

T-regulatory cells in primary immune deficiencies

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Purpose of review

To summarize studies on the development and function of T-regulatory (T_R) cells in primary immune deficiencies (PIDs).

Recent findings

PIDs are associated with high rates of autoimmunity. T_R cells, which are critical to the control of autoimmunity, appear involved in the pathogenesis of PID-related autoimmunity. A number of PIDs, including Omenn's syndrome and Wiskott-Aldrich syndrome, have been associated with impaired production and/or function of thymus-derived (natural) T_R cells. Recently defined primary immunodeficiencies, including Stim1 deficiency, IL-10 receptor deficiency, and xLAP deficiency, have been associated with defects in T_R cells. De-novo generated T_R cells from peripheral CD4⁺ conventional T cells is impaired in the hyper IgE syndrome.

Summary

Gene defects underlying PIDs may also compromise the T_R cell, leading to breakdown of peripheral tolerance.

Keywords

autoimmunity, Foxp3, hyper IgE syndrome, IL-10 and IL-10 receptor deficiency, natural regulatory T cells and induced regulatory T cells, Omenn's syndrome, STAT3

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Introduction

The maintenance of peripheral tolerance is critically dependent on natural CD4⁺CD25⁺ T-regulatory (nT_R) cells, which act to control the magnitude of immune responses to foreign antigens and to prevent autoimmunity [1–3]. The majority of nT_R cells are generated in the thymus as a committed regulatory cell population that expresses the lineage-specific transcription factor Foxp3 and are specific for self-antigens [4–6]. Foxp3⁺ T_R cells can be generated *in vitro* from Foxp3-negative CD4 lymphocytes by T-cell receptor (TCR) activation of CD4 cells in the presence of TGF-β and IL-2 [7–9]. Induced Foxp3⁺ T_R (iT_R) cells are also generated *in vivo* from peripheral Foxp3[−] CD4⁺ cells resulting in a population of cells that have regulatory properties but with a distinct TCR repertoire. nT_R and iT_R act in synergy to induce peripheral tolerance [9,10^{••},11]. Whereas nT_R cells are phenotypically stable, some iT_R cell populations can lose expression of Foxp3 and become effector cells, including Th1 and Th17 cells [10^{••},11–14]. Thus, Foxp3⁺ T_R cells likely consist of dedicated Foxp3⁺ nT_R cells as well as a population of iT_R cells with plasticity. Numerous suppressive mechanisms for T_R cells have been demonstrated, such as CTLA-4 engagement of B7 molecules on target cells, expression of immunosuppressive cytokines such as IL-10, TGF-β

and IL-35, cytotoxicity of target cells through the perforin/granzyme pathway, induction of indoleamine 2,3-dioxygenase (IDO) and the catabolism of tryptophan in target cells, as well as generation of adenosine by expression of CD73 (Table 1) [15–18,19[•],20^{••},21–24].

Immune deficiency versus immune dysregulation: opposite ends of the immune spectrum

A balanced adaptive immune response ensures protection against pathogens while preventing immune responses to self and autoimmunity. Genetic defects that disrupt this homeostatic process results in a spectrum of disorders with varying degrees of immune deficiency, characterized by susceptibility to infections, and immune dysregulation, characterized by autoimmune responses (Table 2). Severe combined immunodeficiency can be thought of at one end of the spectrum and is characterized by a complete lack of an adaptive immune response, resulting in severe life-threatening infections from bacteria, fungi, and viruses within the first year of life. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), the clinical syndrome resulting from genetic mutations in Foxp3⁺, represents the opposite end of the spectrum, presenting with uncontrolled autoimmune response from birth. However, these are

pure archetypical forms, and more commonly patients with primary immune deficiency (PID) express features of both immune deficiency and autoimmunity. This review will address the role of T_R cells in autoimmune manifestations of patients with known PIDs.

Primary defects in T_R cells: IPEX and CD25 deficiency

Although the existence of T-cell populations that suppress immune responses has been postulated and studied for decades, the discovery that mutations in the FOXP3 gene result in IPEX provided proof for the first time that these suppressive populations did indeed exist [25–27]. This X-linked disease presents very early in life with progressive bowel inflammation and failure to thrive. In addition, affected infants experience autoimmune diabetes mellitus, thyroiditis, Addison's disease, severe food allergies, eczema, and autoimmune cytopenias. Although an increased susceptibility to infections is reported in this syndrome, it is difficult to determine if this is due to a defect in controlling infections or due to secondary causes due to the overall ill health of these infants or due to the immunosuppressive mediations that must be used to treat these infants. Hematopoietic stem cell transplant is a curative therapy, and full engraftment is not necessary to provide a cure. This is supported by extensive data that have demonstrated that Foxp3 is essential for the generation, maintenance, and function of T_R cells, and that these cells act in a dominant manner to suppress immune responses [3].

