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Diagnostic and prognostic tests in systemic lupus erythematosus

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A B S T R A C T

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by autoantibodies directed against numerous self-nuclear antigens. Because of the heterogeneous nature of lupus, it has been challenging to identify markers that are sensitive and specific enough for its diagnosis and monitoring. However, with the sequencing of the human genome, rapid development of high-throughput approaches has allowed for a better understanding of the etiopathogenesis of complex diseases, including SLE. Here we present a review of the latest advancements in biomarker discovery during the "omics" era, using these novel technologies, for assisting in the diagnosis and prognosis of patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease, characterized by autoantibodies directed against numerous self-nuclear antigens. Because of the heterogeneous nature of lupus, a broad spectrum of clinical manifestations exists. Disease severity also varies depending on the extent of major organ involvement, including most commonly the brain, kidneys, heart, joints, and skin [1].

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Several pathophysiologic mechanisms leading to the immune dysregulation seen in SLE have been described, including hyperreactive B and T cells, loss of immune tolerance, and defective clearance of apoptotic cells and/or immune complexes [2]. Nevertheless, despite improved understanding of disease pathogenesis, the morbidity and mortality associated with SLE still represent major challenges for patients who face this disease and the clinicians who treat them.

The enhanced focus on the identification of pathogenic pathways in SLE has revealed several novel pharmacologic targets (e.g., B lymphocyte stimulator [BLyS]) that have hastened the development of new and promising therapies (e.g., belimumab) [3]. However, SLE continues to have an unpredictable course with remitting and relapsing episodes, highlighting not only that our understanding of lupus remains incomplete but also that current therapies are not curative.

Although originally not developed as diagnostic but rather as classification criteria, patients today are commonly diagnosed according to the American College of Rheumatology (ACR) or the Systemic Lupus International Collaborating Clinics (SLICC) criteria. In a sample of 690 patients, the ACR criteria had a sensitivity of 83% and a specificity of 96%, whereas the SLICC criteria had a sensitivity of 97% and a specificity of 84% [4]. However, evidence from a tertiary care center suggests that only 60% of patients with SLE meet the ACR criteria [5]; apparently, patients with early signs or limited disease are excluded by this tool. The development of improved diagnostic biomarkers facilitating the early detection of SLE is of utmost importance, not only because this would allow for rapid treatment and subsequent prevention of organ damage but also because of the positive economic impact of early diagnosis [6].

Conventional serologic tests currently used for diagnosis and disease monitoring in SLE, such as anti-nuclear antibodies, anti-double-stranded DNA antibodies (anti-dsDNA), and complement levels, are of limited sensitivity and/or specificity, particularly when used in isolation [7–9]. A more specific and useful test to determine prognosis in patients with renal involvement, kidney biopsy, remains the gold standard; however, this is an invasive procedure that carries additional risk.

The unmet needs described above have urged researchers to search for reliable and non-invasive biomarkers helpful for the diagnosis, classification, prognosis, and treatment of SLE. With the advent of higher throughput and systems biology approaches over the past decade, great advances have been made in this regard. Nevertheless, additional validation is required, and the clinical applicability of such methods needs to be further defined.

This review focuses on novel biomarkers discovered in recent years for the diagnosis and prognosis of SLE, specifically those developed using advanced methodologies, which are beginning to enter clinical practice.

Role of biomarkers in SLE diagnosis and prognosis

Before we review these tests, it is important to understand the concept of biomarkers. A biological marker can be defined as a physical sign or cellular, biochemical, molecular, or gene alteration by which a normal or abnormal biologic process can be recognized and measured [10]. Biomarkers can be diagnostic, prognostic, predictive, pharmacodynamic, or surrogate. Some biomarkers will serve multiple purposes. Specific to this review, a diagnostic biomarker refers to one that confirms the presence or subtype of a disease, whereas a prognostic biomarker identifies a specific disease manifestation, individuals at risk of developing such a disease, or those likely to experience a flare [11].

The post-genomic era, after the completion of the human genome sequencing in 2001 [12], has been characterized by the rapid development of highly efficient molecular tools for the study of complex diseases at the functional level of genes. More holistic and comprehensive approaches (as opposed to those only focused on individual mediators) are now a major route for understanding the underlying pathophysiological processes of complex diseases and can be conducted at any level of the gene expression sequence: genes, messenger RNA (mRNA), proteins, and metabolites [13]. This is what is referred as the “omics” era [14,15]. Below we briefly describe each of these technologies and review their roles in biomarker discovery when applied to the study of SLE. Several years ago, Mohan et al. recognized the contribution of “omics” approaches to biomarker discovery and validation in lupus [14]. In the current review, our focus is mostly on advances described since then in this rapidly progressing field.