

REVIEW

The immunogenetics of immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome

Eva d'Hennezel,^{1,2} Khalid Bin Dhuban,^{1,2} Troy Torgerson,³ Ciriaco Piccirillo^{1,2}

¹Department of Microbiology and Immunology, McGill University, Montréal, Quebec, Canada

²FOCIS Centre of Excellence, Research Institute of the McGill University Health Centre, Montréal, Quebec, Canada

³Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, USA

Correspondence to

Dr Ciriaco Piccirillo, Research Institute of the McGill University Health Centre, Montréal General Hospital, 1650 Cedar Avenue, Room L11.132, Montréal, QC H3G 1A4, Canada; ciro.piccirillo@mcgill.ca

EH and KBD contributed equally to this work.

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ABSTRACT

Immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome is a rare disorder in humans caused by germ-line mutations in the *FOXP3* gene, a master transcriptional regulator for the development of CD4 regulatory T (Treg) cells. This T cell subset has global inhibitory functions that maintain immune homeostasis and mediate self-tolerance. Treg developmental deficiency or dysfunction is a hallmark of IPEX. It leads to severe, multi-organ, autoimmune phenomena including enteropathy, chronic dermatitis, endocrinopathy and other organ-specific diseases such as anaemia, thrombocytopenia, hepatitis and nephritis. In this review, the genetic, immunological and clinical characteristics of IPEX syndrome are described, and the impact of heritable mutations on the function of Treg cells highlighted.

INTRODUCTION

Thirty years ago, Powell *et al* first described the clinical syndrome that has come to be known as immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome in a large non-consanguineous family.¹ The syndrome had a clear X linked recessive pattern of inheritance, with exclusive expression in males. It presented most commonly with early onset diarrhoeal disease, type 1 diabetes (T1D), and an accompanying failure to thrive and dermatitis. Without aggressive treatment the disease was fatal in most affected children within the first two years of life. The devastating clinical outcome of IPEX suggested that the genetic determinant(s) responsible for disease impacted major regulatory processes governing immune homeostasis. An analogous disease process was also observed in a spontaneous mutant mouse known as 'Scurfy'.² Using the Scurfy mouse model, researchers mapped the causative locus to the gene encoding the forkhead box protein 3 (FOXP3), a member of the forkhead/winged-helix family of DNA-binding transcriptional regulators.^{2–3} In humans, the gene is located on the X chromosome at Xp11.23-Xq13.3, near the *WAS* gene, which is responsible for Wiskott–Aldrich syndrome.⁴ The identification of heritable mutations in the *FOXP3* gene as the cause of IPEX and Scurfy provided the clearest demonstration to date, that defects in a single gene could consistently disrupt immune homeostasis and lead to severe autoimmunity.

They also suggested that the *FOXP3* gene was involved in the dominant regulation of immune responses to self-antigens.

The immune system requires a set of 'self-check' control mechanisms that establish a homeostatic balance between the need to generate protective immune responses to various foreign antigens, tolerate self-antigens and suppress the consequences of immune-mediated pathology. IPEX is the result of defective development of a naturally arising CD4 T cell lineage called regulatory T (Treg) cells whose function serves to maintain self-tolerance.⁵ Treg cells develop in the thymus, and represent 1–10% of thymic and peripheral CD4 T cells. They constitutively express high levels of the interleukin 2 receptor α -chain (IL-2R α chain or CD25) and FOXP3 protein. Treg cells are critical mediators of immune homeostasis. They determine the balance between protective immunity and tolerance, mediate peripheral tolerance to self and non-self antigens, and suppress excessive inflammation that can cause pathology. The critical functions of FOXP3 Treg cells in immune homeostasis have been amply demonstrated in several mouse models where abrogation of the development, homeostasis or function of FOXP3 Treg cells simultaneously triggers multi-organ autoimmunity, and provokes immunity to tumours, transplants, infectious and commensal microbes, and allergens.⁶

Numerous studies now show that stable FOXP3 expression is essential for the programming of Treg cell lineage development and function.^{7–9} In the resting state, FOXP3 is expressed almost exclusively in CD4 Treg cells, where it functions in a cell-autonomous fashion. Consistently, Foxp3-deficient or Treg-depleted mice develop a fatal, multi-organ autoimmune syndrome that is similar to the autoimmunity observed in Scurfy mice, which express a non-functional, truncated form of the Foxp3 protein lacking the Forkhead DNA-binding domain.^{2–3–10} Adoptive transfer of CD4/CD25⁺/Foxp3 Treg cells into affected animals readily suppresses the autoimmunity. Moreover, forced overexpression of Foxp3/FOXP3 in conventional murine and human T cells, respectively, redirects their differentiation into the Treg lineage.^{8–11} Of note is that other defects affecting the development and/or function of Treg cells can also break self-tolerance and provoke autoimmunity. Among these, disruption of cytokine and co-stimulatory signalling pathways that are essential for Treg cell development and peripheral homeostasis, can

abrogate Treg cell function and provoke autoimmunity as well. Such is the case in CD25, IL2 or STAT5 deficiencies in humans,^{12–14} or in CD28 or ICOS deficiencies in mice.^{15–17}

Hence, Treg cells are critical mediators of self-tolerance, and their development and function heavily depend on FOXP3. However, there exists a considerable level of heterogeneity of severity among IPEX cases, likely due to the multifaceted nature of the molecular functions of FOXP3. Here, we propose a comprehensive review of the IPEX syndrome, covering both the clinical and molecular aspects of the disease, and providing an analysis of the molecular domains of FOXP3 as a platform for understanding the observed clinical heterogeneity and prognosis.

