The Role of Regulatory T Cells in IgE-Mediated Food Allergy

O Palomares

Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University of Madrid, Spain

Abstract

Immunoglobulin (Ig) E–mediated food allergy is a type 2 helper T cell (T_H2)–dependent disease whose prevalence is increasing in industrialized countries as a direct consequence of reduced tolerance to food antigens. The generation of regulatory T cells (Treg) is a key component of oral tolerance, and compelling experimental evidence has demonstrated that functional allergen-specific Treg cells play a major role in healthy immune responses to allergens and clinically successful allergen-specific immunotherapy. In the particular case of IgE-mediated food allergy, further investigations are required to firmly demonstrate the role of Treg cells during desensitization, induction of tolerance, or both, and several studies have also suggested a key role for these cells in healthy responses to food allergens. Treg cells are able to suppress the sensitization and effector phases of allergic reactions via several mechanisms of action based on multiple soluble and surface-binding molecules. Our knowledge of the mechanisms governing the generation of food allergen–specific Treg cells in the gastrointestinal mucosa, including the specific dendritic cell subsets involved in such processes, has increased significantly over the last decade. The identification of alternative tissues where oral tolerance to food allergens might occur in vivo is crucial, not only for a better understanding of the pathophysiology of food allergy, but also for the development of alternative therapeutic interventions. Recent findings demonstrate that oral tolerance can be induced in the tonsils through generation and maintenance of functional allergen-specific Treg cells. Further investigation in this area could pave the way for novel treatments of food allergy and other immune tolerance–related diseases.

Key words: Allergy. IgE-mediated food allergy. Allergen-specific immunotherapy. Tolerance. Desensitization. Regulatory T cells. Dendritic cells.

Resumen

La alergia a alimentos mediada por IgE es una enfermedad dependiente de linfocitos T colaboradores de tipo 2 (Th2), de incidencia creciente en países desarrollados y que surge como consecuencia de la pérdida de tolerancia a antígenos alimentarios. La generación de células T reguladoras (Treg) constituye un componente esencial en la inducción de tolerancia oral. Diversos estudios demuestran que las células Treg específicas para alérgenos juegan un papel clave tanto en las respuestas de individuos no alérgicos como en la inducción de tolerancia tras inmunoterapia específica de alérgeno. Aunque en el caso particular de la alergia a alimentos se requiere un mayor número de investigaciones que verifiquen el papel real que desempeñan las células Treg durante desensibilización y/o inducción de tolerancia, varios trabajos parecen sugerir que dichas células son también imprescindibles en las repuestas no patológicas frente a alérgenos de alimentos. Las células Treg son capaces de inhibir tanto la fase de sensibilización como provocación de las respuestas alérgicas mediante diferentes mecanismos empleando una gran batería de moléculas solubles y ancladas a membranas. El conocimiento detallado de los mecanismos que operan durante la generación de células Treg específicas para alérgenos de alimentos en la mucosa intestinal, incluyendo las poblaciones de células dendríticas implicadas en dichos procesos, ha aumentado significativamente en la última década. La identificación de tejidos alternativos en los que la inducción de tolerancia oral frente a alérgenos de alimentos pueda ocurrir *in vivo* es fundamental, no sólo para conocer con mayor detalle los mecanismos moleculares implicados en la alergia a alimentos sino también para poder desarrollar tratamientos alternativos. En este sentido, estudios recientes demuestran que las amígdalas humanas constituyen una primera línea de defensa donde la inducción de tolerancia oral ocurre mediante mecanismos que implican la generación y mantenimiento de células Treg específicas para alérgenos. Estos hallazgos abren nuevos horizontes para el desarrollo de tratamientos novedosos para la alergia y otras enfermedades relacionadas con la pérdida de tolerancia.

Palabras clave: Alergia. Alergia a alimentos mediada por IgE. Inmunoterapia específica de alérgeno. Tolerancia. Desensibilización. Células T reguladoras. Células dendríticas.

Introduction

The immune system uses many mechanisms to protect the host against potentially dangerous pathogens while maintaining a state of tolerance to innocuous exogenous antigens and self antigens. Dysregulation of such mechanisms leads to immune tolerance–related conditions such as development of tumors, organ rejection, autoimmune diseases, and allergy.

Allergy can be defined as the capacity of the immune system to produce high levels of immunoglobulin (Ig) E antibodies against allergens. The term food allergy is widely used to refer any adverse immune response that occurs after the ingestion of a specific food [1,2]. IgE-mediated food allergy is a type 2 helper T cell (T_H2)–dependent disease that is increasingly prevalent in industrialized countries. It affects around 6% of children and 4% of adults [3]. The main clinical manifestations of IgE-mediated food allergy normally occur within 2 hours of ingestion and involve acute symptoms that affect the skin, airways, and gastrointestinal tract and often cause severe anaphylactic episodes. The only cure for food allergy is allergen-specific immunotherapy (allergen-SIT), which consists of the administration of increasing doses of the offending food allergen to induce a state of tolerance [4-7].

