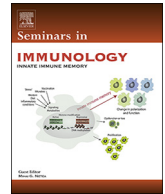




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Review

IL-10 producing T and B cells in allergy

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ABSTRACT

The molecular and cellular mechanisms of allergen tolerance in humans have been intensively studied in the past few decades. The demonstration of epitope-specific T cell tolerance, particularly mediated by the immune suppressor functions of IL-10 led to a major conceptual change in this area more than 20 years ago. Currently, the known essential components of allergen tolerance include the induction of allergen-specific regulatory of T and B cells, the immune suppressive function of secreted factors, such as IL-10, IL-35, IL-1 receptor antagonist and TGF- β , immune suppressive functions of surface molecules such as CTLA-4 and PD-1, the production IgG4 isotype allergen-specific blocking antibodies, and decreased allergic inflammatory responses by mast cells, basophils, and eosinophils in inflamed tissues. In this review, we explain the importance of the role of IL-10 in allergen tolerance.

1. Introduction

Interleukin (IL)-10 family cytokines are considered as the major instrumental cytokines which have both immune suppressive and immune-stimulatory effects [1]. The IL-10 cytokines are produced mainly by monocytes, regulatory T cells (Treg), regulatory B cells (Breg), a small fraction of natural killer (NK) cells, macrophages, dendritic (DCs) cells and innate lymphoid cells (ILCs) [2]. The effects of IL-10 on monocytes and macrophages are inhibition of the production and release of mediators and antigen presentation and the enhancement of phagocytosis. IL-10 directly interacts on CD4⁺ T cells and down-regulates IL-2 and IFN- γ cytokines production by Th1 cells and of IL-4 and IL-5 by Th2 cells [3].

There are nine members in the interleukin-10 (IL-10) family of cytokines including IL-10; IL-20 subfamily members IL-19, IL-20, IL-22, IL-24, and IL-26; and the other related cytokines IL-28A, IL-28B, and IL-29, which are identified as type III interferons (IFNs) [4]. IL-10 binds to a receptor complex comprised of IL-10R1 and IL-10R2 chains [5]. IL-10R1 chain is only expressed on target cells including T cells, B cells, natural killer cells, monocytes, mast cells, and DCs whereas the IL-10R2 is a shared cell surface receptor [8]. In addition, IL-10R associated tyrosine kinase-2 (TYK2) acts as a constitutive reservoir for SHP-1 on IL-10 binding [6]. The tyrosine phosphatase SHP-1 stays linked to TYK2 and gets activated and downregulates the signals via costimulatory molecules, such as CD28, ICOS and CD2 [6]. Moreover, IL-10 receptor

binding activates JAK1 and TYK2, which provide docking sites predominantly recruit and activate, via additional phosphorylation, the transcription factor STAT3, STAT1 and STAT5 [7].

IL-10 plays essential roles as a regulatory molecule in both innate and adaptive immune responses, which often leads to the development of immune tolerance or dampening of tissue inflammation in humans [9]. Immune tolerance is generally established against any immune-activating molecules and several immune-mechanisms mediators [10]. Once the immune tolerance fails, overwhelming immune effector and inflammatory functions often lead to allergies, asthma, tumors, chronic infections, rejection of transplanted organs, graft-versus-host disease, and many autoimmune diseases [11,12]. The low number of natural Treg cells (nTregs) at birth associated with subsequently food allergy [13]. The induction of type 2 immune response, that consists of T helper 2 cells (Th2) and type 2 innate lymphoid cells (ILC2) together with the production of allergen-specific immunoglobulin (Ig) E antibodies and increased eosinophil numbers in the affected tissues and peripheral blood, are a result of allergic diseases [14,15].

Allergen-specific immunotherapy (AIT) is a successful immune tolerance-inducing treatment that reduces symptoms of allergic rhinitis and asthma as well as venom allergy and food allergy [16]. It involves the administration of increasing doses of the causative allergen and induces the establishment of long-term clinical tolerance against allergens [17]. For several decades, the underlying mechanism of AIT has been intensively studied to understand the complexity of allergen-

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Table 1
IL-10-secreting cells and tolerogenic functions.

IL-10 secreting cells	Tolerogenic function
T cells (Treg)	Inhibits eosinophils and basophils cytokine production
B cells (Breg)	Inhibits mast cell activation and cytokine production
dendritic cells (DCreg)	Inhibits dendritic cells maturation and pro-inflammatory cytokine secretion
innate lymphoid cells (ILCreg)	Inhibits antigen presentation by monocyte and macrophages and cytokine production
natural killer cells (NKreg)	Suppresses allergen-specific Th2, Th17 cells
M2-like macrophages	Promotes the generation of Tr1 and Br1 cells
monocyte	Promotes allergen-specific IgG4 and suppresses allergen specific IgE
	Suppresses ILC2 activation and cytokine production

Table 2
Marker of Treg cells function and dysfunction.

Activated suppressive function	Suppressive dysfunction
CCR7	ILT3
CD27	CRTH2
T cells Ig and ITIM domain (TIGIT)	
CTLA-4	
PD-1 (Programmed cell death-1)	
GARP (Glycoprotein A repetitions predominant)	
LAG-3 (CD223)	
CD39, CD73	
Neuropilin (Nrp-1)	
LAP (Latency associated peptide)	
Helios with FOXP3	
CD137 ⁺ CD154 ⁺	
CD69	
ICOS (Inducible costimulatory)	

specific immune responses in both molecular and cellular levels [18,19]. Molecular and cellular mechanisms of actions include the induction of early desensitization of mast cells and basophils, generation of allergen-specific Treg and Breg cells and suppression of allergen-specific type 2 immune cells [10,20], and the decrease in tissue mast cells, eosinophils, and release of their mediators after several months after AIT [21]. Interestingly, allergen-specific Treg and Breg cells and their micro-environmental cytokines are important for determining success in immunotherapy AIT [22,23]. Moreover, IL-10 mRNA levels in whole blood cells revealed the efficacy of AIT in house dust mite allergic patients [24]. Therefore, this review is focused on the role of micro-environment cytokine IL-10 secreting by regulatory cells and other immune regulatory cells in allergy (Table 1).

2. IL-10-secreting Treg cells

Treg cells are represented by the naturally occurring thymus-derived CD4⁺CD25⁺FOXP3⁺ Tregs, also called nTregs, and the inducible Treg cells (iTregs). Three main subsets of iTregs have been characterized; FOXP3-expressing iTregs, CD4⁺FOXP3⁺ IL-10-secreting Tr1 cells, and TGF- β -expressing Th3 cells [1]. Human Tr1 cells suppress effector T cell responses by multiple mechanisms. These mechanisms consist of suppressive cytokines (e.g. IL-10, TGF- β and IL-35) [25], targeted-DCs surface molecules (e.g. cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-L1)) [26], and cytotoxicity (granzymes A, B and K) [27–29]. Furthermore, there are metabolic disruption mechanisms including CD25, cAMP, adenosine receptor 2, histamine receptor 2 (HR2), lymphocyte activation gene 3 (LAG3), CD39 and CD73 [30,31].