THE CLINICAL MANIFESTATIONS OF IPEX

Although patients with IPEX syndrome share many of the hallmark clinical manifestations of the disease, the degree and severity of the expressed phenotypes vary considerably between affected individuals. The most consistent feature of the disorder is enteropathy, which typically manifests as severe, watery diarrhoea. Bowel biopsy often reveals a GVHD-like or coeliac-like pattern with villous-blunting and lymphocytic infiltration of the damaged bowel mucosa.¹⁸ Rash, particularly an eczematous dermatitis, is also a common clinical feature. The rash may vary in severity, taking on a spongiotic psoriasiform appearance at its worst.^{19 20} Pemphigous nodularis has also been described in rare cases.²¹ The endocrinopathies in IPEX are limited almost exclusively to the pancreas and thyroid. The presence of type 1 diabetes is related to inflammatory destruction of the islet cells as evidenced by the presence of lymphocytic infiltrates in and around pancreatic islets. In addition to the enteropathy, dermatitis and endocrine disorders present in most IPEX patients, a number of other clinical conditions including anaemia, thrombocytopenia, lymphadenopathy, hepatitis, nephropathy and alopecia are also present to variable degrees in various patients.²² The usual laboratory evaluation of the immune system most consistently shows elevated immunoglobulin E (IgE) and eosinophilia which is present in most affected patients. IgG and IgM levels are typically normal but can be slightly depressed in older individuals, likely as a result of enteric protein loss. Complement levels are almost universally normal. Neutrophil activity is normal but autoimmune neutropenia has been reported in rare patients.⁵

GENOTYPE-SPECIFIC CONSEQUENCES ON IMMUNE REGULATION AND CLINICAL OUTCOME

A spectrum of *FOXP3* mutations has been identified and characterised in IPEX, each affecting the development and/or function of Treg cells. As discussed below, the impact of individual mutations on FOXP3 expression and function is variable. As a general rule however, point mutations and small in-frame deletions that do not destroy any of the functional domains of the FOXP3 protein are associated with a somewhat milder clinical phenotype. Some of these allow near-normal expression of the FOXP3 protein and do not significantly compromise Treg cell numbers. Interestingly, the disease manifestations can also vary considerably between patients with the same mutation, suggesting that the severity of IPEX may be modulated by other disease-modifying genes that may affect Treg function. This variability might also be due to differences in the TCR repertoire or MHC haplotype between patients. This is supported by the fact that the class II MHC haplotype is one of the primary genetic contributors to autoimmune susceptibility.²³ Exposure to different antigens or infections could also account for the

differential clinical impact on patients with similar mutations. One example to support this possibility is the variability in the outcome of the murine colitis model depending on the level of pathogen-free housing environment.²⁴

IPEX-associated *FOXP3* expression as a clinical tool

Identification of reliable clinical markers that allow rapid diagnosis and/or predict the possible outcomes of IPEX has proven challenging. Flow cytometry to assess FOXP3 protein expression has proven extremely useful but is not particularly sensitive or specific for IPEX disease. Complete absence of FOXP3 is highly suggestive of a *FOXP3* mutation, and patients who entirely lack protein expression often have severe disease. There are however occasional patients who lack FOXP3 expression but do not have an identifiable mutation in the gene.^{25 26} The converse situation in which FOXP3 protein expression is essentially normal, even in the setting of a verified mutation such as M370I,²⁷ A384T²⁸ or E70H²⁹ is even more common (table 1). Consequently, sequencing of the *FOXP3* gene is still considered to be the gold standard for diagnosis of IPEX.²² These issues highlight the need to develop new, practical tools to assess FOXP3 protein function and Treg suppressive capacity on a clinical basis; measures that may prove useful for diagnosing IPEX and predicting disease prognosis.

Coupling IPEX mutations with their impact on *FOXP3* structure and function

IPEX-associated *FOXP3* mutations have been identified in both the non-coding and coding sequences of the *FOXP3* gene.^{3 10 18–20 22 29–63} Point mutations or small in-frame deletions within the coding region of the gene are the most informative for elucidating structure/function relationships of specific domains of the protein. Earlier work relied on these mutations to delineate four functional domains in the molecular structure of FOXP3: (1) N-terminal proline-rich repressor (PRR) domain; (2) zinc-finger domain; (3) leucine-zipper (LZ) domain; and (4) DNA-binding, forkhead/winged helix (FKH) domain (figure 1).⁵⁹ Each of these domains is involved in the molecular function of FOXP3. It is expected that mutations affecting each domain should therefore generate a specific signature of molecular defects (table 2). Understanding the molecular impact of a given mutation in *FOXP3* may provide critical insights into the expected extent, course or prognosis of IPEX.

N-terminal, PRR domain

The N-terminal domain is complex, and involved in various interactions that are critical for multiple aspects of FOXP3 function, including its ability to suppress cytokine production. Mutations positioned between amino acids (a.a.) 1–193, and particularly between a.a. 67–132, disrupt the function of the PRR domain.⁵⁹

In conventional effector T cells, stimulation through the T cell receptor induces activation of NFAT and AP1, transcription factors that are critical for orchestrating the response of T cells to immune stimulation. Together, they regulate expression of genes whose products are involved in cell cycle progression, survival, and the production of inflammatory cytokines such as IL-2 and IFN γ . In contrast, Treg cells are anergic, meaning that they are unable to trigger such TCR-induced responses on stimulation. This anergic state is mediated in part by FOXP3 through its repression of the NFAT/AP1-driven transcriptional programme. The N-terminal proline-rich domain of FOXP3 is specifically required for this function.⁵⁹ As detailed below, FOXP3 also binds directly to NFAT through its FKH domain.^{64 65} In addition,

Table 1 A list of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X linked) mutations reported to date

