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REVIEW

Biomarkers of An Autoimmune Skin Disease—Psoriasis

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Abstract **Psoriasis** is one of the most prevalent autoimmune skin diseases. However, its etiology and pathogenesis are still unclear. Over the last decade, omics-based technologies have been extensively utilized for **biomarker** discovery. As a result, some promising markers for **psoriasis** have been identified at the **genome**, transcriptome, **proteome**, and **metabolome** level. These discoveries have provided new insights into the underlying molecular mechanisms and signaling pathways in **psoriasis** pathogenesis. More importantly, some of these markers may prove useful in the diagnosis of **psoriasis** and in the prediction of disease progression once they have been validated. In this review, we summarize the most recent findings in **psoriasis biomarker** discovery. In addition, we will discuss several emerging technologies and their potential for novel **biomarker** discovery and diagnostics for **psoriasis**.

Introduction

Psoriasis is a common, chronic, and recurrent autoimmune inflammatory skin disease, affecting approximately 2% of the population in the United States [1]. Psoriasis generally manifests as chronic inflammation of the skin and is characterized by circumscribed, scaling, and erythematous plaques. Recurrent episodes occur during a patient's lifetime, which often can be improved through treatment, with few spontaneous remissions. Psoriasis vulgaris (also called plaque psoriasis) is the most common form of the disease, affecting 85%–90% of the patients [2]. Other types of psoriasis include erythrodermic psoriasis, guttate psoriasis, and pustular psoriasis (**Figure 1**). Although psoriasis is considered a skin disease, patients could develop comorbidities, including psoriatic arthritis (PsA), metabolic syndromes, and cardiovascular diseases [3], in addition to skin lesions.

Previous studies on the pathogenic factors and immune mediators of psoriasis have greatly advanced our understanding of disease pathogenesis. Accumulating clinical and experimental evidence points out that the immune system plays a key and central role in disease pathogenesis. Psoriasis has been considered a T helper type 1 (Th1)-mediated disease for many years [4] and recent studies have demonstrated that the

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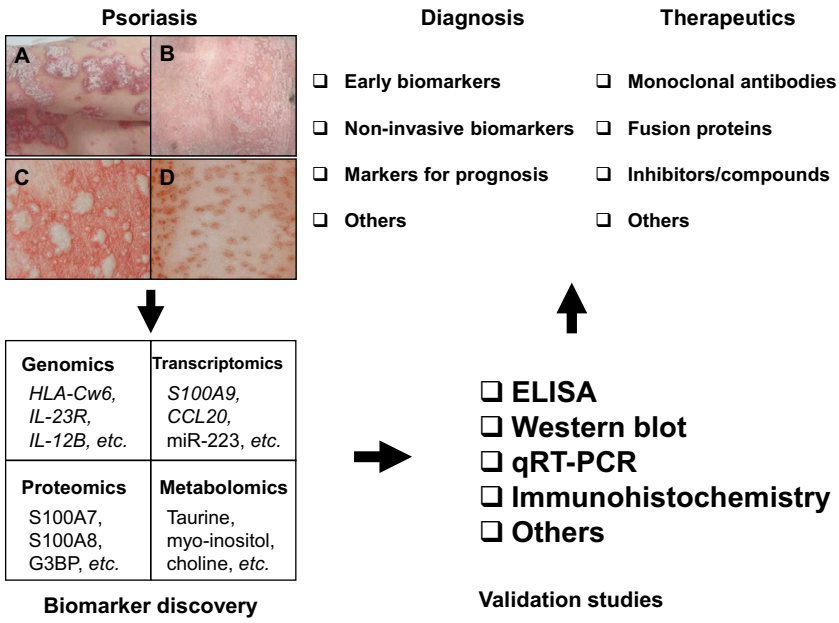

