APECED: is this a model for failure of T cell and B cell tolerance?

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In APECED, the key abnormality is in the T cell defect that may lead to tissue destruction chiefly in endocrine organs. Besides, APECED is characterized by high-titer antibodies against a wide variety of cytokines that could partly be responsible for the clinical symptoms during APECED, mainly chronic mucocutaneous candidiasis, and linked to antibodies against Th17 cells effector molecules, IL-17 and IL-22. On the other hand, the same antibodies, together with antibodies against type I interferons may prevent the patients from other immunological diseases, such as psoriasis and systemic lupus erythematosus. The same effector Th17 cells, present in the lymphocytic infiltrate of target organs of APECED, could be responsible for the tissue destruction. Here again, the antibodies against the corresponding effector molecules, anti-IL-17 and anti-IL-22 could be protective. The occurrence of several effector mechanisms (CD4+ Th17 cell and CD8+ CTL and the effector cytokines IL-17 and IL-22), and simultaneous existence of regulatory mechanisms (CD4+ Treg and antibodies neutralizing the effect of the effector cytokines) may explain the polymorphism of APECED. Almost all the patients develop the characteristic manifestations of the complex, but temporal course and severity of the symptoms vary considerably, even among siblings. The autoantibody profile does not correlate with the clinical picture. One could speculate that a secondary homeostatic balance between the harmful effector mechanisms, and the favorable regulatory mechanisms, finally define both the extent and severity of the clinical condition in the AIRE defective individuals. The proposed hypothesis that in APECED, in addition to strong tissue destructive mechanisms, a controlling regulatory mechanism does exist, allow us to conclude that APECED could be treated, and even cured, with immunological manipulation.

Keywords: AIRE, APECED, endocrine disorders, interleukin 17, interleukin 22, IPEX, T regulatory cells

INTRODUCTION

Autoimmune polyendocrinopathy syndrome type 1 (APS-1) or autoimmune polyendocrinopathy–candidiasis–ectodermal dysplasia type 1 (APECED; OMIM 240300) is a rare recessively inherited disorder (Perheentupa, 2002; Betterle and Zanchetta, 2003; Perheentupa, 2006; Husebye et al., 2009). It is caused by mutations in the autoimmune regulator (AIRE) gene located on locus 21q22.3 (Bjorner et al., 1996; Nagamine et al., 1997; The Finnish–German APECED Consortium, 1997). APECED displays a worldwide distribution, but specific clusters of high prevalence of the disease are observed among Finns (1:25,000; Ahonen et al., 1990) and Sardinians 1 (1:14,500; Rosatelli et al., 1998; Meloni et al., 2012). It is characterized by the variable association of autoimmune endocrine (hypoparathyroidism (HP), Addison’s disease (AD), hypothyroidism, gonadal insufficiency, insulin-dependent diabetes mellitus, atrophic gastritis, and Biermer’s disease] and non-endocrine disorders (keratitis, malabsorption, vitiligo, and alopecia areata) and a specific predisposition to chronic mucocutaneous candidiasis (CMC). A definite diagnosis of APECED is made upon one of the following criteria: (i) the presence of at least two of three major clinical features: CMC, HP, and AD, or (ii) one disease component if a sibling has already a definite diagnosis, or (iii) disease-causing mutations in both alleles of the AIRE gene. However, APECED being highly variable in its presentation, the classical triad may be complete only after years of evolution and diagnosis may be therefore missed. Besides, APECED may appear during adolescence or in the young adult (Husebye et al., 2009). Therefore, criteria for a probable APECED have been defined as follows: (i) presence of one of CMC, HP, AD (before 30 years of age) and at least one of the minor components chronic diarrhea, keratitis, periodic rash with fever, severe constipation, autoimmune hepatitis, vitiligo, alopecia, ename
hypoplasia, (ii) any component and anti-interferon antibodies, or (iii) any component and antibodies against NACHT leucine-rich repeat protein 5 (NLRP5), AADC, tryptophan hydroxylase (TPH), or TH (Huizhong et al., 2019).

**FROM CIRCULATING AUTOIMMUNE ANTIBODIES TO AIRE, FOXP3, APECED, AND IPEX**

Our knowledge of the nature of the condition now called APS-1 or APECED has increased simultaneously with the general development of immunology and autoimmunity. Since the condition was clearly defined in the end of 1950s and early 1960s, the characteristic clinical picture, the immunological abnormalities and the relationship to other autoimmune endocrine diseases were defined in late 1960s and early 1970s. Furthermore, the genetics of APECED, and the fact that the syndrome was caused by a recessive gene defect – as opposed to the HLA-linked genetics seen in the other similarly occurring endocrine diseases – were characterized in the 1980s and the target antigens in the organs affected by APECED were molecularly defined in 1990s. A landmark stage in the study of APECED was reached in 1997, when the long sought APECED gene was cloned by two independent groups (Nagamine et al., 1997; The Finnish–German APECED Consortium, 1997). Finally, a new phase in APECED research occurred during the first decade of the twenty-first century, when the autoantibodies toward soluble mediators if immune response were characterized (Meager et al., 2006; Kisand et al., 2011).

The notion that several diseases affecting endocrine organs and earlier defined as idiopathic, were in fact caused by an autoimmune response toward self antigens, became apparent when novel immunological methods became available in the 1950s and early 1960s (Blizzard et al., 1963; Irvine et al., 1965) and intrinsic factor (IF) in pernicious anemia (Schwartz, 1961; Jeffries et al., 1962), with thyroid epithelium, HP, and AD that were later judged to be the hallmark of the three conditions, immunological methods became available in 1950s and early 1960s. The association of the three conditions, characterized by producing immunoregulatory FOXP3+ T cells, which prevent autoreactive T cell clones escape into the periphery 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. Collectively, several studies in mouse and man have shown that AIRE regulates thymic expression of several genes of ectopic peripheral proteins including many TRAs. Thus, AIRE dysfunction leads to a decrease in the expression of TRAs in the thymus, and consequently, autoreactive T cell clones escape into the periphery (Dobrinski et al., 2005; Morais-Vasconcelos et al., 2008; Gardner et al., 2009; Fierabracci, 2011).

