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Anti-citrullinated protein/peptide autoantibodies in association with genetic and environmental factors as indicators of disease outcome in rheumatoid arthritis

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ABSTRACT

Anti-citrullinated protein/peptide antibodies (ACPA) have recently emerged as sensitive and specific serological markers of rheumatoid arthritis (RA), providing superior alternative of the rheumatoid factor (RF) test in the laboratory diagnostics of RA. Citrullination is a post-translational modification of arginine by deimination, physiologically occurring during apoptosis, inflammation or keratinization. The presence of several citrullinated proteins has been demonstrated in the RA synovium. The identification of citrullinated epitopes as targets led to the development of the first and later second-generation anti-cyclic citrullinated peptide (anti-CCP) antibody assays. The anti-Sa antibody has been identified a decade ago; however, recent studies confirmed that anti-Sa is directed against citrullinated vimentin. The determination of ACPA may have important prognostic significance, since ACPA production can precede the onset of clinical RA symptoms by years. ACPA+ individuals with early, undifferentiated arthritis may have higher risk to develop RA. ACPA has important prognostic role during the progression of RA and it has also been associated with pronounced radiographic progression. ACPA production has been associated with several genetic predisposing factors, including HLA-DRB1 and PTPN22 1858T alleles, as well as with environmental and lifestyle-related factors, primarily smoking and possibly, the use of oral contraceptives and excessive caffeine intake. Thus, the assessment of ACPA, in addition to clinical, radiographic and genetic outcome measures may be important to assess disease prognosis and aids to design effective, early therapeutic strategies.

Contents

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune-inflammatory disease that may lead to joint destruction and disability [1]. Genetic factors including class II major histocompatibility complex (MHC) and

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non-MHC alleles, environmental factors and autoimmune processes are highly involved in the pathogenesis of RA [2]. Early diagnosis and immediate, effective therapy are crucial in order to prevent joint deterioration, functional disability and unfavorable disease outcome [1,3]. Currently, optimal management of RA is needed within 3–6 months after the onset of disease, therefore a very narrow "window of opportunity" is present to achieve remission [3]. Thus, reliable outcome measures are needed in order to establish prognosis early and to conduct good clinical practice.

Significant amount of data have become available suggesting that genetic factors and autoimmune-inflammatory markers are good indicators of outcome [2,4]. In this review, we aim to summarize recent data regarding the predictive and prognostic value of genetic and laboratory markers in RA.

2. Anti-citrullinated protein/peptide antibodies

2.1. Synovial citrullination and production of ACPA

Citrulline is the post-translationally modified, deiminated derivative of arginine [4,5]. The arginine-to-citrulline transition is catalyzed by the peptidylarginine-deiminase (PAD) enzyme that has five isoforms in mammals, PAD1-4 and PAD6 [5,6]. Tissue citrullination is a physiological process underlying epithelial keratinization, inflammation and increased apoptosis [4–7]. Inflammatory leukocytes including RA synovial T and B cells, macrophages, neutrophils and synovial fibroblasts express both the PAD2 and PAD4 isoforms [4,6,8]. There is relatively small amount of citrullinated proteins in the normal synovial tissue, whereas active citrullination has been associated with synovitis [6–8]. Citrullinated protein epitopes have been identified in extravascular fibrin deposits and extracellular fibrinogen aggregates within the RA synovium [6,7]. Filaggrin, the first citrullinated protein identified, as potential autoantigen in RA is an epidermal protein usually absent from the synovium [9]. Thus, other citrullinated proteins, such as fibrin or vimentin that are abundantly expressed and citrullinated in synovial tissues may drive autoantibody responses [8–12]. Indeed, citrullinated fibrin (CF) has been detected in RA synovial fluid [12], whereas citrullinated vimentin is expressed by synovial macrophages [10,13]. These autoantigens induce the production of anti-citrullinated protein/peptide autoantibodies (ACPA) that have been associated with autoimmunity underlying RA [4,8,13,14]. *In vivo*, deiminated α and β chains of fibrin may be the dominant autoantigen in RA, while other citrullinated proteins may cross-react with CF during antibody production [15]. Although, most studies suggest high diagnostic specificity and sensitivity of ACPAs in RA [4,8,10,16], tissue citrullination and ACPA production have been detected in patients with other types of arthritis, yet less frequently [16,17]. In comparative studies, 74–97% of RA, but only 6–7% of psoriatic arthritis (PsA) patients were anti-cyclic citrullinated peptide (anti-CCP) positive [16,17].

