ACPA [ANTI-CITRULLINATED PROTEIN ANTIBODIES] AND RHEUMATOID ARTHRITIS

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Abstract

It has recently been discovered that anti-citrullinated protein antibodies (ACPA) are present in 50% of patients with early rheumatoid arthritis (RA). Assays for detecting ACPA have been shown to have very good diagnostic and predictive characteristics, and they may facilitate the identification of patients with early arthritis who need aggressive treatment.

In addition to their diagnostic and predictive properties, ACPA have also provided new insights into the pathophysiology of RA. The specific association of certain genetic and environmental risk factors with ACPA-positive but not with ACPA-negative RA, has led to new concepts of the underlying pathogenetic mechanisms. The fact that ACPA--positive patients have a more severe disease course with greater joint destruction has also fueled the hypothesis that ACPA themselves may be pathogenic. Although there is no direct proof for this intriguing theory so far, it is clear that ACPA allow the classification of RA patients into two different disease subsets that are associated with distinct pathophysiological mechanisms and clinical outcomes.

Rheumatoid arthritis (RA) is a chronic, potentially destructive, arthritis which has a large impact on patients' quality of life[1]. It has become clear that in order to be able to prevent disease progression and joint destruction, RA needs to be diagnosed early, which requires diagnostic markers which can reliably predict disease development and progression[2]. Some of the most attractive diagnostic markers are autoantibodies.

Rheumatoid factor (RF) has long been known to be a marker of future RA development[3], but more recently, a better diagnostic and predictive marker has emerged in the form of anti-citrullinated protein antibodies (ACPA).

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Development of anti-citrullinated protein immunity

ACPA were first described as anti-perinuclear factor over 45 years ago, but it was not until several years later that recognition of this antigen was found to be exclusively dependent on the presence of citrulline-residues[4,5]. Based on these findings, several commercial assays that test for the presence of antibodies to cyclic citrullinated proteins (CCP) have been developed and successfully introduced in clinical practice[6].

Several studies have investigated at what point in time individuals develop ACPA. Using pre-disease samples from blood bank donors who later developed RA, it was shown that ACPA can be detected years before disease manifestation[7,8]. Furthermore, ACPA titers were found to increase up to the point of disease onset. However, once present, ACPA almost never disappear, but tend to persist in the vast majority of patients in whom they have developed. Likewise, ACPA-negative RA-patients hardly ever sero-convert, indicating that ACPA are a stable biomarker that does not demand re-testing once ACPA-status is known.

The fact that ACPA appear in the pre-clinical phase of RA, together with the finding that ACPA can exacerbate arthritis in mice, suggest that anti--citrulline immunity may play a role in the pathogenesis of the disease[9]. This notion is further supported by investigations into the risk factors that are associated with RA.

Genetic risk factors for RA

The risk of developing rheumatoid arthritis is known to be influenced by several genetic risk factors, of which the HLA-DRB1 shared epitope (SE) alleles confer the highest risk[10]. After the first descriptions of ACPA, it soon became clear that the SE alleles were only associated with ACPA-positive RA and thus only predisposed to ACPA-positive di-

sease[11]. Intriguingly, no apparent contribution of the SE alleles to the progression towards RA or the progression of RA is found when the analyses are stratified for the presence of ACPA in a patient--population with early arthritis[12,13]. Thus, the SE alleles do not independently contribute to the progression to or of RA, but rather predispose to the development of ACPA. The latter is also reflected by the observation that the presence of HLA-SE-alleles influences the profile of the antigens recognized by ACPA, indicating that they are a risk factor for ACPA-development[14].

Conversely, there are other genetic risk factors, which have been described to be exclusively associated with ACPA-negative RA, such as HLA-DR3[15]. Because there are no markers available that are specific for this disease subset, it is currently not feasible to determine if this genetic risk factor predisposes to specific immunological alterations in these patients.

Not only genetic, but also environmental risk factors are known to contribute to the etiology of RA. Many epidemiological studies have shown an association between cigarette smoking. Smoking was found to interact with the HLA SE alleles in the predisposition for RA[16,17]. Interestingly, this association is also predominantly associated with ACPA--positive RA, mainly in the context of the presence of the HLA-SE-alleles[18,19]. Together, as distinct genetic-and environmental factors associated with ACPA-positive and negative disease, these findings indicate that ACPA-positive- and negative RA are distinct disease entities. Nonetheless, at first clinical presentation, no apparent clinical differences seem to be present, although it is clear that ACPA--positive patients will suffer from a more progressive disease course as compared to ACPA-negative subjects[20].

Conclusion

The discovery of the RA-specific anti-citrullinated protein immune response has had great implications, not only for diagnosis and disease prediction, but also for the way we think about the pathophysiology of the disease. Recognition of the distinct genetic and environmental risk factors involved in ACPA-positive versus ACPA-negative disease, has allowed us to view rheumatoid arthritis in a more differentiated way. Even though there is no conclusive proof as yet that ACPA themselves are pathogenic, they allow a useful distinction of disease subsets, each with associated risk factors and prognosis. For the ability to serologically confirm the diagnosis of RA, as well as with regards to the pathophysiologic understanding of the disease, the identification of ACPA has been a great step forward.

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