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Natural regulatory T cells in autoimmunity

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Abstract

The suppressive/immunomodulatory function of CD4+CD25+Foxp+ regulatory T (Treg) cells is crucial for the maintenance of immune homeostasis, which helps to prevent autoimmunity and reduce the inflammation induced by pathogens and environmental insults. This review summarizes the current knowledge on the types and mechanisms of action of Treg cells and their role in the immune tolerance to self antigens, with a particular focus on naturally occurring Treg cells.

Introduction

The mechanisms that control immune responses against self-antigens for the prevention of autoimmunity fall into two broad categories: central tolerance and peripheral tolerance. Central tolerance is achieved in thymus and bone marrow and associates with the blockage of developing lymphocytes that encounter self-antigens. Peripheral tolerance controls the activity of mature lymphocytes that have left their generative organs and encounter self-antigens in peripheral tissues. The mechanisms of peripheral tolerance are multiple and include the lack of immune response to self-antigens (ignorance), the deletion of self-reactive cells by apoptosis, the hyporesponsiveness (anergy) to antigenic stimulation, and the activity of regulatory/suppressor cells - whose existence was postulated decades ago and now represents a key element in the understanding of the regulatory network of responses that maintain immune homeostasis, so that Treg cells are currently regarded as key players in the mechanisms of peripheral immune tolerance.

Types of Tregs

Treg cells are classified on the basis of their origin, generation, and mechanisms of action. Based on their origin, a distinction is made between natural (constitutive) and inducible (adaptive) CD4+CD25+Foxp3+ regulatory T (Treg) cells (Figure 1). These two types of cells appear to have complementary and overlapping functions in the control of immune responses. Natural Treg cells develop in thymus and seed peripheral tissues where they can suppress the activation of effector cells [1]. Adaptive regulatory T cells comprise different subtypes of cells including IL-10-producing Tr1 cells [2], transforming growth factor- β (TGF- β)-producing Th3 cells [3], and FOXP3+ inducible T cells. Adaptive Treg cells that derive from CD4+ T cells in the periphery [4] often have similar phenotype and function as natural Treg cells, yet they may use different mechanisms of immune regulation. Indeed, natural Treg cells require a cell–cell interaction to suppress (as shown in transwell experiments where the supernatants from activated Treg cells do not have suppressive properties) [5], whereas soluble factors (e.g. TGF- β) may be necessary for the optimal action and maintenance of adaptive Treg cells [6]. This review focuses on the natural Treg cells

that suppress the induction and/or activity of effector target cells, to prevent or terminate exaggerated immune responses. The adaptive Tregs are discussed in detail in another review in this issue of the journal [7].

Tr1 regulatory T cells

IL-10-producing Tr1 cells were originally isolated from patients with severe combined immunodeficiency who had undergone successful HLA-mismatched bone marrow transplantation [9-10]. Subsequently, they were generated from naïve CD4⁺ T cells by repeated stimulation with IL-10 or with immature dendritic cells (DC), vitamin D3 and dexamethasone [11]. Interestingly, IL-10-producing suppressive Tr1 cells generated *in vitro* from naïve CD4⁺ T cells in the presence of dexamethasone and vitamin D3 did not express FOXP3, a transcription factor that has a key role in the suppressive function of Treg cells (as discussed later) [12].

Antigen-specific Tr1-cell clones could also be generated during infection of mice with *B. pertussis* or murine leukemia virus, and in humans infected with Epstein-Barr virus (EBV), *M. tuberculosis*, HIV, HCV or with the nematode *Onchocerca volvulus* [13-17].

Th3 regulatory T cells

TGF- β -expressing Th3 cells were originally identified in mice following induction of oral tolerance to myelin basic protein (MBP) [18-19]. Th3 cells suppress MBP-specific Th1 effector cells *in vivo* and *in vitro* in a TGF- β -dependent, antigen non-specific manner [18]. They can be also induced *in vitro* upon exposure of naïve CD4⁺ T cells to TGF- β , and produce IL-4 and IL-10 and, like Tr1 cells, can be generated in the periphery from naïve CD4⁺ T cells after encounter with antigen presented by DC [1].