The most common AIRE mutation, the “Finnish mutation,” R257X, affects 82% of Finnish APECED alleles (Nagamine et al., 1997; The Finnish–German APECED Consortium, 1997). Interestingly, this mutation occurs also in 70% of the Russian APECED patients studied (Olova et al., 2010). The same mutation, R257X, was also detected in Swiss patients on a different haplotype with closely linked polymorphic markers (Nagamine et al., 1997) and in...
| Diagnosis | Clinical findings | Autoantibodies | HLA | Gene defect | Cellular immune response |
|-----------|------------------|----------------|------|-------------|-------------------------|
| APECED (APS-1) | Candidiasis and multiple failure of most endocrine organs and non-endocrine autoimmunity | Against all affected organs | No association (?) | Close to 100 mutations described in the AIRE gene | CTL against affected organs? Failure in Treg population |
| APS-2 | Addison’s disease with insulin-dependent type I diabetes or thyroid diseases | Against adrenal cortex, pancreatic beta cells, thyroid | Risk haplotypes HLA DR3: DRB1*0301, DQA1*0501, DQB1*0201 DR4 DR1, DR2 DR13, and DR14: protective | No single gene defect | CTL against affected organs? |
| Addison’s disease | Low levels of glucocorticoids | Against P450c21, P450sccc | HLA-DRB1-DQA1-DQB1 | No single gene defect | CTL against affected organs? |
| IPEX | Enteropathy, diabetes skin disease (mainly eczema), failure to thrive, thyroiditis, recurrent infections | Against enterocyte (autoimmune enteropathy-related 75kDa antigen) pancreatic islet cells, insulin, and glutamic acid decarboxilase (GAD), and thyroid (antithyroid microsomal antibody) | Defective FOXP3 gene | Impaired function of regulatory T cells, defective IL-2, IFNγ, and TNFα production. Increased production of IL-17 |
northern Italian APECED patients. Nonsense mutation R139X was found as the predominant haplotype among Sardinian patients (18/20 independent alleles; Rossetti et al., 1998). Other hotspots have been identified such as the Y85C missense mutation in an isolated Iranian Jewish community (Zlotogora and Shapiro, 1992; Björses et al., 2000). A 13-bp deletion in exon 8 [1085–1097(del)] is ubiquitous and can be found in Norwegians, but also Anglo–Saxons descendant (Zlotogora and Shapiro, 1992) and south Americans (Moraes-Vasconcelos et al., 2008). Today, over 60 different mutations have been described throughout the coding region of AIRE (Akirav et al., 2011).

**CLINICAL PICTURE OF APECED**

The clinical picture of APECED is characterized by sequentially occurring diseases, with great variation among the patients as to the severity and time course of the various conditions. In most cases, the affected individual starts suffering from CMC in early infancy or childhood. In most cases, the next organs to be affected are the parathyroid glands, followed by AD at puberty, hypogonadism mainly in female teens or young adults. Additional clinical features are less common, and include diabetes type I, hypothyroidism, atrophic gastritis with or without pernicious anemia (Biermer’s disease), cutaneous manifestations (alopecia areata, vitiligo, transient skin rash during fever episodes, non-infectious nail dysplasia), ocular symptoms (keratoconjunctivitis, dry eye, iridocyclitis, cataract, retinal detachment, and optic atrophy; Merenemies and Tarikkanen, 2000), enamel dysplasia, hypoplasmenism/asplenia (implying vaccination against Streptococ- cus pneumonia, Haemophilus influenzae, and Hepatitis B as well as antibiotic prophylaxis), autoimmune hepatitis, tubulo-interstitial nephritis, or organized pneumonitis. Involvement of the gastrointestinal (GI) tract may be responsible for chronic diarrhea, constipation, and malabsorption leading sometimes to malnutrition. GI involvement is difficult to assess as it can be due to numerous various causes that may be associated or follow each other during the life of the patients.

**CANDIDIASIS**

Chronic mucocutaneous candidiasis infection by *Candida albicans* is one of the major characteristic of APECED, usually one of first symptoms and most likely the most disabling features of APECED. CMC is naturally not specific for APECED but any child with CMC should be suspected of APECED. According to the Finnish experience, almost all adults with APECED display symptoms of CMC, up to 78% of the patients at the age of 10, up to 94% at age of 20, and 97% at the age of 30 (Perheentupa, 2002, 2006; Betterle and Zanchetta, 2003, Husebye et al., 2009). However, the course and severity vary widely. Oral candidiasis affects the tongue, the buccal mucosa, the gingival, and the pharynx. It ranges in severity from mild form with redness, soreness, angular cheilitis, pseudemembranous lesions, erosions, ulceration and pain to severe chronic inflammation with dysphagia, and development of hyperkeratotic plaques. In the absence of active antifungal treatment and careful follow-up, chronic oral candidiasis may lead to the development of squamous cell carcinoma with potential lethality by metastatic dissemination. Candida esophagitis has been reported to affect 15–22% of the patients (Perheentupa, 2012; Kusand et al., 2011) with pain while swallowing, retrosternal pain, and dysphagia (Ahonen et al., 1998; Husebye et al., 2009). Chronic esophagitis can lead to local stricture and exceptional esophageal cancer (Rautema et al., 2007).

Intestinal candidiasis may cause chronic diarrhea. It should be stressed that esophageal and intestinal candidiasis may occur without any active oral candidiasis. Genital candidiasis affects mainly women with pruritus and vaginal whitish discharge while genital candidiasis seems less frequent in males, possibly underreported due to discrete signs of balanitis. Lastly, Candida may affect the nails with chronic paronychia and onychomycosis (Collins et al., 2006). Fingernails are more commonly affected than toenails and the thumbs are the commonest digit affected. This can be explained as infection occurs during the “thumbsucking” period. Management of candidiasis in APECED patients implies an excellent oral hygiene with a careful and regular dental follow-up. Candidiasis should be treated aggressively with antimicrobial therapy and regular prophylaxis should be given.

Any clinically suspicious, chronic thickening or erosion of the mucosa that does not heal should be biopsied to rule out a potential underlying lesion of squamous cell carcinoma. Any difficulties in swallowing or eating or retrosternal pain should prompt to perform esophagoscopy (Rautema et al., 2007).

**HYPOPARATHYROIDISM**

Hypoparathyroidism is one of the first endocrine features of APECED. Symptoms are related to hypocalcemia, muscle cramps, parathesia, clumsiness, seizures, and diarrhea. The diagnosis is simply based on blood calcium, phosphorus, and parathormone (PTH) levels: hypocalcemia, hyperphosphatemia, inadapted normal/low PTH without any kidney failure. It is considered that APECED should be systematically considered in cases of primary HP (Husebye et al., 2009). Antibodies against NALP5 as well as...
against the calcium-sensing receptor of parathyroid epithelial cell
have been identified in APECED patients (Gavalas et al., 2007; 
Kemp et al., 2009, 2010). Patients who are free of HP need an 
annual monitoring of blood calcium and phosphorus levels. Man-
agement of HP relies on daily oral supplementation of vitamin D 
derivatives and calcium.

