

Interferon Signature Genes in Early Diagnosis of Systemic Lupus Erythematosus: Current Value and Limitations

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Abstract

Systemic lupus erythematosus (SLE) is a highly heterogeneous autoimmune disease, and early diagnosis remains a major clinical challenge. Abnormal activation of the type I interferon (IFN) pathway is one of the core mechanisms in the pathogenesis of SLE. The IFN signature, as a biomarker reflecting activation of this pathway, has received extensive attention in recent years. This review systematically summarizes the definition and detection methods of the IFN signature and research progress in its use for early diagnosis of SLE. For predicting conversion from undifferentiated connective tissue disease (UCTD) to SLE, current evidence shows that patients with incomplete SLE have significantly increased IFN scores that are closely related to autoantibody profiles, indicating its potential use as a risk stratification tool. For supplementary diagnosis in antinuclear antibody (ANA)-negative or low-positive patients, the IFN signature may provide additional differential information beyond traditional serological tests. In addition, the IFN signature also shows certain value in the differential diagnosis of SLE and other autoimmune diseases, but it must be judged comprehensively together with clinical and other laboratory indicators. However, clinical application of the IFN signature still faces multiple challenges, including insufficient threshold standardization, marked ethnic differences, inadequate longitudinal stability, and relatively high testing cost. This review considers that the IFN signature has a clear biological basis and preliminary clinical evidence as an auxiliary tool for early diagnosis of SLE, but it cannot currently be used alone for confirmed diagnosis. Future work should focus on establishing standardized testing systems, developing multidimensional composite scoring models, and exploring rapid point-of-care testing technologies to promote the translation of the IFN signature from the laboratory to clinical practice.

Keywords

systemic lupus erythematosus, interferon signature genes, early diagnosis, biomarker, undifferentiated connective tissue disease, differential diagnosis

1. Introduction

1.1 Clinical Difficulties in Early Diagnosis of SLE

Systemic lupus erythematosus (SLE) is a highly heterogeneous autoimmune disease with diverse clinical manifestations, ranging from mild skin and joint symptoms to life-threatening renal and nervous system

involvement. This heterogeneity makes early diagnosis of SLE extremely difficult. Studies have shown that the disease course of SLE can be divided into different clinical patterns, from early-onset disease to late-onset lupus, with significant differences in clinical manifestations and prognosis [13-14]. Late-onset SLE, usually defined as disease onset after 50 years of age, often has less typical symptoms and is more likely to be misdiagnosed or diagnosed late. Therefore, searching for biomarkers that can support early and accurate diagnosis has important clinical significance.

1.2 Core Association Between Interferon Pathway Abnormality and SLE Pathogenesis

The type I IFN pathway occupies a core position in the pathogenesis of SLE. A large number of studies have confirmed that patients with SLE have persistent excessive production of type I IFN and abnormal signal transduction. Plasmacytoid dendritic cells (pDCs) are the main source of type I IFN. After Toll-like receptors (TLRs) recognize self-nucleic acid-antibody complexes, pDCs secrete large amounts of IFN- α and then activate the expression of downstream interferon-stimulated genes (ISGs) [12]. This positive feedback loop is considered an important driving factor of immunopathological injury in SLE. Postal et al. [8] systematically summarized the multiple roles of type I IFN in the pathogenesis of SLE in their review, including promoting autoantibody production, activating T cells and B cells, inducing chemokine expression, and participating in organ injury.

In recent years, the discovery of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway has provided a new perspective for understanding the formation of the IFN signature. Through integrative analysis, Zhang et al. [1] found that the IFN signature driven by the cGAS-STING pathway has context-dependent roles in SLE. It not only participates in disease occurrence and progression, but may also have different functions at different disease stages. This suggests that interpretation of the IFN signature needs to consider the specific disease context.

1.3 Aim of This Review

Given the increasingly prominent potential value of the IFN signature in SLE diagnosis, this review aims to systematically evaluate the current research status of the IFN signature as an early diagnostic tool, analyze its advantages and limitations, and provide a reference for future clinical application.