Natural Treg cells

Natural CD4⁺CD25⁺Foxp3⁺ regulatory (or suppressor) Treg cells are the most-studied subset of suppressor CD4⁺ T cells. They are engaged in the control of immune self-tolerance, allograft rejection and allergy, and are also important in inhibiting the effector functions during infection and in tumors. The removal or a functional defect of Treg cells from normal rodents leads to the development of various autoimmune diseases [19], because these cells actively suppress the activation and expansion of autoreactive immune cells.

Natural Treg cells represent 5-10% of the peripheral CD4⁺ T cell population in mice and are characterized by the constitutive expression of CD25, (the interleukin 2 (IL-2) receptor α -chain), and low expression levels of CD45RB [20-21]. In humans, they represent 1%-2% of total CD4⁺ T cells, particularly the ones with highest CD25 expression (CD25^{high} or CD25^{bright}) [22]. However, CD25 is not a unique marker for Treg cells because it is also present on activation T cells and is thus also expressed by effector Th1 and Th2 cells. As a consequence, a suppressive function has also been documented for CD25⁺ T cells [1].

A seminal advance in the understanding of Treg cell biology came with the identification of the X chromosome-encoded member of the forkhead/winged-helix family of transcription regulators FOXP3 (also known as scurf or forkhead box P3) [23]. Mice and humans that harbor a loss-of-function mutation in the FOXP3 gene are affected by fatal lymphoproliferative immune-mediated disease - IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome in humans, and the scurfy phenotype in mice [24-26]. FOXP3 appears required for the development, maintenance and suppressor function of Treg cells [23,27], and the loss of FOXP3 in Treg cells - or its reduced expression - leads to the acquisition of effector T cell properties including the production of non-Treg cell-specific cytokines [28-29]. However, the expression of FOXP3 per se is not

sufficient for a regulatory cell function, as human activated T cells can also express FOXP3 without possessing suppressive activities [30-31]. Furthermore, the induction of FOXP3 in human T cells by TGF- β does not confer a regulatory phenotype, possibly in contrast with the mouse data [31]. Since FOXP3, like CD25, may not represent an adequate marker for Treg cells, particularly in humans, additional markers have been sought to possibly identify a unique Treg cell phenotype. Despite the finding of numerous additional markers including the 4 cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), glucocorticoid-induced TNF receptor (GITR), CD62Lhigh, neuropilin-1, CD103 (integrin α E β 7), CD5, CD27, CD38, CD39, CD73, CD122, OX-40 (CD134), TNFR2, lymphocyte activation gene 3 (LAG-3), CD45RBlow, CCR4, CCR7 and CCR8 [32], none has been found exclusive for these cells. At present, to discriminate Treg cells from conventional (activated) CD4+ T cells, particularly in humans, the inclusion of a low expression of CD127 (the α chain of the IL-7 receptor) and a modulated CD45RB expression [33] have been proposed as co-markers together with the expression of FOXP3 and CD25 [34].

Recently, two subsets of thymus-generated FOXP3+ Treg cells have been identified on the basis of their differential expression of the costimulatory molecule ICOS [35]. The ICOS+FOXP3+ phenotype is endowed with high IL-10-producing capacity, while the ICOS-FOXP3+ subset is endowed with high TGF- β production [35]. Both cell subsets appear to use cell contact-dependent and independent mechanisms for immune suppression in the periphery.

In terms of repertoire, natural Treg cells have a broad one that recognizes various self and non-self antigens [36]. Natural Treg cells are generated in thymus (Figure 1) through high avidity MHC class II-dependent/T cell receptor (TCR) interactions [37-40]. TCR engagement associates with the induction of FOXP3 during thymic differentiation of Treg cells [41], whereas TCR-induced expression of FOXP3 in the periphery may depend or can be influenced by intracellular signaling, cell proliferation, and the synergy with TGF- β and IL-2 [42]. In addition to the TCR, CD28 costimulation seems to also play an important role in the differentiation of Treg cells, and a marked decrease in the frequency of Treg cells is found in CD28 deficient and CD80/CD86 deficient mice [43-44]. Yet these signals may not be sufficient for FOXP3 upregulation and other signals may be required, e.g. IL-2 and, to a lesser degree, two other common γ -chain (γ c) cytokines, IL-7 and IL-15 (mice lacking IL-2 or the IL-2R α chain have an approximately 50% decrease in FOXP3+ thymocytes, while IL-15 or IL-7 deficiency does not affect the generation of FOXP3+ cells).

