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Are Anti-Ribosomal P Protein Antibodies Relevant in Systemic Lupus Erythematosus?

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Abstract

Systemic lupus erythematosus (SLE) is a prototypal auto-immune disorder characterized with multiple organ involvement resulting in disability and increased mortality. Immune regulatory disturbances cumulate in activation of B cells and consequent auto-antibody production. Antigens for these auto-antibodies can be nuclear components and cytoplasmic elements. Anti-P antibodies react against acidic phosphorylated ribosomal proteins P0, P1, and P2 (with molecular mass of 38, 19, and 17 kDa, respectively) and are located on the S60 subunit of ribosomes. Ribosomal P proteins share a common 22-amino acid sequence that is present in the carboxyl-terminal. Anti-P antibodies can be detected in approx 15 to 20% of patients with lupus by several immunoassays, most frequently by enzyme-linked immunosorbent assay (ELISA) and/or Western blotting. However, no standardized assay is available. Auto-antibodies against eukaryotic P proteins appear highly specific for SLE; therefore, they can be used as diagnostic marker for the disease. Furthermore, association has been described with particular manifestations of lupus, especially with neuropsychiatric, renal, and hepatic involvements. Anti-P positivity and the titer of anti-P antibodies also fluctuate with clinical disease activity. Despite several lines of evidence, results are conflicting regarding the existence of such associations. Discrepancies can be explained by different study set-up or study population; it also can be attributed to the different sensitivity of tests used for the detection of anti-P antibody.

Index Entries

CNS; lupus; autoantibodies; ribosomes; ELISA.

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Introduction

Epidemiological studies raise the issue of possible pathogenic role of anti-P antibody in different manifestations of lupus. Although several in vitro studies have been performed, less is known about the biological function of anti-P antibodies. They can bind to and penetrate into different cells and then influence cell viability and cell functions. This article summarizes the results of the most relevant studies, published previously or recently, mainly regarding the clinical importance and biological functions of anti-ribosomal P protein antibodies.

Clinical Associations

Frequency of Anti-P Antibodies and Specificity to Lupus

Anti-P antibodies are present in 15 to 20% of patients with SLE. The frequency can be modified by the technique (gel immunoprecipitation, immunofluorescens, radio-immunoassay, immunoblot, ELISA) *(1)* and the antigen source (highly purified synthetic peptides of the carboxyl terminal 22-amino acid sequence, a multiple antigen format and purified native, or recombinant proteins) *(2)* used for the detection of anti-P antibodies. Ethnic background, genetic factors, age at the onset of the disease, clinical manifestations, and activity of the disease may also account for the different frequency of anti-P antibodies among patients with SLE. Patients of Asian origin have anti-P antibodies more frequently (approx 38%) than other ethnic groups *(2)*. It can be partly attributed to different expression of major histocompatibility (MHC) class II antigens *(3)*. Early and recent (disease duration of 1 yr or less) onset of the disease and activity also appear to increase the frequency of positive anti-P antibody test results *(4,5)*.

Anti-ribosomal P-protein antibodies are highly specific for SLE. In the study published by Ghirardello *(6)*, 20% of patients with lupus and 5% of patients with undifferentiated/overlap CTD were positive for anti-P antibody, but none of the control sera presented the same result. Anti-P antibodies were found in SLE by Western blotting with a sensitivity of 20 and 100% specificity, respectively. Teh *(7)* also confirmed specificity of anti-P antibodies to lupus. Anti-P antibodies have been detected only occasionally in disorders different from SLE or SLE overlap conditions *(8)*. Hamasaki et al. *(9)* proved that the presence of anti-P antibody is predictive for the development of lupus. To summarize, we can conclude that the high specificity of anti-P antibodies for SLE makes them a potential diagnostic marker. However, the low prevalence of these auto-antibodies is the limitation for their use as a new diagnostic or classification criterion *(1)*.

