Classical primary immunodeficiencies (PIDs) are usually monogenic (Mendelian) disorders affecting host defenses. More than 200 clinical phenotypes of PID have been described, and about 100 of them now have a well-defined molecular genetic basis. The classical example is X-linked agammaglobulinemia, in which disease-causing variants in the gene (BTK, Bruton agammaglobulinemia tyrosine kinase) coding for Bruton’s tyrosine kinase lead to arrest of B-cell development at the pre–B-cell stage. Identification and characterization of such monogenic diseases are not only helpful for diagnosis and genetic counseling but will be valuable in development of mechanism-based therapies or gene therapy. Gene therapy has been used to insert a functional gene in hematopoietic stem cells in children with severe combined immunodeficiency, and it is hoped that this procedure will supplement or even replace allogeneic bone marrow transplantations as a treatment option in many diseases in the future. Typically PIDs are rare, life-threatening recessive disorders of leukocytes. PIDs are associated with recurrent infections that often appear in early childhood and are caused by weakly virulent microorganisms.

In daily clinical practice we encounter a large group of children with clinical manifestations of immunodeficiency but without obvious molecular explanations or with only discrete paraclinical findings. Obviously, more and more single-gene diseases will be discovered, but it has also become evident that common variations in certain genes important for immune defense may be associated with an increased tendency to infection. The non-Mendelian inheritance patterns of these conditions indicate that they are part of a complex network of components, which become clinically relevant only when two or more are present at the same time. One such component is a defect in mannose-binding lectin MBL. MBL is a liver-derived complement-activating opsonin that recognizes repetitive sugar structures present on a variety of microorganisms. The MBL gene [MBL2, mannose-binding lectin (protein C) 2, soluble (opsonic defect)] harbors several common polymorphisms that affect the concentration or function of the protein.

Many immunodeficient children who do not have a single-gene defect probably suffer from a complex disease with a combination of two or more partial immunodeficiencies. Indeed, this theory was strongly supported by the study by Bossuyt et al. (4) in the January issue of Clinical Chemistry. In that study, 55 children with recurrent infections were evaluated for several factors of the immune system: IgG, IgA, IgM, and IgG subclass concentrations; MBL2 genotype; IgG2 subclass allotype (GM); partial C4 and C2 deficiency; FCGR2A [Fc fragment of IgG, low affinity IIa, receptor (CD32)] polymorphism; and the specific antibody response to the pneumococcal vaccine Pneumovax. Deficiency of any one of these factors has been described or suggested to increase susceptibility to infection. A substantial fraction of healthy people, however, have a single partial immunodeficiency without any clinical symptoms of immunodeficiency. In the study by Bossuyt et al. (4), the most striking result was that the coexistence of two or more partial immunodeficiencies was significantly higher in the patient group than among healthy controls, suggesting that the combination of partial deficiencies is a strong trigger of the clinical manifestations of immunodeficiency.

Even in patients who have an immunodeficiency that is, by itself, adequate to trigger disease, the coexistence of a partial immunodeficiency in another pathway of defense may worsen the clinical manifestations of the disease. Indeed, among common variable immunodeficiency patients, who by definition have a marked decrease (at least 2 SD below the mean for age) in one of the major isotypes (IgM, IgG, or IgA), the fraction of severe respiratory tract infections before immunoglobulin substitution is higher among patients with MBL2 deficiency.

For evaluation of immunodeficient patients, the single-gene or single-pathway approach is still applicable for immunodeficient patients with a familial history of immunodeficiency and/or susceptibility to atypical infections as demonstrated recently by Picard et al. in patients with mycobacterial disease (6), and we will undoubtedly learn more about the host defense system from these patients in the future. Yet the study of Bossuyt et al. shows that by focusing on partial deficiencies in different pathways of the host defense, we may be able to identify patients with combinational immunodeficiency and eventually keep them free of symptoms with medical correction of one of the partial deficiencies.

References

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