

## Viewpoint

# Autoantibodies in normals – the value of predicting rheumatoid arthritis

Thomas Dörner and Arne Hansen

Charite University Medicine Berlin, Free University and Humboldt University Berlin, Berlin, Germany

Corresponding author: Thomas Dörner, thomas.doerner@charite.de

Published: 15 October 2004

*Arthritis Res Ther* 2004, **6**:282-284 (DOI 10.1186/ar1456)

© 2004 BioMed Central Ltd

## Introduction

The cause of rheumatoid arthritis (RA) remains elusive, however, a study demonstrating synovitis in clinically uninfamed joints [1] and several studies reporting the presence of characteristic autoantibodies (IgM rheumatoid factor [RF] and anti-cyclic citrullinated peptide [CCP] antibodies) prior to the appearance of disease manifestations [2–7] have provided evidence of a preclinical, asymptomatic, phase of the disease. Detection of autoimmune T cells has not yet reached routine diagnostics, but with the development of tetramer and ELISPOT technologies it seems likely that autoantibody detection will serve as the method of choice for the identification of autoimmunity and breaches of tolerance (Fig. 1). In patients with early RA, the frequency of RF is 50–66% and the prevalence of anti-CCP 41–48%, compared to 7–13% and 3–9% respectively in normals [8–10]. Several recent studies have regenerated interest in the value of positive titres of autoantibodies as markers of rheumatic diseases [11–15]. Autoantibody positivity prior to symptom development/disease manifestation has also been identified in other autoimmune diseases, such as systemic lupus erythematosus, insulin-dependent diabetes mellitus (IDDM), autoimmune polyendocrine syndromes and celiac disease [11–20].

## Putative role of protein citrullination in rheumatoid arthritis

Celiac disease is a chronic intestinal disease with an immune response to antigens in wheat gluten. Disease occurs after the target antigen gliadin has been modified by the enzyme tissue transglutaminase, which allows subsequent presentation in the context of specific HLA molecules [19]. It is likely that RA is also the result of post-translational modifications of antigens by enzymatic activity (deiminases), and subsequent immune-mediated

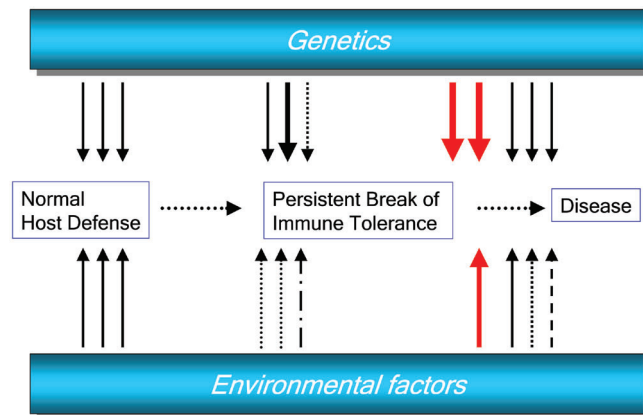
destruction of the synovium [9]. Regulation of peptidyl arginine deiminase (PADI) activity appears also to be involved in the maintenance of immunological tolerance to antigens. Thus, citrullination of proteins in RA patients may unmask essential epitopes that bind strongly to HLA class II molecules and result in initiation of an autoimmune response.

## Early antibody production: prognosis and diagnosis

Two recent studies [14,15] address different aspects of the value of anti-CCP antibodies as a risk factor for the development of RA. A longitudinal study [14] in a cohort of 79 RA patients in whom blood donations were available prior to the development of the disease showed that half of the patients produced anti-CCP antibodies and IgM-RF before the onset of RA. At a similar frequency, 10 of 16 patients who developed systemic lupus erythematosus or mixed connective tissue disease were positive for antinuclear antibodies 0.7–4.5 years before the onset of symptoms [16]. In comparison, 82% of IDDM patients have antibodies to glutamic acid decarboxylase 10 years prior to the disease [17]. In the RA study [14], antibody positive patients proved to develop more severe RA. These data indicate that 50% of the RA patients had a detectable abnormality in immune tolerance before the early clinically detectable disease stages.

The autoimmune response in immune-mediated diseases, such as RA appears to develop at different stages in each individual – this has several important implications. Autoantibodies serve as early indicators of a definite break in tolerance and may provide insight into the pathogenesis of RA. This raises the possibility to predict RA development in high-risk populations and may further allow a more precise “window of opportunity” for early and

CI = confidence interval; CCP = cyclic citrullinated peptide; HLA = human leukocyte antigen; IDDM = insulin dependent diabetes mellitus; MHC = major histocompatibility complex; PADI = peptidyl arginine deiminase; OR = odds ratio; RA = rheumatoid arthritis; RF = rheumatoid factor.