The generation and maintenance of functional allergen-specific regulatory T (Treg) cells is a key event for healthy immune responses to allergens and for successful allergen-SIT [6,8,9]. Compelling experimental evidence supports this concept for allergic diseases involving aeroallergens or venom allergens [6,10-14]. Although recent reports also suggest that the induction of allergen-specific Treg cells might play a pivotal role in healthy immune responses to food allergens and clinically successful allergen-SIT for food allergy [15], further investigations are needed to fully elucidate the contribution of Treg cells to desensitization and induction of tolerance during food allergen-SIT [1,7,15]. In this review, we discuss the phenotypic and functional features of allergen-specific Treg cells in the context of food allergy with emphasis on their role in establishing tolerance against food allergens.

Immune Mechanisms Underlying IgE-Mediated Food Allergy

Our understanding of the mechanisms underlying allergic diseases has increased significantly during recent decades [6,14,16,17]. Allergy can be divided into 2 main stages, namely, the sensitization phase and the effector phase. During sensitization, clonal expansion of allergen-specific $CD4^+$ T_H2 cells that produce interleukin (IL) 4 and IL-13 plays a key role in promoting B-cell class switching and the production of allergen-specific IgE able to bind to the high-affinity FcεRI on the surface of mast cells and basophils. The effector phase occurs after new contacts with the causative allergens, which induce cross-linking of allergen-IgE-FcεRI complexes on effector cells, leading to their activation and subsequent release of the anaphylactogenic substances responsible for the symptoms associated with immediate responses. When late-phase reactions occur, activated allergen-specific memory T_H2 cells produce IL-4, IL-5, IL-9, and IL-13, which help to maintain allergen-specific IgE levels, recruitment of inflammatory cells to tissues, eosinophilia, production of mucus, and contraction of smooth muscle cells, thus eliciting very severe clinical manifestations [8,14]. In addition, other T_H2 cytokines, such as IL-25, IL-31, and IL-33, and other effector T-cell subsets such as T_H1, T_H17, T_H9, and T_H22, might also contribute at different levels to ongoing allergic reactions [9,18,19].

In the case of IgE-mediated food allergy, primary sensitization occurs in the gastrointestinal tract after initial contact with the ingested allergen. Many dietary proteins come into contact with the immune system, but only a small number are able to induce sensitization through the gastrointestinal tract and trigger allergic symptoms [20-22]. Although the process by which a food protein becomes an allergen remains unclear [23], several studies have shown that food antigens with the capacity to induce primary allergic sensitization reach the gastrointestinal tract in an immunologically active form [22,24-27]. Food allergens with the capacity to induce primary sensitization are frequently very stable proteins with high resistance to heat denaturation, enzymatic digestion, or both [22,27-30]. The availability of purified food allergens, as well as recombinant and mutated forms, makes it possible to identify molecules able to induce primary sensitization and distinguish them from cross-reactive agents, thus improving diagnosis and management of food-allergic patients [31-38].

Mouse models of food allergy have shown that allergic sensitization to food antigens delivered through the oral route required the presence of specific adjuvants such as cholera toxin or staphylococcal enterotoxin B [15,39-41]. The detailed mechanisms by which these adjuvants contribute to T_H2 sensitization are not completely understood, although intestinal dendritic cells (DCs) play a key role in this process. In the intestinal lamina propria, 2 subsets of $CD11c^+$ DCs ($CX3CR1^+$ and $CD103^+$) have the capacity to capture and process antigens [42]. Given their capacity to intercalate and extend dendrites between epithelial cells, $CD11c^+$ DCs scan antigens directly from the intestinal lumen but do not transport them [43]. However, $CD11c^+$ $CD103^+$ DCs are able to uptake food antigens and transport them to the closest lymph nodes, where they induce appropriate immune responses depending on specific environmental signals [44]. As shown in Figure 1, under normal homeostatic conditions, migrating $CD103^+$ DCs promote generation of allergen-specific Treg cells through mechanisms involving soluble molecules such as TGF-β, retinoic acid, and the enzyme indoleamine 2,3-deoxygenase (IDO), and surface-binding costimulatory molecules such as 4-1BB, thus contributing to induction of tolerance [45-47]. In contrast, in the presence of cholera toxin or other specific adjuvants, $CD103^+$ DCs capture food allergens, migrate to mesenteric lymph nodes, and prime the differentiation of allergen-specific T_H2 cells through mechanisms that partially depend on the expression of the costimulatory molecules OX40L and TIM-4, thus promoting allergic sensitization (Figure 2) [39,40]. In humans, intestinal $CD103^+$ DCs displaying similar phenotypic and functional properties and different mechanisms contributing to T_H2 allergic sensitization have also been described [48-51]. For example, epithelial