Figure 1 Pipeline of biomarker discovery and therapeutic targeting in psoriasis
Psoriasis is one of the most prevalent autoimmune inflammatory skin diseases. The four main clinical types are plaque (vulgaris) (**A**), erythrodermic (**B**), pustular (**C**), and guttate (**D**). Potential biomarkers of psoriasis could be identified using various technologies including genomics, transcriptomics, proteomics, and metabolomics. Some promising biomarkers of psoriasis have been identified with different "omics" platforms as shown in the figure, and more exciting findings could be expected with the advancement of these technologies. Valuable biomarkers should be validated using orthogonal techniques such as ELISA, Western blot, qRT-PCR, and IHC with a larger cohort of subjects, in order to achieve statistically meaningful results. The validated biomarkers could potentially be useful in the clinical diagnostics and therapeutics of psoriasis.

interleukin (IL)-23/Th17 cell axis plays a crucial role in psoriasis pathogenesis [5]. In the initiation phase, keratinocytes release antimicrobial peptide LL37 after trauma or infection, which can bind to self-DNA and self-RNA fragments that are released by dying or stressed skin cells [6]. These complexes activate plasmacytoid dendritic cells (pDCs) to produce type I interferons (IFN), like IFN-α [6]. In turn, type I IFNs and immune complexes can activate myeloid DCs (mDCs) through Toll-like receptor 8 (TLR8). IL-23 and IL-12 that are released from activated mDCs can then activate Th17, Th1, and Th22 cells to produce an abundance of cytokines, such as IL-17, IL-22, IFN-γ, and tumor necrosis factor (TNF). These cytokines help to stimulate the keratinocytes to amplify the inflammation typically observed in psoriatic lesions [7].

The diagnosis of psoriasis is primarily focused around the clinical morphologic evaluation of a skin lesion, as there are no other clearly-defined diagnostic criteria. The differential diagnosis of psoriasis is abundant and depends on the clinical subtype. Histopathological analysis of a skin biopsy specimen is currently the most common and efficient clinical identification method. Nonetheless, skin biopsy is invasive and the pathological alterations are not obvious at early stages of psoriasis. Therefore, there is an urgent need to develop non-invasive diagnostic tests or biomarkers with high sensitivity and specificity for psoriasis [8].

Although there is no cure for psoriasis, some biological therapies targeting specific immune components have recently proven to be highly effective [9]. Earlier biological agents, including efalizumab and alefacept, primarily disrupt the activation and migration of T cells, whereas agents like infliximab, etanercept, and adalimumab target TNF-α. Recently, agents like ustekinumab and ABT-874, which target the p40 subunit shared by both IL-12 and IL-23, have been developed, as well as new anti-IL-17 agents and anti-IL-23p19 agents [9,10]. However, approximately 20%–30% of psoriasis patients fail to respond to biological therapies [8]. Therefore, valuable biomarkers for the diagnosis, prognosis, and treatment of psoriasis are of great significance for clinicians in designing effective and personalized therapies.

In this review, we will summarize the most up-to-date research findings in biomarker discoveries for psoriasis, including biomarkers identified with conventional technologies, genomic biomarkers, transcriptomic biomarkers, proteomic biomarkers, and metabolomic biomarkers. In addition, we will discuss several emerging technologies, which have potentials in novel biomarker discovery validation and diagnostics in psoriasis.

Biomarkers identified with conventional technologies

Conventional assays, such as bioplex assays, ELISA, Western blotting, and immunohistochemistry (IHC), have been used to identify potential biomarkers for psoriasis. Early studies have found that serum levels of nonspecific inflammation markers, including C-reactive protein (CRP), platelet P-selectin, haptoglobin, complement component 3 (C3), and C4 [11,12], as well as some pro-inflammatory cytokines, such as TNF-α, IFN-γ, IL-6, IL-8, IL-12, and IL-18, were increased in psoriasis patients [8]. However, no elevated serum IL-17A levels were detected in different cohorts of psoriatic patients, although Th17 cells, which produce IL-17, were noted to play an