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Editorial

Introduction to a review series on understanding and treating primary immunodeficiency

Since the first descriptions of inherited immunodeficiency diseases, it has been the science of immunobiology that has driven the design of corrective treatments. The discoveries in the 1960s of the bone marrow origin of lymphocytes, with B cells maturing in that site and in the fetal liver and T cells moving to the thymus for further development, underpinned the first successful correction of severe combined immunodeficiency disease by bone marrow transplantation in 1968 by pioneering work in the United States by Robert Good and in Leiden, The Netherlands by De Vries and colleagues.

Later, clear evidence was provided both in murine models and in human studies that natural killer (NK) cells and T cells may derive from a common precursor. Thus, our understanding of the innate and adaptive immune system expanded far beyond these beginnings to reach a molecular level of definition. The power of genetic analysis to identify mutations has transformed our ability to understand the cellular pathways that are affected in primary immunodeficiency diseases (PID) and is giving insight into the way normal cells behave. Concurrently, treatments have also become more sophisticated and include other types of cellular and molecular therapy with modern technology opening up the possibility of gene therapies to cure these devastating disorders.

In a series of papers by experts in the PID field, we share with you here cutting-edge developments in the biology and management of primary immune deficiencies, as follows:

- "Immune dysregulation in patients with RAG deficiency and other forms of combined immune deficiency" by Ottavia M. Delmonte, Anna Villa, and Luigi D. Notarangelo
- "Virus-specific T-cell therapies for patients with primary immune deficiency" by Michael D. Keller and Catherine M. Bollard
- "A research-driven approach to the identification of novel natural killer cell deficiencies affecting cytotoxic function" by Michael T. Lam, Emily M. Mace, and Jordan S. Orange
- "Increased activation of PI3 kinase-δ predisposes to B-cell lymphoma" by Anne Durandy and Sven Kracker
- "Primary immunodeficiencies reveal the molecular requirements for effective host defense against EBV infection" by Stuart G. Tangye and Sylvain Latour
- "Current genetic landscape in common variable immune deficiency" by Hassan Abolhassani, Lennart Hammarström, and Charlotte Cunningham-Rundles

Delmonte and colleagues from the National Institutes of Health, Bethesda, Maryland describe the current knowledge of the pathophysiology of combined immune deficiency disorders, including deficiencies in the recombination activating genes 1 and 2, which play a critical role in the generation of the T-cell and B-cell receptors. Keller and Bollard from Children's National and The George Washington University, Washington, DC describe the role that virus-specific T-cell cellular therapy can play in the treatment of patients with PID disorders who have life-threatening viral infections pre- or post–bone marrow transplantation. Recently described NK cell deficiencies and novel treatment approaches are described by Lam et al from Columbia University, New York, New York. Two papers cover the complicated relationship between immunodeficiency and the predisposition to B-cell lymphoma: Durandy and Kracker from the Institut Imagine–INSERM U1163, Paris, France describe lymphoproliferation driven by activating mutations in the PI3K δ pathway, which can result in B-cell lymphomas; and Tangye and Latour from the Garvan Institute of Medical Research, Sydney, Australia explore mechanisms of induction of disease by Epstein-Barr virus in primary immunodeficiencies, revealing essential pathways in the normal control of this ubiquitous virus and pointing to strategies that could be developed for the PID setting. Last, Abolhassani and colleagues from Mount Sinai School of Medicine, New York, New York dissect the complex topic of common variable immunodeficiency, indicating that, although some categories have identifiable gene involvement, many do not.

We think the *Blood* readership will appreciate the broad and exciting developments in a field where progress is being rapidly made in the curative treatment of these rare and hitherto dismal inherited disorders.

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