Activity

Anti-P antibodies may take part in the general disease activity *(10)*. Elkon et al. *(11)* found that anti-P antibody was present in 10% of patients with SLE, but the frequency increased up to 40% in those with active disease. Massardo et al. *(5)* detected anti-P antibodies in 23% of patients with active disease, conversely to 4% of those with inactive state. An article from Reichlin *(12)* cited previous studies that evidenced a correlation of anti-P antibodies with general disease activity as well as longitudinal studies anti-P antibodies fluctuated with episodes of psychosis. Sato *(13)* and Gerli *(14)* also found anti-P antibodies with higher frequency in patients with active disease. On the other hand, Wu et al. *(15)* did not find correlation between anti-P antibody and disease activity (SLEDAI). In a lupus cohort with a similar clinical feature and with and without anti-P antibody, Ghirardello *(6)* also could not prove a correlation between anti-P antibody positivity and disease activity, as assessed by the doctor's global assessment.

Neuropsychiatric Manifestations

Neuropsychiatric SLE includes neurological syndromes of the central, peripheral, and

autonomic nervous system as well as psychiatric manifestation. Depression, psychosis, mood disorders, anxiety, cognitive dysfunction, and delirium/encephalopathy consist of psychiatric disorders. Standard nomenclature for 19 neuropsychiatric symptoms associated with SLE (NPSLE) was recently proposed by an *ad hoc* committee of the American College of Rheumatology *(16)*. Patients with NPSLE also can be classified into three different groups—namely, those with psychosis and/or mood disorders, those with other diffuse manifestations, and those with focal neurological events *(2)*. However, the diagnosis, differentiation, and treatment of NPSLE remain challenging. Therefore, a serological marker could help identify NPSLE and to determine a pathogenous auto-antibody that could become the target for immunosuppressive therapy.

Anti-P antibodies are predominantly found in the serum of patients suffering from lupus with neuropsychiatric involvement; however, this association remains controversial and is under investigation. After Bonfa *(17)* observed high titers of anti-P antibodies in lupus psychosis, several studies were performed and published to confirm the possible association between anti-P antibody and psychiatric manifestations, especially psychosis *(5,18–21)*. Reichlin *(12)* reviewed publications that, despite some existing controversies, suggested a meaningful relationship between anti-P antibodies and central nervous system disease *(12)*.

Yoshio et al. *(22)* detected a significantly higher frequency of anti-P antibodies in cerebrospinal fluid (CSF) in patients suffering from SLE with serum anti-P antibodies and in those suffering from NPSLE, particularly complex presentations *(22)*. This observation may confirm the pathogenic role of anti-P antibodies in neuropsychiatric lupus. Although serum (and/or CSF) anti-P antibodies are associated with lupus psychosis, the mechanism by which these antibodies lead to the development of the symptom is not understood. The interaction of anti-P antibodies with neurocytes has not been directly evidenced in vivo. Concordantly, recent epidemiological studies and clinical observations have not confirmed such an association between anti-P antibody and NPSLE *(14,23–25)*. Karassa et al. *(2)* recently published a meta-analysis of data from 1537 patients with lupus thatindicated anti-P antibody testing for the diagnosis of NPSLE overall or for particular manifestations is not helpful and negligible; the weighted sensitivity and specificity of anti-P antibodies for the diagnosis of NPSLE were 26 and 80%, respectively *(2)*. Anti-P testing could not discriminate between patients with diffuse and focal events and those with psychiatric manifestation and other diffuse symptoms.

Hepatic Manifestation

Anti-ribosomal P protein antibodies have been reported to have significant association with lupus hepatitis. In a retrospective study, Arnett et al. *(26)* extensively examined the hepatic manifestation in 131 patients with SLE. Lupus hepatitis appeared to be an infrequent (3%) but distinct manifestation of SLE that correlated strongly with the presence of anti-P antibodies. The course and prognosis were variable, ranging from chronic biochemical abnormalities of liver function to acute clinical hepatitis or hepatic failure. The clinical picture of the liver involvement resembled chronic active hepatitis, but there was no serological evidence of hepatitis B or C infections.

Koren et al. *(27)* described the development of chronic active hepatitis in a patient with lupus together with the appearance of anti-P antibody. Hulsey et al. *(28)* also reported higher frequency of hepatic involvement in patients with SLE who presented with anti-P antibodies compared with those who did not have such antibody. These observations raise the possible pathogenic role of anti-P antibodies in the development of lupus hepatitis; however, it also could be attributed to crossreactivity with anti-DNA antibodies. The article by Caponi et al. *(29)* provided a critical update of the clinical associa-

tions described in patients with lupus. On the other hand, in a prospective study of 141 consecutive Chilean patients with SLE, Massardo et al. *(5)* did not find an association with hepatic involvement. Wu et al. *(15)* found no correlation between anti-P antibody and liver disease in 150 patients with SLE from China.

