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Monogenic Autoimmune Diseases: Insights into Self-Tolerance

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ABSTRACT: Autoimmune diseases affect a significant segment of the population and are typically thought to be multifactorial in etiology. Autoimmune diseases due to single gene defects are rare, but offer an invaluable window into understanding how defects in the immune system can lead to autoimmunity. In this review, we will focus on autoimmune polyendocrinopathy syndrome type 1 and recent advances in our understanding of this disease. We will also discuss two other monogenic autoimmune diseases: immunodysregulation, polyendocrinopathy, and enteropathy, X-linked and Autoimmune lymphoproliferative syndrome. Importantly, the knowledge and principles gained from studying these diseases have been applicable to more common autoimmune diseases and have opened the door to better diagnostic and therapeutic modalities. **(*Pediatr Res* 65: 20R–25R, 2009)**

Autoimmune disease affects approximately 3% of Americans, with many of these diseases arising in childhood (1). Despite its prevalence, the complex, polygenic inheritance of most autoimmune disorders has been an obstacle in understanding the pathogenesis of these diseases. Although recent technical advances, including genome-wide association studies, have allowed for the identification of genetic factors contributing to autoimmunity, the individual impact of each of these genetic factors is low. For example, 8 of the 10 chromosomal regions associated with type I diabetes have an odds ratio of <2.0 (2). The low impact of these genetic factors has made them difficult to study. In contrast, studies of rare monogenic autoimmune diseases have more readily yielded mechanistic insights into autoimmune pathophysiology because of the obvious impact of mutations in these single genes in provoking disease.

An example of a rare monogenic autoimmune diseases is autoimmune polyendocrinopathy syndrome (APS) type I (OMIM 240300), also known as autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy, which is due to a defect in autoimmune regulator (Aire). Studies of monogenic diseases, like APS type I, have played a critical role in informing us on how the immune system normally recognizes self from nonself and how breakdowns in this system can result in autoimmune disease. In this review, we will discuss recent advances in our understanding of the clinical features, genetics, pathophysiology, and diagnosis of this disease. In addition, we will also touch on two other monogenic autoimmune diseases, Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) (OMIM 304790) and autoimmune lymphoproliferative syndrome (ALPS) (OMIM 601859) (Table 1), and discuss recent advances in the study of these syndromes.[1]

Clinical Findings and Molecular Genetics

APS type I is a rare disease, but is more common in certain populations, including Iranian Jews (3), Finns (4), Sardinians (5), and Norwegians (6). Clinically, APS type I is characterized by three major features: adrenal insufficiency, hypoparathyroidism, and mucocutaneous candidiasis (7). A clinical diagnosis is based on the presence of two of these three features. APS type I often manifests with mucocutaneous candidiasis in infancy, followed by hypoparathyroidism and adrenal insufficiency in childhood (7–9). In addition, a number of other organ-specific autoimmune diseases, including ovarian failure, testicular failure, autoimmune thyroiditis, autoimmune diabetes, autoimmune gastritis, and vitiligo, develop in these patients at a lower incidence (8,10). The pace at which disease manifestations are seen is quite variable, requiring patients to be screened throughout their lifetime (7,8). For example, in one series in Norway, the first clinical manifestation of APS type I ranged from the first year of life to age 43 y (6).

Because APS type I is a monogenic disease, classical positional cloning techniques could be used to map the gene defect. In 1997, this defect was mapped to the Aire gene (11,12). Interestingly, the genotype–phenotype correlation is quite variable, with patients in the same family with the same Aire mutation manifesting different organ-specific autoimmune diseases (6). More than 58 mutations have been described in Aire (4). The two most common mutations are the R257X mutation and a 13 bp deletion in exon 8. The frequency of these mutations is population specific, with the R257X mutation seen in the majority of Finnish APS type I patients (12), and a 13 bp deletion in exon 8 (1094-1106del) seen in the majority of APS type I patients in Britain (13) and North America (14). Heterozygous carriers of these mutations in general have not been found to manifest autoimmunity (15).

