An Integrative Approach to Biomarker Development in Psoriatic Arthritis

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ABSTRACT. The recent discovery that the interleukin 23/Th17 pathway is pivotal in the pathogenesis of psoriatic arthritis (PsA) creates new opportunities for the development of mechanistic biomarkers that will assist in the diagnosis and management of this disorder. While biomarkers are still in the discovery phase, new approaches including multiplex panels, fine sequencing of epigenetic and genetic data in non-coding regions of the human genome, and improved imaging modalities will likely foster the development of actionable biomarkers in PsA. In this report, I review the field of biomarkers, underscore the importance of an integrative approach that incorporates both descriptive and mechanistic biomarkers, and discuss the status of biomarker discovery in PsA. (J Rheumatol Suppl. 2015 Nov;93:43–7; doi:10.3899/jrheum.150635)

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In recent years mechanisms have been reported[1] linking specific disease pathways with joint inflammation, enthesitis (inflammation at sites where tendons, ligaments of joint capsules, attach to bone), and joint damage in animal models with strong parallels to human psoriatic arthritis (PsA).

Evidence from preclinical studies and analysis of psoriasis and PsA blood and tissues indicate that the interleukin 23/Th17 pathway is pivotal in disease pathogenesis, and this view is supported by the success of agents that target these cytokines in clinical trials[2]. The congruence of disease mechanisms and treatment response raises the possibility that actionable biomarkers will soon be available to help clinicians better diagnose and manage patients with PsA.

The great diversity in disease presentation and course that is characteristic of PsA greatly complicates diagnosis and treatment. Moll and Wright highlighted the numerous musculoskeletal phenotypes that are often paired with a range of psoriatic skin manifestations and comorbidities that vary markedly from patient to patient[3]. The wide array of clinical characteristics and outcomes offers unique opportunities for application of biomarkers that can identify preclinical and early disease, act as surrogates for subsequent bone damage, predict treatment response to specific agents, and identify early treatment responders. In a review, Robinson, *et al* emphasized the important difference between descriptive biomarkers, which reflect the state of the disease but not pathogenesis [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), imaging], and mechanistic biomarkers that arise from pathogenetic pathways directly related to the disease process (anticyclic citrullinated peptide antibodies)[4]. In this review, the application of both types of biomarkers in the diagnosis and management of PsA, with emphasis on an integrative approach, are discussed. Additionally, recent scientific advances in epigenetics and gene regulation are highlighted, which will strongly influence future strategies to advance PsA biomarkers.

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Biomarkers

A biomarker can be defined as a disease-centered variable that provides insights into the underlying disease process[5]. Biomarkers can represent a wide range of biologic data, which range from disease-centered to patient-centered variables[6].

Disease-centered variables derived from biochemical, cellular, serum, genetic, or imaging sources, may have no inherent significance to the patient or clinician at collection, but the importance of these variables may become apparent as data accumulate over time or after their link to pathologic processes or disease mechanisms is revealed. Examples include blood pressure, laboratory values, and imaging data. Because biomarkers may not have direct relevance to the patient, validation is required.

At the other end of the continuum are patient-centered variables that reflect how a patient feels, functions, and survives, and do not require validation.

A biomarker that can substitute for a clinical endpoint and can predict clinical benefit, harm, or lack of clinical benefit or harm is termed a surrogate marker. One example of a surrogate marker is a T score on dual-energy x-ray absorptiometry scan, which can serve as a partial surrogate of risk for bone fracture.

Two other common terms are risk factor and prognostic factor; these may or may not be biomarkers. These factors

are predictive over time, and patients without disease have risk factors while patients with disease have prognostic factors. Prognostic factors are important for therapeutic stratification because they can identify patient subgroups with characteristics that favor response to specific treatments.

Current sources of biomarkers in PsA are shown in Table 1.

