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Primary Immune Deficiency Disorders Presenting as Autoimmune Diseases: IPEX and APECED

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Abstract
Background Several primary immune deficiency disorders are associated with autoimmunity and malignancy, suggesting a state of immune dysregulation. The concept of immune dysregulation as a direct cause of autoimmunity in primary immune deficiency disorders (PIDDs) has been strengthened by the recent discovery of distinct clinical entities linked to single-gene defects resulting in multiple autoimmune phenomena including immune dysregulation, polyendocrinopathy, enteropathy and X-linked (IPEX) syndrome, and autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED) syndrome.
Conclusion Reviewing recent advances in our understanding of the small subgroup of PIDD patients with defined causes for autoimmunity may lead to the development of more effective treatment strategies for idiopathic human autoimmune diseases.

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Keywords Autoimmunity · autoimmune regulator (AIRE) · autoimmune polyendocrinopathy · candidiasis and ectodermal dystrophy (APECED) · forkhead box P3 (FOXP3) · immune tolerance · immune dysregulation · polyendocrinopathy · enteropathy and X-linked (IPEX) · primary immune deficiency disorders (PIDD)

Introduction

The study of primary immune deficiency diseases (PIDD) indicates that susceptibility to infections is the hallmark of these disorders [1]. However, over the last decade, autoimmune manifestations have emerged as important symptoms of many types of PIDD, providing strong evidence that maintaining tolerance to self is a function of the immune system equally important as the protection from invading microorganisms. Immune dysregulation, polyendocrinopathy, enteropathy and X-linked—OMIM 304930 (IPEX) syndrome and autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia—OMIM 240300 (APECED) are examples of dysregulated immunity resulting in a disturbed tolerance and multiple autoimmune phenomena.

IPEX Syndrome

Clinical Presentation

Frequently fatal in infancy or early childhood, IPEX is caused by mutations in the *FOXP3* gene located in the centromeric region of the X chromosome [2]. Powell et al. [3] described a large family of five generations with multiple affected males. This observation was followed by

numerous reports of similarly affected males from different ethnic groups reflecting the universality of this syndrome (Table I).

We have reviewed the clinical manifestations of 39 patients from 12 independent reports (Fig. 1) [3–14]. Diarrhea was the predominant symptom, present in all patients except one member of the original family described by Powell's group. The autoimmune enteropathy starts early in life as severe watery diarrhea that is at times mucoid or bloody and difficult to control. A few patients are responsive to gluten-free diet; some respond to immunosuppressive drugs or parenteral nutrition and some fail any drug treatment. Diarrhea was also the predominant clinical manifestation in other reviews of IPEX being present in almost all affected males [4, 15].

Table I Facts/Features of IPEX and APECED

	IPEX	APECED
OMIM	304930	240300
Gene	*FOXP3*	*AIRE*
Onset of symptoms	Infancy	Childhood
Infections	*Staphylococcus*, *Enterococcus* species, CMV, *Candida* (infrequent)	*Candida* (up to 100%)
Auto-immune enteropathy	Frequent	10%
Skin involvement	Frequent	Frequent
Alopecia	Rare	30%
Vitiligo	Rare	15%
Nail dystrophy	Rare	50%
Enamel hypoplasia	Absent	75%
Insulin-dependent diabetes mellitus	Frequent	20%
Autoimmune thyroiditis	Frequent	6%
Hypoparathyroidism	Absent	85%
Adrenal failure	Rare	70%
Ovarian failure	Absent	60%
Autoimmune liver disease	Common	15%
Renal disease	Common *	Absent
Autoimmune hematologic diseases	Frequent	Rare
IgG, IgA, IgM	Normal	Normal
IgE	Elevated	Normal
Eosinophils	Increased	Normal
CD3, CD4, CD8, CD19	Normal	Normal
Autoantibodies	Frequent	100%
Antibody production	Normal	Normal
Treatment	Immunossupressive agents HSCT	Antifungal Hormonal replacement
Lethality at early age	High	Low

* It is unclear if this is autoimmune or secondary to treatment with cyclosporin A

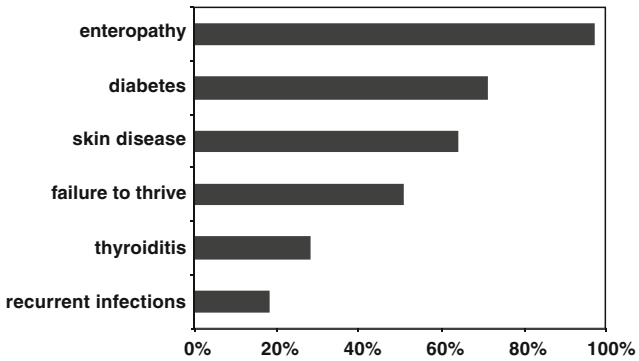

Fig. 1 Main clinical manifestations of 39 IPEX patients from 12 independent reports. Data presented as percentage of patients presenting the different clinical features

Endocrinopathy is a frequently reported complication with insulin-dependent diabetes mellitus the most common endocrine manifestation [4, 5]. Hyperglycemia can start as early as the first week of life, sometimes requiring intravenous insulin infusions to control the difficult to treat blood glucose levels [9]. Autoantibodies against pancreatic-islet cells, insulin, and glutamic acid decarboxilase (GAD) are frequently present [4, 6, 7, 14]. Thyroid disease, either hypo- or hyperthyroidism, was present in 30% of patients. Hypothyroidism, the more frequent thyroid abnormality, is associated with elevated thyroid stimulating hormone levels and/or antithyroid microsomal antibodies [3–5, 7, 9, 11, 12, 14].