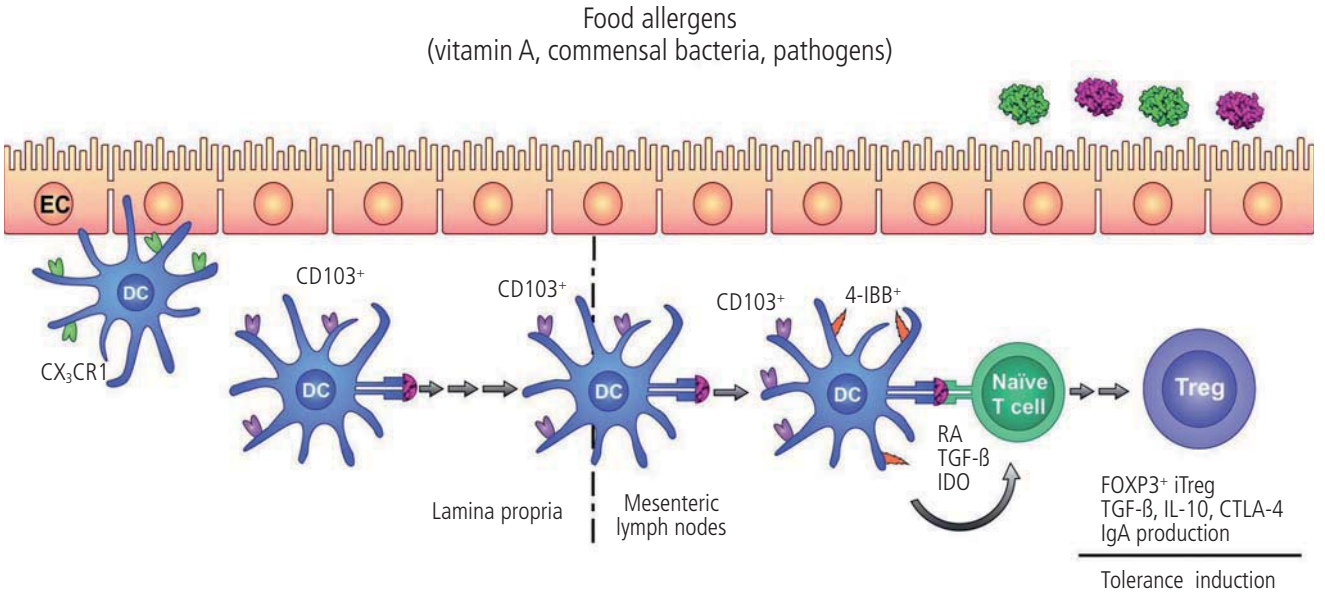

Figure 1. Induction of tolerance in the gastrointestinal mucosa. In mice, intestinal lamina propria CD103+ DCs capture food antigens delivered through the oral route and transport them to mesenteric lymph nodes where, under normal conditions, they polarize naïve CD4+ T cells to Treg cells by mechanisms involving retinoic acid (RA), indoleamine 2,3-dioxygenase (IDO), transforming growth factor ß, and 4-1BB.