2.2. Predictive value of ACPA

Patients presenting with undifferentiated polyarthritis (UDP) may eventually develop definitive RA, remain UDP for years, or may undergo spontaneous remission [3]. Identifying biomarkers, suggesting the transition of UDP to RA are of utmost importance [3,18]. ACPA may be detected in the sera of patients years before the onset of clinical symptoms [4,19]. In the preclinical phase, 25% of patients, who develop RA later than 18 months, while 52% of those that develop RA within 18 months are anti-CCP positive [19]. The positive ACPA serology may predict the development of RA in patients with UDP [3,19].

2.3. ACPA as prognostic marker

Regarding its prognostic value in established RA, ACPA seropositivity has been associated with a more severe, destructive disease course [4,8,19,20]. $ACPA^+$ RA patients developed more erosions after 6–10 years of follow-up [3,18]. Seropositivity has also been associated with sustained inflammatory activity indicated by long-term elevation of erythrocyte sedimentation rate (ESR) and disease activity score (DAS)28 [18,20]. Among various ACPAs, these associations could be confirmed regarding anti-CCP, anti-mutated citrullinated vimentin (MCV), as well as anti-CF [4,10,15,16,19,20].

In an early study, the prognostic value of anti-perinuclear factor (APF) determined by indirect immunofluorescence was assessed in patients with early RA (duration <1 year). APF had additional value in differentiating RF^+ and RF^- patients with respect to radiographic damage [21]. In an inception cohort of 273 patients with RA (disease duration <1 year), anti-CCP^+ patients developed more severe joint destruction after 6 years of follow-up. While radiographic damage was predicted by both ACPA and IgM RF at baseline, functional deterioration was predicted only by RF at entry [22]. In early RA, ACF antibodies also had good prognostic value for radiographic progression after 2 years [8,15]. When serial determination of anti-CCP was performed in 99 early RA patients at baseline and subsequently, within the first 3 years, anti-CCP positivity was associated with 5-year progression of the total Sharp score (OR 3.2), erosion score (OR 5.3) and joint space narrowing score (OR 2.8). In addition, anti-CCP^- patients had less radiographic progression than those with increasing anti-CCP production [23]. The prognostic value of ACPA has also been confirmed in very early RA (duration <3 months) [24].

When four outcome measures were compared with respect to prognostic value for joint destruction after 10 years, anti-CCP was the best indicator (OR 4.0), while the other three indicators (female sex, ESR and RF) showed less potential (OR 3.1–3.3) [25]. Similarly, when anti-CCP and RF were compared with respect to severity of structural damage in the Norfolk Arthritis Register, anti-CCP^+ at baseline was strongly associated with both prevalent erosions (OR 2.5) and developing erosions after 5 years (OR 10.2). Anti-CCP exerted better performance than IgM RF (OR 1.6 and 3.4, respectively) [26]. In another comparative study, anti-CCP had higher positive predictive value for erosive RA than RF, C-reactive protein (CRP), ESR or matrix metalloproteinase-3 (MMP-3) [27].

3. Prognostic value of genetic factors

3.1. MHC genes as outcome measures

Certain HLA-DRB1*01 (HLA-DR1) and HLA-DRB1*04 (HLA-DR4) alleles, also known as "shared epitopes" (SE), has been associated with susceptibility to and/or progression of RA [2,28–30]. SE is a risk factor for more severe, destructive RA, as well as for the development of extraarticular manifestations [2,28]. It is likely, that the SE itself may not be directly responsible for poorer prognosis, but it may rather influence outcome indirectly, via ACPA production [2,4,31]. Indeed, SE is probably the primary risk factor for increased ACPA production in RA [4,28,29,31,32]. SE was not only associated with positive ACPA titers, but also with absolute serum ACPA levels [29]. Among HLA-DRB1 alleles, ACPA production has been associated with HLA-DRB1*04, rather than HLA-DRB1*01 [2,11,29]. Among HLA-DRB1*04 subtypes, DRB1*0401, *0404, *0405 and *0408 SE exerted the closest association with positive ACPA [2,33]. In a recently published study, among 2221 single-nucleotide polymorphisms (SNPs) within the MHC region, 299 SNPs showed significant associations with $ACPA^+$ RA, while none of these SNPs could be associated with seronegative RA [34]. Among non-SE HLA-DRB1 alleles, HLA-DRB1*13 and DRB1*15 have also been implicated in ACPA production [29]. Regarding various ACPAs, positive SE has been associated with anti-CCP, anti-CV and anti-CF production [2,4,8,15,33,35]. In contrast, HLA-DRB*03 (HLA-DR3) may rather be associated with $ACPA^-$ RA and milder disease course [2].