The molecular mechanisms by which IL-2 facilitates Treg cell differentiation are not clear. IL-2 may not be required for thymic development of FOXP3+ Treg cells because normal amounts of FOXP3 mRNA are present in CD4+CD25+ thymocytes of young IL-2 deficient mice [45-46]. Studies with CD25 deficient mice indicated that IL-2 is dispensable for the generation of natural Treg cells in the thymus [47-48], whereas CD122 deficient mice (defective of IL-2 and IL-15 signaling) have a profound reduction in Treg cell development. Treg cell defects have also been reported in IL-2/IL-15 double deficient mice [49,46]. Thus, it seems that the absence of IL-2 is likely to be compensated by IL-15 for the generation of natural Treg cells in thymus [46,50-51]. For TGF- β , a role in the differentiation of adaptive Treg cells is clear - not so for natural Treg cells. Studies with T cell-specific deletion of the TGF- β RII receptor suggested that TGF- β may not be involved in thymic Treg cell development [46,52-53], as young TGF- β 1 deficient mice display normal number of thymic Treg cells [46].

Mechanisms of action

The mechanisms of action of human and mouse Treg cells have been studied mostly using *in vitro* systems. However, it is not clear how these studies *in vitro* reproduce the activity of Treg cells *in vivo*. Targets of Treg cell activity include CD4⁺CD25⁻ T cells, CD8⁺ T cells, B cells, monocytes and DC [54-57]. Cell-to-cell contact mechanisms of suppression involve cytotoxic factors including perforin, granzymes, and LAG-3 expression [58]. Treg cells appear to inhibit target cells via: (1) inhibitory cytokines, (2) cytotoxicity, (3) metabolic disruption, and (4) modulation of DC maturation and/or function [58-59]. These mechanisms are analyzed in detail below.

1. Suppression by inhibitory cytokines

IL- 10, TGF- β , and IL-35 are cytokines that stimulate the development of adaptive Treg cells [60]. The role of IL- 10 and TGF- β as suppressive mediators is well known, but their contribution to the function of natural Treg cells is still debated [61]. This is due both to the observation that natural Treg cells operate in a contact-dependent manner and to *in vitro* studies that have suggested that humoral activities related to these cytokines may not be essential for Treg cell suppression [62-64]. However, *in vivo* studies in allergy and asthma models have shown evidence that both natural and adaptive Treg cells can control disease through mechanisms that depend, at last in part, on IL-10 and sometimes on both IL-10 and TGF- β [65-67]. Furthermore, IL- 10 produced by Treg cells is essential for the prevention of autoimmunity in mouse models, in tumors and in IL-10-mediated tolerance [68-74].

For TGF- β , *in vitro* studies that used neutralizing antibodies to this cytokine - or that employed Treg cells that lacked TGF- β - indicated that TGF- β , even as autocrine production, was dispensable for the Treg suppressive function [63,59,75]. However, some studies found a relevant role for cell membrane-tethered TGF- β on the Treg cells in their suppressive activity, both *in vitro* and *in vivo* [76-77]. Although TGF- β appears to play a nonredundant role in the control of intestinal inflammation, Treg cells from TGF- β 1 deficient mice or from mice expressing a dominant negative form of the TGF- β R11 are capable to inhibit colitis [78]. Since the function of TGF- β 1 deficient Treg cells is abrogated by anti-TGF- β antibodies, it seems that the TGF- β that may be required for protection can derive from a non-Treg cell source.

Finally, the newly described inhibitory cytokine IL- 35 (a member of the IL-12 heterodimeric cytokine family) has recently been found expressed by Treg cells, in which it may contribute to the suppressive capacity of these cells, or operate on the target cells [60].

2. Suppression by cytotoxicity

Cytotoxic mechanisms include granzyme A and granzyme B-dependent and perforin-dependent mechanisms. Gene expression arrays showed that granzyme B was upregulated in mouse Treg cells [79-80], where the upregulation of this cytotoxic molecule following cellular activation associated with the killing of target cells by a granzyme B-dependent, perforin-independent mechanism [81]. Of note, granzyme B-deficient Treg cells also display a reduced suppressive activity. Furthermore, 5%-30% of Treg cells in a tumor microenvironment express granzyme B and can suppress NK cells and cytotoxic T lymphocytes (CTL) that fight tumors [82]. Also, activated human Treg cells express granzyme A and can lyse activated CD4⁺ and CD8⁺ T cells in a perforin-dependent, Fas/FasL independent manner [55]. Treg cells can also kill B cells in a granzyme-B-dependent and partially perforin-dependent manner [83]. Activated Treg cells can also induce apoptosis of effector T cells through the upregulation of TRAIL-DR5 (tumor necrosis factor related

apoptosis inducing ligand–death receptor 5) pathway [84] or galectin-1 (galectin-1-deficient Treg cells have reduced regulatory activity *in vitro* [85]).