Nucleotide change	Amino acid change	Exon or Intron	Domain	Reported ex vivo % FOXP3+ cells	Molecular defect	References	Endocrinopathy	Enteropathy	Skin manifestations	Reported onset	Immunosuppression	Response to immuno-suppression	HSCT	Outcome
g.-6247-4859del	NA	Exon-1 Intron-1	Non-coding	Diminished	Accumulation of unspliced mRNA	Gavin <i>et al</i> , 2006 ³⁰ , Torgerson <i>et al</i> , 2007 ³¹ , Moes <i>et al</i> , 2010 ³²	N	Y	Y	<2 mth	Steroids, tacrolimus, Sirolimus, azathioprine	Y	N	Treated patients stable at 6, 9 years
c.1-7G>T	NA	Upstream of initiation codon	Non-coding	NA	New translation initiation site. Stop codon at 61aa	Myers <i>et al</i> , 2006 ³³	T1D	Y	N	Birth	None	NA	N	Died at 54 days
2T>C	M1T	Exon 1	PRR	Diminished	Predicted abnormal reading frame	Gambineri <i>et al</i> , 2008 ²²	T1D	Y	N	Birth	Steroids, tacrolimus	N	N	Died at 3 mth
3G>A	M1I	Exon 1	PRR	Diminished	Predicted abnormal reading frame	Bacchetta <i>et al</i> , 2006 ³⁴ , Gambineri <i>et al</i> , 2008 ²²	T1D	Y	Y	Birth	Steroids, CsA	N	Y	Stable at 5 years
200G>T	Q70H	Exon 1	PRR	NA	Predicted abnormal reading frame	Heltzer <i>et al</i> , 2007 ³⁵ , Yong <i>et al</i> , 2008 ²⁹	N	Y	Y	1 mth	Sirolimus	Y	N	Stable at 8 years
210+1G>A	NA	Intron 1	Non-coding	NA	Predicted splicing defects	Tsuda <i>et al</i> , 2010 ³⁶ , Bae <i>et al</i> , 2011 ³⁷	T1D	Y	Y	11 mth	Steroids	Y	N	Stable at 14 years
210_210 +1delGinsAC	NA	Intron 1	Non-coding	Diminished	Predicted splicing defects	Gavin <i>et al</i> , 2006 ³⁰	HTH	Y	Y	2 mth	Steroids, tacrolimus	Y	N	Stable at 5 mth
210+2delTT	NA	Intron 1	Non-coding	Diminished	Predicted splicing defects	Burroughs <i>et al</i> , 2010 ³⁸	T1D	Y	N	2 mth	Steroids, tacrolimus	N	Y	Stable at 4 years
210+2T>G	NA	Intron 1	Non-coding	NA	Predicted splicing defects	Gambineri <i>et al</i> , 2008 ²²	T1D	Y	Y	Birth	Steroid, CsA, tacrolimus, IVIG	N	Y	Stable at 18 mth
227delT	L760fsX53	Exon 2	PRR	Diminished	Predicted stop codon at 128aa	Kobayashi <i>et al</i> , 2001 ³⁹ , Fuchizawa <i>et al</i> , 2007 ⁴⁰ , Rubio-Cabezas <i>et al</i> , 2009 ⁴¹	HTH	Y	N	(1) 5 days (2) Birth	(1) Steroids, tacrolimus (2) NA	(1) Y (2) NA	(1) N (2) NA	(1) Stable at 15 years (2) Died at 8 mth
303_304delTT	F102fsX103	Exon 2	PRR	NA	Predicted stop codon at 205aa	Moudgil <i>et al</i> , 2007 ⁴² , Rao <i>et al</i> , 2007 ⁴³	T1D	Y	Y	Birth	Steroids, CsA, rituximab	N	Y	Stable at 2.5 years
323C>T	T108M	Exon 3	PRR	NA	Predicted to yield full length FOXP3	De Benedetti <i>et al</i> , 2006 ⁴⁴	HTH	Y	N	14 mth	Steroids, azathioprine	Y	N	Stable at 7 years
454+4A>G	NA	Intron 3	Non-coding	NA	Skipping of exons 2 and 3	De Benedetti <i>et al</i> , 2006 ⁴⁴	N	Y	Y	11 days	Steroid, CsA, tacrolimus	Y	N	Stable at 22 years
543C>T	S181S	Exon 5	PRR	Elevated	Premature stop codon in exon 7	Gambineri <i>et al</i> , 2008 ²²	N	Y	N	Birth	Steroid, CsA, IVIG	N	N	Died at 5 mth
560C>T	P187L	Exon 5	PRR	Normal	Silent mutation. May affect RNA stability and splicing	Moes <i>et al</i> , 2010 ³²	N	Y	Y	Birth	Tacrolimus	N	Y	Died due to severe GVHD at 8 years

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Table 1 Continued

Nucleotide change	Amino acid change	Exon or Intron	Domain	Reported ex vivo % FOXP3+ cells	Molecular defect	References	Endocrinopathy	Enteropathy	Skin manifestations	Reported onset	Immunosuppression	Response to immuno-suppression	HSCT	Outcome
725T>C	L242P	Exon 6	LZ	Reduced	Missense mutation. Predicted to yield full length FOXP3	Gambineri <i>et al</i> , 2008 ³² ; Passerini <i>et al</i> , 2011 ⁴⁵	N	Y	Y	4 mth	Steroid, CsA, tacrolimus	N	Y	Stable at 14 years
736-1G>A	ΔL246_V272	Intron 6	LZ	NA	Splicing defect. Exon 7 skipping	Halabi-Tawil <i>et al</i> , 2009 ²⁰	T1D	Y	Y	NA	NA	NA	NA	NA
748_750delAAG	ΔLys250	Exon 7	LZ	NA	Disrupts FOXP3 oligomerisation	Wildin <i>et al</i> , 2002 ⁴⁶ ; Li <i>et al</i> , 2007 ⁴⁷	T1D	Y	N	2 mth	Steroid, CsA, tacrolimus	N	Y	Died at 9 years due to BMT complications
750_752delGGA	ΔGlu251	Exon 7	LZ	Reduced	Disrupts FOXP3 oligomerisation	Gavin <i>et al</i> , 2006 ³⁰ ; Moes <i>et al</i> , 2010 ³²	T1D	Y	Y	(1) 6 mth (2) 4 wk	(1) Steroids, tacrolimus (2) Tacrolimus, sirolimus	(1) Y (2) N	(1) N (2) Y	(1) Stable at 6, 9 years (2) Stable at 10 years
816+2del	NA	Intron 7	Non-coding	NA	Predicted splicing defect	Passerini <i>et al</i> , 2011 ⁴⁵	N	Y	Y	5 mth	Yes. Drugs not specified	Y	N	Stable at 27 years
816+4A>G	NA	Intron 7	Non-coding	NA	Predicted skipping of exon 7	Harbuz <i>et al</i> , 2010 ⁴⁸	N	Y	Y	2 mth	Steroids	N	N	Died at 3 years
816+5G>A	NA	Intron 7	Non-coding	NA	Predicted splicing defect	Gambineri <i>et al</i> , 2008 ²²	T1D	Y	Y	Birth	Steroids, Azathioprine	N	N	Died at 9 mth
816+7G>C	NA	Intron 7	LZ	Reduced	Splicing defect. Exon 7 skipping, affecting the leucine-zipper domain	Harbuz <i>et al</i> , 2010 ⁴⁸ ; Burroughs <i>et al</i> , 2010 ³⁸	T1D	Y	Y	(1) 2 wk (2) NA	(1) No (2) IVIG	(1) NA (2) N	(1) N (2) Y	(1) Died at 3.5 years (2) Stable at 16 years
817-1G>A	NA	Intron 7	Non-coding	NA	Predicted skipping of exon 7	Heltzer <i>et al</i> , 2007 ³⁵	T1D	Y	Y	Birth	Tacrolimus	N	N	Died at 79 days
817G>T	A273S	Exon 8	LZ-FKH loop	NA	Predicted impact on RUNX1 binding	Tsuda <i>et al</i> , 2010 ³⁶	HTH	Y	Y	NA	NA	NA	NA	Alive at 6 years
968+4A>G	NA	Intron 8	Non-coding	NA	Skipping of exon 8. Predicted impact on RUNX1 binding	Gambineri <i>et al</i> , 2008 ²²	T1D	Y	Y	Birth	Steroids, Tacrolimus, azathioprine	Y	N	Stable at 4 years
970T>C, 972C>T	F324L	Exon 9	LZ-FKH loop	Normal	Predicted impact on RUNX1 binding	Bacchetta <i>et al</i> , 2006 ³⁴ ; Gambineri <i>et al</i> , 2008 ²²	N	Y	Y	4 mth	No	NA	N	Stable at 7 years
1010G>A	R337Q	Exon 9	FKH boundary	NA	Missense mutation. Likely to affect DNA binding affinity	Rubio-Cabezas <i>et al</i> , 2009 ⁴¹	T1D	Y	N	1 mth	NA	NA	N	Died at 13 mth
1015C>G	P339A	Exon 9	FKH	Reduced	Missense mutation. Predicted to yield full length FOXP3	Gambineri <i>et al</i> , 2008 ²² ; Rubio-Cabezas <i>et al</i> , 2009 ⁴¹ ; Moes <i>et al</i> , 2010 ³²	T1D	Y	Y	(1) Birth (2) 7 days	Steroids, tacrolimus, azathioprine, sirolimus	N	N	(1) Death at 8 mth (2) Died at 6 mth

