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HLA-Disease Associations in Rheumatoid Arthritis

Vincent van Drongelen, Ph.D. and **Joseph Holoshitz, M.D.***

Department of Internal Medicine, University of Michigan, Ann Arbor, MI, 48109, USA

Abstract

The etiology and pathogenesis of rheumatoid arthritis (RA) are influenced by environmental and genetic risk factors. Shared epitope-coding HLA-DRB1 alleles increase RA risk and severity; however, the underlying mechanisms of action remain unclear. In contrast, several other DRB1 alleles protect against RA. Additionally, genome-wide association studies suggest that RA associates with other, HLA and non-HLA, genes but the relative contributions of such risk loci to RA are incompletely understood. Future research challenges include integrating the epidemiological and genomic data into validated arthritogenic pathways, and determining the mechanisms of interaction between RA risk genes and environmental influences.

Keywords

HLA; rheumatoid arthritis; autoimmunity; shared epitope

Introduction

Rheumatoid arthritis (RA) is a common inflammatory disease in which both genetic and environmental factors play a role in disease development. Based on twin studies, the heritability of the disease was estimated at around 60%.[1] Among all the genetic risk factors found to date, the human leukocyte antigen (HLA) locus is the most significant one. A particularly strong association between RA and *HLA-DRB1* alleles that encode a HLA-DRβ chain containing a five amino acid sequence motif called the 'shared epitope' (SE) has long been documented.[2] Here we review salient immunogenetic, clinical and mechanistic features of RA association with the HLA locus, focusing primarily on the SE.

HLA genes and their products

The immune system is composed of various cells that work together to protect the host against invading pathogens without harming its own tissues. Therefore, the host has to recognize which antigens are self and which are foreign. To discriminate between such self- and foreign antigens, the major histocompatibility complex (MHC) antigens, known in humans as HLA, have evolved. MHC molecules have the ability to recognize and present foreign antigens to the immune system, but at the same time disregard self-antigens. This ability to discriminate between self and foreign is established through a process called

*Correspondence should be addressed to Joseph Holoshitz, University of Michigan, 5520D MSRB1, SPC 5680, 1150 West Medical Center Drive, Ann Arbor, MI 48109-5680. Telephone: 734-764-5470, Fax: 734-763-4151, jholo@umich.edu.

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"MHC restriction".[3] During the development of T cells in the thymus, T cells that react to self-antigens are eliminated, while those that respond to foreign antigens that are presented by a self-HLA molecule are preserved. This selection results in $CD4^+$ and $CD8^+$ T cells that only respond to foreign antigens that are presented by self-HLA molecules. Despite their ability to selectively recognize and respond to foreign antigens, a number of HLA alleles has been found to confer susceptibility to various diseases, the majority of which involve dysregulated immunity or autoimmunity.

The HLA locus is located on the short arm of chromosome 6 and covers a 7.6 Mb region that contains over 250 highly polymorphic genes.[4] The region is organized in three sub-regions: class I, class II and class III, which all have different functions. Both class I and II regions encode for glycoproteins that are expressed as cell surface receptors, whereas the class III region contains genes that encode for a variety of secreted immune system proteins, including complement factors and cytokines.

The class I region encodes for three main subsets of HLA molecules; HLA-A, HLA-B and HLA-C. Class I HLA molecules are composed of an HLA-coded heavy α-chain and an invariant light chain, beta-2 microglobulin (β_2m), which is essential for functional expression of the HLA molecule at the cell surface. The α-chain is folded to form a peptide-binding cleft that is "closed" and can accommodate short antigenic peptides, typically 8-10 amino acids long. These class I molecules are expressed on all nucleated cells and specialize in presentation of intracellular antigens, including viral antigens, to cytotoxic ($CD8^+$) T cells. Genes in the class II region encode for HLA-DR, HLA-DP and HLA-DQ molecules as well as a few other related proteins. Class II HLA molecules are composed of an α-chain and a β-chain, both coded by the HLA class II region. Unlike the class I molecules, the peptide-binding cleft of class II molecules are "open" which allows the accommodation of larger peptides of 15-20 amino acids long. Class II molecules are initially expressed on the cell surface of immune cells, in particular antigen presenting cells such as macrophages or dendritic cells, as well as B cells and activated T cells. These molecules present antigens from outside the cell to ($CD4^+$) T cells which in turn stimulate B cells to produce antibodies towards that specific antigen. This results in an antigen specific immune response. After activation of the immune system, the HLA class II molecules can be expressed on other cells.

