Published in final edited form as:
Curr Opin Pediatr. 2013 December ; 25(6): 708–714. doi:10.1097/MOP.0000000000000029.

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) and IPEX-Related Disorders: an Evolving Web of Heritable Autoimmune Diseases

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Abstract

Purpose of review—To summarize recent progress in our understanding of Immune Dysregulation, Polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders.

Recent findings—A number of Mendelian disorders of immune dysregulation and autoimmunity have been noted to result from defects in T regulatory (T_R) cell development and function. The best characterized of these is Immune Dysregulation, Polyendocrinopathy, enteropathy, X-linked (IPEX), resulting from mutations affecting *FOXP3*. A number of other gene defects that affect T_R cell function also give rise to IPEX-related phenotypes, including loss of function mutations in *CD25* and *STAT5b and ITCH*. Recent progress includes the identification of gain of function mutations in *STAT1* as a cause of an IPEX-like disease, emerging *FOXP3* genotype/phenotype relationships in IPEX, and the elucidation of a role for the microbiota in the immune dysregulation associated with regulatory T cell deficiency.

Summary—An expanding spectrum of genetic defects that compromise T_R cell function underlies human disorders of immune dysregulation and autoimmunity. Collectively, these disorders offer novel insights into pathways of peripheral tolerance and their disruption in autoimmunity.

Keywords

FOXP3; CD25; STAT5; STAT1; ITCH; T regulatory cells; autoimmunity; Tolerance

Introduction

A number of Mendelian disorders of immune dysregulation and autoimmunity have been noted to result from defects in T regulatory cells development and function. The best-characterized of these is Immune Dysregulation, Polyendocrinopathy, enteropathy, X-linked

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The authors declare no conflict of interest.

(IPEX), resulting from mutations affecting *FOXP3*. A number of other gene defects that affect T_R cell function also give rise to an IPEX-like phenotype, including loss of function mutations in *CD25*, *STAT5b* and *ITCH* and gain of function mutations in *STAT1* (Table 1). This review highlights recent progress in the study of these disorders and the identification of underlying genetic and functional causative abnormalities.

IPEX

IPEX is a heritable autoimmune lymphoproliferative disease caused by loss of function mutation in *FOXP3* [1–3] [reviewed in [4–6]]. In most patients, IPEX presents early in life with a triad of autoimmune enteropathy, autoimmune endocrinopathy, and eczematous dermatitis [1–5]. Other autoimmune phenomena include autoimmune cytopenias, liver, and kidney disease. Allergic dysregulation with eczema and food allergy is common, with extremely elevated IgE levels accompanied by intense peripheral eosinophilia and evidence of overt Th2 skewing [1,7].

The immunopathogenesis of IPEX relates to the loss of functional $CD4^+CD25^+$ T regulatory (T_R) cells, a subset that is critical to the prevention of autoimmunity [8,9]. The majority of T_R cells are generated in the thymus, express the transcription factor Foxp3, are selected on high affinity TCR interactions with self antigens, and are referred to as natural T_R (nT_R) cells[10] [11,12]. Some $Foxp3^+$ T_R cells can be also be induced de novo *in vivo* from peripheral $Foxp3^-$ $CD4^+$ cells resulting in a population of cells (iT_R cells) that have regulatory properties but with a TCR repertoire distinct from nT_R cells [13,14]. This process can also be recapitulated *in vitro* by TCR activation of naïve $CD4^+$ T cells in the presence of TGF-β and IL-2. iT_R cells are particularly enriched at the mucosal surfaces, especially in the gastrointestinal tract, where they are endowed with a TCR repertoire specific for bacterial antigens [15,16]. nT_R and iT_R cells act in synergy to induce peripheral tolerance [13]. Some iT_R cell populations can lose expression of Foxp3 and become effector cells, including Th1 and Th17 cells [17].

Several suppressive mechanisms for T_R cells have been demonstrated. These include CTLA4 engagement of B7 molecules on target cells [18,19], expression of immunosuppressive cytokines such as IL-10, TGF-β, and IL-35 [20–22], cytotoxicity of target cells through the perforin/granzyme pathway [23], induction of indoleamine 2,3-dioxygenase (IDO) and the catabolism of tryptophan in target cells, as well as consumption of adenosine by expression of CD73, and competition with effector T cells for IL-2 since T_R cells constitutively express the high affinity IL-2 receptor CD25 [24–27]. Several of these pathways are targeted by mutations in human subjects, including the IL-2 receptor alpha chain (CD25; discussed below), IL-10/IL-10 receptor, and the perforin/granzyme pathway [28–30]. Abnormal T_R cell function is a key feature of these diseases [31].

