



Antigen-specific Treg cells in immunological tolerance: implications for allergic diseases

The Harvard community has made this
article openly available. [Please share](#) how
this access benefits you. Your story matters

Citation	Abdel-Gadir, Azza, Amir H. Massoud, and Talal A. Chatila. 2018. "Antigen-specific Treg cells in immunological tolerance: implications for allergic diseases." F1000Research 7 (1): 38. doi:10.12688/f1000research.12650.1. http://dx.doi.org/10.12688/f1000research.12650.1 .
Published Version	doi:10.12688/f1000research.12650.1
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:34868722
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA



REVIEW

Antigen-specific Treg cells in immunological tolerance: implications for allergic diseases [version 1; referees: 3 approved]

Azza Abdel-Gadir ^{1,2}, Amir H. Massoud^{1,2}, Talal A. Chatila^{1,2}

¹Division of Immunology, Boston Children’s Hospital, Boston, USA

²Department of Pediatrics, Harvard Medical School, Boston, USA




v1 **First published:** 10 Jan 2018, 7(F1000 Faculty Rev):38 (doi: [10.12688/f1000research.12650.1](https://doi.org/10.12688/f1000research.12650.1))
Latest published: 10 Jan 2018, 7(F1000 Faculty Rev):38 (doi: [10.12688/f1000research.12650.1](https://doi.org/10.12688/f1000research.12650.1))

Abstract

Allergic diseases are chronic inflammatory disorders in which there is failure to mount effective tolerogenic immune responses to inciting allergens. The alarming rise in the prevalence of allergic diseases in recent decades has spurred investigations to elucidate the mechanisms of breakdown in tolerance in these disorders and means of restoring it. Tolerance to allergens is critically dependent on the generation of allergen-specific regulatory T (Treg) cells, which mediate a state of sustained non-responsiveness to the offending allergen. In this review, we summarize recent advances in our understanding of mechanisms governing the generation and function of allergen-specific Treg cells and their subversion in allergic diseases. We will also outline approaches to harness allergen-specific Treg cell responses to restore tolerance in these disorders.

Open Peer Review

Referee Status: 

	Invited Referees		
	1	2	3
version 1 published 10 Jan 2018			

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 **Tobias Bopp**, University Medical Center of the Johannes Gutenberg-University Mainz, Germany
- 2 **Megan K Levings**, University of British Columbia & British Columbia Children’s Hospital Research Institute, Canada
- 3 **Jagadeesh Bayry**, Centre de Recherche des Cordeliers, France

Discuss this article

Comments (0)

Corresponding author: Talal A. Chatila (talal.chatila@childrens.harvard.edu)

Author roles: **Abdel-Gadir A:** Writing – Original Draft Preparation, Writing – Review & Editing; **Massoud AH:** Data Curation; **Chatila TA:** Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Abdel-Gadir A, Massoud AH and Chatila TA. **Antigen-specific Treg cells in immunological tolerance: implications for allergic diseases [version 1; referees: 3 approved]** *F1000Research* 2018, 7(F1000 Faculty Rev):38 (doi: [10.12688/f1000research.12650.1](https://doi.org/10.12688/f1000research.12650.1))

Copyright: © 2018 Abdel-Gadir A *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: This work was supported by National Institutes of Health grants (5R01AI065617 and R01AI126915) to TAC. *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

First published: 10 Jan 2018, 7(F1000 Faculty Rev):38 (doi: [10.12688/f1000research.12650.1](https://doi.org/10.12688/f1000research.12650.1))

Introduction

Regulatory T (Treg) cells play a key role in the maintenance of immunological self-tolerance and in restraining deleterious immune responses to both self and foreign antigens¹. Treg cell-mediated tolerance is an active process that requires antigen specificity^{2,3} and this dependence on antigen recognition by Treg cells for their regulatory function can be harnessed to provide promising approaches for immunotherapy of diseases such as allergy and autoimmunity.

Sakaguchi *et al.* originally described a population of CD4⁺ T cells expressing the cell surface marker CD25—interleukin-2 (IL-2) receptor alpha chain—that maintained peripheral immunological tolerance in mice. The deficiency of these cells engenders autoimmunity⁴. The discovery of a key role for the transcription factor Forkhead Box P3 (FOXP3) in controlling the differentiation and functions of CD4⁺CD25⁺ Treg cells provided an essential molecular framework for elucidating their physiological functions⁵. It is now appreciated that Treg cells have a broader function than previously thought. In addition to maintaining tolerance to self-tissues, Treg cells are implicated in sustaining tolerance to fetal and transplanted tissues and in promoting tissue

repair⁶⁻⁹. Furthermore, Treg cells promote tolerance to components of the ‘extended self’, encompassing the commensal microbiota and innocuous agents such as nutrients and other environmental exposures^{10,11}. Although additional Foxp3⁻ Treg cell populations have been described¹², this review is focused on CD4⁺CD25⁺Foxp3⁺ Treg cells, the most well-characterized subset of Treg cells whose deficiency in both humans and mouse models precipitates lethal autoimmunity and inflammatory disorders.

What are the niches that promote antigen-specific regulatory T cells formation?

There are two major subtypes of CD4⁺Foxp3⁺ Treg cells¹³. The first encompasses thymic or natural Treg (nTreg) cells, which originate as a separate cell lineage during T-cell development in the thymus (Figure 1)^{14,15}. The second type includes peripheral or induced Treg (iTreg) cells that differentiate from conventional T (Tconv) cells in specialized extra-thymic niches¹⁶⁻²⁰ (reviewed in 18). nTreg cells are biased toward immune recognition of self-antigens, whereas iTreg cells are biased toward recognizing non-self-antigens, reflecting their derivation from Tconv cells^{18,21}. The two subtypes are complementary in their actions in promoting peripheral tolerance²²⁻²⁴.

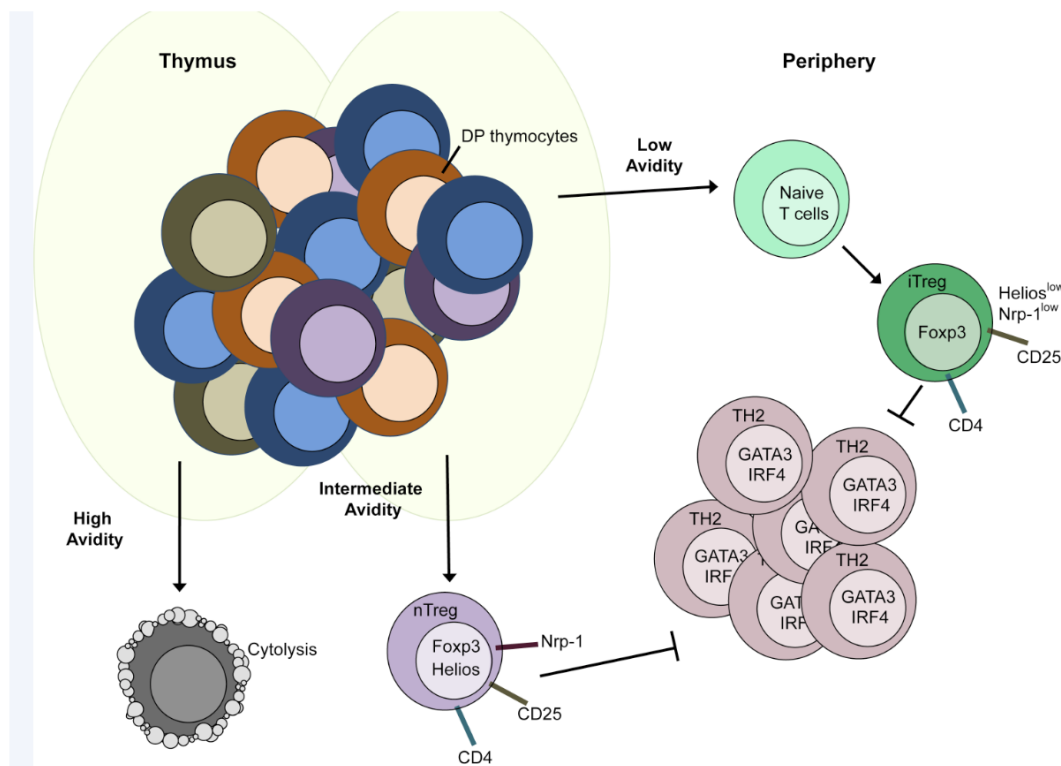


Figure 1. Generation of natural regulatory T (nTreg) and induced Treg (iTreg) cells. Schematic representation of nTreg and iTreg cell developmental pathways. Naturally occurring Treg cells develop upon intermediate-avidity interaction between developing thymocytes and self-antigen-presenting medullary epithelial cells. High-level expression of Neuropilin (Nrp-1) and Helios is maintained on nTreg cells after their migration from the thymus. Naïve conventional T cells that have undergone positive and negative selection in the thymus and have low avidity for self-antigens may develop into iTreg cells upon encountering antigens presented by tolerance-inducing antigen-presenting cells in specialized niches in the periphery. These cells express low levels of Helios or Nrp-1. Both nTreg and peripheral Treg cells are able to suppress CD4⁺ effector helper T 2 (TH2) cell responses. High-avidity T-cell receptor interaction in the thymus results in cytolytic T cells (negative selection). DP, double positive; IRF4, interferon gamma regulatory factor 4.

