

## Emerging Biomarkers in Psoriatic Arthritis

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**ABSTRACT**

Psoriasis is an immune-mediated skin disease which affects 2-4% of the worldwide population. Approximately 20-30% of patients with psoriasis develop psoriatic arthritis (PsA), a frequently destructive and disabling condition. Since skin manifestations precede joint symptoms in nearly all PsA patients, identification of biomarkers for early prediction of joint damage is an important clinical need. Because not all PsA patients respond to treatment in the same fashion, identification of biomarkers capable of predicting therapeutic response is also imperative. Here, we review existing literature and discuss current investigations to identify potential biomarkers for PsA disease activity, with particular emphasis on microRNAs as novel markers of interest. Serum (soluble) biomarkers, peripheral osteoclast-precursor (OCP) as cellular biomarkers, and genetic loci associated with skin and joint disease are also reviewed.

Key Words: Biomarkers, Psoriatic Arthritis, microRNAs

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## Introduction

Advances in our understanding of immune-mediated inflammatory diseases have fueled the development of targeted therapies that alter the course of disease progression, imparting significant beneficial effects on prevention of disease-associated morbidity. However, the pathophysiology of many autoimmune skin and joint diseases remains an enigma. This frequently results in significant morbidity and mortality, whether from the condition itself or due to the treatment.

Psoriasis is a common immune-mediated skin disease, affecting 2-4% of the worldwide population, and has been associated with various co-morbidities, including cardiovascular disease, metabolic syndrome, cancer, and depression (1, 2). Genetic, immunologic, and environmental factors are postulated to contribute to disease phenotype. Although traditionally considered a Th1-mediated disease, recent advances have identified a role for Th17 cells in psoriasis (3).

Approximately 20-30% of patients with psoriasis develop psoriatic arthritis (PsA), but little is known about the immunopathogenesis of these diseases and prognostic factors that lead to their development (4). Skin lesions of psoriasis are generally observed 5-10 years prior to the development of PsA, although joint disease may present first or may never develop (5). PsA can be divided into five clinical subsets, as first described by Moll and Wright in 1973: spondyloarthritis, distal arthritis, oligoarthritis, symmetrical polyarthropathy similar to rheumatoid arthritis (RA), and arthritis mutilans. Patients may demonstrate transitions between these subsets throughout the course of the disease. Early diagnosis and intervention are key to preventing permanent joint deformation. However, no standardized method exists for early detection of PsA, and many patients with psoriasis also have undiagnosed PsA (6). Furthermore, psoriasis and PsA have been associated with various co-morbidities, including cardiovascular disease, metabolic syndrome, cancer, and depression; thus, interventions that beneficially impact disease may also significantly affect morbidity and mortality (1, 2).

Biomarkers, or measurable biological indicators of disease activity, may be used to predict future disease, measure current disease activity, or quantify therapeutic efficacy (7). For example, in rheumatoid arthritis, rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) are utilized to diagnose and prognosticate disease. Ideally, biomarkers should be easy to obtain, sensitive, specific, reproducible, and prognostic. Broadly, they can be classified into soluble biomarkers, cellular biomarkers, and genetic biomarkers. Biomarkers in psoriatic arthritis have been identified as a relevant research gap, and the

development of cohort and longitudinal studies have been proposed to address this need (8). Currently, there are no validated biomarkers to predict the progression of PsA or prognosticate response to available therapies. We review ongoing investigations to identify potential target biomarkers for PsA and discuss future directions for exploration.

### **Soluble biomarkers**

Due to ease of accessibility, circulating biomarkers obtained from peripheral blood are optimal indicators of disease activity. In psoriasis, they are broadly categorized into non-specific inflammatory markers, indicators of metabolic processes, and immunologic markers. Elevated levels of non-specific inflammatory markers, including haptoglobin, C-reactive protein (CRP), and P-selectin, and pro-inflammatory cytokines, such as interleukin (IL)-6, IL-8, IL-12, IFN-gamma, and TNF-alpha, have been identified in serum of patients with psoriasis (9). In addition, circulating Th1, Th17, and Th22 cells and increased expression of IL23R in T cells have been reported (10, 11). Serum adiponectin, a cytokine that improves insulin resistance, is decreased in psoriatic patients, while serum lipocalin, leptin, and resistin are increased (12-14). Adiponectin has also been found to be strongly associated with PsA and TNF-alpha therapy (12). These metabolic markers may provide clues to the link between psoriasis, metabolic syndrome, and cardiovascular disease.

