



Inborn errors of T cell immunity underlying autoimmune diseases

László Maródi

To cite this article: László Maródi (2017) Inborn errors of T cell immunity underlying autoimmune diseases, Expert Review of Clinical Immunology, 13:2, 97-99, DOI: [10.1080/1744666X.2017.1256204](https://doi.org/10.1080/1744666X.2017.1256204)

To link to this article: <http://dx.doi.org/10.1080/1744666X.2017.1256204>



Accepted author version posted online: 01 Nov 2016.
Published online: 18 Nov 2016.



[Submit your article to this journal](#)



Article views: 242



[View related articles](#)



[View Crossmark data](#)

EDITORIAL

Inborn errors of T cell immunity underlying autoimmune diseases

László Maródi^{a,b}

^aDepartments of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary; ^b2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary

ARTICLE HISTORY Received 13 March 2016; Accepted 31 October 2016

KEYWORDS Primary immunodeficiencies; T cell defects; autoimmune diseases; APS 1; IPEX

Immunopathological diseases have traditionally been classified as autoimmune/inflammatory, allergic, and primary immunodeficiency (PID) conditions. Different clinical disciplines have been established along with these classifications resulting in artificial separation of immune disorders in clinical practice and the establishment of professional societies and journals focusing on these seemingly different areas of clinical medicine. Understanding better the genetics of human immunity and immunopathology has changed our approach to such a classification. Monogenic autoimmunity best exemplified by autoimmune polyendocrine syndrome type 1 (APS-1) and immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) has taught us how to re-evaluate previously existing dogmas. Discovery of various genetic errors of immunity has provided powerful insight into a better understanding of disease mechanisms and tolerance to self and non-self. We describe here a few monogenic primary T cell deficiencies as examples that PIDs may actually underlie autoimmune diseases (Table 1).

APS-1 is a rare monogenic disorder caused by autosomal recessive mutations in the autoimmune regulator (AIRE) gene leading to dysregulation of central tolerance [1]. During differentiation of immature lymphocytes in the thymus, central tolerance develops by clonal deletion and inactivation of self-reactive T cells. Most high-affinity T lymphocytes recognizing self-antigens are eliminated by negative selection. Promotion of clonal deletion of self-reactive thymocytes is achieved by ectopically expressed peripheral tissue antigens (PTAs) by medullary epithelial cells. As a result, the T cell pool of the adaptive immune system is rendered tolerant to the body's own constituents, which assures protection against destructive autoimmune responses. AIRE is a major regulator of thymus expression and presentation of PTAs and as such controls tolerance of T cells and protection to autoimmunity. APS-1 is characterized by chronic mucocutaneous candidiasis (CMC), autoimmune endocrinopathies like hypoparathyroidism, Addison disease, hypothyroidism, and insulin-dependent diabetes mellitus [1]. APS-1 patients typically generate various neutralizing autoantibodies against interferon (IFN)- α 2a, IFN- ω , IL-17A and IL-17F, and anti-IL-22 [1,2]. Anti-cytokine antibodies are thought to interfere with host defense against candida,

predisposing patients to CMC. Thus, APS-1 is an inborn error of immunity showing clearly that monogenic PIDs may result in multi-organ autoimmune diseases. Incomplete APS-1, characterized by heterozygous, dominant negative mutations affecting the PHD1 zinc-finger domain of AIRE, may also lead to organ-specific autoimmune diseases [3]. In heterozygous patients, autoimmunity presents later and progresses more slowly than in patients with classical APS-1. The penetrance in heterozygous cases is incomplete like in patients with heterozygous mutations of *CTLA* and *FAS* [3]. It is likely that many patients with heterozygous *AIRE* mutations are diagnosed with organ-specific autoimmune disease [3]. Future research should reveal how modifier genes or environmental factors may be accounted for by the incomplete penetrance in non-classical APS-1 patients in particular and other autosomal dominant PIDs in general.