Eczema is the predominant manifestation of skin disease, but erythematous and psoriasiform dermatitis, urticaria, alopecia universalis, trachyonychia, and pemphigoid nodularis have been described [7, 12]. Some infants present with an erythematous rash involving the entire body, which improves with topical steroid and immunomodulatory agents.

Other manifestations occur less frequently, such as lymphadenopathy, hepatosplenomegaly, cholestatic hepatitis, nephropathy, hemolytic anemia, thrombocytopenia, neutropenia, seizures, sarcoidosis, vasculitis, arthralgia, and arthritis [3, 4, 8, 9, 10, 11, 13]. As the patients get older they develop more clinical manifestations. Comparing reviews with larger patient numbers [4, 15, 16] for clinical manifestations, the triad enteropathy, diabetes and skin disease is clearly predominant.

Despite recurrent infections being the hallmark of primary immunodeficiencies, not all IPEX patients presented with this manifestation. Torgerson and Ochs [17] reported that approximately half of 50 patients with mutations of *FOXP3* had a history of multiple severe infections such as sepsis, meningitis, pneumonia, and

osteomyelitis. The most common pathogens observed were *Enterococcus, Staphylococcus* species, *Cytomegalovirus*, and *Candida* spp. These infections seem to be as much related to a decreased barrier function of the skin and the gut as to an underlying immune defect.

Laboratory Findings

Serum immunoglobulin levels except for elevated IgA and IgE are generally within normal values. The numbers of neutrophils and lymphocytes are normal, but eosinophilia is frequently observed [15]. Patients are able to make protective antibody responses to immunization [3], but studies are limited because most patients are treated with immunosuppressive drugs. Because of immune dysregulation, IPEX patients generate a variety of autoantibodies against a long list of antigens affecting different organs and cell types including the small intestine, pancreatic islet cells, thyroid, kidney, neutrophils, platelets, and erythrocytes [4, 5, 8, 9, 11, 13].

$CD3^+$T lymphocytes including $CD4^+$ and $CD8^+$ subsets are present in normal numbers and proliferation to mitogens, and specific antigens are normal or slightly decreased [5]. Bakke et al. [8] observed, in a prospective study of one patient, a decreased number of B cells, a normal number of $CD8^+$, and variations in $CD4^+$ T cell numbers with a high frequency of HLA-DR^+ and $CD25^+$ cells. The latter finding can be attributed to the absence of FOXP3 function and lack of regulatory T cells, leading to autoaggressive lymphoproliferation [15]. Despite this activation, cells from IPEX patients have defective IL-2, IFN-γ and TNF-α production [7, 18]. The relative proportion of naïve and memory T cells varies between reports [8, 14]. *Foxp3* gene transfer confers suppressor function upon naïve human $CD4^+$T cells and a diminished suppressor activity in memory T cells [19], suggesting that Foxp3-dependent implementation of a functional T_{reg} cell program represents a differentiation pathway distinct from those directing T_H1, T_H2 or memory T-cell fate [20].

Pathology

The IPEX phenotype variably affects multiple organs resulting in tissue damage and severe functional deficits. The most striking and consistent feature is the loss of normal small bowel mucosa caused by total or partial villous atrophy. Involvement of the large intestine is common with lymphocytic (predominantly $CD3^+$) and plasma cell infiltrates in the lamina propria [3, 6, 10, 21]; eosinophils may also be present [13]. There is mucosal and submucosal destruction throughout the intestine but the muscular layer is not involved [10]. The diagnosis of Crohn's disease, ulcerative colitis or celiac disease is often suggested and disaccharidase deficiency was mentioned in one report [3–5, 7, 10] leading to specific treatment of these conditions. Improvement of the diarrhea can usually be achieved only with immunosuppressive agents.

Histologic examination of the pancreas typically reveals lymphocytic infiltrates with destruction of exocrine tissue (in addition to loss of islet cells) with the rare chromogranin, synaptophysin, and insulin positive cells replaced by loose fibrosis [2–4, 6, 9, 10, 14]. The extensive lymphocytic infiltrate observed in the pancreas suggests an autoimmune mechanism mediated by T cells. The lymphocytic infiltrates observed in the thyroid gland also suggest a T-cell mediated autoimmune mechanism, but antithyroid antibodies have been found in some patients [2].

The thymus, often atrophic or dysplastic, cannot easily be distinguished from the mediastinal fat and may be depleted not only of lymphocytes but may also show an absence or severe reduction of Hassall's corpuscles [3, 10, 14]. Recently, Watanabe and colleagues [22] suggested that Hassall's corpuscles express and secrete thymic stromal lymphopoietin (TSLP) leading to the activation of dendritic cells. TSLP are instrumental in the differentiation of $CD4^+CD25^+$ $Foxp3^+$Tregs.

Treatment

Immunosuppressive drugs such as cyclosporine A, tacrolimus (FK506), sirolimus, and steroids have been used with some success [13, 17]. Unfortunately, these drugs do not maintain long-term remission of symptoms, and chronic immunosuppressive therapy may be toxic and may facilitate opportunistic infections.

Hematopoietic stem cell transplantation (HSCT) is the best option for a cure. Originally, the results were not favorable [4, 6], but complete remission of symptoms after HSCT and reduced-intensity conditioning has recently been reported in four patients [23]. If performed early, this therapy can avoid organ toxicity and the increased risk of infections associated with chronic immunosuppression. It may also prevent autoimmune endocrine organ destruction. Identification of the *FOXP3* mutation in a kindred allows carrier diagnosis, prenatal testing, and early postnatal treatment with HSCT [24].

