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REVIEW

Allergen-Specific T Cells in IgE-Mediated Food Allergy

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Abstract
Food allergy is the major reason for severe anaphylaxis in childhood and adolescence. Currently, effective and safe treatments for food allergy are unavailable. Allergen-specific $CD4^+$ T cells have a pivotal role in causing and maintaining the allergic response to food allergens. The purpose of this review is to provide an overview on the role of allergen-specific T cells in food allergy during allergic sensitization, natural tolerance development and allergen immunotherapy. Allergen-specific T cells in the context of food allergy are predominantly of a Th2 type with slightly different surface marker expression patterns in different food allergies. During the process of reverting food allergy to a status of tolerance or sustained unresponsiveness there is a loss of this Th2 committed compartment with an asymptotic approximation to a regulatory and Th0/Th1 dominated compartment seen in non-allergic individuals. This process is accompanied by a significant reduction of absolute frequencies of allergen-specific T cells. Particularly, regulatory T cells may provide significant help to achieve sustained control of the effector cell populations via suppression of effector cell function and possibly induction of blocking antibodies.

Keywords Allergy · IgE-mediated food allergy · Helper T cells · Th2 cells · Regulatory T cells

Introduction

The prevalence of food allergy has reached a level of up to 8% among children and up to 5% in adults (Kattan 2016; Mahesh et al. 2016). However, the true prevalence of food allergies varies strongly depending on the geographic location and the definitions of methods applied.

Despite substantial progress in the concepts and strategies for primary (Greenhawt and Fleischer 2017; Muraro et al. 2014; Werfel et al. 2015) and secondary prevention (Bahnson et al. 2017; Du Toit et al. 2016; Togias et al. 2017), the prevalence of food allergy is expected to further increase (Lanser et al. 2015; Sampson et al. 2014). This is reflected in increased numbers of individuals reacting to a low threshold and/or displaying severe, life-threatening to fatal reactions upon exposure (Hochstadter et al. 2016). As reported by the recent European anaphylaxis registry and World Allergy Organization (WAO) anaphylaxis guidelines 2015, foods are considered as main anaphylaxis elicitors among children and adolescence. Two-thirds of the fatal reactions in children in their first 2 years of life were due to food products, mainly hen's egg and cow's milk. Cashew and hazelnut were the primary elicitors in the preschool children, while peanut triggered anaphylaxis in all ages (Grabenhenrich et al. 2016; Simons et al. 2015; Worm et al. 2014). Depending on the underlying mechanism, there are three types of food allergies: IgE-mediated, mixed and cell-mediated (Chinthrajah et al. 2015). This review will focus on IgE-mediated food allergy. The exact sequence of events, the process of sensitization and all the molecules and cell subsets involved in the sensitization process to a food allergen remain to be explored. However, the fundamental principles of the sensitization process at the cellular level are defined. Antigen-presenting cells (APCs), T cells and B cells are identified as key players and the outcome of the effector

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cell populations mainly depends on the microenvironment the allergen is embedded in. Thus, allergen-intrinsic factors, allergen-associated (Obersteiner et al. 2016) and allergen-bound (Bublin et al. 2014) factors may significantly promote/facilitate sensitization. In addition, numerous environmental factors, such as infectious agents, barrier disruption, the microbiome, metabolic factors shaping the immune repertoire, damage-associated factors and detergents and toxins contribute to or protect from allergic sensitization (Knaysi et al. 2017; Poulsen et al. 2014; Subbarayal et al. 2015).

Upon contact with the antigen, APCs take up the antigen and present it to naïve $CD4^+$ cells, initiating their differentiation into different subclasses defined by their function: T-regulatory (Treg), T helper 1 (Th1), Th2, Th9, Th17 or Th22 type memory and effector cells (Jutel and Akdis 2011; Ruiter and Shreffler 2012) (Fig. 1). As mentioned above, the context/microenvironment defines the type of T cell response. One of the key events in IgE-mediated allergies is the process of the IgE class-switch in B cells mainly driven by interleukin (IL)-4. Most likely allergen-associated molecules, such as glycans, lipids, glycolipids or allergen-intrinsic features (e.g. protease activity, lipid binding, glycosylation patterns…) contribute to allergenicity at the mucosal sites (Bublin et al. 2014; Smith et al. 2017). Cytokines and chemokines which are considered to play important roles in IgE-mediated reactions are IL-4, IL-5, IL-9, IL-13, IL-25, IL-33, thymus and activation-regulated chemokine and thymic stromal lymphopoietin (TSLP) (Akdis et al. 2016) (Fig. 2).

