

Autoimmune enteropathy: molecular concepts

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Purpose of review

Enteropathies causing temporary or permanent intestinal failure are a big diagnostic and therapeutic challenge for pediatric gastroenterologists. A now well-recognized and distinct entity is in the form of "autoimmune enteropathy (AIE)". Recent advances in the molecular workup of AIE gave first insight into the pathophysiology of AIE. In this review, we discuss new molecular concepts of AIE resulting in new diagnostic and therapeutic possibilities.

Recent findings

The identification of disease-causing mutations in the *FOXP3* gene as a basic defect resulting in AIE points to a defect in regulatory T-cell homeostasis. *FOXP3*, primarily expressed by CD4+CD25+regulatory T cells, is a potent transcriptional suppressor and key modulator of T-cell functions. Nonfunctional *FOXP3* leads to a tremendous hyperactivation of T cells, resulting in autoimmune aggression, such as seen in patients with immune dysregulation, polyendocrinopathy autoimmune enteropathy X-linked (IPEX) syndrome, a subgroup of AIE. There is recent evidence suggesting that a defect of regulatory factors other than *FOXP3* might cause AIE. Anti-enterocyte autoantibodies, another main characteristic of AIE, seem to be of a secondary nature and can no more be considered as directly disease causing.

Summary

Based on the profound immune dysregulation, new treatment strategies emerged for AIE. The use of T-cell immunosuppressive drugs, such as tacrolimus combined to steroids, seems to be beneficial in some patients; however, long-term remission is not always possible. Bone marrow transplantation might be the treatment of choice in those patients who do not respond to immunosuppression; however, the first encouraging results remain to be confirmed since to date long-term outcome remains mixed.

Keywords

autoimmune enteropathy, IPEX, *FOXP3*, tacrolimus, bone marrow transplantation

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Introduction

Enteropathies causing temporary or permanent intestinal failure are a big diagnostic and therapeutic challenge for pediatric gastroenterologists. The development of new molecular and immunologic diagnostic tools over the past few years has allowed us to distinguish different types of enteropathies with onset of intestinal symptoms within the first weeks or months of life. A now well-recognized and distinct entity is in the form of "autoimmune enteropathy (AIE)". The first report suggesting the possibility of an intestinal autoimmune pathology dates back to 1978 when McCarthy [1] described an adolescent boy with immunoglobulin A (IgA) deficiency who showed a severe enteropathy with total villous atrophy and circulating gut autoantibodies. Unsworth and Walker-Smith [2] introduced in 1985 the term "autoimmune enteropathy" for severe persistent diarrhea associated with autoimmune disorders without any signs of immune deficiency. A historic keystone in the description of protracted, immune-mediated diarrhea is the report of Powell *et al.* [3] who observed 17 boys with various autoimmune disorders in the same family over three generations. Eight of them died of severe protracted diarrhea, suggesting an X-linked mode of transmission. Over the past few years, several different groups reported the association of early-onset immune-mediated profuse diarrhea, to neonatal insulin-dependent diabetes mellitus and other endocrinopathies in boys. These observations suggested that AIE might be a systemic, X-linked autoimmune disease and not an isolated GI disease [4–6]. However, AIE can also occur in girls indicating other modes of transmission [7,8].

During the past few years, the somewhat vague concept of AIE became more and more precise due to new diagnostic tools allowing a molecular approach. In the present review, we discuss the most recent advances in the field of autoimmune enteropathies in terms of genetic and immunologic evaluation, giving a new pathophysiological and conceptual view. AIE must be clearly distinguished from other immune-mediated GI diseases, such as celiac disease or inflammatory bowel diseases (Crohn disease, ulcerative colitis) as well as other inflammatory disorders such as collagenous colitis. At present,

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three different forms of AIE can be distinguished based on the genetic, immunologic, and clinical presentation, a classification we recently proposed [9]:

- (1) an X-linked form of AIE associated to different endocrinopathies and a severe eczematous skin disease, now well characterized as immune dysregulation, polyendocrinopathy, autoimmune enteropathy, X-linked (IPEX) syndrome
- (2) an isolated GI-form of AIE with typical anti-enterocyte antibodies but without any extraintestinal manifestations
- (3) any form of AIE in girls most often in association to multiple other autoimmune phenomena.