IPEX-like Phenotype

Recently, Zuber et al. [25] described a young female patient from a Turkish consanguineous family, with a polyautoimmune syndrome resembling a mild form of IPEX, associated with susceptibility to infections. Autoimmune enteropathy was diagnosed at the age of 16 years, accompanied by vitiligo and an interstitial nephritis. Anti-islet cell

antibodies were detected. The patient showed a reduced number of $CD4^{+}FOXP3^{+}$ T cells in the circulation and in the highly inflamed intestinal mucosa affecting in particular the $FOXP3^{high}CD25^{high}CD127^{low}$ subset. Other individuals with an IPEX-like phenotype and normal FOXP3 by sequence analysis have been recognized [26]. Recently, Caudy and collaborators [27] identified a patient with CD25 (IL-2 R alpha) deficiency caused by a compound heterozygous mutation of CD25, who presented with clinical features similar to IPEX, but with autosomal recessive inheritance. This patient had severe, chronic diarrhea and villous atrophy in infancy, early onset insulin-dependent diabetes mellitus, autoantibodies and multiorgan lymphoid infiltrates. In addition to these IPEX-like autoimmune features, this and another patient described earlier by Roifman's group [28] had a significant T-cell deficiency and developed opportunistic infections including CMV pneumonitis, as a result of defective signaling via the IL-2 receptor complex.

Chronic Mucocutaneous Candidiasis and APECED/APS-1

Chronic mucocutaneous candidiasis (CMC) is a clinical syndrome with selectively altered immune responses against *Candida*. Patients with CMC display recurrent or persistent yeast infections of the skin, nails, and mucous membranes caused by organisms of the genus *Candida*, mainly *Candida albicans.* Several unique syndromes are part of this entity based on the extent and locations of the *Candida* infections and characteristic associated findings such as polyendocrinopathies, autoimmune disorders, thymoma, and interstitial keratitis. CMC may be sporadic or familial. Isolated familial CMC is distinct from candidiasis with endocrinopathy and can be autosomal recessive (OMIM 212050) or autosomal dominant (OMIM 114580). Frequently, CMC is associated with isolated thyroid disease (OMIM 606415), or with endocrine and autoimmune disorders, such as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome (OMIM 240300) [29, 30, 31] suggesting immune dysregulation as part of the syndrome. The age at onset and the clinical spectrum of Candidal infections are variable. The prognosis of isolated CMC is relatively good because candidiasis can generally be controlled by antifungal drugs; for this reason, prophylaxis with imidazol derivatives is recommended. The clinical manifestations seem to be more severe in patients who present early in infancy [32, 33], especially if they have disseminated disease, a rare event [34, 35]. Intracranial mycotic aneurysms have been reported [36]. CMC affects both sexes, with a discrete predominance of females (1.4:1) in the variants associated with endocrinopathies. Most reports suggest a cellular immune defect affecting the specific responses to antigens of *Candida* species [37]. However, defects of macrophage chemotaxis [38] and humoral immunity—IgA and IgG2/IgG4 deficiencies—were described [39]. An acquired form of asplenia has been observed in some patients with APECED [40]. A decreased production and secretion of IL-2, IFN-gamma and other lymphokines, when patients' lymphocytes were stimulated with *Candida* antigens has been reported [41–43]. However, the central mechanisms leading to CMC are unknown. The diagnosis of CMC is suggested by a history of persistent candidiasis affecting skin, appendages, and mucous membranes. An important differential diagnosis of CMC is myeloperoxidase deficiency (OMIM 254600), which is characterized by mucocutaneous candidiasis and *Candida* abscesses [44], sometimes associated with diabetes mellitus [45]. It is essential to rule out other diseases such as AIDS, Di George syndrome, severe combined immunodeficiency, diabetes mellitus, cancer, and other conditions that could cause persistent mucocutaneous candidiasis [46].

APECED

A molecularly defined group of patients with CMC also suffer from autoimmune polyendocrinopathy and ectodermal dysplasia (APECED). This rare autosomal recessive disorder, also known as autoimmune polyglandular syndrome type 1 (APS-1), has a high incidence in certain isolated populations such as Finns (1:25,000 individuals), Iranian Jews (1:9,000), and Sardinians (1:14,500) [47, 48]. The first description of this syndrome with hypoparathyroidism and CMC was reported by Thorpe and Handley [49] in 1929. In 1938, Söderlund reported a patient with insulin-dependent diabetes mellitus and candidiasis [50]. Subsequent case reports confirmed the association of endocrine disorders such as hypoadrenalism, hypoparathyroidism, and hypothyroidism with chronic mucocutaneous candidiasis [51–53]. Over the years, the classic triad of APECED—hypoparathyroidism, hypoadrenalism, and CMC—has been expanded to a highly variable combination of autoimmune diseases affecting endocrine and non-endocrine organs, including the parathyroid glands, adrenal cortex, gonads, pancreatic β-cells, and gastric parietal cells. This expanded phenotype is often associated with ectodermal manifestations such as dystrophic dental enamel and nails. The clinical features of APECED have been reviewed by Ahonen et al. [54] and are compared to those of IPEX in Table I.

