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Editorial overview: Autoimmunity: New genomics approaches are improving our understanding of autoimmunity

Bernice Lo,
Sidra Medical and Research Center

Michael J Lenardo
Washington University in St. Louis, Mo

Next-generation sequencing and other technological advances are revolutionizing the way we study autoimmune diseases. The discovery and study of monogenic forms of autoimmune or autoinflammatory disorders have helped elucidate several of the molecular pathways involved in disease pathogenesis. Genomic, transcriptomic, proteomic, as well as epigenetic analyses are being used to increase our understanding of immunologic regulatory mechanisms, diagnose patients, discover new targets for therapeutic development, and determine biomarkers that can assist in matching or tailoring the optimal therapies to each patient. These approaches are also yielding key insights into helping us understand the molecular mechanisms that underlie autoimmunity in both experimental animal and human patients. In this issue, the reviews cover the exciting progress in the study of monogenic and complex disorders of autoimmunity and autoinflammation. This editorial overview will briefly highlight some of the major findings discussed in this issue.

AIRE is an essential regulator of central tolerance. Loss-of-function mutations in AIRE lead to Autoimmume Polyglandular Syndrome Type-I (APS-1/APECED), generally characterized by multiorgan autoimmunity, however, the actual clinical phenotypes of patients can vary broadly. The review by Proekt *et al*. discusses the recent findings from patient studies and mouse models that demonstrate a role for additional modifiers of central and peripheral tolerance that may synergize with AIRE defects leading to the various antigen-specific or tissue-specific autoimmune manifestations. Proekt *et al*. also speculate that mild AIRE dysfunction may contribute as a susceptibility factor to complex autoimmune diseases. As our understanding of the factors that can modulate AIRE function and expression expands, the future of immunotherapy for cancer or autoimmunity may involve the manipulation of central tolerance.

Another major player in the maintenance of immune tolerance are $FoxP3^+$ regulatory T cells (Treg). In this issue, Kitagawa and Sakaguchi review the novel insights into how Treg cells develop, function and are maintained. They describe how defects in any of these processes can lead to autoimmunity. They especially focus on the regulation of Tregs at the transcriptional and epigenetic level and discuss the importance of Treg-specific enhancer activation and DNA hypomethylation for the development and lineage stability of Tregs.

The study of monogenic autoimmune disorders has revealed additional molecules involved in immune regulation or new facets to their function. Although CTLA-4 knockout mice

had revealed the crucial role of CTLA-4 in regulating immune homeostasis, the discovery of CTLA-4 haploinsufficiency in humans showed the importance of CTLA-4 levels in the quantitative control of immune responses, as reviewed by Lo and Abdel-Motal. Investigations into LRBA deficiency and the function of LRBA led to the discovery of its role in regulating CTLA-4 protein turnover. The loss of CTLA-4 protein levels in LRBA deficiency and the development of autoimmunity suggests that preserving an intracellular pool of CTLA-4 in Tregs and/or activated T cells is critical for maintaining T cell homeostasis.

As reviewed by Kretschemer and Lee-Kirsch and Costa-Reis and Sullivan, the study of monogenic lupus and the type I interferonopathies, respectively, have uncovered novel protective mechanisms for preventing aberrant activation of viral DNA/RNA sensors by self nucleic acids. Defects in these regulatory mechanisms lead to inappropriate activation of the interferon pathway and autoinflammation. For the development of autoimmunity or lupus-like disease, additional mechanisms that contribute to disease pathogenesis include aberrant clearance of apoptotic bodies or immune complexes and impaired B and T cell tolerance.

Another autoinflammatory or hyperinflammatory condition is hemaphagocytic lymphohistiocytosis (HLH). HLH is a life-threatening syndrome caused by excessive immune activation and the development of a cytokine storm. Primary HLH predominantly results from genetic defects impairing lymphocyte cytotoxicity. However, as reviewed by Sepulveda and de Saint Basile, mutations in genes unrelated to cytotoxic function have recently been identified, demonstrating that other disease mechanisms can also lead to HLH. Genetic defects causing aberrant inflammasome activation or impaired control of EBV infections have been found to result in HLH. Additionally, lymphomas, persistent infections, inflammatory disorders, and primary T cell deficiencies have been found to predispose or trigger secondary forms of HLH.

The study of monogenic autoimmune diseases has not only helped define the molecular pathways involved in immune regulation but have also shed light on potential mechanisms that may explain the ‘missing heritability’ of complex diseases. As reviewed by Rieux-Laucat, autoimmune lymphoproliferative syndrome generally results from dominantly-inherited genetic defects in the FAS apoptosis pathway, however, disease especially that due to haploinsufficient mutations often presents with incomplete penetrance. Somatic mutations affecting the second allele or loss of heterozygosity has been found to be associated with the onset of disease. In mouse models, heterozygous mutations in two different genes of the FAS apoptosis pathway could lead to disease implicating digenic or multigenic inheritance to be a potential mode for disease development.

