skin and joint in PsA share common inflammatory pathways. One particularly intriguing immune mechanism, the Th17 response, plays a dominant role in psoriasis but the importance of this pathway in PsA remains to be determined. The understanding that the BME MRI signal is provided in part by CD11b+ monocytes underscores the importance of the underlying marrow and altered myelopoiesis in the process of joint inflammation. Lastly, compelling data point to impaired lymphatic drainage as a potential mechanism in joint flare, although additional studies are needed in humans to determine the applicability of these findings to rheumatoid and psoriatic joint disease.

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