

Factors that regulate naturally occurring T regulatory cell-mediated suppression

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T regulatory (Treg) cells play a key role in the modulation of allergic and autoimmune responses. This review will discuss the factors that regulate naturally occurring Treg (nTreg) cell-mediated suppression. The involvement of cytokines, costimulatory molecules, and ligands on antigen-presenting cells in the inhibition of nTreg cell-mediated suppression *in vitro* is summarized. Understanding the events that control suppressive function of nTreg cells will allow manipulation of these cells to inhibit or enhance their functions in the development of novel therapies for autoimmune and allergic diseases. (J Allergy Clin Immunol 2005;116:1094-100.)

Key words: T regulatory cells, immune suppression, superantigens, atopic dermatitis

CD4⁺CD25⁺ naturally occurring T regulatory (nTreg) cells represent a population of T cells that are highly specialized for suppression of immune responses.^{1,2} A deficiency in number and function of these cells can lead to the development of autoimmune and inflammatory diseases, including asthma.³⁻⁸ These cells are produced by the normal thymus as a functionally distinct and mature

Abbreviations used

APC:	Antigen-presenting cell
CTLA-4:	Cytotoxic T lymphocyte-associated antigen 4
GITR:	Glucocorticoid-induced TNF receptor-related protein
GITR-L:	Glucocorticoid-induced TNF receptor-related protein ligand
HTLV-1:	Human T-cell lymphotropic virus type 1
IPEX:	Immune dysregulation polyendocrinopathy, enteropathy, X-linked
NFAT:	Nuclear factor of activated T cells
NF-κB:	Nuclear factor κB
nTreg cell:	Naturally occurring CD4 ⁺ CD25 ⁺ regulatory T cell
TLR:	Toll-like receptor
Treg cell:	Regulatory T cell

population of T cells.^{9,10} Specific cell markers have been identified that allow accurate isolation and manipulation of nTreg cells in mice and human subjects (Table I).¹¹ These advances have contributed greatly to our understanding of nTreg cell development and function.

Unraveling the events that control the suppressive function of nTreg cells is extremely important because it will enable investigators to manipulate T regulatory (Treg) cells to inhibit or enhance their functions as necessary. Manipulation of these cells might have great therapeutic benefit.^{4,12} For instance, it might be possible to specifically suppress immune responses in autoimmune and allergic disorders by improving activity of nTreg cells. Conversely, it could be possible to boost immunity required for antimicrobial and antitumor responses by decreasing suppressor function of nTreg cells (Fig 1).

Distinct from nTreg cells is a distinct population of Treg cells that are induced in the periphery after encounter with foreign antigens and pathogens.¹³ These inducible Treg cells are defined by their cytokine profile, namely Treg type 1 (T_R1) cells that secrete high levels of IL-10 and T_H3 cells that secrete high levels of TGF-β.¹⁴ The current review will focus on the mechanisms that control nTreg suppressive function and highlight the molecules

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TABLE I. Properties of nTreg cells

1. Thymic derived
2. Constitutively express:
a. IL-2R α chain (CD25)
b. CTLA-4
c. GITR
3. 5%-10% of CD4 ⁺ T cells in periphery
4. Express FoxP3 transcription factor gene
5. Anergic to <i>in vitro</i> stimulation with:
a. anti-CD3
b. antigen (ConA)
c. allogeneic splenic APC
6. Suppress autoreactive T-cell and CD4 ⁺ CD25 ⁻ T effector cell proliferation and cytokines
7. Suppressive function requires:
a. cell-cell contact
b. TCR ligation
c. cytokines?
8. Maintain peripheral self-tolerance

ConA, Concanavalin A; TCR, T-cell receptor.

that play a role in loss of nTreg cell-mediated suppression, including genetic mutations and environmental factors that subvert nTreg cell activity.