Studies of complex autoimmune diseases have further revealed the various components of the immune system that interplay, leading to disease. As reviewed by Liang *et al.*, the various clinical subtypes of psoriasis are associated with varying degrees of T cell-mediated adaptive immune responses versus innate and autoinflammatory responses. In rheumatoid arthritis, novel CD4+ T cell populations associated with disease have been discovered. As reviewed by Fonseka *et al.*, the advances in single cell profiling technologies has allowed

for the identification of specific disease-associated cell populations that may drive or act as biomarkers of pathologic processes. In myasthenia gravis, humoral autoimmunity is the driver of the neuromuscular autoimmune disease. Romi *et al.* discuss the role of thymomas and the various autoantibodies involved in the different subtypes of myasthenia gravis. The aberrant presentation of epitopes in thymomas or thymic tissue is thought to trigger the disease. For other autoimmune diseases, infections often precede the onset of disease. Cross-reacting epitopes between the pathogen and the host could be the trigger of autoimmunity, however, there are only a few clear cases in humans in which microbial epitopes mimicking autoantigens were linked to disease, as reviewed by Rose.

Studies assessing efficacy and outcomes of the various new therapies have also shed light on the role of particular pathways or cell types in disease pathogenesis. Naushad *et al.* review the recent progress in the treatment of type 1 diabetes. Therapies targeting T cells or B cells or involving Treg expansion and infusion have shown promising results and the goal remains to suppress disease sufficiently to reduce the insulin treatment requirement. For multiple sclerosis, reviewed by Dendrou and Fugger, the B-cell-depleting antibody ocrelizumab has recently been approved. Immunomodulatory therapies have been used for over two decades in multiple sclerosis, however, the various drugs show efficacy in only a proportion of patients, which differs depending on the targeted pathway. Better ways of determining the most effective or appropriate therapy for individual patients need to be developed. Ivison *et al.* review the various tools and approaches for identifying biomarkers that can assist in predicting which treatments are most suited for each patient. Although still in the beginning stages, the future in therapy for autoimmune diseases lies in personalized medicine.

In summary, new investigative technologies have brought in their wake a number of new insights and concepts that raise hope for improved treatment and less suffering from immunological diseases in the future.

Biographies

Bernice Lo, Ph.D. is an investigator at Sidra Medical and Research Center. She has contributed to the discovery, diagnosis, and molecular understanding of inherited autoimmune disorders, most notably, CTLA-4 haploinsufficiency and LRBA deficiency. Dr. Lo’s laboratory is focused on understanding the molecular pathways involved in immune regulation and tolerance.

Michael Joseph Lenardo, M.D. Michael Lenardo was born in Chicago, Illinois on December 1, 1955. He attended the Johns Hopkins University and graduated with a Bachelor of Arts in Natural Sciences in 1977 and obtained his Doctor of Medicine (M. D.) from Washington University in St. Louis, Mo. He carried out clinical and research training at the University of Iowa from 1981–1985 and became a Research Fellow at the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology. During this time, he carried out molecular biology research under the mentorship of Nobel laureates David Baltimore and Philip Sharp. He was appointed Section Chief in the National Institute of Allergy and Infectious Diseases, National Institutes of Health from 1989 to the present, directing research on T-lymphocyte regulation, HIV-1, and genetic diseases of the immune system. He has served on the editorial boards for the European Journal of Immunology, the Journal of Experimental Medicine, Science magazine, and Biology Direct. He is an Adjunct Professor of Pathology at the University of Pennsylvania School of Medicine, and a Visiting Fellow at Cambridge University. He has founded or co-founded several joint research programs including the NIH-Oxford-Cambridge Biomedical Research Scholars, the NIH-University of Pennsylvania Immunology Program, the NIH-Marshall Scholars, the NIH-Rhodes Scholars, the National M.D./Ph.D. partnership program, and the NIH-Institut Pasteur Infectious Disease and Immunology Program. Dr. Lenardo has published over 240 scholarly works and holds a number of medical patents. He discovered the propriocidal mechanism of immune regulation and his work has defined several genetic diseases of the immune system including the Autoimmune Lymphoproliferative Syndrome, Caspase-8 deficiency syndrome, X-linked magnesium deficiency with EBV and neoplasia (XMEN) disease, and CD55 deficiency with hyperactivation of complement, angiopathic thromboses and protein-losing enteropathy (CHAPLE) disease. He is currently the Director of the Clinical Genomics Program and Chief of the Molecular Development of the Immune System Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Among his honors and awards, he is Officer of the Most Excellent Order of the British Empire (O.B.E.), conferred by Queen Elizabeth II, March, 2006 and a Fellow of the American Association for the Advancement of Science and the American Academy of Arts and Sciences.