HLA-associated diseases

The HLA locus is a highly polymorphic region. Its high gene density, presence of clusters of genes with related functions, enormous polymorphism and a strong linkage disequilibrium (LD) between alleles, renders it difficult to unravel the comprehensive HLA functions. During the last several decades, various conditions such as infectious diseases[5], cancer[6] or autoimmune diseases[7] have been found to be more prevalent in individuals that carry certain HLA alleles. The majority of the HLA associated diseases can be classified as autoimmune or immune-mediated disease and have been observed with merely HLA class I alleles (e.g. ankylosing spondylitis (AS))[8] or merely class II alleles (e.g. seropositive RA).[9] Additionally, some autoimmune diseases have been found to be influenced by both HLA class I and class

II genes (e.g. diabetes mellitus type I).[10] In addition to HLA alleles that predispose to disease, there are also a number of HLA alleles that are protective against disease.

How certain HLA alleles predispose to or protect against (autoimmune) diseases and what the underlying molecular mechanisms are is currently unclear. The hypotheses that have been proposed over the years commonly implicate atypical presentation of self-antigens[11,12], an immune response to “altered self” antigens[13] or cross reactivity with foreign or self-antigens.[14,15] These hypotheses may seem plausible based on HLA function and their role in the immune response. However, despite their plausibility, the mechanistic and epidemiologic evidence that is currently available is difficult to reconcile with presentation of specific antigens being the underlying mechanism for HLA-disease association.

Several examples of HLA alleles are associated with more than one disease with completely different target tissues and pathogeneses, which defies the notion that antigen presentation should be specific for both the antigen and the presenting HLA molecule. Examples of such HLA alleles are *HLA-DRB1*04:01* which is associated with both RA and type-1 diabetes[16] and *HLA-DQB1*03:02* which is associated with both type-1 diabetes and celiac disease.[17,18] In addition, there are certain HLA alleles that predispose to one disease but protect against another, e.g. *HLA-DRB1*04:02* has been found to confer susceptibility to pemphigus vulgaris (PV) but at the same time protect against RA (discussed below).

Furthermore, the most significant HLA-disease association to date has been found for a brain disorder (narcolepsy), which is not known to involve antigen presentation.[19] Also, certain HLA molecules have been found to have functions unrelated to antigen presentation, including cognition[20], olfaction and the activation of innate immune signaling (reviewed in [21]).

In addition, some disease-associated alleles have been shown to demonstrate ‘cross-species susceptibility’, e.g. *HLA-DRB1*04:01* associates with human RA and also confers susceptibility to inflammatory arthritis in mice.[22]

Moreover, despite extensive efforts to identify target antigens in autoimmune diseases, they have only been identified for a very small number of diseases. Also, presence of T cell clonality, a phenomenon that can be expected in case of the presence of a specific antigen has not been convincingly demonstrated in HLA associated diseases.

Lastly, RA disease severity has been shown to correlate with HLA allele dose, i.e. two allele copies confer greater susceptibility, severity and penetrance compared to one copy (discussed below). Such allele-dose impact on RA disease severity cannot be explained by antigen presentation-based hypotheses.

HLA-RA associations

The SE

RA association with HLA has been known since 1969[23], and the associations with specific DR4 allotypes were identified in the late 1970s.[24,25] The term ‘shared epitope’[2] was coined in the late 1980's following the discovery that the majority of RA patients share a 5 amino

acid sequence motif (*i.e.* QKRAA, QRRAA, or RRRAA) in residues 70-74 of the DRβ chain, coded by several distinct *DRB1* alleles in individuals expressing DR4 and non-DR4 allotypes. Recent genomic imputation analyses suggest that in addition to residues 70-74 in the α helical rim of DRβ chain, the classically defined "SE", residues 11 and/or 13, located in the 'floor' of the HLA-DR groove, are also associated with RA susceptibility,[26,27] suggesting that presentation of peptidic antigens may play a role in RA etiology. However, this imputation-based hypothesis awaits experimental validation and the relevance of these statistical data to RA etiology has recently been questioned.[28] Additionally, despite several decades of research, the identity of putative arthritogenic peptides remains elusive. The findings of a recent study raise further doubts on the notion of specific antigen presentation by SE-expressing RA-associated DR molecules since a comparative analysis identified only negligible overlaps in the repertoires of peptides eluted from different SE-expressing HLA-DR molecules.[29] The epidemiological and clinical aspects of RA genetics, including the SE, have been reviewed elsewhere.[30,31]