Disease Pathways in PsA

Experimental data derived from *in vitro* studies of murine and human skin plaques, preclinical models of psoriasis, and from clinical studies support a pivotal contribution of both Th1 and Th17 cells in the pathogenesis of psoriasis[7]. Studies in PsA revealed enrichment of Th17 cell subsets in psoriatic joints[8], and more recently Menon, *et al* demonstrated an increased frequency of IL-17+CD8+ and IL-17+CD4+ cells in synovial fluid (SF)[9]. The presence of the IL17+CD8+ cells correlated with 28-joint Disease Activity Score and CRP levels and musculoskeletal ultrasound score and this subset was low or absent in rheumatoid arthritis (RA) SF. In a preclinical model, Sherlock, *et al* demonstrated the presence of enthesitis coupled with inflammatory synovitis and a bone phenotype characterized by erosion and new bone formation[10]. They showed that this inflammatory pathway was driven by resident innate lymphocytes through the release of IL-23, IL-22, IL-17, and tumor necrosis factor (TNF). These results were confirmed over the last year in several different animal models[11,12,13]. These findings implicate both TNF and cytokines in the IL-23/Th17 pathway as master regulators of inflammation and bone remodeling in PsA. Support for the clinical significance of this pathway is also evident in the efficacy of agents that block IL-23 or IL-17 and its receptor in psoriasis and PsA[14,15,16]. Thus, it is highly likely that molecules in this pathway will serve as important mechanistic biomarkers in the diagnosis and management of psoriatic disease.

Diagnosis of PsA

The diagnosis of PsA is based entirely on clinical presentation and imaging results because we lack a diagnostic marker of the disease. Extensive efforts have been under way to elucidate differences in the genetic risk factors for psoriasis and PsA. This differentiation is of clinical importance because most patients with PsA initially develop psoriasis. Using a large scale, fine-mapping study of the MHC region in 3038 patients with psoriasis, 3039 with PsA, and 13,589 controls, Okada, *et al* showed that the risk for PsA was driven by the presence of glutamine at HLA-B amino acid position 45[17]. This site is located in the binding groove of HLA-B and is one of the regions involved in antigen binding or presentation. For some time, investigators have been interested in correlating musculoskeletal phenotypes (peripheral arthritis, axial disease, enthesitis, dactylitis, and arthritis mutilans) with specific biomarkers. With this goal in mind, Haroon, *et al* analyzed clinical phenotypes of 282 patients with PsA for associations with specific HLA-B and HLA-C haplotypes[18]. In this analysis, B*27.05.02 was associated with enthesitis, dactylitis, and symmetric sacroiliitis in contrast to B*08.01.–C07*.01.01 and related alleles, which were associated with joint fusion, asymmetric sacroiliitis, and dactylitis. Divergent combinations of HLA susceptibility genes were associated with severe or milder musculoskeletal phenotypes. These studies provide intriguing insights into how genetic data can aid in the diagnosis and stratification of PsA phenotypes.

A unique aspect of PsA is that the majority of patients with this disease develop psoriasis on average about 10 years before the diagnosis of joint disease[19]. This lag time provides a unique opportunity to identify subclinical joint inflammation in a psoriasis population. Clinical factors associated with increased risk of PsA in psoriasis patients include nail disease, obesity, extensive psoriasis, and scalp disease[20,21]. Over the last 30 years, imaging studies [scintigraphy, magnetic resonance imaging (MRI) and most recently Doppler ultrasound] have demonstrated that patients with psoriasis and no musculoskeletal disease have abnormal findings suggestive of subclinical inflammation in bone, entheses, and synovium not observed in patients with other inflammatory skin disorders or in healthy controls (reviewed in[22]). In a recent study, patients with psoriasis showed significantly more enthesophytes on high resolution computerized tomographic scanning than controls[23]. Moreover, power Doppler ultrasound studies (PDUS) have demonstrated that the prevalence of enthesitis is significantly higher in patients with psoriasis than in controls[24]. Our group previously demonstrated that osteoclast precursors (OCP) are upregulated in patients with PsA[25]. In a subsequent study, we enrolled 44 psoriasis patients without arthritis and combined analysis of OCP frequency with scintigraphy, MRI (if scintigraphy was positive), and PDUS analysis of joints and entheses to examine whether the imaging findings, cellular biomarkers or both, correlate with the development of PsA[26]. Interim analysis of 39 patients followed from 3–36 months identified 5 patients who developed PsA according to CASPAR (ClASsification for Psoriatic Arthritis) Criteria[27].