Human IL-10-secreting Treg cells and their allergen-specific suppressive function have been first suggested in 1998 [32]. During AIT and natural allergen exposure, IL-10 was primarily produced by allergen-specific Treg cells, subsequently by allergen-specific Breg cells (Br1 cells), and monocytes. The immunosuppressive properties of Treg cells are also regulated by IL-10-secreting Tr1 cells and CD4⁺CD25⁺Treg cells [33]. IL-10, together with TGF- β revealed the inhibitory functions through inducible T cell costimulator (ICOS) [34].

IL-10 suppresses T cells via CD28- and ICOS-dependent T cell co-stimulation by precisely blocking proliferation and cytokines production [35]. In mice model, the transfer of ovalbumin peptide-specific CD4⁺CD25⁺T cells to OVA-sensitized mice was determined to be IL-10 dependent. They demonstrated a decrease in airway hyperreactivity and the recruitment of eosinophils and Th2 cytokines to airways after an allergen challenge. As a result, IL-10 expression was increased in the lung after the transfer of CD4⁺CD25⁺T cells and anti-IL-10R antibody confirmed the reverse expression [36].

Tr1 cells are also generated in response to other immunotherapies such as sublingual immunotherapy, other allergens such as grass pollen and house dust mites, and peptide immunotherapies in allergy and autoimmune diseases [37–39]. IL-10-secreting Treg cells suppress Th2-type immune response (IL-4, IL-5, and IL-13) and IL-17-secreting Th cells [40–42]. Meanwhile, AIT also promotes the generation of IL-22 and interferon (IFN)-gamma-secreting Th cells [17,43,44]. Moreover, Treg cells regulate the tissue repairing process by secreting amphiregulin and IL-22. The amphiregulin is an epidermal growth factor family member and IL-22 is a cytokine that promotes tissue healing [45–47]. In addition, allergen-specific Tr1 cells and IL-10⁺IL-22⁺T cells increase during AIT and correlate with the improvement of allergic symptoms in patients [43]. A sustained Treg response after AIT associated with the clinical response, maintenance of lower eosinophil counts and serum specific IgE levels [48].

The marker of Treg cells activation and dysfunction is shown in Table 2. In vivo, CD27 and CCR7 are required for Treg cells immunosuppressive function [49,50]. CCR7 can be used to define 2 distinct subsets; CCR7(+) central memory and CCR7(-) effector memory T cells [51]. T cells expressing the coinhibitory molecule (TIGIT), control Treg cell subsets to selectively suppress Th1 and Th17 cell but not Th2 cell responses [52]. Indeed, programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) expression on Treg cells are known to be involved in allergen tolerance [53]. Helios is a transcription factor that expresses in Treg cells. It activates Treg cells via STAT5 which promotes the expression of FOXP3 [54]. Other Treg cells activation marker is glycoprotein A repetitions predominant (GARP), LAG-3 (CD223), CD39, CD73, neuropilin (Nrp-1), latency associated peptide (LAP), CD137⁺CD154⁺, CD69 and inducible costimulatory (ICOS) are involved in Treg cell suppressive function [55–57]. In addition, CRTH2 and ILT3 expression on Treg cells are dysfunction and related to allergic symptoms [43,58].

3. IL-10-secreting Breg cells

Breg cells (Br1 Cells) represent an immunosuppressive B cell subset that regulates excessive inflammation via the release of IL-10, which induces the differentiation of regulatory T cells, inhibits pro-inflammatory responses and augments IgG4 production [59–63]. IL-10 alone was sufficient in the induction of IgG4 and suppress of IgE [61]. Allergen is captured by IgE which mediated an allergic reaction through cross-linking of IgE bound to Fc ϵ R1 on mast cells or basophils. IgG4 is the least abundant subclass of IgG in serum, accounting for approximately 4% of total IgG, whereas its levels can reach up to 75% of total

IgG after AIT [61]. Allergen-specific IgG4 acts as a blocking antibody and antagonizes the mast cell and basophil degranulation-related effector functions by blocking of IgE binding to allergens and avoiding its cross-linking [61]. Moreover, cross-linking of Fc γ RIIb by the IgG4 subclass can downregulate M2 macrophage and increase IL-10, IL-6, TNF- α and CCL1 production [64].

Br1 cells are characterized by high expression of CD25 and CD71 and low expression of CD73 on the cell surface [65]. The prominent immunoregulatory profile of IL-10- and IL-1RA-secreting Bregs characterized by up-regulation of CD25 (IL-2 receptor α chain), programmed death-ligand 1 (PD-L1), suppressor of cytokine signaling 3, and glycoprotein A repetitions [66]. The other B cell subsets secreting IL-10 include CD24^{hi}CD38^{hi} B cells, CD24^{hi}CD27⁺ B cells (B10), CD38⁺CD1d⁺IgM⁺CD147⁺GrB⁺ B cells, CD27^{int}CD38^{hi} plasmablasts, and CD19⁺TIM1⁺ B cells which have all been shown to suppress proinflammatory responses [67]. Without stimulation, it is hard to detect IL-10-secreting B cells. CpG oligonucleotide and recombinant CD40L are usually used to enhance IL-10-secreting B cells. We demonstrated recently that activated, CD40L-expressing ILC3s reside on the border of the T cell-B cell areas in tonsils and are in close contact with B cells *in vivo*. Furthermore, we showed that CD40L⁺ ILC3s and B cells are in a mutually beneficial relationship with each other: ILC3s induce IL-15 production in B cells via BAFF-receptor, while IL-15, a potent growth factor for ILC3s, upregulate CD40L expression on ILC3s. IL-15-activated CD40L⁺ ILC3s help B cell survival, proliferation, and differentiation of IL-10 secreting and PD-L1-expressing, functional Breg cells [68].

In patients with allergic asthma and rhinitis, reduced expansion of IL-10-secreting CD24^{hi}CD27⁺ Bregs was reported in response to LPS stimulation [69–71]. The patients with cow's milk allergy also demonstrated a decrease in IL-10-producing CD5⁺ B cells upon *in vitro* restimulation with casein [72]. In asthmatic mice, the adoptive transfer of CD9⁺ B cells normalized airway inflammation and lung function by inhibiting Th2- and Th17-driven inflammation in an IL-10-dependent manner, restoring a favorable immunological balance in lung tissues. They further showed that injection of CD9⁺ Bregs controls the expansion of lung effector T cells allowing the establishment of a favorable regulatory T cells/effector T cells ratio in the lungs [73]. Activation of PAR2 inhibits the expression of IL-10 in B cells, which can be reversed by treating B cells with Bcl2L12 shRNA-carrying liposomes. The regulation of Bcl2L12 may be a novel approach in the treatment of allergic rhinitis [74].