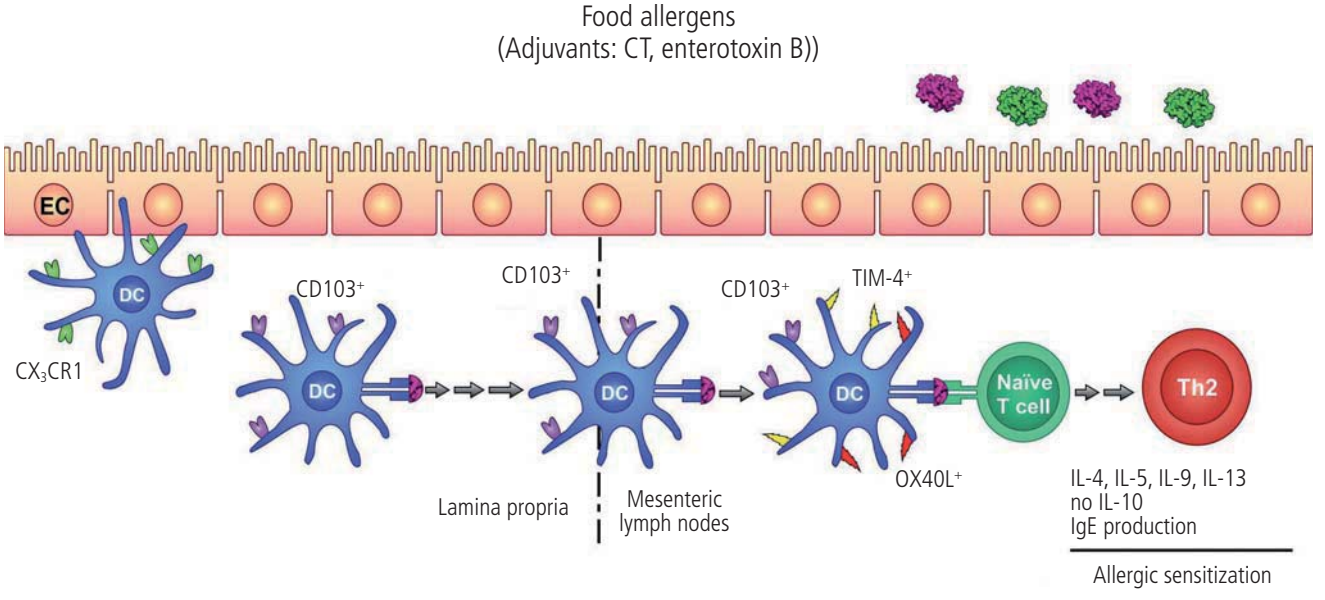

Figure 2. Allergic sensitization in the gastrointestinal mucosa. In mice, in the presence of adjuvants such as cholera toxin (CT) or enterotoxin B, intestinal lamina propria CD103+ DCs capture food antigens delivered through the oral route and transport them to mesenteric lymph nodes where they polarize naïve CD4+ T cells to T_H2 cells by mechanisms involving OX40L and TIM-4. IL, indicates interleukin; Ig, immunoglobulin.

cells can produce thymic stromal lymphopoietin (TSLP), which directly induces expression of OX40L on DCs. TSLP-activated DCs are able to promote the generation of T_H2 immune responses in the absence of IL-12 [51]. The major peanut glycoallergen Ara h 1 was shown to bind the C-type lectin receptor DC-SIGN on human monocyte–derived DCs, thus contributing to the polarization of Ara h 1–specific T_H2 responses and demonstrating that biochemical features of food allergens might well act as T_H2-skewed adjuvants [49,50].

Role of Treg Cells in the Induction of Oral Tolerance to Food Allergens

The generation of tolerance to self antigens and to innocuous nonself antigens such as those derived from food or commensal bacteria is key to ensuring an appropriate immune response. Although several mechanisms are known to mediate immune tolerance, including deletion or anergy of antigen-specific T-cell clones, both generation and maintenance of allergen-specific Treg cells are crucial for induction of oral tolerance to food allergens [2,8,15,44].

Treg cells are a heterogeneous population of T cells with suppressive and immunoregulatory properties that are essential for maintaining tolerance to innocuous substances and preventing excessive or misguided immune responses to pathogens. Treg cells can be broadly classified into 2 main groups: the thymus-derived naturally occurring $CD4^+CD25^+$ forkhead box protein 3 $(FOXP3)^+$ Treg cells, termed natural Treg (nTreg) cells, and the inducible Treg (iTreg) cells, which are generated in the periphery after antigenic stimulation [52,53]. iTreg cells can be further subdivided into 3 main subsets: *(1)* induced $FOXP3^+$ Treg cells, *(2)* $CD4^+FOXP3^-$ IL-10–producing Treg (Tr1) cells, and *(3)* transforming growth factor (TGF) β–expressing T_H3 cells [9]. FOXP3 is the master switch transcription factor for the differentiation of functional nTreg cell development [54]. FOXP3 is a relevant protein in both humans and mice. In humans, different types of mutations in *FOXP3* lead to the immunodysregulation polyendocrinopathy enteropathy X-linked syndrome [55]. Patients with this syndrome frequently display a strong typical autoimmune and allergic phenotype owing to alterations in the functional capacity of nTreg cells. Likewise, scurfy mice with impaired capacity to generate functional nTreg cells due to deletion in the forkhead domain of FOXP3 are characterized by a lifespan of approximately 3 weeks, severe lymphoproliferative disease, elevated IgE levels, and eosinophilia [56].

Treg cells are able to suppress the sensitization and effector phases of allergic reactions through different mechanisms of action. Treg cells directly or indirectly suppress allergen-induced degranulation of effector cells [57] and inhibit the influx of eosinophils and other effector T cells into inflamed tissues [58]. Treg cells interact with resident tissue cells, thus contributing to tissue remodeling [59,60], and promote the generation of tolerogenic DC phenotypes [61]. In addition, Treg cells directly inhibit the activation of allergen-specific T_H2 cells, thus blocking all the effects mediated by these cells during allergic reactions [9] and promoting the production of allergen-specific IgG4 while inhibiting IgE by directly acting on B cells [62]. To perform these functions, Treg cells use a large number of soluble and membrane-bound suppressor factors and 4 main mechanisms of suppression: inhibitory cytokines (eg, IL-10, TGF-β, and IL-35), cytolysis (secretion of granzymes A and B), metabolic disruption mechanisms (through CD25, cAMP, adenosine, CD39, and CD73), and mechanisms that target DCs through CTLA-4, PD-1, or histamine receptor 2 [54,63,64].

As discussed above, in the gastrointestinal tract, the default immune response against food antigens delivered through the oral route is the development of allergen-specific Treg cells that contribute to oral tolerance. The results of initial experiments in ovalbumin-sensitized mice suggested that administration of high doses of allergens through the oral route predominantly induced deletion of antigen-specific effector T cells, whereas administration of low doses favored the generation and/or expansion of antigen-specific Treg cells [65]. Recent data showed that allergen-specific Treg cells might also be induced and expanded in response to high doses of antigen administered orally [66,67], thus supporting the critical role played by Treg cells in oral tolerance. Although the detailed mechanisms operating in induction of tolerance at the gastrointestinal level are not yet fully elucidated, many studies highlight the role played by TGF-β [44,68,69]. The role of IL-10 is more controversial [68,70]. Several studies demonstrated that thymic nTreg cells are dispensable, whereas iTreg cells are essential for induction of tolerance [68,71]. These results are supported by the recent finding that extrathymic iTreg cells but not nTreg cells control mucosal T_H2 inflammation [72]. Elucidation of the mechanisms operating during induction of tolerance could improve our understanding of the pathophysiology of food allergy and enable us to design more efficient and safer immunotherapy approaches aimed at restoring healthy immune responses to food allergens.

