

Commentary

Reshaping Cinderella's slipper: the shared epitope hypothesis

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Abstract

This issue of *Arthritis Research and Therapy* contains a succinct and elegant paper by Michou and colleagues that advances our understanding of the genetic basis of rheumatoid arthritis (RA) by reclassifying the contribution of RA susceptibility alleles according to their structure. This line of research is potentially important in our conceptualization of the mechanism of disease in RA, in predicting disease course and severity, and as a model for further studies on this topic. The author's approach to reassessing the molecular structure of the shared epitope redirects attention to using the binding properties of the major histocompatibility complex molecules associated with susceptibility to search for the peptides driving the autoimmune process underlying rheumatoid arthritis

This issue of *Arthritis Research and Therapy* contains a succinct and elegant paper by Michou and colleagues [1] that advances our understanding of the genetic basis of RA by reclassifying the contribution of RA susceptibility alleles according to their structure. This line of research is potentially important in our conceptualization of the mechanism of disease in RA, in predicting disease course and severity, and as a model for further studies on this topic.

More than 10 different HLA-DRB alleles predispose to the development of rheumatoid arthritis (RA) and this number alone distinguishes RA from many other autoimmune diseases. Over two decades ago the existence of common structural features of the HLA-DR4 and DR1 molecules encoded by these multiple susceptibility alleles emerged from pioneering sequencing efforts and this structure was termed the shared epitope (SE) [2]. The SE hypothesis was a simple conceptual framework that sought to redirect thinking about disease susceptibility towards a unifying molecular susceptibility structure that would aid in the search for peptides driving the T cell immune response underlying RA, a sort of Cinderella's slipper. The original notion of SE was modified by the concepts of protective alleles [3] and 'homozygosity' or allelic interaction [4]. Additional support for

the SE hypothesis came from other unrelated alleles in different populations that encode a SE motif that were identified as RA susceptibility alleles, for example, DRB1*1402 [5] and DRB1*1001 [6].

Although a Google search reveals over 40,000 hits for 'shared epitope', reflecting the efforts by many to advance RA genetics, both knowledge of the inciting peptide, and how the nature and conformation of the peptide-binding groove predispose to RA eludes our grasp. Difficulties in identifying which alleles are implicated in RA susceptibility or protection and which regions of molecules encoded by these alleles are functionally important has resulted in several different allele classifications that yield contrasting notions of the shape and significance of a unifying molecular structure. Indeed, using some of these classifications, the question has been raised whether the so-defined SE concept is correct.

The study of Michou and colleagues [1] began with Tezenas du Montcel and colleagues [7], who rejected the then current view of the contribution of various alleles to the SE as not fitting observed RA inheritance and proposed a new classification of the SE: S1 alleles, for example, DRB1*0402, where negatively charged glutamic acid (E-R-A-A), negates the susceptibility effect of the R-A-A motif; S2 alleles associated with highest disease susceptibility, for example, DRB1*0401 and *1303, with lysine (K-R-A-A) that are independent of the residue at position 70; and S3 arginine (R-R-A-A), further subdivided according to position 70 into R/Q-R-R-A-A S3P alleles associated with intermediate susceptibility to RA, including DRB1*0101, *0102, *0404, *0405, *0408, *1001 and *1402 and S3D alleles including DRB1*1101, and *12 with the D-R-R-A-A motif. Important features of this new classification include: the distinction of the S1 and S3D, allowing study of their protective effect; elimination of the influence of the glycine/valine polymorphism at position 86, thereby reducing the number of SE

MHC = major histocompatibility complex; OR = odds ratio; RA = rheumatoid arthritis; SE = shared epitope.

categories; and reclassification of alleles, notably DRB1*1303, a K-R-A-A allele, as a S2 allele. X alleles lack the SE motif. The predictive power of this SE classification to identify RA susceptibility was cross-validated in this report by Michou and colleagues [1].

What sets this study [1] apart is that the cross validation experimental design and statistical analysis embody thoughtful and powerful contemporary approaches that should become the norm in this field. This transmission disequilibrium study design has a marked advantage over case-control designs when dealing with major histocompatibility (MHC) loci because the extremely polymorphic alleles increase the ever-present risk of ethnic stratification in independently selected control groups.

