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Editorial overview: Autoimmunity

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Our understanding of the cellular and biochemical underpinnings of the pathogenesis of systemic and organ specific autoimmune disorders has increased dramatically in the last decade. Not only are these diseases caused by aberrant adaptive and innate immune responses, but they are also correlated with genetic and epigenetic factors and dependent on microbiota and environmental factors. It has become clear that multiple genetic components contribute to disease risk in autoimmune diseases; each individual component having only a modest effect on disease susceptibility. In spite of exciting progress, the number of people worldwide suffering from autoimmune disorders is increasing, especially in the in more developed countries. A number of key issues still need to be resolved in order to predict and prevent disease in at risk individuals, and develop, firstly, better diagnostic tools to complement currently used indexes; secondly, reliable specific biomarkers to monitor and hopefully predict disease activity and finally, novel treatment protocols to replace or add to generic immunosuppressive drugs. Per example, what are the contributions of genetic variations in different populations, environmental factors, microbiota, infectious agents and diet? How do aberrant signaling networks develop during the sometimes lengthy process of pathogenesis of the disease, for instance due to the plasticity of these networks and the interaction between environmental and genetic factors. The collection of reviews in this edition of Current Opinion of Immunology focus on how the interplay of genetics/genomics and microbiota/environment govern innate and adaptive immune response mechanisms that maintain tolerance, which is broken as autoimmunity develops.

Jessica Brinkworth and Luis Barreiro evaluate general principles that appear to govern the persistence of chronic inflammatory and autoimmune diseases and their uneven distribution across populations. From the outcomes of genome-wide association studies (GWAS) it would appear that ‘pathological’ inflammation is controlled by a small network of genes. Because many chronic inflammatory/autoimmune risk alleles occur in regions of positive selection their association might be the consequence of an evolutionary trade-off. The authors argue that pathogen-mediated selection of genes that critically function in other bodily systems might have driven the increase in frequency of inflammatory/autoimmune risk alleles. In addition, diversifica-tion of human immunity has also been influenced by the major cultural changes such as the advent of agriculture and changes in diet in different parts of the world. Finally, the authors discuss that differences in genetic contribution to disease between individuals of African descent and Europeans may be due to the interbreeding between archaic human and modern human populations.

Vinod Kumar, Cisca Wijmenga and Ramnik Xavier further examine conclusions from GWAS studies and the outcomes of post-GWAS studies. The authors find that the majority of the single nucleotide polymorphisms (SNPs) associated with immunemediated diseases, which are often located in non-coding regions, primarily impact gene expression. In addition, there is growing evidence for the concept that infectious and immune-mediated diseases share genetic factors. Indeed, several autoimmune SNPs are stimulation or condition specific expression quantitative trait loci [*eQTLs*]. The authors make a strong case for more integrative strategies based upon genetics, genomics, immunology, infection and bioinformatics in the post-GWAS era.

Genetic factors confer a predisposition to the development of Systemic lupus erythematosus [SLE]. Although in SLE is sometimes associated with the deficiency of a single gene, for example, complement components, the disease mostly results from the combined effect of variants in a large number of genes. Shu Man Fu and colleagues review selected aspects of GWAS studies that identify candidate genes in human lupus. Whereas genetic/genomic research has historically focused more on aberrant innate and adaptive immune responses in SLE, genes conferring end organ resistance to damage are of importance as well. Excitingly, genes that contribute directly to susceptibility to end organ damage are identified in humans and mice allowing more precise pathway analyses of the complex relationships between SLE-associated genes in animal models.

In almost all GWAS studies associations of MHC with autoimmune diseases supersede the contributions of the non-MHC genes. Ludvig Sollid, Wouter Pos and Kai Wucherpfennig not only discuss the general principles of disease associations with MHC Class I, Class II, or both, they also evaluate the emergence of HLA dependent autoantibodies and epistatic interactions of aminopeptidase genes in Class I associasted diseases. Extremely exciting progress has been made in defining critical molecular events through which MHC proteins confer susceptibility to human autoimmune diseases. In addition to our better understanding of the molecular underpinnings of effect of key polymorphisms on MHC structure and peptide specificity, new mechanisms for induction of autoimmunity to self-peptide/MHC complexes have been discovered. For instance, post-translational modification of peptides leading to changes in their affinity for MHC Class II molecule with specific physicochemical properties, and small molecules induced changes in peptide repertoire presentation leading to activation by neo-self epitopes of normally tolerant T cells. Indeed, studies aimed at understanding how particular MHC alleles confer susceptibility to autoimmunity will remain and active field of research for the near future. Several of these molecular interactions of MHC-linked disease susceptibility should suggest therapeutic strategies that benefit patients with autoimmune diseases.