PROPERTIES OF nTreg cells

nTreg cell function is typically analyzed by assessing proliferation of responder CD4⁺ T cells alone or in combination with CD4⁺CD25⁺ nTreg cells.¹⁵ It has been found that nTreg cells are anergic *in vitro* and do not proliferate or produce IL-2 in response to conventional T-cell stimuli, such as anti-CD3, concanavalin A, or allogeneic splenic antigen-presenting cells (APCs).¹¹ In addition, anti-CD3-stimulated nTreg cells suppress proliferation of responder T cells.¹⁶ In contrast to inducible Treg cells, this process is not IL-10 or TGF- β dependent because nTreg cells from IL-10- or TGF- β -deficient mice efficiently suppress proliferation of responder T cells. Suppression, mediated by nTreg cells, requires T-cell receptor ligation and direct cell-cell contact or close range mediators and is not APC dependent.^{1,15,16} These nTreg cells target IL-2 production by responder T cells, thereby inhibiting T-cell proliferation.^{17,18} The discovery that nTreg cells constitutively express CD25 (IL-2 receptor α chain), as well as specifically express the FoxP3 transcriptional factor, which appears to be the key factor that controls nTreg cell development and function, has made isolation and characterization of these cells more reliable (Table I).¹⁹ Recently, it has been found that polyclonally activated nTreg cells express granzymes (granzyme A in human subjects²⁰ and granzyme B in mice²¹) and can suppress proliferation of effector T cells in a granzyme-dependent cytolytic manner.²⁰ This process was found to be CD18 dependent in the human system.²⁰ nTreg cells from perforin-deficient mice, however, efficiently suppress proliferation of responder T cells, suggesting that granzyme-mediated suppression is perforin independent.²¹

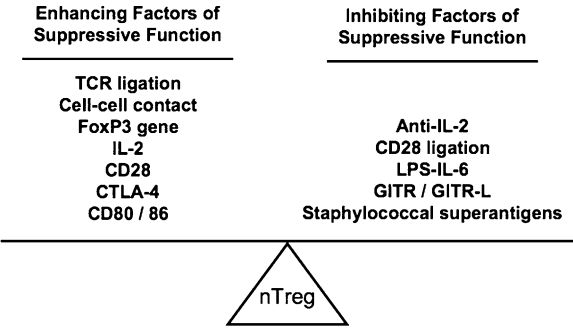


FIG 1. Factors that influence nTreg properties. The *left side* of the balance lists factors that are required for survival and suppressive function of nTreg cells. The *right side* of the balance lists factors that are known to inhibit nTreg suppressive function. Therapeutic benefits might come from shifting the balance toward the left for autoimmune and allergic disorders and shifting the balance toward the right for improved antimicrobial and antitumor responses. TCR, T-cell receptor.

INDIVIDUAL FACTORS THAT INFLUENCE nTreg CELL ACTIVITY

There are several key molecules, including CD25 and FoxP3, whose deficiency or functional alteration affects the generation or function of nTreg cells. Environmental factors that regulate nTreg cell-mediated suppression are only starting to be understood but include microbial superantigens. The involvement of cytokines, costimulatory molecules, and ligands on APCs in the inhibition of nTreg cell-mediated suppression *in vitro* will be discussed (Fig 1).

FoxP3

Recently, it has been shown that CD4⁺CD25⁺ nTreg cells highly express the FoxP3 transcriptional factor.²² Furthermore, virally transduced FoxP3 can convert murine naive T cells into regulatory cells, such that the cells phenotypically and functionally resemble naturally occurring nTreg cells.²³ Increased attention to the function of this molecule and its importance for nTreg cells occurred after identification of natural mutations in the gene encoding FoxP3. Indeed, mutations in *FoxP3* cause a fatal autoimmune disorder known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) in human subjects. Onset of this disease starts early in life, with patients presenting with massive lymphoproliferation, insulin-dependent diabetes mellitus, thyroiditis, eczema, enteropathy, and food allergies. In addition, autoimmune pathologies, such as hemolytic anemia, occur, as well as thrombocytopenia and severe infections.²⁴⁻²⁷ An analogous disease was characterized in a spontaneous mutant mouse, scurfy, which is also caused by mutation in the *FoxP3* gene.^{28,29} FoxP3 belongs to the family of transcriptional factors that are characterized by the presence of winged helix-forkhead DNA-binding domain (forkhead box [Fox]). There is high homology between human, mouse, and rat *FoxP3*, which suggests a conserved function for FoxP3.

