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T Regulatory Cell Biology in Health and Disease

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Abstract

Regulatory T (Treg) cells that express the transcription factor Forkhead box protein P3 (FoxP3) play an essential role in enforcing immune tolerance to self tissues, regulating host-commensal flora interaction and facilitating tissue repair. Their deficiency and/or dysfunction triggers unbridled autoimmunity and inflammation. A growing number of monogenic defects have been recognized that adversely impact Treg cell development, differentiation and/or function, leading to heritable diseases of immune dysregulation and autoimmunity. In this article, we review recent insights into Treg cell biology and function, with particular attention to lessons learned from newly recognized clinical disorders of Treg cell deficiency.

Keywords

Regulatory T cell (Treg); T conventional cell (Tconv); Immune dysregulation; Autoimmunity; IPEX; IPEX like

Introduction

T lymphocyte has a fundamental role in fighting foreign pathogens by generating a diverse repertoire of antigen receptors through antigen receptor genes rearrangement [1]. Unfortunately, this diversity might leads to generation of T cell populations that recognize self-antigen and might cause autoimmunity [2]. One way of protection from these self-reactive T cells is by the process called negative selection that prevents such harmful cells from maturation by successful inactivation or clonal deletion in thymic tissue. Several studies have shown high rate of autoimmunity in genetic mutations affecting thymic central tolerance [3, 4]. As some of these autoreactive T cells might escaped medullary thymic epithelial tissue to the periphery or might be exclusively expressed in the peripheral organs, another way of immune tolerance is necessary for the elimination of these self-reactive cells. For that reason, dominant tolerance ensured by regulatory T cells has been documented as

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Compliance with Ethics Guidelines

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an important strategy to maintain peripheral tolerance in human and mice [5, 6]. The importance of this population in mice have been delineated by neonatal thymectomy performed at day 3 of life that resulted in autoimmunity and production of autoantibodies, while transferring thymic or splenic T cells to these thymectomized mice from adult wild type prevented the development of the immune mediated inflammation and tissues damage [7, 8]. Compelling evidence has shown these thymic suppressive population expresses CD4 and IL-2 receptor α chain (CD25) and has been characterized as $CD4^+CD25^+$ Treg cells [9]. Subsequently, Forkhead box protein P3 (FOXP3) was identified as a transcription factor indispensable for Treg cell development and function [10–12]. Deleterious mutations in *FOXP3* lead to immune dysregulation, polyendocrinopathy and enteropathy X-linked (IPEX) syndrome in human as well as fatal autoimmunity in scurfy mice [13, 14]. The aim of this review is to highlight current information of the defining features of T regulatory cells as well as their phenotypic and functional heterogeneity with particular emphasis on the consequences of this compartment deficiency and or dysfunction in the development of immune dysregulation and autoimmunity.

Treg cell Subsets and markers

Treg cells represent 5% to 10% of peripheral $CD4^+$ T cell compartment in humans and in mice. The two key populations of Treg cells are those that develop in the thymus, referred to as natural or thymic Treg (nTreg or tTreg) cells and induced Treg that develop in the periphery from naïve conventional $CD4^+$ T cells (iTreg or pTreg cells, respectively) [15].

In general, $FOXP3^+$ Treg cells express high levels of interleukin-2 receptor α (CD25) and a low level of IL-7 receptor α (CD127) on the cell surface [16]. The majority of Treg cells constitutively express high level of the inhibitory molecule cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the glucocorticoid-induced TNFR family related (GITR), as well as the regulatory cytokines IL-10 and transforming growth factor-beta (TGF-β) [17–20]. While FOXP3 staining is best available marker for Treg cells, it may also be transiently induced at low levels in human (but not mouse) T conventional (Tconv) cells upon their activation. Expression of other Treg cells markers such as CD25 and CTLA4, and down regulation of CD127, may similarly be effected upon activation of Tconv cells. Accordingly, employment of combinatorial markers such as $FOXP3^{high}CD25^{high}CD127^{low}$ may better discriminate human Treg cells from otherwise activated Tconv cells. Human Treg cells can be further classified based on their activation profile using FOXP3 and CD45RA/RO. Resting Treg cells are $CD45RA^+FOXP3^{low}$, activated Treg cells are $CD45RA^-FOXP3^{high}$ while the $CD45RA^-FOXP3^{low}$ population reflects effector cytokine-producing non-Treg cells [21].