In patients response to AIT is characterized by increased the frequencies of IgA- and IgG4-expressing Der p 1-specific B cells, plasmablasts, and IL-10⁺ and/or IL-1RA⁺ Breg cells [75]. The same study also found the increased frequency of Der p 1-specific IgG4 related to the frequency of IL-10-secreting Br1 cells. Moreover, IL-10-secreting and dual IL-10- and IL-1RA-secreting Br1 cells significantly correlated with improved clinical symptoms over the course of AIT [75]. Allergen-specific Breg cells have maintained allergen tolerance together with allergen-specific Treg cell-induced by AIT.

4. IL-10 secretion by dendritic cells, macrophages, monocyte, and natural killer cells

DCs function depends on the balance between immune effector and immune regulatory cytokine pattern and expression of suppression- and stimulation-relevant co-stimulatory molecules [76]. Treg cells strongly interact with DC and support their tolerance inducing capacity. Allergen-specific CD4⁺CD25⁺Foxp3⁺ Treg cells can enhance IL-10-secreting DCs to suppress allergic Th2-responses [77]. DCs that are differentiated in the presence of IL-10 and allergen-enhanced tolerogenic DCs have the capacity to stimulate allergen-specific Tr1 cells [78]. The induction IL-10 and TGF- β -secreting Treg cells by IL-10-secreting DCs can also prevent excessive immune response and reduce type 2 airway inflammation [36,79].

Allergic patients show a tendency to produce less tolerogenic DCs. IL-10-secreting DCs have been shown to diminish in allergic rhinitis and asthmatic children compared to healthy [80]. Also, IL-10 levels in the supernatants of DCs in the presence of activated aryl hydrocarbon receptor (AhR) from allergic patients were significantly lower than healthy controls [81]. In allergic rhinitis patients, myeloid DCs and plasmacytoid DCs were increased in the allergen-exposed airway and skin tissues but decreased in the IL-10 production both locally and in blood [82]. Their functional studies indicated that myeloid DCs support Th2/Th17-cell polarization and biased T-cell responses. Induction of immune tolerance during AIT has also increased tolerogenic DCs [83]. AIT enhanced regulatory dendritic cells (DCreg) and type 1 DC (DC1) meanwhile decreasing DC2 and DC17 in responder AIT patients [83].

Macrophages are important in maintaining lung homeostasis and protecting against lung inflammation. The inhibition of M2-like macrophage polarisation interferes with the remodeling and development of eosinophilic or neutrophilic lung inflammation in asthma [84]. In addition, the M2-like macrophage is an anti-inflammatory state with the expression of IL-10. Both human and mice asthma showed low number of IL-10⁺ M2-like macrophages compared to control and correlated with lung function [85].

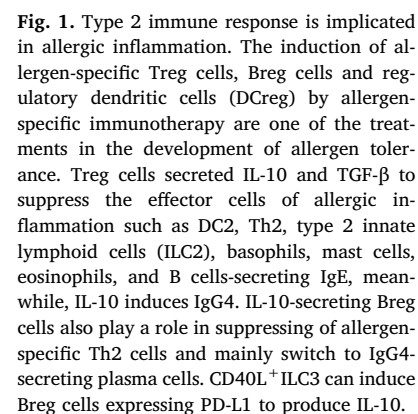
The evidence of monocyte produces IL-10 in allergic immune tolerance is limited. PD-L1 can trigger monocyte to produce IL-10 [86]. Moreover, mesenchymal stem cells administration in mouse model recruited IL-10⁺ and CCR2⁺ monocyte to suppress allergic airway inflammation [87]. IL-10 secreting monocyte induced by LPS stimulation increased in atopic patients than healthy [88].

NK cells are an effective producer of IFN- γ . NK cells are able to polarize into 2 functional distinct subsets, NK1 or NK2 cells *in vitro*. These NK1 or NK2 cell subsets are analogous to the T-cell subsets Th1 or Th2 [89]. Moreover, TGF- β and IL-10-secreting NKreg cells might have a role in immune regulation of allergic inflammation. IL-10-secreting NKreg cells reveal significantly suppressed both allergen/Ag-induced T cell proliferation, IL-13 and IFN- γ -secreting T cells and reduced IgE production [89,90]. However, its role in immune tolerance in allergic patients remains to be investigated.

5. A recently discovered IL-10 secreting innate lymphoid cell subset

Regulatory innate lymphoid cells (ILCreg) are a new group of cells within regulatory cells, which might have an important role in the balance between immune tolerance or allergy development in the same manner as other regulatory cells. In humans, IL-10⁺ ILCreg were induced from ILC2s by using retinoic acid which expressed CTLA-4, CD25, and downregulated effector type 2-related markers, including CRTH2 and ST2 [91]. IL-10-secreting ILC can suppress the activation of CD4⁺ T cells and ILC2 [91]. An increase in ILCregs was detected in nasal tissue from patients with chronic rhinosinusitis with nasal polyps and in lung tissue from house dust mite-treated mice [91]. iTreg can suppress ILC2 via inducible T-cell costimulator (ICOS)-ICOS ligand cell contact for Treg cell-mediated ILC2 suppression alongside the suppressive cytokines TGF- β and IL-10 [92]. Function and regulation of ILCregs in allergy and AIT warrants future investigation.

IL-10-producing ILCs in mice are mostly present in the gut tissue. The differentiation of mature IL-10-producing ILCs can be induced by pathogen stimulation [93]. ILCreg expressed various phenotypic ILC markers, including CD25 (IL-2R α), Sca-1, and CD90 (Thy1), but not ILC1 (NK1.1 and Nkp46), ILC2 (ST2 and KLRG1), or ILC3 markers (Nkp46, and ROR γ t) [93]. The ILCreg inhibited the activation of ILC1 and ILC3 by secretion of IL-10 but did not affect ILC2 with undetectable Il10rb expression [93]. IL-10-secreting lung ILC2 cells (ILC2₁₀) are Thy1.1-positive which produce IL-10 to exert modulating roles upon the stimulation of IL-33 [94]. IL-2 enhances ILC2₁₀ generation and associated with a decreased in eosinophil recruitment to the lung [94].



Allergic disease is caused by an imbalance between type 2 immune response to harmless allergens and regulatory cells. The induction of allergen tolerance by AIT induces allergen-specific Treg cells, Breg cells, and other regulatory cells. IL-10-secreting cells in the innate (DCreg, ILcReg) and adaptive (Treg and Breg) immune system can suppress the activation of type 2 immune response including IgE production and instead increase allergen-specific IgG4 isotype antibody response (Fig. 1). Future directions in scientific research should focus on the role of IL-10, particularly in the innate immune systems such as DCs, ILcs, and monocyte. A better understanding of the development of effector (allergenic) and tolerogenic immune response in allergic diseases will significantly help the development of precise prevention strategies and effective therapeutic options.