At present, although FoxP3 is predicted to be a transcriptional repressor, little is known about the biochemical pathways by which FoxP3 acts. A report by Bettelli et al³⁰ demonstrated that transgenic expression of FoxP3 in conventional T cells inhibits endogenous cytokine expression driven by nuclear factor of activated T cells (NFAT) and nuclear factor (NF) κ B. FoxP3 physically associates with the REL domain proteins of NFAT and NF- κ B and suppresses their transcriptional activity. In addition, *FoxP3*-deficient T cells from scurfy mice have a dramatic increase in NFAT and NF- κ B transcriptional activity compared with that seen in wild-type T cells.³⁰ *FoxP3* expression is thought to be regulated by the estrogen receptor, which has a direct binding site in the promoter region of *FoxP3*.³¹ It has been reported that TGF- β can induce *FoxP3* expression through activation of SMAD (small mother against decapentaplegic) transcriptional factors.³¹

Interestingly, there are a growing number of reports that show downregulation of *FoxP3* mRNA and protein expression by nTreg cells interferes with nTreg cell function, making these cells less efficient in the suppression of inflammation.³¹⁻³⁵ For instance, compared with that from healthy control subjects, the thymus of patients with autoimmune myasthenia gravis was found to have decreased expression of *FoxP3*, which corresponds with a functional defect in the regulatory activity of nTreg cells.³² In another study looking at patients with myelopathy–tropical spastic paraparesis caused by infection with the human T-cell lymphotropic virus type 1 (HTLV-1), *FoxP3* mRNA and protein expression in nTreg cells was found to be lower than in nTreg cells of healthy control subjects. The nTreg cells of the patients with this disease demonstrated loss of nTreg function.³³ The virus-encoded transactivating HTLV-1 *tax* gene was demonstrated to have a direct inhibitory effect on *FoxP3* expression and function of CD4⁺CD25⁺ nTreg cells. This is the first report demonstrating the role of a specific viral gene product (HTLV-1 Tax) on the expression of genes associated with nTreg (in particular, *FoxP3*) resulting in inhibition of nTreg function. These results suggest that direct human retroviral infection of nTreg cells might be associated with the pathogenesis of HTLV-1-associated neurologic disease.³³

IL-2

It has become clear that high expression of CD25 is not only an identification marker of nTreg cells but is also important for functional development of nTreg cells. Experiments indicate that IL-2 is essential for nTreg cell homeostasis.³⁴ It is required for *in vivo* and *in vitro* activation of nTreg cells and for expression of CD25.³⁵ IL-2-deficient mice have reduced numbers of CD4⁺CD25⁺ nTreg cells in the thymus and periphery; these mice experience fatal lymphoproliferative disorders with autoimmune features.² In addition, administration of IL-2–neutralizing antibody to normal mice selectively reduces the number of nTreg cells in the thymus and periphery, resulting in the development of autoimmune disorders similar to those produced by depletion of CD4⁺CD25⁺ nTreg cells.³⁶

nTreg cells do not proliferate when stimulated with anti-CD3 or antigens unless supplemented with high doses of IL-2. nTreg cells do not produce IL-2, but they need IL-2 for survival.^{37,38} Activated T cells are the main source of IL-2 for nTreg cells. Coculture experiments indicate that nTreg cells compete with responder T cells for IL-2.³⁹ During coculture of nTreg cells with responder T cells, nTreg cells upregulate CD25 expression, whereas induction of CD25 expression on responder T cells is suppressed. Upregulation of CD25 expression by nTreg cells is inhibited by addition of anti-IL-2; addition of IL-2 restores CD25 expression on responder T cells, demonstrating that IL-2 regulates the differential expression of CD25.³⁹ Therefore IL-2 mediates a feedback loop between nTreg cells and responder T cells: IL-2 secreted by responder T cells maintains and activates nTreg cells (Fig 1), and nTreg cells in turn inhibit IL-2 production by responder T cells.⁴⁰

Although IL-2 and its receptor clearly play a critical role in the homeostasis of nTreg cells, the contribution of IL-2 to the suppressive function of nTreg cells is considered a controversial issue. The molecular basis for suppression of T-cell activation by nTreg cells is inhibition of IL-2 gene transcription in CD4⁺CD25[−] responder T cells. On the other hand, addition of IL-2 or anti-CD28 abrogates CD4⁺CD25⁺-mediated suppression of proliferation and has been assumed to break suppression. Recently it has been found that transcription of IL-2 mRNA remains fully suppressed in the presence of high concentrations of exogenous IL-2, despite the proliferation of both CD4⁺CD25⁺ and CD4⁺CD25[−] cells.¹⁸ Thus abrogation of the anergic state of CD4⁺CD25⁺ nTreg cells does not break suppression, as previously thought. Most importantly, addition of anti-IL-2 completely abrogates the suppressive effects of nTreg cells on IL-2 mRNA transcription by responder T cells and demonstrates that IL-2 is not only required for the homeostasis of nTreg cells but is also required for the acquisition of suppressor function.¹⁸

Glucocorticoid-induced TNF receptor-related protein ligand and costimulatory molecules from the TNF receptor superfamily

