EDITORIAL

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Anti-citrullinated protein antibodies in rheumatoid arthritis: a bridge between genetic predisposition and autoimmunity

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovial inflammation and subsequent joint destruction. The interaction of genetic, immunological, and environmental factors contributes to the development of RA. The genetic contribution to RA is 50% to 60% and the concordance rate of monozygotic twins is up to 15% [1,2]. A recent Swedish study of a large population showed that the standardized incidence ratio (SIR) is 3.02 in offspring of RA patients, 4.64 in siblings, 9.31 in multiplex families (both a patient and a sibling diagnosed with RA), and 6.48 in twins [2].

Genetic risk factors for RA are major histocompatibility complex (MHC) genes and non-MHC regions, such as the *PTPN22* and *STAT4* genes. Among the MHC genes, the HLA-DRB1 shared epitope alleles, which encode a common amino acid sequence, are the most important risk factors for disease susceptibility and progression. HLA-DRB1 shared epitope alleles are strongly associated with anti-citrullinated protein antibody (ACPA)-positive RA [3,4]. HLA-DRB1 shared epitope alleles contribute 18% to the heritability of ACPA-positive RA, whereas the HLA-DRB1 shared epitope alleles contribute only 2.4% to the heritability of ACPA-negative RA [3]. The relationship between HLA-DRB1 shared epitopes and ACPA in the development of RA is explained by the fact that citrullinated peptide binds in the pocket of DRB1 molecules containing the shared epitope, and this binding causes activation of $CD4^+$ T cells and polarization to Th17 cells, which are involved primarily in autoimmune processes [5]. HLA-DRB1 shared epitope alleles are present in 64% to 70% of RA patients and in 55% of their first-degree relatives; this frequency is significantly higher than in control populations (35.8%) [6,7]. In ACPA-positive RA patients, 80% have at least one shared epitope, while 49% of ACPA-negative RA patients have shared epitopes. This interaction among genetic risk factors and the presence of autoantibodies increases the risk of developing RA in first-degree relatives of RA patients [7,8].

Anti-cyclic citrullinated peptide (anti-CCP) is the antibody used most commonly for detection of ACPA.

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Citrullination is the post-translational modification of arginine to citrulline by pepdidyl arginine deiminase (PAD). This is a normal process that occurs in dying cells, but active PAD is released when the clearance mechanism of apoptosis is damaged [8]. The production of ACPA leads to the formation of immune complexes and the induction of inflammation, followed by the development of RA [9]. The antibodies against citrullinated peptides and proteins were first described in 1998 and anti-CCP was developed as a commercial enzyme-linked immunosorbent assay for diagnosis of RA in 2000. Since the anti-CCP2 test improved the diagnosis of RA, anti-CCP was included as one of the serologic criteria in the new 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA [10]. In the new criteria, the replacement of rheumatoid nodules and radiographic changes with ACPA positivity increases the sensitivity of the diagnosis of RA in short-duration disease. Early diagnosis and prompt aggressive therapy using disease-modifying anti-rheumatic drugs leads to an improved therapeutic response and the prevention of irreversible joint destruction. Since anti-CCP can be detected up to 10 years before clinical disease, it is useful for predicting the development of RA in patients with undifferentiated arthritis. After 1 year of follow-up, 75% to 90% of undifferentiated arthritis patients who are anti-CCP positive at baseline progress to RA versus 25% of patients who are anti-CCP negative at baseline. Moreover, ACPA predicts RA disease outcome, and ACPA positivity is associated with severe, destructive disease. Although the serum rheumatoid factor (RF) is a sensitive method for diagnosing RA, it has low specificity, with 10% to 30% false positivity. By contrast, anti-CCP has a high specificity of 98%, with false positivity less than 5%, so the combination of RF and anti-CCP is poised to be the gold standard for the diagnosis of RA [8].