Two markers have been used to discriminate nTreg from iTreg cells. Helios, a member of the Ikaros family of transcription factors, is highly enriched in nTreg as compared to iTreg cells and is commonly used as a marker of Treg cells of thymic origin [22]. Furthermore, Neuropilin-1 is similarly enriched in nTreg versus iTreg cells. However, expression of both markers can be altered by T cell activation and they should be judiciously used in discriminating those populations under conditions of inflammation or generalized T cell activation [23].

Finally, Treg cells that become unstable and lose their FOXP3 expression are referred to as ex-Treg cells [24]. They acquire effector functions and may contribute to pathology in inflammatory and autoimmune diseases [25•].

Treg cell development

nTreg cell development in the thymus proceeds through discrete steps including intermediate avidity interactions between self reactive TCR on developing thymocytes and their cognate antigens presented in specialized thymic niches. These interactions, in the context of optimal input from co-stimulatory molecules and cytokines, enable the acquisition of CD25 expression, epigenetic modification of *FOXP3* and other Treg cell-related genetic loci, leading to upregulation of FOXP3 and other Treg cell markers[26].

The interaction of the T cell receptor (TCR) with self-antigens in the thymus is pivotal for Treg cell differentiation. Typically, conventional thymocytes that receive high strength TCR signals undergo apoptosis while those that pass positive selection and receive low affinity signals will eventually develop into mature T cells. In contrast, the development of Treg cells in the thymus appears to require intermediate strength interactions between their TCRs and self-peptide/MHC ligands. These interactions, in the context of specialized niches in the thymic medulla, including medullary thymic epithelial cells (mTecs) and hematopoietic antigen presenting cells, lead to the upregulation of CD25 and also enabling subsequent developmental steps in thymic Treg cell development [27].

In addition to TCR, co-stimulatory molecules, including CD28 and members of the tumor-necrosis factor receptor superfamily, including GITR, OX40 and TNFR2, all make important contributions to Treg cell differentiation [28•, 29]. These pathways converge on downstream signaling intermediates, most notably NF-κB, STAT5, mTOR and others, to promote Treg cell development [30].

FOXP3 is upregulated at terminal stage in thymic Treg cells differentiation under the action of IL-2 via the CD25 containing high affinity IL-2R complex that provide the critical stimulus inducing its expression. FOXP3 itself is dispensable for thymic Treg cell development. However, it plays an indispensable role in enabling Treg cell function in the periphery. FOXP3 expression directly regulates a sizeable component of the Treg cell transcriptome, including further upregulation of CD25 and high expression of suppressor genes as well as repression of pro-inflammatory cytokines. It also shapes the Treg cell transcriptome by stabilizing the interaction of its different component, including those induced by TCR and cytokine signaling. On the other hand, a large fraction of the core Treg cell transcriptome is maintained in the absence of FOXP3, consistent with the FOXP3-independent development of Treg cells. Nevertheless, the mutant Treg cells de novo acquire the phenotype and the relevant genetic circuitries of activated, unstable cytotoxic T cell like-cells that lack regulatory functions [31].

Beside FOXP3 expression, epigenetic (external DNA modifications that affect the gene function without changing DNA sequencing) has an important impact on Treg cell development and function. These epigenetic marks show some heterogeneity between Treg

and Tconv cells. Indeed, most of nTreg cells have a completely demethylated CNS2 (conserved non-coding region 2) at the *FOXP3* locus while, the Tconv cells ($CD4^+CD25^{low}$) posses partial methylated pattern even after transient FOXP3 upregulation. Treg-type DNA hypomethylation is exclusively imprinted in nTregs cells and found to be important in their suppressor function, lineage stability and controlling Treg cell-specific genes expression [32–35•].