Recently, there has been increasing interest in the role of glucocorticoid-induced TNF receptor-related protein (GITR) and its ligand (GITR-L) in the control of nTreg cell activity. The costimulatory molecule GITR, a member of the TNF receptor superfamily, was originally identified and cloned by comparing untreated and dexamethasone-treated murine T-cell hybridoma cells.⁴¹ The authors found that the GITR gene could be induced in T cells during T-lymphocyte activation and by treatment with dexamethasone. In addition, the GITR gene was found to have a T-cell antiapoptotic effect when T cells were treated with anti-CD3 mAb. These results were later confirmed in the human model when the human GITR and its ligand were isolated by 2 separate groups and found to inhibit T-cell apoptosis by inducing NF- κ B activation.^{42,43}

GITR has been found to be a constitutively expressed marker for nTreg cells, but it is also upregulated on conventional activated CD4⁺ T cells (Table I).⁴⁴ Blocking GITR with an anti-mouse GITR mAb is able to inhibit nTreg cell suppression *in vitro*,^{45,46} and its injection into mice leads to the induction of autoimmunity *in vivo*.⁴⁶ Originally, it was presumed that triggering of GITR on the surface of nTreg cells transmits a suppression-blocking signal to these cells.⁴⁶ Recent data suggest instead that ligation of GITR on activated responder T cells, and not on nTreg cells, renders them resistant to suppression.⁴⁷ Of interest, it was noted that triggering of GITR substantially inhibited granzyme B production by nTreg cells.²¹

The natural ligand for GITR has been cloned recently.⁴³ It was found that the soluble recombinant form of mouse GITR-L induces GITR-dependent NF- κ B activation and blocks *in vitro* suppression mediated by nTreg cells.⁴⁸ GITR-L upregulates IL-2 secretion by activated responder T cells and in the presence of IL-2 breaks the anergic state of nTreg cells. It was found that although soluble GITR-L was able to block nTreg cell-mediated suppression, its functional capability was substantially enhanced by cross-linking of GITR–GITR-L complexes,⁴⁸ suggesting that natural scaffolding of GITR-L on the cell surface could be a mechanism for sufficient engagement of GITR.

An active area of research is extending the data on the role of GITR-L reversing suppression in the murine system to human subjects. If *in vivo* studies prove that GITR–GITR-L interactions can break Treg cell suppressive activity, then the potential for blocking this signaling pathway could lead to treatment of inflammatory conditions.⁴⁹ In this regard more than 90% of atopic dermatitis lesions are colonized with *Staphylococcal aureus*, with the severity of skin inflammation correlating with the density of colonization with superantigen-secreting bacteria.^{50,51} In addition, recent evidence demonstrates that superantigens subvert Treg cells in atopic dermatitis,⁵² but the mechanism by which this occurs is unknown. A recent report by Cardona et al⁵³ shows that staphylococcal enterotoxin B subverts naturally occurring nTreg cell activity through mechanisms that require direct cell-cell contact between monocyte APCs and nTreg cells. Staphylococcal enterotoxin B induces GITR-L expression on the surface of monocytes. When GITR-L activity was neutralized with a blocking antibody, nTreg cell suppressive activity was restored, despite the presence of superantigen.⁵³ The data above suggest that relative distribution patterns of GITR on activated responder T cells and nTreg cells and of GITR-L on APCs represent a complex dynamic interaction that modulates the activity of nTreg cells. Note as well that several other TNF receptor superfamily members (4-1BB and OX40) have also been shown to influence the suppressor function of nTreg cells.^{54,55}

CD28, cytotoxic T lymphocyte–associated antigen 4, and B7 family proteins

In terms of percentage and number, CD28 is critical for thymic generation of nTreg cells, as well as for their

renewal and survival in the periphery.⁵⁶ The number of CD4⁺CD25⁺ nTreg cells is substantially reduced in the thymus and periphery of CD28- or B7-deficient mice. Deficiency in CD28 and B7 molecules alters activation of conventional T cells, thereby resulting in lower levels of IL-2 production. This in turn controls nTreg cells and their proliferation status.¹⁶ On the other hand, strong *in vitro* ligation of CD28, together with T-cell receptor stimulation, abrogates anergy and suppressor function of nTreg cells and induces their proliferation, presumably by stimulating the production of endogenous IL-2.¹⁵