Foxp3 is a transcription factor with a winged helix (Forkhead) DNA binding domain, a proline rich N-terminal domain, a C2H2 zinc finger motif, and a leucine zipper domain. The leucine zipper domain has been implicated in the formation homo and heterodimers and higher order assembly of Foxp3 complexes [1,32]. A number of proteins interact with Foxp3 at its N-terminus, including the transcription factors Hif1a, IRF4, and Eos, the histone

acetyltransferases Tip60 and p300, and the histone deacetylase HDAC7, which help regulate the levels of Foxp3 protein [32,33]. A linker region between the leucine zipper and c-terminal Forkhead domain interacts with the transcription factor AML1/RUNX1, which cooperates with Foxp3 in the suppression of IL-2 expression [34]. The Forkhead domain itself interacts with the transcription factor NFAT, relevant to the expression in components of the T_R cell transcriptome, including IL-2 receptor alpha chain (CD25), GITR and CTLA-4 [35]. FOXP3 may act to induce (e.g. CD25) or suppress (e.g. IL2) gene expression depending on the nature of the interactions with different transcriptional partners at the respective promoter region [8].

Regarding *FOXP3* genotype/phenotype relationships in IPEX some conclusions can be drawn from the clinical phenotypes reported for different human FOXP3 mutations [6,36]. Missense mutations, small in-frame deletions, and deletions and mutations in the promoter and 5′ untranslated regions of Foxp3 can be associated with near-normal expression of Foxp3 protein, normal T_R cell numbers but with compromised regulatory function, and a milder clinical phenotype. For example, a 1388-bp deletion (g.del–6247–4859) affecting the first untranslated exon and the adjacent intron of FOXP3, a region relevant to the formation of induced T_R cells, gave rise to enteropathy, eczema and food allergies and elevated IgE but no endocrinopathy or cytopenias [37]. Similarly, some N-terminal Foxp3 mutations (e.g. Q70H and T108M) gave rise to a milder phenotype without endocrinopathy [38,39]. Leucine zipper domain and Forkhead domain mutations are usually associated with more severe phenotypes [6,36]. It is also likely that the genetic background may affect organ involvement as demonstrated in Foxp3-deficient mice where organ involvement and disease manifestations vary depending on the strain background [40].

The immunopathology of Foxp3 deficiency results from unchecked T cell activation secondary to loss of T_R cells that act in a dominant manner to suppress T cell activation [41,42]. This is evidenced by the capacity of perinatal adoptive transfer of $CD4^+CD25^+$ T_R cells to cure Foxp3-deficient mice from disease [13]. Left untreated, disease in Foxp3 deficient mice evolves aggressively and death ensues within a few weeks after birth [43–46]. Disease progression is associated with lymphoid and myeloid hyperplasia and a concomitant intense mixed inflammatory infiltrates involving several organs including the liver, lung pancreas, stomach, skin and the gut [43–46]. The overwhelming majority of $CD4^+$ and $CD8^+$ T cells are activated, and Th1, Th2, and Th17 cytokines are abundantly expressed [40]. Inflammation at the mucosal surfaces, including the gut, skin and lungs, may be driven by unrestrained T cell reactivity to antigens of the commensal flora [47,48]. It is attenuated in germ-free Foxp3 deficient mice and by deficiency of the toll-like receptor adaptor MyD88 [48]. In contrast the systemic autoimmunity of Foxp3 deficiency is unaffected by these interventions.

CD25 Deficiency

CD25 deficiency in humans manifests similarities to IPEX but is distinguished by a profound susceptibility to infections. The first description of CD25 deficiency was in a male subject of consanguineous parents who presented with CMV pneumonitis, oral and esophageal candidiasis, adenoviral gastroenteritis, diarrhea and failure to thrive [49,50]. A

second case of CD25 deficiency was described in a boy born to unrelated parents who developed severe diarrhea, insulin-dependent diabetes mellitus, and eventual respiratory failure within the first months of life [30]. CMV pneumonitis, enteritis, and EBV lymphoproliferative disease developed. More recently, a third case of CD25 deficiency was described in a female child of consanguineous parents who developed early onset eczema and autoimmune enteropathy that was complicated by CMV, bullous pemphigoid, autoimmune thyroiditis, and alopecia universalis.[51].

The presentation of CD25 deficiency has many features of IPEX, but exhibits unique features including chronic viral, fungal, and bacterial infections [30,49,51]. The autoimmune findings are consistent with the pivotal role of CD25 in T_R cell biology [52,53]. 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 [54,55]. However, two of the reported patients with CD25 deficiency were found to have relatively normal percentages of $Foxp3^+$ cells in the peripheral blood, suggesting that CD25 signaling is not required for the development of T_R cells, which is supported in mouse models [55]. Although CD25 is dispensable for the generation of T_R cells, deficiency of CD25 leads to widespread immune dysregulation, arguing that functional responses of T_R cells critically depend on IL-2. In support of this, *in vivo* and *in vitro* treatment of T regulatory cells with IL-2 appears to enhance their suppressive abilities [55–57]. In addition, the constitutive expression of CD25 on T_R cells allows them to effectively compete for IL-2 and act as a cytokine sink that promotes apoptosis in a Bim-dependent manner in effector cells[58,59]. Finally, IL-2 is essential to the generation of induced T_R cell populations [60,61].