**GASTRITIS AND PERNICIOUS ANEMIA**

Chronic gastritis, with or without concomitant pernicious anemia 
belongs to the APECED complex but is found only in a fraction of 
cases. In non-APECED population, two types of chronic gastritis 
occurred, divided by Strickland into type A and B gastritis. Type A 
gastritis was known to be caused by autoimmune and the B gastritis 
was suspected to be the results of environmental factors. In 
early 1980s, it was shown by Warren and Marshall (1984) that 
the major environmental factor was in fact a chronic infection with 
Helicobacter pylori.

The type A chronic gastritis, with and without pernicious ane-
mia that occur in non-APECED individuals, is clearly linked 
to certain HLA risk haplotypes, in analogy to isolated AD. In 
APECED patients, the chronic gastritis differs from the above 
also in time of occurrence and the speed of the progression. In 
non-APECED patients, the time needed for progression from the 
early stage of gastritis, the superficial form to diffuse gastritis, to 
atrophic gastritis and to full gastric atrophy is a slow process, taking 
up several decades. Also, the process usually starts in the adult 
life. In contrast, an APECED-associated gastric process is much 
faster and can start in the first decade of life. Thus, one of 
the authors of this review was able to follow such a gastric process 
in two 8-year-old girls with sequential gastric biopsies and could 
see how, within the time period of only 2 months, the superficial 
process lead to complete gastric atrophy of the fundus and corpus 
(K. Krohn, personal experience).

The target molecule for the parietal cell antibodies were shown 
to be the sodium-potassium channel molecule of the parietal cells 
on corpus and fundal part of the stomach (Karlsson et al., 1988). 
In antral gastritis, the antigen are the gastrin-producing cells 
(Ulbo and Krohn, 1994).

Pernicious anemia is the end stage of the gastric immunological 
destruction, caused partly by the lack of IF; that in addition to the 
hydrochloric acid is the main product of parietal cells, but also by 
the autoantibodies recognizing this vitamin B12-binding protein. 
There are two types of antibodies to IF: one blocking vitamin 
B12 binding to IF and another type, binding to the IF molecule 
without interfering with vitamin B12 binding (Tob et al., 1997). 
Both antibody types prevent the binding of IF to its receptor on 
the ileal mucosa and subsequent translocation of the vitamin B12 
from ileum to circulation.

**ADDISON’S DISEASE**

Adrenocortical failure or AD, described by Thomas Addison in 
the nineteenth century, is considered one of the three hallmarks 
of APECED, but it occurs also as a solitary disease, or as part of 
the APS-2 complex. Today, in western word, most cases of AD 
are caused by autoimmunity, but adrenal cortical destruction and 
subsequent cortical failure can be caused by several other factors, 
notably by secondary tuberculosis or other chronic infections. In 
retrospect, the cases described by Thomas Addison was most 
likely caused by tuberculosis.

The clinical signs and symptoms of AD are mostly similar in 
APECED and in solitary AD as well as in APS-2 complex. These 
include decreased levels of gluco- and mineralocorticoids and ele-
vated ACTH concentrations. The most severe consequence of AD 
is the life-threatening Addisonian crisis, characterized by general 
fatigue, dizziness, diarrhea, and death, if the patient is not quickly 
substituted with corticosteroids, mainly hydrocortisol.

Autoantibodies to adrenal cortex are the characteristic 
immunological feature in AD, be it part of APECED or APS-2 
or the solitary form. These antibodies can be easily demonstrated 
by immunofluorescence. However, in APECED, but not in the 
other forms of AD, the autoantibodies are precipitating, and this 
phenomenon can be demonstrated by Ouchterlony’s immunod-
iffusion (Andrada et al., 1968; Krohn et al., 1974; Heinonen et al., 
1976). In immunodiffusion with APECED serum against adrenal 
homogenate three precipitating lines were observed, and one of 
these were shown to represent a mitochondrial antigen while the 
two others were microsomal.

The nature of the adrenal cortical autoantigens were revealed 
early 1990s and shown to be the three main steroidogenic 
enzymes, CYP11A1, CYP17, and cytochrome p450 side-chain cleavage enzyme 
(CYP17), and cytochrome p450 17α-hydroxylase (CYP17A1).

In males, testicular failure is less common and occurs later. 
The prevalence of hypogonadism in males is three times lower 
(8–28%) than in females (35–70%; Perheentupa, 2008). It leads to 
clinical hypogonadism or isolated azoospermia (Hausenloy et al., 
2009). It has been hypothesized that the blood-testis barrier 
protects the Leydig cells from an autoimmune attack. However,
Various other endocrine disorders have been described such as diabetes mellitus, hypothyroidism, and pituitary failure, the latter diagnosed by a growth hormone deficiency. The diagnosis and management of these conditions does not differ from the standard guidelines for each disorder separately (Perheentupa, 2002; Betterle and Zanchetta, 2003; Husebye et al., 2009).

Enamel hypoplasia affect mainly permanent teeth (Perheentupa, 2002, 2006; Pavlic and Waltimo-Sirén, 2009). Pavlic and Waltimo-Sirén (2009) recently suggested that an inadequate process of enamel formation might affect all ameloblasts in phase. Ameloblasts have an epithelial origin with parenchymal cells of odontogenic origin. It is speculated that ameloblasts or secreted protein in the extracellular matrix may be the target of autoantibodies leading to hypoplasia. Thereby, APECED would be the first model of dental hard tissue autoimmune disease (Pavlic and Waltimo-Sirén, 2009).

Ocular manifestations affect 25% of the patients and include mainly keratitis that can lead to blindness. It is asumed that the origin of keratitis is the result of autoimmunity against corneal epithelium (Meremmies and Tarkkanen, 2000; Perheentupa, 2006). However, to our knowledge no specific antibodies have been identified in APECED patients. Only antibodies against ORBP1 have been found in the AIRE mouse model against lacrimal glands (DeViss et al., 2010).

Hypersplenism or asplenia is often diagnosed upon the development of thrombocytosis, circulating Howell-Jolly bodies, abdominal ultrasound imaging or in case of severe S. pneumoniae infection (Pollak et al., 2009). Destruction of the spleen in APECED has been related to an autoimmune attack against the spleen (Perheentupa, 2002, 2006; Betterle and Zanchetta, 2003; Husebye et al., 2009) although the exact mechanism remains obscure. Again, the mechanisms proposed by Schaller et al. (2008) and by Matsumoto (2011) are of interest, as AIRE expression has also been described in lymphoid tissue and skin. A speculative hypothesis to the evolution of splenic atrophy could thus be disturbance of differentiation, due to lack of AIRE expression.