Table 1. Sources of biomarkers in psoriatic arthritis.

1. Peripheral blood cells
   a. Cell subset analysis
   b. Genome-wide association scans
   c. Transcriptome analysis
2. Skin tissue, synovial tissue, synovial fluid, lymph node
   a. Cell subset analysis
   b. Immunohistochemistry
   c. Transcriptome analysis
3. Serum
   a. Quantitative analysis of cytokines, chemokines, microRNA and molecules involved in bone and cartilage turnover
4. Microbiome skin, bowel
   a. High throughput 16S ribosomal RNA pyrosequencing

All 5 patients had imaging abnormalities (synovitis, enthesitis) and the average OCP frequency in these patients was 1209 ± 492 OCP/10^6 monocytes compared to 168 ± 96 OCP/10^6 monocytes in patients with psoriasis who did not develop PsA and had normal imaging findings. Taken together, the results of the genetic studies and the combination of imaging and cellular biomarkers may help to differentiate psoriasis from PsA, provide an approach to stratify risk factors for specific musculoskeletal subsets of PsA, and identify patients with psoriasis who are at risk for arthritis.

Assessment of Disease Activity

A major unmet need in the treatment of PsA are biomarkers that accurately and reliably assess disease activity. Acute-phase reactants are elevated in a minority of patients with PsA and may not accurately reflect disease activity. In a recent systematic review of candidate serum soluble bone turnover biomarkers, Jadon, *et al* found 10 studies that met eligibility criteria[28]. These studies reported that C1-2C (a type 2 collagen neoepitope) was associated with tender and swollen joint counts and bone morphogenetic protein-4 with patient global disease assessment, pain score, and the Bath Ankylosing Spondylitis Disease Activity Index. Bone alkaline phosphatase was associated with disease activity and receptor activator of nuclear factor-kappa B ligand (RANKL) was associated with several radiographic features. Multibiomarker panels developed in RA have demonstrated utility for revealing disease activity, particularly in patients who do not show high clinical activity[29], but these panels have not been developed in PsA. Recently, a chaperone molecule 14-3-3η was shown to be elevated in the sera of patients with RA, and expression was higher in patients with radiographic damage and progression[30]. Interestingly, levels of this marker were also reported to be increased in patients with erosive PsA[31]. Additional studies are required to confirm this interesting observation.

Prognostic Markers of Severity

Clinical risk factors for radiographic progression include age, time in clinic, initial ESR, number of tender and swollen joints at previous visit, and number of deformed joints[32].

Identification of rapid progressors is essential given that almost half of patients demonstrate erosions in the first 2 years of disease[33]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is planning to analyze data from a large therapeutic clinical trial comparing methotrexate or anti-TNF monotherapy to methotrexate in combination with an anti-TNF agent, to identify candidate serum surrogates of bone damage.

Predictive Biomarkers of Treatment Response

Therapeutic options for patients with PsA have greatly increased over the last several years. The 2 new alternative agents (ustekinumab and apremilast) are particularly appealing because they represent alternative targets to the TNF pathways. Moreover, secukinumab, recently approved for psoriasis, is also effective in PsA[15]. Currently, we do not have predictors that can stratify which patients are likely to respond to a specific agent. Given the important role of IL-23 and IL-17 in disease models, however, the presence of IL-17+ CD8+ cells in the SF or tissue may correlate with responsiveness to an agent that inhibits the IL-23/Th17 pathway, whereas the absence of these cells may be associated with a higher TNF response. Indeed, analysis of RA synovial tissues revealed 4 different phenotypes: lymphoid, myeloid, low inflammatory, and fibroid, each with a distinct gene expression signature[34]. Those patients with a myeloid signature were more likely to experience a good compared to a poor European League Against Rheumatism clinical response. In addition, specific markers in the tissue correlated with responses to anti-TNF therapies versus IL-6R antagonists. Other potential sites for biomarkers include the bowel, where the presence of chronic colitis detected by ileocolonoscopy was associated with a higher prevalence of sacroiliitis on MRI in patients with ankylosing spondylitis[35]. Another consideration is psoriatic plaques where markers in the dermis or epidermis may assist in the prediction of treatment response to a specific agent in the skin and possibly even the joints.