Interestingly, a G228W point mutation in Aire has been described in an Italian family with an autoimmune syndrome that is inherited in an autosomal dominant manner (16). This autoimmune syndrome differs from the classic APS type I in

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Abbreviations: APS, autoimmune polyendocrinopathy syndrome; **IPEX,** immunodysregulation, polyendocrinopathy, and enteropathy, X-linked; **ALPS,** autoimmune lymphoproliferative syndrome; **Aire,** autoimmune regulator; **mTECs,** medullary thymic epithelial cells

Table 1. *Monogenic autoimmune diseases, altered proteins due to genetic mutations, and clinical findings*

Disease	Altered protein	Clinical manifestations
APS type I	Aire	Major: hypoparathyroidism, adrenal insufficiency, mucocutaneous candidiasis; minor: type I diabetes, hypothyroidism, vitiligo, gonadal failure, gastritis, pernicious anemia, hepatitis, alopecia, keratitis, etc.
IPEX	FoxP3	Diarrhea, dermatitis, hemolytic anemia, diabetes mellitus, and thyroid autoimmunity
ALPS	IA: Fas IB: Fas ligand IIA: Caspase 10 IIB: Caspase 8	Lymphadenopathy, splenomegaly, hemolytic anemia, thrombocytopenia, hypergammaglobulinemia

that some family members have only autoimmune thyroiditis. A mouse model with a knockin of this G228W point mutation in Aire recapitulates the disease seen in this family (17). Thus, Aire-associated mutations can also result in an autoimmune syndrome that differs from APS type I in phenotype and inheritance pattern.

Most studies looking at common, isolated autoimmune endocrinopathies, however, have not identified Aire as a susceptibility gene. Polymorphisms in Aire did not seem to be associated with isolated adrenal insufficiency (18), type I diabetes (19), or vitiligo (20). Additionally, the two most common mutations in Aire were not seen in a large group of patients with isolated adrenal insufficiency, type I diabetes, or autoimmune thyroiditis (21). One small study suggested an association between an Aire intronic polymorphism and systemic sclerosis and thyroiditis (22). Other studies have suggested an association between Aire polymorphisms and alopecia areata (23) and vitiligo (24). Larger scale studies will have to be done to validate these findings because these associations could be due to chance alone.

Pathophysiology of APS Type I

Aire is predominantly expressed in the thymus, suggesting an important role in immune regulation (25). Within the thymus, Aire is expressed in a subset of stromal cells known as medullary thymic epithelial cells (mTECs). mTECs have the unusual property of displaying a variety of peripheral self-antigens, including known autoimmune targets such as insulin and thyroglobulin (26–28) (Fig. 1*A*). This expression of peripheral self-antigens had been proposed to be important in allowing self-reactive T cells that recognize these self-antigens to be deleted. In this process, termed negative selection, T cells that recognize self-antigen in the thymus would be prevented from being released into the body and thus prevented from causing autoimmune disease. It was, therefore, hypothesized that Aire might be playing an important role in driving the expression of these peripheral self-antigens in mTECs.

Indeed, Aire-deficient mice, developed as a model of human APS type I, have decreased expression of a number of organ-specific self antigens in mTECs (29). Additionally, these mice also have defective negative selection of T cells in the thymus (30,31). Like humans with homozygous null mutations in Aire, these mice develop tissue-specific autoimmune disease in multiple organs. The autoimmune disease is characterized both by a lymphocytic infiltrate in the targeted organ and the presence of serum autoantibodies reactive against the targeted organ.

These data are consistent with a model in which self-reactive T cells in the thymus are normally removed from the T-cell repertoire (Fig. 1*A*). Aire plays an important role in the normal thymus in that it increases the expression of thymic self-antigens, and the presentation of these antigens drive the negative selection of self-reactive T cells (32). Without Aire, a number of self-antigens are no longer transcribed in mTECs and self-reactive T cells can escape into the periphery to cause autoimmunity (Fig. 1*B*). These self-antigens have been shown to be enriched for organ-specific self-antigens (29), perhaps explaining why APS type I patients develop a number of organ-specific autoimmune diseases.

More recently, Aire has been proposed to play an additional role in guarding against autoimmunity in extrathymic immune sites (33,34). Studies in a mouse that expresses a fluorescent tag in Aire-expressing cells showed that a unique subset of cells in the lymph node and spleen also express Aire (33). Like mTECs, these cells, termed extrathymic Aire-expressing cells (eTACs), are able to delete autoreactive T cells in a transgenic system. Furthermore, these eTACs, like mTECs, express a number of organ-specific antigens in an Aire-dependent manner. The antigens expressed in eTACs were nonoverlapping with mTECs, suggesting that these two cell types may have nonredundant functions and protect against a different repertoire of self-reactive T cells.

