Editorial

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

Guido Valesini and Cristiano Alessandri

Dipartimento di Clinica e Terapia Medica, Reumatologia, Sapienza Università di Roma, V.le del Policlinico 155, 00161 Rome, Italy

Corresponding author: Guido Valesini, guido.valesini@uniroma1.it

Published: 14 September 2009
This article is online at http://arthritis-research.com/content/11/5/125

Arthritis Research & Therapy 2009, **11:**125 (doi:10.1186/ar2786)

See related research by Ursum *et al*., http://arthritis-research.com/content/11/3/R75

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 vimentine [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.

Acknowledgement

The present work was supported by the Fondazione Umberto Di Mario ONLUS.

References

1. Ursum J, Bos WH, van de Stadt RJ, Dijkmans BAC, van Schaardenburg D: **Different properties of ACPA and IgM-RF derived from a large dataset: further evidence of two distinct autoantibody systems. A cohort study.** *Arthritis Res Ther* 2009, **11:**R75.
2. Rönnelid J, Wick MC, Lampa J, Lindblad S, Nordmark B, Klareskog L, van Vollenhoven RF: **Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression.** *Ann Rheum Dis* 2005, **64:**1744-1749.
3. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, Saigo K, Morinobu A, Koshiba M, Kuntz KM, Kamae I, Kumagai S: **Meta-analysis: diagnostic accuracy of anticyclicncitrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis.** *Ann Intern Med* 2007, **146:**797-808.
4. Avouac J, Gossec L, Dougados M: **Diagnostic and predictive value of anti cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review.** *Ann Rheum Dis* 2006, **65:**845-851.
5. Vossenaar ER, Després N, Lapointe E, van der Heijden A, Lora M, Senshu T, van Venrooij WJ, Ménard HA: **RA specific anti-Sa antibodies target citrullinated vimentin.** *Arthritis Res Ther* 2004, **6:**R142-R150.
6. Spadaro A, Riccieri V, Scrivo R, Alessandri C, Valesini G: **Anticyclic citrullinated peptide antibody determination in the synovial fluid of patients with rheumatoid arthritis.** *Arthritis Rheum* 2006, **55:**681-682.
7. Kuhn KA, Kulik L, Tomooka B, Braschler KJ, Arend WP, Robinson WH, Holers VM: **Antibodies against citrullinated proteins enhance tissue injury in experimental autoimmune arthritis.** *J Clin Invest* 2006, **116:**961-973.
8. Humby F, Bombardieri M, Manzo A, Kelly S, Blades MC, Kirkham B, Spencer J, Pitzalis C: **Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium.** *PLoS Med* 2009, **6:**e1.
9. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR: **The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis.** *Arthritis Rheum* 2006, **54:**1117-1121.
10. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, Habibuw MR, Vandenbroucke JP, Dijkmans BA: **Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors.** *Arthritis Rheum* 2004, **50:**380-386.
11. Li W, Wang M, Irigoyen P, Gregersen PK: **Inferring causal relationships among intermediate phenotypes and biomarkers: a case study of rheumatoid arthritis.** *Bioinformatics* 2006, **22:**1503-1507.
12. Chibnik LB, Mandl LA, Costenbader KH, Schur PH, Karlson EW: **Comparison of threshold cut-points and continuous measures of anti-CCP antibodies in predicting future RA.** *J Rheumatol* 2009, **36:**706-711.
13. Nowak UM, Newkirk MM: **Rheumatoid factors: good or bad for you?** *Int Arch Allergy Immunol* 2005, **138:**180-188.