Research Article

HLA Susceptibility Genes In Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune condition that results due to the association of both genetic and environmental factors, for instance, smoking and HLA-DRB1. The progression of disease is marked by the onset of autoimmune reactions and mucous membrane inflammation that leads to synovitis, pannus development, as well as the degeneration of cartilages and bones through T cell/B cell and cytokine cross-talks such as tumor necrosis factor-α (TNF-α) and Interleukin 6 (IL-6). While the exact contribution of susceptibility loci to the disease remains unclear, there have been many instances where DRB1 alleles, in addition to other non-HLA loci, affected the predisposition of individuals to disease. Future studies should concentrate on the combination of both epidemiologic and genetic evidence in the framework of current models of arthritogenic pathways. HLA-DRB1 alleles have been identified as some of the major genetic risk factors associated with disease and are responsible for about 30% of the disease genetics. HLA-DRB1 alleles are generally called the "shared epitope" and have considerable links with RA, especially those associated with the presence of ACPA for alleles *04, *01, and *10. There are other HLA settings, including HLA-A, HLA-B, and HLA-DPB1.

Keywords: HLA, rheumatoid arthritis, autoimmunity, epitope.

Introduction

The chronic inflammatory disease known as rheumatoid arthritis (RA) mostly affects the joints. The affected joints are often painful, swollen, and warm. The affected joints are usually swollen, hot, and painful. Usually the limbs and the wrist areas will be affected, and this will happen bilaterally in similar parts of the body. Infections may even develop in other parts of the body such as the skin, sweat glands, eyes, the heart, the lungs, the nerves and the bloodstream. Other symptoms include anemia, myocarditis/pericarditis, interstitial lung disease, as well as tiredness and/or fatigue. In some patients the development of the symptoms may take several weeks to months [1, 2].

The initial studies showing that HLA-DR4 became extra typical in RA patients have found that the foremost histocompatibility complex (MHC) genes are concerned within the susceptibility to rheumatoid arthritis (RA) [3]. However, studies showing any association or association with DRi led to the exclusion of DR4 because the RA susceptibility allele [4]. According to recent studies, the hypothetical susceptibility gene for HLA-DRfI is additionally significantly associated with the DR4 subtypes Dw4 and Dw14 [5] than with DR4. The seemingly uncommon populations are defined via the shared-epitope speculation [6] which postulates that common sequences are present inside the 0.33 hypervariable vicinity of the DROI gene, present in DR4 prone suballeles and other non-DR4 alleles such as DR41, DRW1 alleles]. Although it may play a role, the DROI locus does not entirely explain RA susceptibility. Populations associated with RA have different frequencies of epitopes [8].

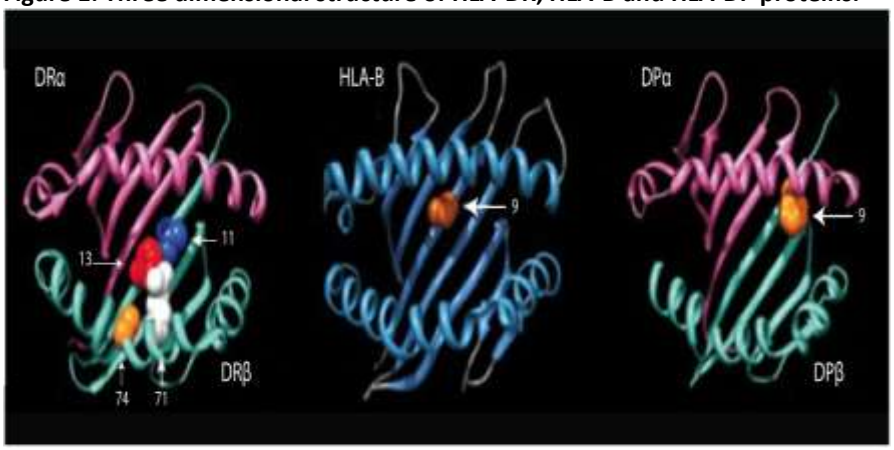
HLA genes associated with RA susceptibility include HLA-DRB1*04:01, *04:04, *04:08 in Caucasians, HLA-DRB1*04:05 in Spaniards and Japanese, HLA-DRB1*01:01 and *01:02 in Israelis, HLA-DRB1*14:02 in some Native Americans, HLA-DRB1*10:01 in Greeks and HLA-DRB1*01:01, *04:01, *04:04, *04:05 in Latin Americans [9, 10]. The involvement of the above allelic variants in the development of the disease is not clear so far, yet there have been formulated several hypotheses, including the following: (1) the alleles present arthritogenic antigens; (2) the alleles affect the T-cell receptor repertoire in terms of peptide affinity; and (3) the alleles present molecular mimicry with peptide residues of microorganisms. Gregersen et al. [11] suggested another hypothesis due to the fact that in the third hypervariable region (positions 70-74) of the abovementioned HLA-DRB1 allelic variants one may find a common sequence: L-LE-[Q/R]-[R/K]-R-A-A (L-LE indicates leucine-leucine or leucine-glutamate; [Q/R] refers to the glutamine or lysine residue; [R/K] corresponds to the arginine or lysine residue; A-A is alanine or threonine).

