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Annals of the Rheumatic Diseases collection on autoantibodies in the rheumatic diseases: new insights into pathogenesis and the development of novel biomarkers

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Abstract

The rheumatic diseases are a diverse group of conditions that can display autoantibody production, functional immune disturbances and systemic disease manifestations. These antibodies can serve as markers for classification, diagnosis, prognosis and disease activity. Among specificities prominently expressed by patients, those directed to nuclear antigens (antinuclear antibodies or ANAs) are markers for specific rheumatic diseases. ANAs can bind to DNA, RNA and complexes of proteins with nucleic acids. Other autoantibodies expressed in the rheumatic diseases are directed to proteins, including IgG, post-translational modifications of proteins, and soluble mediators such as cytokines. While autoantibodies have been investigated for over 50 years, recent studies published in the *Annals of the Rheumatic Diseases (ARD)* have provided an exciting perspective on the mechanisms of autoantibody production and the power of new technologies to identify novel autoantibody targets to elucidate etiology and underpin patient evaluation. Furthermore, in-depth serological studies have demonstrated a phenomenon known as clustering; clustering defines sets of autoantibodies that are commonly expressed together in patients with a given rheumatic disease. Other research reported in *ARD* has used B cell phenotyping and genotypic analysis to subtype patients, and have explored the relationship of autoantibodies, complement activation and the patterns of gene expression as exemplified by the interferon gene signature. Together, these studies provide important new insights into disease mechanisms as well as actionable information to facilitate personalized patient care.

Keywords

rheumatic diseases; autoantibodies; antinuclear antibodies; biomarker; complement; B cells

Introduction

Autoimmunity is central to the pathogenesis of many rheumatic diseases and has therefore been the focus of many papers published in *Annals of the Rheumatic Diseases* (*ARD*). These papers have been exciting and insightful and have addressed important topics such as the mechanisms of autoantibody induction, the molecular properties of autoantibodies and

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autoantigens, new autoantibody specificities, and the role of autoantibodies as biomarkers. This review will consider papers on these topics that have appeared in *ARD* primarily since 2020. As the discussion will indicate, new technology is revealing a more deep, detailed and nuanced picture of disease mechanisms. Importantly, papers in *ARD* have provided actionable information on serological testing for diagnosis, prognosis, disease activity and response to therapy

Rheumatoid arthritis

Rheumatoid factors (RF) are sensitive markers for rheumatoid arthritis (RA) and a characteristic immunological feature of this disease. Primarily IgM antibodies, RFs bind to IgG but lack a single, discrete specificity; rather, RFs bind to diverse antigenic determinants in the Fc region of the IgG molecule. Although present in approximately 80% of RA patients, RFs can occur in patients with other inflammatory diseases as well as infection. These findings have suggested that RFs result from immune system activation and can contribute to host defense, perhaps by augmenting IgG binding to antigen and promoting complement fixation.

To elucidate RF interactions, a study by Oskam et al used a panel of molecularly engineered IgG molecules to define antigenic determinants recognized by RFs from RA compared to those of RFs from other clinical groups, including healthy donors [1]. These findings showed that RFs can bind to a variety of sites on human IgG Fc that had been experimentally mutated to sequences from mouse IgG. Importantly, the sites bound by RA RFs could be distinguished from those of RFs from healthy donors or patients with Sjogren's syndrome. These findings highlight differences in RF specificity depending on clinical settings as well as potential differences in the functional properties of RFs, including their pathogenicity in RA.

Antibodies to citrullinated proteins (ACPAs) are specific markers RA and are usually assayed as antibodies to citrullinated peptides (anti-CCP). To elucidate the relationship of these antibodies to clinical disease activity, important articles in *ARD* have explored ACPA expression in RA in both early and late phases of disease[2 3]. As these studies indicate, by the time a patient displays symptoms, the ACPA response appears mature. Neither the amount nor specificity of ACPAs appears to demarcate a transition from arthralgia to arthritis. Similarly, ACPA responses appear stable with remission and persist despite decreases in synovitis; these findings suggest that elimination of ACPA responses is not an essential goal in treat-to-target approaches.

The persistent expression of ACPAs poses important questions about the pathogenesis. If ACPAs can drive disease, why are these antibodies present in asymptomatic individuals? In the setting of remission, similar questions arise. If ACPAs drive joint inflammation, why does synovitis diminish despite ACPA expression? These issues are especially pertinent in view of studies that anti-CCP antibodies can induce pain by transfer into animals [4]. The absence of pain in serologically positive patients is therefore a striking finding.