Renal Manifestation

Kidney involvement can be detected in approx 30 to 40% of patients with SLE and may progress to end-stage renal disease. Nephritis in patients with lupus was recognized to have increased prevalence with anti-P antibodies. Martin et al. *(30)* described that anti-P antibodies fluctuated simultaneously with anti-dsDNA titers and with the activity of lupus nephritis. Hulsey et al. *(28)* confirmed this finding. Furthermore, glomerular eluates from lupus renal tissue were found to contain anti-P antibodies significantly enriched with respect to their serum level, suggesting specific deposition and possible pathogenic role of these auto-antibodies in the development of glomerular damage *(31)*. In that study by Massardo et al. *(31),* anti-P associated with anti-dsDNA but not with active glomerular disease. In the most recent study, published by Nascimento et al. *(32)* anti-P antibodies were determined in 81 consecutive patients with lupus with biopsy-proven glomerulonephritis. Significant association was found between the frequency of anti-P antibody and class V nephritis as well as with the level of proteinuria.

Because the level of anti-P antibody is known to fluctuate with disease activity, data provide evidence for a novel serological marker of membranous glomerular disease. Conversely, anti-dsDNA associated with proliferative lesions and impaired renal functions. The result appears to be relevant because in class V nephritis, glomerular deposits failed to identify antigen targets previously. Ribosomal P proteins were shown on the renal cell surfaces in auto-immune and normal mice and, therefore, further increases the possibility that anti-P antibodies are involved in renal damage *(33)*.

Serological Associations

The hallmark of SLE is the presence of antinuclear and anticytoplasmic auto-antibodies. Anti-dsDNA, anti-Sm, and anticardiolipin antibodies are included in the diagnostic criteria of systemic lupus erythematosus revised by the American College of Rheumatology *(34)*. These auto-antibodies may associate to particular clinical manifestations of the disease. Not surprisingly, anti-ribosomal P protein antibodies (which are specific markers of lupus) also may associate with different organ involvements, as discussed earlier, as well as with the presence of other peculiar auto-antibodies.

The majority of publications in this regard describe associations between anti-P and anti-dsDNA antibodies *(5,31,35)*. Besides anti-dsDNA, anti-P antibodies were found to correlate with the presence of anti-Sm and anti-RNP antibodies *(15,36)*. Elkon et al. *(37)* found that both the frequency and the titer of anti-P antibodies were higher in anti-Sm positive sera compared to anti-Sm-negative sera *(37)*. Other antibodies may also associate with and modify the effect of anti-P antibodies. In detail, antibodies to lipoprotein lipase (anti-LPL) significantly increase the risk for lupus nephritis when they act in synergy with anti-P antibody (odds ratio [OR] 17.11 vs 3.47) and/or with anti-DNA (OR: 4.2 vs 2.84), as observed in a recent study by Reichlin *(38)*.

On the other hand, anti-P antibodies can also be shown alone in lupus sera. An example was published by Nascimento et al. *(32),* who observed that half of the anti-P-positive patients with lupus nephritis did not have anti-dsDNA antibodies and consequently presented different clinical and histopathological characteristics. According to the case report by Koren *(27)*, anti-ribosomal P antibody and the consequent lupus hepatitis developed after the disappearance of antinuclear antibodies *(27)*. Similarly, in 3 of the 153 subjects in a study by Bonfa *(39)*, lupus sera anti-P antibody was detected without any nuclear immunofluorescence. In the

same work, anti-SSA was found to be the most frequent antibody in anti-P-positive sera *(39)*.

The association between anti-P and other auto-antibodies can be partly attributed to the polyclonal B-cell activation characteristic for SLE; however, it could not be confirmed in all publications. Furthermore, cross-inhibition experiments excluded the presence of shared common epitope on Sm and ribosomal P proteins *(37)*. Conversely, anti-DNA antibody was able to bind to and crossreact with P protein expressed on mesangial cells in kidney affected by lupus glomerulonephritis *(33,40)*. On the other hand, anti-ribosomal antibodies from patients with lupus bind DNA *(41)* as well as Sm proteins *(42)*.