Additionally, other transcription factors, including Helios and GATA3, play an important role in conferring suppressive functions on Treg cells, especially in the context of different inflammatory Cues [36•–38]. Homeostatic proliferation of Treg cells in the periphery is dependent on cytokines, most notably IL-2, which act to maintain Treg cell fitness and maintain their stability and regulatory functions. In contrast, other signals including those delivered by the Notch family of receptors act to restrain Treg cell function in the periphery [39••].

In addition to nTreg cells, de novo generation of iTreg cells contributes to peripheral tolerance [40]. iTreg cells are particularly abundant at the mucosal interface, where they are induced in specialized niches by the action of tolerogenic antigen presenting cells (APCs) such $CD103^+$ dendritic cells in the gut and $CD11c^+$ macrophages in the lung. iTreg cell generation is dependent on TGF-β production by the APCs, and is potentiated by the production of retinoic acid, which acts to stabilize the newly formed iTreg cells [41–43]. These cells posses a TCR repertoire distinct from that of nTreg cells, and the two populations synergize to maintain peripheral immunological tolerance [44]. iTreg cells are enriched at the environmental interfaces, and are enriched in specificities directed at microbial antigens [45]. Microbial sensing by iTreg cells in the gut via the toll like receptor associated adaptor protein MyD88 promotes their function and their differentiation into T follicular cells that regulate anti-commensal IgA production in the Peyer's patches [46•, 47•]. By regulating the anti-commensal IgA response, the Treg cells play an essential role in shaping a healthy commensal flora that contributes to peripheral tolerance.

Under conditions of sustained inflammation and/or lymphopenia, iTreg cells (and to a lesser extent nTreg cells), may acquire attributes of effector T cells and express cytokines and effector molecules that contribute to the inflammatory response such as food allergy [48, 49•]. *In extremis*, this plasticity may lead to the loss of FOXP3 expression, leading as mentioned above to the generation of pathogenic ex-Treg cells that participate in disease pathology [25]. Collectively, these findings indicate that Treg stability, function and fate specification are influenced by multiple mechanisms that might be upstream of FOXP3.

Treg cells: Regulatory Mechanisms and Functional specialization

Regulatory T cells are central players in the area of the peripheral tolerance. By their immunosuppressive capability, they maintain immune homeostasis and prevent autoimmunity in diverse anatomical locations. The suppressive mechanisms of this population may proceed by contact dependent suppressive mechanisms either through inhibitory receptors (e.g. CTLA-4, LAG3, Galectin-1) or by means of perforin and granzyme B-dependent, Treg cell-mediated cytotoxic target cell killing [50–53]. Treg cells

may also mediate contact independent suppression either by acting as IL-2 sink (through Treg cell-bound CD25) or by producing inhibitory cytokines (e.g. IL-10, TGF-β, IL-35) [54–56].

While more than the general suppressive activity, Treg cells might further differentiate in the periphery as a part of Treg plasticity to a specialized fates that specifically control Th1, Th2, Th17, or T follicular helper (Tfh) type immune responses by acquiring the transcriptional program of the specific effector cells they suppress, such as T-bet, IRF4, STAT3, or Bcl-6, respectively [57–60]. It is also important to note that the suppressive function of Treg cells might limit the beneficial effector responses against tumors and chronic infections [61].

Interestingly, Treg cells have an important role in tissue protection both directly by inducing tissue repair through amphiregulin production and indirectly by limiting tissue damage through the down-regulation of the inflammatory response [62••]. Beyond tissue protection, numerous reports have also suggested other Treg cell functions, including protection against allergic disorders; transplant rejection and atherosclerosis as well as controlling metabolic disorders [63–65].