One explanation for these findings relates to the functional properties of ACPAs. A fascinating study by Raposo et al showed that some ACPAs surprisingly can block

inflammation [5]. This study assessed the effects of monoclonal ACPAs in the collagen-antibody induced arthritis model in mice and showed that certain monoclonal antibodies tested could diminish inflammation. It is therefore possible that shifts in the profile of ACPAs and their capacity to modulate disease can occur even if the antibody levels remain unchanged.

The study of ACPAs has been important in elucidating immune responses to post-translational modification (PTM) of proteins, of which citrullination is a prime example. Citrullination converts arginine to citrulline and is catalyzed by enzymes known as peptidylarginine deiminases (PAD). The function of this modification is not well understood although it may arise during inflammation as can occur in RA in the lung. Citrullination is not the only PTM relevant to RA since patient antibodies can also bind to proteins modified by carbamylation with changes lysine to homocitrulline. Antibodies to acetylated lysine also occur in RA. As shown with monoclonal antibodies derived from patients, cross-reactive binding to the various modifications (i.e., citrullination, carbamylation, and acetylation) is a feature of this group of autoantibodies [6]. Of interest, a study by Castellanos et al showed an association of antibodies to carbamylated proteins and interstitial lung disease (ILD), another finding pointing to the lung as a site where PTMs may form [7].

While the presumed origin of PAD enzymes is the host, a study by Jenning et al demonstrated that prokaryotic peptidyl arginine deiminase (PPDA) from *Porhyromonas gingivalis* can also citrullinate proteins including itself; proteins citrullinated by this enzyme can be recognized by patient sera, with antibody levels to citrullinated PPDA correlated with anti-CCP levels as well as ILD [8]. Since *PG* is present in periodontal disease, these findings raise the possibility that citrullination can arise from certain infection and can be mediated by enzymes of the causative organism, a novel mechanism to link infection to autoimmunity.

Systemic lupus erythematosus

The prototype systemic autoimmune disease, systemic lupus erythematosus (SLE) displays a diverse set of autoantibodies to components of the cell nucleus that serve as marker of pathogenesis, classification and disease activity. These antibodies are collectively termed antinuclear antibodies (ANAs) and bind to DNA, RNA and protein complexes of DNA and RNA. ANAs can be detected by a variety of immunochemical assays which produce similar but not identical results; for immunofluorescence assays (IFA) with Hep2 cells, differences can relate to titer, pattern and frequency of positivity in SLE patients [9]. Assay variability is of great significance since the presence of an ANA is now required for the classification of a patient with SLE [10].

An impressive study by Choi et al from the Systemic Lupus International Collaborating Clinics (SLICC) group involved a longitudinal analysis of a large patient cohort to determine comparability of three different ANA assay kits [11]. The study investigated two different IFA assays as well as an ELISA and determined serological status at disease onset and over the subsequent 5 years. As the results indicated, the three different assays all showed a very high frequency of ANA positivity in the initial samples although, by year 5, the frequency of positive results by ELISA had declined. There was a greater than 91% agreement in

positivity at all times tested but only a 71% agreement in IFA patterns between the two IFA assays.

The study involved only 3 ANA kits but many more kits are available. Furthermore, in "the real world," determination of ANA titers and patterns can be imprecise; this study utilized both a digital IFA microscope with verification by a technologist with 30 years of experience, assuring high quality reads. Going forward, it will be important to evaluate changes in ANA responses over longer periods of time. Since ANA expression appears dynamic, the study of Choi et al provides a valuable starting point to delineate the properties of the ANAs that persist and those that dwindle with the passage of time or effective therapy.

In a related study, Choi and colleagues from the SLICC group investigated an intriguing phenomenon called clustering [12]. While SLE is a very heterogenous disease, nevertheless, detailed serological profiling can identify sets of autoantibodies that commonly occur together. Using machine learning, this study defined 4 clusters: 1) cluster 1 had a high frequency of anti-Sm and anti-U1RNP and the highest proportion of patients of African ancestry; 2) cluster 2, the largest cluster, had a low frequency of anti-DNA and the lowest proportion of nephritis; 3) cluster 3, the smallest cluster, had the highest frequency of anti-phospholipid antibodies; and 4) cluster 4 showed many autoantibodies, including antibodies to DNA, ribosomal P, La, Ro52, Ro60, PCNA and centromere.