In psoriatic arthritis, no single validated screening test exists for the detection of joint involvement, but several studies have identified potential soluble biomarkers relating to inflammation and cartilage or bone metabolism. Serum IL-6, a pro-inflammatory cytokine produced by lymphoid and other cells, has been found in greater quantity in patients with PsA versus skin disease alone, correlating with number of joints affected.(15) However, this cytokine may also be up-regulated by other inflammatory processes, and therefore is not a specific screening tool. Rather, a designated panel of soluble biomarkers may best differentiate patients with psoriatic joint involvement from those with only cutaneous lesions. In a Canadian cohort, Chandran et al identified osteoprotegerin (OPG), high sensitivity C-reactive protein (hs-CRP), cartilage oligomeric matrix protein (COMP), matrix metalloproteinase 3 (MMP-3), and the ratio of C-propeptide of Type II collagen (CPII) to collagen fragment neoepitopes Col2-3/4 (C2C ratio) in patients with PsA versus psoriasis alone (16). In another study, Ramonda et al identified MMP-3, hs-CRP, and vascular endothelial growth factor (VEGF) as potential screening tools for the detection of PsA (17).

In addition to serving as screening tools for psoriatic arthritis, soluble biomarkers may measure

disease activity by correlating with temporal changes in other clinical parameters such as radiographic change and response to therapy. Of the markers listed above, a reduction in MMP-3 was associated with response to TNF-alpha inhibitor therapy, suggesting its potential role in measuring disease activity (18). Candidate circulating markers of bone remodeling which may correlate with radiographic change include Dickkopf-1 (Dkk-1), cartilage oligomeric matrix protein (COMP), bone alkaline phosphatase, and macrophage-colony stimulating factor (M-CSF) (19). Higher concentrations of Dkk-1 and M-CSF were seen in patients with PsA, but their levels did not correlate with radiographic changes or number of affected joints.

### **Peripheral blood-derived osteoclast precursors (OCP) as cellular biomarkers for PsA**

Joint damage is carried out by synovial fibroblastoid cells that degrade cartilage through the release of metalloproteinases and osteoclasts (OC), which directly resorb bone. OC are multinucleated cells that arise from OCP or circulating CD14<sup>+</sup> monocytes through a differentiation process referred to as osteoclastogenesis (20). Myeloid-derived cells differentiate into osteoclasts in the presence of macrophage colony stimulating factor (M-CSF) and RANKL. RANK and colony stimulating factor 1 receptor (CSF-1R/c-fms) are both expressed on OCP cells which, upon stimulation with RANKL and M-CSF, develop into mature bone-resorbing cells (21). Activator protein (AP-1), a transcriptional regulator composed of members of the Fos and Jun families, is also required for osteoclast differentiation and has been implicated in PsA (22). Osteoclasts can be generated from RANKL-, RANK- or TRAF6-deficient mice, suggesting that RANKL-RANK-independent osteoclast differentiation pathways also exist (23).

Of particular interest in regards to PsA was the finding of an increased frequency of OCP in one-third of patients with psoriasis without arthritis and in the majority of PsA patients (24, 25). Intriguingly, monocytes circulating in the peripheral blood of PsA patients were able to generate OC in vitro in the absence of exogenous stimulation, a property distinct from OCP in healthy controls. Importantly, the frequency of OCP correlated with the extent of radiographic damage in a cohort of patients with established PsA(24).

The IL-23/IL-17 axis plays a critical role in osteoclastogenesis via a number of direct and indirect effects that both positively and negatively modulate osteoclast formation. IL-23-induced Th17 cell differentiation results in RANKL secretion and thus promotes osteoclastogenesis (26). IL-17 also acts on osteoblasts to secrete RANKL to further enhance bone resorption. IL-17 further modulates the expression of the osteoclast fusion protein, DC-STAMP (dendritic cell-specific transmembrane protein), a potential biomarker for early prognosis of PsA (27).