Once sensitization is achieved, these allergen-specific T cell populations may approach the inflamed area and interact

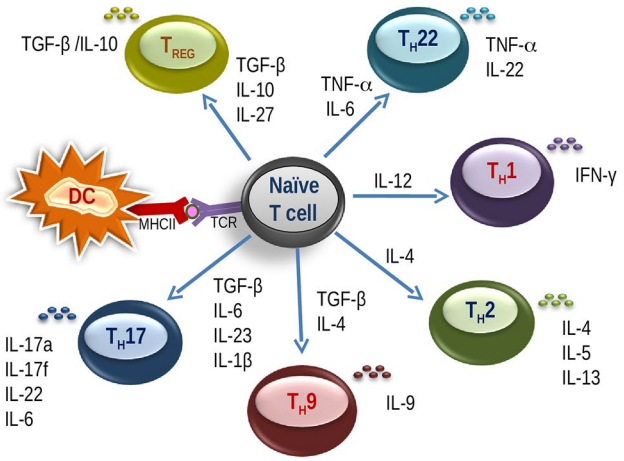

Fig. 1 Differentiation of a naive T cells. After presenting an antigen to the T cell by antigen presenting cells (DC), antigen specific naïve T cell become activated and differentiate into a number of T cell subsets such as Th1, Th2, Th9, Th17, Th22 and regulatory T cells. Depending on their function, they are linked to distinct local inflammatory or suppressive functions

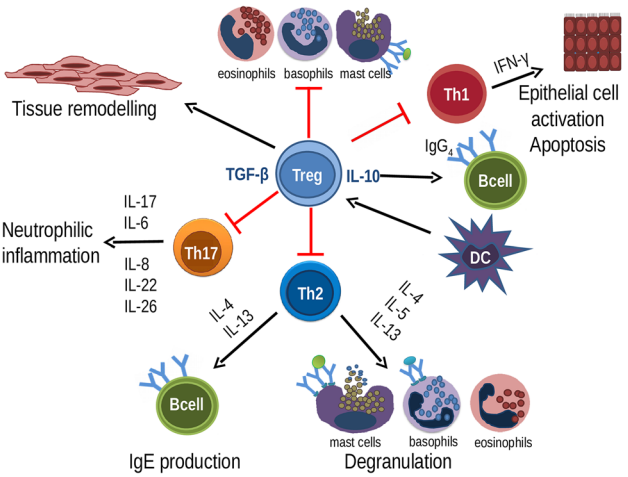

Fig. 2 The role of T cells in immunotherapy in food allergy. Regulatory T cells promote multiple suppressive (red line segment) and activating (black arrows) properties. As a result, the activation and the degranulation of mast cells, eosinophils and basophils are abated, leading to the reduction of the mediator release. Hence, secretion of the cytokines and the response of allergen-specific T cells is down-regulated by the action of allergen-specific Treg cells

with effector cells. Recently, type 2 innate lymphoid cells have been added to the puzzle, though their exact role in human food allergy still is largely unknown (Noval Rivas et al. 2016).

In this review, we will focus on the role of T-helper cells in the context of IgE-mediated reactions to food. Moreover, we will review changes in the T-helper cell compartments during oral immunotherapy and natural tolerance development.

