Editorial

Epitope spreading in animal models: array of hope in rheumatoid arthritis and multiple sclerosis

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Abstract

The paradigm for pathogenic autoimmunity is the generation of high-titre, affinity-matured autoantibodies to a restricted family of autoantigens, in the appropriate genetic context. Genetic determinants of autoimmunity are largely found within the major histocompatibility complex (MHC) and the 'genotype to serotype to phenotype' concept is supported in a number of autoimmune diseases, where both genotype and serotype are well established. The serotype is autoantigen-driven, with evidence of epitope spreading as the disease evolves from asymptomatic to pathogenic autoimmunity. In rheumatoid arthritis and multiple sclerosis, where the autoantigens are poorly characterised, the use of an array in animal models may produce a hint of what happens in human disease. A more complete picture will be obtained from animals transgenic for human MHC, immunised with known human autoantigens.

Epitope spreading in animal models of rheumatoid arthritis and multiple sclerosis

In a recent issue, Kidd and colleagues [1] have attempted an analysis of epitope spreading in murine collagen-induced arthritis and experimental autoimmune encephalomyelitis as models of rheumatoid arthritis (RA) and multiple sclerosis (MS). This is a courageous undertaking, because the major histocompatibility complex (MHC) differs between mouse and man and, therefore, any MHC-dependent autoimmune response may also differ. In the human form of both diseases, the autoantigens remain poorly characterised. In RA, citrullinated antigens are likely to be the major targets of the autoimmune response. This conclusion is supported by the high specificity of antibodies to cyclic citrullinated peptides (CCPs) both in diagnosing and predicting disease. The specific target antigens include citrullinated fibrinogen, citrullinated vimentin, citrullinated collagen type II (reviewed in [2]) and, more recently, citrullinated α-enolase [3]. In α-enolase, there is evidence of an independent immune response to multiple citrullinated epitopes within the molecule [3]. In MS, a number of candidate autoantigens are associated with myelin, though the predictive and diagnostic value of their associated autoantibodies is disappointing [4]. In both murine models, the primary autoantigen is the protein used to induce the disease. However, in RA, it is clear that native collagen is not 'the' autoantigen and the intense antibody response to proteolipid protein, seen in experimental autoimmune encephalomyelitis, is not present in MS.

Kidd and colleagues attempt a non-prejudicial approach to dealing with the range of autoantigens that might be pathogenic in RA and MS by array technology. They used 253 antigens for their synovial array and 406 for their myelin array. This, of course, is a tiny fraction of the proteome and their choice had to be restricted to some of the antigens described as candidates in the previous literature. In spite of these limitations, they showed that antibodies to other candidate antigens, including citrullinated peptides, developed during the course of both diseases. They interpreted this as being due to intermolecular epitope spreading arising from the expression of citrullinated proteins as neoantigens in inflamed tissue. Some support for this hypothesis was provided by anti-citrulline immunoblotting, which demonstrated an increase of citrullinated proteins in both inflamed synovium and brain tissue. Other interpretations, however, include the possibility that antibodies to citrullinated proteins arise as a result of polyclonal activation as part of the 'natural antibody' response to adjuvant. Kidd and colleagues did not use an adjuvant-only immunised group of mice as controls, nor did they distinguish IgM from IgG antibodies. A further control not examined was the testing of the CII immunised mice on the myelin array or *vice versa*. A controversial finding in this study was the demonstration of citrulline specificity for the antibodies to citrullinated peptides. This has also been

CCP = cyclic citrullinated peptides; MHC = major histocompatibility complex; MS = multiple sclerosis; RA = rheumatoid arthritis.

reported in one previous study of collagen-induced arthritis [5], though other studies have found equal binding to both citrullinated and arginine-containing control peptides [6]. In RA, the anti-CCP response reflects the genotype-serotype-phenotype model, with antibodies to citrullinated proteins being closely correlated with the presence of the MHC shared epitope [7] and it has been argued that the shared epitope is required to present citrulline containing peptides to responder T cells [8]. Therefore, the most convincing murine model of RA is that of the recently reported DR4-IE transgenic mouse immunised with citrullinated fibrinogen [9].

The impressive, though often uncontrolled, array of data that arises from this sort of work is often regarded as hypothesis-generating rather than hypothesis-testing. The study from Kidd and colleagues [1] falls in the former group, in that it provides more questions than answers. In the case of RA, some of the answers are already partially addressed by the recent reports of new disease-specific autoantibodies. In MS, the B cell autoantigens remain poorly characterised. Nevertheless, the authors have presented an exciting new model to provide some of the answers in the future. Now that we know more about the citrullinated antigens associated with the anti-CCP response and the requirement for specific MHC alleles, the use of transgenic animals could go a long way to analyse the autoimmune response in RA. In MS, where the autoimmune response appears to be less MHC-restricted, better definition of the human autoantigens is required for further progress.

Competing interests

The authors reference their own work [3] in this editorial. Reference 3 concerns the immunodominant epitope of citrullinated alpha-enolase, denoted CEP-1. The sequence of the CEP-1 peptide is the subject of an international patent application, number WO0890360, published on 31st July 2008. The authors of this editorial, KL and PJV, are named as inventors on this patent application.

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