nTreg cells emerge late in the double-positive stage of thymocyte development²⁵, and the majority of nTreg cells segregate into CD4 single-positive mature thymocytes²¹. The maturation of nTreg cells from thymocytes requires T-cell receptor (TCR)-dependent signals delivered upon its engagement by major histocompatibility complex (MHC) II molecules on specialized antigen-presenting cells²⁶, most notably medullary thymic epithelial cells^{27,28}. Whereas high-avidity TCR/MHC interactions induce negative selection^{29,30} and low-avidity interactions favor thymocyte maturation and egress as conventional naïve T cells, intermediate-avidity interactions favor FOXP3 expression and the differentiation of thymocytes into nTreg cells (Figure 1)^{31–33}. The TCR repertoire expressed by nTreg cells is broad and distinct from Tconv cells. It is enriched in self-reactive TCRs that otherwise would have been eliminated in Tconv cells^{34,35}.

iTreg cells are generated in specialized niches particularly at the environmental interfaces, including the gut and lung^{20,36}. These niches are endowed with specialized antigen-presenting

cells—including CD103⁺CD11c⁺ dendritic cells in the gut and alveolar and interstitial macrophages in the lung—that polarize antigen-responsive T cells into iTreg cells under the influence of transforming growth factor beta 1 (TGF- β 1) and retinoic acid produced by the antigen-presenting cells (Figure 2)^{37–41}. In the intestine, iTreg cells develop primarily in response to the gut microbiota and food antigens, enabling tolerance to both sets of foreign antigens^{42–44}. In germ-free (GF) mice, colonic Treg cells generated in the periphery (iTreg cells) are greatly reduced in numbers, reflecting the critical role of colonic bacteria in promoting colonic Treg cell development⁴⁵. In contrast, GF mice appear to have normal numbers of iTreg cells in the small intestine⁴⁶. Kim *et al.* reported that under normal physiological conditions, proteins from a typical diet lead to iTreg cell generation in the small intestine but not in the colon¹¹. They found that phenotypically and functionally distinct iTreg cells in the lamina propria of the small intestine develop after weaning to suppress strong immunological reactions in response to dietary antigens in solid food. These iTreg cells are important for the maintenance of

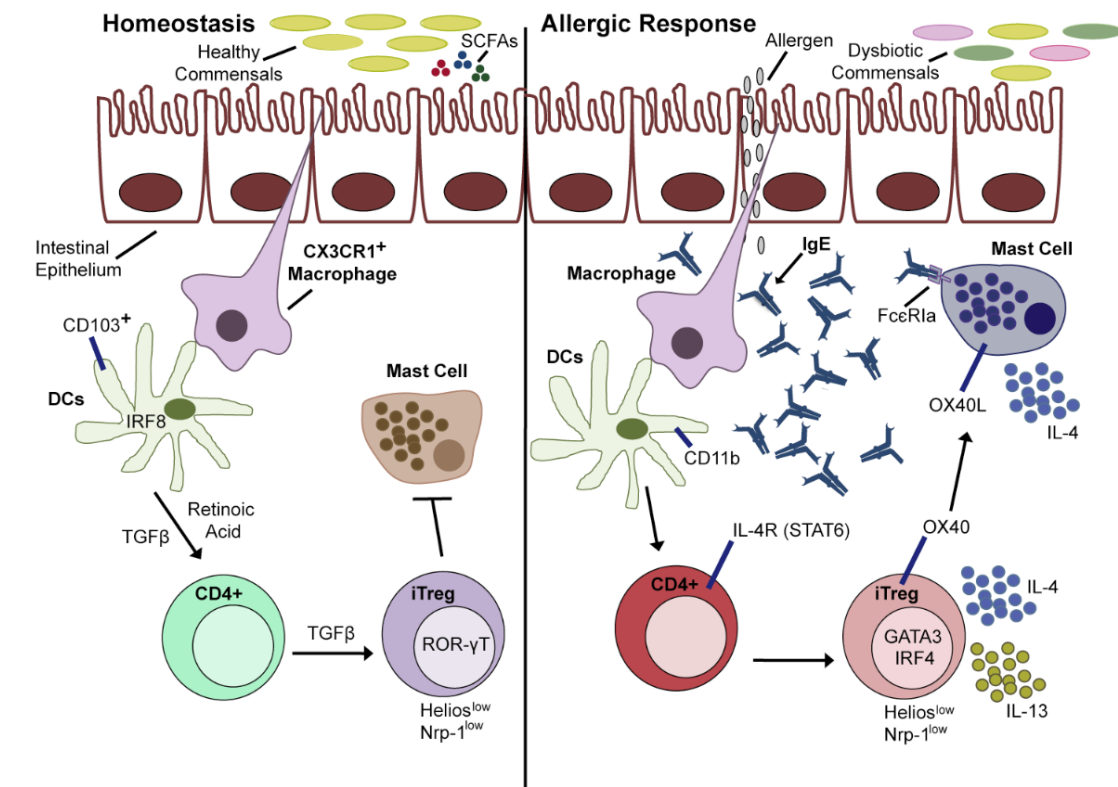


Figure 2. Mucosal tolerance in the gut and its breakdown in food allergy. (Left) Under homeostatic conditions, CX3CR1⁺ macrophages sample components of the gut lumen and transfer luminal antigens to IRF8⁺CD103⁺ dendritic cells (DCs), which in turn promote the formation of antigen-specific induced regulatory T (iTreg) cells. iTreg cells expressing retinoid-related orphan receptor gamma t (ROR- γ t) may regulate tolerance to dietary antigens by a range of mechanisms, including the suppression of mast cell activation. iTreg cells may also prevent the conversion of naïve CD4⁺ T cells to antigen-specific helper T 2 (TH2) cells. **(Right)** Under food allergic conditions, CD11b⁺CD103⁻ DCs encounter allergens that are made more accessible by a permeable epithelial barrier. Allergen-presenting DCs drive the differentiation of naïve T cells into allergen-specific TH2 cells expressing the interleukin-4 receptor (IL-4R). iTreg cells also acquire a TH2 cell-like phenotype characterized by increased GATA3 and IRF4 expression and the release of IL-4 and IL-13. These 'pathogenic' Treg cells are unable to suppress mast cell activation through engagement of the OX40-OX40 ligand pathway. Binding of IgE to the high-affinity receptor for IgE (Fc ϵ R1) leads to uninhibited mast cell degranulation and IL-4 production. IRF8, interferon gamma regulatory factor 8; SCFA, short-chain fatty acid; TGF β , transforming growth factor beta.

immune tolerance at mucosal surfaces. Compared with nTreg cells, they express lower levels of the markers Neuropilin-1 and Helios and higher levels of the retinoid-related orphan receptor gamma t (RoR- γ T)¹¹.

The lung is another important site for the induction of antigen-specific Treg cells^{20,47,48}. Although alveolar macrophages are defective in their capacity to activate T effector (Teff) cells, they are particularly adept at driving the differentiation of naïve allergen-specific T cells into iTreg cells in a TGF- β 1- and retinoic-dependent manner^{37,38}. Similar to that of the gut, the microbiota of the lung has been implicated in promoting airway tolerance to allergens early in life by enabling the production of allergen-specific induced Treg cells⁴⁹. High frequencies of Treg cells targeting innocuous environmental aero-antigens (such as house dust mite or plant pollen) have been reported in human adult peripheral blood mononuclear cells but are absent in cord blood, suggesting that Treg cell expansion is specific to antigen encounter in the periphery⁵⁰. Aero-antigen-targeted responses were also found to be less pronounced in Tconv cells as Treg cells outnumbered effector memory T (TM) cells and expressed chemokine receptors essential for lung homing⁵⁰.