The mechanism by which Aire functions to up-regulate thymic self-antigen expression in mTECs remains to be fully elucidated. The Aire protein contains a number of domains that suggest that it plays a role in transcription (32). In particular, Aire contains two PHD (plant homeodomain) domains, which have recently been shown in a number of proteins to bind trimethylated histone H3 (H3K4me3) (35,36). Unlike the PHD domains in these other proteins, PHD1 in Aire seems to bind histone H3 in the unmethylated state (37,38). Despite this difference, this finding nevertheless suggests a link between Aire and chromatin pattern recognition. Additionally, Aire has been shown to bind to three proteins with described roles in transcription: 1) positive transcription elongation factor b (pTEFb) (39), 2) DNA-dependent protein kinase (DNA-PK) (40), and 3) cAMP response element-binding protein (CBP) (41,42). How these proteins interact together in Aire-mediated transcription remains to be determined.

Identification of Novel Autoantigens in APS Type I

Much headway has recently been made in identifying the autoantigens associated with the clinical features seen in APS type I. Utilizing sera from APS type I patients with hypoparathryoidism, investigators recently identified NACHT

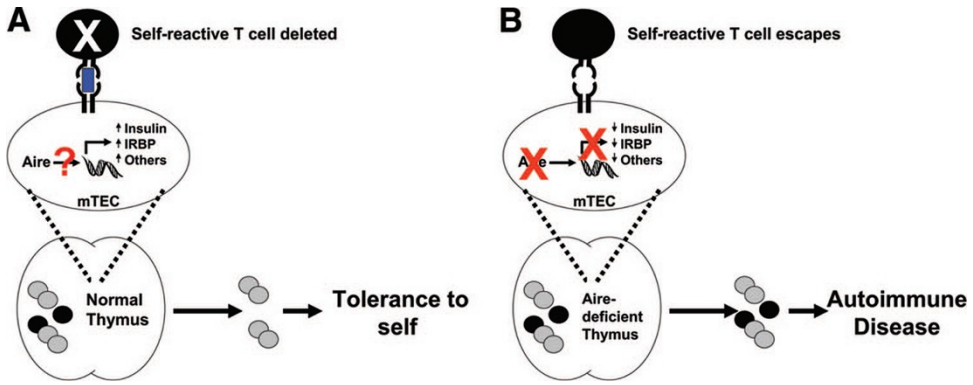

Figure 1. Negative selection of T cells in normal and Aire-deficient thymi. *A*, Thymic negative selection in the normal state. Progenitor T cells undergo T-cell receptor rearrangement in the thymus, which generates by chance a subset of self-reactive cells (*black circles*). These progenitor T cells undergo negative selection in the thymus to eliminate these self-reactive cells. In the normal thymus, mTECs express Aire, a putative transcription factor that drives the expression of a large number of organ-specific self-antigens. The expression of these self-antigens (*e.g.*, insulin, and IRBP) allows self-reactive T cells that recognize the self-antigens displayed on mTECs to be deleted. This negative selection of self-reactive T cells is a key element of self-tolerance. *B*, A defect in thymic negative selection in APS type I. Aire-deficient individuals do not up-regulate the expression of organ-specific self-antigens, thus preventing the deletion of self-reactive T cells that recognize these self-antigens. These self-reactive T cells can escape into the periphery and cause organ-specific autoimmune disease. *Gray ovals* represent T cells; *black ovals* represent self-reactive T cells.

(*NA*IP [neuronal apoptosis inhibitory protein], *C*IITA [MHC class II transcription activator], *H*ET-E [incompatibility locus protein from *Podospora anserina*] and *T*P1 [telomerase-associated protein]) leucine-rich-repeat and pyrin protein 5 (NALP5) as a parathyroid autoantigen (43). Autoantibodies to NALP5 seem to be present specifically in APS type I patients with hypoparathyroidism, making the autoantibody response against NALP5 a potential diagnostic marker for parathyroid involvement in APS type I. Whether Aire-deficient mice also share serum reactivity against NALP5 and whether NALP5 is Aire regulated in the thymus remain to be addressed.

In Aire-deficient mice, a number of antigens important in preventing organ-specific autoimmunity have been identified (44–46). Identification of these antigens in mice have played an important role in understanding the pathophysiology of APS type I. Interphotoreceptor retinoid-binding protein, IRBP, for example, has been identified as the antigen important in preventing eye autoimmunity (44). Remarkably, loss of expression of this antigen in the thymus results in eye autoimmunity in mice, demonstrating that lack of a single thymic antigen is sufficient to result in disease.