The SE not only confers a higher risk for RA, but also increases the likelihood of developing earlier disease onset, more severe bone erosions[9,32-34] and anti-citrullinated protein antibodies (ACPA).[35] SE-RA association and disease severity are gene-dose dependent. For example, in individuals carrying one SE-coding allele the odds ratio (OR) of developing joint damage compared to SE-negative individuals is 2.38. With two SE-coding alleles, the OR increases to 3.92.[36] Furthermore, there is additional evidence of an allele-dose effect, in which early disease onset, severity of bone destruction and higher disease concordance among monozygotic twins all correlate with the number of SE-coding *HLA-DRB1* alleles.[9,33,34]

It is worth to mention that not only inherited genes confer SE-RA association. Non-inherited maternal HLA antigens (NIMA) carrying SE motifs have been shown to confer RA risk in SE-negative individuals[37], especially in younger onset RA in women.[38] Thus minute amounts of maternal SE acquired during the fetal period is sufficient to determine RA susceptibility. This mechanism may account for some of the SE-negative subset of RA.

Ethnic and racial factors that affect SE-RA association

Considerable ethnic and racial stratification exist within the SE-positive RA subset in terms of association with specific SE-coding *DRB1* alleles (reviewed in [39]). For example, in European RA patients, *DRB1*04:01; *04:04; *01:01*, and **10:01* are the predominant SE-coding alleles, while in East Asians the most common SE-coding allele is *DRB1*04:05.* In Pima, Tlingit, Yakima and Chippewa Native American individuals a SE-coding allele *DRB1*14:02* has been found to be a significant genetic risk factor for severe RA.[40,41]

RA is generally less common among Africans compared to populations of European descent[42,43] and the frequency of SE-coding alleles in African Americans RA patients is approximately one third of that reported in European RA patients.[44] Nonetheless, SE-coding *DRB1* alleles are almost twice as common in African American RA patients, compared to healthy control subjects.[44] This indicates that the SE is a significant risk factor in African Americans, albeit to a lesser extent than in Caucasians. Importantly, the prevalence of SE-coding alleles in African Americans correlates positively with the extent of estimated

European ancestry, regardless of RA status, suggesting that genetic admixture between European and African American populations is responsible for introducing RA risk in the latter population.[44]

SE and ACPA

ACPA (or anti-cyclic citrullinated peptide (anti-CCP)) are a useful disease marker in RA. These antibodies associate with severe, erosive disease[45,46] and, relevant to this review, they are strongly associated with SE-coding *DRB1* alleles.[35,47] Among different SE-positive RA patients, those carrying the *DRB1*04* group of alleles display higher ACPA titers of compared to those carrying *DRB1*01* alleles.[48] An early study on RA patients in the Netherlands[49] demonstrated an odds ratio (OR) of 3.3 for anti-CCP positivity in RA patients with a single SE-coding allele (*DRB1*01, *04, *10*). The OR in RA patients with two SE-coding alleles was 13.3, suggesting a SE gene-dose effect on anti-CCP positivity. In anti-CCP-negative European RA patients, on the other hand, a significant RA association (OR= 1.84) with the DR3 allotype was reported [50] In Japanese individuals, who rarely carry the *DRB1*03:01* allele, a significant association with DR14 and DR8 was found.[51] Thus, the ACPA-positive and –negative subsets of RA associate with different *HLA-DRB1* alleles and should be therefore considered immunogenetically distinct diseases.

The strong association between SE-coding alleles and ACPA suggest a cause-effect relationship, although the precise underlying mechanism remains unknown. A common hypothesis states that the SE represents an obligatory amino acid sequence in the HLA-DR antigen presentation pocket that is critically necessary for antigen-specific presentation of citrullinated antigen-derived peptides to citrullinated protein-specific helper T cells, which help B cells to produce ACPA. According to this scenario, ACPA react against tissue citrullinated proteins which results in autoimmunity.[52,53] While this hypothesis is plausible, it is difficult to reconcile with the findings that ACPA can be detected in RA patients, years before disease onset.[54,55] Furthermore, ACPA in RA sera display promiscuous specificity against multiple citrullinated proteins which do not share sequence homology, such as vimentin[56], a-enolase[57], collagen type II[58], or fibrin[59], amongst other candidate self-proteins. Such promiscuity is inconsistent with the HLA-restricted antigen presentation concept.