Role of DCs in the Generation of Treg Cells

The intestinal lamina propria is constantly subjected to high antigenic loads (pathogens, commensal bacteria, and food-derived antigens); therefore, the immune system must mount proper immune responses to clear potentially dangerous pathogens while maintaining a state of tolerance to innocuous self antigens and nonself antigens. DCs play an essential role in these processes owing to their capacity for orchestrating adequate immune responses linking innate and adaptive immunity [73,74]. The mechanisms used by DCs to polarize Treg cells during induction of peripheral tolerance constitute an important area of research [6,9,45].

Initial experiments demonstrated that immature or partially mature DCs have the ability to generate Treg cells that promote oral tolerance [75], whereas mature DCs polarize different effector T_H subsets depending on the stimuli they encounter in specific environments [76]. The results of several studies demonstrated that under certain circumstances, fully mature

DCs are also able to induce functional Treg cells [9,77,78]. As shown in Figure 3, the capacity of mature DCs to polarize Treg cell responses is determined by exogenous signals (eg, vitamin D3 metabolites, retinoic acid, adenosine, and histamine), by specific probiotic or pathogen-derived molecules, and by FOXP3+ Treg cells [79-81]. In order to polarize Treg cells, DCs use a large battery of soluble and costimulatory molecules. Soluble molecules include cytokines with tolerogenic capacity (eg, TGF–β and IL-10), specific enzymes (eg, IDO or retinal aldehyde dehydrogenase), and distinct metabolites (eg, retinoic acid). Different costimulatory molecules with immunoregulatory capacity such as ICOS-L, PD-L1, ILT-3, ILT-4, CD80, CD86, and MHC-II can imprint specific Treg cell programs on naïve CD4+ T cells and expand existing functional Treg cells [54,63]. Human circulating DCs can be divided into 2 groups, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). Both are equipped with a different pattern of toll-like receptors (TLRs) and display different functional roles in the initiation of immune responses [78]. mDCs express TLR2-6 and 8 and pDCs express TLR7 and 9, thus enabling them to respond to specific pathogens. mDCs respond to bacterial and viral infections by producing large amounts of IL-12, whereas pDCs are the main producers of type I interferons after viral infections [78,82]. Several studies in humans demonstrated that fully mature pDCs are able to generate functional Treg cells, thus indicating their pivotal role in oral tolerance [77,78,83]. In a mouse model of asthma, depletion and adoptive transfer of pulmonary pDCs demonstrated that this DC subset is crucial for the prevention and development of allergic asthma [84]. Other studies in mouse models of allergic contact dermatitis showed that pDCs can also contribute to the initiation of oral tolerance in gut-associated lymphoid tissue or in the liver by inducing anergy or deletion of antigen-specific T cells. These data support the idea that pDCs represent a unique DC subset with intrinsic tolerogenic capacity able to promote oral tolerance through various mechanisms. Although further investigations are needed to confirm the role of pDCs in the context of food allergy, especially in humans, the design of specific vaccines targeting pDCs might well represent an alternative strategy for induction of peripheral tolerance to food allergens.