The infectious complications in CD25 deficiency also confirm a role for IL-2 in generating effective immunity of T cells [reviewed in [62]]. IL-2 promotes the proliferation and development of TH1 and TH2 cells [63–65] [66]. In contrast, IL-2 appears to inhibit Th17 development, but once generated Th17 cells may utilize IL-2 to expand [67,68]. IL-2 also inhibits T follicular helper T cells development [69,70]. IL-2 is important in generating cytotoxic CD8 effector cells as well as memory CD8 cells through the induction of IFN-γ, perforin and granzyme expression[71]. [72]. IL-2 can activate NK cells to become lymphokine-activated killer cells, and IL-2 has been reported to promote B cell response [73,74]. The pleiotropic effects of IL-2 on the effector function of the adaptive immune response helps to explain why individuals lacking CD25 exhibit increased susceptibility to infections, including fungus, bacteria, and viruses.

STAT5b Deficiency

STAT5 consists of two close related proteins, STAT5a and STAT5b, that are the product of two distinct genes and are 90% homologous [75,76]. Complete deficiency in STAT5 proteins in mice results in perinatal lethality since these proteins are involved in the signal transduction of a variety of growth factors, including growth hormone, prolactin, erythropoietin, IL-3, IL-5, and GM-CSF [77,78]. Defects in Stat5a have not been described. Defects in Stat5b have been described to result from deletion, missense and splice junction mutations, and are inherited in an autosomal recessive manner.

The original description of STAT5b deficiency was of an Argentinean girl with growth failure, delayed puberty, prominent forehead, saddle nose, and high pitched voice, all features of growth hormone deficiency [79]. Since then, several other patients have been described [80–85]. Common clinical presentations include failure to thrive and growth failure, recurrent infectious pneumonias due to bacterial and viral infections, lymphoid interstitial pneumonitis, severe varicella and recurrent bouts of herpes zoster, and chronic diarrhea and eczema. Laboratory studies usually demonstrate hypergammaglobulinemia, with normal T, B, NK cells number, although the T cells may show severe memory skewing. $Foxp3^+$ T_R cells may be normal or slightly decreased. Mitogenic responses may be low, Low IGF-1, low IGFBP-3, and high prolactin are usually present, reflecting defective growth hormone receptor signaling.

Many of the features of STAT5b deficiency are similar to findings in CD25 deficiency, including eczema, chronic diarrhea, thyroiditis, and increased susceptibility to infections, likely due to the fact that IL-2 receptor signaling requires STAT5. Pulmonary disease appears more prominent in STAT5b deficiency, although it is unclear whether this is driven by infectious processes, or is the result of defective immune regulation. Similar to CD25 deficiency, signs of immune activation may be apparent, including hypergammaglobulinemia and increased percentages of CD45RO positive T cells. The severity of disease in STAT5b deficiency appears more variable and less severe compared to CD25 deficiency, likely due to the fact that STAT5a may substitute for some of the functions of Stat5b deficiency. The increased susceptibility to infections and autoimmune manifestations of STAT5b deficiency is likely due to defects in responsiveness to IL-2 as outlined in CD25 deficiency above.

IPEX-like disease due STAT1 Mutations

Autosomal dominant heterozygous gain of function mutations in STAT1 have been found in subjects with mucocutaneous candidiasis. Some of the affected subjects suffered from autoimmunity, mainly autoimmune thyroiditis, but otherwise lacked other characteristics of the AEPECD phenotype, including characteristic end-organ targets of autoimmunity and ectodermal dysplasia [86–88]. By screening patients with IPEX like phenotype with or without mucocutaneous candidiasis, Uzel et al identified 5 patients heterozygous gain of function STAT1 mutations [89]. The mutations involved the coiled-coil (R210I, V266I) and DNA binding domains (L358W, T385M (two patients) of STAT1. These mutations resulted in increased STAT1 phosphorylation at the regulatory tyrosine 701, consistent with the gain of function phenotype of the mutations.