In addition to the antigen specificity paradox discussed above, the hypotheses that postulate an effector role for ACPA in disease pathogenesis seem to dismiss a sizable body of literature implicating presence of polymorphisms in the peptidyl arginine deiminase 4 (*PADI4*) gene in certain populations[60,61] and evidence for enzyme dysregulation and overabundance of citrullinated proteins in RA.[62-64] These data suggest that citrullinated proteins, independent of ACPA, are at least partially accountable for RA pathogenesis. While definitive explanations of this paradox are absent, it is worth mentioning that the HLA Cusp Theory[65,66] has previously proposed that in addition to antigen presentation, HLA-DR molecules may perform other, non-antigen presentation allele-specific functions, through the third allelic hypervariable region of the DRβ chain, as depicted graphically in Figure 1. Our group has demonstrated that the SE acts as a signal transduction ligand that leads to immune dysregulation and osteoclast activation, independent of its putative antigen presentation

role.[67-74] It remains to be seen if a non-antigen presentation mechanism, such as SE ligand-activated signaling could shed light on the SE-ACPA association paradox.

SE-environment interaction

Approximately two-thirds of RA risk is attributed to genetic factors, of which the SE is the most significant one. The remaining one third of disease susceptibility is attributed to non-genetic mechanisms that are most likely triggered by environmental factors. Over the years, ample evidence has been gathered to support the role of environmental factors in disease onset. For example, the disease is historically believed to have gained higher prevalence in the Old World concomitant with the Industrial Revolution; prevalence of the disease is higher in urban populations; the disease incidence varies by birth cohort; and most importantly, conclusive evidence has been established for an association between RA and exposure to cigarette smoke.[75] Several studies have identified interactions between the SE and tobacco exposure.[76-78] For example, a Swedish group reported a strong interaction between the SE and smoking in RA risk, particularly in SE homozygous individuals.[77] Similar conclusions have been reached by a Danish study[78], and a very large US survey has demonstrated strong interaction between heavy smoking and the SE in RA.[76] In African Americans, the contribution of cigarette smoking to RA was found to be limited to those with more than 10 years of exposure, particularly among patients carrying SE-coding *DRB1* alleles.[79] Thus, there is compelling evidence for interaction between the SE and tobacco exposure in the etiology of RA in diverse populations.

The mechanistic basis of SE-smoking interaction in RA etiology and pathogenesis is unknown. A popular model for the etiology of RA suggests that the association between smoking and RA is due to the ability of the former to enhance SE-dependent immune reaction to citrullinated proteins, which, in turn trigger disease.[80] According to this model, smoking increases the abundance of citrullinated proteins in the lung, which in SE-positive individuals may provide an antigenic stimulus for ACPA generation. More recently, another group has reported that SE-smoking interaction does not shape the reactivity of the ACPA response, suggesting that smoking activates antigen-nonspecific citrullination.[81]

Bacterial infection has long been proposed as an environmental etiologic factor for RA.[82] Given that ACPA may be found years before disease onset in RA, it has been speculated that prior to RA, extra-articular infections may be the culprit. For example, recently, there has been a growing interest in the possible contribution of smoking-induced lung infection as an extra-articular source of disease-triggering infection. A recent study suggested that smoking-associated bronchiectasis might be an RA-triggering etiology due to enhanced production of ACPA in such individuals.[83] Periodontal disease (PD), another extra-articular chronically infected site, has been proposed as a culprit in RA due to the known association between the two diseases[84], and the fact that a well-studies PD-triggering bacterium, *Porphyromonas gingivalis*, expresses the bacterial PAD enzyme.[85] In the context of this review, however, it should be pointed out that PD has been shown to associate with SE-coding alleles independent of RA.[86,87] How this confounding factor affects the interpretation of studies focusing on the etiologic role of oral bacterial agents on RA etiology is currently unclear.