Surveying longitudinal ANA responses, this study indicated that frequency of anti-Sm and anti-RNP responses declined over time. While the variability of anti-DNA levels provides a biomarker for disease activity, the change in the antibody levels to Sm and RNP is surprising and provide further evidence for the dynamic nature of ANA production. Along with other studies on clustering, the findings of Choi et al raises questions about the origin of the phenomenon, including the role of ancestry and possible environmental exposures. Assessing clustering also has practical application since the clusters differ in clinical features such as nephritis or thrombosis. As such, clustering can help predict disease course and prognosis. Both studies by Choi et al also suggest the utility of periodic reassessment of ANA responses to determine any gain or losses of ANAs, especially in response to particular therapies.

The interferon gene signature (IGS) is a characteristic feature of SLE and other rheumatic diseases and may also result from immune complexes (ICs) containing nucleic acids, either DNA or RNA. Along with anti-DNA, antibodies to RNA binding proteins (RBPs) such as Sm, RNP, Ro and La are associated with increased interferon gene expression A study by Hubbard et al explored the relationship between different ANAs, complement levels and the IGS in a large patient cohort and showed that, while anti-RNP is associated with the IGS, it is not clearly associated with decreased complement levels [13]. This finding is intriguing since ICs comprised of an ANA and its target nuclear antigen would be expected to activate complement. This study therefore suggests that ICs in SLE are structurally and functionally heterogeneous and that complement activation may occur with ICs with comprised of only certain ANA (e.g., anti-DNA) and that those with anti-RNP lacking some critical property.

In the diseases in the lupus spectrum, chronic cutaneous lupus erythematosus (CCLE) encompasses serious skin manifestations such as discoid lupus (DLE). Although DLE can occur in patients without systemic disease, transitions from DLE to SLE can also occur. In an elegant paper in *ARD* in 2021, Jenks and colleagues used state-of-the-art immunological techniques to characterize B cell abnormalities in patients with CCLE in comparison with those with systemic disease [14]. As the data indicate, like SLE, CCLE is clinically and immunological heterogeneous although some patients have B cell disturbances (decreased unswitched memory B cells and increased effector B cells) like those in SLE. By stratifying patients into those with SLE-like B cells and those with normal B cells, Jenks et al showed that patients with more serological activity were more likely to show disseminated skin lesions.

Sjogren Syndrome

Sjogren syndrome (SS) is a systemic autoimmune disease characterized by sicca symptoms (dry mouth, dry eyes) in association with the production of antibodies to Ro/SSA (Ro 52 and Ro 60) and La/SSB. Since many patients with SS lack either anti-Ro or anti-La. Identifying new antibody markers would be valuable for diagnosing SS especially in those who are negative for conventional ANAs. In an application of novel techniques for antigen discovery, Longobardi and colleagues used a proteome array with over 19,500 proteins to analyze sera from patients with SS, those with and without antibodies to Ro [15]. In this way, the investigators identified a series of new antigens which were found in 87% of the anti-Ro subset compared with 7% with anti-La. In the discovery cohort, patients bound a mean of 3 to 4 of the novel antigens.

In addition to developing a predictive model for SS using machine learning of the serological data, the authors tested the expression of the new, so-called non-canonical specificities, in a rheumatology practice as a validation cohort. The results of this study indicated that patients could bind many of the newly discovered autoantigens, suggesting the value of an extended analysis of binding to canonical and non-canonical biomarkers. Furthermore, the investigators showed that the newly discovered antigens were related to leukemia cells, ubiquitin conjugation and antiviral defense pathways. The analysis also revealed enrichment of antigenic proteins in tissues affected by SS.

This paper is important clinically by providing markers to help diagnose and classify patients with SS especially those who lack anti-Ro and anti-La. The enrichment of proteins in the category “leukemia cells” is notable and suggests that autoantibodies may arise during surveillance of cancer cells. Since SS is associated with lymphoma, perhaps an immune response to nascent hematological malignancy can initiate immunological events in SS.

