Synovitis in Psoriatic Arthritis: Immunohistochemistry, Comparisons With Rheumatoid Arthritis, and Effects of Therapy

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Abstract Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis that affects the peripheral joints, spine, and entheses. Most patients with PsA present with peripheral synovitis of the oligoarticular or polyarticular subtype. As one of the targets of this disease, studies on the synovium may provide insight into the mechanisms involved in this condition. Key findings from the available studies comparing synovial tissue of PsA and rheumatoid arthritis patients are discussed in this review. Also, changes in the synovial infiltrate, expression of proinflammatory cytokines and adhesion molecules, and vascularity in synovial tissue after treatment with various medications are addressed. Finally, a model for proof-of-principle study design using serial synovial biopsies is described, which could be used to predict clinical (in)efficacy in early clinical trial design in PsA.

Keywords Psoriatic arthritis · Synovium · Immunohistochemistry · Synovitis · Rheumatoid arthritis · Therapy · Treatment

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology that is associated with psoriasis. It can affect the peripheral joints, spine, and entheses. Belonging to the spondyloarthritis (SpA) family, PsA is distinguished from rheumatoid arthritis (RA), the most common inflammatory arthropathy, by infrequent seropositivity for rheumatoid factor and anti-citrullinated peptide antibodies, as well as the presence of distinctive clinical features. These features include the involvement of the distal interphalangeal (DIP) joints; an asymmetric distribution of the inflamed joints; the presence of dactylitis (inflammation of an entire digit [finger or toe]), enthesitis, sacroiliitis, or spinal involvement; and, of course, psoriasis. Radiological changes in PsA can present as erosive lesions or osteolysis but also as periarticular new bone formation. Joint destruction is often progressive, with almost 50% of PsA patients from an early arthritis clinic showing radiological damage 2 years after first presentation [1], and the the degree of radiological damage in PsA is comparable to RA [2].

More than 35 years ago, Moll and Wright [3] described a large case series of patients with PsA on which they based a subdivision into five clinical phenotypes: polyarthritis, asymmetrical oligoarthritis, spondylitis, predominant DIP arthritis, and arthritis mutilans. This clinical heterogeneity and the difficulty classifying patients with PsA correctly has been a major concern over the years and may have hampered our pathophysiologic understanding of the disease. Most patients of the original cohort of Moll and Wright [3] were classified in the oligoarticular subgroup (70%), and a minority in the other subgroups. In later cohorts, polyarticular PsA was usually the largest subgroup, at about 60% of the patients, as was put forward by Helliwell and Taylor [4]. The reasons for this discrepancy are not completely clear, but some have argued that these later cohorts may have included patients with seronegative RA with coincident psoriasis [4]. Moreover, the disease pattern in an individual patient can change over time as a result of evolution of the disease or treatment [5]. Recently, data from a large cohort were prospectively

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collected in the CASPAR (Classification Criteria for Psoriatic Arthritis) study (588 PsA patients, 525 controls with other inflammatory diseases, 70% of whom had RA) with the aim of constructing new classification criteria from patient-derived data [6]. Interestingly, when the collected data from this large cohort were investigated, it turned out that the patients with polyarticular PsA resembled those with oligoarticular PsA in several ways, much more so than they resembled patients with RA [7]. Thus, misclassification of seronegative RA as polyarticular PsA does not seem to be a major problem.

It has been hypothesized by some authors that PsA is mainly an entheseal disease [8]. Anatomically linking mechanical stress (entheses) to immunologically active tissue (synovium), the concept of the synovioenthesial complex (SEC) supports this hypothesis [9, 10•, 11•]. Imaging studies have suggested that tendon and ligament insertion points to bone (entheses) are commonly subject to microdamage. Although the normal enthesis is avascular in its fibrocartilaginous region, micro-damage to the entheses is associated with local cytokine release, tissue repair responses, and vessel ingrowth, which may evolve into subsequent inflammation. It also has been suggested that adjuvant molecules derived from bacteria may be preferentially deposited at the site of the SEC; hence, microdamage and propensity for bacterial molecule deposition in the context of certain genetic factors may lead to the characteristic inflammatory changes seen at the entheses in SpA, including PsA [11•]. Furthermore, because the nail is functionally integrated with the SEC associated with the DIP joints, this model provides a rationale for the combination of DIP arthritis and nail involvement that is often observed in PsA patients [9].