Monogenic Diseases resulting in Treg cell Deficiency/Dysfunction

Treg cells play a key role in immune homeostasis by maintaining a balanced adaptive immune response. Human congenital defects that affect Treg cell number and or function disrupt this balance and result in autoimmunity, lymphoproliferation, allergic dysregulation and ongoing lymphocytic infiltration in different organs, which lead to disease progression and impact patient survival. The spectrum of manifestations due to Treg cell defect might range from mild allergy or autoimmunity to lethal immune dysregulation disorders. Interestingly, several human genetic disorders have been described recently and noted to have a tremendous impact on Treg cell development and functional activity. A loss of function mutation in *FOXP3*, the key transcriptional factor for Treg cell differentiation, lead to IPEX phenotype. Subsequently, a number of other gene defects have been described to cause IPEX-related phenotypes including loss of function mutations in *CD25, STAT5b, LRBA and CTLA4* (Fig. 1).

IPEX

IPEX is a rare genetic disorder resulting from lack of functional Treg cells due to loss of function mutations in *FOXP3*. It exclusively affects males given its X-linked recessive pattern of inheritance, and is often fatal within the first few years of life unless rescued with bone marrow transplantation [66]. Clinically, IPEX presents with a triad of autoimmune enteropathy, autoimmune endocrinopathy, and eczematous dermatitis. The commonest manifestation is enteropathy followed by endocrinopathy especially insulin-dependent type 1 diabetes mellitus. Additional described manifestations include immune-mediated cytopenia, which may present as neutropenia, anemia and/or thrombocytopenia, and autoimmune nephropathy, hepatitis and lung disease. Food allergy with elevated serum IgE and peripheral eosinophilia are very common in this disorder, reflecting a breakdown in oral tolerance. Patients with IPEX usually have a wide range of autoantibodies due to adaptive

immune dysregulation. As more than 60 *FOXP3* mutations have been reported to date, it has been observed from the clinical phenotype reported for these mutations that there is genotype/phenotype relationships [67]. The only available curative treatment for this disease is allogeneic hematopoietic stem cell transplant with reduced-intensity chemotherapy. Before transplant, patients require nutritional support and immunosuppressive therapy, which may include glucocorticoids and/or steroid-sparing agents such as calcineurin inhibitors, the mechanistic target of rapamycin (mTOR) inhibitor and others [68•].

IPEX like disorders

IPEX-like disorders have been described in many patients, both males and females, who lack detectable mutations in *FOXP3* [69]. Putative mutations in this syndrome may involve genes that adversely affect Treg cell differentiation and function and that present with an overlapping clinical picture with that of FOXP3 deficiency. To date, the most well characterized IPEX-like disorders include mutations along the IL-2Rα/STAT5b and CTLA4/LRBA pathways, detailed below.

CD25 and STAT5b deficiency

Fatal autoimmunity was initially described in mice lacking IL-2, IL-2Rα, IL-2Rβ or STAT5 isoforms. Reconstitution of these mutant mice with Treg cells from wild type mice rescues disease [70–73]. These observations confirmed the critical role for the IL-2R-STAT5 signaling pathway in Treg cell homeostasis and function. Interleukin-2 (IL-2) receptor is formed by three subunits namely α (CD25), β (CD122) and γ (CD132) subunit. Among those, CD25, the high affinity IL-2 receptor, is a unique subunit that exclusively binds IL-2 and constitutively expressed at high levels by Treg cells. CD25 deficiency in human leads to both autoimmunity and immunodeficiency with recurrent infections. Features of CD25 deficiency that shared with IPEX include chronic eczema, enteropathy, lymphoproliferation and autoimmunity disorders such as alopecia, diabetes mellitus, thyroiditis and autoimmune hemolytic anemia [74–77]. CD25 deficiency is permissive to Treg cell differentiation, with normal count of $FOXP3^+$ Treg cells found in circulation [78]. However, loss of CD25 expression impairs Treg cell suppressive function by several mechanisms. These include the defective production by Treg cells of the suppressive cytokine IL10, and their failure to provide an IL-2 “sink” that deprives Tconv cells of IL-2, leading to their apoptosis in a Bim-dependent manner [54, 75, 79]. Finally, the decreased sensitivity of CD25-deficient Treg cell to IL-2 impairs their metabolic fitness in the context of an immune response [80].