Autoantigens as Targets of Autoimmune Attack in APECED

A characteristic finding relevant to the endocrinopathies of APECED is the existence of high-serum antibody titers reacting specifically with components of the affected endocrine organs (Table II). Using a human fetal cDNA

expression system, antibodies against the key enzyme in steroid biosynthesis, 17 alpha-hydroxylase (P450c17) were identified in serum from patients with APECED, strongly suggesting that this enzyme acts as an autoantigen and is involved in the pathogenesis of adrenocortical failure in APECED [55]. Subsequently, three enzymes, P450c17, P450c21 and P450scc, belonging to the cytochrome P450 superfamily and involved in steroid synthesis, were found to be targets of autoantibodies present in sera from APECED patients with Addison Disease (81%), but less frequent in those without this complication (21%). Whereas P450c21 is adrenal cortex specific, P450c17 and P450scc are specific for all steroid producing cells and are also expressed in gonads. The presence of autoantibodies to the latter two enzymes was strongly associated with hypogonadism in patients with APECED [56]. Many other autoantibodies have been reported in APECED patients, often associated with a particular clinical manifestation. These include autoantibodies to pancreatic islet-cell specific autoantigens such as GAD65, insulin, and IA2 in those with type 1 diabetes, thyroid peroxidase, and thyroglobulin in patients with thyroiditis, and possibly to parathyroid antigen (calcium-sensing receptor) in some patients with hypoparathyroidism [57]. Antibodies to another pancreatic islet cell protein, aromatic L-amino acid decarboxylase, were identified in sera from the majority of APECED patients with chronic active hepatitis, vitiligo, or type 1 diabetes [58]. Interestingly, malabsorption appears to be the result of intestinal endocrine cell destruction as gastrointestinal dysfunction in APECED patients was strongly associated with the presence of antitryptophan hydroxylase in serotonin-producing enterochromaffin cells in the gastric antrum [59] and antihistidine decarboxylase in histamine producing enterochromaffin-like cells in the gastric fundus [60]. Importantly, patients with autoantibodies against these enzymes lacked serotonin and histamine producing enterochromaffin-like cells in the gut mucosa.

It has been hypothesized that autoantibodies are induced in response to tissue destruction, whereas the pathogenic effect is mediated by T cells. Little is known, however, about the role cell mediated immunity plays in the pathogenesis of APECED. Nevertheless, autoantibodies are useful diagnostic markers as there is generally a good correlation between the presence of autoantibodies and clinical disease, and their appearance often precedes the clinical manifestation.

Genetics of APECED

APECED results from mutations in the autoimmune regulator (*AIRE*) gene [30, 31, 62]. There are hotspot mutations that can be related to a founder effect, such as the nonsense mutation (R257X) prevalent in the Finnish and Eastern European population, the Y85C missense mutation observed in an isolated Iranian Jewish community [63, 64] and a nonsense mutation (R139X) frequently found among Sardinian patients [48]. The 13-bp deletion in exon 8 (1085–1097(del)) is ubiquitous and can be found in Norwegians, British, and North Americans [64] as well as South Americans (Moraes-Vasconcelos, personal observation). The missense mutation G228W in exon 6 of AIRE was found in an Italian kindred with an autosomal dominant (AD) form of APECED [65]. Ilmarinen et al. [66] analyzed multiple proteins with amino acid substitutions in the SAND domain of AIRE and found that only the *G228W* mutation, when coexpressed with wild type, changed the subcellular localization and severely disrupted the transactivating capacity of wild-type AIRE. They concluded that the G228W protein acts with a dominant-negative effect by binding to wild-type AIRE, preventing the protein from forming the complexes needed for transactivation.

Another form of CMC associated with hypothyroidism, apparently with AD inheritance, has been mapped to

Table II Autoantigens in APECED (Modified from [61])

APECED components	Tissue	Antigens
Addison's disease	Adrenals (cortex)	P450c21, P450c17a, P450scc
Hypoparathyroidism	Parathyroid glands	Ca^{++} sensing receptor*
Hypothyroidism	Thyroid gland	Thyroid peroxidase, Thyroglobulin
Type 1 diabetes	Endocrine pancreas	GAD65, GAD67, ICA, IA-2 tyrosine phosphatase like protein, L-amino acid decarboxylase (L-AADC)
Autoimmune hepatitis	Liver	P450 CYP1A2, P450 CYP2A6, L-AADC
Vitiligo	Skin	SOX10, L-AADC
Alopecia	Scalp	Tyrosine hydroxylase
Malabsorption	Gastrointestinal tract	Tryptophan hydroxylase Histidine decarboxylase
Autoimmune gastritis	Stomach	H^+K^+ ATPase
Pernicious anemia	Gastric mucosa, red blood cells	Intrinsic factor

* This autoantigen has not been unequivocally proven in APECED [57]

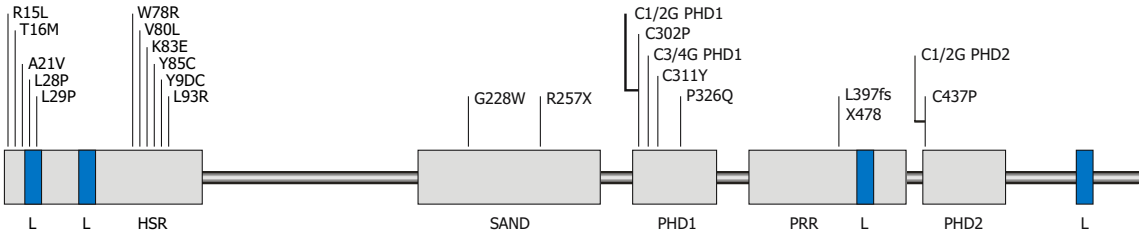

Fig. 2 Schematic view of the AIRE protein showing the functional protein domains and the distribution of the APECED-causing mutations. *HSR* homogenously staining region, *SAND* Sp100, *AIRE* NucP41/75 and DEAF-1, *PHD* plant homeodomain zinc finger, *PRR* proline rich region, *L* LXXLL nuclear receptor interaction motif

chromosome 2q (OMIM 606415) [67]. None of the other variants of CMC has been molecularly defined [68, 69], and are lumped into the category of chronic and recurrent mucocutaneous infections by *Candida* species [33].

