COLITIS, AUTOIMMUNITY, AND PRIMARY IMMUNODEFICIENCIES

Several PIDs (most of which are T cell–related) can cause severe gut inflammation. The prototypic example is *immunodysregulation polyendocrinopathy enteropathy X-linked syndrome* (IPEX), characterized by a widespread inflammatory enteropathy, food intolerance, skin rashes, autoimmune cytopenias, and diabetes. The syndrome is caused by loss-of-function mutations in the gene encoding the transcription factor FOXP3, which is required for the acquisition of effector function by regulatory T cells. In most cases of IPEX, CD4+CD25+ regulatory T cells are absent from the blood. This condition has a poor prognosis and requires aggressive immunosuppression. The only possible curative approach is allogeneic HSCT. IPEX-like syndromes that lack a FOXP3 mutation have also been described. In some cases, a CD25 deficiency has been found. Defective CD25 expression also impairs regulatory cell expansion/function. This functional T cell deficiency means that CD25-deficient patients are also at increased risk of opportunistic infections. It is noteworthy that abnormalities in regulatory T cells have been described in other PID settings, such as in Omenn syndrome, STAT5b deficiency, STIM1 (Ca flux) deficiency, and WAS; these abnormalities may account (at least in part) for the occurrence of inflammation and autoimmunity. The autoimmune features observed in a small fraction of patients with DiGeorge syndrome may have the same cause. Recently, severe inflammatory gut disease has been described in patients with a deficiency in the IL-10 receptor or IL-10.

A distinct autoimmune entity is observed in *autoimmune polyendocrinopathy candidiasis ectodermal dysplasia* (APECED) syndrome, which is characterized by autosomal recessive inheritance. It consists of multiple autoimmune manifestations that can affect solid organs in general and endocrine glands in particular. Mild, chronic *Candida* infection is often associated with this syndrome. The condition is due to mutations in the autoimmune regulator (*AIRE*) gene and results in impaired thymic expression of self-antigens by medullary epithelial cells and impaired negative selection of self-reactive T cells that leads to autoimmune manifestations.

A combination of hypogammaglobulinemia, autoantibody production, cold-induced urticaria or skin granulomas, or autoinflammation has been reported, and has been termed the *PLCβ2-associated antibody deficiency and immune dysregulation* (PLAID or APLAID).

CONCLUSION

The variety and complexity of the clinical manifestations of the many different PIDs strongly indicate that it is important to raise awareness of these diseases. Indeed, early diagnosis is essential for establishing an appropriate therapeutic regimen. Hence, patients with suspected PIDs must always be referred to experienced clinical centers that are able to perform appropriate molecular and genetic tests. A precise molecular diagnosis is not only necessary for initiating the most suitable treatment, but is also important for genetic counseling and prenatal diagnosis.

One pitfall that may hamper diagnosis is the high variability that is associated with many PIDs. Variable disease expression can result from the differing consequences of various mutations associated with a given condition, as exemplified by WAS and, to a lesser extent, X-linked agammaglobulinemia (XLA). There can also be effects of modifier genes (as also suspected in XLA) and environmental factors such as EBV infection that can be the main trigger of disease in XLP conditions. Furthermore, it has recently been established that somatic mutations in an affected gene can attenuate the phenotype of a number of T cell PIDs. This has been described for ADA deficiency, X-linked SCID, RAG deficiencies, NF-κB essential modulator (NEMO) deficiency, and, most frequently, WAS. In contrast, somatic mutations can create disease states analogous to PID, as reported for ALPS. Lastly, cytokine-neutralizing autoantibodies can mimic a PID, as shown for IFN-γ.

Many aspects of the pathophysiology of PIDs are still unknown, and the disease-causing gene mutations have not been identified in all cases (as illustrated by CVID and IgA deficiency). However, our medical understanding of PIDs has now reached the stage where scientifically based approaches to the diagnosis and treatment of these diseases can be implemented.