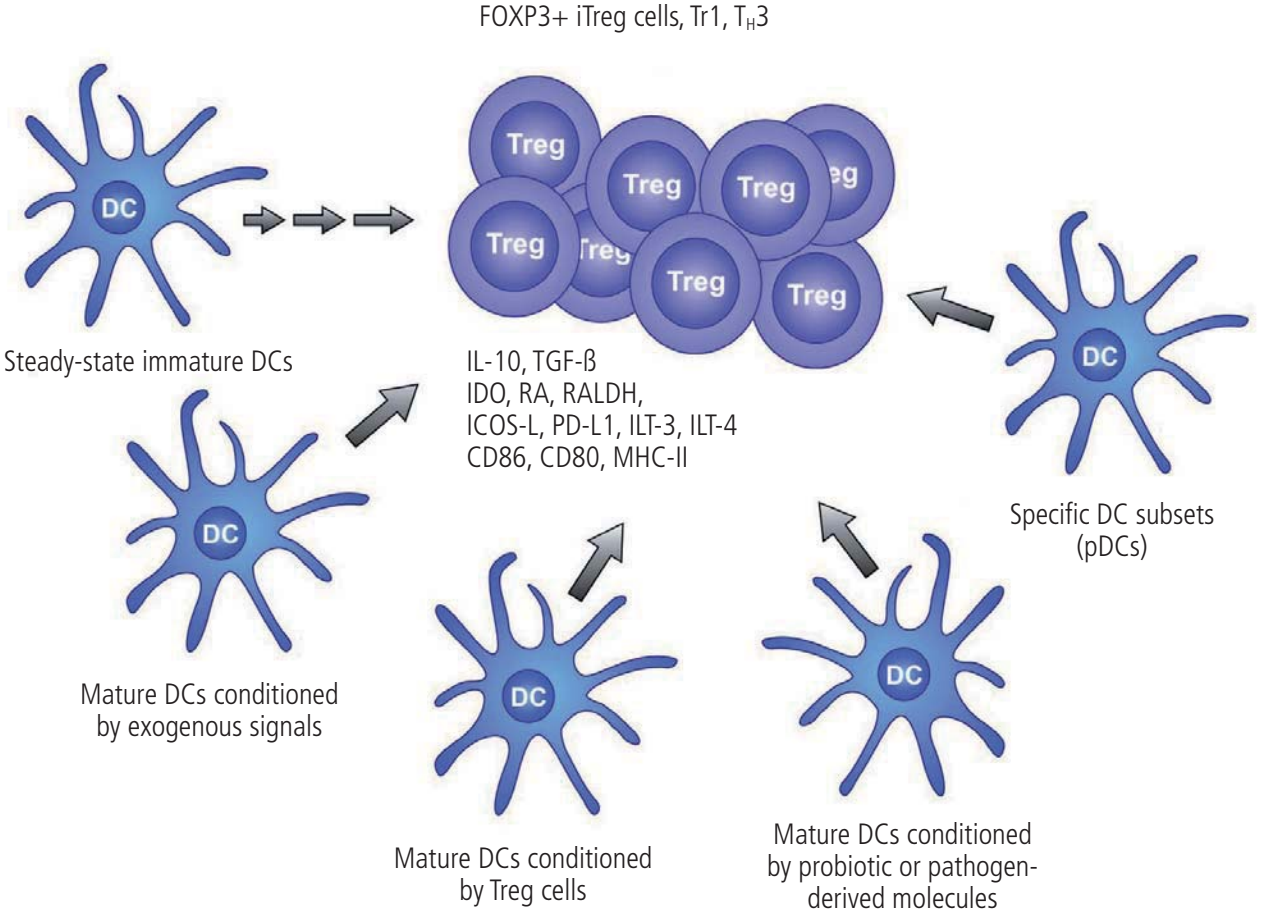

Figure 3. DCs polarize Treg cell through different mechanisms. Immature and mature DCs are able to generate iTreg cells. Under certain circumstances, specific DCs or mature DCs conditioned by exogenous signals, Treg cells, and probiotic or pathogen-derived molecules prime the generation of iTreg cells by the action of several tolerogenic molecules. DC indicates dendritic cells; Treg, regulatory T cells; IL, interleukin.

Treg Cells in Healthy Immune Responses to Food Allergens

Treg cells play a central role in controlling healthy immune responses to allergens. In humans, several studies show that the balance between allergen-specific T_H2 and Treg cells recognizing the same T-cell epitopes determines whether an individual develops allergy (T_H2) or has a healthy response (Treg) [6,8]. Allergen-specific T-cell lines derived from the peripheral blood mononuclear cells (PBMCs) of food-allergic patients display a predominant T_H2 phenotype characterized by high production of IL-4 and IL-13 but not of IFN-γ [85,86]. However, it has not always been possible to generate food allergen–specific Treg cell lines from the PBMCs of healthy controls. In the case of peanut, healthy individuals display significantly lower numbers of peanut-specific T cells than patients allergic to peanut [87,88]. This observation, together with the intrinsic anergy frequently observed in Treg cells, could explain why Treg cell lines from healthy donors are not easily generated. Nevertheless, it remains unclear whether Treg cells target specific tissues where they orchestrate and execute suppressive functions after allergen exposure. In addition, the profile of food allergen–specific T cells derived from healthy individuals display a predominantly T_H0/T_H1 phenotype compared to the T_H2 profile observed in allergic patients [86,87].

Exposure to high quantities of the causative allergen has been shown to promote tolerance in 2 human models [13,89]. Children who outgrew their milk allergy had fewer in vitro allergen-specific proliferative responses and a higher frequency of Treg cells than children who are allergic to milk [90,91]. Furthermore, Shreffler et al [92] showed that milk-allergic patients who tolerated heated milk had a higher frequency of proliferative allergen-specific Treg cells than patients who did not tolerate heated milk and healthy controls [92]. No differences were found between healthy controls and milk-allergic patients, suggesting that the expansion of Treg cells might play an important role during induction of tolerance, since milk-allergic patients who tolerate heated milk are supposed to be in the process of outgrowing their allergy. The protective role of allergen-specific Treg cells in preventing and controlling the development of food allergy is supported by the finding that Treg cells and TGF-β signaling played a very important role during induction of tolerance in a mouse model of breast milk–mediated transfer of antigens to the neonate [69]. Moreover, Bottema et al [93] showed that single-nucleotide polymorphisms in *FOXP3* are associated with development of allergy in childhood. However, and despite these findings, further research is still required to confirm whether food allergy is indeed caused by impaired function of Treg cells.