Gain of function STAT1 mutations inhibit Th17 cell differentiation, a phenotype associated with heightened susceptibility to mucocutaneous candidiasis. However, the mechanism of IPEX-like disease in some of the patients remains unclear. The number of T_R cells and their *in vitro* suppressor function appeared normal [89]. It is possible that the gain of function STAT1 mutant destabilizes the T_R cells by reprograming them into Th1-like cells, but that remains to be determined. IL-10 production by peripheral blood lymphocytes was profoundly decreased, suggesting a role for functional IL-10 deficiency in certain aspects of disease manifestation (such as enteritis).

All five patients presented with eczema and enteropathy, [89]. Three of the patients developed type 1 diabetes, three developed hypothyroidism and or thyroid autoantibodies, and one patient developed growth hormone insufficiency. All patients suffered recurrent infections, with various combinations of sinopulmonary infections and pneumonias (with or without bronchiectasis), herpes virus infections, and blood-borne infections. The patients also suffered form a variety of cardiovascular problems including hypertension, vascular aneurysms and calcifications. Four of the five patients exhibited mucocutaneous candidiasis, suggesting that the disease may occasionally present in the absence of (or cryptic presence) of candidiasis [89]. Disseminated aspergillosis and candidemia have been noted in two patients under conditions of immunosuppression and catheter related, respectively.

ITCH

Human ITCH deficiency was discovered in an extended Amish family with findings of multisystem autoimmunity, dysmorphic features, and developmental abnormalities due to a single adenine nucleotide insertion in codon 132 of *ITCH* was found, resulting in a frame-shift and premature stop [90]. Ten affected individuals were found to carry this mutation. Autosomal recessive inheritance was apparent in this extended family, and prominent consanguinity was noted. A naturally occurring mutation in *Itch*, the mouse homologue of human *ITCH*, recapitulates many features of the human disease, including a severe autoimmune disorder characterized by dermatitis, chronic pulmonary inflammation, alveolar proteinosis, and lymphoid hyperplasia [91]. Studies with Itch-deficient mice have elucidated some of the potential mechanisms of immune dysregulation in these mice. ITCH is a ubiquitin ligase with diverse function in T cells [91]. T cells from $Itch^{-/-}$ mice show an activated phenotype with enhanced proliferation and expression of the TH2 cell cytokines interleukin 4 and IL-5 [92]. IgG1 and IgE levels were elevated, consistent with a prominent TH2 response in these mice. These studies identified JunB, a transcription factor that is involved in TH2 differentiation, as a target of ITCH [93,94]. Other studies have shown that ITCH is upregulated in anergic T cells, and ITCH associates with PLC-γ1 and PKC-θ, two key signaling molecules induced by Ca^{2+}/ calcineurin signaling [95]. Following ITCH-mediated ubiquitination, PLC-γ1 and PKC-θ are targeted to the lysosome for degradation, leading to reduced levels of PLC-γ1 and PKC-θ and defective T cells activation.

ITCH has also been implicated in T_R cell function and generation, mainly through its affects on TGF-β signaling and Foxp3 expression in CD4 T cells [96]. The loss of ITCH compromises TGF-β–induced Foxp3 expression and TGF-β–mediated inhibition of T-cell proliferation through the ubiquitination of the transcription factor TIEG1. Upon ubiquitination by ITCH, TIEG1 translocates to the nucleus, and binds GC rich sequences in the Foxp3 promoter [96].

Summary and Future Directions

Despite the progress in identifying several IPEX like diseases and establishing their genetic causations, the underlying defects in a large proportion of subjects who present with IPEX like disorders remain obscure. The advent of global sequencing approaches such as whole

genome and exome sequencing promises to identify novel gene defects and exciting new pathways operative in tolerance and autoimmunity.

Acknowledgments

The authors acknowledge grant support by the National Institutes of Health to T.A.C. (5R01AI085090) and J.W.V. (1K08AI072023).

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Key Points

- A number of heritable Mendelian disorders of autoimmunity and immune dysregulation involve genes that control various T regulatory (T_R) cell functions, including *FOXP3*, *IL2RA*, *STAT5B*, and *ITCH*.
- A life-long risk of autoimmune complications attends mutations affecting *FOXP3* and related pathways.
- Gain of function mutations in STAT1, normally associated with mucocutaneous candidiasis, may manifest as an IPEX-like phenotype.

Table 1

Clinical and laboratory features of IPEX and IPEX-like disorders.

	IPEX	CD25	Stat5b	STAT-1	ITCH
Autoimmunity					
Ezcema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic Disease	+++	+	+	++	++
Cytopenias	++	++	++	−	
Lung Disease	+	++	+++	+	+++
Infections					
Yeast	−	++	−	+++	−
Herpes virus	−	+++(EBV/CMV)	++(VZV)	++	−
Bacterial	+/−	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic Growth failure
Serum Immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
CD4+CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
Foxp3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

EBV, Epstein Barr Virus; CMV, cytomegalovirus; VZV, varicella zoster virus