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Review article

Cellular and molecular mechanisms of immune dysregulation and autoimmunity

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ABSTRACT

Primary immunodeficiencies (PIDs) constitute a large group of rare disorders that affect the function of the immune system. A specific group of PIDs entitled "diseases of immune dysregulation" are developed due to mutation in the genes which have critical roles in the regulation of immune responses and immunological tolerance. This group of PID patients develop autoimmune and inflammatory disorders as a result of their impaired immunity, therefore they could be considered as a model for analyzing the link between immune dysregulation and autoimmunity. In this article, our aim is to describe the function of the mutated gene, the molecular and cellular mechanisms underlying the immune dysregulation and review the literature in regard with the reported autoimmune disorders in the main types of immunodysregulatory diseases including genetic defects of regulatory T cells, familial hemophagocytic lymphohistiocytosis syndromes, autoimmunity without lymphoproliferation, autoimmune lymphoproliferative syndrome, immune dysregulation with colitis, and type 1 interferonopathies.

Contents

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1. Introduction

Primary immunodeficiencies (PIDs) are classified into diverse groups of clinical disorders with various genetic defects that affect both the development and the function of the immune system [1–8]. Paradoxically, a considerable proportion of PID patients develop autoimmunity in addition to having augmented susceptibility to infections as a result of their impaired immunity [9–17]. One of the main mechanisms for autoimmunity is defects in the development and breakdown of self-tolerance (Table 1). Generally, defects in T cells and their tolerance induction, defects in B cells, immunoglobulins and class-switch recombination, as well as defects in the genes which affect multiple cellular subsets are the most common defects which predispose PID patients to autoimmunity [18–21]. Furthermore, alteration in frequency and function of regulatory T (Treg) cells and B (Breg) cells might be responsible for loss of self-tolerance and subsequently destructive immune responses and autoimmunity [12,22,23]. On the other hand, in some types of PID, the major reason of autoimmunity is the inability of the host to eradicate microbial antigens. This is often accompanied by exaggerated and chronic inflammatory responses by ineffective alternative immune pathways, which may damage not only the infected cells, but also the adjacent tissue. Accordingly, autoimmunity is not necessarily a disrupted tolerance to self-antigens; it is rather tissue damage as the host attempts to get rid of foreign antigens [24–28]. Recently, there are numbers of well-characterized PIDs, entitled diseases of immune dysregulation; these have improved our knowledge of the pathways that drive autoimmunity in PIDs [29]. Based on the 2014 International Union of Immunological Societies (IUIS) classification [30], diseases of immune dysregulation are categorized as: (1) Familial hemophagocytic lymphohistiocytosis (FHL) syndromes, (2) Lymphoproliferative syndromes, (3) Genetic defects of regulatory T cells, (4) Autoimmunity without lymphoproliferation, (5) Autoimmune lymphoproliferative syndrome (ALPS), (6) Immune dysregulation with colitis and (7) Type 1 interferonopathies [31–35]. It has been shown that these disorders can also predispose PID patients to autoimmune diseases (Table 2). In the last few years great strides have been made toward understanding the pathogenesis of autoimmunity in diseases of immune dysregulation [36]. With this brief description, the aim of this article is to review the available literature in respect of autoimmune disorders and their proposed mechanisms in each type of aforementioned immunodysregulatory diseases.

2. Diseases of immune dysregulation

2.1. Genetic defects of regulatory T cells

2.1.1. Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX)

IPEX is a PID caused by mutations in the gene *FOXP3*, which encodes an essential transcription factor required for maintenance of thymus-derived Treg cells. Induction of the *FOXP3* gene in normal naive T cells induces them into Treg-like cells with suppressive function, which is required for maintaining peripheral tolerance [37,38]. Another function of FOXP3 is to suppress the function of NFAT and NFκB and this leads to suppression of expression of some genes including *IL-2* and effector T-cell cytokines. FOXP3 also acts as a transcription activator for many other genes including *CD25*, *CTLA4*, *GITR* and *FR4* [39]. In animal models, FOXP3 mutant mice show an activated phenotype in the majority of $CD4^+$ and $CD8^+$ T cells, also Th1/Th2/Th17 cytokine profiles are abundantly expressed [40]. Therefore, immunopathology of IPEX syndrome arises as a result of unchecked T cell activation secondary to loss of Treg cells which are dominant suppressors of T cell activation [41].

IPEX syndrome is characterized by early onset diarrhea, eczema, allergic diseases, susceptibility to infections and development of several autoimmune disorders in affected individuals. In most patients, the clinical features of autoimmunity include autoimmune enteropathy, and autoimmune endocrinopathy such as thyroiditis, and/or early-onset type 1 diabetes. This syndrome is also associated with other symptoms such as autoimmune cytopenias, liver inflammation and nephritis which may be caused by an autoimmune response [42]. Nearly, all individuals with IPEX syndrome develop enteropathy which is characterized by refractory and severe diarrhea. It is suggested that severe autoimmune

Table 1
Tolerance mechanisms in T cells and B cells.

Process	Cells			
	T cell		B cell	
	Central tolerance	Peripheral tolerance	Central tolerance	Peripheral tolerance
AICD		√		√
Anergy		√	√	√
Receptor editing			√	
Clonal Deletion	√	√	√	√
Clonal Ignorance		√	√	√
Clonal Exhaustion		√		
nTreg development	√			
Development into iTreg		√		
Development into Breg				√
Tolerogenic dendritic cells		√		
Suppression by Tregs and immunoregulatory cytokine		√		√
Regulation by inhibitory receptors*				√

nTreg; natural regulatory T cell, Breg; regulatory B cell, AICD; Activation-Induced Cell Death.
* FcγRIIb.