Protective DRB1 alleles

While the QKRAA, QRRAA or RRRAA sequences in position 70-74 of the DRβ chain have been shown to increase RA risk, alleles that code for D instead of Q or R in position 70[88,89], particularly the 70-DERAA-74 sequence which is coded by several alleles, including *DRB1*01:03, DRB1*13:01*, *DRB1*13:02* or *DRB1*04:02* exert a protective effect.[90,91] Interestingly, diametrically opposite of the pro-RA effect of SE-expressing NIMA[37,38], DERAA-expressing NIMA have been shown to protect against the disease.[92]

The mechanism of this allele-based protection is unknown, although it was recently proposed that this association is due to cross-reactivity between citrullinated-vinculin and microbial proteins, due to presentation of the DERAA sequence by *DQB* alleles that are in linkage disequilibrium with SE-coding *DRB1* alleles.[15] Nonetheless, besides the fact that this intriguing hypothesis awaits experimental validation, it also appears to contradict published data from the same group which indicate that DERAA-expressing alleles are protective against RA independent of a SE-coding *DRB1* allele[90] and the dominant protective effect of a DERAA-expressing transgene on CIA development independent of any DQ molecules.[93] Moreover, this hypothesis does not explain why exposure of SE-positive haplotypes to the DERAA sequence, ubiquitously expressed by microbial proteins, cannot mount a similar immune protective effect in individuals without DERAA-coding alleles. Finally, DERAA-coding *DRB1* alleles have been shown to be protective against several other autoimmune diseases besides RA[94,95], suggesting an antigen-nonspecific modulatory effect, rather than antigen presentation-based mechanism.

The 70-DERAA-74 sequence coded by *HLA-DRB1*0402*, as well as by several other alleles, exerts a dominant protective effect in RA[90,91], presence of one DERAA-coding *HLA-DRB1* allele provides protection against RA even in the presence of predisposing SE-positive alleles.[90]

However, this allele has been shown to predispose to pemphigus vulgaris (PV), an potentially lethal autoimmune disease that is characterized by blistering of the skin and the mucosal membranes. Although this disease is relatively rare, it is associated with considerable morbidity and mortality.[96] Little is currently known about the mechanistic basis of the association of *HLA-DRB1*04:02* with PV, but some have postulated that this allele binds and allows presentation of desmoglein 3, an identified auto-antigen in PV. However, the evidence supporting this hypothesis is ambiguous. The dual role of *HLA-DRB1*04:02* in HLA-disease association, being protective in RA and at the same time being a genetic risk factor for PV, is currently not understood.

Non-SE-coding HLA alleles in RA

As mentioned above, while ACPA-positive RA strongly associates with SE-coding *DRB1* alleles, the ACPA-negative subset has been shown to associate with other, non-SE-coding HLA alleles, such as *DRB1*03:01*, *DR14* or *DR8*. In East Asians, associations of RA with a homozygous non-SE-coding allele *DRB1*09:01*[97], or a heterozygous combination of*DRB1*04:05/09:01* alleles[98] have been anecdotally reported. While the prevalence and

mechanistic basis of these associations remain to be better explored, it is clear that there is more to learn about the stringency of the SE motif as a RA genetic risk factor.

The *DR* and *DQ* loci are inherited in strong linkage disequilibrium. It is therefore not surprising that both loci are statistically found to associate with RA. RA-associated *DRB1* alleles have been particularly demonstrated in haplotypes with certain *DQ* loci. For example, the SE-coding *DRB1*04:01* has been found in haplotypes that include *DQA1*03-DQB1*03:01* or *DQA1*03-DQB1*03:02* alleles, the SE-coding *DRB1*04:04* has been shown to form haplotypes with *DQA1*03-DQB1*03:02*.[99] However, while extensive evidence exists to substantiate a direct role of the *DRB1* locus in RA, evidence to support such role for the *DQ* locus remains to be conclusively shown.

Associations with non-HLA genes

With the advent of GWAS technologies over the past decade, the field has seen major expansion in the number of single nucleotide polymorphism (SNP) sites that identify RA susceptibility gene candidates. A large meta-analysis of multiple independent GWAS data sets[100], covering over 100,000 subjects of European or Asian ancestries, identified 101 RA risk loci corresponding to 98 biological candidate genes.