To date, there have been several reports characterizing the entity of osteoclast precursors, although whether there are specific monocytoid populations committed to differentiating exclusively into osteoclasts remains to be elucidated (28). Chiu et al found PsA patients have an elevated percentage of CD14<sup>+</sup>CD16<sup>+</sup> pro-inflammatory monocytes in the peripheral blood (29). Based on the observation of CD16 up-regulation in cells cultured in OC-promoting (M-CSF and RANKL) but not DC-promoting conditions (GM-CSF and IL-4), they further found OC arise from circulating CD16<sup>+</sup> monocytes in PsA, whereas OC were generated from the CD16<sup>-</sup> subset in healthy controls. Finally, they showed a positive correlation between the level of CD16 cell surface expression and the extent of bone resorption. These studies indicate that the major reservoir of OCP in PsA is CD16<sup>+</sup> cells, a finding that may catalyze the development of susceptibility biomarkers for arthritis in Ps patients and a treatment response marker in PsA patients with erosive arthritis. In considering all of these potential biomarkers, it should be noted that the majority are associated with ongoing disease activity/damage, which may be helpful in the diagnosis of arthritis and monitoring response to therapy. However, at this time, these biomarkers provide little insight in the prediction of arthritis prior to its onset, which is where the greatest potential impact on disease and future disability may be imparted.

### Genetic biomarkers for PsA

Genetic factors play a significant role in psoriasis, as initially reported by identification of *PSORS1* (psoriasis susceptibility-1) in family studies, and association with MHC (major histocompatibility complex) haplotypes in case-control studies (30, 31). The *HLA-Cw\*0602* allele has been well established as the *PSORS1* risk variant associated with early development of psoriasis with a family history of psoriatic disease in Caucasians (32). Genome-wide association studies (GWAS) have led to candidate gene identification in psoriatic disease (33). Outside the MHC, novel genetic loci have been associated with psoriasis and PsA; these include the SNP rs4795067 encoding *NOS2*, rs10782001 encoding *FBXL19*, and rs12586317 encoding *PSMA6-NFKBIA* (34). In particular, the SNP rs10782001, which encodes the *FBXL19* gene and activates NF-kappaB, is more strongly associated with psoriatic joint disease than cutaneous psoriasis. The SNPs rs20541 and rs1800925, both encoding IL-13, have been associated with increased susceptibility to PsA in Caucasian patients (35), while rs1800629 has been reported in cases of early-onset psoriasis and joint erosions in PsA (36). Finally, a locus on chromosome 4q27 expressing the interleukin 2 (IL-2) and IL-21 genes was found to be linked with PsA and other autoimmune diseases, including Type 1 diabetes mellitus, rheumatoid arthritis, Grave's disease, and Celiac disease (37).

In addition to determining genetic risk, SNPs have been linked with therapeutic efficacy and may serve as markers to predict treatment response. Polymorphisms in the tumor necrosis factor (TNF), TNF receptor superfamily 1B (TNFR1B), and TNF alpha-induced protein 2 gene (TNFAIP3) have been associated with response to anti-TNF therapy (38, 39). The SNP in the promoter of the *TNF* gene at position 857T was found to be a risk factor for PsA independent of the *PSORS1* allele (36). Carriers of the minor allele of *TNF-308* polymorphism have also been reported to experience an aggressive course of PsA (40). SNPs mapping to the interleukin-23 receptor (IL-23R) and IL-12beta gene confer susceptibility to both cutaneous psoriasis and PsA, which supports the rationale for treatment with ustekinumab, a monoclonal antibody against IL-12 and IL-23, in these conditions (41).

Genetic biomarkers utilize single nucleotide polymorphisms (SNPs) within genome-wide association studies (GWAS) to identify genetic susceptibility. However, the predictive potential for individual genes in psoriatic disease is minimal, and weighted genetic risk scores (wGRS) based on known psoriasis loci currently have limited efficacy as biomarkers (42). Chen et al attempted to improve predictive ability by combining 10 psoriasis risk loci into a simple risk alleles count (cGRS) or weighted genetic risk score (wGRS) (43). The wGRS was able to capture more risk than individual SNPs and was linked to early disease onset and family history of psoriatic disease. In spite of these findings, analysis of multiple genetic loci only accounted for 15% of psoriasis heritability.

Despite the identification of potential genetic markers in PsA, the inability to accurately differentiate skin versus joint disease, the low odds ratios for these target genes, and the relatively modest risks associated with these loci, limit their current utility.