Role of AIRE in Autoimmunity

The genesis of autoimmunity involves environmental and genetic mechanisms, both contributing to the disruption or imbalance of central or peripheral tolerance, allowing autoreactive T- and B-cell clones to escape negative selection or post thymic deletion. Among genetic factors, mutations of the autoimmune regulator gene, *AIRE,* correlate with the development of organ-specific autoimmune diseases with monogenic autosomal recessive inheritance. The *AIRE* gene, approximately 13 kb in length, contains 14 exons that encode a polypeptide of 545 amino acids (Fig. 2). Initial characterization of the AIRE protein, based on the amino acid sequence, revealed a conserved nuclear localization signal (NLS) in the N terminus followed by a SAND domain; two plant homeodomain (PHD) type zinc fingers located in the C terminus and a proline-rich region lying between the two PHDs; and four LXXLL motifs, typical of nuclear receptor binding proteins [30, 31, 70]. It was soon discovered that the N terminus of AIRE also harbors a homogeneous staining region (HSR) domain, which defines a protein family including speckled protein 100 (SP100) that mediates homodimerization [71]. The AIRE protein undergoes homomultimerization and functions as a transcription factor. The PHD1 domain of AIRE, which contains a leucine zipper motif, acts as an E3 ubiquitin ligase, mediating transfer of ubiquitin to specific proteins, which results in proteasome degradation, downregulation of cell surface receptors, and proteolysis-independent activities [72]. AIRE expression is limited to medullary thymic epithelial cells (mTECs) and cells of the monocyte/dendritic cell lineage of the thymus, where it is thought to play a unique role in the establishment of immune tolerance [73]. Interestingly, mTECs express MHC class II (MHC-II) and the costimulatory molecule CD80, and are endowed

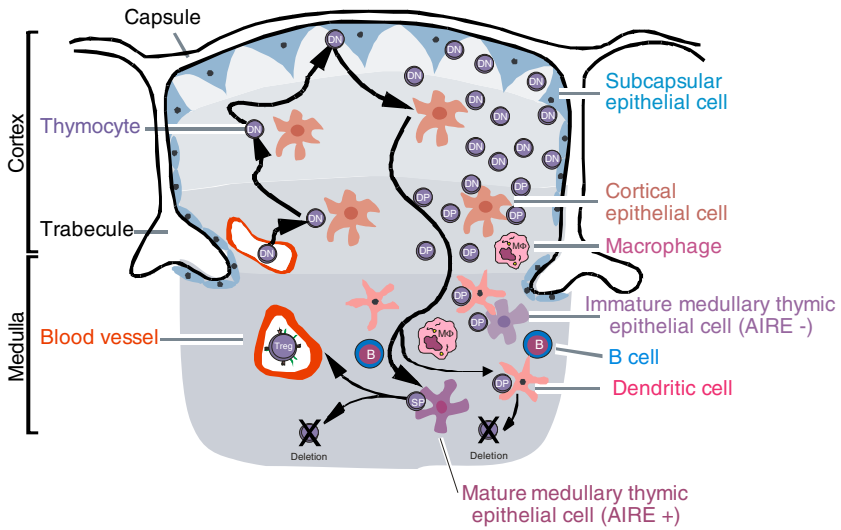

Fig. 3 Cellular composition of the thymus. The major cell types and the sequential cell–cell interactions along the migratory route of developing thymocytes are depicted. The sequential stages of differentiation of thymocytes: double-negative (DN); double-positive (DP), and single-positive (SP) T-cell precursors are highlighted. Mature medullary thymic epithelial cells (mTECs) expressing AIRE play an essential role in self-tolerance induction toward tissue-restricted self-antigens by deleting high-avidity T cells or inducing T-reg differentiation

with the remarkable ability to "promiscuously" express a wide array of tissue-restricted antigens (TRAs) derived from nearly all organs in the body [74]. TRAs comprise self-proteins with patterns of expression restricted to a single or small handful of organs. Self-reactive thymocytes develop naturally as a consequence of random T-cell receptor (TCR) gene rearrangement, and TRA expression in the thymus probably serves as an important source of self-antigens responsible for the negative selection of autoreactive T cells [75]. Both mTEC and thymic monocyte/dendritic cells are considered to play a major role in the establishment of self-tolerance by eliminating autoreactive T cells (negative selection) and/or by producing immunoregulatory $FOXP3^+$ T cells, which prevent $CD4^+$ T-cell-mediated organ-specific autoimmune diseases [76] (Fig. 3). It has been demonstrated that AIRE regulates thymic expression of several mRNA genes of ectopic peripheral proteins including many TRAs [77] in a dosage-dependent manner [78]. Therefore, a decrease in AIRE function can consequently lead to a decrease in the expression of tissue restricted antigens in the thymus, allowing the escape of autoreactive T-cell clones into the periphery [79]. Deficiency of AIRE expression affects negative selection in a aire $^{-/-}$ mouse model by complete failure to delete organ-specific thymocytes [78].

Conclusions

The rare syndromes of IPEX and APECED prove to be unique models to study immune tolerance—AIRE contributing primarily to central tolerance mechanisms and FOXP3 to peripheral tolerance mechanisms. Recent findings demonstrating that AIRE controls thymic expression of peripheral self-antigens have opened new directions in research, but also raised important questions [80]. Considering that AIRE is regulated by the lymphotoxin–RelB pathway in thymic epithelial cells, other members of this pathway may influence the ectopic expression of self-antigens in the thymus. In addition to central tolerance, the possible role of AIRE in peripheral tolerance, presumably by its expression in dendritic cells of secondary lymphoid organs, requires further study [81]. The recognition that AIRE expression is sustained by effective thymopoiesis has recently led to investigations of AIRE expression in the thymus of human severe combined immunodeficiency (SCID) patients. These studies suggest that the autoimmunity observed in Omenn syndrome, a combined immunodeficiency caused by defective V(D)J recombination, may result from defective expression of AIRE in the thymus [82]. In the case of FOXP3, understanding the mechanism by which it confers a regulatory phenotype upon T cells will be an ongoing focus of future investigation. Understanding the molecular mechanisms of autoimmunity by studying these rare monogenic syndromes has important implications for the way we approach autoimmune phenomena both in immunocompetent and immune compromised hosts and may lead to novel therapeutic opportunities.