IPEX is characterized by early onset diarrhea, autoimmune endocrinopathies, eczema, autoimmune thyroiditis, immune cytopenias, allergic diseases, and susceptibility to infections [4]. IPEX is caused by loss-of-function mutation in *FOXP3*. Functional defect of *FOXP3*, a forkhead/winged-helix family transcriptional factor, results in decreased expression of this protein in CD4+CD25+ regulatory (Treg) cells which are highly enriched with suppressive activity. The primary role of Treg cells is to control auto-reactive immune responses, immune-mediated inflammation, and lymphoproliferative diseases. Treg differentiation is promoted in the thymus (tTreg cells) by remarkable affinity interactions with self-peptide-MHC complexes. On the other hand, differentiation of inducible Treg cells (iTreg) is promoted at the periphery by interaction with non-self-antigens. Not surprisingly, the immunological consequence of *FOXP3* mutation is unchecked T-cell activation because of the functional defect of CD4+CD25+ Treg cells to maintain peripheral tolerance. Unrestrained reactivity of T cells and the abundant secretion of Th1, Th2, and Th17 cytokines result in massive inflammation at body surfaces in the gut, lung, and skin induced by the commensal flora [4]. Phenotypic expression of IPEX is similar to that of CD25 deficiency [5] (Table 1).

Table 1. Primary T cell immunodeficiencies (PTIDs) associated with autoimmune (AI) diseases.

PTID disease	Gene mutated	Inheritance	AI disease manifestation	Mechanistic explanation
APS-1	<i>AIRE</i>	AR	Endocrinopathies Anti-cytokine Ab; anti-NALP5 Organ-specific auto-Ab	Impaired central tolerance
IPEX	<i>FOXP3</i>	XL	Endocrinopathies Enteropathy; atopic diseases Immune cytopenias	Impaired peripheral tolerance
CD25 deficiency	<i>IL2RA</i>	AR	Enteropathy	Impaired generation of iTreg cells
CTLA4 deficiency	<i>CTLA4</i>	AD	Eczema Lymphocytic infiltration of organs Cytopenias	Impaired function of Treg cells Impaired Treg function
ALPS	<i>FAS*</i> , <i>FASL</i> , <i>CASP10*</i>	*AD, *AR	Cytopenias; Evans syndrome Organ-specific autoantibodies	Impaired apoptosis of lymphocytes
RAG deficiency	<i>RAG1</i> , <i>RAG2</i>	AR	Autoreactive T cells	Impaired VDJ recombination
LRBA deficiency	<i>LRBA</i>	AR	ITP, AIHA, LIP, atrophic gastritis	Autophagy; susceptibility to apoptosis
PGMA3 deficiency	<i>PGMA3</i>	AR	Leukocytoclastic vasculitis, AIHA, neutropenia, glomerulonephritis	CD8 lymphopenia
Artemis deficiency	<i>DCLRE1</i>	AR	Cytopenia	Impaired DNA double strand repair
DNA PKcs deficiency	<i>PRKDC</i>	AR	ANA positive arthritis	Impaired VDJ recombination
ZAP-70 deficiency	<i>ZAP70</i>	AR	Nephrotic syndrome, Bullous pemphigoid, anti-factor VIII	CD8 lymphopenia
TCRαβ deficiency	<i>TRAC</i>	AR	ANA, IgA tissue transglutaminase	Impaired T cell proliferation Lack of TCRαβ+ cells
MST1 deficiency	<i>STK4</i>	AR	Cytopenias	Restricted T cell repertoire Impaired T cell proliferation
LCK deficiency	<i>LCK</i>	AR	Retinal vasculitis Anti-platelet antibodies	Restricted T cell repertoire CD4 lymphopenia; low Treg number Impaired TCR signaling

APS: autoimmune polyendocrine syndrome; AR: autosomal recessive; Ab: antibody; NALP: NACHT leucine-rich repeat protein; IPEX: immunodeficiency, polyendocrinopathy, enteropathy, X-linked; XL: X-linked; iTreg: inducible Treg; CTLA: cytotoxic T lymphocyte antigen; AD: autosomal dominant; ALPS: autoimmune lymphoproliferative syndrome; RAG: recombinase activating gene; LRBA: lipopolysaccharide responsive beige-like anchor protein; ITP: immune thrombocytopenia; AIHA: autoimmune hemolytic anemia; LIP: lymphocytic interstitial pneumonia; PGM: phosphoglutamase; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; ANA: anti-nuclear antibody; ZAP: zeta-associated protein; TCR: T cell receptor; MST: mammalian sterile 20-like kinase; LCK: T lymphocyte-specific SRC tyrosine kinase.