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Table 1 Continued

Nucleotide change	Amino acid change	Exon or Intron	Domain	Reported ex vivo % FOXp3+ cells	Molecular defect	References	Endocrinopathy	Enteropathy	Skin manifestations	Reported onset (2) < 1 year	Immunosuppression	Response to immunosuppression	HSCT	Outcome
1040G>A	R347H	Exon 9	FKH	Reduced	Effect on nuclear targeting. Abrogation of IL-2 repression	Gambineri <i>et al</i> , 2006 ²² ; McMurchy <i>et al</i> , 2010 ⁴⁹ ; Passerini <i>et al</i> , 2011 ⁴⁵	T1D	Y	Y	(1) Birth (2) < 1 year	Steroids, CsA	Y	N	Stable at 10, 19 years
1044+4A>G	E323GfsX14	Intron 9	FKH	NA	Skipping of exon 9. Abnormal FKH domain	Chatila <i>et al</i> , 2000 ⁵⁰	T1D	Y	Y	Infancy	NA	NA	NA	NA
1045-3C>G	NA	Intron 9	Non-coding	Reduced	Retention of intron 9. Abnormal FKH domain	Costa-Carvalho <i>et al</i> , 2008 ⁵¹	T1D, HTH	Y	Y	Birth	Steroids	N	N	Died at 10 mth
1061delC	Frameshift	Exon 10	FKH	NA	Deletion and frameshift. Premature stop codon. Truncated FKH domain	Heltzer <i>et al</i> , 2007 ³⁵ ; Yong <i>et al</i> , 2008 ²³	N	Y	Y	2 years	(1) Steroids (2) Steroids, sirolimus	Y	N	(1) Stable at 4 years (2) Stable at 6 years
1080_1081insA	N361KfsX2	Exon 10	FKH	Diminished	Truncated FKH domain	An Yf <i>et al</i> , 2011 ²⁷	T1D	Y	Y	20 days	No	NA	N	Died at 1 mth
1087A>G	I363V	Exon 10	FKH	NA	Missense mutation. Predicted to yield full length FOXp3	Kobayashi <i>et al</i> , 2001 ³⁵	T1D, HTH	Y	N	Early infancy	No	NA	N	Died at 3 years
1100T>G	F367C	Exon 10	FKH	Normal	Full length FOXp3 with abnormal FKH domain	Patey-Mariaud de Serre <i>et al</i> , 2009 ¹⁸	T1D	Y	N	15 mth	NA	NA	NA	NA
1101C>G, c.1099T>C	F367L	Exon 10	FKH	NA	Full length FOXp3 with abnormal FKH domain	Suzuki <i>et al</i> , 2007 ⁵³ ; Halabi-Tawil <i>et al</i> , 2009 ²⁰	T1D, HTH	Y	Y	8 days	No	NA	N	Died at 4 mth
1110G>A	M370I	Exon 10	FKH	Normal	Full length FOXp3 with abnormal FKH domain	An Yf <i>et al</i> , 2011 ²⁷	N	Y	Y	14 days	No	NA	N	Died at 11 mth
1113T>G	F371C	Exon 10	FKH	Normal	Full length FOXp3 with abnormal FKH domain	Wildin <i>et al</i> , 2001 ¹⁰ ; Baud <i>et al</i> , 2001 ⁵⁴ ; Patey-Mariaud de Serre <i>et al</i> , 2009 ¹⁸	T1D	Y	Y	4 wk	Steroids	N	Y	Stable at 2 years
1117T>G	F373V	Exon 10	FKH	Reduced	Full length FOXp3 with abnormal FKH domain	Tanaka <i>et al</i> , 2004 ⁵⁵ ; Tanaka <i>et al</i> , 2005 ⁵⁶ ; Fuchizawa <i>et al</i> , 2007 ⁴⁰	N	Y	N	2 mth	Steroids, CsA, IVIG	Y	N	Stable at 3.2 years