2. Research Progress on the IFN Signature in Early Diagnosis of SLE

2.1 Definition and Detection Methods of the IFN Signature

The IFN signature usually refers to the expression profile of a group of interferon-stimulated genes (ISGs) regulated by type I IFN. The gene combinations used in different studies vary, ranging from 3 to 21 genes. Commonly used ISGs include IFI27, IFI44L, IFIT1, MX1, OAS1, ISG15, and LY6E. Shen et al. [2] identified key ISGs through bioinformatics analysis and constructed an index system that can be used to evaluate the disease status of patients with SLE. This study provided a valuable reference for selecting ISGs. In terms of detection methods, real-time quantitative polymerase chain reaction (qPCR) is currently the most commonly used method, followed by RNA sequencing and microarray chips. However, no unified standard has been formed among studies in detection platforms, data analysis methods, or threshold setting. Renaudineau et al. [5] pointed out in a review of lupus nephritis biomarkers that although the IFN signature shows good diagnostic performance in research, threshold standardization remains one of the main bottlenecks hindering clinical translation.

2.2 Predictive Value in Conversion from Undifferentiated Connective Tissue Disease (UCTD) to SLE

Undifferentiated connective tissue disease (UCTD) and incomplete SLE refer to patient groups that have some clinical or laboratory features of SLE but do not yet meet classification criteria. Approximately 10%-20% of these patients progress to definite SLE during follow-up, and early identification of high-risk individuals is important for timely intervention.

The study by Lambers et al. [10] showed that the IFN score of patients with incomplete SLE was significantly higher than that of healthy controls and was positively correlated with the level of myxovirus-resistance protein A (MxA) in blood and skin. MxA is a direct effector protein of the type I IFN pathway, and its expression level can indirectly reflect the degree of IFN pathway activation. This finding suggests that the IFN score may serve as a potential tool for identifying high-risk patients with incomplete SLE.

Li et al. [11] further found that, in patients with incomplete lupus, expression of IFN signature genes was closely related to specific autoantibody profiles. Some autoantibody-positive patients with incomplete lupus showed higher levels of IFN gene expression, which may indicate a higher risk of progression. Together, these studies indicate that the IFN signature has important value in risk stratification and early prediction.

2.3 Supplementary Diagnostic Role in ANA-negative or Low-positive Patients

Antinuclear antibody (ANA) testing is a traditional cornerstone of SLE diagnosis, but a portion of ANA-negative SLE patients does exist clinically, especially in the early stage of disease. In addition, low-titer ANA positivity is quite common in the general population. How to distinguish true SLE patients from individuals with benign ANA positivity is an urgent problem to solve.

The study by Slight-Webb et al. [3] provides a new perspective on this problem. They found that, among healthy individuals with positive autoantibodies, those with lower genetic risk for lupus showed a unique immune endotype. This finding suggests that ANA positivity alone is not sufficient to predict disease occurrence and that other biomarkers need to be combined for comprehensive evaluation. As a biological indicator independent of ANA, the IFN signature may play a role in this differentiation process.

Although studies directly targeting the IFN signature in ANA-negative SLE patients are still uncommon, existing evidence shows that activation of the IFN pathway can be independent of the classical autoantibody pathway. Therefore, the IFN signature is expected to become an important supplementary tool for diagnosis in ANA-negative or low-positive patients.

3. Current Status of IFN Signature Standardization

3.1 Differential Diagnostic Ability for Other Autoimmune Diseases

SLE overlaps with other systemic autoimmune diseases, such as Sjogren syndrome, dermatomyositis, and rheumatoid arthritis, in clinical manifestations and laboratory examinations, and differential diagnosis can sometimes be very difficult. Because the type I IFN pathway can be activated in various autoimmune diseases, the specificity of the IFN signature has always been a focus of research.

Suspitsin et al. [9] systematically analyzed the value of the type I IFN signature for differential diagnosis of immune system diseases in their review. They pointed out that although the IFN signature is not specific to SLE, the pattern and intensity of the IFN signature may differ among diseases. For example, both SLE and dermatomyositis show strong IFN signatures, but there may be subtle differences in their gene expression profiles. In addition, combining other clinical and laboratory indicators can improve the accuracy of differential diagnosis.