Key points

- Defects in regulatory T-cell generation and/or function are important contributors to autoimmunity in primary immunodeficiency diseases.
- Defective generation of thymus-derived 'natural' regulatory T cells is a feature of Omenn's syndrome due to hypomorphic RAG1/2 gene mutations.
- Impaired generation of 'induced' regulatory T cells, derived *de novo* from peripheral, conventional T cells, has been recognized in the hyper IgE syndrome.
- Human genetic defects in the IL-10/IL-10 receptor system, critically important for regulatory T-cell function at mucosal surfaces, are associated with early-onset inflammatory bowel disease.
- Reconstitution of the regulatory T-cell compartment is an important endpoint of definitive therapies for primary immunodeficiency diseases, including stem cell transplants and gene therapy.

One of the defining characteristics of T_R cells is the expression of CD25, the high-affinity IL-2 receptor, and this marker was the first to define the Foxp3⁺ T_R cell population [28]. Thus it was not surprising that deficiency in this protein resulted in a syndrome with many features of IPEX. For example, the initial description of CD25 deficiency demonstrated a syndrome that included severe immune enteropathy, eczema, and lymphoproliferation [29]. We have described an additional

Table 1 Proposed mechanisms of suppression by T_R cells

T_R derived factor	Mechanism of suppression	References
CD25	Competition with effector cells for IL-2	[15]
	Utilization of IL-2 for cytokine expression and growth	[16]
CTLA-4	Competition with effector cells for CD80/CD86	[17]
	Induction of indolamine deoxygenase in DCs	[18]
IL-10	Inhibition of dendritic cells	[19 [*]]
	Promote survival/fitness of T_R cells	[20 ^{••}]
TGF- β	Inhibition of effector T cells	[21]
CD39/CD73	Generation of adenosine	[22]
Perforin/granzymes	Cytotoxicity of effector cells (T cells, DCs)	[23]
IL-35	Suppression of T cells	[24]

Table 2 Mechanism of immune dysregulation of recently described primary immune deficiencies

Mechanism of immune dysregulation	Omenn	STIM1	WAS	STAT3	CD25	χ IAP	STAT5b	IL10R	APECED	IPEX
Expansion of oligoclonal T cells	+									
Apoptosis/loss of T_R cells	+	+			+	+	+	+/-		+
Defective IL-2 expression/responsiveness		+	+		+		+			
Defective responsiveness to T_R suppression				+				+		
Defective suppression by T_R cells			+		+		+			
Defective AIRE expression in thymus	+								+	



case of CD25 deficiency in a child with early-onset diabetes mellitus, thyroiditis, and aggressive autoimmune hemolytic anemia in addition to severe enteropathy and eczema [16]. These reports highlight several features of IPEX or CD25 deficiency. First, inflammatory responses at sites of constant microbial exposure, sites in which iT_R cells are most effectively induced and particularly enriched, such as the skin and gut, appear to be universal in these disorders. Second, some of the other manifestations of IPEX may vary depending on the individual, as may the severity of symptoms as has recently been shown in patients with point mutations in Foxp3 [30]. Although endocrinopathies are common in IPEX, they are not seen in every individual, which may explain why the initial description of CD25 deficiency lacked endocrinopathies.

Importantly, patients with CD25 deficiency exhibit several unique features not seen in IPEX, namely chronic herpetic viral infections and an increased susceptibility to infections [16,29]. These results provide unique insights into the function of CD25 and IL-2, and demonstrate that this important cytokine has both immune-activating and immune-regulating properties. For example, IL-2 appears critical for the growth of T_R cells, and it has been proposed that one of the key features of IL-2 is to expand T_R cells [31]. However, a patient with CD25 deficiency was found to have relatively normal percentages of Foxp3⁺ cells in the peripheral blood, although CD4 cells from this patient failed to produce IL-10 *in vitro*, raising the possibility that CD25 deficiency results in defective function of T_R cells [16]. In support of this, studies [15,32] have shown that T_R cells utilized CD25 as a cytokine sink that promotes apoptosis in a Bim-dependent manner in effector cells. In addition, IL-2 has been shown to be critical for the generation of memory CD8 cells, which may help to explain why individuals lacking CD25 exhibit difficulties controlling chronic herpetic viruses [33].