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References

1. Stiehm ER, Johnston RB Jr. A history of pediatric immunology. Pediatr Res 2005;57:458–67.
2. Bennett CL, Yoshioka R, Kiyosawa H, Barker DF, Fain PR, Shigeoka AO, et al. X-Linked syndrome of polyendocrinopathy, immune dysfunction, and diarrhea maps to Xp11.23–Xq13.3. Am J Hum Genet 2000;66:461–8.
3. Powell BR, Buist NR, Stenzel P. A X-linked syndrome of diarrhea, polyendocrinopathy, and fatal infection in infancy. J Pediatr 1982;100:731–7.
4. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet 2002;39:537–45.
5. Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy and X-linked inheritance (IPEX): a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol 2003;15:430–5.
6. Baud O, Goulet O, Canioni D, Le Deist F, Radford I, Rieu D, et al. Treatment of the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. N Engl J Med 2001;344:1758–62.
7. Nieves DS, Phipps RP, Pollock SJ, Ochs HD, Zhu Q, Scott GA, et al. Dermatologic and immunologic findings in the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. Arch Dermatol 2004;140:466–72.
8. Bakke AC, Purtzer MZ, Wildin RS. Prospective immunological profiling in a case of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX). Clin Exp Immunol 2004;137:373–8.
9. Myers AK, Perroni L, Reardon W. Clinical and molecular findings in IPEX syndrome. Arch Dis Child 2006;91:63–4.
10. Heltzer ML, Choi JK, Ochs HD, Sullivan KE, Torgerson TR, Ernst LM. A potential screening tool for IPEX syndrome. Pediatr Dev Pathol 2007;10:98–105.
11. Kobayashi I, Shiari R, Yamada M, Kawamura N, Okano M, Yara A, et al. Novel mutations of FOXP3 in two Japanese patients with immune dysregulation, polyendocrinopathy, enteropathy, X linked syndrome (IPEX). J Med Genet 2001;38:874–6.
12. McGinness JL, Bivens MM, Greer KE, Patterson JW, Saulsbury FT. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) associated with pemphigoid nodularis: a case report and review of the literature. J Am Acad Dermatol 2006;55:143–8.
13. Bindl L, Torgerson T, Perroni L, Youssef N, Ochs HD, Goulet O, et al. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). J Pediatr 2005;147:256–9.