CD80 and CD86 are also essential in nTreg-mediated suppression. During T-cell responses to alloantigens expressed on dendritic cells, antibodies against CD86 potentially enhance suppression mediated by CD4⁺CD25⁺ nTreg cells. In contrast, blocking CD80 enhanced proliferative responses by impairing nTreg cell suppression. Intriguingly, the relative expression levels of CD80 and CD86 on dendritic cells are modulated during progression from an immature to mature state, and this correlates with the ability of nTreg cells to suppress responses.⁵⁷ Mature CD86^{high} dendritic cells trigger proliferation of nTreg cells, attenuating their suppressor function, and provoke effective immune responses to microorganisms.^{58,59}

nTreg cells constitutively express cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), whereas other types of T cells express it only after activation (Table I). It has been shown that blockade of CTLA-4 *in vitro* inhibits nTreg cell-mediated suppression.⁶⁰ Experiments suggest that CTLA-4 is required as a costimulatory signal to exert suppression by nTreg cells. Another attractive hypothesis is that CTLA-4 in nTreg cells directly mediates suppression: ligation of CTLA-4 with CD80, CD86, or both on dendritic cells triggers induction of the enzyme indoleamine 2,3-dioxygenase, which catalyzes tryptophan into kynurine and other metabolites that have potent immunosuppressive effects in the local environment of nTreg cells.^{61,62} In addition, it has been proposed that CTLA-4 (on nTreg cells) directly ligates CD80 or CD86, which are expressed by responder T cells, leading to suppression of responder T-cell proliferation. On the basis of these observations, an “outside-in” theory of nTreg cell-mediated suppression has been proposed in which nTreg cells (“outside,” expressing CTLA-4) and responder T cells (“outside,” expressing CD80/86) interact by meeting at an APC (“inside”). This facilitates binding of nTreg cell-surface CTLA-4 with CD80, CD86, or both on activated T cells, thus preventing responder T cells from further activation.^{16,63}

ENVIRONMENTAL FACTORS THAT MODULATE nTreg CELL ACTIVITY

Viruses, bacteria, and Toll-like receptors

The amount and type of pathogen might dictate whether nTreg cell suppressive function is favored. For instance, studies involving commensal gut bacteria have shown that nTreg cells are crucial in maintaining gastrointestinal homeostasis. When naive T-cell populations lacking nTreg

cells were transferred to T cell-deficient mice, significant gut inflammation occurred. Thus pathogens that enhance nTreg cell function could serve to dampen the immune response and consequently maintain pathogen survival and possibly long-term persistence, as in hepatitis C infection and *Helicobacter pylori* infection.^{64,65} In the case of HIV, induction of nTreg cell activity might serve to temper a deleterious immune response. For example, HIV-infected patients with strong HIV-specific nTreg cell activity *in vitro* demonstrated significantly lower levels of plasma viremia and higher CD4 to CD8 ratios than patients with lower levels of nTreg activity.⁶⁶

In contrast to the examples above, sometimes microbial products might serve to dysregulate nTreg cell function to boost pathogen-directed immune responses. For instance, Toll-like receptors (TLRs) have been reported to control nTreg suppressor function as well.^{67,68} It was found that polyclonal activation of nTreg cells in the presence of APCs that had been activated through TLRs by LPS or CpGs does not suppress the proliferation of naive T cells *in vitro*.⁶⁸ Supernatants from TLR-activated APCs make T cells resistant to suppression. IL-6 has been identified as one of the essential components that interferes with nTreg cell-mediated suppression, rendering responder T cells resistant to suppression and thus allowing response of cells to the invading microbes.⁶⁸ nTreg cells themselves have been reported to express TLR-4.⁶⁹ *In vitro* stimulation of nTreg cells with high doses of LPS induces their proliferation and augments their suppressive activity.⁶⁹

Unlike LPS,⁶⁸ which might serve to inhibit nTreg cell function to boost pathogen-directed immune responses, staphylococcal superantigens seem to exert a different effect on nTreg cell activity than pathogen-associated molecular patterns recognized by TLR.^{52,53} In a recent study by Ou et al⁵² that characterized the function of nTreg cells in patients with atopic dermatitis, it was found that stimulation of nTreg cells with the superantigen staphylococcal enterotoxin B resulted in abrogation of nTreg cell function, breaking their anergy and inhibiting their suppressor function. These data suggest that superantigen-mediated subversion of nTreg functions might potentially enhance skin inflammation in atopic dermatitis. The clinical presentation of these patients, however, suggests an overactivation of the immune system rather than a pathogen-directed immune response.^{50,51} Interestingly, although the soluble factor IL-6 was shown to interfere with nTreg cell-mediated suppression after LPS-induced activation of the Toll pathway, recombinant IL-6 alone or together with MyD88^{-/-} dendritic cells, conditioned media, despite LPS stimulation, did not lead to blockade of suppression, and nTreg cell-mediated suppression was efficient.⁶⁸ Thus the authors proposed that IL-6 has to act synergistically with another TLR-induced signal for efficient blockade of nTreg cell function. This missing factor could be GITR-L because it has been shown that LPS transiently upregulates GITR-L in murine macrophages⁷⁰ and superantigens transiently upregulate GITR-L in human monocytes.⁵³