Besides, the HLA-DRB1 gene includes some protective alleles, which display a sequence called DERAA at the same position in the third hypervariable region (positions 70-74) of the DRB1 chain. More precisely, this region displays an aspartic acid (D) at the 70th

position. The protective alleles with the DERAA sequence include: HLA-DRB1*01:03, *04:02, *11:02, *11:03, *13:01, *13:02 and *13:04. Patients with HLA-DRB1 alleles expressing the DERAA sequence possess lower risk for RA development; the patients are also likely to have less severe disease if their genotype lacks HLA-DRB1 allele expressing the DERAA sequence [12].
A link has been suggested between the existence of SE-containing allele and triggering of autoreactivity in T-cells. Crystallographically analyzed, the residues of Q and R/K of position 70 and 71, respectively, in the β chains make physical contact with the T cell receptors and may thus recognize the particular T cells referred to as "SE recognizers".
Modifications within the β-chain of the SE alleles at residue 70-seventy-four, resulting in a total shift in the peptide repertoire that these molecules begin to display, have been identified using direct mutagenesis [13]. The alleles of those genes (whether HLA or non-HLA) and the SE residues that depend on a number of these genes are critical. The even genetic conformational distribution is observed inside the threat (based totally on the genotypic conformation). For example, the hazard effect is halved within the homozygous SE system and 30% smaller within the heterozygous SE population, suggesting variability in penetrance related to genotype popularity. Thus, it can be argued that the RR is not sufficiently elevated, however, may be sufficiently extended in one hundred% of SE patients to justify RA in the presence of SE [14].

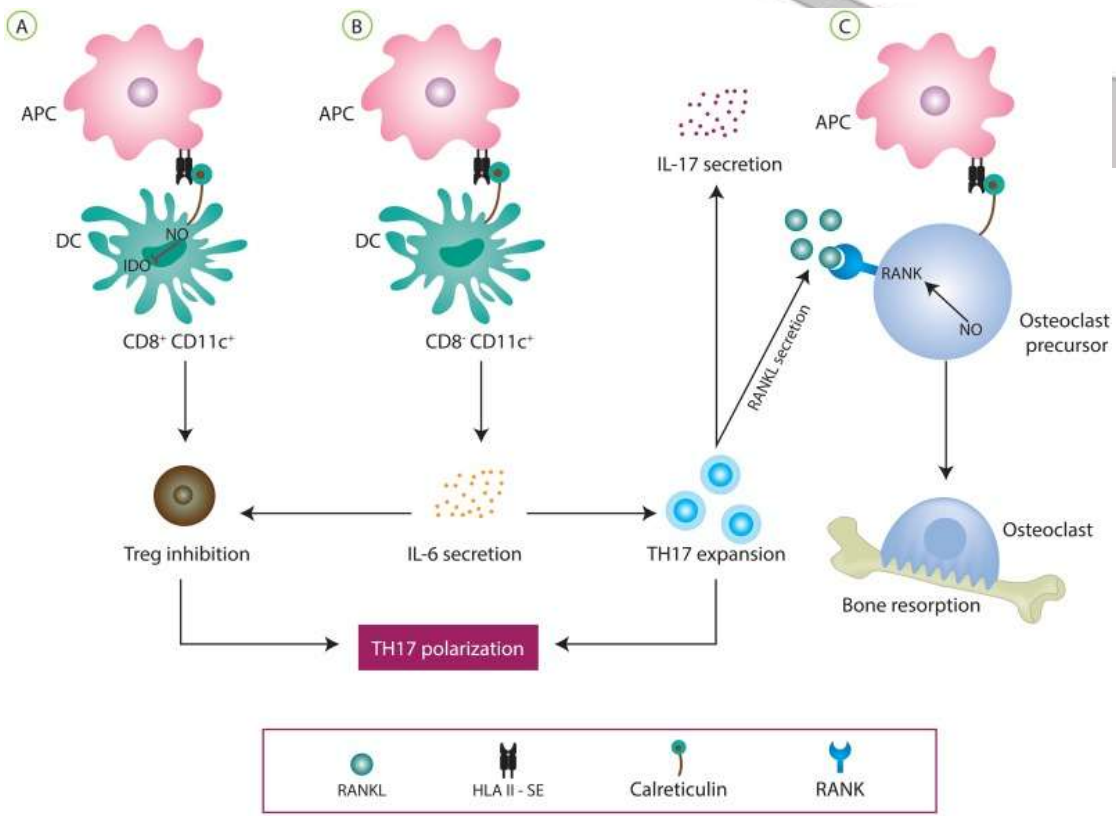
Furthermore, upon analyzing anti-cyclic citrullinated peptide antibodies (ACPA) and HLA-DRB1, the relationship is further restricted to RA patients positive for ACPA, but not to negative ACPA RA patients among all ethnic groups [15]. It may be seen that MHC region contributes about 12.7% phenotypic variance, while the non-MHC region contributes 4% in phenotypic variance. Besides HLA-DRB1 region, few other factors are responsible for explaining the MHC region association in RA [16]. There are also four amino acids (positions 11, 13, 71, and 74) in HLA-DRB1 region of individuals positive for ACPA which are responsible for susceptibility of RA [Figure 1].