3. Suppression by metabolic disruption of target cells

Metabolic disruption includes a mechanism of cytokine deprivation-mediated apoptosis, cyclic AMP (cAMP)-mediated inhibition, and CD39- and/or CD73-generated, adenosine receptor 2A (A_{2A}R)-mediated immunosuppression [58-59]. A debate is open on whether the expression of high-affinity IL-2 receptors would make Treg cells competitors with effector T cells for IL-2, with a resulting cytokine-mediated deprivation for target cell and subsequent apoptosis favored by the proapoptotic factor Bim [62,86-87]. However, the lack of effect of anti-CD25 antibody on human Treg cells suggests that IL-2 depletion may not be sufficient for Treg cells to suppress effector T cells [88-89]. On the other hand, Treg cells have been found to suppress effector T cells by directly transferring the inhibitory second messenger cyclic AMP (cAMP) into effector T cells through gap junctions [90]. Treg cells can also provide intracellular or extracellular release of adenosine nucleosides, and the expression of the ectoenzymes CD39 and CD73 can generate peri-cellular adenosine which inhibits activated T cells or inhibits DC through the activation of the adenosine receptor 2A (A_{2A}R) [91-93]. Importantly, the binding of adenosine to A_{2A}R enhances the generation of adaptive Treg cells by inhibiting IL-6 (an inhibitory cytokine for Treg cells) [94] and by promoting TGF- β secretion [95].

4. Suppression through DC targeting

Treg cells can directly affect antigen presenting cell (APC) function [58-59] through mechanisms involving the expression of CTLA-4 on Treg cells (which downregulates or prevent CD80 and CD86 upregulation, the major costimulatory molecules on APC) [96-99] and LAG-3 (CD223, a CD4 homolog that binds MHC class II molecules with very high affinity). LAG-3 can interact with MHC class II on APC, and the binding of LAG-3 to MHC class II molecules expressed by immature DC can result in an inhibitory signal that suppresses the DC immunostimulatory capacity [100].

Also the expression of neuropilin (Nrp)-1 on Treg cells can promote long interactions between Treg cells and immature DC, and restrict the access of effector cells to the APC. Finally, the hydrolysis of extracellular ATP by CD39 may be used by Treg cells to prevent the deleterious effects of ATP on APC function [92]. Altogether, Treg cells seem capable to limit the capacity of DC to stimulate effector cells.

Natural Treg cells and autoimmunity

We describe below the number, function and role of Treg cells in prevalent autoimmune conditions.

Natural Treg cells and systemic autoimmunity

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is characterized by the loss of immune tolerance to self antigens, activation and expansion of autoreactive lymphocytes, and the production of inflammatory mediators and autoantibodies that cause damage to multiple organs. Several studies have investigated the role of Treg cells in SLE, sometimes with controversial results [101]. Most studies have found a reduced or normal frequency of Treg cells in SLE [102], although other studies may have also shown increased numbers. Yet it seems that the numbers of Treg cells is found decreased during active disease flares [103-104] and in active SLE pediatric patients, with an inverse correlation between Treg cells and disease activity as

well as autoantibody levels [105]. Reduced numbers of Treg cells have also been described in the peripheral blood of patients with active SLE (compared with patients with inactive SLE and normal donors), with reduced levels of FOXP3 and a poor suppressive capacity when compared to inactive SLE patients and controls [106-107]. Therapy with corticosteroids and/or immunosuppressive agents has been found to promote an increase in the number of Treg cells [108], and a significant increase of peripheral Treg cells and increased mRNA levels of CD25, FoxP3, and GITR have been found in B-cell depleted patients treated with rituximab at the time of B cell repopulation - where an increase of FOXP3 expression during early B cell-depletion persisted in those SLE patients with clinically active remission of nephritis, and decreased in patients with active disease [109].