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Table 1 Continued

Nucleotide change	Amino acid change	Exon or Intron	Domain	Reported ex vivo % FOXP3+ cells	Molecular defect	References	Endocrinopathy	Enteropathy	Skin manifestations	Reported onset	Immunosuppression	Response to immuno-suppression	HSCT	Outcome
1117 1118del TTinsGC	F373A	Exon 10	FKH	Normal	Full length FOXP3 with abnormal FKH domain	Bacchetta <i>et al</i> , 2006 ³⁴ ; Gambineri <i>et al</i> , 2008 ²² ; McMurchy <i>et al</i> , 2010 ⁴⁹ ; Passerini <i>et al</i> , 2011 ⁴⁵	T1D	Y	Y	2 wk	MMF	N	Y	Stable at 7 years
1121 T>G	F374C	Exon 10	FKH	Reduced	Full length FOXP3 with abnormal FKH domain	Gambineri <i>et al</i> , 2006 ³² ; Moes <i>et al</i> , 2010 ³²	T1D HTH	Y	Y	Birth	(1) Tacrolimus, sirolimus (2) Steroids, tacrolimus, azathioprine	N	N	(1) Died at 14 mth (2) Died at 11 mth
1139C>T	T380I	Exon 10	FKH	NA	Full length FOXP3 with abnormal FKH domain	Zhan <i>et al</i> , 2008 ⁵⁷	N	Y	N	4 mth	Steroids, tacrolimus, azathioprine	N	Y	Stable at 3 years
1150G>A	A384T	Exon 11	FKH	Reduced	Full length FOXP3 with abnormal FKH domain	Wildin <i>et al</i> , 2001 ¹⁰ ; Nieves <i>et al</i> , 2004 ¹⁹ ; Gambineri <i>et al</i> , 2008 ²² ; d'Hennezel <i>et al</i> , 2009 ²⁸	T1D HTH	Y	Y	Birth	(1) Sirolimus (2) Steroids, IVIG, tacrolimus, sirolimus	(1) N (2) Y	N	(1) Died at 7 wk (2) Stable at 15 years
1157G>A	R386H	Exon 11	FKH	NA	Full length FOXP3 with abnormal FKH domain	Tsuda <i>et al</i> , 2010 ³⁶	N	Y	N	Early infancy	NA	NA	NA	Alive at 4 mth
1169G>A	S390N	Exon 11	FKH	NA	Full length FOXP3 with abnormal FKH domain	Myers <i>et al</i> , 2006 ³³ ; Tsuda <i>et al</i> , 2010 ³⁶	T1D	Y	Y	Day 4	(1) None (2) Not reported	(1) NA (2) Y	N	(1) Died at 1 year (2) Alive at 5 years
1190G>A	R397Q	Exon 11	FKH	NA	Full length FOXP3 with abnormal FKH domain	Tsuda <i>et al</i> , 2010 ³⁶	T1D	Y	Y	NA	NA	NA	NA	Alive at 4 years
1189C>T	R397W	Exon 11	FKH	NA	Full length FOXP3 with abnormal FKH domain. Impaired DNA binding	Levy-Lahad <i>et al</i> , 2001 ⁵⁸ ; Lopes <i>et al</i> , 2006 ⁵⁹	T1D HTH	Y	N	Birth	(1) None (2) Steroids, CsA	N	N	(1) Died at 3–5 wk (2) Died at 5 mth
1222G>A	V408M	Exon 11	FKH	NA	Full length FOXP3 with misfolded FKH domain	Rubio-Cabezas <i>et al</i> , 2009 ⁴¹	T1D HTH	Y	N	3.5 mth	Steroids	Y	N	Stable at 12 years
1226A>G	D409G	Exon 11	FKH	NA	Full length FOXP3 with abnormal FKH domain	Rao <i>et al</i> , 2007 ⁴³	T1D	Y	N	Early infancy	Steroids, tacrolimus, rituximab, alemtuzumab	N	Y	Stable at 6 mth
1271 G>A	C424Y	Exon 11	C-terminal	NA	Missense mutation downstream of FKH domain	Rao <i>et al</i> , 2007 ⁴³ ; Burroughs <i>et al</i> , 2007 ⁶⁰	T1D HTH	Y	Y	NA	Steroids, tacrolimus, MMF	N	Y	Stable at 4 years

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Table 1 Continued

Nucleotide change	Amino acid change	Exon or Intron	Domain	Reported ex vivo % FOXP3+ cells	Molecular defect	References	Endocrinopathy	Enteropathy	Skin manifestations	Reported onset	Immunosuppression	Response to immuno-suppression	H SCT	Outcome
1290 1309delinsTGG	G430fsX22	Exon 11	Stop codon	NA	Deletion/insertion mutation yielding an elongated amino acid sequence	Peake <i>et al</i> , 1996 ⁶¹ ; Wildin <i>et al</i> , 2001 ¹⁰	T1D	Y	Y	6 wk	No	NA	N	Died at 10 mth
1293 1294delCT	ter432TfsX26	Exon 11	Stop codon	NA	Frameshift/deletion mutation yielding elongated amino acid sequence	Bennett <i>et al</i> , 2001 ³ ; Wildin <i>et al</i> , 2002 ⁴⁶	NA	NA	NA	NA	NA	NA	NA	NA
c.*876A>G (AAUAAA → AAUGAA)	NA	PolyA sequence	PolyA sequence	No FOXP3 mRNA	Polyadenylation defect resulting in unstable FOXP3 mRNA	Bennett <i>et al</i> , 2001 ⁶² ; Tsuda <i>et al</i> , 2010 ³⁶	N	Y	Y	Birth	NA	NA	NA	NA
AAUAAA → AAUAAG	NA	PolyA sequence	PolyA sequence	Diminished	Polyadenylation defect resulting in unstable FOXP3 mRNA	Dorsey <i>et al</i> , 2009 ⁶³	T1D	Y	Y	Birth	Steroids, sirolimus	N	Y	Stable at 8.5 mth

*Not necessarily in combination. FKX, forkhead domain; H SCT, haematopoietic stem cell transfer; HTH, hypothyroidism; PRR, proline-rich region; T1D, type 1 diabetes mth, month; wk, week; N, no; Y, yes; CsA, Cyclosporin A; IVIG, intra-venous Immunoglobulin; NA, not available; aa, amino acid; BMT, bone marrow transplantation; LZ, leucine zipper; Δ, deletion; fs, frameshift; mRNA, messenger RNA; PolyA, Polyadenylation sequence; g, genomic sequence; c., coding sequence; del, deletion; ins, insertion.