Feedback mechanisms from the peripheral niches in the form of local tissue factors have been shown to regulate the function of Treg cells. In the skin, the pro-inflammatory cytokine thymic stromal lymphopoietin (TSLP) produced by keratinocytes acts to activate Treg cells to contain skin inflammation locally and prevent its systemic spread⁵¹. Deletion of TSLP receptor (TSLPR) signaling specifically on Treg cells prevented the upregulation of genes, including *Icos* and *Ctla4*, that mediate their regulatory effects and consequently restricted the capacity of Treg cells to inhibit skin effector T cells and prevent the progression of local skin inflammation systemically.

Treg cell memory

One of the key features of adaptive immunity is the ability to respond effectively and more rapidly to antigens that have been encountered previously. A subset of clonally expanded Teff cells differentiate into long-lived TM cells that are particularly adept at mounting recall responses upon re-exposure to antigens/pathogens⁵². TM cells are endowed with long-term epigenetic, transcriptional, and metabolic changes that enable their long-term survival and rapid response to recall challenges⁵³. The concept of Treg cell memory has been controversial as a long-lasting increase in suppressive function that persists after the resolution of the primary antigenic exposure could severely suppress recall Teff cell responses and lead to persisting immuno-suppression⁵⁴⁻⁵⁷. Van der Veecken *et al.* recently found that the suppressive function of antigen-specific Treg cells is a transient quality⁵⁸. They reported that inflammation-induced Treg cells reversed activation-specific transcriptional changes and reduced suppressive function with time. These changes were associated with stable chromatin modifications that facilitate reactivation and long-lasting preference for non-lymphoid tissue localization. Rested Treg cells exhibited a gene expression signature similar to that of conventional TM cells that was not affected by secondary activation⁵⁸.

In contrast to the above results, other studies on Treg cell responses have supported the concept of Treg cell memory. Rosenblum *et al.* investigated Treg cell responses in the skin by generating transgenic mice that expressed a model antigen in keratinocytes⁵⁹. The model antigen was regulated in the skin but only constitutively expressed in the thymus and the expression could be silenced to assess antigen-specific TM cells without prolonged exposure to antigen. This system revealed that the thymic constitutive expression allowed the expansion of a large subset of antigen-specific Treg cells that spread to secondary lymphoid organs. The induction of antigen in the skin induced potent proliferation of antigen-specific Treg cells and increased expression of CTLA-4 before migrating to the skin to ameliorate antigen-specific effector T-cell inflammation. After antigen expression was switched off, a subset of Treg cells expressing CTLA-4 persisted and upon antigen re-exposure inflammation was attenuated much more rapidly compared with the primary response⁵⁹. Treg cell depletion between primary and secondary exposure saw no protection from inflammation. Overall, these results are relevant to therapeutic applications aimed at boosting tolerance responses, such as immunotherapy for allergic diseases (see below).

What is the role of antigen-specific Treg cells in allergic diseases?

Allergic responses arise in the context of failure to develop tolerance toward specific allergens. These conditions are marked by the production of allergen-specific IgE and the development of CD4⁺ TH2 skewed cell responses (Figure 2)⁶⁰. Conditions that impact the differentiation of allergen-specific Treg cells can give rise to allergic disorders⁶⁰. For example, human subjects with loss-of-function mutations in FOXP3, whose Treg cells fail to appropriately differentiate into effective suppressors, develop an X-linked disorder of immune dysregulation and autoimmunity⁶¹⁻⁶³. A similar phenotype is recapitulated in mice with mutations in *Foxp3*⁶⁴⁻⁶⁷. Human subjects with FOXP3 deficiency suffer from associated severe allergic inflammation and develop food allergy (FA) due to loss of oral tolerance. In mice, manipulations that deplete or inhibit allergen-specific Treg cells also result in the loss of tolerance and the development of allergic responses to said allergen⁶⁸. In human subjects, Treg cells of children with FA fail to suppress responses to the causative food allergens, whereas those of children who outgrow FA develop allergen-specific suppressive capacity⁶⁸.

Derangement of antigen-specific Treg cell responses in allergic diseases

Oral tolerance is specifically associated with the development of iTreg cells from naïve CD4⁺ T cells that are activated in the presence of TGF- β 1 and CD103⁺ classic dendritic cells in the gut that express interferon gamma regulatory factor 8 (IRF8) (Figure 2)^{61,69}. At steady state, macrophages expressing the CX3C chemokine receptor 1 (CX3CR1) sample luminal antigens, including food and microbiota components, by projecting dendrites through the epithelial barrier into the gut lumen⁷⁰⁻⁷². CX3CR1⁺ macrophages transfer the luminal soluble antigen to CD103⁺ dendritic cells, which in turn induce oral tolerance to said antigens by promoting the generation of antigen-specific iTreg cells (Figure 2)⁷³. iTreg

cells regulate TH2 immune responses at mucosal surfaces, are less stable, and exhibit more plasticity than thymic-derived nTreg cells^{74,75}. Noval Rivas *et al.* showed that, in a mouse model of FA marked by IgE-mediated anaphylaxis, the generation of antigen-specific Treg cells was inhibited by increased IL-4 receptor (IL-4R)-STAT6 signaling⁶⁸. The mice in question, *Il4ra*^{F709} mice, carry a gain-of-function mutation in the IL-4R α chain⁷⁶. They mount exaggerated TH2 responses and are particularly susceptible to oral sensitization and anaphylaxis⁷⁷. The antigen-specific Treg cells that did develop underwent TH2 cell reprogramming marked by increased expression of IL-4, IL-13, IRF-4, and GATA-3 when compared with those from wild-type (WT) mice, a phenomenon also observed in human subjects with FA (Figure 2). The impaired induction of food allergen-specific iTreg cells paralleled the excessive IL-4R signaling and could be reversed by the deletion of Stat6.

GATA-3 plays a key role in Treg cell homeostasis, acting to prevent polarization to TH17 cells^{78,79}. Under physiological conditions, TH cell reprogramming is restrained and is lost in the presence of increased STAT6 signaling, thereby contributing to the pathogenic reprogramming of Treg cells into TH2-like cells⁶⁸. Treg cell lineage-specific deletion of *Il4* and *Il13* genes abrogates the induction of FA, thus confirming that IL-4 production by TH2 cell-like reprogrammed Treg cells directly contributes to allergic disease⁶⁸. The *in vitro* suppression of mast cell activation by antigen-specific Treg cells was abrogated in the presence of IL-4 but reversed with the deletion of *Stat6* in Treg cells. This is supported by previous reports that the suppression of mast cell activation and IL-4 production restores tolerance and promotes the induction of Treg cells⁸⁰. Although the programming of iTreg cells into TH2 cell-like cells is pathogenic in FA, it may serve physiological purposes under other circumstances. For example, intense IL-4/IL-4R signaling in the context of helminth infections has been reported to drive the development of TH2 cell-like ex-Treg cells, which contribute to immunity to nematodes⁸¹.

The above concepts of iTreg cell suppression and pathogenic reprogramming into Teff-like cells, developed in the context of FA, have been extended to encompass the pathogenesis of other allergic diseases such as asthma. The frequencies of suppressive allergen-specific Treg cells trend higher in healthy controls as compared with asthmatics⁸². Importantly, there is evidence of pathogenic reprogramming of Treg cells toward effector phenotypes that contribute to asthma severity⁸³. Infection with respiratory syncytial virus induced a TH2 cell-like effector program in Treg cells and impaired their suppressive function⁸⁴. Also, TH2 cell-like reprogramming of iTreg cells due to enhanced STAT6 activation via the IL-4R α in *Il4ra*^{F709} mice is associated with intense TH2 cell-skewed allergic airway inflammation. Other Treg cell pathways have also been implicated in the regulation of the TH2 cell response in allergic airway inflammation. Deletion of the beta subunit of casein kinase 2 (CK2) resulted in the proliferation of a Treg cell subpopulation characterized by the expression of the inhibitory receptor ILT3 (also known as gp49B). This Treg cell population was unable to control the maturation of dendritic cells expressing both the transcription factor IRF4 and the programmed cell death ligand 2 (PD-L2), which drove the development of lung TH2 responses⁸⁵.

