Understanding human immunology through the study of primary immune deficiency disorders
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CONCLUDING REMARKS

Recent conceptual advances and new technologies are driving an unprecedented expansion in the field of primary immunodeficiencies (PIDs). The number of known genetic defects is growing rapidly each year, counting more than 160 in 2011 (ref. 1 and unpublished observations). One recent major technological advance that will have, in the author’s view, strong impact in the coming years is the application of second-generation (“next-gen”) sequencing for the study of primary immunodeficiencies. Several examples of how next-gen will revolutionize the study of PIDs and other monogenic disorders are starting to appear in the literature. This technology makes possible the sequencing of a large number of candidate genes or whole genomes or exomes at a reasonable cost, allowing an unprecedented insight into human genetics. The author’s laboratory is currently sequencing whole exomes in small groups of patients with unexplained recurrent infections or autoimmune disorders, and has already found promising candidate genes, under intense study.

With the widespread use of this technology the author believes that in the next decade the genetic basis of the individual susceptibility to infectious diseases will be mostly defined. By the sequencing of whole genomes in large cohorts of patients one will be able to pinpoint the isolated rare or collection of common genetic events making up the elusive “genetic background” often blamed for the large variation in infectious susceptibility. Obviously such studies will have to take into consideration other relevant factors such as the type and genetic constitution of the pathogen and environmental influences.

The author also believes that some of the rare primary immunodeficiencies seen today will be associated not only with strong mutations in individual genes, but also with a combination of two or more hits, which in isolation are not considered pathogenic, in genes of the same or complimentary signaling pathways. The author’s laboratory is making efforts on that direction by linking every mutation found by whole exome sequencing to correlational databases that classify genes by their function/pathway, and looking for intersections between patients with similar clinical phenotype.
Concluding remarks

Despite the fast pace of these basic discoveries, novel therapies for PIDs are not being developed as expected. Immunoglobulin production defects are still being treated essentially as suggested by Col. Ogden Bruton almost 60 years ago, and the use of antibiotics and hematopoietic stem cell transplant still constitute the cornerstone treatment of most severe PIDs\(^7\)\(^,\)\(^8\). Promising areas, such as gene therapy, have been plagued by serious side effects and will need substantial work before becoming routine practice in the future\(^9\). Likewise, the use of targeted biologicals, common practice in rheumatic disorders, has not made its way into the treatment of PIDs, with the exception of the autoinflammatory syndromes. Attempts such as the use of recombinant CD40L for patients with Hyper IgM syndrome have thus far failed. For these reasons, passed this exciting phase of gene discovery, the community should change focus and employ its best efforts on the therapeutic arena. Early and precise diagnosis, coupled to effective treatment, can undoubtedly save countless human lives.

References