Deficiency in STAT5b, one of two signal transducer and activator of transcription 5 (STAT5) proteins, leads to a syndrome of immune deficiency with autoimmunity since signaling through the IL-2 receptor requires STAT5 [34,35]. Growth failure is also observed since STAT5 is involved in growth hormone signaling. Most patients with these defects also develop pulmonary disease that is described as interstitial lymphocytic pneumonia, although whether this represents an autoimmune phenomenon or a response to infectious episodes is unclear. These infants also suffer from autoimmune diseases such as autoimmune thrombocytopenia and hemolytic anemia, eczema, and idiopathic arthritis implicating a defect in immune regulation similar to what is seen in CD25 deficiency [34,35]. This is partly explained by a low percentage of Foxp3⁺ T_R in these individuals as well as decreased suppressive ability of Tregs [34,35].

Defects in Tregs function

It has been known for some time that deficiency of IL-10 results in inflammatory bowel disease (IBD) in mice, highlighting the suppressive nature of this cytokine [36]. Recently it has been described that IL-10 receptor (IL-10R) defects result in a syndrome characterized by early-onset fistulizing colitis and folliculitis in humans [37]. IL-10 is an important cytokine in the function of T_R as demonstrated by conditional knockouts of IL-10 using a Foxp3-Cre protein to delete IL-10 in T_R cells [38]. These mice suffer from the early onset of IBD similar to mice with complete deficiency in IL-10. This is further supported by studies with IL-10 reporter animals that show that in the gut Foxp3⁺ T_R cells are a predominant cell type expressing IL-10 [39,40]. However, Foxp3⁺ CD4⁺ cells also express IL-10 in this location and this may help to explain why the disease in Foxp3-Cre/IL-10 mice was delayed compared to IL-10-deficient animals [38]. An even more severe form of IBD is incurred upon deletion of the IL-10R in murine T_R cells, resulting in a dysregulated Th17 cell response to gut flora. This experimental murine model indicates a critical role of IL-10R signaling in T_R cells in amplifying the regulatory effects of IL-10 produced by both T_R cells and effector T cells. It also suggests that T_R cells may be the locus of action of IL-10R deficiency in humans [20^{••}].

X-linked lymphoproliferative disease type 2

Recently, defects in the antiapoptotic protein x-linked inhibitor of apoptosis (xIAP) were shown to account for a second cause of X-linked lymphoproliferative syndrome (XLP) [41]. These individuals were detected based on lymphoproliferative disease in men in response to Epstein-Barr virus (EBV) infection. XLP1 results from defects in Slam-associated protein (SAP) – an important protein required for the activation of natural killer (NK) and cytotoxic lymphocytes, which likely accounts for the increased susceptibility to EBV infections [42]. xIAP binds caspase 3 and caspase 9 and prevents their activation, thus inhibiting apoptosis [43–45]. How these functions translate into increased susceptibility to EBV infection is unclear.

One interesting feature of xIAP deficiency is an increased susceptibility to inflammatory colitis, occurring in about 17% of patients [46]. Colitis is not seen in XLP1 deficiency. We have described a patient with early-onset, aggressive fistulizing colitis that was found to have a novel mutation in xIAP detected by whole exome sequencing [47]. The cause of the colitis in these individuals is unclear, but affected individuals have a low percentage of T_R cells, perhaps due to excessive apoptosis of these cells [41,47]. In addition, xIAP has been recently implicated in signaling to NOD2, potentially explaining the early-onset IBD that can occur in these individuals [48,49].

Deficiency in Ora1/Stim1

During T-cell activation, release of intracellular calcium stores activates calcium release activated calcium channels (CRAC channels) that results in the influx of extracellular calcium which is critical to T-cell activation [50–52]. ORA1 and STIM1 are two components of CRAC channels, and defects in these proteins cause severe combined immunodeficiency characterized by profound susceptibility to bacterial, viral and fungal infections [53]. In addition, deficiency of Stim1 also presents with autoimmune hemolytic anemia, autoimmune thrombocytopenia, and hypergammaglobulinemia [53]. Although autoimmunity was not reported in Ora1 deficiency, hypergammaglobulinemia with defective specific antibody production was reported. Lymphocyte numbers were normal, but there was an increase in CD4 lymphocytes expressing the memory marker CD45RO, suggesting immune dysregulation [54].

Autosomal dominant hyper IgE syndrome

Autosomal dominant hyper IgE syndrome (AD-HIES), caused by mutations in STAT3, is a primary immunodeficiency with diverse clinical manifestations including eczema, recurrent skin and lung infections, and bone and teeth abnormalities [55,56]. Several studies [57–60] have demonstrated a defect in the generation of TH17 CD4 T cells in HIES, a consequence of the critical function of STAT3 in signaling via cytokines receptors that instruct Th17 differentiation, including IL-6 and IL-21 receptors. STAT3 is also critical for signaling via the IL-10 receptor, and defects in STAT3 may render target cells resistant to IL-10 produced by T_R cells [61]. In addition, recent data have demonstrated that defective signaling via the IL-10 receptor has been linked to impaired generation of tolerogenic dendritic cells and defective formation of iTreg cells [19[•]]. Decreased iTreg formation, or blunted responsiveness of target cells to T_R-cell-derived IL-10 may contribute to mucosal inflammation in AD-HIES.