More recently, we described a novel mechanism involving a common asthma-promoting human IL-4R α chain variant, by which allergen-specific iTreg cell differentiation is subverted to promote mixed TH2/TH17 cell inflammation, associated with severe, steroid-resistant asthma⁸⁶. When expressed in mice, this variant, which contains a glutamine-to-arginine (Q-to-R) substitution at position 576 of the IL-4R α , promotes exaggerated airway hyper-responsiveness and severe mixed TH2/TH17 inflammation when the mice are sensitized with allergens and subsequently challenged. The R substitution does not impact IL-4R signaling via STAT6. Rather, IL-4 signaling via IL-4Ra-R576 activates IL-6 production by inducing the *de novo* recruitment of the adaptor growth factor receptor-bound protein 2 (GRB2) to the IL-4R α ⁸⁶ (Figure 3). GRB2 activates downstream MAP kinase cascades, including extracellular signal-regulated kinases to induce *IL6* gene expression by activating the transcription factors nuclear factor-kappa B (NF- κ B) and C/EBP- β and p38 MAP kinase, which activates IL-13 production. Newly formed antigen-specific iTreg cells are subsequently destabilized by the confluence of IL-6 and TGF- β 1 signaling, resulting in the degeneration of iTreg cells into TH17 cells that lack suppressive function. This derangement results in the over-production of both TH2 and TH17 cell responses, promoting severe airway hyper-responsiveness and inflammation. Exaggerated allergic inflammation in *Il4ra*^{R576} mice was reversed when Treg cells differentiating into TH17 cells were inhibited by either treatment with an anti-IL-6 antibody or Treg cell-specific deletion of genes that regulate TH17 cell differentiation, including *Rorc* (encoding the TH17 master transcription factor RoR- γ t) and *Il6ra*, encoding the IL-6R α chain⁸⁶.

Downstream abnormalities in allergen-specific Treg cells involving immunomodulatory cytokines, including IL-10 and TGF- β , may also contribute to the pathogenesis of allergic diseases. Rubtsov *et al.* deleted IL-10 in Treg cells and showed increased severity of allergic airway inflammation suggesting that IL-10 production by Treg cells is critical for the induction of immune tolerance⁸⁷. TGF- β production by Treg cells also contributes to the regulation of the immune response⁸⁸. The role of altered Treg cell production of IL-10 and TGF- β in the pathogenesis of allergic diseases and the underlying mechanisms for such alterations remain to be fully elucidated.

Antigenic specificity of allergen-specific Treg cells

The possession by nTreg cells of a distinct TCR repertoire, confirmed by several studies^{22,34,89,90}, suggests that they may recognize a distinct set of peptide antigens as compared with Tconv cells⁹¹. Furthermore, nTreg and iTreg cells exhibit distinct TCR repertoires, which may broaden the scope of antigens recognized collectively by the two Treg cell populations underlying their synergistic function in maintaining peripheral tolerance^{22,92}. More recently, evidence was presented that TCR of iTreg cells may recognize peptide-MHC class II complexes with a reversed polarity as compared with the TCR of Tconv cells, again suggesting the potential for altered recognition of a distinct set of peptide antigens as compared with TCR of Tconv cells⁹³. The allergen specificity of Treg cells in humans has recently been mapped by simultaneously quantifying and characterizing allergen-reactive enriched T cells. Using this approach, Bacher *et al.* identified a population of peripherally expanded,

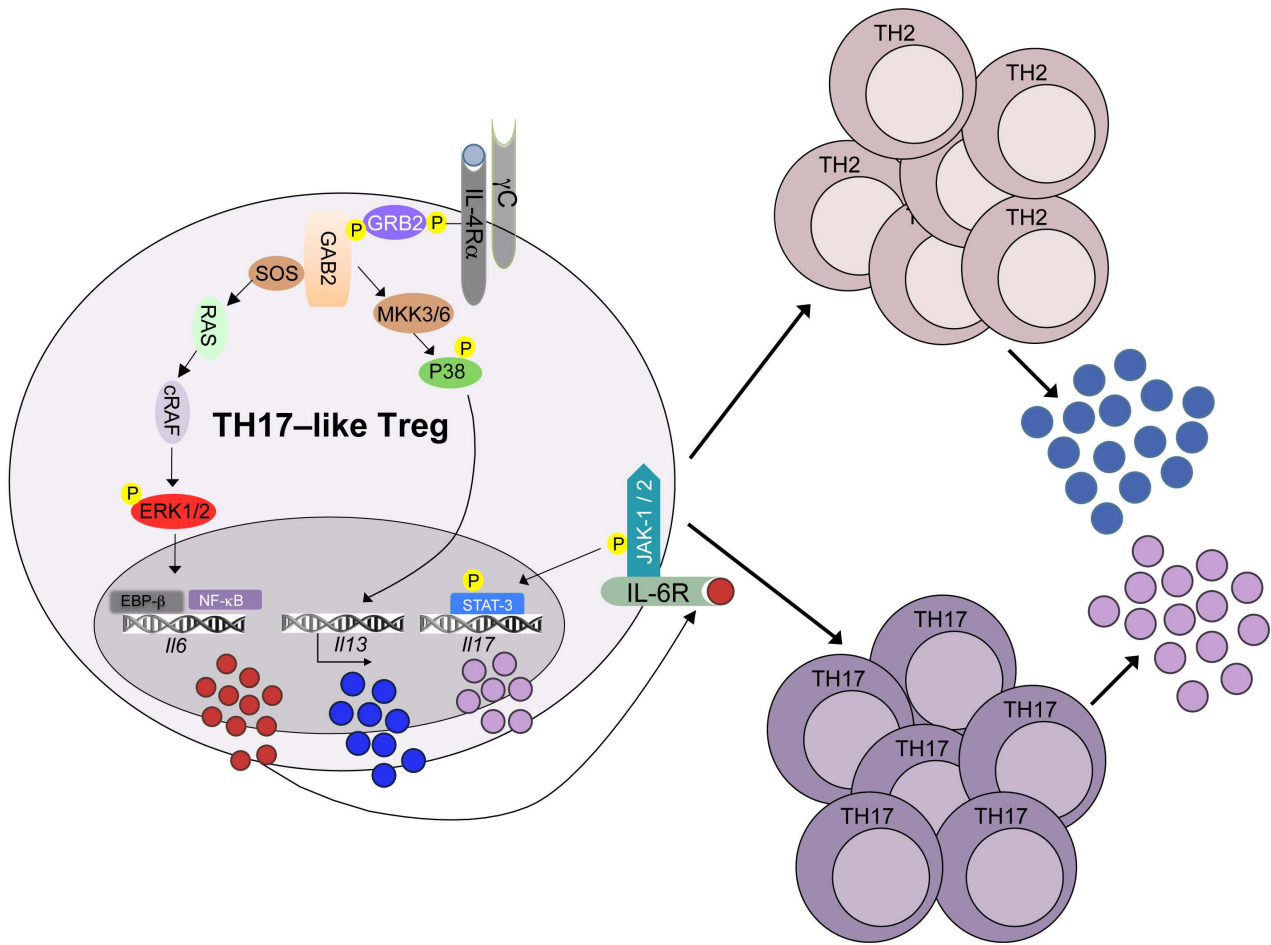


Figure 3. Induced regulatory T (iTreg) cell subversion by the asthma-promoting IL-4R α -R576 variant. Schematic representation of pathways mediating iTreg cell subversion by the asthma-promoting IL-4R α -Q76R variant. The glutamine to arginine substitution at position 576 of IL-4R α chain allows recruitment of the protein adaptor GRB2 upon receptor activation. GRB2 activates downstream MAP kinase cascades, including extracellular signal-regulated kinases, which drive IL-6 production by activating the transcription factors NF- κ B and C/EBP- β , and p38 MAP kinase, which activates IL-13 production. Newly formed antigen-specific iTreg cells are subsequently destabilized, resulting in the generation of excessive TH2 and TH17 cell responses that promote severe airway hyper-responsiveness.

stable Treg cells specific to innocuous aero-antigens in all allergic subjects⁵⁰. This subset of Treg cells served to maintain active tolerance as there was no corresponding clonally expanded high avidity-selected Tconv cell response in healthy controls. Whereas the authors did not address the suppressive influence of these antigen-specific Treg cells on TH2 induction in humans, previous mouse studies support this function.