T-Helper Cells and Allergic Sensitization

Sensitization to a certain food protein requires the interaction between the immune system of the host, the food allergen and a number of environmental factors that facilitate the process (Poulsen et al. 2014). Increasing evidence is pointing towards the skin as the sensitizing organ. This evidence is stronger for peanut allergy. This is supported by several mouse studies (Moghaddam et al. 2014; Noti et al. 2014; Tordesillas et al. 2014). In humans, the association between the usage of peanut-based ointments and peanut allergy has suggested this linkage (Lack et al. 2003). In addition, newer evidence on the early usage of ointments to prevent sensitization and allergies as well as the linkage between skin barrier defects and increased rates of food sensitizations (Ashley et al. 2017; Irvine et al. 2011; Kelleher et al. 2016; Simpson et al. 2016) further support the concept of the skin as a key area for sensitization. Currently, the hypothesis that the concurrence of delayed food introduction preventing oral

tolerance induction in facilitating the sensitization via the skin in atopic dermatitis contributed to significant increase in food allergies has been strongly supported for peanut allergy by the Learning Early About Peanut Allergy (LEAP) study (Du Toit et al. 2015, 2016; Perkin et al. 2016). Studies on early introduction of foods such as egg or milk are less clear, though they point in the same direction (Bellach et al. 2017; de Silva et al. 2014; Perkin et al. 2016). A very recent study by Wambre et al. (2017) identified new subset of Th2 cells with particular functional aspects distinctive from conventional Th2 cells and named them as Th2A cells. Th2A cells showed distinctive phenotypic characteristics expressing CRTH2^{high}, CD161^{high}, CD49d^{high}, CD45RB^{low} and CD27^{neg} in allergic subjects including food-allergic individuals. Peripheral blood mononuclear cells (PBMCs) of allergic and non-atopic subjects demonstrated phenotypically distinc cell expression patterns. These allergen-specific CD4$^+$ T cells were mainly CD45RO$^+$, whereas this population consisted to a lower percentage of CD45RO$^+$CD4$^+$ T cells in non-allergic individuals (Wambre et al. 2017).

Additionally, active tolerance development after sensitization or very early in life occurs as well (Mayer et al. 2012). However, from a conceptual point of view, active tolerance induction of regulatory cell subsets may (Mayer et al. 2012) represent the exception considering the incredible diversity and abundance of environmental antigens and the relatively low number of allergen families (Breiteneder and Radauer 2004) (Fig. 2).

If the allergen is presented in the appropriate Th2-favoring context via activated so-called dendritic cell 2 (DC2) APCs, Th2 or Th9 type cells will be generated from naïve T cells (Chen et al. 2015; Stojadinovic et al. 2014). Mucosal surfaces and the stratum spinosum of the epidermis, where pathogens mainly enter the organism are rich in DCs. These cells are the only cells circulating almost in every organ and tissue. After capturing an antigen at the tissues, DCs migrate to the lymph nodes through lymphatic vessels. In the lymph nodes, by the influence of cytokines and innate signals, DCs mature reflected by their increased ability to present an antigen via MHC class molecules and the expression of co-stimulatory molecules. In conjunction with the antigen, these signals define the type of effector T cell population that is induced. Especially, mucosa and epithelium-derived cytokines, such as IL-25, IL-33, and TSLP shape APC function in favor of Th2 responses which are also capable of enhancing the number and the function of effector cells in the tissue and thereby increase immune cell recruitment and inflammation (Eiwegger and Akdis 2011; Licona-Limon et al. 2013; Soyka et al. 2015; Wang 2016). The induction and the release of these cytokines in the epithelium by the impact of allergens or allergen-associated factors have been reported (Li et al. 2013). Recent trials on humans and mouse models addressed the great influence of TSLP on T cells, inducing allergic response involving lungs, skin, and gastrointestinal tract (Jiang et al. 2012; Noti et al. 2014). Latest study demonstrated that mesenteric lymph nodes from mice sensitized to food allergens lacking TSLP produce lower amounts of IL-4, IL-5, and IL-10 (Frossard et al. 2015). As a result, with the help of IL-4, allergen-specific B cells can mature and IgE production via the Ig-class switch to IgE is promoted. Sensitization in peanut allergy via TSLP has been reported to be IL-4 and IL-33 dependent (Chu et al. 2013).

