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A Golden Anniversary: Recognition That Rheumatoid Arthritis Sera Contain Autoantibodies Specific for Determinants on Native IgG Molecules

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Fifty years ago, when this month's Pillars of Immunology article appeared in *The Journal of Experimental Medicine* (1), the concept of systemic autoimmune disease did not exist, and systemic lupus erythematosus and rheumatoid arthritis were thought to be diseases of connective tissue or collagen. The shift to an autoimmune paradigm that gradually occurred in the late 1950s was based on the demonstration that these diseases were characterized by the presence of Abs directed to self-Ags. In the instance of rheumatoid arthritis, this Pillars of Immunology paper (1) was arguably the central and definitive event in the reconceptualization of rheumatoid arthritis as an autoimmune disease. The paper used techniques that now would be classified as proteomic to examine the nature of unusual macromolecular interactions found in sera of individuals with rheumatoid arthritis. It was written in an understated style that provides an excellent insight into the intellectual creativity of that research era and the profound quality of its scientific inference. However, the terms IgM and IgG were yet to be introduced, and in their place, the descriptive 19s and 7s sedimentation constants of these molecules were used, reflecting the elegant use of analytic and preparative ultracentrifugation.

To summarize the contributions of this paper using the current Ig terminology, Franklin and colleagues made three interrelated observations on the presence and specificity of autoantibodies in individuals with rheumatoid arthritis. The first finding was that rheumatoid arthritis sera were characterized by large quantities, as much as 1.7 mg/ml, of a polyclonal IgM class autoantibody, which was directed to determinants on autologous IgG molecules. This conclusion was based on the demonstration that 19s IgM anti-IgG molecules circulate as an Ag-Ab complex with a sedimentation coefficient of 22s indicating they are bound to five serum IgG molecules, incidentally an elegant direct demonstration of the pentavalence of IgM. This was the first direct visualization and isolation of circulating immune complexes. Franklin and colleagues also provided evidence that this production of large amounts of polyclonal Abs specific for determinants on native IgG distinguished rheumatoid arthritis from other diseases. That the presence of these IgM anti-IgG autoantibodies implied an autoimmune event in rheumatoid arthritis was subtly affirmed in the last sentence of the discussion, "The possibility that the 22 S component might represent a soluble antigen-antibody complex appears worthy of further investigation." In other words, rheumatoid arthritis was being defined as an autoimmune disease where the IgG molecule is the autoantigen and that the formation of autoantibodies to this Ag results in circulating immune complexes. Subsequent work from the Kunkel laboratory by Schrohenloher would complete this part of the story by showing that the anti-IgG specificity, in addition to being present on IgM class Abs, was also found on IgG class Abs (2). The Ag-Ab complexes formed by these IgG antiglobulins typically contained two to three IgG molecules and sedimented intermediate between monomeric IgG and IgM. This finding would be the basis of the identification that the joint fluids contained pathogenically relevant complexes that were in part based on the action of IgG anti-IgG-globulins and that these intra-articular complexes contributed to local activation of innate immune system responses within the joint, including the activation and consumption of complement (3). In the light of many subsequent years of immunologic investigation, we now understand the polyclonality of the IgM autoantibodies to IgG likely indicates epitope spreading and affinity maturation, and along with subsequent evidence of a class switch to IgG class anti-IgG autoantibodies, clearly reflects the operation of T cell help in this disease-specific autoimmune response.

The second observation made by Franklin and colleagues provided an explanation for the intriguing phenomenon identified by Epstein, Johnson, and Ragan (4) that rheumatoid arthritis sera formed precipitin reactions with soluble aggregates of denatured IgG, perhaps suggesting that there was some specificity in rheumatoid arthritis sera that reacted with altered IgG. Franklin and colleagues showed that the addition of monomeric IgG molecules to purified IgM anti-Ig preparations formed the soluble pentameric 22s complex, but that if the same IgG molecules were heat-aggregated to form soluble aggregates of two or three IgG molecules, the aggregated IgG would be precipitated upon mixing with the same purified IgM anti-IgG autoantibodies. Furthermore, they showed that the native monomeric IgG could be competed off the 22s complex by the multivalent IgG aggregates, demonstrating that the specificity of the IgM anti-IgG Abs that formed the 22s complexes was the same as those that precipitated the multivalent IgG aggregates. We now recognize this experiment as an example of increasing reaction avidity of the autoantibody for the aggregated IgG by increasing the valence of the aggregated IgG ligand.