Prediction of Early Treatment Response

Mechanistic biomarkers that drop in the first few weeks after therapy may predict longterm response. Our group is examining whether the decline in OCP frequency, 2 weeks after therapy, is predictive of therapeutic response at 6 months. We are also analyzing the expression of dendritic cell-specific transmembrane protein (DC-STAMP), a marker of OCP expressed by CD14+ monocytes, that can be quantified by flow cytometry[36]. Other candidate cell populations in which early decline may predict longterm response include IL-17 expressing T cell subsets, CD14+16+ monocyte subsets, and markers of bone turnover mentioned above.

Prospective studies that use PDUS to capture imaging data in patients with PsA at early timepoints followed by longitudinal followup of musculoskeletal disease will address the predictive value of suppression of abnormal signals as a marker of treatment response. MRI can also provide useful imaging for longitudinal studies but it is anticipated that PDUS will become the instrument of choice to follow PsA given its increasing presence in rheumatology offices, ease of use, and relatively low cost.

Novel Sources of Biomarkers

Recent links between the gut microbiome and human disease have become apparent, resulting in great anticipation that new pathophysiologic pathways will be unveiled, particularly in regard to spondyloarthritis[37]. Scher, *et al* demonstrated that

the gut microbiota in PsA and psoriasis were less diverse than in healthy controls, and supernatants showed increased soluble IgA levels and decreased RANKL levels[38]. Moreover, the skin also has an extremely varied microbiome with a diversity of fungi, viruses, and bacteria that colonize distinct skin microenvironments[39]. Of particular interest was the finding that species enrichment was varied in the sebaceous, dry, and toenail microenvironments. To date, however, the contribution of the bacterial and nonbacterial taxa in the development of persistence of the psoriatic plaque is unknown[40].

A major challenge with genome-wide association studies is linking single-nucleotide polymorphisms with specific disease mechanisms or pathways, because many of the mutations do not interrupt protein coding sequences. To address this challenge, Farh, *et al* developed a fine mapping algorithm to identify causal variants for 21 autoimmune disorders (including psoriasis)[41]. They found that about 90% of the causal variants are non-coding and most map to immune cell enhancer regions. These types of investigations will undoubtedly reveal a trove of new mechanistic biomarkers that will greatly assist in the diagnosis and management of PsA.

Closing Remarks

Biomarker discovery and validation has been frustratingly slow in the field of PsA, but the environment is changing rapidly in 4 major areas that will facilitate biomarker development for PsA in the near future (Table 2).

1. Increased understanding of the pathways that promote inflammation and altered bone remodeling. The master cytokines in this process include TNF and the IL-23/Th17 pathway. It is highly probable that mechanistic biomarkers will be identified in these cytokine pathways.
2. Improvements in proteomic and metabolomics technologies as well as sophisticated approaches for deep sequencing of gut and skin microbiomes will provide additional sources for biomarkers.
3. Development of well-phenotyped patients in longitudinal databases coupled with the collection of patient-related variables and biomarker sampling from phase III clinical trials will be of central importance in the development of a wide range of mechanistic biomarkers.
4. Lastly, the availability of high-quality genetic and epigenetic data will uncover novel candidate markers (most likely controlling gene regulation) involved in immune homeostasis and disease.

These advances coupled with the growth of bioinformatics and improved quality of imaging instruments will provide unparalleled opportunities to combine descriptive and mechanistic biomarkers to help optimize diagnosis and treatment of patients with PsA.

Table 2. Newer approaches to biomarker discovery in psoriatic disease.

- Metabolomics
- Proteomics
- Integrated genetic and epigenetic fine mapping of the human genome
- Advances in microbiome analysis and interpretation
- Multiplex panels to evaluate multiple biomarkers
- Combination of descriptive (imaging) and mechanistic biomarkers

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