FOXP3 can directly bind AP1, in turn sequestering it away from chromatin and from AP1 DNA-binding sites. As the interaction of FOXP3 with AP1 requires the integrity of its N-terminal region,^{64 65} it follows that IPEX mutations such as E70H²⁹ and T108M⁴⁴ may affect the maintenance of Treg anergy by FOXP3, while not necessarily disrupting other functions of FOXP3. Consistent with this hypothesis, these mutations have been described in association with milder cases of IPEX.^{29 44}

The N-terminal region of FOXP3 also harbours a canonical LxxLL motif within a.a. 70–105, allowing FOXP3 to interact with RORα, thus inhibiting RORα-mediated transcriptional activation.⁶⁶ RORα is a transcription factor that is critically involved in the regulation of inflammatory Th17 cell development.^{66 67} Murine studies have shown Th17 and Treg cells to be reciprocally regulated: abrogation of FOXP3 leads to a spontaneous increase in IL-17⁶⁸ whereas mice deficient for Th17-inducing cytokines such as IL-6 display a dramatic defect in Th17 cells and an increased peripheral Treg compartment.⁶⁹ Direct FOXP3 binding to RORα leads to a mutual inhibition.⁷⁰ Hence, the fate of a given T cell is highly dependent on factors affecting its internal FOXP3/RORα balance,⁷¹ and the loss of FOXP3 expression is expected to lead to an inflammatory Th17 phenotype. Observations in murine studies may however not translate to humans, as it has been shown that normal human memory-like Treg cells can co-express IL-17 and functional FOXP3, all the while maintaining their suppressive function.^{72 73} In addition, an enhanced susceptibility to Th17 conversion in vitro has been recently reported in IPEX patients with mutations outside the a.a. 70–105 region.⁴⁵ This suggests that other mechanisms, likely involving other areas of FOXP3, could affect the regulation of RORα and/or other Th17-regulating factors. Nonetheless, the disruption of FOXP3 binding to RORα by an IPEX mutation is expected to yield a severe Treg/Th17 imbalance.

Amino acids 70–105 of FOXP3 also contain a lysine-rich, nuclear export sequence, which renders it differentially sensitive to lysine acetylation.⁷⁴ Lysine acetylation of FOXP3 may thus represent a pivotal mechanism in regulating its function. Indeed, although portions of the total pool of FOXP3 can exist in diverse nuclear sites, active and acetylated FOXP3 is preferentially, but not exclusively, bound to chromatin.⁷⁵ Such acetylation could be carried out by TIP60, a natural molecular partner of FOXP3, whose association with FOXP3 has been shown to lead to its acetylation.^{74 76 77} Several mutations of FOXP3 have been described, which localise to this segment; however they all result in frameshifts and subsequent truncation of the protein, making it impossible to impute the resulting Treg phenotype to a disruption of FOXP3 binding to RORα (table 1).^{39 42 46}

Lastly, a sequence spanning a.a. 106–190 has been shown to be critically required for FOXP3 binding to histone deacetylases.⁷⁶ Histone acetylase (HAT) and deacetylase (HDAC) proteins, thanks to their ability to regulate chromatin structure and function, have been shown to modulate the chromatin remodelling events instrumental in T cell development and differentiation. They have also been shown to modify non-histone proteins as well as histones.^{78 79} FOXP3 can be co-immunoprecipitated with several HDAC molecules (eg, HDAC1, HDAC7 and HDAC9),^{76 80} suggesting that the function of FOXP3 is at least partially mediated by modulating the configuration of chromatin, thereby regulating access to promoter regions for itself and potentially for other transcription factors. Hence, the function of FOXP3 could depend on its acetylation status, and its association with HDAC and HAT. Mutations located in this region include T108M⁴⁴ and P187L.^{18 32}

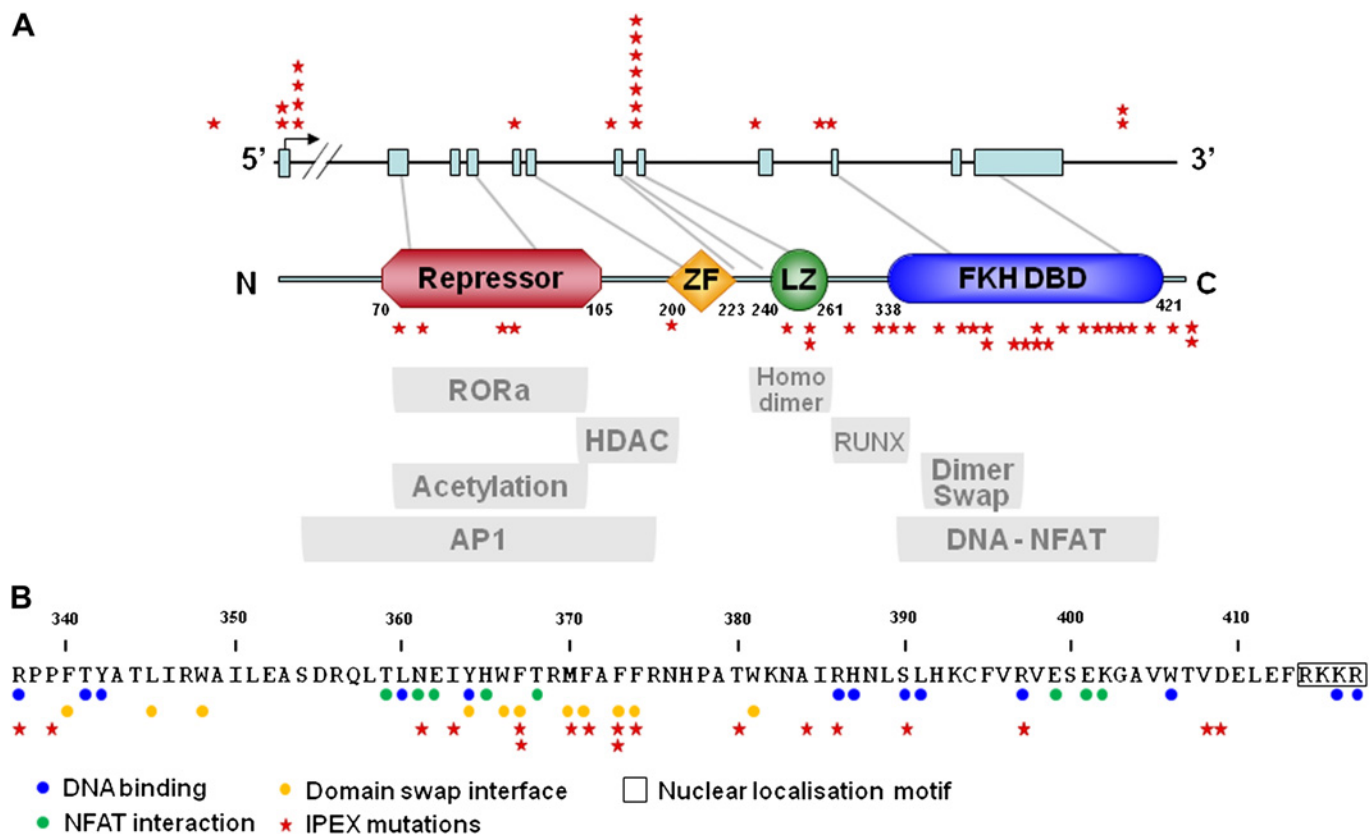


Figure 1 (A) IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X linked) mutations along FOXP3 domains and molecular functions. (B) The forkhead domain.