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The third finding of Franklin and colleagues was to obtain evidence that a subpopulation of the anti-IgM/anti-IgG autoantibodies agglutinated rabbit IgG-coated sheep cells or latex particles coated with human IgG designated as the rheumatoid factor. By way of background, the notion of rheumatoid arthritis as a collagen disease always fit somewhat uncomfortably with the presence of peculiar agglutination reactions in rheumatoid arthritis sera first noted in 1931 by Cecil et al. (5), an author whose name is more familiar to medical students as the editor of a major textbook of medicine, "To our surprise we found that the serum of practically every patient with well-developed rheumatoid arthritis gave a strongly positive agglutination test with the 'typical strains' of streptococci." In the 1940s and 1950s, Waaler, Rose, Vaughan, Epstein, and their colleagues (4, 6–8), along with a number of other investigators, greatly advanced understanding of the agglutinating principle, and they ultimately identified some form of altered human or rabbit Ig as the target of the agglutinating or precipitating activity. However, the nature of the agglutinating factor as an Ab and the relationship of the Ag to native serum IgG was uncertain until the appearance of the study by Franklin and colleagues. They took pains to point out that what was measured in these agglutination reactions as rheumatoid factor was only a portion of the autoantibody reactivity for autologous IgG. Perhaps because of the subtlety of the notions of avidity, valence, and the lack of a simple method to measure these molecular interactions, in the intervening years, usage has grouped the anti-IgG autoantibodies identified by Franklin and colleagues into the concept of rheumatoid factors. While the production of polyclonal IgM anti-IgG present as circulating complexes in serum remains a feature that is specific for rheumatoid arthritis, rheumatoid factor as measured in agglutinating and precipitating tests is not specific for rheumatoid arthritis and may be found in Sjogren's syndrome, hepatitis C infection, and systemic lupus erythematosus. Nevertheless, in these latter diseases, the rheumatoid factor is usually not somatically mutated and is often oligo- or monoclonal, a fundamentally different response that does not suggest these diseases are driven by the sustained and progressive immune response to IgG molecules that characterizes rheumatoid arthritis.

The distinction of the different specificities as a part of the polyclonal nature of the anti-Ig response presaged both the identification of a variety of specificities identified among the anti-Igs for autologous IgG, likely reflecting an epitope spreading phenomenon, as well as the variety of interactions that IgM anti-IgG autoantibodies had with various other circulating IgG complexes, including those based on IgG anti-IgG activity. The lack of a complete parallel between the physical quantity of IgM anti-IgG-globulin as measured by the quantity of 22s complex in ultracentrifugation and the lower titers of rheumatoid factor demonstrable by agglutination measures implies that a proportion of anti-IgG-globulin is either "hidden" high affinity rheumatoid factor, or lower affinity anti-IgG bound to soluble intermediate-sized IgG complexes involving IgG anti-IgG-globulin. The obvious basis in B cell development and differentiation of this panoply of interacting autoantibodies as a central component of rheumatoid arthritis pathogenesis led to the introduction of CD20 immunotherapy for the disease, a currently promising therapeutic approach (9).

A point clearly etched in this pillar of immunology was that the production of these anti-IgG autoantibodies was found in only about one-third of those who met the clinical classification criteria for rheumatoid arthritis. While this finding of heterogeneity, in part, could have been due to the insensitivity of the detection methods, available evidence did not support this possibility as a complete explanation, and no further interpretations were raised. The finding that there was heterogeneity in the immune response of those who met clinical criteria for rheumatoid arthritis presaged the current interest in the relationship between the production of anti-IgG autoantibodies and the closely linked production of autoantibodies to citrullinated proteins and the genetic association of both these traits of autoantibody production with the inheritance of certain HLA-DR alleles distinguished by the presence of a motif at P4 pocket of the HLA-DR molecule termed the shared epitope. The constellation of these three features has been advocated by de Vries et al. (10) to denote what could be considered a different disease with a more adverse prognosis that appears to require more aggressive therapy, distinct from what has been termed "seronegative rheumatoid arthritis."

While much of our current understanding of rheumatoid arthritis and its autoimmune nature rests on this pillar, intriguingly, there are important questions raised in this paper about events in the pathogenesis of rheumatoid arthritis that still remain unanswered. Insufficient attention has been directed to unraveling the intriguing interactions among Ig molecules based on the anti-Ig activity that is a distinctive characteristic of rheumatoid arthritis. We still do not have a complete understanding of how this autoimmune response is implicated in the development of the inflammatory response that we recognize as the disease of rheumatoid arthritis. Of course, the central unanswered question is that after five decades we still have no clear idea why the constant region of IgG molecules become the target of an autoimmune response. Perhaps as the focus of research shifts again to more proteomic approaches with improved technology to measure intermolecular interactions and to a greater recognition of the importance of innate immunity in autoimmune disease, there will be renewed interest in this intriguing and elegantly demonstrated aspect of rheumatoid arthritis pathogenesis.

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