Various types of GI manifestations are common in APECED patients. These include chronic diarrhea that can be related to HP; severe constipation. Intestinal infection by candida and giardia especially, pancreatic insufficiency and autoimmune enteropathy. Several autoactive circulating antibodies directed toward intestinal components have been described. Ekwall et al. (1998) identified TPH as an intestinal autoantigen in APECED patients. TPH is expressed in serotonin-producing cells in the central nervous system and in the intestine. In their series of 80 patients, they were able to relate “GI symptoms” to the presence of circulating TPH antibodies and also to the total absence of enterochromaffin cells in the mucosa of small bowel. These enterochromaffin cells (EECs) are scattered through the intestinal mucosa, from the gastric body and antrum to the rectum. They play a key role in growth of the gut, blood flow, motility, secretion of pancreatic enzymes, bile, and bicarbonate-rich fluid (Posovszky et al., 2012). TPH antibodies were found in 89% of the APECED patients with GI symptoms and in 34% of those without (Ekwall et al., 1998). Antibodies can precede clinical symptoms (Ekwall et al., 1998). Conversely, TPH autoantibodies are absent in other inflammatory or autoimmune intestinal diseases. Additionally, SkoldBerg et al. (2003) identified also autoantibodies against histidine decarboxylase expressed by EEC – like cells in the gastric mucosa. It is noteworthy, that it is not a routine procedure to perform EECs staining on intestinal biopsies in case of diarrhea or malabsorption, as stressed by Ohise et al. (2009). Besides, several studies showed repeatedly that EECs were lacking in the intestinal mucosa and were related to chronic diarrhea (Padeh et al., 1997; Ward et al., 1999; Oliva-Hemker et al., 2006; Posovszky et al., 2012).

Tubulo-interstitial nephritis, life-threatening autoimmune broncholitis and other rare manifestations have also been reported in APECED (Perheentupa, 2002, 2006; Betterle and Zanchetta, 2003; Husebye et al., 2009). The main identified autoantibodies are summarized in Table 2.

**TREATMENT**

Management of APECED relies in education of the patients to know his disease, education of the local physician, and the knowledge that new components of the disease may develop during life. Psychological support is strongly recommended as this disease impairs greatly the quality of life of the patients (Perheentupa, 2006). Except candidiasis treatment that has been explained previously, treatment of APECED relies mostly on hormone replacement therapy according to affected organs (thyroid, parathyroid, pancreas, etc.). In some rare and potentially lethal situations, however, patients may require corticosteroid treatment in association with immunosuppressive therapies. These rare situations include autoimmune hepatitis, especially its fulminant form, which may be lethal and therefore prompt immunosuppressive therapy is needed (Obermayer-Straub et al., 2001). The same is true for intestinal nephritis and broncholitis in association to APECED. Immunosuppressive therapies have been also proposed in case of severe intestinal malabsorption with efficacy (Padeh et al., 1997; Ward et al., 1999). Very recently, Rituximab, a chimeric monoclonal antibody targeting B cell lymphocytes

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**OTHER NON-ENDOCRINE DISORDERS**

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Table 2 | Main identified target of autoimmune antibodies in APECED patients.

| Diagnosis             | Main identified circulating autoantibodies                                                                 |
|-----------------------|-----------------------------------------------------------------------------------------------------------|
| Addison’s disease     | 21-hydroxylase, 17a-hydroxylase                                                                          |
|                       | Side-chain cleavage enzyme antibodies (or steroid cell antibodies)                                        |
| Hypoparathyroidism    | NALP12, Ca2⁺ sensing receptor                                                                          |
| Hypothyroidism        | Thyroglobulin                                                                                           |
| Hypogonadism          | 17a-hydroxylase                                                                                         |
|                       | Side-chain cleavage enzyme antibodies (or steroid cell antibodies)                                       |
| Diabetes type I       | Glutamic acid decarboxylase 65-kDa isofrom (GAD65)                                                       |
|                       | Insulin                                                                                                  |
|                       | Tyrosine phosphatase (IA2)                                                                             |
| Pituitary insufficiency| Tudor Domain containing protein 6 (TDRD6)                                                                |
| Atrophic gastritis/    | Intrinsics factor, gastric parietal cell                                                                  |
| Biermer’s disease     | Glutamic acid decarboxylase 65-kDa isofrom (GAD65)                                                       |
|                       | Histidine decarboxylase                                                                                 |
|                       | Tyroptahin hydroxylase                                                                                 |
| Autoimmune hepatitis  | Aromatic L-amino acid decarboxylase (AADC)                                                              |
|                       | Cytochrome P450 1A2                                                                                     |
|                       | Cytochrome P450 1A6                                                                                     |
|                       | Cytochrome P450 1A1                                                                                     |
|                       | Cytochrome P450 286                                                                                    |
| Vitiligo              | Transcription factors: SOX 9, SOX 10, aromatic                                                          |
|                       | L-amino acid decarboxylase (AADC)                                                                       |
| Alopecia areata       | Tyrosine hydroxylase                                                                                     |
| Nephropathy           | Antibody against tubular basement membrane (Harrigan et al., 1996)                                      |
| Pulmonary disease     | Potassium channel regulatory protein (KCNRG)                                                            |
| Eye                   | POTP1                                                                                                    |
| Non-tissue specific** | FN1α, FN1β, FN1γ, FN1αβ, IL-22, IL-17F, IL-17A                                                           |

*Identified in a mouse model AIRE** – **Main non-tissue-specific antibodies according to Kisand et al. (2011).

expression CD20 has been successfully used in a young patient with bronchialitis (Popler et al., 2012). The rationale for Rituximab use in APECED is supported by the presence of B cell infiltrates in the affected organs (Gavanescu et al., 2008).

AUTOANTIBODIES TOWARD INTERFERONS AND CYTOKINES

At the beginning of this millennium, the antibody responses to the major target organs affected in APECED, and the responsible target antigens were fairly well characterized. A new period in APECED studies started along the publication by Meager et al. (2006), describing high-titer antibodies to several type I interferons in practically all APECED patients studied. This anti-interferon response was exceptionally strong, since serum titers up to 1:1,000,000, and clearly exceeding the titers seen against organ-specific antigens, were found.

Furthermore, high-titer antibodies were seen against the two main mediators secreted by Th17 cells, interleukin-17 and interleukin-22 (IL-17 and IL-22). Responses with lower titers were occasionally seen against other interleukins, too. In our own as yet unpublished observations we have detected occasional high-titer responses against several other interleukins and chemokines, as well, but in contrast to the aforementioned responses, these responses are not characteristic to all APECED patients but rather occur occasionally in only a few patients.