Whereas this model may provide a good explanation for entheseal-related inflammation and arthritis (eg, as observed in the DIP joints), it does not where there is no close relationship between the inflamed joints and enthesis or skin. As reported above, most patients with PsA in the major cohorts seem to have oligoarticular or polyarticular peripheral synovitis. Because the synovium is a primary site of inflammation in this disease, there has been increasing interest in studies of the synovial tissue from patients with RA or PsA. In addition to the use of synovial biopsies for diagnostic purposes [12, 13] and pathogenetic studies [14, 15], serial synovial biopsies could be used to evaluate the effects of treatments [16•, 17]. This approach may have merit in screening for potential efficacy during early drug development.

Immunohistochemistry of Synovial Tissue in Psoriatic Arthritis Compared With Rheumatoid Arthritis

Several studies have characterized the synovium in PsA compared with RA [15, 18–25], with variable results. In general, it is good to realize that there are large differences in synovial infiltrate and expression of proteins on an individual patient level, so all findings reported are on the group level. Confounding factors, such as differences in the use of antirheumatic drugs between both groups and the selection of patients, may have influenced the results of some studies. Also, that synovial tissue was collected in different ways (eg, arthroscopic or needle biopsies vs tissue obtained during joint replacement surgery) may account for some of the observed differences.

It has been suggested by several studies that the PsA synovium is characterized by less pronounced lining layer hyperplasia and fewer monocytes/macrophages than are seen in RA [18, 23]. One group found fewer T and B cells in SpA synovium [22], while others reported fewer T cells in PsA synovial tissue in comparison with RA [15, 23, 25]. This is remarkable because psoriasis and PsA are thought of as T-cell–driven conditions. The lower number of T cells in PsA synovium does not mean, however, that these cells are not important in the pathogenesis, as a subset of specific T cells may be sufficient to promote the inflammatory process, and regulatory T cells may have anti-inflammatory effects. As a matter of fact, T cells are likely to be involved in the pathogenesis of psoriasis and PsA [26]. The infiltrate in lesional psoriasis skin mainly consists of activated T cells. In the synovial infiltrate, T cells are present among other cell types, and oligoclonal T-cell expansions have been demonstrated in both skin and synovium [27], suggesting that an antigen-driven T-cell response could be promoting ongoing inflammation. For T-cell migration to the skin, the chemokine receptor CCR4 is necessary. Interestingly, the ligand for CCR4, macrophage-derived chemokine (MDC, also known as CCL22) was recently demonstrated within the synovial membrane and in high concentrations in the synovial fluid of RA and PsA patients [28]. The presence of MDC facilitates migration of CCR4-expressing memory cells into the inflamed joint, supporting the notion that MDC/CCR4 could play a role in attracting skin-specific memory T cells to the synovial compartment. The role of T cells is further underlined in psoriasis and PsA by the beneficial effect of therapies against T cells, such as cyclosporin A and alefacept [29–31]. Interestingly, a recently published paper on the effects of abatacept, a selective inhibitor of T-cell activation via competitive binding to CD80 or CD86, in PsA demonstrated the efficacy of using abatacept on joints, but a less strong effect on skin [32]. Interleukin (IL)-17–producing T-helper cells (Th17 cells) are a recently recognized effector T-lymphocyte population playing a role in chronic inflammatory conditions. IL-23 is highly expressed in psoriatic plaques [33], and this cytokine is responsible for stimulating Th17 cells that produce IL-17, as well as tumor necrosis factor (TNF)-α, IL-21, and IL-22 [34•]. An important role for Th17 cells has been demonstrated in murine arthritis models [35]. The exact role of Th17 cells in

PsA is not clear at this moment, but the Th17-related cytokines IL-17 and IL-23 are expressed in the joints of PsA and RA patients [36]. Clinical studies targeting the Th17 axis are currently under way to establish the validity of this therapeutic approach in patients with PsA. Moreover, blocking the p40 subunit, which is shared by IL-12 and IL-23, leads to amelioration of arthritis in PsA [37].

Lymphoid aggregates of variable size and organization level are not specific for RA but were observed in the synovial biopsies of the majority of 27 PsA patients as well [38]. Clear T-cell/B-cell segregation could be observed, especially in the larger lymphoid aggregates, with many features of lymphoid neogenesis present. Interestingly, a complete response to treatment was associated with a regression of the lymphoid aggregates.