Anti-mutated citrullinated vimentin (anti-MCV) antibody is another ACPA and recognizes the vimentin isoform in which arginine residues are replaced by glycine. Vimentin is a widely expressed intermediate filament in mesenchymal cells and macrophages. It is usually not citrullinated, but citrullinated vimentin is a consequence of inadequate clearance of apoptosis. Citrullinated vimentin is present in the pannus and synovial fluid of RA patients. The anti-MCV test has a sensitivity of 59% and specificity of 92% for the diagnosis of RA [11]. Although results of comparisons of anti-MCV and anti-CCP have differed, anti-MCV seems to have diagnostic value comparable to that of anti-CCP.

In a study reporting that "seropositivity of anti-CCP is more prevalent in unaffected first-degree relatives with multicase family of RA," Kim et al. [12] measured serum RF, anti-CCP, and anti-MCV in 135 patients with RA and 202 of their first-degree relatives and determined the risk factors associated with the RA-related autoantibodies. The frequency of autoantibodies in first-degree relatives was 14.4% for RF, 5% for anti-CCP, and 13.4% for anti-MCV. The frequency of anti-CCP was higher (17.8%) in first-degree relatives of multi-case families than in those of non-multi-case families (1.3%). They suggested that anti-CCP positivity in multi-case families is associated with a risk factor of developing RA in unaffected first-degree relatives. Recent studies showed that the frequencies of RF and anti-CCP in first-degree relatives of patients with RA were 14% to 33.5% and 8.5% to 26.8%, respectively [6,13]. Inconsistent with this study, there was no significant difference in the prevalence of anti-CCP between small-case and multi-case families [13]. The discrepancy between studies could be explained by differences in the test methods, ethnicity, sex, disease duration, definition of multi-case families, and presence of HLA-DRB1 shared epitopes. To date, there have been few genetic studies of Korean RA patients and no cohort study of first-degree relatives of RA patients in Korea. The report by Kim et al. [12] is important because it is the first study of the prevalence of autoantibodies in RA families in Korea. Genetic and environmental risk factors differ with ethnicity and region, and etiological studies in different countries give distinct results. For example, the most significant HLA-DRB1 allele for RA susceptibility is *0401 in Caucasians, while the HLA-DRB1*0405 allele is significant in Asians, including Koreans [14]. This study is the first step in familial studies of Korean RA; using this family cohort, longitudinal observations can examine the genetics of HLA-DRB1 shared epitopes and non-MHC gene polymorphisms and environmental risk factors for developing RA in a genetically susceptible

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population.

The prevalence of HLA-DRB1 shared epitopes and RA-related autoantibodies is higher in first-degree relatives than in controls, and it is obvious that first-degree relatives of RA patients are genetically predisposed to develop RA. However, the presence of genetic risk factors and autoantibodies is not always associated with disease development in first-degree relatives of RA patients. Besides genetic predisposition and the presence of autoantibodies, environmental factors also contribute to disease development and progression. Environmental and lifestyle-associated risk factors for RA are smoking, infections, oral contraceptives, excessive caffeine consumption, silica exposure, and high body weight at birth [11]. The fact that the familial risk for RA is significant among spouses (SIR, 1.17), although they are not blood relatives, suggests that common environmental exposure is also important in the development of RA [2]. Smoking is the factor that has the greatest influence on RA development and progression. In the pathogenesis of RA, smoking induces apoptosis in lung tissues and the non-specific citrullination of many proteins, followed by the generation of ACPA. Clinically, smoking is associated with more aggressive disease, reduced therapeutic response, and high risk of cardiovascular diseases in RA. HLA-DRB1 shared epitopes combined with smoking is significantly related to anti-CCP in RA patients, while no such relationship is found in first-degree relatives [2]. However, the effect of environmental risk factors on the development of RA in genetically predisposed people has not been studied sufficiently.

Since a family history, anti-CCP positivity, and HLA shared epitopes are associated with the early appearance of joint damage in RA, first-degree relatives of RA patients have the potential to progress to more severe disease after developing RA. A full understanding of genetic risk factors and the control of environmental risk factors are needed to reduce the risk of disease development and progression in first-degree relatives of RA patients.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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