In contrast to FOXP3-deficient patients, CD25 deficiency is distinguished by chronic infections with members of the herpes family of viruses. The susceptibility to viral infections may reflect the importance of IL-2 signaling in generating effective cytotoxic $CD8^+$ effector and memory T cell responses as well as NK cell activation [81–83]. Of note, CD25 deficient patients reported to date lack food allergies and significantly elevated IgE level, reflecting a distinct mechanisms for the control of oral allergic sensitization by Treg cells.

The transcriptional activating factor STAT5b, part of IL2/STAT5 axis, is required for signal transduction of gamma chain cytokines, growth hormone, erythropoietin, prolactin and

granulocyte colony-stimulating factor (G-CSF) [84]. STAT5b deficiency presents with growth failure, delayed puberty, prominent forehead, recurrent infections, chronic diarrhea, eczema and lymphoid interstitial pneumonitis [85, 86]. Autoimmunity is a common manifestation in this monogenic defect due to abnormal Treg cell development and function and most of the patients have hypergammaglobulinemia and increased percentages of memory T cells [87]. Finally, low IGF-1, low IGFBP-3, and high prolactin are usually present, reflecting defective growth hormone receptor signaling [88].

LRBA and CTLA4

Cytotoxic T lymphocyte antigen–4 (CTLA-4) is an inhibitory receptor expressed on both Treg and activated Tconv cells. CTLA4 expression on Treg cells is essential for their contact dependent suppression. CTLA4 regulates the immune response by competing with CD28 for the ligands CD80/CD86 and also removing these ligands from antigen-presenting cells (APCs) via transendocytosis [89], which abrogates subsequent T effector cells activation. Recent report showed that CTLA4 trafficking and expression is regulated by LPS-responsive and beige-like anchor (LRBA) [90]. Both CTLA4 haploinsufficiency and LRBA deficiency leads to severe immune dysregulation and fatal autoimmunity in human and several patients who presented recently with IPEX like phenotype were found to have mutations in *LRBA* [91••] or *CTLA4* gene [92•, 93•]. Collectively, the clinical presentation of those two monogenic defects is similar, ranging from CVID phenotype to severe IPEX-like disorder. These features include recurrent infections, hypogammaglobulinemia, inflammatory bowel disease, lymphoproliferation with Granulomatous lymphocytic infiltration (brain, lung, liver, kidney, bone marrow), solid tumors, intense autoantibody responses, and profound autoimmunity including autoimmune cytopenia, psoriasis, alopecia, arthritis and autoimmune hepatitis [91–97•]. There are many immunosuppressive medications have been tried initially to suppress immune dysregulation and autoimmunity without good clinical improvement. Interestingly, it has been shown recently that medications targeting CTLA4 like CTLA4 fusion proteins and hydroxychloroquine (lysosomal degradation inhibitor) are highly effective in controlling the profound autoimmunity in these disorders [90, 98••]. Finally, the curative treatment option is still hematopoietic stem cell transplantation despite the high risk of mortality and possible recurrence of autoimmunity post transplant [99].

Conclusion

It is now clear that Treg cells play a critical role not only in maintaining peripheral tolerance and preventing autoimmunity (negative regulation) but also in promoting tissue repair, intestinal IgA response and healthy commensalism (positive regulation). Exploring the molecular mechanisms involved in Treg cell dysfunction in IPEX and IPEX-like disorders would provide insights into the biology of Treg cells and their role in common autoimmune and immune dysregulatory diseases. This understanding enables the development of successful therapeutic interventions in these disorders.

