Autoimmune Disease in Primary Immunodeficiency

At the Crossroads of Anti-Infective Immunity and Self-Tolerance

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KEYWORDS

• Primary immunodeficiency • Autoimmunity • Tolerance • Regulatory T cell
• Apoptosis • Common variable immunodeficiency

KEY POINTS

- Identification of gene defects in primary immunodeficiencies complicated by autoimmune diseases has expanded the understanding of central and peripheral self-tolerance.
- This knowledge is in turn expanding the understanding of more complex, polygenic diseases of immunodeficiency and immune dysregulation, such as common variable immunodeficiency (CVID).
- Certain gene mutations, resulting in autoimmune phenotypes with incomplete penetrance, may act as disease modifiers in complex diseases, such as CVID, increasing predisposition toward autoimmunity.

INTRODUCTION

Autoimmunity and primary immunodeficiency (PID) are frequently associated. This seemingly paradoxic relationship highlights the inherent mechanistic links between proper development of the various elements of the immune system, and the selection and regulatory mechanisms that maintain self-tolerance. Here, various immunologic syndromes are discussed in which this paradoxic relationship occurs, and the lesions in self-tolerance and immunoregulation are systematically explored that contribute to autoimmunity in these diseases. The authors have tried to be comprehensive, but, because this topic is broad, certain immunologic syndromes, such as the autoinflammatory syndromes (periodic fever syndromes), were thought to fall outside the scope

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of this review and have been reviewed elsewhere.[1] For defective tolerance mechanisms in various primary immunodeficiencies, the reader is directed to **Table 1** for clinical correlations, and to **Fig. 1** for a mechanistic diagram.

DEFECTIVE TOLERANCE IN PRIMARY IMMUNODEFICIENCIES

Defects in Thymic Central Tolerance

Central tolerance refers to the deletion of autoreactive T cells during development in the thymus. Single positive thymocytes binding with overly high avidity to self-peptide-major histocompatibility complex undergo apoptosis in the thymic medulla, preventing escape of self-reactive T cells to the periphery (reviewed in[2]). This process relies in part on ectopic expression and presentation of proteins usually restricted to peripheral tissues, by medullary thymic epithelial cells (mTEC). Promiscuous expression of tissue-restricted antigens (TRAs) by mTEC is regulated by a transcription factor called the autoimmune regulator, or AIRE.[3] The mechanism through which AIRE activates expression of TRAs is not fully elucidated, but requires oligomerization, nuclear localization, DNA binding, and interactions with other nuclear factors,[4] and mutations affecting these functions cause autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED), also known as autoimmune polyendocrinopathy syndrome type 1 (APS-1),[5,6] a disease characterized by multiorgan autoimmunity with loss of tolerance to AIRE-regulated gene products. The most common organs involved are parathyroid and adrenal glands, β cells in the islets of Langerhans, and the liver. Autoantibody formation against cytokines such as interleukin (IL)-17 and IL-22 may contribute to the immunodeficiency, increasing susceptibility to mucocutaneous candidal infection.[3,7] In addition, lack of expression of TRAs may lead to a failure in development of regulatory T cells (Treg),[8] causing impaired peripheral tolerance.

In animal models, AIRE expression in the thymus was shown to require cross-talk between developing thymocytes and stromal cells.[9] AIRE gene expression was shown to be decreased in the thymi of RAG-deficient patients with T-B-SCID and Omenn syndrome, in conjunction with lymphoid depletion and loss of corticomedullary differentiation.[10] A lack of expression of TRAs was observed, which may permit the few T-cell clones that develop to escape negative selection. The inflammatory manifestations of Omenn syndrome include T-cell-mediated inflammation in skin and intestine. Intestinal goblet cell and hair follicle antigens were shown in a murine model to be among the TRAs regulated by AIRE.[3]

Abnormal thymic development in DiGeorge syndrome (DGS) may result in impaired expression of AIRE, which may contribute to the autoimmunity seen in DGS.[11] Ten to 15% of patients with DGS have autoimmune disease,[12,13] most commonly idiopathic thrombocytopenic purpura, hemolytic anemia, thyroid disease, and juvenile idiopathic arthritis. The pathophysiology is thought to be a multifactorial failure of T-cell development with autoreactive T-cell escape and restricted Treg diversity.[14]

Central deletion can also be evaded due to abnormalities in TCR signaling, leading to defective activation-induced cell death (AICD). Null mutations in ZAP 70, a critical kinase downstream of the TCR, lead to combined immunodeficiency, by impairing positive selection in the thymus. In murine models, hypomorphic mutations in ZAP70 cause a syndrome of autoimmunity because of ineffective negative selection and reduced FoxP3+ Treg formation.[15] A human counterpart to this ZAP70-mediated autoimmune syndrome has not yet been identified. The store operated calcium entry (SOCE)-nuclear factor of activated T cells (NFAT) pathway is another signaling mechanism through which AICD is induced via the TCR. ORAI1, a calcium