### **miRNA Biomarkers**

MicroRNAs (miRNAs) are a class of small noncoding RNAs that negatively regulate the expression of protein-coding genes and degrade target mRNAs. Emerging evidence suggests that miRNA-mediated regulation represents a fundamental layer of epigenetic control of diverse sets of physiological processes and disease development. Studies from our laboratory and others have reported the critical involvement of miRNAs in immune cell development and function. Since miRNAs are expressed in a tissue specific manner and are altered in relation to disease, these noncoding RNAs represent ideal candidates for biomarker discovery. One study evaluated the global miRNA expression profiles of peripheral blood mononuclear cells

(PBMCs) in patients with recent onset of PsA. A comparison of miRNA profiles between PsA and healthy controls identified 16 miRNAs as differentially expressed, including the upregulation of inflammatory linked miRNAs, miR-21, miR-34a, miR-125a-3p, and miR-125a-5p. Recent studies from our lab and others have demonstrated that serum contains stable miRNAs derived from immune cells and various tissues, establishing their potential value as biomarkers for changes in physiologic and pathologic conditions (44-46). In fact, the use of circulating miRNA biomarkers has become an area of great interest; identification of biomarkers for a wide-number of diseases and conditions have been reported to date (45). The ability to readily detect changes in blood-based miRNAs is an attractive biomarker methodology, most notably due to the non-invasive nature of blood collection and relative ease of high-throughput detection systems for processing and analyzing miRNA content. Additionally, circulating miRNAs show remarkable stability and demonstrate consistent expression profiles among individuals. As a result, serum miRNA biomarkers have been reported in cancer, inflammation and cardiovascular disease. Several studies investigating the circulating miRNA profiles of patients with psoriatic disease have found significant changes in expression of several miRNAs when compared to healthy controls. Candidate biomarkers for psoriasis included the upregulated expression of miR-33, miR-369-3p, miR-1266, and miR-128(47) and the downregulation of let-7d, miR-142-3p, and miR-181a (47). Despite these reports, not much is known regarding miRNA expression in PsA patients, and there has been no investigation into the alterations of miRNA expression in the circulation of PsA patients. However, it has been suggested that serum miRNAs may provide a source of candidate biomarkers for PsA (7).

### **Perspective**

Recent advances in targeted biological therapy have allowed a cohort of patients to experience remission from psoriasis and psoriatic arthritis. Anti-TNF therapy, IL-12/23-targeted therapy, and IL-17A blockade have demonstrated efficacy in previously resistant disease (48). However, a minority of patients experience severe side effects or remain resistant to treatment. In addition to measuring disease activity, biomarkers may be able to direct therapy and monitor for development of adverse reactions to specific treatment modalities. Regrettably, no PsA-specific biomarker studied to date has shown clinical relevance, and no large-scale studies have been conducted to determine numeric thresholds for significance.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, known as GRAPPA, is an international consortium of dermatologists and rheumatologists who have made biomarker development a primary goal for psoriatic disease (49). GRAPPA will be essential to the discovery and validation of new



biomarkers through collaborative efforts at patient recruitment, funding, protocol development, study implementation, and data analysis (50). Through investigator-led trials, such as the PsA BioDam study, the goal is to identify sensitive and specific markers of joint disease in PsA. Biomarkers could provide an objective, measurable method of diagnosis, in conjunction with subjective, patient-reported screening questionnaires. In addition to identifying undiagnosed cases of PsA among patients with psoriasis, a goal will be to detect biomarkers that predict future development of PsA. Other potential avenues for future research include use of flow cytometry, bioinformatics and proteomics utilizing high-resolution mass spectrometry, and molecular signaling. Recent advances in proteomic technology are especially promising and may be applied toward development of a validated biomarker panel which incorporates various methodologies for diagnostic, and eventually prognostic, clinical value (51).

Biomarker development is a long and arduous process, involving discovery, validation, and finally, clinical adoption. Only a minority of candidate biomarkers are eventually utilized in the clinical setting due to failure to validate, technical difficulty, inaccessibility, or expense. Despite these obstacles, we are hopeful that our goals of identifying a biologic basis for treatment, recognizing prognostic markers for disease development and treatment response, and developing targeted therapies for disease management will be achieved.

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