Increased vascularity has been reported in both psoriatic skin lesions and synovial tissue. In the dermis of psoriatic skin, an abundance of dilated and tortuous blood vessels is present [39]. Several authors have reported that PsA synovium is characterized by an increase in macroscopically tortuous blood vessels, and this is more pronounced in—but not exclusive to—PsA than it is in RA synovium [18–20, 40]. Consistent with the vascular abnormalities observed, overexpression of vascular endothelial growth factor, which is involved in angiogenesis, has been reported in immunohistochemical analyses of both psoriatic skin [41] and PsA synovial tissue, together with other vascular markers such as von Willebrand's factor, integrin $\alpha V\beta 3$, and basic fibroblast growth factor [15, 20, 21]. Upregulation of vascular adhesion molecule 1, intercellular adhesion molecule 1 (ICAM-1), and E-selectin has been reported in PsA synovium [15, 18]. These adhesion molecules are involved in leukocyte adhesion and penetration through the endothelium at sites of inflammation. Interestingly, E-selectin appears to be upregulated in the skin compared with the PsA synovial membrane, and cutaneous lymphocyte–associated antigen is preferentially expressed on leukocytes "homing" to psoriasis lesions, but not to the PsA synovium [42].

A striking feature of PsA synovium is the abundant overexpression of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-18 [15]. Another interesting proinflammatory cytokine of the TNF ligand superfamily is TNF-like weak inducer of apoptosis (TWEAK), a pleiotropic cytokine that probably plays a physiologic role in tissue repair via its receptor, Fn14, which is highly induced after injury. The TWEAK/Fn14 pathway promotes local chemokine and cytokine production, resulting in additional infiltration of proinflammatory cells, and facilitates angiogenesis and the proliferation of progenitor cells needed for tissue repair. TWEAK and Fn14 seem to be permanently activated in chronic inflammation, however, and the mechanisms that are beneficial for tissue repair can then contribute to persistent inflammation. TWEAK blockade previously has been observed to exert a beneficial effect in an animal model of arthritis. The presence of TWEAK and Fn14 was recently demonstrated in the inflamed synovium of patients with RA and PsA [43]. This raises the possibility that blocking TWEAK/Fn14 signaling could be of therapeutic benefit in inflammatory arthritis.

Another new field of interest is the role of the nervous system in inflammatory arthritis. Considerable evidence indicates that the nervous system can modulate immune responses in several immune-mediated diseases. The cholinergic anti-inflammatory pathway is characterized by neural regulation of systemic inflammation, mediated by the vagus nerve and specific cholinergic stimulation of the nicotinic $\alpha 7$ acetylcholine receptor (α7nAChR) on immune cells. Using immunohistochemistry and double immunofluorescence microscopy, the expression of α7nAChR-positive cells in synovial tissue from patients with RA and PsA was recently demonstrated. The α7nAChR-positive cells were identified as primarily macrophages and fibroblasts in the intimal lining layer and in blood vessels [44•]. This illustrates the potential role of α7nAChR and cholinergic mechanisms controlling arthritis. Another pivotal mediator of neurogenic inflammation is nerve growth factor (NGF). NGF is found in serum, synovial fluid, and cerebrospinal fluid and is highly expressed in inflammatory and degenerative rheumatic diseases. NGF concentrations correlate with the extent of inflammation and clinical disease activity. NGF levels are significantly higher in RA as compared with osteoarthritis [45•]. These findings support the possibility of therapeutic modulation of neurogenic inflammation by intervening with NGF or α7nAChR as a potential anti-inflammatory therapeutic strategy in arthritis.

Taken together, although RA and PsA are clinically separate diseases with different etiologies, the synovial infiltrate in both conditions shows more similarities than differences. On the group level, PsA synovium may have less pronounced intimal lining layer hyperplasia and fewer synovial T cells compared with RA, but the available studies comparing synovial tissue are relatively small and may be biased by several confounding factors. More importantly, there is overexpression of many proinflammatory cytokines in the synovial tissue of active RA and PsA, including TNF-α and IL-6. Future studies will show whether interventions in newly discovered pathways, such as the proinflammatory cytokine TWEAK, or neurogenic inflammation could also be of therapeutic benefit to patients with inflammatory arthritis.

Effects of Therapy on Psoriatic Arthritis Synovium

A few studies have been conducted in PsA to evaluate synovial changes after therapy [46–51]. Open-label treatment of 10 PsA patients with methotrexate resulted in a decrease in

T cells and macrophages, as well as reduced expression of IL-8, E-selectin, ICAM-1, and matrix metalloproteinase 3 (MMP-3) after 6 to 12 months [46]. In another study, 52 SpA patients with peripheral arthritis were included (16 of whom were classified as PsA [47]) and underwent synovial biopsy at baseline and 12 weeks following different treatment regimens (infliximab, etanercept, sulfasalazine, or no disease-modifying antirheumatic drug). Clinical improvement in this study correlated with a decrease in CD163^{+} macrophages, polymorphonuclear cells, and MMP-3 expression. Two other smaller studies demonstrated a significant reduction in the expression of the adhesion molecule ICAM-1 and the vascular markers von Willebrand's factor and $\alpha V\beta$ in 11 and 9 PsA patients, respectively, treated with infliximab [50, 51]. A study on the effects of alefacept revealed a significant decrease in T-cell numbers after 4 weeks of treatment and a significant reduction in both T cells and macrophages after 12 weeks of treatment in 11 PsA patients [48]. Finally, experimental treatment with IL-10 subcutaneously for 4 weeks in 28 patients resulted in decreased T-cell and macrophage infiltration in the synovium [52].