14. Costa-Carvalho BT, Moraes-Pinto MI, Almeida LC, et al. A remarkable depletion of both naïve CD4+ and CD8+ with high proportion of memory T cells in an IPEX infant with a FOXP3 mutation in the forkhead domain. Scand J Immunol 2008;in press.
15. Ochs HD, Ziegler SF, Torgerson TR. FOXP3 acts as a rheostat of the immune response. Immunol Rev 2005;203:156–64.
16. Torgerson TR, Ochs HD. Regulatory T cells in primary immunodeficiency diseases. Curr Opin Allergy Clin Immunol 2007a;7:515–21.
17. Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked: Forkhead box protein mutations and lack of regulatory T cells. J Allergy Clin Immunol 2007b;120:744–50.
18. Bacchetta R, Passerini L, Gambineri E, Dai M, Allan SE, Perroni L, et al. Defective regulatory and effector T cell functions in patients with FOXP3 mutations. J Clin Invest 2006;116:1713–22.
19. Yagi H, Nomura T, Nakamura K, Yamazaki S, Kitawaki T, Hori S, et al. Crucial role of FOXP3 in the development and function of human CD25+CD4+ regulatory T cells. Int Immunol 2004;16:1643–56.
20. Zheng Y, Rudensky AY. Foxp3 in control of the regulatory T cell lineage. Nat Immunol 2007;8:457–62.
21. Bennett CL, Ochs HD. IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena. Curr Opin Pediatr 2001;13:533–8.
22. Watanabe N, Wang YH, Lee HK, Ito T, Wang YH, Cao W, et al. Hassall's corpuscles instruct dendritic cells to induce CD4+CD25+ regulatory T cells in human thymus. Nature 2005;436:1181–5.
23. Rao A, Kamani N, Filipovich A, Lee SM, Davies SM, Dalal J, et al. Successful bone marrow transplantation for IPEX syndrome after reduced-intensity conditioning. Blood 2007;109:383–5.
24. Perroni L, Faravelli F, Cusano R, Forzano F, De Cassan P, Baldo C, et al. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX): report of the first prenatal mutation testing. Prenat Diagn 2006;26:487–9.
25. Zuber J, Viguier M, Lemaitre F, Senée V, Patey N, Elain G, et al. Severe FOXP3+ and naive T lymphopenia in a non-IPEX form of autoimmune enteropathy combined with an immunodeficiency. Gastroenterology 2007;132(5):1694–704.
26. Owen CJ, Jennings CE, Imrie H, Lachaux A, Bridges NA, Cheetham TD, et al. Mutational analysis of the FOXP3 gene and evidence for genetic heterogeneity in the immunodysregulation, polyendocrinopathy, enteropathy syndrome. J Clin Endocrinol Metab 2003;88:6034–9.
27. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol 2007;119:482–7.
28. Sharfe N, Dadi HK, Shahar M, Roifman CM. Human immune disorder arising from mutation of the alpha chain of the interleukin-2 receptor. Proc Natl Acad Sci U S A 1997;94:3168–71.
29. Aaltonen J, Björses P, Sandkuijl L, Perheentupa J, Peltonen L. An autosomal locus causing autoimmune disease: autoimmune polyglandular disease type I assigned to chromosome 21. Nat Genet 1994;8:83–7.
30. The Finnish-German APECED Consortium. An auto-immune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet 1997;17:399–403.
31. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, et al. Positional cloning of the APECED gene. Nat Genet 1997;17:393–8.
32. Kirkpatrick CH, Sohnle P. Chronic mucocutaneous candidiasis. In: Safai B, Good RA, editors. Immunodermatology. New York: Plenum Medical Book; 1981. p. 495–514.
33. Hong R, Clement LT, Gatti RA, Kirkpatrick CH. Disorders of the T-Cell System. In: Stiehm ER, editor. Immunologic disorders in infants and children. Philadelphia: Saunders; 1996. p. 339–408.
34. Kauffman CA, Shea MJ, Frame PT. Invasive fungal infections in patients with chronic mucocutaneous candidiasis. Arch Int Med 1981;141:1076–9.
35. Germain M, Gourdeau M, Hébert J. Case report: familial chronic mucocutaneous candidiasis complicated by deep Candida infection. Am J Med Sci 1994;307:282–3.
36. Loeys BL, Van Coster RN, Defreyne LR, Leroy JG. Fungal intracranial aneurysm in a child with familial chronic mucocutaneous candidiasis. Eur J Pediatr 1999;158:650–2.
37. Valdimarsson H, Higgs JM, Wells RS, Yamamura M, Hobbs JR, Holt PJL. Immune abnormalities associated with chronic mucocutaneous candidiasis. Cell Immunol 1973;6:348–61.
38. Djawari D, Bischoff T, Hornstein OP. Impairment of chemotactic activity of macrophages in chronic mucocutaneous candidosis. Arch Dermatol Res 1978;262:247–53.
39. Bentur L, Nisbet-Brown E, Levinson H, Roifman CM. Lung disease associated with IgG subclass deficiency in chronic mucocutaneous candidiasis. J Pediatr 1991;118:82–6.
40. Friedman TC, Thomas PM, Fleisher TH, Feuillan P, Parker RI, Cassoria F, et al. Frequent occurrence of asplenism and cholelithiasis in patients with autoimmune polyglandular disease type I. Am J Med 1991;91:625–30.
41. Lilic D, Cant AJ, Abinun M, Calvert JE, Spickett GP. Chronic mucocutaneous candidiasis. I. Altered antigen-stimulated IL-2, IL-4, IL-6 and interferon-gamma (IFN-γ) production. Clin Exp Immunol 1996;105:205–12.
42. Kobrynski LJ, Tanimune L, Kilpatrick L, Campbell DE, Douglas SD. Production of T-helper cell subsets and cytokines by lymphocytes from patients with chronic mucocutaneous candidiasis. Clin Diagn Lab Immunol 1996;3:740–5.
43. de Moraes-Vasconcelos D, Orii NM, Romano CC, Iqueoka RY, Duarte AJ. Characterization of the cellular immune function of patients with chronic mucocutaneous candidiasis. Clin Exp Immunol 2001;123:247–53.
44. Lehrer RI, Cline MJ. Leukocyte myeloperoxidase deficiency and disseminated candidiasis: the role of myeloperoxidase in resistance to Candida infection. J Clin Invest 1969;48:1478–88.
45. Cech P, Stalder HS, Widmann JJ, Rohrer A, Miescher PA. Leukocyte myeloperoxidase deficiency and diabetes mellitus associated with Candida albicans liver abscess. Am J Med 1979;66:149–53.
46. Drake LA, Dinehart SM, Farmer MK, Goltz RW, Graham GF, Hordinsky MK, et al. Guidelines of care for superficial mycologic infections of skins: mucocutaneous candidiasis. J Am Acad Dermatol 1996;34:110–5.
47. Vogel A, Strassburg CP, Obermayer-Straub P, Brabant G, Manns MP. The genetic background of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and its autoimmune disease components. J Mol Med 2002;80:201–11.
48. Rosatelli MC, Meloni AL, Meloni AN, Devoto M, Cao A, Scott HS, et al. A common mutation in Sardinian autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients. Hum Genet 1998;103:428–34.
49. Thorpe ES, Handley HE. Chronic tetany and chronic mycelial stomatitis in a child aged four and one-half years. Am J Dis Child 1929;38:328–38.
50. Söderlund S. Några fall av tetani, behandlade med A.T. 10. Finska läkaresällskapets handlingar 1938; 81: 659–87. Apud: Ahonen P. Autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy (APECED): autosomal recessive inheritance. Clin Genet 1985; 27:535–42.
51. Craig JM, Schiff LH, Boone JE. Chronic moniliasis associated with Addison's disease. Am J Dis Child 1955;89:669–84.