Among the SNPs identified there are many that involve immune system genes and/or known targets of approved therapy.[100] For example, a missense variant of protein tyrosine phosphatase nonreceptor 22, coded by *PTPN22* that introduces an R620W substitution is associated with RA as well as with many other autoimmune diseases in Caucasian patients.[101] This variant has been shown to affect immune responses relevant to autoimmunity.[102] Another important RA-associated polymorphism involves *PADI4* [103], the gene that codes for the citrullinating enzyme PAD4. The risk variant is associated with increased *PADI4* transcription stability, and has been shown to associate with RA primarily in Asians. An interesting SNP association has been reproducibly found in the tumor necrosis factor-a protein 3 (*TNFAIP3*) locus.[104] The variant leads to impaired A20, an enzyme that inhibits NF-kB activity. As a result, NF-kB signaling is enhanced, and in mice with ablation of *Tnfaip3* there is spontaneous inflammatory polyarthritis.[105] Additional information about GWAS-based RA association data is discussed elsewhere.[100,106-108]

Finally, it should be added that the contribution of the HLA locus to RA susceptibility is far higher than any of the known non-HLA loci, with the *DRB1*-associated risk alone being greater than the aggregate contribution of all known non-HLA risk loci. Additionally, even when the genetic contributions of the entire list of known HLA and non-HLA risk loci are compiled, there is still a large percentage of heritability that remains unaccounted for. The research challenges in the coming years will be to fill in the missing hereditability gaps, address the role of gene-environment and gene-gene interactions, and validate the functional roles of the SE and a myriad of GWAS-based RA risk loci.

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Key points

- Certain human leukocyte antigen (HLA) alleles have been found to be associated with immune mediated or autoimmune diseases, but the underlying mechanisms are largely unknown
- Rheumatoid arthritis (RA) strongly associates with HLA-DRB1 alleles that encode a sequence motif called ‘shared epitope’ (SE) and there is variability in the strength of RA-SE association among ethnic and racial populations
- The SE shows interaction with environmental factors (tobacco exposure) and together significantly amplify the disease risk
- In contrast to RA risk-conferring SE-coding alleles, there are several other DRB1 alleles that protect against the disease
- Genome-wide association studies discovered many non-HLA RA risk loci, but their aggregate contribution to RA risk is outweighed by that of the SE

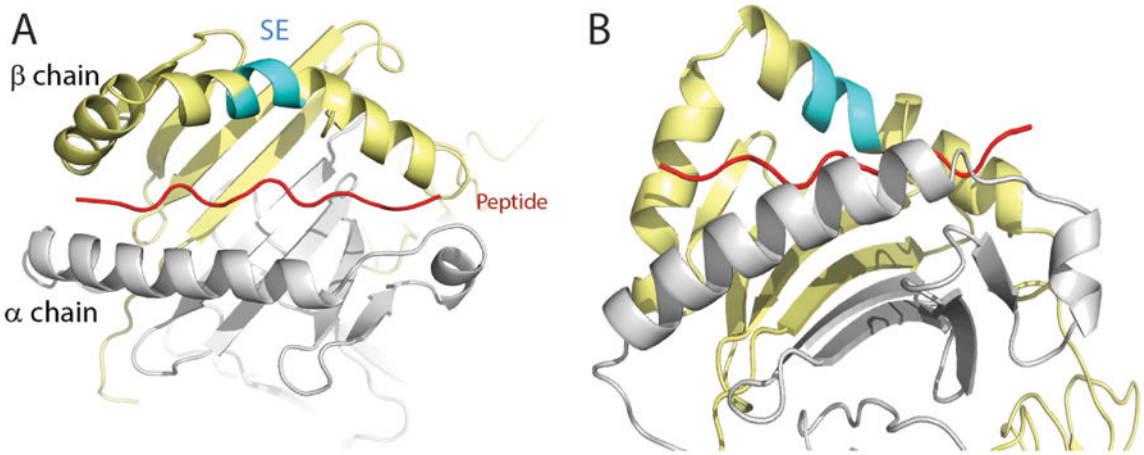

Figure 1. The SE ligand

Crystal structure of HLA-DR4 (*DRB1*04:01*) molecule in a 'top" (A) and 'side' (B) views. The DRα chain is colored in gray; the DRβ chain is shown in yellow and the groove peptide is shown in red. The SE (residues 70-74) is shown in cyan.