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Autoimmunity

Editorial overview

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Yanick Crow is a professor in Genetic Medicine at the University of Manchester, and a consultant in Clinical Genetics at St Mary's Hospital, Manchester. His studies of the rare Mendelian disorder Aicardi-Goutières syndrome have highlighted the relationship between nucleic acid metabolism, type I interferon, and autoimmunity. This work has led to a subsequent focus on Mendelian forms of systemic lupus erythematosus as a tractable approach to understanding disease pathogenesis, and the concept of human 'type I interferonopathies' as a novel set of inborn errors of immunity.

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Edward Wakeland is a professor and Chairman of the Department of Immunology at the University of Texas Southwestern Medical Center. He holds the Edwin L. Cox Distinguished Chair in Immunology and Genetics and is the Director of the Bader Center for Arthritis and Autoimmunity. His research has focused on characterizing the nature of genetic predisposition to autoimmunity via the creation and analysis of mouse models of systemic lupus. More recently, he has moved to the study of human autoimmune disease utilizing next generation sequencing technologies to characterize the allelic architecture of autoimmune risk loci.

Systemic lupus erythematosus (SLE) is an enigmatic autoimmune disease, typically beginning with the development of autoantibodies against nucleic acids and nucleoproteins and progressing to a heterogeneous disease pathology that can cause inflammatory damage in a variety of organs. Multiple immunologic abnormalities contribute to the pathogenesis of SLE, including defects in the clearance of apoptotic cells and immune complexes, altered T and B lymphocyte function, and dysregulation of the innate immune system. SLE patients typically develop high titres of IgG autoantibodies against a plethora of nuclear autoantigens, indicative of a severe breach in the normal immunologic tolerance mechanisms of the adaptive immune system. The innate immune system is also dysregulated in SLE, resulting in the chronic production of several cytokines, notably including the type I interferons. Various lines of evidence indicate that type I interferons are key players in multiple stages of the pathogenesis of SLE, with nucleic acids representing the major factor initiating type I interferon production.

Despite much progress in our understanding of lupus, the disease continues to be associated with significant morbidity and mortality, so that there is an urgent need to develop more effective therapies through new biological insights. This issue of *Current Opinions in Immunology* contains articles covering areas of research that promise to provide significant advances in our understanding of autoimmunity in general, and lupus pathogenesis in particular. We very much hope that the spectrum of articles which we have chosen will provide the reader with a sense of new concepts and novel ways of thinking about old problems, and possibly foster the creation of innovative approaches to the development of targeted therapeutics.

The first contribution to this issue, from [Joe Craft](#), [Jinyoung Choi](#), and [Sang Taek Kim](#), provides a concise and insightful overview of lupus pathology, focusing on recent progress in understanding the complex immune abnormalities that mediate the initiation and progression of lupus pathogenesis. Recent studies of animal models have firmly established that dendritic cells play an essential role in the initiation of a breach in tolerance and humoral autoimmunity. They also discuss the potential importance of extra-follicular germinal centers in disease pathogenesis and effector mechanisms that are involved in generating end organ damage. Their analyses of these processes are put in the context of current and potentially future therapeutic strategies for human disease.

The prominent role of high affinity IgG autoantibodies specific for nuclear antigens in lupus pathogenesis has been recognised for decades. Recent data have indicated that the development of potent humoral autoimmunity is

crucial in driving the progression of disease pathology. [Carola Vinuesa, Rebecca Sweet, and Sau K Lee](#) have contributed an article focusing on the abnormal immunologic mechanisms that underlie the development and persistence of such autoantibodies. Their article focuses on the role of cytokines in dysregulating follicular helper T cells and driving humoral autoimmunity. They also discuss the types of mechanistic variations that mediate this dysregulation and potential therapeutic strategies using monoclonal antibodies to specific cytokines based on patient phenotypes.

The involvement of complement in the pathogenesis of lupus has been recognised for decades. However, the precise mechanisms relating complement to lupus remain unclear. In addition to the well-described role of early classical complement proteins in facilitating apoptotic cell clearance, [Keith Elkon and Deanna Santer](#) discuss other links between complement and lupus through type I interferon induction. Of particular note are recent studies showing that, in the absence of C1q, instead of immune complexes binding to monocytes, they preferentially engage plasmacytoid dendritic cells (pDCs), thus generating interferon alpha. Furthermore, C1q has been shown to impede neutrophil extracellular trap (NET) degradation. NETs are known to promote type I interferon production in SLE by providing a source of antigen for the formation of immune complexes, as well as through direct pDC activation by LL37.

[Simone Caielli, Jacques Banchereau, and Virginia Pascual](#) provide an elegant exposition of the role of neutrophils in inflammation. As they explain, neutrophils are key players in the war against pathogens. However, because they are short-lived and difficult to manipulate *in vitro*, studies on neutrophils in inflammatory disease states have lagged behind those of other leukocytes. Their review discusses how non-infectious types of neutrophil activation and death might contribute to the pathogenesis of chronic human autoimmune and inflammatory diseases, with a particular highlight of recent studies being the elucidation of a link between NETs and lupus. Undoubtedly, better definition of neutrophil biology will provide us with safer and more rational approaches to the treatment of chronic inflammatory disease.

Bruce Beutler and Katharina Brandl have provided an interesting article focused on the nature of the genetic mutations that may mediate susceptibility to inflammatory bowel disease (IBD). Their article provides a concise overview of the genetics of IBD and postulates that disease susceptibility may be strongly impacted by a variety of low frequency or rare variations affecting

intestinal homeostasis. Low frequency or rare variations are not readily detected by genome-wide association studies, which are currently the standard strategy of most genetic analyses of autoimmune disease. The degree to which rare or low frequency alleles contribute to disease susceptibility is an area of intense investigation in many complex diseases. Beutler and Brandl have illustrated a potential mechanism by which such mutations might contribute to disease susceptibility using a series of ENU mutants, each of which are capable of driving the development of severe colitis in a DSS-mediated mouse model. This provocative article has provided an interesting and well-supported rationale for the potential role of rare variants in mediating susceptibility to autoimmunity.

In their article, [Angela Ceribelli, Minoru Satoh and Edward Chan](#) discuss the rapidly evolving field of microRNAs (miRNAs) in autoimmunity. The identification of miRNAs in *C. elegans* in the early 1990s represents a landmark advance in our understanding of gene regulation. Many hundreds of miRNAs have been discovered which regulate various conserved biological systems, including those in mammalian cells. Multiple of these miRNAs have been shown to be overexpressed or underexpressed in autoimmune disease states including SLE and rheumatoid arthritis, and evidence for the relevance of miRNA biology to human autoimmunity is rapidly accruing from both model system and human data. A particular rationale for studies in this area derives from the potential to target miRNAs for therapeutic purposes. Although the miRNA field is still in its infancy, as bioinformatic and experimental approaches develop, it is likely to provide rich insights into the pathogenesis of autoimmunity.

The evolution of mechanisms for recognising and responding to pathogen invasion represents a major biological preoccupation. 'Archaeological evidence' for this ancient conflict exists, in that up to 40% of the human genome is derived from fragments of ancestral viral sequence. A novel, and perhaps controversial, concept suggests a role for endogenous retroelements as triggers of innate immune system activation, type I IFN production, and the initiation of systemic autoimmune disease. In his article, [Dan Stetson](#) discusses the regulation of endogenous retroelement expression, and the pathways through which retroelements might activate the innate immune system. On the basis of insights derived from the study of Mendelian forms of autoimmunity, he posits the intriguing possibility of treating some forms of autoimmunity with drugs that antagonise endogenous retroelement reverse transcriptase activity.