Kennedy et al. [7] found in a multicohort study that the IFN signature metric was associated with serological manifestations of SLE, such as anti-dsDNA antibodies and complement levels, but had weak correlation with global disease activity scores. This finding suggests that the IFN signature may reflect the immunological state of disease more than overall clinical activity. In differential diagnosis, it should be regarded as a biological indicator rather than a simple activity biomarker.

3.2 Current Main Limitations: Inconsistent Thresholds, Ethnic Differences, Dynamic Fluctuation, and High Cost

Although the IFN signature shows great potential in early diagnosis of SLE, its clinical application still faces multiple challenges.

First, threshold standardization is the most prominent obstacle. Different studies use different gene combinations, different calculation methods, and different cutoff values, making results difficult to compare

directly. Renaudineau et al. [5] clearly pointed out that establishing unified testing standards and thresholds is a prerequisite for clinical translation.

Second, ethnic differences cannot be ignored. The study by Chung et al. [4] showed that the risk of adverse renal outcomes in African ancestry patients with SLE was related to APOL1 gene variants, and APOL1 itself is also an IFN-induced gene. There are differences in baseline expression levels and genetic backgrounds of ISGs among different ethnic populations, which means that a unified cutoff value may not be applicable to all populations.

Third, the problem of longitudinal stability limits the application of the IFN signature in disease monitoring. The multicohort study by Kennedy et al. [7] found that the IFN signature metric was related to serological manifestations, but its association with global disease activity scores was inconsistent. In some patients, the IFN score remained relatively stable even when disease activity changed significantly, suggesting that it may be more suitable as a marker of disease susceptibility than as an activity monitoring indicator.

Finally, testing cost and accessibility are also important factors to consider in practical application. Compared with traditional ANA testing, IFN signature testing based on multigene expression has a higher cost and more complex operation, which is especially prominent in resource-limited areas.

4. Summary and Outlook

4.1 Main Conclusion: The IFN Signature is a Potential Auxiliary Diagnostic Tool, but It Cannot yet be Used Alone for Confirmed Diagnosis

Based on current research evidence, the IFN signature has a clear biological basis and preliminary clinical evidence as an auxiliary tool for early diagnosis of SLE. In risk prediction for incomplete lupus, supplementary diagnosis of ANA-negative patients, and differential diagnosis from other autoimmune diseases, the IFN signature shows potential clinical application value. However, the current level of evidence is still insufficient to support its independent use as a diagnostic biomarker.

4.2 Future Directions: Establishing Standardized Testing Systems, Developing Composite Scores, and Exploring Rapid Point-of-care Testing Technologies

First, standardized testing systems and thresholds should be established. International collaborative organizations should promote the development of unified ISG combination schemes, testing procedures, and data analysis methods, and establish normal reference ranges and diagnostic thresholds based on large-sample multicenter studies.

Second, composite scoring models should be developed. The IFN signature should be combined with traditional autoantibody testing, complement levels, clinical features, and other multidimensional information, and methods such as machine learning should be used to build more accurate diagnostic prediction models.

Third, prospective longitudinal cohort studies should be carried out. In particular, long-term follow-up should be conducted in high-risk populations, such as first-degree relatives of patients with SLE and patients with UCTD, to verify the predictive performance of the IFN signature for disease occurrence.

Fourth, rapid point-of-care testing technologies should be explored. Portable IFN signature testing devices based on microfluidic or lateral flow technologies should be developed to reduce cost and shorten testing time, so that more primary medical institutions can apply this technology.

4.3 Recommendation for Clinical Practice: IT May be Used as a Supplementary Indicator for Screening High-risk Populations

At the current stage, the IFN signature may be considered as a supplementary testing method in the following scenarios: patients who are highly suspected of having SLE but are ANA-negative; risk assessment and follow-up monitoring of patients with incomplete lupus; and differential diagnosis between SLE and other IFN-related autoimmune diseases. However, in practical application, its limitations should be fully recognized, and comprehensive judgment should be made according to the specific situation of each patient to avoid overinterpretation of a single IFN signature result.

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Conflicts of Interest

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