The significance of these novel findings is still unclear, but some information concerning the role of IL-17/IL-22 antibodies in the chronic candida infections, characteristic for APECED, has been obtained. Th17 cells secrete IL-17 and IL-22, which are cytokines with potent antifungal properties (Engelhardt and Grimbacher, 2012) and the occurrence of autoantibodies against IL-17/IL-22 were reported to closely correlate to the presence of candida infection (Kisand et al., 2011; Engelhardt and Grimbacher, 2012). However, recent evidence points to a new interaction between AIRE and delin-1, a pattern-recognition receptor that is important in antifungal innate immunity. Pedrosa et al. (2012) recently showed that AIRE participates in the delin-1 signaling pathway, and thus, missing AIRE activity could contribute to fungal susceptibility through this pathway. Delin-1 is expressed on phagocytes and was recently shown to induce a non-canonical caspase-8 inflammasome response to fungal and mycobacterial infection (Girghith et al., 2012). The activation of the delin signaling pathway also leads to expression of IL-17 and 22 and defenses, however. Besides, other mechanisms such Dominant-negative mutations in STAT3, gain of mutation of STAT1, mutations in IL-17F and IL-17R may be alternate causes of CMC (Engelhardt and Grimbacher, 2012).

The significance of the antibody response toward interferons and other cytokines is presently also unclear. One could speculate that some of these antibodies against type I interferons as well as reacting with IL-17 and IL-22 might have a protective function. As pointed out by Waterfield and Anderson (2011), antibodies to type 1 interferons do not seem to lead to increased susceptibility to viral infections. This resistance might be due to redundancy and it has to be seen whether this anti-interferon response is directed only toward certain members of the interferon family.

While Th17 cell response and the release of soluble IL-17 and IL-22 are evidently necessary for the defense against mucocutaneous candida infection, the same cytokines have a role in the development of psoriasis. Similarly, interferons are known to be involved in the pathogenesis of several conditions, and one such chronic ailment is the autoimmune diseases belonging to the systemic lupus erythematosus (SLE) complex. Anti-interferon alpha antibodies are currently being tested as a therapeutic mean against SLE (Merrill et al., 2011). In order to be able to find out if the antibodies against interferons and other cytokines could have a protective role in APECED, large APECED patient cohorts have to be studied in order to find out whether, e.g., psoriasis and SLE are...
significantly less common in APECED patients than in the general population.

The reason for the antibody response toward soluble immune mediators is still unclear, and we do not yet know what exactly elicits them and thus, only speculative scenarios can be presented. It is conceivable to hypothesize, however, that the tissue destruction preceding the failure of the endocrine organs may have a role. Tissue destruction, be it caused by trauma, viral infection or autoimmune attack, would probably lead not only to the release of potential tissue-specific autoantigens and thus, to autoantibody formation against these proteins, but could also lead to an inflammatory response and production of several mediators of inflammation. One key group of molecules in this respect is the acute-phase proteins, notably those belonging to the IL-1 group.

It is generally believed that the destruction of the endocrine organs in APECED is caused by the autoimmune CD8+ cytotoxic T cells, although definitive evidence for this mechanism is still lacking (Bettele and Zanchetta, 2003; Moraes-Vasconcelos et al., 2008). This hypothesis is reinforced by the examination of microscopic examinations of samples, sometimes obtained post-mortem. Indeed, parathyroid, adrenal glands, or ovaries pathology disclosed also atrophy and lymphocytic infiltration that suggest lymphocytic aggression of the organs leading to atrophy and dysfunction (Bettele and Zanchetta, 2003). This is also stressed, indirectly, by the analysis of the AIRE-deficient mouse model, who develop also a lymphocytic infiltration in some inner organs along with atrophy (Ramsey et al., 2002).

However, cell destruction caused by an immune response against the endocrine organ would in fact lead to a similar situation that is thought to happen in viral infections. In fact, several autoimmune diseases, such as diabetes type I or chronic autoimmune liver diseases are thought to be a consequence of preceding viral infection: enterovirus infection in the case of diabetes type I and hepatitis B in the case of chronic active hepatitis. In viral infections, a specific group of intracellular regulatory molecules, TRIMs (tripartite motif-containing proteins), have been shown to have a key role in eliciting an autoimmune or auto inflammatory consequence (Jeffries et al., 2011).

The TRIM protein family is a form of RING domain containing E3 ligases and they exert a variety of biological functions, related to immunity and inflammation (Jeffries et al., 2011). Specifically, of the more than 20 different TRIM proteins, some seem to up-regulate the expression of type I interferons and proinflammatory cytokines, notable interleukin-1beta (IL-1beta). Furthermore, the same mediators of immune response and inflammation are in some cases known to up-regulate the expression of TRIMs. Thus, a vicious circle can theoretically occur and this in turn could lead to autoimmunity. So far, overexpression of TRIMs, or an autoimmune response toward them, has been shown to be linked to autoimmune and autoinflammatory processes in Sjögren’s syndrome or rheumatoid arthritis (Jeffries et al., 2011).

Presently, we have no information how the occurrence of autoantibodies toward the interferons and other mediators of immune response might affect the aforementioned vicious circle, but it is conceivable to speculate that such an antibody response could have an balancing effect. One could thus form a hypothesis, that in APECED, the primary defect outside thymus, where the autoreactive T cells are not destroyed, would be the cell destruction of the endocrine organs by cell-mediated immune response, followed by release of cellular components taken up by professional antigen presenting cells and further stimulating the activation of CD4+ Th-cells and finally resulting in an autoantibody response toward these organ-specific antigens. However, simultaneous over-expression of TRIMs and subsequent up-regulation of a variety of soluble mediators of immune response and inflammation, such as interferons and members of the IL-1 family would lead to autoantibody formation also against these cytokines. Lastly, one reason for the break of tolerance to immune mediators, and subsequent production of autoantibodies could be related the fact that AIRE expression seems to occur, in addition to thymic epithelial cells also outside thymus, notably in dendritic cells, that normally express also such mediators (Health and Carbone, 2009).