Clinical features of autoimmune enteropathies and IPEX syndrome

To date, the best-characterized form of autoimmune enteropathy is the X-linked form of IPEX. These children present with a severe enteropathy combined with insulin-dependent diabetes mellitus, severe eczema, hematological abnormalities, and eventually other endocrinopathies or renal involvement [10–12•]. In many cases, the onset of diabetes is prior to the first intestinal symptoms. Levy-Lahad *et al.* [13] suggested that diabetes is the result of a complete inflammatory destruction of pancreatic islet cells. Equilibration of diabetes with insulin in these patients is sometimes rather difficult.

In our personal series of 11 patients with IPEX followed at Necker Enfants Malades Hospital, the onset of diarrhea was always within the first six months of life; however, later onset forms were occasionally described [14,15]. Diarrhea is watery or sometimes with bloody mucous and it persists despite bowel rest. All patients developed a protein-losing enteropathy with a more severe clinical expression indicating a poor prognosis. Electrolyte imbalances were secondary to diarrhea and its correction was initially only achieved by bowel rest and total parenteral nutrition.

Another clinical feature of IPEX is eczema (atopic dermatitis), often severe in presentation. Eczema is most often diffuse, involving the entire skin and may show follicular dermatitis. Eczema was present in two-thirds of our IPEX patients, in keeping with a recent analysis [10]. Further symptoms, such as thyroiditis, hematological abnormalities (Coombs-positive anemia, neutropenia [15], and thrombocytopenia) or diffuse lymphadenopathy are markedly less frequent. Thyroiditis most often presents in the form of hypothyroidism requiring substitutive treatment. In our personal experience, hypothyroidism occurred in 2 of 11 IPEX patients. Renal involvement, in the form of glomerulonephritis, tubulopathy, or nephrotic syndrome was also described in a subset of IPEX patients [16,17]. In our patients, two cases presented with biopsy-proven membranous glomerulonephritis. Very

few patients with AIE present with an isolated GI disease, in the form of a severe protein-losing enteropathy. However, most often during follow-up, several autoimmune disorders appear, such as celiac disease, hemolytic anemia, and autoimmune neutropenia.

Autoimmune enteropathy and genetic analysis

The overwhelming clinical similarities between scurfy mice and boys with autoimmune enteropathy helped to track down the genetic defect of this autoimmune disorder and gave the first molecular clue in the understanding of this disease. Scurfy mice are a naturally occurring X-linked mutant presenting with massive lymphoproliferation, scaly skin, diarrhea, intestinal bleeding, anemia, thrombocytopenia, and hypogonadism [18–20]. Symptoms occur only in hemizygous mutant males who typically die within 3 to 4 weeks of life; female carriers are asymptomatic. Recently, Brunkow *et al.* [21] identified a disease-causing mutation on the X chromosome in scurfy mice. Based on these observations, major efforts were made in patients and their families suspected to have an X-linked form of autoimmune enteropathy, now called IPEX. In fact, genetic mapping in these families allowed the identification of the human IPEX locus to chromosome Xp11.23-q13.3 [22–24••]. The gene was named *FOXP3*. It encodes a 48 kDa protein of the forkhead (FKH)/winged helix transcription factor family, named scurfy [21]. This protein is predominantly expressed in CD4+/CD25+ T-cell with regulatory functions, at significantly lower levels in CD4+/CD25- T cells and not at all in CD8+ or B220+ cells [21,24••]. There is increasing experimental evidence suggesting that scurfy is implicated in the regulation and suppression of T-cell activation [25]. In a recent analysis of boys with IPEX, Wildin *et al.* [10] reported that in 10 of 11 screened families, loss of function mutations were found within the coding region of *FOXP3*, whereas, in one family, a mutation in the 3'-untranslated region of *FOXP3* was observed. In another series, two patients with typical clinical symptoms of IPEX did not show any mutations within the coding regions of *FOXP3* [23,26], suggesting that regulatory or conditional mutations may occur outside *FOXP3*, such as described by Bennett *et al.* [27] in the polyadenylation signal following the final coding exon of *FOXP3*. This may result in a decreased *FOXP3* messenger ribonucleic acid (RNA) expression, probably owing to nonspecific degradation of the aberrant RNA. Similar to the loss of function mutations in *FOXP3*, this results in a decreased or completely suppressed expression of scurfy leading to an altered biologic function. In addition, it is possible that other forms of IPEX or AIE exist that are not related to mutations in the *FOXP3* gene and that are transmitted either with an X-chromosomal or an autosomatic trait. Owen *et al.* [28•] reported on two families with several members presenting with IPEX. In one family a novel

FOXP3 mutation was identified with a single base deletion at codon 76 of exon 2, resulting in a frameshift mutation, whereas in the second family the *FOXP3* locus was excluded by recombination and mutational analysis was negative. Since one girl was affected in this family, there is clear evidence for an autosomal locus.