The close association between IgG anti-P and anticardiolipin antibodies shown recently by Ghirardello et al. *(6)* appears to be fascinating and highly relevant. Interestingly, none of the anti-P-positive patients with lupus had antiphospholipid syndrome (APS), and none of the patients with primary APS presented anti-P antibodies *(6)*. These observations indicate that the correlation of anti-P antibody with anticardiolipin is strong and specific for SLE, in which it confines to a subset of antibodies to cardiolipin-positive patients with lupus not at risk from antiphospholipid-related thrombotic events. Because no homology exists between these two auto-antibodies, their co-existence suggests a possible common pathogenic pathway (e.g., simultaneous production of antigens and antibody clustering during dysregulated apoptosis) *(6,43,44)*.

The Antigen Binding and Penetration of Auto-Antibody Induction of Apoptosis Cytokine and Other Effects

Besides eukaryotes, fungi, insects, and protozoans possess ribosomal phosphoproteins. Therefore, anti-ribosomal antibodies are usually present in human and experimental chronic infections (e.g. with *Trypanosoma cruzi*); however, these antibodies show weak reactivity toward the C-terminal end of mammalian ribosomal P protein *(45)*. However, because there is a sequence on P proteins that is highly conserved during evolution, in an earlier study, Elkon et al. *(46)* observed similar properties of the ribosomal P2 protein auto-antigen to those of foreign protein antigens.

In eukaryotic cells, the major antigen targets of anti-ribosomal antibodies are the three alanin-rich phosphorylated proteins—P0, P1, and P2, which have molecular weights of 38, 19, and 17 kDa, respectively *(47)*. Rarely, RNA *(47,48)* and other ribosome-bound proteins, such as L7, L12, and L14, can be also recognized *(11,49)*. The immonodominant epitope, which is shared by P0, P1, and P2, is a single sequential epitope consisting of 22 amino acids at the carboxyl terminal, although a conformational epitope may also exist *(29,48,50)*. Recently, an immunogenic epitope was also observed on the N-terminal *(51)*.

The P0, P1, and P2 form a pentamer structure consisting of two P1/P2 heterodimers bound to one P0 molecule. A P protein complex forms the lateral stalk of ribosome and binds the GTPase-associated domain of 28S rRNA of the 60S large ribosomal subunit *(52,53)*, where they interact with elongation factors 1α (EF-1α) and 2 (EF-2) inhibiting protein synthesis *(54,55)*. Ribosomal P proteins catalyse the translocation of peptidyl tRNA. Phosphorylation of ribosomal P proteins is required for the interaction with EF-2; therefore, the phosphorylation of these proteins may act as one of the regulatory mechanisms with the potential of influencing polypeptide synthesis *(1)*. In addition to the function of ribosomal P proteins on translation, it has been reported that a particular ribosomal protein (RPS3A) also control cell growth and apoptosis *(56)*. The control mechanisms of gene expression and the functions of ribosomal proteins are believed to be identical *(57)*.

P proteins in eukaryotic cells are mainly associated with ribosomes, but they also can be found in a ribosome-free cytoplasmic pool *(58)*. Furthermore, the P0 protein has been demonstrated on the surface of different cells, including human hepatoma, neuroblastoma, fibroblast, endothelial, and glomerular mesangial cells as well as T-lymphocytes *(33,59–61)*. On T-cells, the cell surface expression of P protein is activation-dependent because the presence of an epitope that is antigenically related to the carboxyl-terminal 22-amino acid sequence of the protein has not been demonstrated on resting $CD4^+$ and $CD8^+$ T-cells, but the expression a P protein has been induced by activation of these cell types with immobilized anti-CD3. The expression of ribosomal P protein on immunocompetent cells appears to be also cell-type-dependent, because the previously mentioned antigenic P protein was expressed neither on resting nor activated B-cells *(62)*.

Besides activation, apoptosis also can induce the translocation of ribosomal P proteins to the membrane. The strong association and the appropriate exclusion of crossreactivity and homology between anti-P and anticardiolipin antibodies also suggests the possibility of a common pathogenic pathway (e.g., apoptosis) implicated in their concomitant production and such antibody clustering *(6)*. Ribosomes can be detected in small apoptotic blebs together with Ro ribonucleoproteins and rough endoplasmic reticulum after ultraviolet-induced apoptosis of human lupus keratinocytes *(43)*.