Interestingly, while the former mutation was associated with a milder, late-onset form of IPEX,⁴⁴ the P187L mutation led to loss of Treg function and disease onset shortly after birth.³²

Zinc-finger domain

Amino acids 200–223 encode a classic C2H2 zinc finger. The role of this domain in the normal function of FOXP3 is unknown. It does not appear to be involved in homo-oligomerisation of the protein, and mutations that destroy the structure of the zinc-finger do not appear to significantly affect the ability of FOXP3 to repress gene transcription from the IL-2 promoter.⁵⁹ Interestingly, there have also been no IPEX mutations described in this domain of FOXP3 that could provide a clue to its function.

LZ domain

The LZ domain extends between a.a. 240–261. Several IPEX mutations are found in this short interval, the most studied of which is the Δ E251 mutant.^{18 20 22 30 46 77 81} Studies show that the LZ domain is required in order for FOXP3 to homo-oligomerize,^{59 82} but not for FOXP3 to form high molecular weight protein complexes.⁷⁷ In addition, either IPEX-derived or experimental disruption of the LZ domain leads to a loss in transcriptional regulation by FOXP3, and subsequently of suppression by Treg cells.^{59 82 83} In particular, a naturally-occurring splice variant of FOXP3 lacking both exons 2 and 7, which encodes the LZ domain, lacks regulatory properties and has been suggested to play a role in regulating the function of the other FOXP3 isoforms by a dominant negative effect.⁸³ Finally, the association of FOXP3 with HAT and HDAC proteins is partially abrogated in LZ mutants, and the resulting complex also partly loses its ability to bind DNA.⁴⁷ Functionally, this

translates into a partial abrogation of the repressive function of FOXP3. As such, LZ mutations in IPEX are expected to result in severe deficiencies in the immunoregulatory properties of FOXP3.

The LZ–FKH loop

The amino acids between the LZ and FKH domains of FOXP3 (a.a. 261–337) do not constitute a defined functional domain, but have been shown to be essential for the binding of FOXP3 to RUNX.⁸⁴ The RUNX transcription factors are critical enhancers of IL-2 expression in T cells and have been suggested to play a role in autoimmunity.^{84 85} Disrupting the binding of FOXP3 to RUNX1 impairs the FOXP3-dependent suppression of IL-2 production and attenuates its suppressive activity.⁸⁵ Knockdown of Runx1 in Treg cells abrogates their suppressive activity, suggesting the interaction between Runx1 and Foxp3 is essential for Treg function in vitro.⁸⁵ Not all mutations affecting this area have proven equally deleterious. For instance, transduction of the F324L mutant into T cells has been reported to induce essentially normal expression of surface and secreted Treg markers (eg, CD25, cytokines), and to drive normal suppressive potency in Teff cells.⁴⁹ Consistently, this mutation is associated with a milder form of IPEX (table 1).

DNA-binding, FKH domain

The FKH domain spans a.a. 337–421 in the C-terminal region of the protein. Like the N-terminal region, the FKH domain is necessary for most aspects of FOXP3 function. Accordingly, the majority of mutations found within the coding sequence of FOXP3 lie within the FKH domain (table 1, figure 1). Deletion of the FKH domain (truncated after a.a. 327) abrogates FOXP3's

Table 2 The various domains of the FOXP3 protein, and the predicted functional impact of mutations on FOXP3 regulatory function

Sequence	Affected molecular domains	Expected mechanistic dysfunctions	Expected functional consequence
1–69	Repressor domain	Partial loss of transcriptional repression	Activation-induced inflammatory cytokine production by Treg
70–105	NFAT:AP1 repression	Partial loss of transcriptional repression	Activation-induced inflammatory cytokine production by Treg
	ROR α binding	Loss of Th17 control	Overzealous Th17 responses
	Lysine acetylation	Deregulated subcellular localisation	Deficient transcriptional regulation.
106–132	NFAT:AP1 repression	Loss of transcriptional repression	Activation-induced inflammatory cytokine production by Treg
	Association with HDAC	Impaired access to chromatin	Deficient transcriptional regulation
133–190	Association with HDAC	Impaired access to chromatin	Deficient transcriptional regulation
200–223	Zinc finger domain	NA	NA
240–261	Leucine zipper domain	Loss of FOXP3 oligomerisation	Deficient transcriptional regulation
		Partial loss of DNA binding and HDAC association	Deficient transcriptional regulation
261–337	LZ-FKH loop	Binding to RUNX1	Activation-induced inflammatory cytokine production by Treg
337–421	DNA binding	Impaired binding to DNA	Deficient transcriptional regulation
	NFAT/AP1 repression	Loss of transcriptional repression	Activation-induced inflammatory cytokine production by Treg
	Swap dimer formation	Unstable FOXP3 dimers	Deficient transcriptional regulation

ability to bind DNA as measured by various in vitro DNA-binding assays.⁸⁶ The importance of the FKH domain for in vivo Foxp3 function is demonstrated by the Scurfy mouse in which a two-nucleotide insertion in exon 8 of the *Foxp3* gene causes a frameshift and premature termination codon that deletes the FKH domain. This domain also interfaces with the transcription factors NFAT and NFkB,⁸⁷ and targeted mutations of the NFAT-binding residues in the FKH domain lead to a loss of IL-2 repression.⁶⁴ However, of eight residues currently identified as NFAT-binding (figure 1), none have been identified as causative mutations in IPEX patients, possibly due to their extreme deleterious effect.

In addition, the recently reported partial crystal structure of the FOXP3/DNA complex demonstrated that a segment of the FKH domain forms a domain-swap conformation that is required for FOXP3 to form a stable dimer. This conformation was shown to be critical to its function.⁸⁸ Predictably, several IPEX mutations directly affect residues that are at the domain-swap interface, including F367C, F367L, M370L, F371C, F373V, F373A and F374C, many of which are associated with severe clinical outcomes.^{10 18 20 22 27 34 40 45 46 49 53–55} Notably, the FKH domain also directs the nuclear localisation of FOXP3 through an RKKR nuclear localisation motif found between a.a. 414–417.⁵⁹ However, no IPEX mutation has yet been described in this interval.