Presenting an antigen to CD4$^+$ and CD8$^+$ lymphocytes is one of the primary mechanisms of the DC. Some of these subsets express the high-affinity IgE receptor that can result in a phenomenon called cross-presentation with much higher efficacy. This is, however, of unclear relevance in the context of the allergic disease since mice do not express the high-affinity IgE receptor on DC populations. Recently, a murine model expressing the humanized FcεRI was generated. Humanized mice exposed to antigen having only DC in the absence of mast cells and basophils could not induce the allergen-specific T cell response (Platzer et al. 2015).

Allergen-Specific CD4$^+$ T Cells in Food Allergy

During the development of food allergy, Th2 cells are the major cell type contributing to the pathological changes by producing cytokines, such as IL-4 and IL-13 (Michaud et al. 2014), and IL-5 and perhaps other Th2-type cytokines like IL-9 and IL-25 (Chen et al. 2015) (Fig. 3). In addition to an increased number of Th2 cells, IL-10, interferon (IFN)-γ,

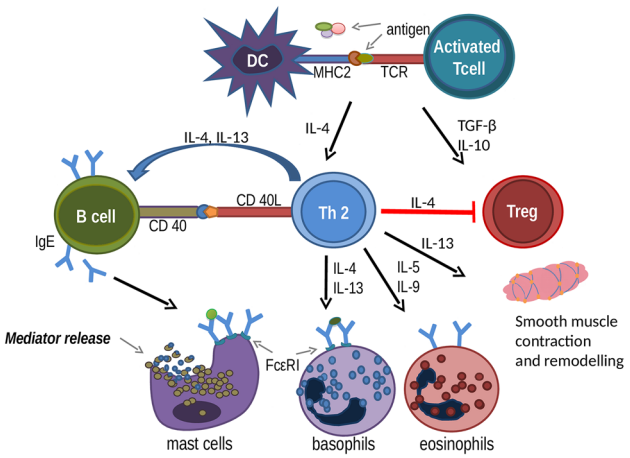

Fig. 3 The role of a Th2 cells in allergic disease. Antigen presented by type 2 dentritic cells via MHC class II to the TCR, activates T cells, which in turn up-regulate IL-4, leading to Th2 differentiation. With the help of IL-4 and IL-13 secreted by Th2 cells, allergen-specific B cells mature and IgE class-switching is promoted. Secreted IgE bind to the high affinity IgE receptor on mast cells and basophils and causes mediator release

and IL-17 secreting cells are also detected at lower frequencies in food-allergic subjects (DeLong et al. 2011).

Peanut-specific $CD4^+$ T cells have been calculated in the range of 100–200/million (Prussin et al. 2009), allergen-specific frequencies resulted in numbers of 20–60 $CD4^+$ T cells/million and in some allergic individuals, frequencies of more than 100/million $CD4^+$ T cells were reported. (Archila et al. 2015, 2016; DeLong et al. 2011; Renand et al. 2014). However, for the highest level of precision, sometimes epitope-specific investigations are required. Because of the low frequency of epitope-specific T cells in the periphery of food-allergic individuals (< 20/million $CD4^+$ T cells) and due to the risk of unspecific activation, MHC class II/peptide tetramer complexes are considered to be a gold standard. HLA-class II tetramers allow the identification of allergen-specific T cells with high specificity, but with low sensitivity. Since large amounts of blood and HLA-genotyping are needed, MHC II tetramers are reserved for research to generate mechanistic data at a single cell level. In this regard, $CD4^+$ T cell epitopes of Ara h 1 utilizing MHC class II tetramers in peanut and also cashew allergy have been generated (Archila et al. 2016; DeLong et al. 2011). Comparable characterization of Ara h 1-specific T cells revealed similar surface marker expression showing that the majority of the allergen-specific T cells were memory subtype, expressing CD45RO, CCR4, and CD25. CRTH2 was expressed only by a minority and did not provide any additional information. Interestingly, the gut-homing marker, $\alpha_4\beta_7$ was down-regulated or expressed at a very low level in Ara h 1, Ana o 1 and Ana o 2-specific T cells. Neither showed the skin homing marker CLA significant up-regulation in Ara h 1-specific T cells. The uniform cytokine pattern was a Th2 type, albeit. A certain percentage of Ara h 1-specific cells were IFN-γ, IL-10, and IL-17 producing cells (DeLong et al. 2011). In the case of the cashew allergens, an almost exclusive Th2 or Th2/Th17 skewed profile was observed (Archila et al. 2016). The T cell response against tropomyosin and arginine kinase in shrimp-allergic individuals revealed epitope-specific $CCR4^{pos}CXCR3^{low}$, $CD45RA^{neg}CD4^+CD27^+$ T cells. Again, CRTH2 expression was almost absent. Interestingly, the frequency of Pen m1 or Pen m 2 specific T cells was extremely low (< 5/million CD4 T cells) and allergen-specific cytokine responses did not provide a clear Th2 skewing of Pen m 1 and Pen m 2 with significant responses of IFN-y and IL-10 in the allergic population, particularly in Pen m 1 epitope-specific cells (Renand et al. 2014). Data from experiments using this technology revealed allergen-specific Th2 cell deletion as the main mechanism that drives the change in Th1/Th2 allergen-specific T cell ratios and governs the restoration of tolerance to inhalant allergens during immunotherapy. Allergen-specific $CD4^+$ T cells in allergy acquire various phenotypes and the quantity of these cells and their response depend on the allergen epitope and the atopic condition of the individual (Wambre et al. 2014).

