

Can Anti-Ribosomal Antibodies Improve Systemic Lupus Erythematosus Diagnosis?

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Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology. The only means of reducing its morbidity and mortality remains early diagnosis followed by timely medical treatment. SLE affects all populations worldwide, although prevalence rates differ between population groups, with higher rates among women of reproductive age and for African, Asian, and Hispanic ethnicities.[1]

The possibility of SLE diagnosis should be kept in mind during daily medical practice, not because of its high frequency, but because of the pronounced heterogeneity of its clinical presentation; of all autoimmune diseases, SLE probably has the greatest diversity in clinical manifestations. Biomarkers that can diagnose and differentiate SLE from other rheumatic autoimmune diseases are needed. However, in more than 50 years of research, no single biomarker has emerged capable of identifying SLE in diagnostic tests.

SLE's serological hallmark is the presence of circulating antinuclear antibodies (ANA). A positive ANA test is the starting point for diagnosing and classifying SLE, but by itself is not conclusive, because although ANA are expressed in virtually all SLE patients, they also occur in other autoimmune and non-autoimmune conditions. Consequently, SLE diagnosis and classification also require that patients meet certain clinical and immunological criteria defined by the American College of Rheumatology (ACR), and more recently by the European League Against Rheumatism (EULAR).[2]

ANAs have been the largest pool of serological biomarkers for SLE. Of the dozens of antinuclear specificities associated with SLE, only two have been included in the condition's diagnostic criteria: the double-stranded deoxyribonucleic acid antibodies (anti-dsDNA) and the Smith spliceosome antibody (anti-Sm). Both autoantibodies traditionally have been used to confirm an SLE diagnosis due to their high specificity for the disease. Nevertheless, their specificity—as well as sensitivity in the 90–98% range—depends on the assay used and the population in which it is employed. Recent studies reveal that presence of dsDNA antibodies is not exclusive to SLE. Considerable amounts of anti-dsDNA are found in other rheumatic diseases, neoplasms, infections and endocrine disorders, as well as in healthy older adults, which lessens specificity, and thus utility, of dsDNA antibodies in diagnosing SLE.[3]

In addition to the autoantibodies noted above, a number of novel immunological markers have been suggested as criteria for inclusion in the most recent SLE classification. The nominated biomarkers include cytokines such as B lymphocyte stimulator (BLyS) and tumor necrosis factor (TNF); chemokines including monocyte chemoattractant protein 1, or chemokine (C-C motif) ligand 2 (MCP-1/CCL2) and interferon gamma-induced protein 10, also known as C-X-C motif chemokine ligand 10 (IP10/CXCL10); the expression of genes regulated by interferon I (type I IFN) and markers of the T helper 17 cell (Th17) subpopulation.[4] Although

these markers have been associated with SLE pathogenesis or activity, the lack of technical wherewithal for their measurement in clinical settings—especially in low-resource contexts—has kept them from practical employment. Thus, the proposed novel immunologic markers may be important for classifying SLE in the future, but serological evidence of autoantibody production is still the prevalent diagnostic criteria for SLE.[2]


A subset of antibodies directed against ribosomal P proteins has proven useful for SLE diagnosis in Cuba and elsewhere

A subset of antibodies directed against ribosomal P proteins (referred to as anti-RibP) has proven useful for SLE diagnosis in Cuba and elsewhere. Anti-RibP reactivity is localized in three phosphoproteins: P0, P1 and P2 (with molecular masses of 38, 19 and 17 kDa, respectively) of the 60S ribosomal subunit. These phosphoproteins are located mainly in cell cytoplasm in the form of a pentameric protein complex whose functions likely include intervention in the elongation step of protein synthesis. RibP antibodies show intriguing pathogenic potential based on evidence of their ability to penetrate living cells and inhibit *in vivo* and *in vitro* protein synthesis.[5]

Antibodies to ribosomal proteins have not fared as well as other nuclear antibodies like anti-dsDNA and anti-Sm. Although ribosomal antibodies' specificity to SLE was evident early on, RibP antibody determinations only became widespread in clinical laboratories in this century.[6] The late emphasis on the value of RibP antibodies in diagnosing SLE is likely due to the fact that the most widely-used method for ANA screening, indirect immunofluorescence assays (IFA), is of limited value in detecting RibP antibodies. The low sensitivity of IFA in detecting RibP antibodies has been aggravated by omission of IFA cytoplasmic staining patterns (resulting from antibodies against cytoplasmic components like ribosomal P) by laboratories focused on ANA, which underestimated the utility of anti-cellular antibodies (ACA) as diagnostic agents.[7]

More recently, enzyme-linked immunosorbent assay (ELISA) kits have been used to detect RibP antibodies, allowing for high diagnostic flow at relatively low cost. Certainly, the current variety of diagnostic platforms with different antigenic preparations requires greater standardization, but most available assays rely on the specificity of RibP antibodies even within diverse populations of SLE patients. The ELISA test has shown the most consistent and least heterogeneous results among laboratories. [6,8] Detection of RibP antibodies using the ELISA method in human P0, P1 and P2 ribosomal proteins in both Cuban SLE patients and healthy controls have shown extraordinary specificity for SLE, exceeding that of dsDNA and Sm antibodies.[9] RibP antibodies are not abundant in patients with SLE—in the Cuban population, as in other populations, they were only found in a fifth of SLE patients. Rather, their diagnostic value lies in their great specificity, allowing for a definitive SLE diagnosis when

they are detected. The high specificity of RibP antibodies is of particular importance in the diagnosis of anti-dsDNA– and anti-Sm–negative patients, representing a significant proportion of patients with anti-RibP–positive SLE.[10] Failure to consider the presence of RibP antibodies in these patients may delay diagnosis and medical treatment.

The high specificity of RibP antibodies for SLE, now confirmed in multiple studies from different geographical regions, merits their inclusion in SLE classification and diagnostic criteria. Furthermore, since anti-RibP specificity exceeds that of other serological markers for SLE, it is time to make greater use of this marker in establishing early SLE diagnosis. 

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Submitted: August 19, 2020

Approved for publication: January 6, 2021

Disclosures: None

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