Figure 1: Three dimensional structure of HLA-DR, HLA-B and HLA-DP proteins.



The side chains of these amino acids are very big in the groove and play a crucial role in the binding of peptides by the HLA protein. In addition, amino acids in SE (71 & 74) were previously associated with the risk of RA. These 4 loci are otherwise related to RA patients and the HLA-DRB1 polymorphisms have an impact on these populations. ACPA-legacy RAs therefore contain the alleles that can be most tenuously linked to the European population. Similar associations have also been found with other alleles of HLA-DP1, as well as a second HLA-B*08 alleles. Both molecules produced with these HLA genes have a substitution with function nine, which had a functional effect with the presentation of the antigenic peptide to the T cell [17].
This was due to recent advances in SE signaling recognition in the chronic intestinal pathology of RA and is an example of innate reaction transduction. De Almeida and colleagues advise that the protein calreticulin (CRT) can induce the production of beneficial cells, which is the handiwork that controlled SE signal transduction in dendritic cells (DCs). The SE can be defended by connecting the CRT to its P slot. Sometimes the traits of these optimal commodities can be found, including nitric oxide (NO) and reactive oxygen species (ROS). SE suppresses the properties of enzyme indoleamine 2,3 dioxygenase (IDO) that are essential for immunological tolerance and T mobile regulation in CD11c + CD8- DCs, while also triggering IL-6 and IL-17 in CD11c+ CD8 + DCs, leading to NO and ROS in OC. The latter is confirmed by the discovery that SE may trigger the formation of IL-17 the development of T cells followed by the production of RANKL, which is associated with Th17-based osteoclastogenesis [19].

Figure 2: Proposed model of the new insights in the functional role of the SE in RA pathogenesis



The cell surface CRT binds the SE ligand, expressed on the APC. Increased SE-CRT affinity, polarization of Th17 and onset of disease can lead to an abnormal activation of SE pathway in RA. The SE is able to inhibit the enzyme, IDO, which has been shown to be required for activation of regulatory T cells in CD8+CD11c+ DC. B) SE increases IL-6 production resulting in activation and expansion of Th17 cells. C) induced the differentiation of OC and production of proosteoclastogenic substances. Consequently, there was greater bone loss that was perceived. Abbreviations are: calreticulin (CRT); shared epitope (SE); cluster of differentiation (CD); indoleamine-pyrrole 2, 3-dioxygenase (IDO); and osteoclasts (OC).

Finally, RA has a substantial genetic component throughout alleles. A risk score for RA should be able to be established using clinical prediction based on human genetics. The most direct therapeutic use is to advance the use of human genetics in RA therapy development. It will be crucial to ascertain whether a combination of RA risk alleles can be used to identify patients who will benefit from biological medication therapy for RA as well as those who develop specific clinical outcomes, such as myocardial infarction, severe infection/inflammation, or lymphoma.

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