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3.2. The prognostic value of non-MHC genes

Regarding non-HLA genes, the 1858C/T allele (rs2476601) polymorphism of PTPN22 has been associated with anti-CCP$^+$ and RF$^+$ RA [30,36,37]. This has also been confirmed in UDP and early RA [37].

Fcγ receptors are key players in antigen presentation and inflammation. In a cohort of 945 RA patients, Fcγ receptor IIIA (FcγRIIIA) 158V/F polymorphism was assessed and the VV genotype showed clear association with ACPA$^+$ RA [38].

In conclusion, SE, possibly other MHC genes including HLA-DRB1*13 and DRB1*15, and non-MHC genes including PTPN22-1858C/T and FcγRIIIA-158V/F alleles are associated with ACPA production and thus, they may serve as indirect outcome measures. The use of multiple indices, such as HLA-DRB1 + PTPN22 + ACPA may exert even higher prognostic value. In contrast, HLA-DRB1*03 may confer ACPA seronegativity and better prognosis. However, there may be geographical differences in the prognostic value of genetic factors described above [2,11,29,30,32,33,35–38].

Regarding the comparison between genetic and immunological markers as outcome measures, ACPA may have better predictive/prognostic value than SE or PTPN22 polymorphism [30].

4. Environmental and lifestyle-associated prognostic factors

Numerous studies have been performed with respect to the role of environmental and lifestyle-related factors, primarily smoking, in susceptibility to the development and progress of RA. At least in some geographical regions, smoking has been associated with the development of extraarticular manifestations, including nodulosis and cardiovascular complications, as well as with more progressive disease course [33,39,40]. Yet, smoking may not be related to radiographic progression [39]. It is likely, that smoking forms a "Bermuda triangle" with SE and ACPA. Smoking promotes the citrullination of synovial proteins and thus ACPA production [33,39]. In Scandinavian, Dutch and French cohorts, a high risk for the development of ACPA$^+$ RA was observed in patients carrying one or two SE alleles [33,39,40]. In SE$^+$ patients, smoking is not only associated with positive ACPA, but also with absolute serum anti-CCP levels [33]. While, as described above, primarily HLA-DRB1*04 alleles have been associated with ACPA production [2,11,29], in smokers, HLA-DRB1*0101, *0102 and *1001 alleles showed the closest association with positive anti-CCP [33]. Smoking confers increased disease progression [39,40].

Regarding other environmental factors, based on studies, conducted in Scandinavian cohorts, higher body weight at birth, the use of oral contraceptives and excessive caffeine consumption (>10/day) conferred higher risk to develop ACPA$^+$ RA. Interestingly, obesity was associated with higher risk to seronegative RA. Red meat, vitamin D and estrogen intake may be neutral in this respect, while moderate wine consumption may decrease susceptibility [39,40]. In a Danish cohort, SE$^+$ heavy coffee drinkers had 53-times, contraceptive users had 45-times higher risk to develop anti-CCP$^+$ RA [40].

5. Conclusion

In conclusion, RA patients may be classified into ACPA$^+$ and ACPA$^-$ subpopulations that may have important prognostic significance. The terms "seropositive" and "seronegative", originally based on the evaluation of IgM RF, have undergone major transition. The development of ACPA may precede the onset of clinical symptoms by years. ACPA has predictive role in early, undifferentiated arthritis and ACPA$^+$ individuals with UDP may have higher risk to develop RA. ACPA has important prognostic role during the progression of RA and it is also associated with more pronounced structural damage of the joints indicated by radiographic progression. ACPA production has been associated with certain genetic makeup, including the presence of SE, or PTPN22 gene polymorphisms, as well as with environmental and lifestyle-related factors. Individuals carrying SE, or the PTPN22 1858T allele, in addition to smoking exert increased radiographic progression and unfavorable prognosis. Other factors, such as the use of oral contraceptives, or excessive caffeine intake my also have relevance for the development of ACPA$^+$ RA. In clinical practice, a combination of autoantibodies and genetic factors, in addition to clinical and radiographic outcome measures should be determined in order to better assess the outcome of RA and to enable optimal, early treatment.

Take-home messages

- Synovial citrullination and the production of ACPA are crucial for the pathogenesis and prognosis of rheumatoid arthritis.
- ACPA production has been associated with genetic factors including the shared epitope, PTPN22 polymorphism, as well as with lifestyle-related factors, primarily, smoking.
- The determination of ACPA in association with genetic and environmental factors at the onset of the disease may serve as a complex outcome measure in RA.

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