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HLA and anti-citrullinated protein antibodies: Building blocks in RA

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A B S T R A C T

Antibodies against citrullinated proteins (ACPAs) are specific for rheumatoid arthritis (RA). ACPA-positive RA is a chronic inflammatory disease resulting from the complex interaction between genetic (mainly HLA class II genes) and environmental factors (mainly smoking). Recent findings have offered new insights into where, when and how anti-citrulline immunity develops. Some studies have found that a mucosal site, such as the lungs, may function as the initiating site for the immune response against citrullinated proteins, in line with the known association between smoking and ACPA. Other studies, focusing rather on the HLA associations, have suggested that cross-reactivity between microbial sequences and citrullinated self-proteins may lead to ACPA formation. Once ACPAs have developed, they can circulate throughout the body and upon reaching the joints exert direct pathogenic effects themselves. ACPAs can target first the bone compartment of the joints to activate osteoclasts and release interleukin (IL)-8 that in turn will promote bone loss and pain-like behaviour. In the current review, we will present the current understanding of the genetic associations in RA contributing to ACPA occurrence and offer insight in the latest findings explaining how and why autoimmunity generated in the lungs of genetically susceptible hosts might lead to chronic inflammation in the joints.

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Rheumatoid arthritis (RA) is a chronic disease mainly characterized by inflammation of small joints of hands and feet. The underlying pathogenic abnormality is systemic autoimmunity with main clinical manifestations on the level of joints, tendons and bursae. Several markers of the underlying immunological aberrancies can be detected in the blood of RA patients, including autoantibodies, in particular. Among the autoantibodies, anti-citrullinated protein antibodies (ACPAs) have been found to be more specific for RA than the traditionally used rheumatoid factor (RF) [1]. Based on several findings, which will be discussed in more detail in this review, ACPA appears to have a closer link to the underlying immunopathogenesis compared to, for example, RF.

ACPAs can be found up to 10 years before RA onset and can predict the development of RA. Prior to disease onset, the ACPA response matures with a rise in ACPA levels, increased isotype usage and epitope spreading to a broader range of citrullinated antigens [2,3]. This results in a broad, mature autoantibody response at the time of disease onset, which does not expand any further later. The discovery of ACPA has led to a paradigm shift in the pathophysiological hypotheses concerning the development of RA. Nearly all genetic and environmental risk factors known for RA have been found to be exclusively associated with ACPA-positive disease. This also applies to the most potent genetic risk factor encoded in the human leukocyte antigen (HLA) class II locus.

In this review, we will first provide an in-depth description of the HLA alleles and their relationship to RA, followed by a presentation of the most recent current pathogenic views linking HLA genes to the development of ACPA-positive RA.

HLA molecules: structure and function

Molecules belonging to the major histocompatibility complex (MHC), known in humans as HLA, are best known for their antigen-presenting function. For a complete understanding of the current hypotheses about the role of HLA in the development of RA, we need to take a closer look at the exact structure and function of these molecules and the genomic organization of their encoding locus [4].

HLA molecules are divided into two classes differing in the site of expression, structure and function (Table 1). HLA class I molecules are present on all nucleated cells, whereas HLA class II molecules are only expressed on immune cells, and especially those cells involved in antigen presentation such as dendritic cells, B cells and macrophages. The overall protein structure of HLA class I and class II molecules is similar in that one side of these molecules is attached to the cell membrane and the other side has a long cleft or groove to bind peptides. On a lower structural level of the subunit, however, the class I and II molecules do differ. Class I molecules consist of two polypeptide chains, of which only the longer alpha chain encoded in the HLA genetic locus is polymorphic. It is bound to the non-polymorphic molecule beta2-microglobulin. The peptide-binding cleft is formed entirely by the alpha chain. Class II molecules, however, consist of two equally large chains: the alpha and beta chain, both of which are polymorphic and encoded in the HLA genomic region. Both contribute to the peptide-binding cleft. The composition of class II molecules consisting of two chains adds a higher degree of variability, but the alpha chains of these molecules are generally less polymorphic than the beta chains. Furthermore, the combination of alpha and beta chains encoded on different chromosomes can increase the number of different HLA molecules expressed by a cell, with two alpha and two beta chains leading to four different molecules. Murine studies have shown, however, that not all combinations lead to stable dimers.

The way in which peptides are bound by the different molecules is a key aspect to understanding how some HLA molecules may predispose to RA. Crystallography has revealed that the major difference between class I and II molecules is the 'openness' at the ends of the peptide-binding cleft, that is, the ends of a peptide bound to class I are buried within the class I molecule, while the ends of a peptide bound to class II can dangle out. Peptides bound to class I are generally of length 8–10 amino acids because contacts between their free amino-terminus and carboxy-terminus on one side and the peptide-binding cleft on the other side are very important for stable binding. Longer peptides can therefore not be readily accommodated. Besides the termini, amino acid residues at two or three particular positions (called anchor residues) are essential for binding to a given HLA class I molecule. Class II molecules, however, can bind to much longer peptides of at least 13 amino acids held in the peptide groove by side chains that protrude into shallow and deep pockets of the class II molecules.