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Review

Organ-specific biomarkers in lupus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex and highly heterogeneous disease, which affects multiple organs, including joints, skin, kidneys, heart, hematopoietic system, and nerve system. While the etiopathogenesis of SLE still remains unclear, genetic susceptibilities and aberrant epigenetic modifications are believed to be involved. For precision therapy, it is necessary to assess accurately and objectively organ involvements and disease activity, which is difficult by current clinical laboratory tests. Biomarkers, which are a biologic, genetic, epigenetic or a chemical characteristic and conveniently detectable, serve as measures of disease diagnosis, activity, prognosis, and manifestation prediction, thereby providing instruction for individualized therapy. In addition, biomarkers differ according to different manifestations, since the disease activity index and treatments vary significantly. For example, unlike other non-renal SLE, lupus nephritis requires significant immunosuppressive drugs. Over the past decades, the research on biomarkers in lupus has been strengthened and numerous promising biomarkers have been identified at levels of genomics, transcriptomics and proteomics. In this review, we summarize the conventional and novel biomarkers in the tissue-specific manner, and discuss their roles in specific organ diagnosis, future manifestation prediction, disease activity assessment and their correlation with histology results. By doing so, it aims to shed a light on individualized treatment.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a complicated autoimmune disease that affects multiple systems and displays a variable clinical signs and symptoms, leading to the extremely difficult to diagnosis and treatment. It is characterized by a presence of abundant autoantibodies in the circulation of patients [1], together with abnormal T and B lymphocytes [2,3]. Although the direct cause of SLE remains unclear, many factors are believed to contribute to pathogenesis of SLE, including genetic susceptibility, epigenetic, and environmental factors [4–6]. SLE occurs when an individual with genetic susceptibility to lupus encounters environmental triggers such as sunlight, drugs or infection. Then, the immune tolerance is broken down such that T cells recognize self-antigens and provide assistant to auto-reactive B cells, which produce a diverse set of autoantibodies. These autoantibodies bind to self-antigens, form immune complex, and reside in multiple organs, leading to organ inflammation, dysfunction and failure [7–10].

The current diagnosis criterion for SLE mainly bases on the combination of clinical manifestations such as cutaneous rash, joint pain, glomerular nephritis, and neuropsychiatric symptoms, and laboratory tests such as antinuclear antibodies, especially ANA and anti-dsDNA antibodies [11]. However, The current available laboratory markers for SLE diagnosis have been restricted. For example, ANA tests have a very high sensitivity (100%) but a relatively low specificity (65%) [12]. In the contrast, anti-dsDNA antibody is highly specific for SLE (94%); however, low sensitivity was due to the transient appearance [12]. Same phenomena have been found in *anti*-Sm antibodies (high specificity and low sensitivity) [13]. Besides, biomarkers should be differed in various manifestations due to the pathogenesis of each clinical symptom, and non-invasive markers for organ-specific diagnosis are much easily accepted by patients compared to biopsy. In addition, only corticosteroids and hydroxychloroquine have been approved to treat SLE patients [14] and cyclophosphamide, azathioprine and mycophenolate are standard treatment for lupus nephritis patients [15], even the newly approved Belimumab [16], but data from the past decades showed no improvement in outcomes. For more effectively treating the patients with present drugs before the new one available, it is important to assess the current disease activity and predict the future disease course. Thus, a more reliable biomarker for SLE, which can play a critical role no matter in diagnosis, especially in an organ-specific manner, monitoring the disease progress, evaluating the response to treatment, and predicting the future flare is in great need. In this review, we summarize the novel organ-specific biomarkers, discuss their merit and shortage, and provide the scenario of novel biomarkers in lupus.

2. Biomarkers in lupus nephritis

Among diverse manifestations of SLE, lupus nephritis (LN) remains the most common severe manifestation with the mortality of >50% [17]. Renal biopsy remains the gold standard for LN diagnosis, prognosis and provides the guidance for the treatment of LN. However, biopsy has various complications, bleeding being the most common, and it cannot be conducted routinely and may not reflect the whole renal pathological status of LN due to the very small specimens from kidney. Besides, the current available clinical routine tests, such as 24-hour proteinuria, cell composition of urine sediments, anti-dsDNA antibodies, C3 and *C*4 levels in sera, also have restriction due to the low sensitivity and specificity to reflect the real-time renal disease activity and have no correlation to the pathological alterations [18]. Therefore, there is an unmet need to identify and develop LN specific biomarkers, which can help with diagnosis, accurately assess disease activity, maybe replace the biopsy and predict the future flare of LN.