Another paper on SS provided an intriguing picture of local autoantibody production in salivary glands [16]. To generate monoclonal autoantibodies for analysis, most studies have utilized peripheral blood as a source of B cells. As shown by Takeshita et al, this approach is potentially limited and can miss the contribution of autoantibodies produced in the affected tissue. Takeshita et al termed these locally produced antibodies as lesion antibodies. Because salivary gland tissue can readily be obtained, SS provides an apt model for comparing the repertoire of antibodies in peripheral blood B cells and those in a lesion.

The results of these studies indicate that antibodies to Ro52, Ro60 and La are produced in the lesions and that these antibodies have somatic mutations indicating antigen selection. Among lesion antibodies, Takeshita et al also identified antibodies to centromeres (ACAs) and delineated a novel pattern of reactivity to components of a complex denoted as MIS12. Further studies suggested that these antibodies recognize sites dependent on the conformation of the MIS12 complex, with some of the monoclonal antibodies binding only when all complex components are present.

Two other important concepts emerge from this paper. The first is that the antibody repertoire of B cells in the periphery and the lesions are not identical and that disease-related antibodies may be produced preferentially in the affected tissue. Second, the paper suggests the value of classifying disease in terms of serology, with ACA-related diseases encompassing SS, limited scleroderma (SSc) and primary biliary cholangitis (PBC).

A related study extended the molecular dissection of anti-centromere antibodies [17]. Although the binding to the CENP-B protein is used to assay for ACAs, the centromere is an enormously complicated “antigen” as it comprises 16 principal subcomplexes built with 41 different proteins. To understand the specificity of ACA, Kajio et al assayed sera from patients with SS, SSc and PBC for binding to individual proteins as well as complexes. While the pattern of reactivity of sera from the different disease groups was similar, clustering analysis indicated major and minor clusters of specificities. Furthermore, monoclonal antibodies derived from SS salivary glands showed reactivity to the newly defined autoantigens.

The paper further bolsters the idea that autoantigens, rather than simple proteins, can be large complexes that can induce similar responses in different diagnoses. As such, the papers by Kajio et al and Takeshita et al suggest that, to understand autoimmunity, new models for antibody induction are needed to go beyond the reductionist approaches commonly used by immunologists to dissect the response to a single, structurally well-defined proteins.

Systemic sclerosis

One promising approach for elucidating the B cell contribution to autoreactivity is to determine the effects of therapy on autoantibody levels. the mode of action of many anti-rheumatic drugs is not well understood and some may act on both B and T cells; these drugs may also be given in combination which further complicates the analysis. Few studies therefore are able to relate the effect of a therapy to the autoantibody response to illuminate underlying immune cell disturbances.

The SCOT trial is a notable exception to this situation. The SCOT trial (Scleroderma: Cyclophosphamide or Transplantation) compared the effects of cyclophosphamide with myeloablative CD34-selected hematopoietic stem cell transplantation (HSCT) and demonstrated increased efficacy of HSCT on a variety of clinical outcomes. While cyclophosphamide (CYC) can suppress B cells and deplete certain T cell populations, HSCT depletes both lymphocytes and stems cells, potentially eliminating the autoimmune repertoire and facilitating the repopulation with new cells that become tolerant. Since HSCT

is more effective than CYC, a comparison of the changes in B cell populations can help elucidate the critical cellular changes that lead to a better treatment outcome.

Two papers published in *ARD* provide unique molecular data to explicate the treatment effect. Admaska and colleagues sequenced peripheral blood immunoglobulin heavy (IgH) chain repertoires of treated patients and demonstrated notable changes in patients with HSCT: increases in IgM antibodies with a low mutation rate, a reduction of clonal expression in the IgH repertoire, and underutilization of the heavy chain V gene 5–51 [18]. Together, these findings suggest that HSCT can reset the immunoglobulin gene repertoire into a more naïve state as exemplified by the IgM B cell population. The reset in turn could be associated with a diminution of pathogenic B cells.

A study by Ayoglu et al tested the hypothesis that a reset can change the expressed B cell repertoire [19]. Using a bead-based array with common rheumatic disease antigens, viral antigens and secreted proteins, Ayoglu and colleagues surveyed the sera of treated patients at baseline and at regular intervals up to 48 months. The findings at baseline were notable in demonstrating at low levels the presence of antibodies to “traditional autoantigens” such as Ro 52, Ro60 and Sm; in addition, baseline samples showed antibodies to cytokines, chemokines and growth factors.