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References

- [1] C.A. Akdis, M. Akdis, Mechanisms of immune tolerance to allergens: role of IL-10 and Tregs, *J. Clin. Invest.* 124 (11) (2014) 4678–4680.
- [2] M. Akdis, A. Aab, C. Altunbulakli, K. Azkur, R.A. Costa, R. Cramer, S. Duan, T. Eiwegger, A. Eljaszewicz, R. Ferstl, R. Frei, M. Garbani, A. Globinska, L. Hess, C. Huitema, T. Kubo, Z. Komlosi, P. Konieczna, N. Kovacs, U.C. Kucuksez, N. Meyer, H. Morita, J. Olzhansen, L. O'Mahony, M. Pezer, M. Prati, A. Rebane, C. Rhyner, A. Rinaldi, M. Sokolowska, B. Stanic, K. Sugita, A. Treis, W. van de Veen, K. Wanke, M. Wawrzyniak, P. Wawrzyniak, O.F. Wirz, J.S. Zakzuk, C.A. Akdis, Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: receptors, functions, and roles in diseases, *J. Allergy Clin. Immunol.* 138 (4) (2016) 984–1010.
- [3] M. Jutel, M. Akdis, K. Blaser, C.A. Akdis, Mechanisms of allergen specific immunotherapy—T-cell tolerance and more, *Allergy* 61 (7) (2006) 796–807.
- [4] W. Ouyang, S. Rutz, N.K. Crellin, P.A. Valdez, S.G. Hymowitz, Regulation and functions of the IL-10 family of cytokines in inflammation and disease, *Annu. Rev. Immunol.* 29 (2011) 71–109.
- [5] S.V. Kotenko, C.D. Krause, L.S. Izotova, B.P. Pollack, W. Wu, S. Pestka, Identification and functional characterization of a second chain of the interleukin-10 receptor complex, *EMBO J.* 16 (19) (1997) 5894–5903.
- [6] A. Taylor, M. Akdis, A. Joss, T. Akkoc, R. Wenig, M. Colonna, I. Daigle, E. Flory, K. Blaser, C.A. Akdis, IL-10 inhibits CD28 and ICOS costimulations of T cells via src homology 2 domain-containing protein tyrosine phosphatase 1, *J. Allergy Clin. Immunol.* 120 (1) (2007) 76–83.
- [7] M.R. Walter, The molecular basis of IL-10 function: from receptor structure to the onset of signaling, *Curr. Top. Microbiol. Immunol.* 380 (2014) 191–212.
- [8] O. Palomares, M. Martin-Fontecha, R. Lauener, C. Traidl-Hoffmann, O. Cavkaytar, M. Akdis, C.A. Akdis, Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF-beta, *Genes Immun.* 15 (8) (2014) 511–520.
- [9] W. Ouyang, A. O'Garra, IL-10 family cytokines IL-10 and IL-22: from basic science to clinical translation, *Immunology* 50 (4) (2019) 871–891.
- [10] C.A. Akdis, M. Akdis, Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens, *World Allergy Organ. J.* 8 (1) (2015) 17.
- [11] H. Breiteneder, Z. Diamant, T. Eiwegger, W.J. Fokkens, C. Traidl-Hoffmann, K. Nadeau, R.E. O'Hehir, L. O'Mahony, O. Pfaar, M.J. Torres, Y. Wang, L. Zhang, C.A. Akdis, Future research trends in understanding the mechanisms underlying allergic diseases for improved patient care, *Allergy* (2019).
- [12] I. Agache, C.A. Akdis, Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases, *J. Clin. Invest.* 130 (2019) 1493–1503.
- [13] F. Collier, A.L. Ponsonby, M. O'Hely, M.L.K. Tang, R. Saffery, J. Molloy, L.E. Gray, S. Ranganathan, D. Burgner, K.J. Allen, S. Brix, P.J. Vuillermin, B.I.S.I. Group, Naive regulatory T cells in infancy: associations with perinatal factors and