In contrast to epitope-specific tetramers, CD154 (CD40L) is a promising alternative that allows studying allergen-specific or even allergen extract-specific T cells (Chattopadhyay et al. 2005). Data on direct comparison exist and show encouraging results (Wambre et al. 2008). Meanwhile, CD154 *ex vivo* assay helps to identify allergen-specific $CD4^+$ T cells independent from the type or kinetics of the cytokine they produce. Monitoring immune changes at a single cell level using tetramer technology and other technologies will allow a better understanding of the pathophysiology of allergic immune inflammation, the nature of protective responses and the sequence of events in individuals who become allergic or tolerant (Wambre et al. 2014). Recently, CD154 positive peanut-specific Th2 cells have been identified as CD161 and CD200R positive (Blom et al. 2017; Mitson-Salazar et al. 2016). The specificity of these markers for food allergy remains to be elucidated.

The third method that is often applied takes advantage of the dye carboxyfluorescein succinimidyl ester (CFSE). It is less time-consuming and relatively inexpensive in comparison to the method of tetramer technology. This method uses a cellular dye that is integrated into the cell and reduced upon cell division. Hence, it allows gating on the population of T cells that proliferate in response to the respective allergen ($CFSE^{low}$) and make them distinguishable from non-proliferating cells (Eiwegger et al. 2006; Turcanu et al. 2003). Nevertheless, the CFSE method also has a high potential of auto-proliferation confounding the results. These methods and data from allergen-specific T cell clones provided uniform evidence that allergen-specific T cells of allergic individuals are mainly of a Th2 type.

Allergen-Specific $CD4^+$ T Cells in Oral Allergen Immunotherapy

Allergen-specific oral (OIT), sublingual (SLIT) and epicutaneous immunotherapy to treat food allergies have been tested in phase 2 (Burks et al. 2012; Jones et al. 2017; Nurmatov et al. 2017) and currently ongoing phase 3 trials. Although, children with the most severe responses or concomitant severe or uncontrolled asthma are in general excluded from these trials and a significant number of patients do not develop sustained unresponsiveness (tolerating the respective food after a period of 4–8 weeks of avoidance). OIT trials have significantly contributed to a better understanding of the underlying immunological processes that take place during immunotherapy and will provide treatment options for food-allergic individuals. This also increased the knowledge on the nature of food allergen-specific T cells.