Primary Immunodeficiency Diseases (PIDs) are experiments of nature, whose study is extremely valuable in understanding the function of the immune system. An increasing number of PID patients with distinct inheritable mutations appear to develop autoimmunity. For instance, whereas genetic disruption of the core elements of either the RAG1 or RAG2 proteins abruptly blocks early development of T and B cells, hypomorphic mutations of the RAG1 and RAG2 genes lead to a variety of milder disease manifestations, including autoimmunity. Luigi Notarangelo reviews recent discoveries of proximal defects of T cell

receptor (TCR) signaling in patients with immune deficiency and immune dysregulation. Altered TCR signaling strength may affect positive and negative selection of thymocytes, development and function of regulatory T cells, lymphostromal cross-talk in the thymus, and peripheral T cell function, and thus cause immune dysregulation. Identification of thresholds of TCR signaling that differentially impact on effector and regulatory T cell functions may guide toward development for novel immunosuppressive agents

Dysregulated sensing of self-DNA is acknowledged as a cause for the development of autoimmune disorders. Jeonghyun Ahn and Glen N. Barber review the identification of the sensor STING (stimulator of interferon genes) as critical for induction of pro-inflammatory cytokines including type-1 IFN in response to the presence of microbial cytosolic double-stranded DNA and cyclic dinucleotide. In addition, they discuss the role of STING in the recognition of accumulated self-DNA as a result of a defect in DNAse III (Trex 1) and discuss recent discoveries pointing to mutations in STING as responsible for vascular and pulmonary syndrome. Finally, the authors put forward the intriguing possibility that inflammation-induced cancer may be mediated by STING recognizing damaged-associated DNA.

It is now well accepted that genetics, environmental factors and microbiota, greatly contribute to susceptibility autoimmune disorders. Vanessa Leone, Candace Cham and Eugene Chang discuss our current understanding of autoimmunity in the context of IBD. Their research, as well as that of others, leads to the concept that in addition to genetics, environmental factors and microbiota, diet determines susceptibility to inflammatory bowel diseases [IBD]. Western diet promotes dys-biosis, which can lead to disease in certain individuals. Thus, in addition to specific microbial products that affect host immunity and promote an inflammatory milieu, dietary specific components determine how humans or animals control inflammation. The authors argue that future treatments for IBD might include microbial and/or dietary intervention

Although we know that microbiota are implicated in the development of autoimmunity true causality in humans remains elusive. Ashley Steed and Thaddeus Stappen-beck review our increased understanding of chronic viral infections and commensal microbial relationships, which is requisite for deciphering the pathogenesis of microbialhost induced autoimmunity. Principles of immune tolerance with a focus on the breakdown of immune tolerance during pathogenic as well as commensal relationships between the host and bacteria and chronic viruses are discussed. As the relationship between microbiota and autoimmune disease development is further complicated by host genetic susceptibility, these considerations need to be further verified by the study of well-defined animal models.

The eight reviews in this issue of Current Opinions in Immunology propose working models based on the interplay between genetics and microbiota in autoimmune disorders. The concepts proposed should aid in designing specific experimental approaches that will lead to new diagnostic approaches and therapeutic modalities for these autoimmune diseases.

Biographies

Dr Bana Jabri obtained her MD and PhD at the University of Paris VII, Paris, France. She is a professor of Medicine, Pathology, and Pediatrics at the University of Chicago. She is vice chair for basic research in the Department of Medicine, director of research at the University of Chicago Celiac Disease Center, and co-director of the University of Chicago NIDDK P30 Digestive Disease Research Core. Her research program aims at understanding the mechanisms underlying the development of complex inflammatory and autoimmune disorders, with a focus on celiac disease, inflammatory bowel disease and type-1 diabetes. Her laboratory studies the interplay between mucosal tissues, the microbiota and the immune systems using interdisciplinary and integrated approaches in human and mouse models of disease. She was awarded the William K. Warren, Jr Prize for Excellence in Celiac Disease Research for her seminal work on the role of innate immunity and intraepithelial lymphocytes in the pathogenesis of celiac disease.

Dr Cox Terhorst received his PhD degree in molecular biology from the University of Leiden, The Netherlands. He is professor in the Department of Medicine/Immunology at the Harvard Medical School in Boston, Massachusetts. He is chief of the Division of Immunology at the Beth Israel Deaconess Medical Center in Boston and Associate Director of the Harvard Center for the Study of Inflammatory Bowel Diseases. He has authored over 320 research articles, reviews, and book chapters. His laboratory studies pathway analyses in selected Primary Immunodeficiencies, Inflammatory Bowel Diseases and Systemic Lupus Erythematosus.