Allergen-specific Treg cells and the microbiome

Substantial increases in the prevalence of allergic/atopic disease have been attributed to environmental factors coupled with genetic susceptibility. The hygiene hypothesis states that recent increases in the prevalence of allergic diseases are caused by reduced microbial exposure early in age due to the use of antibiotics and improved hygiene (more sterility)^{94–96}. Microbial colonization of neonates is initiated at birth, and the microbiotic composition of vaginally delivered infants is similar to that of the mother's vagina.

However, infants born by caesarean section obtain their microbiota from maternal skin and have been shown to have higher incidences of asthma and allergy^{97–99}. The direct role of the microbiota in the development of allergen-specific responses is evident in GF mice that cannot be tolerized to oral antigens¹⁰⁰. We recently demonstrated that the development of FA is correlated with dysbiosis in a mouse model of allergic dysregulation¹⁰¹. Food allergic *Il4ra*^{F709} mice exhibited reduced abundance in members of the Firmicutes phylum and an increase in Proteobacteria phylum as compared with WT mice. The transfer of allergen-specific Treg cells blocked the development of allergic responses in mice while also preventing the food allergic dysbiosis observed in control mice¹⁰¹.

Although the mechanisms by which the microbiota direct the differentiation and function of allergen-specific Treg cells remain to be fully elucidated, progress has been made in identifying

potential pathways involved. Commensal bacteria induce the expression in iTreg cells of the transcription factor RoR- γ ^{102,103}. Ohnmacht *et al.* proposed that RoR- γ iTreg cells may regulate allergic diseases by restraining TH2 cell-mediated responses in the gut by a CTLA-4-dependent mechanism¹⁰². Other studies have implicated short-chain fatty acids, including acetate, propionate, and butyrate, produced by commensals such as *Clostridial* species in stabilizing Treg cells in the gut^{104–106}. Other microbiotic products could also be directly influencing iTreg cell differentiation and function in the gut. *Bacteroides fragilis* is a commensal bacteria that has been found to promote the upregulation of Foxp3⁺ Treg cells using its product, polysaccharide A (PSA), to signal through Toll-like receptor 2 in T cells^{107–109}. *B. fragilis* lacking PSA was unable to maintain tolerance induction and upregulated TH17 cell differentiation¹¹⁰. Failure of MyD88-dependent signaling in Treg cells severely restricted the evolution of antigen-specific Treg cell responses in the gut, consistent with the action of microbiotic products through innate immune signaling mechanisms in Treg cells promoting their expansion and function¹¹¹. The loss of these and other mechanisms through dysbiosis may compromise the development of Treg cells in FA and other gut dysbiotic disorders.

Resetting pro-inflammatory antigen-specific Treg cells to promote tolerance in human subjects

The plasticity of Treg cells becomes a critically relevant issue when contemplating interventions aiming to employ Treg cells in cellular therapies or to promote Treg cell function in chronic inflammatory and autoimmune disorders. Because of the instability of Foxp3 expression in Treg cells, especially iTreg cells, under intense inflammatory conditions, these cells may acquire Teff cell phenotypes and express TH cytokines relevant to the ongoing immune response¹¹². *In extremis*, they may lose their Foxp3 expression to become pathogenic Teff cell-like ex-Treg cells¹¹³. In that regard, therapies that neutralize key inflammatory cytokines have been shown to promote Treg cell stability and function under inflammatory conditions. For example, in experimental models of chronic inflammatory disorders, including arthritis and asthma, treatment with anti-IL-6 or anti-tumor necrosis factor (anti-TNF) monoclonal antibodies appears to enhance Treg cell stability and function^{114,115}. Genetic manipulations of iTreg cells aimed to improve their stability when employed in cellular therapies may prove useful in enabling effective use of these therapies in inflammatory disorders. Conversely, therapies that are currently used in other indications to block Treg cell function such as anti-CTLA-4 and anti-PD-1 antibodies in cancer¹¹⁶ may predispose patients to allergic diseases by inhibiting and destabilizing Treg cells, especially iTreg cells.

The induction of antigen-specific Treg cells is particularly relevant to allergen-specific immunotherapy, which aims to reduce the allergic symptoms and maintain a long-term tolerance to allergen exposure¹¹⁷. It typically consists of gradual introduction of escalating doses of the offending allergen, leading to a state of allergen desensitization and ultimately, when successful, to a state of long-term tolerance that persists upon discontinuation of immunotherapy. A case in point is oral immunotherapy (OIT) for FA, which has the potential to modify disease outcome and, in

some cases, provide a long-term cure. OIT may impact the responses of allergen-specific T cells by (a) reversing the TH2 phenotype of Teff cells or inducing their deletion or both and (b) upregulating the effectiveness of allergen-specific Treg cells¹¹⁸. Foxp3 Treg cells and induced type 1 Treg cells have both been implicated in clinical effectiveness of OIT¹¹⁹. For example, a role for peanut-specific Treg cells has been demonstrated in peanut-allergic patients successfully treated with OIT. Syed *et al.* reported an increase in antigen-specific Treg cells in patients who reacted well to treatment compared with those who failed to tolerate¹²⁰. These Treg cells were characterized with increased suppressive behavior and epigenetic modifications within the Foxp3 locus. Similarly, we observed an initial decline in Treg cells when first treated with OIT supplemented with anti-IgE therapy that were recovered over time as the patients were desensitized (Abdel-Gadir *et al.*, manuscript submitted)^{121,122}. Recovered Treg cells had increased suppressive function and reduced production of IL-4. Blockade of IL-4R signaling appeared to rescue the suppressive function of peanut-specific Treg cells isolated from untreated patients (Abdel-Gadir and Chatila, manuscript submitted). These findings suggest a possible role for IL-4R signaling blockade as an adjunct therapy in promoting long-term tolerance in OIT.

Notwithstanding these encouraging results, OIT has had varying success in conferring long-term tolerance—defined as tolerance to the ‘offending’ food for up to six months after cessation of daily OIT—in patients with FA¹²³. Moran *et al.*¹²¹ and Sicherer¹²² both report that long-term tolerance is achieved in only 13 to 28% of OIT-treated patients. The reasons for these limited long-term successes remain obscure but may have to do with the persistence of a pro-TH2 inflammatory environment in the gut that promotes the reemergence of disease upon cessation of therapy. Adjunct efforts that attempt to limit TH2 inflammation either by neutralizing effector TH2 molecules or by employing immunomodulatory bacterial therapies that promote Treg cell stability in the face of inflammation may be effective in increasing the rates of long-term tolerance acquisition in this disorder.

Patch-based immunotherapy has recently been employed as an alternative approach to OIT in inducing allergen-specific oral tolerance in FA. Tordesillas *et al.* used a non-oral desensitization route involving epicutaneous antigen delivery and showed that mice thus treated were protected from FA-related anaphylaxis¹²⁴. A population of gut-homing (tissue-specific) Treg cells that lacked Foxp3 protein but expressed latency-associated peptide was found to be selectively expanded, and these Treg cells did not suppress IgE production but inhibited mast cell activation. This report showed that skin-gut immune interaction is important for the induction of long-term oral tolerance in FA.

Future directions

It is now clear that antigen-specific Treg cells play a key role in mediating peripheral tolerance to specific allergens in healthy individuals, but there are many questions left unanswered. First, the molecular mechanisms underlying the generation of pathogenic TH2 cell-skewed Treg cells in the periphery remain to be fully deciphered. Elucidating such mechanisms would enable therapeutic interventions that ‘reset’ the TH2 cell-like reprogramming

of allergen-specific Treg cells to promote their tolerogenic functions⁶⁸. Such a reset may be further extended to cellular therapies in which allergen-specific Treg cells are expanded from the peripheral blood, modified away from the TH2 cell-like reprogramming and subsequently transferred back to patients. More broadly, the environmental factors associated with changes in lifestyle over the last decade may foster the loss of tolerance to allergens and need to be more specifically mapped. Particularly relevant is the role of altered microbial exposure early in life in shaping the Treg cell response^{101,107}. A better understanding of how commensal microorganisms or their metabolites influence the generation of Treg cells and how dysbiosis may impact allergic responses would be highly informative in this regard. Thus, translating these advances to more effective manipulations of the

allergen-specific Treg cell responses may offer novel therapeutic approaches in allergic disorders.

Competing interests

The authors declare that they have no competing interests.