Studies on allergen immunotherapy (AIT) with inhalant allergens demonstrated a modification of the allergen-specific T cell compartment that is characterized by a loss of Th2 cells and the increase of the Treg cells and the generation of blocking antibodies. Thus, changes in the immune system at both, humoral and cellular levels occur (reviewed by Akdis and Akdis et al. 2015) (Fig. 3). Based on the sequence of events that have been described during immunotherapy activation of Tregs and Bregs and suppression of Th2 cells starts after an initial phase of mast cell deactivation and desensitization (Hussain et al. 2017). Milk-allergic subjects treated with OIT under the umbrella of omalizumab showed a substantial reduction of milk-specific $CD4^+$ T cells. In these patients, the ratio Th1 (IFN-γ^{pos})/Th2 (IL-4^{pos}, IL-13^{pos}) increased during OIT (Bedoret et al. 2012). In line with this finding, another group reported a relative reduction of $CD8^-CD3^+$ IL-4 producing cells upon Ara h 2 and Ara h 1 stimulation during peanut OIT (Wisniewski et al. 2015). Peanut-specific $CD4^+$ T cells (crude peanut extract) co-cultured with myeloid DCs or plasmacytoid DCs and T cells showed a significant reduction in IL-5 and IL-13 production in OIT and SLIT treated individuals in comparison to baseline with a temporary down-regulation of activation marker expression on the DC subsets (Gorelik et al. 2015). Another trial using peanut SLIT observed a reduction of IL-5 in peanut-allergic individuals after 1 year of SLIT. However, there were no significant differences in IL-13 and IFN-γ production in comparison to baseline (Kim et al. 2011a). A randomized double-blind placebo-controlled study of OIT also showed insignificant alterations in allergen-specific cytokine production of PBMCs. Specifically, IL-5 and IL-13 were significantly down-regulated (Varshney et al. 2011).

Among T cell subsets, Treg cells are considered to play a fundamental role in suppressing effector cell populations via direct inhibition or via the generation of inhibitory cytokines such as IL-10 and transforming growth factor (TGF)-β (Akdis and Akdis 2015; Zhang et al. 2014) and also contribute to the generation of blocking antibodies (Fig. 2). This IL-10 induction has also been observed in the context of peanut OIT (Wisniewski et al. 2015). In peanut OIT Syed et al. (2014) reported the induction of allergen-specific suppressive cells of a $CD4^+CD25^{high}FOXP3^+$ phenotype. However, the role of $FOXP3^+$ Treg or induced IL-10 producing regulatory T cells in food oral immunotherapy has not been completely confirmed in humans. Bedoret et al. (2012) observed a significantly reduced, almost absent allergen- specific T cell response to milk during milk OIT under omalizumab protection. Whether this was due to a suppression or reduction in allergen-specific clones could not be clarified since they did not assess allergen-specific Treg cells without *in vitro* expansion/stimulation by techniques such as tetramer staining. There was no upregulation of $CFSE^{low}CD4^+FOXP3^+$ milk-specific Treg cells in milk-allergic patients in response to allergen-specific immunotherapy. As a result, they concluded that desensitization occurred not by reduction/suppression of IL-10, simply because of skewing of cytokine production from IL-4 towards IFN-γ (Bedoret et al. 2012). A reduction of the proliferation of allergen-specific T cells in the process of specific oral tolerance achieved with OIT showed significant elevation of $CD4^+CD38^+CD45RO^-$ and $CD3^+CD4^+CD45RA^+CD31^+$ cells in egg allergy (Fuentes-Aparicio et al. 2012).

A common immunological phenomenon reported during AIT is the increase of allergen-specific IgG, and specifically IgG4. This is paralleled by a transient increase of IgE followed by a decline (Jones et al. 2009). In particular, IgG4 may be key blocking antibody due to the lack of complement binding sides and induction of IL-10. OIT induced Treg cells are considered to be relevant. Specifically, these changes are described in a longitudinal egg OIT study demonstrating the marked increase of egg white-specific IgG4, IgA, and IgA2 in the egg OIT group. In addition, substantial changes in the ratios of the IgG4/IgE, IgA/IgE, and IgA2/IgE have been identified (Wright et al. 2016). Similar results (increased ratios of IgG4/IgE) in peanut OIT were observed by Vickery et al. (2014) in patients with sustained unresponsiveness after 5 years of OIT. Another pilot study by Wisniewski et al. (2015) described the allergen-specific T cell profiles after OIT in peanut-allergic children.