2.1. Potential biomarkers from circulation for LN

Increasing evidence has revealed that intricate serum autoantibodies and immune regulators may involve in particular tissue/organ damages. The current clinical parameters and pathogenic antibodies, including *anti*-dsDNA, anti-cardiolipin, *anti*-ribosomal P, anti-SSA/Ro, anti-Sm, anti-endothelial cells, anti-epithelial cells, anti-glomerular matrix, and anti-glomerular basement membrane antibodies combined with reduced serum complement C3 and C4 levels have been found associated with LN [19–21]. In recent studies, some genetic, epigenetic and protein markers in serum have been shown promising in guidance for the diagnosis and treatment of LN.

2.1.1. Genetic biomarkers in circulation for LN

A genetic component likely increases the risk of developing SLE, which is supported by a higher concordance rate in monozygotic (MZ) twins than in dizygotic (DZ) twins [22,23]. Until now, various candidate genes of LN predisposition have been identified, such as histocompatibility complex (MHC) and Fcγ receptor (FcγR) IIA and IIIA which are associated with SLE and LN [24,25]. FcγRIIA gene is important disease susceptibility factors for SLE, particularly for LN, suggesting that the Fcc receptor may influence clinical manifestation of LN, as well as show prognostic and therapeutic implications [26]. More recently, the programmed cell death-1 (PD-1), which is the negative regulatory molecule in T cells, PD1.3A has been found to be a risk factor for LN in European population [27] and a study has confirmed PDCD1 as a LN potential biomarker by the findings of the association of PDCD1 gene variation and LN [28].

Besides the molecules from blood cells, genetic polymorphisms of some cytokines, chemokines and proteins have been revealed to be associated with LN. Inflammatory mediator monocyte chemoattractant protein-1 (MCP-1), for example, has been identified as a biomarker for LN at protein level. The −2518 A/G polymorphism of MCP-1 has also shown a strong correlation to LN [29]. Another large study has also confirmed integrin alpha M (ITGAM) as a susceptibility gene for LN [30]. Collectively, defective function caused by these variants may lead to lamely clearance of glomerular deposits. In addition, the low frequencies of the risk alleles of ITGAM gene identified that it is a risk factor correlated to disease susceptibility and even severe manifestations of SLE [31]. Recently, several studies showed that ITGAM gene variants, encoding CD11b–integrin (alpha M), was association with SLE susceptibility and renal involvement [32–34]. Among diverse LN susceptible genes, further studies showed that angiotensin-converting enzyme (ACE) and angiotensinogen (AGT) were the best renal-specific risk factors. The serum levels of ACE positively associated with LN activity, and reflected the disease progress and sensitivity to drugs [35,36]. Two polymorphisms in the ACE gene, Alu insertion/deletion (I/D) and 23,949 $(CT)_{2/3}$, were found to be correlated with serum ACE levels and therefore be believed to be associated with LN. Data from meta-analysis shows D allele or DD genotype in ACE gene as predictive markers for LN [37].

However, all the genetic biomarkers, mentioned above (summarized in Table 1), are not suitable to be applied to evaluate the disease activity as biomarkers, since their presence is perpetual and cannot be altered by treatments. Therefore, they may be good predictors for LN possibility, even the future flare, but not markers for disease activity.

2.1.2. DNA methylation biomarkers in circulation for LN

Genetic elements clearly play predisposing role in the pathogenesis of lupus, but incomplete concordance in identical twins and the fact that most causes of lupus are sporadic rather than familial indicate the requirement for an additional factor and mechanisms. In recent years, accumulating evidences suggest that aberrant epigenetic modifications contribute to the pathogenesis of the disease. Epigenetics is a study of