Mechanisms of autoimmunity in primary immune deficiencies

The above observations demonstrate that PIDs are associated with significant autoimmune manifestations. Several mechanisms can be invoked to explain this paradoxical observation. One feature of several of the above-discussed PIDs is the observation of the expansion of autoreactive clones of T cells and resulting oligoclonality. Omenn's syndrome, a primary immunodeficiency presenting with increased susceptibility to infections, failure to thrive with diarrhea, early-onset rash, and high IgE levels, is a clear example. Omenn's syndrome occurs due to hypomorphic mutations in the recombinase activating genes (RAGs) resulting in defective TCR rearrangement and the emergence of oligoclonal T cells that expand in the periphery and display a memory

phenotype [62,63]. Why this occurs is unclear, but the concept of homeostatic proliferation can be considered. This phenomenon shows that in a lymphopenic environment, naïve lymphocytes will expand utilizing low-affinity TCR contacts and cytokines, in particular IL-7 [64,65]. One function of T_R cells is to control this homeostatic proliferation of lymphocytes, as shown in mouse models in which transfer of naïve CD4 cells into a lymphopenic animal results in IBD and other autoimmune phenomenon [66]. Interestingly, T_R cells express low levels of CD127, the IL-7 receptor binding subunit, and it is possible that in lymphopenic environments, T_R cells have a competitive disadvantage compared with effector T cells [67].

In addition, recent work has demonstrated that Omenn's syndrome is associated with defective thymic expression of the autoimmune regulator (AIRE), likely due to a complex interplay between lymphocytes, LT- α , and thymic stroma [68,69]. It is possible that any disease with defective T-cell development and T-cell lymphopenia could result in defective AIRE expression. AIRE deficiencies cause autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED) due to defective expression of peripheral antigens in the thymus, a process that is critical to the deletion of autoreactive lymphocytes [70,71]. Similarly, studies on T_R receptor diversity have demonstrated that T_R cells express a highly diverse repertoire that is distinctive from that of conventional T cells [72]. This diverse repertoire is likely critical to the generation of a diverse population of T_R cells that see self as well as nonself antigens which are necessary for these cells to be activated in the periphery and inhibit T-cell responses. The expression of peripheral antigens in the thymus by AIRE is likely critical to the generation of a diverse repertoire of T_R cells, and patients with AIRE deficiency have been shown to have decreased numbers, impaired suppressive function and altered repertoire of T_R cells [73]. When TCR diversity is limited, such as in Omenn's syndrome, thymic Foxp3⁺ cells may be absent [68]. However, this is not the entire answer since other patients with Omenn's syndrome were found to have a relatively normal percentage of Foxp3⁺ cells as well as a normal mRNA levels of Foxp3 in peripheral blood [74[•],75].

Although decreased numbers of T_R cells have been described in PIDs, it is also likely that impaired function of T_R cells contributes to the autoimmunity seen in these disorders. For example, Wiskott-Aldrich syndrome (WAS) is a rare X-linked syndrome consisting of thrombocytopenia, eczema, recurrent infections, autoimmunity, and defective function of T_R [76,77]. WAS and other immunodeficiency disorders, such as Stim1/Ora1 deficiency, are associated with defective IL-2 production [76,78,79]. Paracrine IL-2 is critical for the expansion and

function of T_R cells, since these cells express high levels of CD25 but low levels of the IL-7 receptor, and these cells do not express IL-2 unlike most T cells. Failure to produce IL-2 in these disorders may prevent T_R cell expansion and expression of immunosuppressive factors, ineffective inhibition of effector T cells, and resulting autoimmunity. In support of this, incubation of T_R cells defective in WASP with IL-2 corrects the suppressive defects of these cells [76].

Conclusion

A critical role for T_R cell deficiency/dysfunction has emerged in recent studies on autoimmunity associated with PIDs. The mechanisms by which T_R cell deficiency develops in PID and its precise role in the autoimmune phenomena associated with these disorders will require further studies involving humans and experimental animal models. Monitoring of T_R cell recovery and function post therapy, including transplant and gene therapy, would be one important end measuring the success of those interventions.

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Conflicts of interest

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There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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