- development of food allergy, *Allergy* (2019).
- [14] C.A. Akdis, Therapies for allergic inflammation: refining strategies to induce tolerance, *Nat. Med.* 18 (5) (2012) 736–749.
 - [15] K. Sugita, C.A. Steer, I. Martinez-Gonzalez, C. Altunbulakli, H. Morita, F. Castro-Giner, T. Kubo, P. Wawrzyniak, B. Ruckert, K. Sudo, S. Nakae, K. Matsumoto, L. O'Mahony, M. Akdis, F. Takei, C.A. Akdis, Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients, *J. Allergy Clin. Immunol.* 141 (1) (2018) 300–310 e11.
 - [16] A. Globinska, T. Boonpiyathad, P. Satitsuksanoa, M. Kleuskens, W. van de Veen, M. Sokolowska, M. Akdis, Mechanisms of allergen-specific immunotherapy: diverse mechanisms of immune tolerance to allergens, *Ann. Allergy Asthma Immunol.* 121 (3) (2018) 306–312.
 - [17] W. van de Veen, O.F. Wirz, A. Globinska, M. Akdis, Novel mechanisms in immune tolerance to allergens during natural allergen exposure and allergen-specific immunotherapy, *Curr. Opin. Immunol.* 48 (2017) 74–81.
 - [18] H. Fujita, M.B. Soyka, M. Akdis, C.A. Akdis, Mechanisms of allergen-specific immunotherapy, *Clin. Transl. Allergy* 2 (1) (2012) 2.
 - [19] M. Jutel, C.A. Akdis, Immunological mechanisms of allergen-specific immunotherapy, *Allergy* 66 (6) (2011) 725–732.
 - [20] W. Mitthamsiri, P. Pradubpong, A. Sangasapaviliya, T. Boonpiyathad, Decreased CRTH2 expression and response to allergen Re-stimulation on innate lymphoid cells in patients with allergen-specific immunotherapy, *Allergy Asthma Immunol. Res.* 10 (6) (2018) 662–674.
 - [21] M. Akdis, C.A. Akdis, Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens, *J. Allergy Clin. Immunol.* 133 (3) (2014) 621–631.
 - [22] O. Palomares, M. Akdis, M. Martin-Fontecha, C.A. Akdis, Mechanisms of immune regulation in allergic diseases: the role of regulatory T and B cells, *Immunol. Rev.* 278 (1) (2017) 219–236.
 - [23] M.B. Soyka, D. Holzmann, C.A. Akdis, Regulatory cells in allergen-specific immunotherapy, *Immunotherapy* 4 (4) (2012) 389–396.
 - [24] C. Gueguen, S. Luce, V. Lombardi, V. Baron-Bodo, P. Moingeon, L. Mascarell, IL-10 mRNA levels in whole blood cells correlate with house dust mite allergen immunotherapy efficacy, *Allergy* (2019).
 - [25] M. Jutel, M. Akdis, F. Budak, C. Aebischer-Casaulta, M. Wrzyszc, K. Blaser, C.A. Akdis, IL-10 and TGF- β cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy, *Eur. J. Immunol.* 33 (5) (2003) 1205–1214.
 - [26] M. Akdis, J. Verhagen, A. Taylor, F. Karamloo, C. Karagiannidis, R. Cramer, S. Thunberg, G. Deniz, R. Valenta, H. Fiebig, K. Kegel, R. Disch, C.B. Schmidt-Weber, K. Blaser, C.A. Akdis, Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells, *J. Exp. Med.* 199 (11) (2004) 1567–1575.
 - [27] J. Loebbermann, H. Thornton, L. Durant, T. Sparwasser, K.E. Webster, J. Sprent, F.J. Culley, C. Johansson, P.J. Openshaw, Regulatory T cells expressing granzyme B play a critical role in controlling lung inflammation during acute viral infection, *Mucosal Immunol.* 5 (2) (2012) 161–172.
 - [28] S. Velaga, S.N. Ukena, U. Dringenberg, C. Alter, J. Pardo, O. Kershaw, A. Franzke, Granzyme a is required for regulatory T-Cell mediated prevention of gastrointestinal graft-versus-Host disease, *PLoS One* 10 (4) (2015) e0124927.
 - [29] P. Gruarin, S. Maglie, M. De Simone, B. Haringer, C. Vasco, V. Ranzani, R. Bosotti, J.S. Noddings, P. Larghi, F. Facciotti, M.L. Sarnicola, M. Martinovic, M. Crosti, M. Moro, R.L. Rossi, M.E. Bernardo, F. Caprioli, F. Locatelli, G. Rossetti, S. Abbrignani, M. Pagani, J. Geginat, Eomesodermin controls a unique differentiation program in human IL-10 and IFN- γ coproducing regulatory T cells, *Eur. J. Immunol.* 49 (1) (2019) 96–111.
 - [30] F. Meiler, J. Zunker, S. Klunker, B. Ruckert, C.A. Akdis, M. Akdis, In vivo switch to IL-10-secreting T regulatory cells in high dose allergen exposure, *J. Exp. Med.* 205 (12) (2008) 2887–2898.
 - [31] R. Ferstl, R. Frei, W. Barcik, E. Schiavi, K. Wanke, M. Ziegler, N. Rodriguez-Perez, D. Groeger, P. Konieczna, S. Zeiter, D. Nehrass, R. Lauener, C.A. Akdis, L. O'Mahony, Histamine receptor 2 modifies iNKT cell activity within the inflamed lung, *Allergy* 72 (12) (2017) 1925–1935.
 - [32] C.A. Akdis, T. Blesken, M. Akdis, B. Wuthrich, K. Blaser, Role of interleukin 10 in specific immunotherapy, *J. Clin. Invest.* 102 (1) (1998) 98–106.
 - [33] C. Baecher-Allan, V. Viglietta, D.A. Hafler, Human CD4+CD25+ regulatory T cells, *Semin. Immunol.* 16 (2) (2004) 89–98.
 - [34] T. Ito, S. Hanabuchi, Y.H. Wang, W.R. Park, K. Arima, L. Bover, F.X. Qin, M. Gilliet, Y.J. Liu, Two functional subsets of FOXP3+ regulatory T cells in human thymus and periphery, *Immunity* 28 (6) (2008) 870–880.
 - [35] A. Joss, M. Akdis, A. Faith, K. Blaser, C.A. Akdis, IL-10 directly acts on T cells by specifically altering the CD28 co-stimulation pathway, *Eur. J. Immunol.* 30 (6) (2000) 1683–1690.
 - [36] J. Kearley, J.E. Barker, D.S. Robinson, C.M. Lloyd, Resolution of airway inflammation and hyperreactivity after in vivo transfer of CD4+CD25+ regulatory T cells is interleukin 10 dependent, *J. Exp. Med.* 202 (11) (2005) 1539–1547.
 - [37] C.A. Akdis, I.B. Barlan, N. Bahceci, M. Akdis, Immunological mechanisms of sublingual immunotherapy, *Allergy* 61 (Suppl. 81) (2006) 11–14.
 - [38] G. Ciprandi, D. Fenoglio, I. Cirillo, M. Milanese, P. Minuti, Sublingual immunotherapy and regulatory T cells, *Allergy* 61 (4) (2006) 511–513.
 - [39] J.U. Shin, S.H. Kim, J.Y. Noh, J.H. Kim, K.H. Kim, K.Y. Jeong, K.H. Park, J. Lee, H. Chu, J.H. Lee, T.S. Yong, J.W. Park, K.H. Lee, Allergen-specific immunotherapy induces regulatory T cells in an atopic dermatitis mouse model, *Allergy* 73 (9) (2018) 1801–1811.
 - [40] M. Berings, C. Karaaslan, C. Altunbulakli, P. Gevaert, M. Akdis, C. Bachert, C.A. Akdis, Advances and highlights in allergen immunotherapy: on the way to sustained clinical and immunologic tolerance, *J. Allergy Clin. Immunol.* 140 (5) (2017) 1250–1267.
