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Evolution of autoantibody responses in individuals at risk of rheumatoid arthritis

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A B S T R A C T

Autoantibodies such as rheumatoid factors (RFs), anti-citrullinated protein antibodies (ACPAs), and other anti-modified protein antibodies are important risk factors for the development of rheumatoid arthritis (RA) and probably play an important role in its pathogenesis. In the phase before clinical arthritis becomes apparent, different autoantibody responses can evolve because of increases in their level, isotype switching, affinity maturation, epitope spreading, and a changing glycosylation profile. This evolution may be crucial for the pathogenic properties of the autoantibody responses, and interfering with this process in individuals at risk may become a route to prevent RA. Recent data suggest that interactions between RFs and ACPAs further amplify their inflammatory potential.

Introduction

It has been recognized for some time now that in the natural history of rheumatoid arthritis (RA), there is a phase of developing autoimmunity that precedes the onset of clinical symptoms in a large proportion of patients. The most prominent players in this pre-clinical phase are the autoantibodies, and although no definitive causal link with the development of arthritis has been established,

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autoantibodies have been shown to induce arthritis in mouse models [1–3]. While the presence of autoantibodies is an important risk factor for future RA and part of the ACR/EULAR RA classification criteria [4], it does not always lead to the development of disease. This may be explained by the heterogeneous character of the various autoantibody responses that can be present in individuals at risk for RA, with different intrinsic properties such as affinity, specificity, isotype composition, and glycosylation. These properties translate into different capabilities for causing inflammation. Furthermore, autoantibody responses can evolve their pathogenic properties in the period leading up to the clinical manifestations of autoimmunity.

In this chapter, we discuss the recent developments in research on autoantibody responses in individuals at risk of RA, with a focus on work that has investigated how specific autoantibody responses change and evolve over time to become more pathogenic and recent work on interactions between different autoantibody systems. The implications of these findings for clinical practice are briefly discussed.

Spectrum of autoantibodies in patients at risk of RA

Autoantibodies present in RA and the pre-clinical phase can be divided into antibodies that bind to immunoglobulin G (IgG) and anti-modified protein antibodies (AMPAs). Antibodies binding IgG are known as rheumatoid factors (RFs) and recognize epitopes in the fragment crystallizable (Fc) region of IgG, which is responsible for the effector functions of IgG such as complement binding and engagement of Fc receptors on effector cells.

The main AMPAs are the anti-citrullinated protein antibodies (ACPAs), which bind to proteins in which arginine amino acid residues have been enzymatically converted into citrulline residues [5], and anti-carbamylated protein antibodies (anti-CarP Abs), which bind to proteins in which lysine has been chemically converted into homocitrullines [6]. The chemical structure of homocitrulline is very similar to that of citrulline. Although anti-CarP Abs have been found in 16% of ACPA-negative RA patients [6], there is evidence of cross-reactivity between ACPAs and anti-CarPs, as may be expected because of the similarity of their targeted antigens [7]. Multiple studies have shown that RF and ACPAs, as well as anti-CarP Abs, can be found in serum samples taken years before the onset of clinical RA [8–14]. Recently, antibodies recognizing acetylated vimentin were found in RA patients [15], but these AMPAs have not yet been demonstrated in patients at risk of RA.

Using a cDNA phase display library that expresses antigens from RA synovial pannus tissue, a Belgian team identified RA-specific reactivity against two novel peptides [16]. These antibodies were also detected in a small proportion of ACPA-negative patients, showing promise of this technique in identifying new markers for patients considered to be autoantibody negative. Future studies using this technique may also identify new autoantibody marker in individuals at risk of RA.

Finally, anti-hinge antibodies (AHAs) can be found in healthy individuals, but more frequently and at higher levels in patients with established RA and arthralgia patients at risk of RA [17–19]. AHAs recognize neoepitopes exposed after the cleavage of IgG in the hinge region that connects the Fc domain of IgG to its antigen-binding domains [20] and can therefore also be classified as AMPAs. Various proteases that can specifically cleave the IgG hinge have been shown to be upregulated in RA [21–24]. AHAs might play a role in the phase leading up to RA by forming immune complexes and activating the complement system [18].

Isotype switching

In a physiological immune response, the first antibody produced by B cells is of the IgM isotype, shaped as a pentamer made of 5 IgM monomers and a joining (J-) chain or as a hexamer with 6 IgM monomers lacking a J-chain. Under the influence of antigenic stimulation, combined with T-cell help and cytokines, B cells can switch their isotype from IgM to other immunoglobulin classes (IgA, IgG, IgE). Autoimmune responses can also start with the production of IgM autoantibodies. However, as these responses can also arise from cross-reactivity, sometimes autoantibody responses may already be highly mutated and isotype-switched. Most research on RFs has focused on IgM-RF, and detection of IgM-RF, but not IgA- or IgG-RF, is part of the routine work-up in diagnosing RA in most clinics.

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