**Figure 1**

Proposed model of the development of autoimmunity influenced by genetic and environmental factors at certain stages.

effective treatment interventions. Moreover, modulation of the immune response to a given antigen might alter the future disease course. A further important recent lesson learned is that serologic prediction of the disease can be greatly improved by considering the presence of combinations of autoantibodies [20]. Although a clear pathogenic link between RF and anti-CCP antibody is missing, their co-presence is highly indicative of RA [21]. Likely antibody combinations reflect a spreading of the immune response to include more than one antigenic determinant with an associated increase in the risk of progression to disease [21]. Spreading of this immune response is probably genetically determined [22].

The value of positive autoantibodies in RA can only be considered amidst a complex pattern of additional predictive markers. Another recent prospective study [15] evaluated patients with undifferentiated early arthritis. Of the 936 patients, 21.9% had RA at inclusion, 32% after 1 year, 38% after 2 years and 40% after 3 years of follow-up. Importantly, the presence of anti-CCP antibodies was identified as a significant risk factor for RA with an odds ratio (OR) of 37.8 (95% confidence interval [CI] 13.8–111.9) while IgM-RF had an OR of 9.8 (95% CI 4.1–23.4). Major predictive clinical variables were morning stiffness, polyarthritis, symmetric arthritis and erosions on radiographs. Although serologic abnormalities had a high OR, these data emphasize the importance of a clinical pattern that needs to be identified for preclinical conditions with antibody positivity.

### Associated genetic markers

Genetic factors, for example HLA-DR haplotypes and PADI gene polymorphisms, represent further intriguing candidates for prediction. Hill *et al.*, identified the specific

role of MHC class II molecules in presenting citrullinated peptides to the immune system by studying T-cell responses to citrulline-containing peptides in HLA-DRB1\*0401 transgenic (DR4-IE tg) mice [22]. They demonstrated that the conversion of arginine to citrulline at the peptide side-chain position interacting with the shared epitope significantly increased peptide-MHC affinity and led to the activation of CD4<sup>+</sup> T cells. These data could, therefore, explain how DRB1 alleles with the shared epitope initiate an autoimmune response to citrullinated peptides in RA patients. Further studies [23,24] focussed on an involvement of peptidylarginine deiminases citrullinating enzymes (encoded by PADI genes). In a Japanese case-control linkage disequilibrium study [23], PADI type 4 was identified as a susceptibility locus for RA; this was not found in a UK population of RA patients [24] indicating the need for further studies. The role of genetics in RA is further supported by the observation that an anti-CCP+ member of a multicase RA family has an estimated 69.4% risk of developing RA within 5 years [15].

### Open questions/conclusions

A number of questions have been raised by these studies: (1) Since only 50% of RA patients develop autoantibodies before the onset of disease, the question remains whether other unknown humoral disturbances might be present in the remaining patients or if there are different subgroups of patients independent of the presence of RF and/or anti-CCP antibodies before disease develops; (2) The American College of Rheumatology criteria [25] for RA are commonly used for classification based on patient's history, physical examination, laboratory and radiographic findings. Early diagnosis of RA in patients with arthritis of recent onset [26,27] is often difficult. New aspects of the prognostic value of autoantibodies lead us to question whether our current diagnostic standard in RA needs re-evaluation; (3) Although we have progressed remarkably in our therapeutic armamentarium as well as in identifying high-risk subjects for RA through antigen-specific autoantibodies, screening the appropriate population for RA susceptibility remains a challenging task.

Identification of an autoimmune response to specific autoantigens in the pre-RA period raises the prospect of prediction and prevention. This may allow early treatment interventions (secondary prevention) and potentially disease prevention (primary prevention). However, accurate disease prediction is vital for secondary prevention in the context of clinical manifestations. At last, this will require not only a reliable view through the "window of opportunity" but also a subsequent successful step through a "gate of new opportunities".

### Competing interests

The author(s) declare that they have no competing interests.