Interestingly, the presence of autoantibodies against type I interferon (IFN-α and ω) has been independently reported by five groups (6,47–49). In all five studies, there was a striking correlation (nearly 100%) between the presence of antitype I interferon antibodies and the presence of Aire mutations. Notably, patients heterozygous for the dominant negative G228W point mutation also demonstrated type I interferon autoantibodies (49). These antibodies seem to appear early in the disease course, thus making this a useful diagnostic tool in identifying APS type I patients.

The actual contribution of anti-interferon autoantibodies to APS type I has been the subject of much speculation. Type I interferons are important in defense against pathogens and adaptive immunity (50). Given that many APS type I patients present with mucocutaneous candidiasis, the possible role of anti-interferon autoantibodies in causing an immune dysregulation that results in this infection has been proposed (51). In support of this proposal, monocytes and dendritic cells from APS type I patients have been shown to down-regulate a number of genes that are known to be driven by interferon (52). Furthermore, sera from APS type I patients seem to down-regulate these genes in monocytes in a cell culture system. However, this hypothesis does not explain why APS type I patients are not more susceptible to other fungal or viral infections. Thus, further study will be needed to elucidate the role of these autoantibodies in disease pathogenesis.

The Role of Thymic Antigen Expression in More Common Autoimmune Diseases

The importance of identifying thymic self-antigens extends beyond understanding the pathogenesis of APS type I. In addition to APS type I, more common autoimmune diseases have also been linked to decreases in thymic antigen expression. In type I diabetes, decreased levels of thymic insulin expression are linked to disease. Polymorphisms in the Variable Number of Tandem Repeats region upstream of the insulin promoter result in variation in the amount of insulin expression in the thymus. Population studies show that alleles that result in higher levels of insulin expression in the thymus is associated with protection against the development of type I diabetes (53,54). This protection is thought to be conferred by the promotion of negative selection of T cells reactive to the autoantigen insulin. Furthermore, in mice, the loss of thymic expression of proinsulin 2 also predisposes to autoimmune diabetes (55).

An analogous situation occurs with the α chain of the acetylcholine receptor (CHRNA1) and Myasthenia Gravis. The relative thymic expression level of this antigen varies relative to a single nucleotide polymorphism in the promoter region. Additionally, increased expression of this thymic antigen is correlated with later age of onset of disease (56,57). Interestingly, a correlation seemed to exist between level of Aire expression and CHRNA1 expression in purified human mTEC samples, suggesting that Aire may play a role in thymic

expression of CHRNA1 in the thymus. *In vitro* studies also indicated that Aire is able to drive the expression of a CHRNA1 reporter construct.

Other Monogenic Autoimmune Diseases

IPEX. IPEX is a very rare X-linked disorder that results in a severe autoimmunity syndrome that is lethal in infancy unless treated with immunosupression (58) and/or bone marrow transplantation (59). This severe autoimmunity manifests as a constellation of diarrhea, dermatitis, diabetes mellitus, thyroiditis, and hemolytic anemia (Table 1) (60,61). Importantly, an exaggerated response to viral infections is seen, further suggesting an over-activation of the immune system in general.

In 2001, patients with the IPEX syndrome were found to harbor mutations in the Foxp3 gene (62,63). These patients were noted to have mutations in the same gene as scurfy mice, a mouse strain with severe autoimmunity and lymphoproliferation (64). Studies in mice have shown that Foxp3 plays an important role in the development and function of regulatory T (Treg; [65,66]) cells. This regulatory T-cell population has been shown to dampen immune responses in a variety of settings, including autoimmune diseases.

More recently, the pathogenesis of IPEX has been further defined. First, selective ablation of Foxp3-expressing cells in mice results in severe autoimmunity and lymphoproliferation, demonstrating that a decrease in the number of these Foxp3-expressing cells is sufficient to cause severe autoimmune disease (67). Second, the suppressive function of Tregs seems to depend on the expression of cytotoxic T lymphocyte antigen (CTLA)-4 by Tregs (68), because selective loss of CTLA-4 in FoxP3-expressing cells results in a severe autoimmunity. Third, loss of expression of interleukin (IL)-10 by Foxp3-expressing cells results in inflammation in the gut and lung (69), suggesting that expression of specific cytokines by Tregs may have specific, nonredundant functions.