Corticosteroids

If the goal one day is to treat allergic and autoimmune diseases by clinically manipulating the factors that regulate nTreg suppressive activity, it will likely occur in conjunction with corticosteroids. With this in mind, 2 groups recently investigated the effects of corticosteroids on Treg cells. Dao Nguyen and Robinson⁷¹ found that fluticasone propionate increases nTreg cell suppression of allergen-stimulated T effector cells by means of an IL-10-dependent mechanism. These findings corroborated the results of Karagiannidis et al,⁷² who focused on the effects of inhaled or systemic glucocorticoids on inducible T regulatory cells. They found that *FoxP3* mRNA expression both correlated with IL-10 mRNA expression and was significantly induced in asthmatic patients receiving either glucocorticoid treatment.⁷² Thus evidence suggests that corticosteroids inhibit T-cell activation by multiple mechanisms,⁷³ one of which is through induction of Treg cells.

CONCLUSIONS AND FUTURE DIRECTIONS

In the past few years, there has been an increase in the number of publications on the topic of Treg cells, with a specific focus on understanding the factors that affect their suppressive function. These factors can be summarized by the following. The key molecule for the development and function of nTreg cells is FoxP3.⁹ A mutation in this transcription factor gene is the cause of IPEX disease, the first human disease described that is caused by a direct dysfunction of nTreg cells.²⁶ The murine model has shown that IL-2 is another essential molecule necessary for the survival and homeostasis of nTreg cells.^{34,37,38} Similar to IL-2, studies have shown that CD28 is critical for the survival of nTreg cells, and like FoxP3, CD28 is necessary for the thymic development of nTreg cells.⁵⁶ Strong *in vitro* ligation of CD28 subverts nTreg suppressive function.¹⁵ Ligation of GITR on T effector cells by GITR-L renders them resistant to nTreg suppression, forming another mechanism by which nTreg suppressive activity is abrogated.⁴⁷ The interplay between the costimulatory molecules CTLA-4, CD80, and CD86 also seems to be important for the suppressive function of nTreg cells.⁵⁷⁻⁶⁰ Factors in the environment, such as viral and microbial products, have been implicated to modulate nTreg cell activity (eg, HIV, LPS, and superantigens).^{52,66,68} Interestingly, one of the most used classes of medications, corticosteroids, was recently found to have the ability to induce Treg suppression.^{71,72}

The hope is that one day all or some of these factors discussed above that influence nTreg cell-mediated suppression would be exploited for potential therapeutic applications. Finding ways to turn on Treg cells in autoimmune diseases that have known defects in Treg function, such as multiple sclerosis and autoimmune polyglandular syndrome type II,^{74,75} or poor expression of *FoxP3*, such as IPEX disease, will hopefully lead to new therapeutic options. Indeed, the *FoxP3*-deficient

mouse is highly allergic and highlights the importance of FoxP3 and Treg cells in controlling allergic disease (see article by Chatila⁷⁶). Moreover, the importance of environmental factors that might augment allergic inflammation, such as staphylococcal superantigen subversion of nTreg activity,⁵² will hopefully lead to further studies on superantigen-driven diseases. Perhaps neutralizing GITR-L activity could block this from occurring.⁵³ Finally, although not discussed in this article, inducible Treg cells have already been shown to be important in the mechanism behind immunotherapy, as well as in amelioration of airway hyperresponsiveness and allergic airway inflammation (see article by Chatila⁷⁶). This knowledge, coupled with the factors reviewed in this article, might one day lead to preventive and therapeutic vaccines that induce Treg activity in allergic and autoimmune diseases.

The experimental data summarized in this review, along with future investigations, will form the foundation for translatable and clinically useful manipulations of Treg cell function in human subjects. The use of nTreg cells as a therapeutic strategy will require a thorough understanding of the factors that influence nTreg cell-mediated suppression.

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