The consequences of such cytokine-directed antibody response are still an open question. In case of the Th17 type interleukins (IL-17 and IL-22) there is convincing evidence that such antibod-

### CELL-MEDIATED IMMUNE RESPONSES

Although it is now a generally accepted view that the consequence of the AIRE-defect in APECED will lead to the escape of the potentially autoaggressive T cells, there is in fact rather little direct evidence to show that the tissue destruction in the endocrine organs affected in APECED is caused by cytotoxic CD8+ T cells. Furthermore, most studies describing the phenotype of the lymphocytes infiltrating affected organs is not from APECED patients directly, but from patients suffering of solitary lesions that are similar to the ones seen in APECED, such as solitary AD or diabetes. However, the solitary endocrine diseases, such as isolated thyroid disease or AD are remarkably similar in their clinical picture as well as immunological findings as those of APECED. Thus, in solitary AD and in APECED with adenocortical failure, autoantibodies recognize the p450c21 steroidogenic enzyme. Interestingly, in this disease complex CD8+ T cells that reach against specific T cell epitopes in p450c21 has been demonstrated (Bratland et al., 2009; Rottembourg et al., 2010) Likewise, in thyroid diseases, thyroglobulin and thyroid peroxidase are recognized by the autoantibodies, irrespective if the condition is occurring alone, in association of APS-2 or as part of the APECED complex. The similar synergism in terms of the nature of autoantigens occurs in chronic immunological liver diseases, too.

In chronic aggressive hepatitis the lymphocytic infiltrating cell population has been shown to be of the CD8+ lineage (Si et al., 1984). In a murine model of Graves’ disease, the CD8+ cell population contains also the recently identified CD8+CD122+ T cells that are functionally similar to the CD4+CD25+ regulatory T cells (Ryan et al., 2005). Furthermore, studies in thyroid and
other affected organs show that one of the main cell population in the lymphotic infiltrate are in fact the CD4+ Th17 cells that secrete as effector molecules, the cytokines IL-17 and IL-22. In experimental autoimmune disease, the balance between the Th17 effector cells and the regulatory T cells, CD8+CD122+ and CD4+CD25+, seems to regulate both the occurrence and severity of tissue destruction and functions. 

There could thus be two distinct mechanisms operating in the pathogenesis of autoimmunity in the endocrinopathies: one mediated by soluble effector molecules, such as IL-17 and IL-22 as well as type I interferons, and another one mediated by effector T cells, which are either of the CD8+ CTL cell or of the Th17 effector cell lineage. To counteract these, again two distinct biological processes would occur to the production of new cells and to the emergency of the regulatory T cells. As to the regulatory T cell response, it is to note that one key immunological failure in APECED is the dysregulation of the T cell maturation (Ryan et al., 2005; Kekäläinen et al., 2007; Saitoh et al., 2007; Laakso et al., 2010, 2011; Wolff et al., 2010).

In normal thymus, Treg maturation follows a preprogrammed scheme, and the immature CD8+CD4+FOXP3+ seems to be prone to apoptosis, whereas the more mature form CD4+CD8+FOXP3+ cells form the active Treg population (Lehovtova et al., 2009). According to Endharti et al. (2011) the CD8+CXCR3+ Tregs in humans are functionally similar to murine CD8+CXCR3+ Treg. Furthermore, in APECED patients the recent thymic emigrant (RTE) pool of T cells shift to the activated pool and the RTE reservoir is depleted. Most importantly, in APECED patients these cells express less FOXP3 than in the healthy controls (Laakso et al., 2010). Thus, in APECED the newly formed Treg cells have a developmental defect and their function is therefore impaired. Data concerning the CD8+ regulatory T cells in APECED patients is missing, however.

The finding that the regulatory T cell population in APECED is functionally defective and that the expression of the key molecule for Treg function, the FOXP3, is impaired, is consistent with clinical findings in IPEX syndrome, caused by a defect in the function of the FOXP3 gene. However, it should be noted that the expression of FOXP3 mutations in Treg population also in IPEX patients is highly variable. Also, in contrast to APECED there seems to be a genotype-phenotype correlation in IPEX, as different mutations are associated in variable clinical picture, that show differences in severity as well as the types of clinical components that are present (Torgerson et al., 2007; d’Hennezel et al., 2009) A consistent finding in IPEX is however the inability of the CD4+CD25 high Tregs to suppress the function of autologous effector T cells (Bacchetta et al., 2008). There are, thus, several differences in the clinical picture of APECED and IPEX, but both conditions show clear immune destruction of at least some endocrine organs. Both conditions also share some similarities in the GI symptoms.

The proposed hypothesis that in APECED both tissue destructive mechanisms and controlling regulatory mechanisms exist raises a question whether APECED could be treated or even cured by immunological manipulations. To find an answer for this question is one of the further challenges for APECED research.

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REFERENCES

Aikens, P., Kanduri, S., Spyla, L., and Perhoentupa, J. (1990). Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 16 patients. N. Engl. J. Med. 322, 1829–1836.

Akira, S., Uematsu, S., and Takeda, K. (2006). Toll-like receptor signalling. Nat. Rev. Immunol. 6, 499–511.

Andrada, J. A., Bigazzi, P. L., Andrada, M. A., Romo, G., and Chance, P. F. (2000). X-Linked syndrome of polyendocrinopathy, immune dysfunction, and diabetes maps to Xp11.23–Xp11.3. Am. J. Hum. Genet. 67, 222–231.

Bacchetta, C., and Zanchetta, R. (2003). Aire in human autoimmune disease. Am. J. Hum. Genet. 73, 725–733.

Bennett, C. L., Yoshioka, R., Kiyokawa, A. O., Shigeoka, A., and Chance, P. F. (2006). Clinical relevance of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome. Am. J. Med. 119(Suppl. 1), 37–50.

Bennet, C. L., Yoshioka, R., Kiyo-oka, A., Shigeoka, A. O., and Chance, P. F. (2008). The role of FOXP3 mutations. Nat. Rev. Immunol. 8, 1535–1541.

Björses, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (2000). Mutations in AIRE cause APECED. Am. J. Hum. Genet. 67, 1829–1836.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (1999). Genotype homogeneity of autoimmune polyendocrine disease type 1. J. Clin. Endocrinol. Metab. 84, 1171–1172.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (2000). Mutations in the AIRE gene: effects on subclassical location and transcription function of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protein. Am. J. Hum. Genet. 67, 378–392.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (1999). Genotype homogeneity of autoimmune polyendocrine disease type 1. J. Clin. Endocrinol. Metab. 84, 879–886.

Bratlid, E., Skinningsrud, B., Uvdal, D. E., Menné, E., and Husebye, E. S. (2001). Human monocytes respond to matrix metalloproteinase-9 by increasing haptoglobin production and decreasing haptoglobin cDNA expression. J. Immunol. 167, 5137–5144.