Activation of cytotoxic T lymphocyte antigen 4 (CTLA4) stimulates the suppressor function of Treg cells [6]. Such activation occurs after binding of CTLA4 expressed by T cells to B7 molecules expressed on the surface of antigen-presenting cells and help to maintain tolerance to self-antigen. Patients with heterozygous mutation in the gene encoding for *CTLA4* suffer from severe autoimmune disease [6,7]. Patients typically develop uncontrolled infiltration by T and B lymphocytes of various organs including the lungs, brain, and gut, a clinical phenotype similar to that of autoimmune lymphoproliferative syndrome (ALPS).

The classical initial manifestation of ALPS is persistent, benign, non-tender lymphadenopathy and hepatosplenomegaly without severe infections or malignancy [8]. Non-Hodgkin lymphoma may develop in 10–20% of patients. Homozygous and compound heterozygous Fas receptor (CD95) mutations were described as common genetic causes of ALPS in humans. Mutations in genes encoding for the Fas-ligand (FasL, CD95L) and caspases 10 may also cause ALPS, suggesting heterozygous genetic basis of a unique clinical syndrome [8]. The immunological findings in ALPS include increased number of CD4⁺CD8⁺ T cells, the production of autoantibodies including anti-cardiolipin, anti-nuclear antibodies (ANA), anti-red blood cell autoantibodies, and rheumatic factor. Autoimmunity in patients with ALPS may affect several organs including the eyes, kidneys, liver, joints, nerve system, and skin [9].

The inappropriate contraction of the immune response due to impaired apoptosis of lymphoid cells may be the major mechanism for autoimmunity in patients with ALPS. During immune activation driven by high antigenic load, Fas-

mediated cell death is promoted by unregulated expression of FasL on T cells triggering active apoptosis. Chronic antigen presentation due to defective apoptosis of dendritic cells and autoreactive B cells may contribute to humoral autoimmunity, a prominent phenotype of ALPS.

Autosomal recessive recombinase-activating gene 1 and 2 (RAG 1/2) deficiencies are genetic disorders causing severe combined immunodeficiency characterized by the T⁺B⁺NK⁺ immunological phenotype [10]. However, hypomorphic RAG mutations also may result in variable phenotypes including autoimmune diseases and common variable immunodeficiency [11]. Patients with compound heterozygous RAG mutations and CVID phenotype with autoimmune cytopenias have recently been reported [12]. Population genetic analysis showed that the incidence of immunoregulatory defect caused by RAG mutations may be higher than thought before. In patients with RAG deficiency, the mechanisms of autoimmunity, in general, and the generation of autoantibodies, in particular, may relate to impaired development of the thymus resulting in decreased AIRE expression and Treg differentiation (vide supra).

Lipopolysaccharide response beige-like anchor protein (LRBA) deficiency has been described as a cause of PID associated with autoimmunity in four consanguineous family [13]. Affected individuals presented with typical clinical manifestations of antibody deficiency, including recurrent bacterial infections of the respiratory tract. Immunological findings in LRBA-deficient patients include low IgG and IgA levels, and low or normal serum IgM concentration (Table 1).

Phosphoglutamase 3 (PGM3) *deficiency* is a multi-systemic disorder with developmental delay, seizures, ataxia and dysarthria, characteristic features of primary immunodeficiency, and autoimmunity (Table 1) [14]. PGM3 deficiency is caused by autosomal recessive, hypomorphic mutations in *PGM3*. Immunological findings include CD8+ T cell lymphopenia, decreased CD27+ B cell number and neutropenia.