Treg Cells in Allergen-SIT for Food Allergy

Allergen-SIT consists of the repeated administration of increasing doses of the offending allergen to induce tolerance. It is currently the only available treatment that is capable of modifying disease course. Approaches such as subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), and peptide immunotherapy to treat allergies triggered by aeroallergens or venom allergens demonstrated that the generation and maintenance of functional allergen-specific Treg cells are critical steps in successful allergen-SIT [7,94,95]. The reported mechanisms by which these iTreg cells contribute to the restoration of tolerance include suppression of effector cells, decreased infiltration of inflamed tissues by eosinophils, reduction in allergen-specific IgE with increases in allergen-specific IgG4 levels in serum, and IL-10–mediated or TGF-β–mediated suppression of T_H1 and T_H2 cell responses [8,96-100].

Over the last decade, tremendous advances have been made in the field of allergen-SIT for patients with food allergy [1,7,15]. These advances are due in part to the application of alternative strategies aimed at minimizing the adverse reactions previously observed during SCIT for peanut allergy [101,102]. Some of these strategies include the use of alternative routes of administration such as oral immunotherapy (OIT) or SLIT [103-107]. Other immunotherapy approaches being evaluated for food allergy include diets containing extensively heated foods to reduce allergenicity, treatments with modified antigens, epicutaneous administration of allergens, and combination of OIT with anti-IgE monoclonal antibodies [7,108,109]. When assessing successful outcomes of allergen-SIT, it is important to distinguish between desensitization and tolerance. Desensitization is defined as clinical nonresponsiveness to the specific food allergens while allergen-SIT is maintained, whereas tolerance refers to the induction of permanent clinical nonresponsiveness, even after discontinuation of treatment [1,2,15]. The ability of OIT and SLIT for food allergy to induce tolerance is currently under investigation, and the areas that have yet to be clarified include the relative risks of therapy versus allergen avoidance, optimal dosing regimens, and appropriate patient populations [7]. Clinical trials with patients who are allergic to milk, egg, and peanut undergoing OIT and SLIT showed that these approaches are safer than SCIT and able to induce desensitization [105,107,110-113]. Although the capacity of these treatments to induce permanent tolerance remains open to debate and requires further research, several clinical trials have already reported the capacity of OIT to induce tolerance [103,114-116]. Immunological data on successful OIT and SLIT for food allergy are still scarce. Some clinical trials showed that successful OIT is associated with increases in serum IgG4 and IgA levels, reduction in basophil and mast cell reactivity, and changes in the ratio of Treg and T_H2 cells [105,107,110,112,117-120]. However, the actual contribution of food allergen–specific Treg cells to desensitization and tolerance after OIT and SLIT for food allergy needs to be confirmed.

Tissues Where Allergen-Specific Treg Cells Are Generated

The gastrointestinal tract has several mechanisms to generate tolerance to food antigens delivered through the oral