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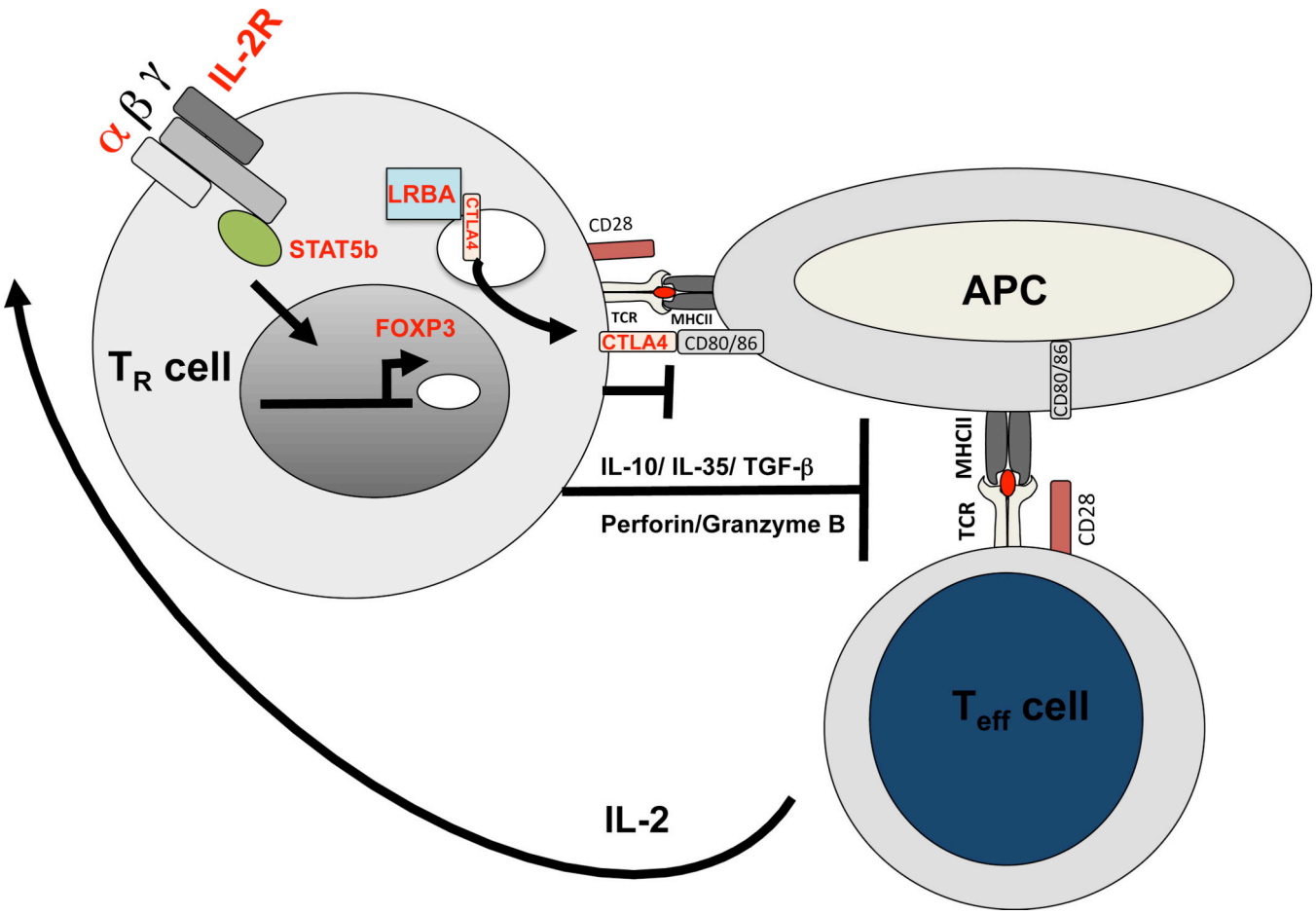

Fig. 1.

Defective Treg cell suppressive mechanisms in IPEX and IPEX-like disorders. Shown are key pathways for maintaining Treg cell homeostasis and function highlights human monogenic defects that lead to severe immune dysregulation due to altered Treg cell function. The engagement between IL-2 and IL-2R and the initiation of signal transduction through Stat5b phosphorylation are important for FOXP3 expression. While FOXP3 deficiency leads to IPEX, loss of function mutations in IL2Rα or STAT5b manifest with IPEX like phenotype. LRBA-CTLA4 pathway is indispensible for Treg cell suppressive activity. LRBA controls CTLA4 expression and the later provides a negative feedback both directly by competing CD28 for binding to CD80/CD86 ligands and indirectly by down-regulating the co-stimulatory molecules on APCs. Both LRBA and CTLA4 deficiency cause IPEX-like disorder.