What structures are seen by a T cell in the immune response to a lupus autoantigen?

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In this decade we have witnessed substantive progress in solving a number of the fundamental enigmas in systemic lupus erythematosus (SLE) that thwart progress towards achieving the goal of inducing disease remission in all patients with this challenging disease. This issue of the *Annals of the Rheumatic Diseases* contains a paper by Zhao *et al*¹, 'Nature of T cell epitopes in lupus antigens and HLA-DR determines autoantibody initiation and diversification', which greatly advances understanding of four critical aspects of SLE that are included among these enigmas: Why is the susceptibility to develop SLE associated with the Major Histocompatibility class II allele designated HLA-DR3? What role does the recognition by specific T cell clones of self-peptides presented by HLA-DR3 molecules play in the process of epitope spreading that drives the progressive intensification of a seemingly inconsequential autoimmune response to become a virulent life-threatening autoimmune disease? What roles do the peptides of the diverse commensal and environmental antigens of a person's environment play in this progressive intensification? Lastly, what events are involved in the transition from asymptomatic autoimmunity to the heterogeneous organ involvement of clinical disease? The paper addresses these questions by analysing in detail the characteristics of both the B cell and T cell immune response to Smith antigen (Sm). It especially focuses on the particular peptides recognised by the clonally specific T cell receptors (TCRs) of the T cell clones proliferating in HLA-DR3 transgenic mice during the response to immunisation by Sm, by elegantly exploiting the property of murine T cells to be readily immortalised as hybridomas.

Several intriguing findings in this paper that address these questions provide insight into the ever-accelerating incendiary spiral of autoimmune responsiveness in SLE:

1. The authors show that the immune response of the mouse to Sm triggers the proliferation of a large number of different T cell clones, which recognise a number of different amino acid sequences (epitopes) located on different peptides of the SmD molecule, when these peptides are presented by HLA-DR3. This finding extends the earlier study from Fu and colleagues that among transgenic mice with diverse HLA-DR and DQ alleles, those expressing HLA-DR3 make the greatest antibody responses to Ro60 and Sm.² Moreover, in parallel Zhao *et al*¹ demonstrate that normal blood donors who have HLA-DR3 make significantly more anti-Sm and anti-Ro60 antibodies than those without this allele, indirectly supporting the thesis that the diversity of T cell recognition of different peptides with HLA-DR restriction is important in the generation of antibodies to these classic lupus autoantigens. These results suggest the property of HLA-DR3 to select a T cell repertoire enriched in clones with TCRs that recognise Sm peptides could be a direct molecular explanation for why both the susceptibility to develop SLE and the presence of antibodies to Sm and Ro60 are associated with the MHC.
2. These authors further showed that many of the individual Sm peptide reactive T cell clones responded to more than one peptide on the Sm molecule, indicating that they recognise and respond to cross-reacting intramolecular epitopes when presented by HLA-DR3 molecules. Furthermore, some of these clones cross-reacted with peptides derived from other small nuclear ribonucleoprotein, including those on peptides from proteins in the Ro60/La/Ro52 complex, a demonstration of T cell clonal recognition of intermolecularly shared epitopes. This elegant and striking demonstration of extensive cross-reactive recognition of different autoantigen peptides by the same TCR clone was interpreted to suggest

that an intricate and extensive clonal recognition network underlies the development and maturation of the autoimmune response to Sm. These data highlight the role that T cells can play in the process of intermolecular epitope spreading among autoantibodies, a process that is at the heart of the progressive intensification of the immune response underlying SLE. Indeed, this phenomenon could underlie the deeper significance of the presence of Sm autoantibodies in patients with SLE.

3. Provocatively, Zhou *et al*¹ observed that many T cell clonal members of this recognition network, which likely entered the T cell repertoire by being selected by self-Sm peptides during thymic development, also identified and responded to a variety of non-self-peptides encoded within the proteomes of a large number of different commensal and environmental microbes. Indeed, in some instances this cross-recognition was mirrored by the presence of antibodies that reacted with the parent microbial molecule. It is important to emphasise that this finding of cross-reactive recognition of microbial peptides differs from two previous views on potential mimicry between self and microbial non-self. First, this is not the description of a single canonical microbial mimic that might drive the entire T cell response, as in older concepts of molecular mimicry, but rather that any given T cell clone participating in the response against Sm that recognises an Sm peptide might cross-react with one particular microbially encoded peptide, while other T cell clones in the same response with different TCRs that each recognises different Sm peptides also cross-recognise and respond to entirely different microbial peptides contained in the proteins of different micro-organisms. Intriguingly, the affinity of some of the T cell clones for microbial peptides was considerably greater than that for the peptides of the autoantigen. Second, this hypothesis differs from the B cell mimicry hypothesis of James and Harley,³ which contributes to SLE-related antibody diversification since it addresses the role of T cells and incorporates the importance of T cell dependence in the generation of SLE-related antibodies such as anti-Sm and anti-Ro60 that are restricted by HLA-DR, a major lupus susceptibility gene.

This report by Zhao *et al*¹ did not address the important next question of whether this cross-reactivity is

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incidental to the vastness of microbial diversity or might play an important direct role in the initiation or in the progression of the autoimmune response. One can envision that the T cells in the repertoire of DR3 individuals responding to these cross-reacting microbial structures might be the starting point for the provision of help to autoantibody secreting B cells. Similarly, these diverse, cross-reacting microbial peptides that mimic different autoantigen epitopes could also drive the progressive maturation of the autoantibody response that eventuates in clinical disease. However, this report is clearly relevant to the emerging studies on the role of the microbiome and dysbiosis in autoimmune disease. Additional work engendered by the findings of this study is required to sort out the relevance, mechanisms and consequences of this unanticipated extensive T cell cross-recognition to the immune response occurring in SLE.

4. This innovative study makes an additional point of particular relevance to the progression from asymptomatic autoimmunity to the development of an autoimmune disease with injury in target organs. Zhao *et al*¹ showed that the spreading autoimmune antibody response induced by immunising with

SmD peptides ultimately includes novel autoantibodies that react directly with organs that are the targets of injury in lupus. This raises the question of whether the generation of novel tissue-specific autoantibodies as a consequence of this network of autoantigen recognition plays a role in the eventual development of tissue injury of target organs responsible for clinical disease and whether the diversity of this process contributes to the heterogeneous clinical presentation and course in SLE.

A final thought is that this paper's study of the manner in which T cells could fundamentally contribute to the interconnected aberrant adaptive immune responses to nucleic acid antigens that underlie lupus, and potentially additionally react with environmental and microbiological structures, is a compelling call for further investigation of this exciting and therapeutically promising aspect of the immunobiology of lupus. It will remain for this future work to rigorously demonstrate the extent to which the fascinating capability of a T cell receptor to engage in the network of recognition events elegantly delineated in this paper is indeed a critical component of the immune response occurring in patients with SLE.

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