## References

- Kraan MC, Versendaal H, Jonker M, Bresnihan B, Post WJ, t Hart BA, Breedveld FC, Tak PP: **Asymptomatic synovitis precedes clinically manifest arthritis.** *Arthritis Rheum* 1998; **41**:1481-1488.
- Silman AJ, Hennessy E, Ollier B: **Incidence of rheumatoid arthritis in a genetically predisposed population.** *Br J Rheumatol* 1992; **31**:365-368.
- Aho K, Heliövaara M, Maatela J, Tuomi T, Palosuo T: **Rheumatoid factors antedating clinical rheumatoid arthritis.** *J Rheumatol* 1991; **18**:1282-1284.
- Kurki P, Aho K, Palosuo T, Heliövaara M: **Immunopathology of rheumatoid arthritis: antikeratin antibodies precede the clinical disease.** *Arthritis Rheum* 1992; **35**:914-917.
- Halldorsdóttir HD, Jonsson T, Thorsteinsson J, Valdimarsson H: **A prospective study on the incidence of rheumatoid arthritis among people with persistent increase of rheumatoid factor.** *Ann Rheum Dis* 2000; **59**:149-151.
- Del Puente A, Knowler WC, Pettitt DJ, Bennett PH: **The incidence of rheumatoid arthritis is predicted by rheumatoid factor titer in a longitudinal population study.** *Arthritis Rheum* 1988; **31**:1239-1244.
- Walker DJ, Pound JD, Griffiths ID, Powell RJ: **Rheumatoid factor tests in the diagnosis and prediction of rheumatoid arthritis.** *Ann Rheum Dis* 1986; **45**:684-690.
- Goldbach-Mansky R, Lee J, McCoy A, Hoxworth J, Yarburo C, Smolen JS, Steiner G, Rosen A, Zhang C, Menard HA, Zhou ZJ, Palosuo T, Van Venrooij WJ, Wilder RL, Klippel JH, Schumacher HR Jr, El-Gabalawy HS: **Rheumatoid arthritis associated autoantibodies in patients with synovitis of recent onset.** *Arthritis Res* 2000; **2**:236-243.
- Schellekens GA, Visser H, de Jong BAW, van den Hoogen FHJ, Hazes JMW, Breedveld FC, van Venrooij WJ: **The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide.** *Arthritis Rheum* 2000; **43**:155-163.
- Jansen LMA, van der Horst Bruinsma IE, van Schaardenburg D, van de Stadt RJ, de Koning MHMT, Dijkmans BAC: **Rheumatoid factor and antibodies to cyclic citrullinated peptide differentiate rheumatoid arthritis from undifferentiated polyarthritis in patients with early arthritis.** *J Rheumatol* 2002; **29**:2074-2076.
- Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, Harley JB: **Development of autoantibodies before the clinical onset of systemic lupus erythematosus.** *N Engl J Med* 2003; **349**:1526-1533.
- McClain MT, Arbuckle MR, Heinlen LD, Dennis GJ, Roebuck J, Rubertone MV, Harley JB, James JA: **The prevalence, onset, and clinical significance of antiphospholipid antibodies prior to diagnosis of systemic lupus erythematosus.** *Arthritis Rheum* 2004; **50**:1226-1232.
- Arbuckle MR, James JA, Kohlhase KF, Rubertone MV, Dennis GJ, Harley JB: **Development of anti-dsDNA autoantibodies prior to clinical diagnosis of systemic lupus erythematosus.** *Scand J Immunol* 2001; **54**:211-219.
- Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, Habibuw MR, Vandembroucke 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.
- van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, Toes RE, Huizinga TW: **Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study.** *Arthritis Rheum* 2004; **50**:709-715.
- Aho K, Koskela P, Makitalo R, Heliövaara M, Palosuo T: **Antinuclear antibodies heralding the onset of systemic lupus erythematosus.** *J Rheumatol* 1992; **19**:1377-1379.
- Tuomilehto J, Zimmet P, Mackay IR, Koskela P, Vidgren G, Toivanen L, Tuomilehto-Wolf E, Kohtamaki K, Stengard J, Rowley MJ: **Antibodies to glutamic acid decarboxylase as predictors of insulin-dependent diabetes mellitus before clinical onset of disease.** *Lancet* 1994; **343**:1383-1385.
- Eisenbarth GS, Gottlieb PA: **Autoimmune polyendocrine syndromes.** *N Engl J Med* 2004; **350**:2068-2079.
- Mowat AM: **Coeliac disease – a meeting point for genetics, immunology, and protein chemistry.** *Lancet* 2003; **361**:1290-1292.
- Leslie RDG, Atkinson MA, Notkins AL: **Autoantigens IA-2 and GAD in type I (insulin dependent) diabetes.** *Diabetologia* 1999; **42**:3-14.
- Dörner T, Egerer K, Feist E, Burmester GR: **Rheumatoid factor revisited.** *Curr Opin Rheumatol* 2004; **16**:246-53.
- Hill JA, Southwood S, Sette A, Jevnikar AM, Bell DA, Cairns E: **Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1\*0401 MHC class II molecule.** *J Immunol* 2003; **171**:538-541.
- Suzuki A, Yamada R, Chang X, Tokuhiko S, Sawada T, Suzuki M, Nagasaki M, Ohtsuki M, Ono M, Furukawa H, Nagashima M, Yoshino S, Mabuchi A, Sekine A, Saito S, Takahashi A, Tsunoda T, Nakamura Y, Yamamoto K: **Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis.** *Nat Genet* 2003; **34**:395-402.
- Barton A, Bowes J, Eyre S, Spreckley K, Hinks A, John S, Worthington J: **A functional haplotype of the PADI4 gene associated with rheumatoid arthritis in a Japanese population is not associated in a United Kingdom population.** *Arthritis Rheum* 2004; **50**:1117-1121.
- Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS: **The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.** *Arthritis Rheum* 1988; **31**:315-324.
- Huizinga TWJ, Machold KP, Breedveld FC, Lipsky PE, Smolen JS: **Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis.** *Arthritis Rheum* 2002; **46**:1155-1159.
- El-Gabalawy HS, Duray P, Goldbach-Mansky R: **Evaluating patients with arthritis of recent onset: studies in pathogenesis and prognosis.** *JAMA* 2000; **284**:2368-2373.