Grant information

This work was supported by National Institutes of Health grants (5R01AI065617 and R01AI126915) to TAC.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References



- Sakaguchi S, Yamaguchi T, Nomura T, *et al.*: **Regulatory T cells and immune tolerance.** *Cell.* 2008; **133**(5): 775–87.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Harrison OJ, Powrie FM: **Regulatory T cells and immune tolerance in the intestine.** *Cold Spring Harb Perspect Biol.* 2013; **5**(7): pii: a018341.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Legoux FP, Lim JB, Cauley AW, *et al.*: **CD4⁺ T Cell Tolerance to Tissue-Restricted Self Antigens Is Mediated by Antigen-Specific Regulatory T Cells Rather Than Deletion.** *Immunity.* 2015; **43**(5): 896–908.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Sakaguchi S, Sakaguchi N, Asano M, *et al.*: **Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases.** *J Immunol.* 1995; **155**(3): 1151–64.
[PubMed Abstract](#) | [F1000 Recommendation](#)
- Hori S, Nomura T, Sakaguchi S: **Control of regulatory T cell development by the transcription factor Foxp3.** *Science.* 2003; **299**(5609): 1057–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Samstein RM, Josefowicz SZ, Arvey A, *et al.*: **Extrathymic generation of regulatory T cells in placental mammals mitigates maternal-fetal conflict.** *Cell.* 2012; **150**(1): 29–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Burzyn D, Kuswanto W, Kolodin D, *et al.*: **A special population of regulatory T cells potentiates muscle repair.** *Cell.* 2013; **155**(6): 1282–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Arpaia N, Green JA, Moltedo B, *et al.*: **A Distinct Function of Regulatory T Cells in Tissue Protection.** *Cell.* 2015; **162**(5): 1078–89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Di Ianni M, Falzetti F, Carotti A, *et al.*: **Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation.** *Blood.* 2011; **117**(14): 3921–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Russler-Germain EV, Rengarajan S, Hsieh C: **Antigen-specific regulatory T-cell responses to intestinal microbiota.** *Mucosal Immunol.* 2017; **10**(6): 1375–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Kim KS, Hong SW, Han D, *et al.*: **Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine.** *Science.* 2016; **351**(6275): 858–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Sakaguchi S: **Naturally arising Foxp3-expressing CD25⁺CD4⁺ regulatory T cells in immunological tolerance to self and non-self.** *Nat Immunol.* 2005; **6**(4): 345–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Pellerin L, Jenks JA, Bégin P, *et al.*: **Regulatory T cells and their roles in immune dysregulation and allergy.** *Immunol Res.* 2014; **58**(2–3): 358–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Curotto de Lafaille MA, Lafaille JJ: **Natural and adaptive foxp3⁺ regulatory T cells: more of the same or a division of labor?** *Immunity.* 2009; **30**(5): 626–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sakaguchi S, Miyara M, Costantino CM, *et al.*: **FOXP3⁺ regulatory T cells in the human immune system.** *Nat Rev Immunol.* 2010; **10**(7): 490–500.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Chen W, Jin W, Hardegen N, *et al.*: **Conversion of peripheral CD4⁺CD25⁺ naive T cells to CD4⁺CD25⁺ regulatory T cells by TGF-beta induction of transcription factor Foxp3.** *J Exp Med.* 2003; **198**(12): 1875–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Huehn J, Hamann A: **Homing to suppress: address codes for Treg migration.** *Trends Immunol.* 2005; **26**(12): 632–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bilate AM, Lafaille JJ: **Induced CD4⁺Foxp3⁺ regulatory T cells in immune tolerance.** *Annu Rev Immunol.* 2012; **30**: 733–58.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mucida D, Kutchukhidze N, Erazo A, *et al.*: **Oral tolerance in the absence of naturally occurring Tregs.** *J Clin Invest.* 2005; **115**(7): 1923–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Josefowicz SZ, Niec RE, Kim HY, *et al.*: **Extrathymically generated regulatory T cells control mucosal T_H2 inflammation.** *Nature.* 2012; **482**(7385): 395–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Hsieh CS, Lee HM, Lio CW: **Selection of regulatory T cells in the thymus.** *Nat Rev Immunol.* 2012; **12**(3): 157–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Haribhai D, Williams JB, Jia S, *et al.*: **A requisite role for induced regulatory T cells in tolerance based on expanding antigen receptor diversity.** *Immunity.* 2011; **35**(1): 109–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Haribhai D, Lin W, Edwards B, *et al.*: **A central role for induced regulatory T cells in tolerance induction in experimental colitis.** *J Immunol.* 2009; **182**(6): 3461–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mayne CG, Williams CB: **Induced and natural regulatory T cells in the development of inflammatory bowel disease.** *Inflamm Bowel Dis.* 2013; **19**(8): 1772–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liston A, Nutsch KM, Farr AG, *et al.*: **Differentiation of regulatory Foxp3⁺ T cells in the thymic cortex.** *Proc Natl Acad Sci U S A.* 2008; **105**(33): 11903–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Wirnsberger G, Mair F, Klein L: **Regulatory T cell differentiation of thymocytes does not require a dedicated antigen-presenting cell but is under T cell-intrinsic developmental control.** *Proc Natl Acad Sci U S A.* 2009; **106**(25): 10278–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Akiyama T, Maeda S, Yamane S, *et al.*: **Dependence of self-tolerance on TRAF6-directed development of thymic stroma.** *Science.* 2005; **308**(5719): 248–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cowan JE, Jenkinson WE, Anderson G: **Thymus medulla fosters generation of**