The paper confirmed that the weight of contribution to RA susceptibility is not equal for each SE virtual allele. S2 and S3P respectively confer high or moderate risk for RA, while X, S1 and S3D do not influence risk and were grouped together as L alleles. The high risk SE conformation of the K-R-A-A motif is independent of the contribution of position 70, while the lower risk R-R-A-A motif (e.g. in DRB1*0101 or *0404 Q-R-R-A-A) is strongly influenced by the charge of position 70. The work strongly confirms that virtual genotypes involving certain SE combinations differ in the risk they contribute to the development of RA. S2/S3P and S2/S2 in grouped analysis provide remarkably high risks (odds ratios (ORs) 22.2 and 20.5, respectively). The other three genotypes confer lower risks: S3P/S3P, OR 8.7; S2/L, OR 5.3; and S3P/L, OR 3.1. The two levels of risk suggest that two differing disease mechanisms operate and that epistatic interactions with other non-MHC genes might preferentially occur with only one of these. In the 'hemizygous' situation of S2/X or S3P/X, the SE acts like a conventional dominant immune response gene in regulating peptide binding. Why certain compound SE genotypes provide a multiplicative risk over single alleles or their attendant haplotypes is harder to explain. Some of these allelic combinations have previously been associated with vasculitis [4,6,8], suggesting the new classification will better predict those likely to develop more severe disease, which could require more intense therapy.

Michou and colleagues did not obtain evidence supporting a protective effect for S3D or S1 alleles, although this might be due to their lower frequency in this particular study population. The new classification provides a clear approach for additional studies to examine the apparent protective effect of S1 and S3D virtual alleles reported in some studies [3]. While the paper of Michou and colleagues [1] was in press, another report appeared by Gourraud and colleagues [9], also demonstrating that the classification proposed by Tezenas du Montcel and colleagues [7] was also superior to older classifications of SE alleles in predicting radiological progression to erosive disease and also supporting the identification of a protective effect on progression. This cross-

sectional study from Toulouse in Southern France used a Midi-Pyrenees patient population exhibiting a rather different composition of HLA-DR alleles, presumably reflecting Basque and Mediterranean influences; for example, S2 allele frequency increased from 9 to 21.5 and X alleles decreased from 36% to 19.4% compared to the study of Michou and colleagues [1]. Notably, a protective role was identified for S3D alleles on progression to erosive disease. However, the cross-sectional study design format limited the conclusions that could be made concerning genetic susceptibility and protection.

The triad study design of Michou and colleagues [1], requiring both parents to be typed, necessarily included younger age onset RA (31 ± 9 years). This appears to have selected a distinctive study population as there was a marked female preponderance (90%), and rheumatoid factor detectable in 76% of subjects, nodules in 19% and erosions in 79%, indicative of classic, severe RA. This of course raises the old and unanswered question of whether the current syndromic classification criteria for RA are non-specific and whether anti cyclic-citrullinated peptide (CCP) antibody-negative and rheumatoid factor-negative patients with non-erosive arthritis who are SE-negative might contain a large proportion of individuals with milder arthritis of an etiology different from RA.

The Michou and colleagues report is a major advance and a template for future studies, but there is still insufficient information to develop a comprehensive conformational understanding of how the DRB1 molecules confer RA susceptibility in terms of motif, charge and other properties of the amino acids and whether this implies two or more conformations that bind different peptides. The exact shape of the glass slipper still eludes us. Studies in populations in addition to French Caucasoids that have differing frequencies of susceptibility alleles or potentially protective alleles are necessary to refine the SE model by addressing questions such as the contribution to the SE of DRB1*0901 or *0411 that have RAE motifs and the role of ARAA motif alleles. As of April 2006, there are some 522 HLA-DRB alleles, so there is still much to discover about their role in RA.

Of course, the MHC is characterized by its haplotypic organization and the pervasive linkage disequilibrium among various alleles of the MHC loci and non-DRB1 alleles in linkage disequilibrium with DRB1 alleles also contribute to RA susceptibility, as emphasized by Jawaheer and colleagues [10]. This SE classification, by pointing out that different haplotypes encode a structure that may make them identical by state, and that the inheritance of two SEs confers multiplicative risk, directs attention to a different, more functional axis on which to conceptualize and model the role of the MHC gene effect. Indeed, stratification of patients according to SE genotype may facilitate better identification and analysis of haplotype specific effects. Challenged by this

new classification of RA susceptibility alleles [1] and in concert with the efforts of major genomic consortia focused on RA, one senses we are poised for a period of very fruitful insight into this enigmatic disease.

Competing interests

The author declares that he has no competing interests.

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