 - [41] G.W. Scadding, M.A. Calderon, M.H. Shamji, A.O. Eifan, M. Penagos, F. Dumitru, M.L. Sever, H.T. Bahnson, K. Lawson, K.M. Harris, A.G. Plough, J.L. Panza, T. Qin, N. Lim, N.K. Tchao, A. Togias, S.R. Durham, G.S.T. Immune tolerance network, effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: the GRASS randomized clinical trial, *JAMA* 317 (6) (2017) 615–625.
 - [42] D. Russkamp, A. Aguilar-Pimentel, F. Alessandrini, V. Gailus-Durner, H. Fuchs, C. Ohnmacht, A. Chaker, M.H. de Angelis, M. Ollert, C.B. Schmidt-Weber, S. Blank, IL-4 receptor alpha blockade prevents sensitization and alters acute and long-lasting effects of allergen-specific immunotherapy of murine allergic asthma, *Allergy* (2019).
 - [43] T. Boonpiyathad, M. Sokolowska, H. Morita, B. Ruckert, J.L. Kast, M. Wawrzyniak, A. Sangasapaviliya, P. Pradubpong, R. Fuengthong, P. Thantiworasit, S. Sirivichayakul, W.W. Kwok, K. Ruxrungtham, M. Akdis, C.A. Akdis, Der p 1-specific regulatory T-cell response during house dust mite allergen immunotherapy, *Allergy* 74 (5) (2019) 976–985.
 - [44] I. Soria, J. Lopez-Relano, M. Vinuela, J.I. Tudela, A. Angelina, C. Benito-Villalvilla, C.M. Diez-Rivero, B. Cases, A.I. Manzano, E. Fernandez-Caldas, M. Casanovas, O. Palomares, J.L. Subiza, Oral myeloid cells uptake allergoids coupled to mannan driving Th1/Treg responses upon sublingual delivery in mice, *Allergy* 73 (4) (2018) 875–884.
 - [45] M. Noval Rivas, T.A. Chatila, Regulatory T cells in allergic diseases, *J. Allergy Clin. Immunol.* 138 (3) (2016) 639–652.
 - [46] D. Burzyn, W. Kuswanto, D. Kolodin, J.L. Shadrach, M. Cerletti, Y. Jang, E. Sefik, T.G. Tan, A.J. Wagers, C. Benoist, D. Mathis, A special population of regulatory T cells potentiates muscle repair, *Cell* 155 (6) (2013) 1282–1295.
 - [47] J.Y. Hong, M. Kim, I.S. Sol, K.W. Kim, C.M. Lee, J.A. Elias, M.H. Sohn, C.G. Lee, Chitotriosidase inhibits allergic asthmatic airways via regulation of TGF- β expression and Foxp3(+) Treg cells, *Allergy* 73 (8) (2018) 1686–1699.
 - [48] R. Varona, T. Ramos, M.M. Escribese, L. Jimeno, A. Galan, P.A. Wurtzen, F. Vega, A. Marin, S. Martin, A.C. Carrera, C. Blanco, D. Barber, Persistent regulatory T-cell response 2 years after 3 years of grass tablet SLIT: links to reduced eosinophil counts, sIgE levels, and clinical benefit, *Allergy* 74 (2) (2019) 349–360.
 - [49] M.A. Schneider, J.G. Meingassner, M. Lipp, H.D. Moore, A. Rot, CCR7 is required for the in vivo function of CD4+CD25+ regulatory T cells, *J. Exp. Med.* 204 (4) (2007) 735–745.
 - [50] R.C. Duggleby, T.N. Shaw, L.B. Jarvis, G. Kaur, J.S. Gaston, CD27 expression discriminates between regulatory and non-regulatory cells after expansion of human peripheral blood CD4+CD25+ cells, *Immunology* 121 (1) (2007) 129–139.
 - [51] V. Tosello, K. Odunsi, N.E. Souleimanian, S. Lele, P. Shrikant, L.J. Old, D. Valmori, M. Ayyoub, Differential expression of CCR7 defines two distinct subsets of human memory CD4+CD25+ Tregs, *Clin. Immunol.* 126 (3) (2008) 291–302.
 - [52] N. Joller, E. Lozano, P.R. Burkett, B. Patel, S. Xiao, C. Zhu, J. Xia, T.G. Tan, E. Sefik, V. Yajnik, A.H. Sharpe, F.J. Quintana, D. Mathis, C. Benoist, D.A. Hafler, V.K. Kuchroo, Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses, *Immunity* 40 (4) (2014) 569–581.
 - [53] E. Giancchetti, A. Fierabracci, Inhibitory receptors and pathways of lymphocytes: the role of PD-1 in Treg development and their involvement in autoimmunity onset and Cancer progression, *Front. Immunol.* 9 (2018) 2374.
 - [54] C. Chougnet, D. Hildeman, Helios-controller of Treg stability and function, *Transl. Cancer Res.* 5 (Suppl. 2) (2016) S338–S341.
 - [55] L. Sun, H. Jin, H. Li, GARP: a surface molecule of regulatory T cells that is involved in the regulatory function and TGF- β releasing, *Oncotarget* 7 (27) (2016) 42826–42836.
 - [56] A. Nowak, D. Lock, P. Bacher, T. Hohnstein, K. Vogt, J. Gottfreund, P. Giehr, J.K. Polansky, B. Sawitzki, A. Kaiser, J. Walter, A. Scheffold, CD137+CD154-expression As a regulatory T cell (Treg)-Specific activation signature for identification and sorting of stable human tregs from in vitro expansion cultures, *Front. Immunol.* 9 (2018) 199.
 - [57] M. Yadav, C. Louvet, D. Davini, J.M. Gardner, M. Martinez-Llordella, S. Bailey-Bucktrout, B.A. Anthony, F.M. Sverdrup, R. Head, D.J. Kuster, P. Ruminski, D. Weiss, D. Von Schack, J.A. Bluestone, Neuropilin-1 distinguishes natural and inducible regulatory T cells among regulatory T cell subsets in vivo, *J. Exp. Med.* 209 (10) (2012) 1713–1722 S1–S19.
 - [58] T. Boonpiyathad, G. Capova, H.W. Duchna, A.L. Croxford, H. Farine, A. Dreher, M. Clozel, J. Schreiber, P. Kubena, N. Lunjani, D. Mirer, B. Ruckert, P. Satitsuksanoa, G. Tan, P.M.A. Groenen, M. Akdis, D.S. Strasser, E.D. Renner, C.A. Akdis, Impact of high altitude therapy on Type-2 immune responses in asthma patients, *Allergy* (2019).
 - [59] W. van de Veen, The role of regulatory B cells in allergen immunotherapy, *Curr. Opin. Allergy Clin. Immunol.* 17 (6) (2017) 447–452.
 - [60] W. van de Veen, B. Stanic, O.F. Wirz, K. Jansen, A. Globinska, M. Akdis, Role of regulatory B cells in immune tolerance to allergens and beyond, *J. Allergy Clin. Immunol.* 138 (3) (2016) 654–665.
 - [61] W. van de Veen, M. Akdis, Role of IgG4 in IgE-mediated allergic responses, *J. Allergy Clin. Immunol.* 138 (5) (2016) 1434–1435.
 - [62] P. Satitsuksanoa, K. Jansen, A. Globinska, W. van de Veen, M. Akdis, Regulatory immune mechanisms in tolerance to food allergy, *Front. Immunol.* 9 (2018) 2939.
 - [63] F. Braza, J. Chesne, S. Castagnet, A. Magnan, S. Brouard, Regulatory functions of B cells in allergic diseases, *Allergy* 69 (11) (2014) 1454–1463.
 - [64] R. Bianchini, F. Roth-Walter, A. Ohradnova-Repic, S. Flicker, K. Hufnagl,