The membrane form of P0 protein acts as a cellular receptor, mediating the binding and penetration of antibodies into the cytoplasm *(63)*. However, the mechanism by which the penetration occurs was not clear until recently. If anti-P antibodies have once penetrated into the cell, they influence different cell functions. For example, Koscec *(64)* found evidence that affinity-purified anti-P antibodies penetrated into living HepG2 cells and affected protein synthesis, particularly those of lipoprotein B. Monoclonal antibodies against human ribosomal P proteins also could penetrate into normal mice brain astrocytes, lung cancer cells, and Jurkat T-cells. Treatment of Jurkat T-cells with monoclonal anti-P antibody increased the percentage of cells in sub-G1 phase and those undergoing apoptosis, suggesting that anti-P auto-antibodies may play a role in the pathogenesis of lymphopenia and lymphocyte dysfunction *(65)*. Apoptosis of T-cells may also occur in human SLE because of anti-P antibodies. Although anti-P antibodies can bind to different cell types, the concentration and the expression of P antigens or their reactivity and sensitivity may vary in different tissues, partially explaining the association of anti-P antibodies with certain organ involvements. Sensitivity to anti-P antibodies can be influenced by the stage of the cell cycle as well *(65)*.

Recently, a few studies have described modulation of cytokine network. Sun *(66)* demonstrated that the treatment of LPS-stimulated murine macrophages with monoclonal anti-P antibody significantly inhibited the production of interleukin (IL)-12, tumor necrosis factor (TNF)-α, and inducible nitric oxide synthetase (iNOS) both at messenger RNA (mRNA) and protein levels, whereas the production of IL-10 increased. These changes are consistent with T-helper 2 dominance, which enhances autoantibody formation. Results have also suggested that the decrease in iNOS and TNF-α production is the consequence of the reduction of IL-12 release. Equivocally, another team observed the upregulation of TNF-α together with IL-6 in human peripheral blood monocytes after treatment with anti-P antibodies. This process did not require FcγR crosslinking.

Similarly to T-cells, human peripheral blood monocytes expressed ribosomal P antigen upon activation but irrespectively of induction of apoptosis *(67)*. Authors have discussed that these changes in the cytokine milieu may modify the collaboration between monocytes and endothelial cell and may contribute to vascular damage. The observed cytokine pattern also can influence the cooperation between

lymphocytes and endothelium, because they may promote transendothelial migration of activated lymphocytes. Furthermore, IL-6 is known to increase adherence of endothelium for lymphocytes, facilitating the recruitment of lymphocytes into other nonlymphoid tissues (e.g., the place of inflammation), and this may have a pathogenic role in NPSLE. Using a molecular cloning strategy, ribosomal P0 protein also was identified as an endothelial antigen *(68)*.

Based on these experiments, our hypothesis to explain the association of the higher frequency of anti-P antibodies in patients with active lupus is the following: in the active phase of SLE, activated T-cells express P0 protein on their surfaces. Furthermore, P proteins are also presented in apoptotic blebs, because the rate of programmed cell death is also enhanced in active lupus. Increased concentration of the auto-antigenic P proteins induces and drives auto-antibody formation, and anti-P autoantibodies further augment the apoptosis and cause a T-helper 2 dominance in the cytokine network that is responsible for increased autoantibody production. This could result in a self-perpetuating process; however suppressor/regulator mechanisms downregulates and stops this vicious circle.

Anti-idiotypic antibodies are important elements of regulatory mechanisms. Specific suppression of harmful immune response can be reached by the regulation of idiotype–anti-idiotype interactions. The immune system recognizes private and/or public idiotypes on certain auto-antibodies and, consequently, produces anti-Id. Zhang et al. *(69)* isolated a human monoclonal single-chain Fv IgG anti-idiotypic antibody from a phage display library that specifically inhibited anti-P antibody activity in immunoassays and also inhibited anti-P antibody binding to Jurkat cells. Such autologous or synthetic anti-Id antibodies can be potentially used as therapeutic agents *(69)*.

Further research work is needed to clarify the exact mechanisms by which anti-ribosomal P protein antibodies participate in the development of systemic lupus erythematosus and its special organ manifestations, and work is also needed to investigate the cellular effects of these interesting auto-antibodies.

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