The impact of various IPEX mutations located in the FKH domain on FOXP3 transcriptional activity and on Treg function has been extensively studied. Lopes *et al* identified several mutations that disrupt the transcriptional repression activity of FOXP3 (eg, R337P, R347H, F371C and R397W). In a more recent study, McMurchy *et al* reported that the F373A mutant also lacked transcriptional repression activity.⁴⁹ In addition, we have shown that cells from an IPEX patient with a A384T mutation are significantly reduced in their suppressive activity.²⁸ These studies also report mutations within the FKH domain, that do not affect the transcriptional repression of IL-2 by FOXP3 (eg, I363V, C424Y),⁵⁹ or its capacity to drive the suppressive activity of Treg cells (eg, R347H).⁴⁹

Despite recent insights into the functions of each FOXP3 domain, the role that each plays in mediating and maintaining Treg suppressive capacity under normal physiological circum-

stances remains unclear. Indeed, it has been reported that complementing the N-terminal region of FOXP3 with a nuclear localisation sequence suffices to provide Treg cells with a phenotype of anergy, but not suppressive function.⁶⁵ These findings suggest that FOXP3-driven transcriptional regulation is mediated cooperatively by its N-terminal region and its FKH domain.^{64 65} One problem may be that many of the assays used to evaluate FOXP3 function in vitro using ectopic expression systems may not be able to discern subtle functional abnormalities that are evident in vivo when the protein is expressed at physiological levels. For example, some mutations associated with a severe disease course, do not necessarily translate into an abrogation of FOXP3 function, as their ectopic overexpression results in T cells adopting a Treg-like phenotype.⁴⁹ Moreover, the impact these mutations have on FOXP3 function does not show any correlation with the severity of the resulting disease (table 1). Mutations such as A384T, for instance, have been described in association with both milder and severe cases of IPEX^{19 28} (see also d'Hennezel *et al*, manuscript in preparation). On the other hand, siblings affected with the same mutation tend to develop the disease with a course, timeline and severity that are strikingly similar.³¹ Hence, it is likely that the genetic background, in combination with epigenetic and environmental variables, has a decisive role in determining the disease course. While it is not yet known which particular aspect of the background is most influential on IPEX, several loci have previously been shown to correlate with autoimmunity, the most important of which is HLA.⁸⁹ Polymorphisms in these and other genes encoding immunoregulatory proteins may play a significant role in shaping the ultimate severity of IPEX disease.

THERAPEUTIC OPTIONS AND FUTURE DIRECTIONS

By the time a diagnosis of IPEX is suspected or confirmed, patients are often quite ill with significant nutritional deficits, and initial therapies are focused on stabilisation. These may include bowel rest and initiation of total parenteral nutrition, correction of electrolyte and glucose abnormalities, correction of endocrine deficits, treatment of infections and aggressive immunosuppression. Consistent with murine studies demonstrating that the disease phenotype can be adoptively transferred from an affected Scurfy mouse to a lymphopenic mouse using

just the CD4 T cells, initial immunosuppressive therapy directed at T cells is generally most effective. While there are no large clinical trials, our experience is that calcineurin inhibitors (tacrolimus and cyclosporine) are the most effective initial therapies to control disease. Typically in the early stages, these are most effectively administered intravenously to avoid problems with malabsorption and to obtain consistent, therapeutic drug levels. Sirolimus has also been used effectively in IPEX, particularly in patients who may not tolerate calcineurin inhibitors.^{29–30} There are anecdotal reports that T cell depletion using alemtuzumab or anti-thymocyte globulin may be effective to stabilise patients prior to initiating haematopoietic stem cell transplantation (HSCT). Glucocorticoids may be useful initially as an adjunctive immunosuppressant, although they complicate diabetes management and are associated with significant side effects with long-term use. In patients with auto-antibody mediated disease (pemphigus nodularis, autoimmune haemolytic anaemia/thrombocytopenia, etc) B cell depletion therapy (rituximab) has proven effective.²¹

Given that lifespan is significantly curtailed, even for the mildest cases of IPEX, long-term therapy revolves primarily around HSCT for most patients. The minimal goal of HSCT is to restore normal numbers of competent Treg cells. This can be achieved even with low-level mixed donor chimerism because of the selective advantage conferred on Treg cells by expression of normal FOXP3, as further evidenced in studies in carrier mothers.^{91–93} To this end, a variety of transplant conditioning regimens have been utilised, ranging from minimal intensity to fully myeloablative.^{38–43–54–57–63–92–94} In general, reduced intensity conditioning regimens have been most successful and have been associated with less morbidity and mortality, although there have not been enough patients transplanted to specifically recommend a particular regimen.^{38–43–63–92–94} In terms of donor stem cell source, matched sibling, matched unrelated, and cord blood stem cells have all been used successfully. If transplantation is performed early in the course of disease, before the onset of diabetes or thyroiditis, it is entirely curative. If done after the onset of endocrinopathy, the bowel disease and other autoimmunity is cured but in most cases, the endocrine problems persist because of the inability of these organs to regenerate.

In the future, there is hope that gene therapy or gene repair approaches may be used to treat IPEX. The Treg cells certainly have the appropriate selective growth advantage that appears to be critical for successful treatment by gene therapy. The great challenge of gene therapy will be finding a gene delivery approach that delivers the appropriate level of FOXP3 expression. Too little will generate insufficient numbers of Treg cells to cure disease, and too much will lead to an overly immunosuppressed state similar to that observed in Foxp3 transgenic mice expressing multiple copies of the gene. Because of this, gene repair approaches that seek to merely correct the mutation in the endogenous locus are more appealing, but also face technical challenges that will make them more difficult to bring to fruition.

SUMMARY

As discussed in this review, FOXP3 plays a central role in the generation of functionally suppressive Treg cells. It likely does this through a number of complex interactions with other proteins that are yet to be fully understood. The impact of the various IPEX-associated FOXP3 mutations on its association with these other proteins remains to be systematically elucidated and may explain why the clinical phenotype of IPEX can

be somewhat variable. In addition, there are likely disease modifying genes and possibly environmental factors that affect Treg cell function and may explain some of the variability in clinical phenotype that is observed in different patients with the exact same mutation. We believe that increasing our understanding of how various FOXP3 mutations impact protein–protein interactions, transcriptional regulatory function and Treg generation will make it possible to understand the elements that shape the clinical phenotype and prognosis of IPEX. We also believe that this will help us understand in a broader sense how Treg cell dysfunction may occur and how this may impact the course of other autoimmune disorders.

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Eva d'Hennezel, Khalid Bin Dhuban, Troy Torgerson, et al.

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