- M.B. Fischer, H. Stockinger, E. Jensen-Jarolim, IgG4 drives M2a macrophages to a regulatory M2b-like phenotype: potential implication in immune tolerance, *Allergy* 74 (3) (2019) 483–494.
- [65] W. van de Veen, B. Stanic, G. Yaman, M. Wawrzyniak, S. Sollner, D.G. Akdis, B. Ruckert, C.A. Akdis, M. Akdis, IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses, *J. Allergy Clin. Immunol.* 131 (4) (2013) 1204–1212.
- [66] B. Stanic, W. van de Veen, O.F. Wirz, B. Ruckert, H. Morita, S. Sollner, C.A. Akdis, M. Akdis, IL-10-overexpressing B cells regulate innate and adaptive immune responses, *J. Allergy Clin. Immunol.* 135 (3) (2015) 771–780 e8.
- [67] C. Mauri, M. Menon, Human regulatory B cells in health and disease: therapeutic potential, *J. Clin. Invest.* 127 (3) (2017) 772–779.
- [68] Z.I. Komlosi, N. Kovacs, W. van de Veen, A.I. Kirsch, H.B. Fahrner, M. Wawrzyniak, A. Rebane, B. Stanic, O. Palomares, B. Ruckert, G. Menz, M. Akdis, G. Losonczi, C.A. Akdis, Human CD40 ligand-expressing type 3 innate lymphoid cells induce IL-10-producing immature transitional regulatory B cells, *J. Allergy Clin. Immunol.* 142 (1) (2018) 178–194 e11.
- [69] R. Kamekura, K. Shigehara, S. Miyajima, S. Jitsukawa, K. Kawata, K. Yamashita, T. Nagaya, A. Kumagai, A. Sato, H. Matsumiya, N. Ogasawara, N. Seki, K. Takano, Y. Kalkai, H. Takahashi, T. Himi, S. Ichimiya, Alteration of circulating type 2 follicular helper T cells and regulatory B cells underlies the comorbid association of allergic rhinitis with bronchial asthma, *Clin. Immunol.* 158 (2) (2015) 204–211.
- [70] L.E. van der Vlugt, E. Mlejnek, A. Ozir-Fazlalikh, M. Janssen Bonas, T.R. Dijkman, L.A. Labuda, R. Schot, B. Guigas, G.M. Moller, P.S. Hiemstra, M. Yazdanbakhsh, H.H. Smits, CD24(hi)CD27(+) B cells from patients with allergic asthma have impaired regulatory activity in response to lipopolysaccharide, *Clin. Exp. Allergy* 44 (4) (2014) 517–528.
- [71] O.F. Wirz, A. Globinska, U. Ochsen, W. van de Veen, E. Eller, E.S. Christiansen, S. Halken, C. Nielsen, C. Bindselev-Jensen, J.M. Anto, J. Bousquet, C.A. Akdis, M. Akdis, Comparison of regulatory B cells in asthma and allergic rhinitis, *Allergy* 74 (4) (2019) 815–818.
- [72] J.H. Lee, J. Noh, G. Noh, H.S. Kim, S.H. Mun, W.S. Choi, S. Cho, S. Lee, Allergen-specific B cell subset responses in cow's milk allergy of late eczematous reactions in atopic dermatitis, *Cell. Immunol.* 262 (1) (2010) 44–51.
- [73] F. Braza, J. Chesne, M. Durand, S. Dirou, C. Brosseau, G. Mahay, M.A. Cheminant, A. Magnan, S. Brouard, A regulatory CD9(+) B-cell subset inhibits HDM-induced allergic airway inflammation, *Allergy* 70 (11) (2015) 1421–1431.
- [74] J.M. Xue, L.T. Yang, G. Yang, X.R. Geng, Z.Q. Liu, S. Wang, H.L. Zhao, Z.G. Liu, C.Q. Zhao, P.C. Yang, Protease-activated receptor-2 suppresses interleukin (IL)-10 expression in B cells via upregulating Bel2L12 in patients with allergic rhinitis, *Allergy* 72 (11) (2017) 1704–1712.
- [75] T. Boonpiyathad, W. van de Veen, O. Wirz, M. Sokolowska, B. Ruckert, G. Tan, A. Sangasapaviliya, P. Pradubongsas, R. Fuengthong, P. Thantiworasi, S. Sirivichayakul, K. Ruxrungtham, C.A. Akdis, M. Akdis, Role of Der p 1-specific B cells in immune tolerance during 2 years of house dust mite-specific immunotherapy, *J. Allergy Clin. Immunol.* 143 (3) (2019) 1077–1086 e10.
- [76] S. Schulke, Induction of Interleukin-10 producing dendritic cells As a tool to suppress allergen-specific t helper 2 responses, *Front. Immunol.* 9 (2018) 455.
- [77] X. Han, S. Wang, Y. Fan, J. Yang, L. Jiao, H. Qiu, X. Yang, Chlamydia infection induces ICOS ligand-expressing and IL-10-producing dendritic cells that can inhibit airway inflammation and mucus overproduction elicited by allergen challenge in BALB/c mice, *J. Immunol.* 176 (9) (2006) 5232–5239.
- [78] V. Pacciani, S. Gregori, L. Chini, S. Corrente, M. Chianca, V. Moschese, P. Rossi, M.G. Roncarolo, F. Angelini, Induction of anergic allergen-specific suppressor T cells using tolerogenic dendritic cells derived from children with allergies to house dust mites, *J. Allergy Clin. Immunol.* 125 (3) (2010) 727–736.
- [79] J.W. Oh, C.M. Seroogy, E.H. Meyer, O. Akbari, G. Berry, C.G. Fathman, R.H. Dekruyff, D.T. Umetsu, CD4 T-helper cells engineered to produce IL-10 prevent allergen-induced airway hyperreactivity and inflammation, *J. Allergy Clin. Immunol.* 110 (3) (2002) 460–468.
- [80] D.A. Gentile, R. Schreiber, J. Howe-Adams, J. Trecki, A. Patel, B. Angelini, D.P. Skoner, Diminished dendritic cell interleukin 10 production in atopic children, *Ann. Allergy Asthma Immunol.* 92 (5) (2004) 538–544.
- [81] P. Wei, G.H. Hu, H.Y. Kang, H.B. Yao, W. Kou, H. Liu, C. Zhang, S.L. Hong, An aryl hydrocarbon receptor ligand acts on dendritic cells and T cells to suppress the Th17 response in allergic rhinitis patients, *Lab. Invest.* 94 (5) (2014) 528–535.
- [82] C. Pilette, M.R. Jacobson, C. Ratajczak, B. Detry, G. Banfield, J. VanSnick, S.R. Durham, K.T. Nouri-Aria, Aberrant dendritic cell function conditions Th2-cell polarization in allergic rhinitis, *Allergy* 68 (3) (2013) 312–321.