***FOXP3* and immune regulation**

The structure of the *FOXP3* protein, scurfin, suggests that it has deoxyribonucleic acid (DNA) binding activity and may serve as nuclear transcription factor. Schubert *et al.* [25] demonstrated that scurfin acts as a repressor of transcription and regulator of T-cell activation. Intact scurfin represses transcription of a reporter containing a multimeric FKH binding site. Such FKH binding sites are located adjacent to nuclear factor of activated T cells (NFAT), regulatory sites in various cytokine promoters such as IL-2, or granulocyte-macrophage colony-stimulating factor enhancer. Therefore, intact scurfin seems to be capable to directly repress NFAT-mediated transcription of the IL-2 gene in CD4⁺ T cells upon activation [25]. In addition, scurfin may play an important role in the control and maturation of regulatory T cells [29,30•].

Overexpression of scurfin in mice results in a tremendous repression of immune functions, supporting the hypothesis of scurfin as a repressor of transcription in T cells [31]. On the other hand, depletion of CD4⁺/CD25⁺ lymphocytes in healthy mice results rapidly in the development of different T-cell mediated auto-immune disorders, such as thyroiditis, gastritis, or diabetes. Upon reconstitution with CD4⁺/CD25⁺ T cells these depleted mice enter into complete remission [32]. These data indicate that *FOXP3* is an essential regulatory factor guaranteeing a normal regulatory function of T reg cells. However, the exact molecular mechanisms of an altered function of *FOXP3* protein (scurfin) resulting in IPEX are not yet fully understood. It is important to stress that heterozygous females are completely asymptomatic or in other words, no intermediate phenotype of IPEX exists. Tommasini *et al.* [33] recently analyzed X-chromosome inactivation in peripheral blood lymphocytes from a healthy heterozygous female with a child affected by IPEX. Interestingly, only one single *FOXP3* transcript (either wild type or diseased) was expressed by CD4⁺ T cell clones as assessed by RT-PCR, clearly confirming the hypothesis of X-inactivation for this gene. These findings further support the notion that only few regulatory cells are required to guarantee a homeostatic situation.

Immune dysregulation and autoantibodies

Almost all patients with IPEX or AIE generate a variety of autoantibodies. Therefore, a major characteristic and essential element in the diagnosis of autoimmune enteropathies is the presence of autoantibodies against human enterocytes or colonocytes. These antibodies are present

in the vast majority of IPEX patients; however, in a few patients the search for autoantibodies remains negative [5,15,34]. On the other hand, anti-enterocyte antibodies at low titers can also be found in other inflammatory gut conditions, such as Crohn disease, ulcerative colitis, or cow's milk allergy [5]. Therefore, the sole presence of anti-enterocyte antibodies does not allow the diagnosis of autoimmune enteropathy. Only in the context of severe diarrhea requiring parenteral nutrition, positive testing for anti-enterocyte (human duodenum, jejunum) and/or anti-colonocyte antibodies of the IgG type is highly suggestive of AIE. Indirect immunofluorescence studies showed that these autoantibodies are directed against components of the cytoplasm of mature enterocytes, with an increasing intensity towards the villus tip. Positive staining of the intestinal brush border membrane can also be observed. High titers and the complement-fixing ability of anti-enterocyte antibodies were correlated to a poor prognosis; however, these observations must be challenged. A pathogenetic role of these antibodies in the onset of intestinal inflammation—as suspected in the past—is unlikely [2,14,35]. The occurrence of anti-enterocyte/anti-colonocyte antibodies is rather an epiphenomenon of intestinal inflammation. A precise kinetic study performed in one patient with autoimmune enteropathy showed that autoantibodies occurred after the onset of intestinal lesions [35]. Anti-goblet cell antibodies are also encountered in AIE patients [36]. Another highly specific antibody often detected in IPEX patients is directed against a novel gut and kidney-specific 75 kDa antigen, named AIE75 [16,37]. This antigen shares over 99% identity with NY-Co-38, a colon cancer-related autoantigen [38]. Other circulating autoantibodies observed in IPEX are antibodies against gastric parietal cells, pancreatic islets, insulin, glutamic acid decarboxylase (GAD), as well as anti-smooth-muscle, anti-endoplasmic reticulum, anti-reticulin, anti-gliadin, anti-adrenal, anti-ANA, and anti-DNA-antibodies. Finally, antithyroglobulin or antimicrosomal antibodies can be seen without clinical symptoms of hypothyroidism.