From these studies, it can be concluded that successful treatment in the long run always leads to deactivation of endothelium, reduced vascularity, and a reduction in infiltrating immune cells. Identical to the approach that we have previously described in RA patients [53], we designed a randomized, placebo-controlled study to determine which early changes in synovial markers are associated with active treatment on the group level [16•]. For this purpose, 24 patients with active PsA were treated with adalimumab or matched placebo at baseline and day 15. Synovial biopsies were taken before and after 4 weeks of treatment. We observed (trends toward) reduced numbers of macrophages and macrophage subsets after active treatment, but a statistically significant effect of treatment was only observed for the reduction in CD3^{+} T cells and the expression of MMP-13 using analysis of covariance. In addition, clinical improvement was strongly correlated with a decrease in CD3^{+} T cells, CD4^{+} cells, and MRP8^{+}, as well as MMP-13 and MMP-3. Thus, particularly the reduction of T cells was correlated with effective therapy and clinical improvement, which was confirmed by another recently published study [54]. This underscores the importance of T cells in the pathogenesis of PsA [26], consistent with the observation that specific targeting of T cells may result in clinical benefit in this disease [31, 48, 55].

Model for Proof-of-Concept Study Design

The rise in newly discovered drugs and potential therapeutic targets currently under investigation will have consequences for the way potential novel therapies are tested in clinical trials. It will be increasingly difficult to include large numbers of patients with active disease in large, placebo-controlled trials because of the growing number of compounds to be tested and the fact that effective treatment is now available for many patients. Therefore, in an early stage of drug development, it could be useful to perform intensive trials with a small number of patients in which large amounts of data are collected to study the effects of the compound tested. The identification of biomarkers that could be used for prediction of the clinical response to treatment and evaluation of biological effects of potential novel therapies is of the utmost importance for this development. Because synovial inflammation is one of the key manifestations of PsA, we and others have focused on the identification of synovial biomarkers [16•, 54]. Sensitive synovial biomarkers could be used as predictors of clinical effects in small proof-of-principle trials for selection purposes, similar to the approach used in RA [17]. Our study indicates that the reduction in the number of CD3^{+} cells and the expression of MMP-13 may be candidate synovial biomarkers to screen for potentially active drugs in small proof-of-concept studies of short duration. As arthroscopic synovial biopsy is not available in all centers, ultrasound-guided biopsy may be another approach [56]. Alternatively, the identification of relevant soluble biomarkers that can be measured in blood would further facilitate the feasibility of small high-density-of-data clinical trials that are conducted to screen for efficacy. We propose that analysis of serial biopsies may be used as a screening method to test new compounds requiring relatively small numbers of participants. The absence of changes in the synovial tissue after treatment on the group level would suggest that the therapy is probably not effective.

Conclusions

Most patients with PsA present with peripheral synovitis of the oligoarticular or polyarticular subtype. Therefore, the synovium is, as a primary site of inflammation in this disease, an important tissue to study. Several descriptive immunohistochemical studies of the synovial tissue of patients with RA and PsA show more similarities than differences between the two inflammatory arthropathies, which could point to the activation of common final pathways and similarities in synovial infiltrate in established disease. On the group level, PsA synovium might have less pronounced intimal lining layer hyperplasia, more pronounced vascularity, and fewer synovial T cells compared with RA, but the available studies comparing synovial tissue are relatively small and may be biased by several confounding factors. Effective treatment of patients with PsA in the long run

will lead to a resolution in synovial inflammation, including deactivation of endothelium, fewer blood vessels, and a reduction in infiltrating immune cells. Two recent studies demonstrated that an early reduction in synovial T cells after TNF blocking therapy correlated with clinical improvement. We propose a model for early proof-of-concept studies in which sensitive (synovial) biomarkers are used as predictors of clinical effect for selection purposes during early drug development. A reduction in the number of $CD3^+$ cells and the expression of MMP-13 are interesting candidate synovial biomarkers to screen for potentially active drugs in small proof-of-principle studies of short duration, alongside clinical outcome and imaging measures.

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