A number of studies have investigated whether Treg defects can also contribute to more common autoimmune diseases. Although the loss of Treg cells due to Foxp3 mutations have been well linked to the IPEX syndrome, subtle changes in the number and function of Tregs in other more common, polygenic autoimmune diseases are less clear. For example, the role of Tregs in the pathogenesis of type I diabetes mellitus has been controversial. One article reported a reduction in the percentage of Tregs in CD4+ lymphocytes in patients with type I diabetes (70), whereas several others have reported no differences in Treg frequency between these patients and controls (71–73). Thus, the generalizability of decreased Treg numbers as a common pathogenic mechanism in autoimmune disease remains to be determined.

A syndrome related to IPEX has been described in two patients with mutations in the IL-2 receptor alpha (CD25) gene (74,75). The Foxp3 gene was found to be wild type in both of these patients. In one patient, homozygous mutations in CD25 resulted in defective secretion of IL-10 by CD4+ T lymphocytes (75). Because IL-10 is important in the down-regulation of inflammation, this finding suggests a possible mechanism by which homozygous mutations in CD25 may phenocopy IPEX.

ALPS. As its name suggests, ALPS is characterized by lymphadenopathy, splenomegaly, hypergammaglobulinemia, and autoimmune diseases (76). The autoimmune features often manifest as hemolytic anemia and thrombocytopenia, and can also include a number of additional autoimmune diseases such as hepatitis, uveitis, and vasculitis. Like APS type I and IPEX, the pathophysiology of ALPS was largely worked out utilizing a mouse model that phenotypically resembled patients with ALPS (76).

This mouse model, the MRL lpr/lpr mouse, played a key role in demonstrating that ALPS patients have a defect in the ability of their lymphocytes to undergo apoptosis. Patients with ALPS were noted to have an increase in double-negative T cells (developing T cells that have not yet expressed CD4 or CD8 on their cell surface) much like MRL lpr/lpr mice (77). Because MRL lpr/lpr mice have defective expression of Fas, a key mediator of apoptosis, ALPS patients were also suspected of having this defect (78,79). Indeed, subsets of patients were found to have heterozygous mutations in TNFRSF6, the gene encoding Fas (ALPS type Ia) (78) (Table 1).

Additionally, mutations in the Fas-mediated apoptosis pathway were also found (Table 1). A patient with Systemic Lupus Erythematosus and lymphoproliferation was found to have a mutation in the TNFSF6 gene encoding Fas ligand, the binding partner for Fas. This disease subtype was termed ALPS type Ib (80). Patients with ALPS type IIa have mutations in the gene encoding caspase 10, a protein downstream of Fas in the apoptotic pathway (81). ALPS type IIa patients seem to be distinguishable from the other subtypes in that they manifest a more severe lymphoproliferation and autoimmunity, and a resistance to apoptosis in both lymphocytes and dendritic cells is seen. Finally, patients with homozygous mutations in caspase 8, another downstream mediator of the apoptosis pathway, have been termed ALPS type IIb (82). Unexpectedly, however, these patients seem to have immunodeficiency rather than autoimmunity (83).

The mechanism by which defects in apoptosis results in autoimmunity still awaits clarification. The increased numbers of double negative T cells points to an aberrant contraction of the immune response. It has been postulated that lymphocytes that recognize self-antigens may be more dependent on Fas-mediated apoptosis than lymphocytes that recognize external antigen (82). This assertion, however, remains to be proven.

Summary

Despite the rarity of monogenic autoimmune diseases, these diseases have played an invaluable role in our understanding of the pathophysiology of autoimmune diseases in general. Mouse models of these diseases have been instrumental in unraveling the cellular and molecular pathways at play in these diseases. Out of these basic science advances may come more targeted diagnostic and therapeutic approaches to autoimmune diseases. An example of a promising antigen-targeted

therapeutic is the utilization of Tregs as a treatment for type I diabetes. In a mouse model for type I diabetes, transfer of a small number of antigen-specific Tregs could reverse disease (84,85). Similarly, studies in Aire-deficient mice and APS type I patients have resulted in the identification of new antigens that may be useful in the diagnosis and prediction of autoimmune disease. Taken together, these basic science advances in the study of monogenic autoimmune diseases are making major contributions to our ability to diagnose and treat patients with autoimmunity.

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