Treatment options of autoimmune enteropathy

Treatment is extremely challenging and the mortality rate was reported to be high in patients with IPEX [39]. In the initial phase, all patients are highly dependent on parenteral nutrition. Different treatment strategies were attempted; however, to date only two approaches seem to be successful: immunosuppressive drugs or bone marrow transplantation. Over the past few years, some experience was gained in treating AIE patients with steroids alone or in combination with azathioprine, cyclosporine A, or tacrolimus [40–43]. Other approaches include the use of immunoglobulins, antilymphocytic immunoglobulin, or cyclophosphamide, which were all rather inefficient [44]. Recently, Vanderhoof and Young

[45] reported the successful use of anti-TNF-antibodies in the treatment of a patient with AIE. However, upon three injections, the treatment was stopped and high-dose steroid medication was again required to maintain remission. Therefore, no information on the long-term beneficial effect of anti-TNF treatment exists so far.

To date, the most efficient immunosuppressor seems to be tacrolimus, markedly improving the outcome of AIE, whereas only very few patients respond to Cyclosporine A (CsA) [10,40]. In our personal experience, no patient responded to CsA, whereas 7 of 8 boys came into remission when combining tacrolimus to steroids. In fact, T cells from scurfy mice are highly resistant to CSA suppression, indicating that agents inhibiting TCR signaling may be of limited benefit [21]. Given the serious side effects and the toxicity of immunosuppressive medication and its limited efficacy for long-term remission, there is a major need for new therapeutic approaches for IPEX and AIE. To date, the most promising treatment is in the form of bone marrow transplantation (BMT). In our center, the first successful HLA identical allogeneic BMT was performed on a 4-month-old boy who failed to respond to tacrolimus [39]. The donor was his HLA-identical 18-year-old sister. BMT was followed by a complete remission over 2.5 years. It is important to underline that the conditioning regimen itself already controlled the disease, further confirming that IPEX is a T-cell-mediated disease [18]. After BMT, not only the enteropathy remained in remission but also diabetes and eczema were clinically silent. Insulin therapy could be stopped 7 days after BMT; PN was reduced 4 weeks after BMT and stopped within 6 months. Unfortunately, 29 months after BMT the child died of a rapidly progressive hemophagocytotic syndrome, which remained completely unexplained. Meanwhile, two other boys received BMT as ultimate treatment option for IPEX [10]. In both cases, BMT was initially successful; however, lethal, infectious complications occurred 3 and 5 months post BMT, respectively. These three cases indicate that BMT is potentially successful in otherwise treatment-resistant IPEX. However, this treatment remains quite difficult. Therefore, further experience with BMT must be gained by particularly experienced teams before it could be recommended as rescue therapy for AIE. On the other hand, with the increasing understanding of the pathophysiology of IPEX, there is good hope that in the near future new immunosuppressive strategies will be available to treat this T-cell-mediated autoimmune disorder.

Conclusion

The development of new diagnostic tools has allowed us to advance markedly in the understanding of the pathophysiology and in parallel to advance in the diagnosis of AIE. With the identification of disease-causing mutations in the FOXP3 gene, one clue in the understanding

of the immune dysregulation in AIE was found. FOXP3 codes for a protein called scurf, which plays an important role in the control of T-cell activation. Recent data point towards a defect of regulatory T cells secondary to nonfunctional FOXP3 protein or scurf, at least in a subtype of patients, now identified as IPEX syndrome. However, there is some evidence to believe that regulatory factors others than FOXP3 may cause the immune dysregulation resulting in AIE or IPEX. Therefore, the search for other potential candidate genes is open. It is now well accepted to consider AIE as a systemic disease and therapeutic attitudes are based on the recent knowledge of immune dysregulation. During the initial phase, all children are dependent on parenteral nutrition to stabilize their course without changing the evolution. To date, the only two therapeutic approaches that seem to be successful are potent immunosuppressive drugs or bone marrow transplantation. The only drug that allowed us to control this T-cell-mediated disease was the T-cell immunosuppressor tacrolimus combined to steroids. However, long-term remission with immunosuppressors is difficult to obtain and drug toxicity limits their use. Based on the immunologic nature of IPEX, early BMT looks like the treatment of choice. However, more experience with BMT for IPEX is needed to be sure that it will allow permanent remission, since the first results with BMT are mixed.

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