- [83] C. Gueguen, J. Bouley, H. Moussy, S. Luce, M. Duchateau, J. Chamot-Rooke, M. Pallardy, V. Lombardi, E. Nony, V. Baron-Bodo, L. Mascarelli, P. Moingeon, Changes in markers associated with dendritic cells driving the differentiation of either Th2 cells or regulatory T cells correlate with clinical benefit during allergen immunotherapy, *J. Allergy Clin. Immunol.* 137 (2) (2016) 545–558.
- [84] C. Draijer, P. Robbe, C.E. Boersma, M.N. Hylkema, B.N. Melgert, Dual role of Ym1+ M2 macrophages in allergic lung inflammation, *Sci. Rep.* 8 (1) (2018) 5105.
- [85] C. Draijer, C.E. Boersma, P. Robbe, W. Timens, M.N. Hylkema, N.H. Ten Hacken, M. van den Berge, D.S. Postma, B.N. Melgert, Human asthma is characterized by more IRF5+ M1 and CD206+ M2 macrophages and less IL-10+ M2-like macrophages around airways compared with healthy airways, *J. Allergy Clin. Immunol.* 140 (1) (2017) 280–283 e3.
- [86] E.A. Said, F.P. Dupuy, L. Trautmann, Y. Zhang, Y. Shi, M. El-Far, B.J. Hill, A. Noto, P. Ancuta, Y. Peretz, S.G. Fonseca, J. Van Grevenynghe, M.R. Boulassel, J. Bruneau, N.H. Shoukry, J.P. Routy, D.C. Douek, E.K. Haddad, R.P. Sekaly, Programmed death-1-induced interleukin-10 production by monocytes impairs CD4+ T cell activation during HIV infection, *Nat. Med.* 16 (4) (2010) 452–459.
- [87] K. Takeda, T.L. Webb, F. Ning, Y. Shiraishi, D.P. Regan, L. Chow, M.J. Smith, S. Ashino, A.M. Guth, S. Hopkins, E.W. Gelfand, S. Dow, Mesenchymal stem cells recruit CCR2(+) monocytes to suppress allergic airway inflammation, *J. Immunol.* 200 (4) (2018) 1261–1269.
- [88] A. Prasse, M. Germann, D.V. Pechkovsky, A. Markert, T. Verres, M. Stahl, I. Melchers, W. Luttmann, J. Muller-Quernheim, G. Zissel, IL-10-producing monocytes differentiate to alternatively activated macrophages and are increased in atopic patients, *J. Allergy Clin. Immunol.* 119 (2) (2007) 464–471.
- [89] G. Deniz, W. van de Veen, M. Akdis, Natural killer cells in patients with allergic diseases, *J. Allergy Clin. Immunol.* 132 (3) (2013) 527–535.
- [90] G. Deniz, G. Erten, U.C. Kucuksezer, D. Kocacik, C. Karagiannidis, E. Aktas, C.A. Akdis, M. Akdis, Regulatory NK cells suppress antigen-specific T cell responses, *J. Immunol.* 180 (2) (2008) 850–857.
- [91] H. Morita, T. Kubo, B. Ruckert, A. Ravindran, M.B. Soyka, A.O. Rinaldi, K. Sugita, M. Wawrzyniak, P. Wawrzyniak, K. Motomura, M. Tamari, K. Orimo, N. Okada, K. Arae, K. Saito, C. Altunbulakli, F. Castro-Giner, G. Tan, A. Neumann, K. Sudo, L. O'Mahony, K. Honda, S. Nakae, H. Saito, J. Mjosberg, G. Nilsson, K. Matsumoto, M. Akdis, C.A. Akdis, Induction of human regulatory innate lymphoid cells from group 2 innate lymphoid cells by retinoic acid, *J. Allergy Clin. Immunol.* 143 (6) (2019) 2190–2201 e9.
- [92] D. Rıgas, G. Lewis, J.L. Aron, B. Wang, H. Banie, I. Sankaranarayanan, L. Galle-Treger, H. Maazi, R. Lo, G.J. Freeman, A.H. Sharpe, P. Soroosh, O. Akbari, Type 2 innate lymphoid cell suppression by regulatory T cells attenuates airway hyperreactivity and requires inducible T-cell costimulator-inducible T-cell costimulator ligand interaction, *J. Allergy Clin. Immunol.* 139 (5) (2017) 1468–1477 e2.
- [93] S. Wang, P. Xia, Y. Chen, Y. Qu, Z. Xiong, B. Ye, Y. Du, Y. Tian, Z. Yin, Z. Xu, Z. Fan, Regulatory innate lymphoid cells control innate intestinal inflammation, *Cell* 171 (1) (2017) 201–216 e18.
- [94] C.R. Seehus, A. Kadavallore, B. Torre, A.R. Yeckes, Y. Wang, J. Tang, J. Kaye, Alternative activation generates IL-10 producing type 2 innate lymphoid cells, *Nat. Commun.* 8 (1) (2017) 1900.
- [95] C.A. Akdis, M. Akdis, T. Blesken, D. Wymann, S.S. Alkan, U. Muller, K. Blaser, Epitope-specific T cell tolerance to phospholipase A2 in bee venom immunotherapy and recovery by IL-2 and IL-15 in vitro, *J. Clin. Invest.* 98 (7) (1996) 1676–1683.
- [96] U. Muller, C.A. Akdis, M. Fricker, M. Akdis, T. Blesken, F. Bettens, K. Blaser, Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom, *J. Allergy Clin. Immunol.* 101 (6 Pt 1) (1998) 747–754.
- [97] M.C.P. Santos, A. Serra-Caetano, E. Pedro, A. Melo, I. Caramalho, M.P. Barbosa, R.M.M. Victorino, A.E. Sousa, Expansion of FOXP3(+) regulatory CD4 T cells upon exposure to hymenoptera venom during the beekeeping season, *Allergy* 74 (6) (2019) 1182–1184.
- [98] M. Sokolowska, J. Stefanska, K. Wodz-Naskiewicz, M. Gieslak, R. Pawliczak, Cytosolic phospholipase A2 group IVA is overexpressed in patients with persistent asthma and regulated by the promoter microsatellites, *J. Allergy Clin. Immunol.* 125 (6) (2010) 1393–1395.
- [99] M. Sokolowska, M. Borowiec, A. Ptasińska, M. Cieslak, J.H. Shelhamer, M.L. Kowalski, R. Pawliczak, 85-kDa cytosolic phospholipase A2 group IVA gene promoter polymorphisms in patients with severe asthma: a gene expression and case-control study, *Clin. Exp. Immunol.* 150 (1) (2007) 124–131.
- [100] E. Pniewska, M. Sokolowska, I. Kuprys-Lipinska, M. Przybek, P. Kuna, R. Pawliczak, The step further to understand the role of cytosolic phospholipase A2 alpha and group X secretory phospholipase A2 in allergic inflammation: pilot study, *Biomed Res. Int.* 2014 (2014) 670814.
- [101] T. Boonpiyathad, N. Meyer, M. Moniuszko, M. Sokolowska, A. Eljaszewicz, O.F. Wirz, M.M. Tomasiak-Lozowska, A. Bodzenta-Lukaszyk, K. Ruxrungtham, W. van de Veen, High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers, *Allergy* 72 (3) (2017) 407–415.