- natural Treg cells, invariant $\gamma\delta$ T cells, and invariant NKT cells: what we learn from intrathymic migration. *Eur J Immunol.* 2015; 45(3): 652–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Bains I, van Santen HM, Seddon B, *et al.*: Models of self-peptide sampling by developing T cells identify candidate mechanisms of thymic selection. *PLoS Comput Biol.* 2013; 9(7): e1003102.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Margulies DH: TCR avidity: it's not how strong you make it, it's how you make it strong. *Nat Immunol.* 2001; 2(8): 669–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. van Santen H, Benoist C, Mathis D: Number of T reg cells that differentiate does not increase upon encounter of agonist ligand on thymic epithelial cells. *J Exp Med.* 2004; 200(10): 1221–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
32. Huppa JB, Gleimer M, Sumen C, *et al.*: Continuous T cell receptor signaling required for synapse maintenance and full effector potential. *Nat Immunol.* 2003; 4(8): 749–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
33. Alegre ML, Frauwirth KA, Thompson CB: T-cell regulation by CD28 and CTLA-4. *Nat Rev Immunol.* 2001; 1(3): 220–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Relland LM, Williams JB, Relland GN, *et al.*: The TCR repertoires of regulatory and conventional T cells specific for the same foreign antigen are distinct. *J Immunol.* 2012; 189(7): 3566–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. Nishio J, Baba M, Atarashi K, *et al.*: Requirement of full TCR repertoire for regulatory T cells to maintain intestinal homeostasis. *Proc Natl Acad Sci U S A.* 2015; 112(41): 12770–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
36. Hadis U, Wahl B, Schulz O, *et al.*: Intestinal tolerance requires gut homing and expansion of FoxP3⁺ regulatory T cells in the lamina propria. *Immunity.* 2011; 34(2): 237–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Soroosh P, Doherty TA, Duan W, *et al.*: Lung-resident tissue macrophages generate Foxp3⁺ regulatory T cells and promote airway tolerance. *J Exp Med.* 2013; 210(4): 775–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Coleman MM, Ruane D, Moran B, *et al.*: Alveolar macrophages contribute to respiratory tolerance by inducing FoxP3 expression in naive T cells. *Am J Respir Cell Mol Biol.* 2013; 48(6): 773–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
39. Benson MJ, Pino-Lagos K, Roseblatt M, *et al.*: All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. *J Exp Med.* 2007; 204(8): 1765–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, *et al.*: A functionally specialized population of mucosal CD103⁺ DCs induces Foxp3⁺ regulatory T cells via a TGF- β and retinoic acid-dependent mechanism. *J Exp Med.* 2007; 204(8): 1757–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Esterházy D, Loschko J, London M, *et al.*: Classical dendritic cells are required for dietary antigen-mediated induction of peripheral T_{reg} cells and tolerance. *Nat Immunol.* 2016; 17(5): 545–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
42. Chistiakov DA, Bobryshev YV, Kozarov E, *et al.*: Intestinal mucosal tolerance and impact of gut microbiota to mucosal tolerance. *Front Microbiol.* 2015; 5: 781.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Lathrop SK, Bloom SM, Rao SM, *et al.*: Peripheral education of the immune system by colonic commensal microbiota. *Nature.* 2011; 478(7368): 250–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
44. Chai JN, Peng Y, Rengarajan S, *et al.*: *Helicobacter* species are potent drivers of colonic T cell responses in homeostasis and inflammation. *Sci Immunol.* 2017; 2(13): pii: eaal5068.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Weiss JM, Bilate AM, Gobert M, *et al.*: Neuropilin 1 is expressed on thymus-derived natural regulatory T cells, but not mucosa-generated induced Foxp3⁺ T reg cells. *J Exp Med.* 2012; 209(10): 1723–42, S1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. Tanoue T, Atarashi K, Honda K: Development and maintenance of intestinal regulatory T cells. *Nat Rev Immunol.* 2016; 16(5): 295–309.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
47. Duan W, Croft M: Control of regulatory T cells and airway tolerance by lung macrophages and dendritic cells. *Ann Am Thorac Soc.* 2014; 11 Suppl 5: S306–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Jaffar Z, Ferrini ME, Girtsman TA, *et al.*: Antigen-specific Treg regulate Th17-mediated lung neutrophilic inflammation, B-cell recruitment and polymeric IgA and IgM levels in the airways. *Eur J Immunol.* 2009; 39(12): 3307–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. Gollwitzer ES, Saglani S, Trompette A, *et al.*: Lung microbiota promotes tolerance to allergens in neonates via PD-L1. *Nat Med.* 2014; 20(6): 642–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
50. Bacher P, Heinrich F, Stervbo U, *et al.*: Regulatory T Cell Specificity Directs Tolerance versus Allergy against Aeroantigens in Humans. *Cell.* 2016; 167(4): 1067–1078.e16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. Kashiwagi M, Hosoi J, Lai JF, *et al.*: Direct control of regulatory T cells by keratinocytes. *Nat Immunol.* 2017; 18(3): 334–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. Jameson SC, Masopust D: Diversity in T cell memory: an embarrassment of riches. *Immunity.* 2009; 31(6): 859–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
53. Rosenblum MD, Way SS, Abbas AK: Regulatory T cell memory. *Nat Rev Immunol.* 2016; 16(2): 90–101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
54. Wakim LM, Bevan MJ: From the thymus to longevity in the periphery. *Curr Opin Immunol.* 2010; 22(3): 274–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. Rowe JH, Ertelt JM, Xin L, *et al.*: Pregnancy imprints regulatory memory that sustains energy to fetal antigen. *Nature.* 2012; 490(7418): 102–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Gratz IK, Rosenblum MD, Maurano MM, *et al.*: Cutting edge: Self-antigen controls the balance between effector and regulatory T cells in peripheral tissues. *J Immunol.* 2014; 192(4): 1351–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
57. Brincks EL, Roberts AD, Cookenham T, *et al.*: Antigen-specific memory regulatory CD4⁺Foxp3⁺ T cells control memory responses to influenza virus infection. *J Immunol.* 2013; 190(7): 3438–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. van der Veecken J, Gonzalez AJ, Cho H, *et al.*: Memory of Inflammation in Regulatory T Cells. *Cell.* 2016; 166(4): 977–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
59. Rosenblum MD, Gratz IK, Paw JS, *et al.*: Response to self antigen imprints regulatory memory in tissues. *Nature.* 2011; 480(7378): 538–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
60. Noval Rivas M, Chatila TA: Regulatory T cells in allergic diseases. *J Allergy Clin Immunol.* 2016; 138(3): 639–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Chatila TA, Blaeser F, Ho N, *et al.*: JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic dysregulation syndrome. *J Clin Invest.* 2000; 106(12): R75–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
62. Bennett CL, Christie J, Ramsdell F, *et al.*: The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet.* 2001; 27(1): 20–1.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Wildin RS, Ramsdell F, Peake J, *et al.*: X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet.* 2001; 27(1): 18–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Brunkow ME, Jeffery EW, Hjerrild KA, *et al.*: Disruption of a new forkhead/winged-helix protein, scurfy, results in the fatal lymphoproliferative disorder of the scurfy mouse. *Nat Genet.* 2001; 27(1): 68–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Lin W, Truong N, Grossman WJ, *et al.*: Allergic dysregulation and hyperimmunoglobulinemia E in Foxp3 mutant mice. *J Allergy Clin Immunol.* 2005; 116(5): 1106–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Lin W, Haribhai D, Relland LM, *et al.*: Regulatory T cell development in the absence of functional Foxp3. *Nat Immunol.* 2007; 8(4): 359–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
67. Gavin MA, Rasmussen JP, Fontenot JD, *et al.*: Foxp3-dependent programme of regulatory T-cell differentiation. *Nature.* 2007; 445(7129): 771–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Noval Rivas M, Burton OT, Wise P, *et al.*: Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy. *Immunity.* 2015; 42(3): 512–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
69. Huang G, Wang Y, Chi H: Control of T cell fates and immune tolerance by p38 α signaling in mucosal CD103⁺ dendritic cells. *J Immunol.* 2013; 191(2): 650–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Niess JH, Brand S, Gu X, *et al.*: CX₃CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science.* 2005; 307(5707): 254–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
71. Chieppa M, Rescigno M, Huang AY, *et al.*: Dynamic imaging of dendritic cell extension into the small bowel lumen in response to epithelial cell TLR engagement. *J Exp Med.* 2006; 203(13): 2841–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. Hapfelmeier S, Müller AJ, Stecher B, *et al.*: Microbe sampling by mucosal