52. Whitaker J, Landing BH, Esselborn VM, Williams RR. The syndrome of familial juvenile hypoadrenocorticism, hypoparathyroidism, and superficial moniliasis. J Clin Endocrinol 1985;16:1374–87.
53. Hung W, Migeon CJ, Parrott RH. A possible auto-immune basis for Addison's disease in three siblings, one with idiopathic hypoparathyroidism, pernicious anemia and superficial moniliasis. N Engl J Med 1963;269:658–63.
54. Ahonen P, Myllärniemi S, Sipilä I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 1990;322:1829–36.
55. Krohn K, Uibo R, Aavik E, Peterson P, Savilahti K. Identification by molecular cloning of an autoantigen associated with Addison's disease as steroid 17 alpha-hydroxylase. Lancet 1992;339:770–3.
56. Uibo R, Aavik E, Peterson P, Perheentupa J, Aranko S, Pelkonen R, et al. Autoantibodies to cytochrome P450 enzymes P450scc, P450c17, and P450c21 in autoimmune polyglandular disease types I and II and in isolated Addison's disease. J Clin Endocrinol Metab 1994;78:323–8.
57. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev 2002;23:327–64.
58. Husebye ES, Gebre-Medhin G, Tuomi T, Perheentupa J, Landin-Olsson M, Gustafsson J, et al. Autoantibodies against aromatic L-amino acid decarboxylase in autoimmune polyendocrine syndrome type I. J Clin Endocrinol Metab 1997;82:147–50.
59. Ekwall O, Hedstrand H, Grimelius L, Haavik J, Perheentupa J, Gustafsson J, et al. Identification of tryptophan hydroxylase as an intestinal autoantigen. Lancet 1998;352:279–83.
60. Sköldberg F, Portela-Gomes GM, Grimelius L, Nilsson G, Perheentupa J, Betterle C, et al. Histidine decarboxylase, a pyridoxal phosphate-dependent enzyme, is an autoantigen of gastric enterochromaffin-like cells. J Clin Endocrinol Metab 2003;88:1445–52.
61. Peterson P, Pitkänen J, Sillanpää N, Krohn K. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): a model disease to study molecular aspects of endocrine autoimmunity. Clin Exp Immunol 2004;135:348–57.
62. Villaseñor J, Benoist C, Mathis D. AIRE and APECED: molecular insights into an autoimmune disease. Immunol Rev 2005;204:156–64.
63. Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome type I among Iranian Jews. J Med Genet 1992;29:824–6.
64. Björses P, Halonen M, Palvimo JJ, Kolmer M, Aaltonen J, Ellonen P, et al. Mutations in the AIRE gene: effects on subcellular location and transactivation function of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protein. Am J Hum Genet 2000;66:378–92.
65. Cetani F, Barbesino G, Borsari S, et al. A novel mutation of the autoimmune regulator gene in an Italian kindred with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, acting in a dominant fashion and strongly cosegregating with hypothyroid autoimmune thyroiditis. J Clin Endocrinol Metab 2001;86:4747–52.
66. Ilmarinen T, Eskelin P, Halonen M, Ruppell T, Kilpikari R, Duran Torres G, et al. Functional analysis of SAND mutations in AIRE supports dominant inheritance of the G228W mutation. Hum Mutat 2005;26:322–31.
67. Atkinson TP, Schaffer AA, Grimbacher B, Schroeder HW Jr, Woellner C, Zerbe CS, et al. An immune defect causing dominant chronic mucocutaneous candidiasis and thyroid disease maps to chromosome 2p in a single family. Am J Hum Genet 2001;69 (4):791–803.
68. Coleman R, Hay RJ. Chronic mucocutaneous candidosis associated with hypothyroidism: a distinct syndrome? Br J Dermatol 1997;136(1):24–9.
69. Lehner T, Wilton JMA, Ivanyi L. Immunodeficiencies in chronic mucocutaneous candidiasis. Immunology 1972;22:775–87.
70. Mittaz L, Rossier C, Heino M, Peterson P, Krohn KJ, Gos A, et al. Isolation and characterization of the mouse Aire gene. Biochem Biophys Res Commun 1999;255:483–90.
71. Sternsdorf T, Jensen K, Reich B, Will H. The nuclear dot protein sp100, characterization of domains necessary for dimerization, subcellular localization, and modification by small ubiquitin-like modifiers. J Biol Chem 1999;274:12555–66.
72. Uchida D, Hatakeyama S, Matsushima A, Han H, Ishido S, Hotta H, et al. AIRE functions as an E3 ubiquitin ligase. J Exp Med 2004;199:167–72.
73. Kogawa K, Nagafuchi S, Katsuta H, Kudoh J, Tamiya S, Sakai Y, et al. Expression of AIRE gene in peripheral monocyte/dendritic cell lineage. Immunol Lett 2002;80:195–8.
74. Derbinski J, Schulte A, Kyewski B, Klein L. Promiscuous gene expression in medullary thymic epithelial cells mirrors the peripheral self. Nat Immunol 2001;2:1032–9.
75. Kyewski B, Klein L. A central role for central tolerance. Annu Rev Immunol 2006;24:571–606.
76. Kuroda N, Mitani T, Takeda N, Ishimaru N, Arakaki R, Hayashi Y, et al. Development of autoimmunity against transcriptionally unrepressed target antigen in the thymus of Aire-deficient mice. J Immunol 2005;174:1862–70.
77. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science 2002;298:1395–401.
78. Liston A, Gray DH, Lesage S, Fletcher AL, Wilson J, Webster KE, et al. Gene dosage-limiting role of Aire in thymic expression, clonal deletion, and organ-specific autoimmunity. J Exp Med 2004;200:1015–26.
79. Kont V, Laan M, Kisand K, Merits A, Scott HS, Peterson P. Modulation of Aire regulates the expression of tissue-restricted antigens. Mol Immunol 2008;45:25–33.
80. Mathis D, Benoist C. A decade of AIRE. Nat Rev Immunol 2007;7:645–50.
81. Cheng MH, Shum AK, Anderson MS. What's new in the Aire? Trends Immunol 2007;28:321–7.
82. Cavadini P, Vermi W, Facchetti F, Fontana S, Nagafuchi S, Mazzolari E, et al. AIRE deficiency in thymus of 2 patients with Omenn syndrome. J Clin Invest 2005;115:728–32.