Due to the considerable side effects of oral immunotherapy, some trials additionally implemented anti-IgE treatment, omalizumab during the up-dosing period. Indeed, OIT was much better tolerated, up-dosing could be performed faster and consequently the applicability in an outpatient setting seems much more feasible compared to conventional desensitization protocols. However, no additional information regarding omalizumab on sustained unresponsiveness and on the allergen-specific T cell compartment beyond those that have been seen during OIT (Frischmeyer-Guerrerio et al. 2017; Wood et al. 2016). Nevertheless, further mechanistic investigations are needed to finally conclude on this issue.

Allergen-Specific T Cells in Natural Tolerance Development

The likelihood of outgrowing or losing food allergy also often referred to as natural tolerance development depends on the food source, allergen-specific IgE levels and individual risk factors (Savage et al. 2016), such as genetics, age, skin barrier function and inflammation and gut microbiota (Chinthrajah et al. 2016). Many children with milk and egg allergy outgrow their food allergy without intervention by the time reaching school-age (Luyt et al. 2014; Nwaru et al.

2014; Ponce et al. 2016). Most likely mechanisms that occur during sustained unresponsiveness development also apply during natural tolerance development.

Children that tolerated extensively heated milk may have a higher chance to become tolerant to cow's milk (Kim et al. 2011b). This may be explained by a significantly higher percentage of milk-specific $CD25^{+}CD27^{+}CD4^{+}$ T cells (Shreffler et al. 2009) that also display features of Treg cells ($FOXP3^{pos}$, $CD127^{low/neg}$, $CD25^{high}$).

An amelioration of symptoms and the induction of tolerance in allergic individuals in association with an increase of allergen-specific IgG4 antibodies (Mobs et al. 2012; van de Veen et al. 2013) has been reported for food, hymenoptera and respiratory allergies. Furthermore, skin prick test, specific immunoglobulin E (sIgE), sIgG4, and IL-4 are also considered to be predictive markers in natural tolerance manifestation (Caubet et al. 2017; Fishbein et al. 2014; Savage et al. 2016). Specific IgE/IgG4 ratios for food allergens, namely, for milk, egg and peanut drop down in those subjects who are facing resolution from their food allergy, whereas the ratio was considerably elevated in individuals who could not tolerate food allergens (Caubet et al. 2012; Michaud et al. 2014; Santos et al. 2015). Allergen-sIgG4 antibodies are considered to compete with the existing allergen-sIgE antibodies for the allergen and thereby prevent the degranulation of mast cells. This shift away from IgE to IgG4 antibodies is hypothesized to be at least partly mediated by IL-10 producing T cells or B cells with regulatory function (Santos et al. 2015; Sommanus et al. 2014). Unfortunately, allergen-sIgG4 does not allow to predict resolution of the disease activity (tolerance development) and consequently does not enable the cessation of allergen-specific therapy (Burks et al. 2012; Sicherer et al. 2014; Vickery et al. 2014; Wood et al. 2013). Comparing T- and B-cell responses in peanut-allergic individuals revealed a considerable positive correlation of sIgE among both IL-4 and IL-13 and a negative correlation observed of sIgE between both IFN-γ and tumor necrosis factor (TNF)-α, whereas there were no detectable correlations in non-atopic subjects (Turcanu et al. 2008).

Compelling evidence for a strong role of the regulatory T cell compartment during natural tolerance development was provided by Karlsson et al. (2004) by demonstrating an up-regulation of $CD4^{+}CD25^{+}$ T cells *in vitro* after oral food challenge in patients who became tolerant. In contrast to allergic individuals these individuals had T cells with suppressive functions that were of a memory type (Karlsson et al. 2004). In this context, Qamar et al. (2015) showed that natural tolerance to foods in children who were allergic in the past is an antigen-specific process with an up-regulation of Treg cells. In mice, low-dose IL-2 induced Treg expansion and activation that offered protection against clinical features of food allergy (Bonnet et al. 2016). Additional evidence for an important role of Tregs in IgE-mediated cow's milk allergy (CMA) tolerance acquisition in childhood is accompanied by epigenetic regulation of the FOXP3 (Paparo et al. 2016). Beta-lactoglobulin (BLG) stimulated PBMCs of children who resolved CMA or had persistent CMA displayed $CD4^{+}CD25^{high}CD127^{low}$ phenotype T-helper cells with a higher FOXP3 protein and mRNA expression in CMA children in comparison to healthy children. No statistical difference in the percentage of $CD25^{high}CD127^{low}$ or $CD25^{high}CD127^{low}FOXP3^{pos}$ T-helper cells was observed upon BLG stimulation. This suggests that the loss of response (i.e. anergy) reflects what happens in patients that lose their CMA as compared to an active mechanism of suppression via expansion of the allergen-specific Treg pool (Savilahti et al. 2010).

