

Editorial

Anticitrullinated protein/peptide antibodies and rheumatoid factors: two distinct autoantibody systems

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Abstract

In a previous issue of *Arthritis Research and Therapy*, Ursum and colleagues report the relative stabilities of anticitrullinated protein/peptide antibodies (ACPAs) and IgM rheumatoid factors during the course of rheumatoid arthritis and their differential correlation with markers of the acute-phase response. These findings add to a growing body of evidence highlighting the distinct nature of these two autoantibody systems and the role of ACPAs as a disease-specific marker of rheumatoid arthritis.

In a previous issue of *Arthritis Research and Therapy*, Ursum and colleagues report data showing that the anticitrullinated protein/peptide antibody (ACPA) status is significantly more stable than that of IgM rheumatoid factors (RFs) during the course of rheumatoid arthritis (RA) [1] – a finding that is fully consistent with previous reports [2]. They also found that the frequency of ACPA positivity is unrelated to age in RA patients and in the few ACPA-positive patients with non-RA disease, whereas RF positivity displayed age-related increases in patients with non-RA disease and it was also more closely correlated with acute-phase inflammatory markers. These findings, which are based on serological studies in over 18,000 patients attending outpatient rheumatology clinics, add to a steadily growing body of evidence highlighting the distinct natures of these two autoantibody systems.

Differential accuracy in the diagnosis of RA

ACPAs are considered the most accurate serological marker for RA [3]. ACPA seropositivity is rarely detected in non-RA patients, although it is occasionally associated with psoriatic arthritis, tuberculosis, leprosy, and autoimmune hepatitis, and its specificity for RA (over 96% when measured with second-generation ELISA) [4] is clearly superior to that of RF. In contrast, IgG RF, IgA RF, or IgM RF are a frequent finding in patients with other autoimmune disorders, in those with infectious diseases (where its prevalence depends on the

primary/secondary nature of the infection, as well as on its duration), and even in healthy individuals, especially those who are elderly. The sensitivity of ACPAs is less impressive (around 68%) [4], but better results (82%) have been reported with assays measuring anti-Sa, the subset of ACPAs directed against modified citrullinated vimentin [5]. Anti-Sa positivity also appears to be a better predictor of radiographic progression in patients with early RA.

Anticitrullinated protein/peptide antibody role in synovial injury

Citrullinated proteins originate in the synovium, and ACPAs are produced in the inflamed synovium by local plasma cells. ACPAs [6] and ACPA-producing B cells have both been detected in synovial fluid from RA patients. The central role of these autoantibodies in the pathogenesis of RA has been demonstrated in a mouse model [7]. More recently, ectopic lymphoid structures in the synovia of some RA patients have been shown to support ongoing production of class-switched ACPAs [8].

Correlation between anticitrullinated protein/peptide antibodies and genetic determinants of RA

The HLA-DRB1 shared epitope alleles are a major genetic risk factor for RA. Their presence is associated with ACPA-positive forms of RA, and they also influence the magnitude of the ACPA response [9]. IgM RF has not been linked to any of the genetic risk factors for RA.

Temporal characteristics of anticitrullinated protein/peptide antibodies and RF expression in RA

ACPAs and RFs are both potential components of the specific autoantibody response that characterizes the pre-

ACPA = anticitrullinated protein/peptide antibody; ELISA = enzyme-linked immunosorbent assay; RA = rheumatoid arthritis; RF = rheumatoid factor.

clinical phase of RA [10], but ACPA positivity is likely to develop earlier and its presence may contribute to the subsequent appearance of RFs [11]. Later, with the onset of clinical RA, ACPA titers rise as a reflection of immune response maturation and increasing epitope dominance [12].

Conclusions

Together with the new data of the Ursum group, the findings discussed above strongly support the view that ACPAs are a disease-specific marker of RA detectable early in the preclinical phase of the disease. In contrast, IgM-RF seropositivity is generally a somewhat later event, and it is primarily a reflection of an inflammatory process that amplifies the tissue injury already underway. As Nowak and Newkirk have noted, the RF response may well be part of a normal host defense that – in this particular setting – is transformed into a threat to tissue integrity [13]. An interesting focus for future studies would be the characterization of ACPA (particularly anti-Sa) patterns in RA patients with partial responses to treatment consisting of the remission of signs and symptoms of inflammation coupled with ongoing radiographic progression.

Competing interests

The authors declare that they have no competing interests.

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