In summary, several genetically defined primary T cell deficiencies have been described to cause autoimmunity (Table 1) [15–19]. Patients with primary B cell defects or inborn errors of innate immunity (not discussed here) may also develop autoimmune diseases. These Mendelian disorders shed light on PIDs underlying immunological diseases traditionally considered to be autoimmune. Further identification of PID genes in patients with systemic or organ-specific autoimmunity is expected to enlighten autoimmune diseases as a result of monogenic inborn errors of immunity.

Funding

This paper was funded by the Foundation for Children with Immunodeficiencies.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. *J Clin Immunol*. 2015;35:463–478.
2. Puel A, Döffinger R, Natividad A, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med*. 2010;207:291–297.
3. Oftedal BE, Hellesø A, Erichsen MM, et al. Dominant mutations in the autoimmune regulator AIRE are associated with common organ-specific autoimmune diseases. *Immunity*. 2015;42:1185–1196.
4. Ochs HD, Gambineri E, Torgerson TR. IPEX, FOXP3 and regulatory T-cells: a model for autoimmunity. *Immunol Res*. 2007;38:112–121.
5. Roifman CM. Studies of patients' thymic aid in the discovery and characterization of immunodeficiency in humans. *Immunol Rev*. 2005;203:143–155.
6. Schubert D, Bode C, Kenefeck R, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat Med*. 2014;20:1410–1416.
7. Kuehn HS, Ouyang W, Lo B, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. *Science*. 2014;345:1623–1627.
8. Oliveira JB, Bleesing JJ, Dianzani U, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH international workshop. *Blood*. 2010;116:e35–e40.
9. Shah S, Wu E, Rao VK, et al. Autoimmune lymphoproliferative syndrome: an update and review of the literature. *Curr Allergy Asthma Rep*. 2014;14:462.
10. Villa A, Sobacchi C, Notarangelo LD, et al. V(D)J recombination defects in lymphocytes due to RAG mutations: severe immunodeficiency with a spectrum of clinical presentations. *Blood*. 2001;97:81–88.
11. Avila EM, Uzel G, Hsu A, et al. Highly variable clinical phenotypes of hypomorphic RAG1 mutations. *Pediatrics*. 2010;126:e1248–52.
12. Chen K, Wu W, Mathew D, et al. Autoimmunity due to RAG deficiency and estimated disease incidence in RAG1/2 mutations. *J Allergy Clin Immunol*. 2014;133:880–882.e10.
13. Lopez-Herrera G, Tampella G, Pan-Hammarström Q, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am J Hum Genet*. 2012;90:986–1001.
14. Stray-Pedersen A, Backe PH, Sorte HS, et al. PGM3 mutations cause a congenital disorder of glycosylation with severe immunodeficiency and skeletal dysplasia. *Am J Hum Genet*. 2014;95:96–107.
15. Mathieu AL, Verronese E, Rice GI, et al. PRKDC mutations associated with immunodeficiency, granuloma, and autoimmune regulator-dependent autoimmunity. *J Allergy Clin Immunol*. 2015;135:1578–88.e5.
16. Chan AY, Punwani D, Kadlecik T, et al. A novel human autoimmune syndrome caused by combined hypomorphic and activating mutations in ZAP-70. *J Exp Med*. 2016;213:155–165.
17. Morgan NV, Goddard S, Cardno TS, et al. Mutation in the TCRα subunit constant gene (TRAC) leads to a human immunodeficiency disorder characterized by a lack of TCRαβ+ T cells. *J Clin Invest*. 2011;121:695–702.
18. Halacli SO, Ayvaz DC, Sun-Tan C, et al. STK4 (MST1) deficiency in two siblings with autoimmune cytopenias: a novel mutation. *Clin Immunol*. 2015;161:316–323.
19. Hauck F, Randriamampita C, Martin E, et al. Primary T-cell immunodeficiency with immunodysregulation caused by autosomal recessive LCK deficiency. *J Allergy Clin Immunol*. 2012;130:1144–1152.