Asymptomatic sensitization in children with peanut allergy is reflected in a shift of allergen-specific T cells mostly towards Th1 as compared to clear Th2 profile in peanut allergy (Eiwegger et al. 2006; Turcanu et al. 2003). In this context, Tiemessen et al. (2004) demonstrated notable discrepancies in the correlation of the production of CD25 and IL-4, IL-13, IL-10, and IFN-γ expression. The expression of CD25 and Th2 signature cytokines, namely, IL-4 and IL-13 were positively correlated in CMA individuals, whereas no correlation was observed in the control group (Tiemessen et al. 2004). Both T cell lines and PBMCs exposed to crude peanut extract of peanut-allergic, peanut-sensitized and non-atopic children showed significant increase of IL-13, IFN-γ and TNF-α only in peanut-allergic group, whereas no significant differences observed among peanut-sensitized and non-atopic group, with insignificant increase of IL-13 in peanut-sensitized children. Ara h 1 peptide-specific T cells of peanut-allergic subjects with absent allergen-sIgE expressed higher levels of IFN-γ in comparison to subjects with positive sIgE (Ramesh et al. 2016). More recently, IL-9 has been linked to allergen-specific T cells in food-allergic individuals (Brough et al. 2014; Xie et al. 2012). Proliferation of T cells in response to crude peanut extract and peanut components, namely, Ara h 1, Ara h 3 and Ara h 6 was notably high in peanut allergic versus peanut sensitized and non-atopic subjects (DeLong et al. 2011; Flinterman et al. 2010; Pascal et al. 2013). Clustering subjects into different groups by dextramer positive and dextramer negative sorting of the Ara h 2-specific $CD4^{+}$ T cells showed the differential expression of the genes among allergen-specific and unspecific cells. IL-4 and IL-13 were specific for allergic individuals, whereas IFN-γ was predominant in non-allergic, $FOXP3^{pos}CD25^{pos}IL\text{-}10^{pos}$ in regulatory phenotype and $CD28^{neg}CD38^{neg}IFN\text{-}\gamma^{neg}IL\text{-}4^{neg}IL\text{-}13^{neg}IL\text{-}10^{neg}$ in anergy in both allergic and non-allergic groups (Ryan et al. 2016).

Moreover, there is a strong influence of a gut and skin microbiota in both, the development of normal immune system and keeping normal immune function later on (Belkaid

and Segre 2014). Regulatory T cells preserve homeostasis between the microbiota and the host by interaction of adaptive and innate immune system (Westerholm-Ormio et al. 2010). In mice, microbiota composition was associated with protection from food allergy (Diesner et al. 2016). Recently, bacterial signatures have been linked to multi-sensitization at the age of two. In particular, the metabolome derived from stool samples of multi-sensitized atopic children seems to be decisive in this context and it is capable of inducing a Th2 phenotype in naïve T cells (Fujimura et al. 2016). Similar results have been generated from a Canadian birth cohort in the context of asthma development (Arrieta et al. 2015).

Conclusion

Recent advances in characterizing food allergen-specific T cells strongly supported the assumption that these cells are of a Th2 type. $CD4^+$ T cells have a strong impact on sensitization, allergy and tolerance, depending on the generation and the cytokines they produce. Notwithstanding significant progress in the understanding of allergen-specific T cells has been made, there is still a strong need to better understand the extent and the relevance of T cells in tolerance development. This is vital to generate novel treatment approaches that also address high risk patients with food allergy who are currently excluded from oral immunotherapy trials.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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