Bratlid, E., Skinningsrud, B., Uvdal, D. E., Menné, E., and Husebye, E. S. (2001). Human monocytes respond to matrix metalloproteinase-9 by increasing haptoglobin production and decreasing haptoglobin cDNA expression. J. Immunol. 167, 5137–5144.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (1999). Genotype homogeneity of autoimmune polyendocrine disease type 1. J. Clin. Endocrinol. Metab. 84, 1171–1172.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (1999). Genotype homogeneity of autoimmune polyendocrine disease type 1. J. Clin. Endocrinol. Metab. 84, 1171–1172.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (1999). Genotype homogeneity of autoimmune polyendocrine disease type 1. J. Clin. Endocrinol. Metab. 84, 1171–1172.

Bouza, P., Halonen, M., Palvimo, J. J., Perheentupa, J., Ben-Zion, G., Chiaretti, S., Solyom, J., Zlotogora, J., and Peltonen, L. (1999). Genotype homogeneity of autoimmune polyendocrine disease type 1. J. Clin. Endocrinol. Metab. 84, 1171–1172.
and thyroid autoimmunity in relation to hemato poetic autoimmunity. Scand. J. Immunol. 1, 313–343.

D. O., Hodstrad, H. Grinwis, L., Harat, J., Perpeutama, J. Grunthson, J., Ha, E., Koppel, D., and Rozeman, F. (1998). Identification of transplanted thyroid hormone as an intracellular autoantigen. J. Autoimmun. 15, 279–284.

Einhardt, A. T., Okumura, S., Shi, Z., Minami, K., Toyama, S., Ho, W., and Saito, H. (2011). CD8(+) T cells positively prevent and cure CD4(+) cell-induced colitis. J. Immunol. 186, 41–52.

Engelhardt, K. R., and Grimbacher, B. (2012). Malignant tumors causing susceptibility to mucocutaneous fungal infections in human subjects. J. Allergy Clin. Immunol. 129, 299–305.

Falkovits, A. (2014). Recent insights into the role and molecular mechanisms of the autoimmune regulator (AIRE) gene in autoimmune diseases. Autoimmun. Rev. 13, 137–141.

Garrod, J. M., Fletcher, A. L., Anderson, M. S., and Turley, S. J. (2009). AIRE in the thymus and beyond. Curr. Opin. Immunol. 21, 582–589.

Garcia, N. G., Kemp, E. H., Krohn, K. J., Brown, E. M., Watson, P. F., and Watt, A. P. (2007). The calcium-sensing receptor is a target of autoantibodies in patients with autoimmune polyendocrine syndrome type 1. J. Clin. Endocrinol. Metab. 92, 2107–2114.

Garrodot, I., Benetos, C., and Mathis, D. (2008). B cells are required for autoimmune polyendocrine syndrome type 1: an extensive longitudinal study in Sardinian patients. J. Clin. Endocrinol. Metab. 97, 1116–1124.

M. E., Kawahara, Y., Tanaka, T., and Kurimoto, K. (2008). Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type 1. J. Autoimmun. 32, 116–120.

Kahaleh, A. (1979). Autoantibodies to tolit cells in diabetes mellitus. Dia metabolism 103, 106–107.

Karlsson, F. A., Baurain, P., Lof, L., and Mårdh, S. (1988). Major premal cell antigen in autoimmune gastritis with pernicious anemia. Scand. J. Gastroenterol. 23, 475–479.

Kekäläinen, E., Tuirinen, H., Joensuu, J., Gehring, H., Frantzen, R., Pirinen, N., Järvenpää, K., Perheentupa, J., Merenmies, L., and Arstila, T. P. (2007). A defect of regulatory T cells in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J. Immunol. 179, 1265–1273.

Kemp, E. H., Garrod, N. G., Allcroft, S., Krohn, K. J., Brown, E. M., Watson, P. F., and Watt, A. P. (2010). Mapping of human autoimmune thyroid binding sites on the calcium-sensing receptor. J. Bone Miner. Res. 25, 132–140.

Kemp, E. H., Garrod, N. G., Krohn, K. J., Brown, E. M., Watson, P. F., and Watt, A. P. (2009). Activating autoantibodies against the calcium-sensing receptor are detected in two patients with autoimmune polyendocrine syndrome type 1. J. Clin. Endocrinol. Metab. 94, 4744–4749.

Kendal, R., Ly, C., Gunawara, J. L., Peterson, P., Meager, A., and Wilcox, A. (2011). Macrophage-candida and autoimmunity against cytokines in APECED and thymoma patients. Clinical and pathological implications. J. Immunol. 181, 1517–1527.

Kogawa, K., Nagaduki, S., Kato, H., Kudoh, J., Tamai, S., Sakai, Y., Shimizu, N., and Harada, M. (2002). Expression of AIRE gene in peripheral mononuclear cells. J. Immunol. 168, 105–108.

Krohn, K., Perpeutama, J., and Heinonen, E. (1974). Preventing autoantibodies in Addison’s disease. Clin. J Immunol. J. Immunol. 91, 1329–1334.

Laakso, S. M., Lauloheli, T. T., Rossi, L. H., Lehtovirta, M., Sairanen, H., Haapasalo, M., and Perheentupa, J. (2010). Regulatory T-cell defect in APECED patients is associated with loss of naive FOXP3(+) precursors and impaired activated population. J. Autoimmun. 35, 351–357.

Laakso, S. M., Kekäläinen, E., Rossi, L. H., Lauriläri, T. T., Mannisto, O., Hekkas, N., Lehtovirta, A., Perpeutama, J., Jurva, H., and Arstila, T. P. (2011). IL-7 dysregulation and loss of CD95: T cell homeostasis in the monogenic human disease autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J. Immunol. 187, 2023–2030.

Lehtovirta, A., Ross, L. H., Kekäläinen, E., Sairanen, H., and Arstila, T. P. (2010). The CD4(+)CD95(-) subset of FOXP3(+) T cells differs in their response to growth factor deprivation or stimulation. J. Immunol. 184, 377–383.

Matsumoto, M. (2011). Contrasting models for the role of Aire in the differentiation program of epithelial cells in the thymic medulla. J. Immunol. 84, 121–127.

Mayer, A., Vromans, K., Pleiter, P., Moll, K., Mummajos, A., Krohn, K., Elkadi, P., Perpeutama, J., Ha, E., Kasaka, Y., and Willcox, N. (2008). Anti-interferon autoantibodies in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Gastroenterology 132, 1288–1297.

Molenaar, C., Desjardins, C., Ouwens, G., van Doorn, W., and Frijhoff, R. (2004). Pernicious anemia in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J. Rheumatol. 31, 18–22.
malabsorption. J Clin Endocrinol Metab 91, 2835–2838.