Analysis of samples from the CYC and HSCT treatment groups indicated differences in the response to six self-antigens and two viral antigens. Of these antigens, increases in antibodies to HBsAg, CCL3 and EGRF occurred in the HSCT group whereas levels of these antibodies were unchanged in the CTX group. Nevertheless, in both CYC and HSCT groups, levels of autoantibodies showed clustering which was stable over time in individual patients. On the other hand, the study also found evidence for the emergence of autoantibodies to other self-antigens including thyroid specific molecules. While HSCT may lead to “autotolerant stabilization,” new onset autoimmunity can nevertheless emerge during repopulation.

Of interest, this analysis demonstrated the presence of autoantibodies to cytokines in patients with SSc at baseline. Since baseline levels of these anti-cytokine antibodies were higher in patients with survived event-free, anticytokine antibodies may attenuate pathogenicity. Anti-cytokine antibodies occur in other clinical settings, where they may promote immunodeficiency. This study thus suggests the value in a more detailed analysis of the role of antibodies to cytokines, growth factors and other soluble proteins in SSc and other rheumatic diseases.

Myositis

Among the immune mediated myopathies (IIM), autoantibodies can define disease subtypes and can be categorized into those specific for these diseases (myositis specific antibodies or MSA) and those associated with these diseases (myositis associated antibodies or MAA). Among the IIM subtypes, the anti-synthetase syndrome (ASyS) displays myositis, interstitial lung disease, and Raynaud’s phenomenon among other findings. Autoantibodies to aminoacyl -tRNA synthetase (ARS) is the serological hallmark, with anti-Jo1 (anti-histidyl-tRNA synthetase) the most common

Since some patients with ASyS features lack known ARs, Vulsteke and colleagues searched for new antibodies using unbiased immunoprecipitation and mass spectrometry [20]. In this approach, serum is mixed with HeLa cell cytoplasmic extracts, immune complexes isolated by protein A/G beads and proteins eluted from the complexes sequenced by mass spectrometry. Results of this analysis indicated that the serum of a patient with clinical features of ASyS, a positive cytoplasmic HEp2 IFA but no known ARSs could contain antibodies to cysteinyl-tRNA synthetase as well as valyl-tRNA synthesis. The findings thus identified two novel ARSs called CARS1 and VARS1, with the dominant specificity CARS1 denoted as anti-Ly. This paper substantiates the relationship of antibodies to tRNA synthetases with features of ASyS and provides the basis of new assays to screen for antibodies from patients with suspected ASyS. While enlarging the family of ARSs, the association of these antibodies with a set of clinical features remains a mystery.

As in the case of other rheumatic diseases, the pathogenesis of IIM can result from genetic factors of which genes in the HLA complex have prime importance. Within the HLA complex, the genes for the C4 complement protein vary in terms of gene copy number variation (GCN); gene size with long and short genes reflecting the insertion of a retrovirus; functional differences between the acidic C4A and basic C4B proteins; and polymorphisms in immunochemical properties of C4A and C4B proteins.

In a detailed genetic and serological analysis, Zhou et al showed low GCNs with dermatomyositis and polymyositis in adults and children; HLA-DR3 with C4A and C4B with inclusion body myositis; and low plasma protein levels of C4 and C3 in patients with anti-Jo1 and other MAAs [21]. While the role of complement deficiency in SLE is well studied, the findings on myositis are novel and point to unexpected roles of the complement system in either autoantibody induction or the effector phase of disease. While monitoring of complement is not usually a part of the disease assessment in IIM, this paper suggests its utility.

Assay variation is always important in the clinical arena. In a very informative correspondence, Mahler and colleagues summarized differences in assays of MSAs using either a line immunoassay (LIA) or an immune precipitation assay [22]. Depending on antibody, the correlation between the two assays varied from weak to strong to almost perfect. When ordering tests, clinicians should therefore understand the performance characteristics of the laboratory assay used and be alert to the possibility of false negative results.

Conclusions

The papers on autoantibody expression in the rheumatic diseases in *ARD* demonstrate the vibrancy and vitality of the field of serology and the unique value of autoantibody testing to elucidate disease heterogeneity. As such, data in these papers provided a framework for personalized therapy based on autoantibody profile (i.e., cluster), IGS, complement activation and B cell phenotypes. Given the exciting findings reported in *ARD* the past few years, the future of the field is very bright and should witness further progress in revealing

fundamental disease mechanisms and the best approaches for using the laboratory to guide patient evaluation and treatment

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