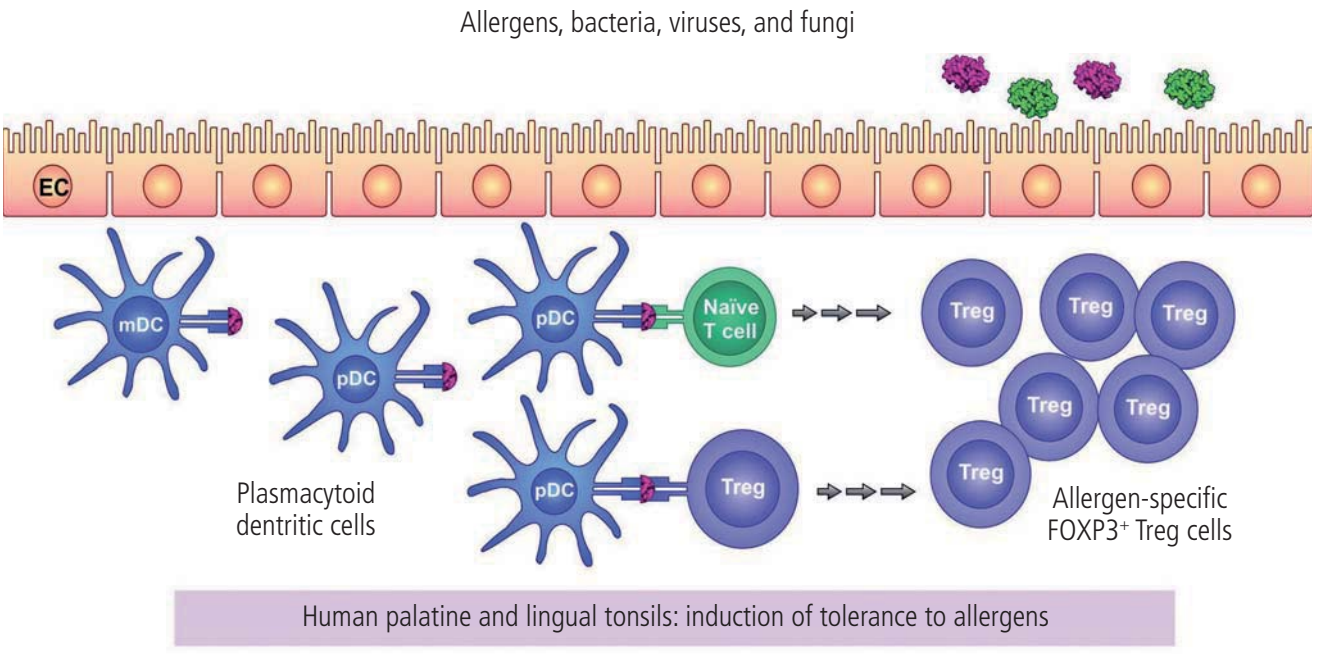

Figure 4. Human tonsils are organs of immune tolerance. The generation and maintenance of allergen-specific FOXP3+ Treg cells is controlled by pDCs in the palatine and lingual tonsils.

route, including the generation of food allergen–specific Treg cells by the action of specialized DC subsets [15,45]. The gastrointestinal mucosa is not the only site where functional Treg cells are generated, and tolerance has been induced in the respiratory tract, skin, and buccal mucosa [121-123]. Recent findings also demonstrated that human tonsils are key organs for induction of oral tolerance to food and aeroallergens through mechanisms that partially depend on the generation and maintenance of functional allergen-specific Treg cells mediated by pDCs (Figure 4) [77]. The tonsils have also been shown to be a site where extrathymic T cells develop [124,125]. The tonsils are secondary lymphoid organs that constitute part of the mucosa-associated lymphoid tissue [126]. Therefore, they are the first point of contact between the immune system and ingested food allergens before their degradation by digestive enzymes [126,127]. In addition, during deglutition, food particles are squeezed between the oropharynx wall and lingual or palatine tonsils, where food allergens are retained for a long period by highly cryptic surface structures. In the study by Palomares et al [77], major histocompatibility complex class II tetramer molecules coupled to specific peptides of the major birch pollen allergen Bet v 1 enabled the identification of higher numbers of Bet v 1–specific $CD4^+FOXP3^+$ Treg cells in human tonsils than in peripheral blood. The Bet v 1 peptides used in the study were T-cell epitopes previously involved in cross-reactivity with various food allergens [128,129]; therefore, it seems plausible that these tonsillar Bet v 1–specific Treg cells also play a role in suppressing allergic reactions triggered by homologous Bet v 1 counterparts from these food allergens. Kucuksezer et al [130] recently showed that triggering of TLR4 or TLR8 and proinflammatory cytokines breaks allergen-specific T-cell tolerance in human tonsils and peripheral blood. The authors also demonstrated that the immune profile of tonsils from allergic patients indicated atopic status, thus supporting the role of the tonsils as organs where immunoregulation takes place [130]. Consequently, and given that the palatine tonsils and, sometimes, adenoids are removed by tonsillectomy without disturbing the integrity of the relatively large lingual tonsil, these organs could well be ideal targets in novel immunotherapy protocols for the treatment of food allergy.

Conclusion

The generation and maintenance of functional allergen-specific Treg cells are key processes in healthy immune responses to allergens, as well as in successful allergen-SIT for reactions triggered by venom or aeroallergens. Treg cells are able to suppress both the sensitization phase and the effector phase of allergic reactions by means of multiple soluble and surface-binding molecules through different mechanisms. In the particular case of IgE-mediated food allergy, recent advances seem to indicate that functional allergen-specific Treg cells are also essential in the induction, restoration, and maintenance of tolerance to food allergens. Our understanding of the mechanisms operating during the generation of food allergen–specific Treg cells in the gastrointestinal mucosa, including the specific DC subsets involved in such processes, has significantly increased over the last decade. However, it

remains unclear whether IgE-mediated food allergy is a direct consequence of impaired function of Treg cells. Furthermore, the role of these cells during desensitization and induction of tolerance after OIT and SLIT has yet to be defined. Identification of easily accessible tissues where induction of tolerance is generated is crucial for developing alternative therapeutic interventions. In this regard, recent findings demonstrate that oral tolerance can be induced in the tonsils through generation and maintenance of functional allergen-specific Treg cells. Further investigation in this area could pave the way for novel immunotherapy protocols in food allergy.

Funding

Oscar Palomares is a Ramon y Cajal Scholar funded by Ministerio de Economía y Competitividad (MINECO) and the European Social Fund. The author's laboratory is supported by grants SAF2011-26716 and IPT-2012-0639-090000 from MINECO and RD12/0013/0015 from Fondo de Investigación Sanitaria.

Conflicts of Interest

The author declares that he has no conflicts of interests.

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Oscar Palomares

Department of Biochemistry and Molecular Biology
School of Chemistry
Complutense University of Madrid
Ciudad Universitaria, s/n
28040 Madrid, Spain
E-mail: oscar.palomares@quim.ucm.es