Functionally, a reduced suppressive capacity of Treg cells is present in patients with active SLE compared to healthy controls [106,110-111] and in patients with inactive SLE [106], whereas a normal suppressive capacity of Treg is found in SLE patients with either active or inactive disease [104,112-113].

In murine models of SLE, a deficit of Tregs can contribute to the loss of self-tolerance and the development of lupus-like disease [114], whereas the adoptive transfer of Tregs can slow the progression of renal disease and decrease mouse mortality [115]. Lupus-prone mice have lower frequency of Treg cells when compared to non-autoimmune strains [115]. Interestingly, the low prevalence of Treg cells in peripheral tissues found in young lupus-prone mice is followed by an increased in the number of these cells with aging. Since this expansion of Treg cells does not prevent end-organ damage, it is not clear whether it associates with a reduced suppressive function or with an inability of functional Treg cells to efficiently suppress and/or contrast over time continuously expanding autoreactive cells [115].

Autoimmune rheumatic diseases

In the collagen-induced arthritis model of systemic joint inflammation, the adoptive transfer of Treg cells protects from disease [116], whereas the depletion of Treg cells accelerates it [117]. In patients with early rheumatoid arthritis (RA), a reduced number of peripheral Treg cells is observed [118], although the synovial fluid can often contain increased numbers of Treg cells [119].

In patients with oligoarticular juvenile idiopathic arthritis, Treg cells are present in higher frequency than in patients with oligoarticular juvenile arthritis (a disease with clinical similarities to the former but with a less favorable prognosis) [120].

Natural Treg cells and organ-specific autoimmunity

Multiple sclerosis

A functional deficit and a reduced number of Treg cells have been described in patients with multiple sclerosis [121-122]. In the mouse model of multiple sclerosis known as experimental autoimmune encephalomyelitis (EAE), Treg cells protect from disease by suppressing the proliferation and production of pro-inflammatory cytokine by autoreactive Th1 cells [123]. Also, a failure of Treg cells to control pathogenic T cells associated with an increased incidence of disease is observed in mice that harbor T cells reactive to neural antigens [124].

Type-1 diabetes

Treg cells have functional deficits in type-1 diabetes patients [125]. Importantly, rapamycin seems to favor the expansion of functional Treg cells while depleting at the meantime the effector T cells in the disease [126].

In mice, female nonobese diabetic (NOD) animals spontaneously develop type-1 diabetes together with a peripheral deficit of Treg cells [127-129] - whose function and proliferative potential decline with age [130]. The transfer of Treg cells from diabetes-resistant animals [131] or Treg cells expanded *in vitro* suppress the disease [132]. Interestingly, Treg cells from pancreatic lymph nodes - but not from peripheral lymph nodes - delay the progression of diabetes, suggesting that antigen specificity may be required by Treg cells to optimally inhibit pathogenic autoreactivity in the disease [133]. Finally, Treg cells have been recently found capable to regulate pancreatic autoimmunity through the local control of NK cells [134].

Inflammatory bowel disease

A reduced number of peripheral Treg cells in patients with inflammatory bowel disease correlates with changes in disease activity (it increases during remission and decreases with active disease) [135]. In murine models of human inflammatory bowel disease, Treg cells can suppress effector T cells in the intestinal lamina propria [136] through cytokine deprivation-induced apoptosis [87]. Finally, the induction of colitis following transfer of naïve CD4⁺CD45RB^{high} T cells into syngeneic immuno-deficient mice [137] can be prevented by the co-transfer of regulatory CD4⁺CD45RB^{low} T-cells [138].

Experimental autoimmune thyroiditis

Patients with autoimmune thyroiditis have a reduced function of Treg cells, and Treg cells seem to exert protective roles in experimental autoimmune thyroiditis, an animal model for Hashimoto's thyroiditis [139].

Conclusions

Natural Treg cells have gained great interest in autoimmunity because of their well-established ability to suppress autoreactive immune responses. Important information has been obtained on key molecules, pathways and mechanisms adopted by the Treg cells in their functional activities in normal and pathologic conditions. New challenges that remain despite the intense investigations include the finding of unique phenotypic markers that may allow purification of these cells without contaminants, and the possibility to develop safe and effective modalities of Treg cell-based intervention in the therapy of human autoimmune conditions.

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Figure 1. Schematic representation of the distinction between natural and adaptive Treg cells