Oliveira, E., Bakir, A. M., Kamekura, E. S., Kaveva, M. A., Zakharkova, S. E., Potekhin, V. A., and Dedon, P. I. (2010). Autoimmune polyendocrine syndrome type 1 in Russian patient: clinical variants and autoimmune regulator mutations. Horm Res Paediatr 73, 449–457.

Pajamäki, S., Tholander, R., Jonas, A., and Paukkonen, I. H. (1997). Severe malabsorption in autoimmune polyendocrine-candidiasis-ectodermal dystrophy syndrome successfully treated with immunosuppression. Arch Dis Child 76, 532–534.

Posovszky, C., Lahr, G., von Schnurbein, Popler, J., Alimohammadi, M., Kämpe, Pollak, U., Bar-Sever, Z., Hoffer, V. , Mar-A, Debatin, K. M., W abitsch, M., and Dedov, I. I. (2010). Autoimmunity to Dectin-1-induced TNF-α in a marker of active pulmonary disease and therapy. J Allergy Clin Immunol 126, 444–472, 472.e1–3.

Rautemaa, R., Hietanen, J., Niissalo, A. R., Arkwright, P. D., Isaacs, J. D., Warren, J. R., and Marshall, B. J. (1994). Unidentified causal factor in the onset of stomach pain in patients with gastric atrophy and peptic ulceration. Lancet 1, 1131–1133.

Risso, M., Deul, C., Lambert, M., Rottembourg, D., Deal, C., and Le Deist, F. (2010). 21-Hydroxylase epitopes are targeted by CD8 T cells in autoimmune polyendocrine syndrome type 1. J Immunol 184, 6156–6162.

Sawaya, L., Whitehead, T. L., Van Thiel, D. H., and Rubin, B. S. (1984). Lympohocytic subpopulations at the site of “punched” necrosis in end stage chronic liver disease and recovering liver allografts in cyclosporine-treated patients. Lab Invest 54, 341–347.

Schildberg, F., Portela-Gomes, G. M., Guttmann, L., Nilsson, G., Perhoentupa, J., Betferle, C., Haubry, E. S., Gustafsson, J., Römböhm, A., Rovam, E., and Kämpf, O. (2003). Histidine decarboxylase, a pyridol-phosphate-dependent enzyme, is an autoantigen in gastric enterochromaffin-like cells. J Clin Endocrinol Metab 88, 1449–1452.

Soderberg, A., Meigo, A. G., Ekkro, O., Grøbe-Mehlin, G., Headland, H., Landgren, E., Matts, A., Eskelin, P., Halonen, M., Tuomainen, T., Gustafsson, J., Hauhoy, E. S., Perhoentupa, J., Fejling, M., Mann, M., Rorvén, F., Kämpe, O., and Nilsson, T. (2004). Prevalence and clinical association of 11 defined autoantibodies in autoimmune polyendocrine syndrome type 1. J Clin Endocrinol Metab 89, 357–362.

The Finnish–German APECED Consortium. (1997). An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PDZ-domain-encoding regions. Nat Genet 17, 1054–1057.

Timms, L., Barten, G., Lavery, T., Pirinen, S., and Perheentupa, J. (2003). Two different cytotoxic T405 epitopes are the adrenal antigens in autoimmune polyendocrine syndrome type 1 and Addison’s disease. J Clin Endocrinol Metab 88, 2377–2385.

Utikal, E., Rose, R. N., Paine, J. R., and Eagen, R. W. (1997). Thyroid-specific autoimmune. Annu. N. Y. Acad. Sci 839, 669–677.

Verkade, P., van Rooijen, N. E., Kruis, K., Enserink, J. M., and Husebye, E. S. (2001). Flow cytometry study of blood cell subtypes reflects autoimmune and inflammatory processes in autoimmune polyendocrine syndrome type 1 and Addison’s disease. J Clin Invest 109, 1041–1051.

Verkade, P., Oost, L., van Rooijen, N. E., and Husebye, E. S. (2000). Flow cytometry study of blood cell subtypes reflects autoimmune and inflammatory processes in autoimmune polyendocrine syndrome type 1 and Addison’s disease. J Clin Invest 108, 1041–1051.

Verkade, P., van Rooijen, N. E., and Husebye, E. S. (2000). Flow cytometry study of blood cell subtypes reflects autoimmune and inflammatory processes in autoimmune polyendocrine syndrome type 1 and Addison’s disease. J Clin Invest 108, 1041–1051.

Viljo, L., Vuolteenaho, O., Eskelin, P., Halonen, M., Tuomainen, T., Gustafsson, J., Hauhoy, E. S., Perhoentupa, J., Fejling, M., Mann, M., Rorvén, F., Kämpe, O., and Nilsson, T. (2004). Prevalence and clinical association of 11 defined autoantibodies in autoimmune polyendocrine syndrome type 1. J Clin Endocrinol Metab 89, 357–362.

Ward, L., Paquet, J., Sundman, E., Hurt, A., Crotty, E., Crook, P., Delvin, E., Kämpf, O., and Deul, C. (1999). Severe autoimmune polyendocrine-candidiasis-ectodermal dystrophy in an adolescent girl with a novel AIRE mutation: response to immunosuppressive therapy. J Clin Endocrinol Metab 84, 844–852.

Warden, J. R., and Marshall, B. J. (1994). Unidentified causal factor in the onset of stomach pain in patients with gastric atrophy and peptic ulceration. Lancet 1, 1131–1133.

Waterfield, M., and Anderson, M. S. (2011). Autoimmunity’s collateral damage: Immunodeficiency hints at autoimmunity to cytokinins. Nat Med 17, 1054–1057.

Wynigt, O., Gustafsson, J., Rorvén, F., Karlsson, E. A., and Kämpf, O. (1993). Two different cytotoxic T405 epitopes are the adrenal antigens in autoimmune polyendocrine syndrome type 1 and Addison’s disease. J Clin Endocrinol Metab 88, 2377–2385.

Yabuki, T., Suzuki, T., Higuchi, A., Kihara, S., and Tsuchiya, K. (1990). Severe food allergy as a variant of DEX syndrome caused by a deletion in a gene encoding DEX receptor. N Engl J Med 327, 1441–1448.

Yang, J., Kemp, R. S., Linana, A., Moss, N., Anver, S., Mateo, V., Ruxton, L., Harriman, O., Vignjevic, J., Gambineri, E., Cott-Brunnan, N., Fischer, A., Och, H. D., Gauder, O., and Bruemmel, E. M. (2007). Severe food allergy as a variant of DEX syndrome caused by a deletion in a gene encoding DEX receptor. N Engl J Med 327, 1441–1448.
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