- dendritic cells is a discrete, MyD88-independent step in DeltainvG S. Typhimurium colitis. *J Exp Med*. 2008; 205(2): 437–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. **F** Mazzini E, Massimiliano L, Penna G, *et al.*: Oral tolerance can be established via gap junction transfer of fed antigens from CX3CR1⁺ macrophages to CD103⁺ dendritic cells. *Immunity*. 2014; 40(2): 248–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
74. **F** Zhou X, Bailey-Bucktrout SL, Jeker LT, *et al.*: Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells *in vivo*. *Nat Immunol*. 2009; 10(9): 1000–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
75. **F** Yang XO, Nurieva R, Martinez GJ, *et al.*: Molecular antagonism and plasticity of regulatory and inflammatory T cell programs. *Immunity*. 2008; 29(1): 44–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
76. **F** Tachdjian R, Al Khatib S, Schwinglschack A, *et al.*: *In vivo* regulation of the allergic response by the IL-4 receptor alpha chain immunoreceptor tyrosine-based inhibitory motif. *J Allergy Clin Immunol*. 2010; 125(5): 1128–1136.e8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. **F** Mathias CB, Hobson SA, Garcia-Lloret M, *et al.*: IgE-mediated systemic anaphylaxis and impaired tolerance to food antigens in mice with enhanced IL-4 receptor signaling. *J Allergy Clin Immunol*. 2011; 127(3): 795–805.e1-6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
78. Wohlfert EA, Grainger JR, Bouladoux N, *et al.*: GATA3 controls Foxp3⁺ regulatory T cell fate during inflammation in mice. *J Clin Invest*. 2011; 121(11): 4503–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Wang Y, Su MA, Wan YY: An essential role of the transcription factor GATA-3 for the function of regulatory T cells. *Immunity*. 2011; 35(3): 337–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. **F** Burton OT, Noval Rivas M, Zhou JS, *et al.*: Immunoglobulin E signal inhibition during allergen ingestion leads to reversal of established food allergy and induction of regulatory T cells. *Immunity*. 2014; 41(1): 141–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. **F** Pelly VS, Coomes SM, Kannan Y, *et al.*: Interleukin 4 promotes the development of ex-Foxp3 Th2 cells during immunity to intestinal helminths. *J Exp Med*. 2017; 214(6): 1809–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
82. **F** Raedler D, Ballenberger N, Kluecker E, *et al.*: Identification of novel immune phenotypes for allergic and nonallergic childhood asthma. *J Allergy Clin Immunol*. 2015; 135(1): 81–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
83. Lloyd CM, Hawrylowicz CM: Regulatory T cells in asthma. *Immunity*. 2009; 31(3): 438–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. **F** Krishnamoorthy N, Khare A, Oriss TB, *et al.*: Early infection with respiratory syncytial virus impairs regulatory T cell function and increases susceptibility to allergic asthma. *Nat Med*. 2012; 18(10): 1525–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
85. **F** Ulges A, Klein M, Reuter S, *et al.*: Protein kinase CK2 enables regulatory T cells to suppress excessive T_H2 responses *in vivo*. *Nat Immunol*. 2015; 16(3): 267–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
86. **F** Massoud AH, Charbonnier LM, Lopez D, *et al.*: An asthma-associated IL4R variant exacerbates airway inflammation by promoting conversion of regulatory T cells to T_H17-like cells. *Nat Med*. 2016; 22(9): 1013–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
87. **F** Rubtsov YP, Rasmussen JP, Chi EY, *et al.*: Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. *Immunity*. 2008; 28(4): 546–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
88. Li MO, Sanjabi S, Flavell RA: Transforming growth factor-beta controls development, homeostasis, and tolerance of T cells by regulatory T cell-dependent and -independent mechanisms. *Immunity*. 2006; 25(3): 455–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. **F** Hsieh CS, Liang Y, Tyznik AJ, *et al.*: Recognition of the peripheral self by naturally arising CD25⁺ CD4⁺ T cell receptors. *Immunity*. 2004; 21(2): 267–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
90. Kuczma M, Pawlikowska I, Kopij M, *et al.*: TCR repertoire and Foxp3 expression define functionally distinct subsets of CD4⁺ regulatory T cells. *J Immunol*. 2009; 183(5): 3118–29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. Pacholczyk R, Kern J: The T-cell receptor repertoire of regulatory T cells. *Immunology*. 2008; 125(4): 450–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
92. Lathrop SK, Santacruz NA, Pham D, *et al.*: Antigen-specific peripheral shaping of the natural regulatory T cell population. *J Exp Med*. 2008; 205(13): 3105–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
93. **F** Lechner TM, Satake A, Kambayashi T: TCR signaling by conventional CD4⁺ T cells is required for optimal maintenance of peripheral regulatory T cell numbers. *Immun Inflamm Dis*. 2016; 4(2): 148–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
94. Okada H, Kuhn C, Feillet H, *et al.*: The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol*. 2010; 160(1): 1–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
95. Droste JH, Wieringa MH, Weyler JJ, *et al.*: Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy*. 2000; 30(11): 1547–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
96. Lack G, Fox D, Northstone K, *et al.*: Factors associated with the development of peanut allergy in childhood. *N Engl J Med*. 2003; 348(11): 977–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
97. **F** Jakobsson HE, Abrahamsson TR, Jenmalm MC, *et al.*: Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut*. 2014; 63(4): 559–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
98. Marrs T, Bruce KD, Logan K, *et al.*: Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol*. 2013; 24(4): 311–320.e8.
[PubMed Abstract](#) | [Publisher Full Text](#)
99. Legatzki A, Rösler B, von Mutius E: Microbiome diversity and asthma and allergy risk. *Curr Allergy Asthma Rep*. 2014; 14(10): 466.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Walton KL, Galanko JA, Balfour Sartor R, *et al.*: T cell-mediated oral tolerance is intact in germ-free mice. *Clin Exp Immunol*. 2006; 143(3): 503–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
101. **F** Noval Rivas M, Burton OT, Wise P, *et al.*: A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. *J Allergy Clin Immunol*. 2013; 131(1): 201–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
102. **F** Ohnmacht C, Park JH, Cording S, *et al.*: MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through ROR γ ^T T cells. *Science*. 2015; 349(6251): 989–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
103. **F** Sefik E, Geva-Zatorsky N, Oh S, *et al.*: MUCOSAL IMMUNOLOGY. Individual intestinal symbionts induce a distinct population of ROR γ ^T regulatory T cells. *Science*. 2015; 349(6251): 993–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
104. **F** Furusawa Y, Obata Y, Fukuda S, *et al.*: Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013; 504(7480): 446–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
105. **F** Park J, Kim M, Kang SG, *et al.*: Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. *Mucosal Immunol*. 2015; 8(1): 80–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
106. Brestoff JR, Artis D: Commensal bacteria at the interface of host metabolism and the immune system. *Nat Immunol*. 2013; 14(7): 676–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
107. **F** Round JL, Mazmanian SK: Inducible Foxp3⁺ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci U S A*. 2010; 107(27): 12204–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
108. **F** Telesford KM, Yan W, Ochoa-Reparaz J, *et al.*: A commensal symbiotic factor derived from *Bacteroides fragilis* promotes human CD39⁺Foxp3⁺T cells and T_{reg} function. *Gut Microbes*. 2015; 6(4): 234–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
109. **F** Round JL, Lee SM, Li J, *et al.*: The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science*. 2011; 332(6032): 974–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
110. **F** Mazmanian SK, Round JL, Kasper DL: A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature*. 2008; 453(7195): 620–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
111. **F** Wang S, Charbonnier LM, Noval Rivas M, *et al.*: MyD88 Adaptor-Dependent Microbial Sensing by Regulatory T Cells Promotes Mucosal Tolerance and Enforces Commensalism. *Immunity*. 2015; 43(2): 289–303.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
112. Beres A, Komorowski R, Mihara M, *et al.*: Instability of Foxp3 expression limits the ability of induced regulatory T cells to mitigate graft versus host disease. *Clin Cancer Res*. 2011; 17(12): 3969–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
113. Zhou X, Jeker LT, Fife BT, *et al.*: Selective miRNA disruption in T reg cells leads to uncontrolled autoimmunity. *J Exp Med*. 2008; 205(9): 1983–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

114. Thiolat A, Semerano L, Pers YM, *et al.*: **Interleukin-6 receptor blockade enhances CD39+ regulatory T cell development in rheumatoid arthritis and in experimental arthritis.** *Arthritis Rheumatol.* 2014; **66**(2): 273–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
115. **F** Nadkarni S, Mauri C, Ehrenstein MR: **Anti-TNF-alpha therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-beta.** *J Exp Med.* 2007; **204**(1): 33–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
116. Baumeister SH, Freeman GJ, Dranoff G, *et al.*: **Coinhibitory Pathways in Immunotherapy for Cancer.** *Annu Rev Immunol.* 2016; **34**: 539–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
117. Burks AW, Laubach S, Jones SM: **Oral tolerance, food allergy, and immunotherapy: implications for future treatment.** *J Allergy Clin Immunol.* 2008; **121**(6): 1344–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
118. Bedoret D, Singh AK, Shaw V, *et al.*: **Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab.** *Mucosal Immunol.* 2012; **5**(3): 267–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
119. **F** Zeng H, Zhang R, Jin B, *et al.*: **Type 1 regulatory T cells: a new mechanism of peripheral immune tolerance.** *Cell Mol Immunol.* 2015; **12**(5): 566–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
120. Syed A, Garcia MA, Lyu SC, *et al.*: **Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3).** *J Allergy Clin Immunol.* 2014; **133**(2): 500–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
121. Moran TP, Vickery BP, Burks AW: **Oral and sublingual immunotherapy for food allergy: current progress and future directions.** *Curr Opin Immunol.* 2013; **25**(6): 781–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
122. Sicherer SH: **Epidemiology of food allergy.** *J Allergy Clin Immunol.* 2011; **127**(3): 594–602.
[PubMed Abstract](#) | [Publisher Full Text](#)
123. Begin P, Chinthrajah RS, Nadeau KC: **Oral immunotherapy for the treatment of food allergy.** *Hum Vaccin Immunother.* 2014; **10**(8): 2295–302.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
124. **F** Tordesillas L, Mondoulet L, Blazquez AB, *et al.*: **Epicutaneous immunotherapy induces gastrointestinal LAP+ regulatory T cells and prevents food-induced anaphylaxis.** *J Allergy Clin Immunol.* 2017; **139**(1): 189–201.e4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Referee Status: 

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

- 1 **Jagadeesh Bayry** Immunopathologie et Immunointervention Thérapeutique, Centre de Recherche des Cordeliers, Paris, France
Competing Interests: No competing interests were disclosed.
- 1 **Megan K Levings** Department of Surgery, University of British Columbia & British Columbia Children's Hospital Research Institute, Vancouver, Canada
Competing Interests: No competing interests were disclosed.
- 1 **Tobias Bopp** Institute for Immunology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research