ALLERGY IS AN IMMUNE DISORDER RELATED TO A LACK OF REGULATION: THE GLUING ROLE OF IL-2

by

José Mengel

[1]Laboratory of Basical and Clinical Immunology, Petrópolis Medical School, UNIFASE, Petrópolis, RJ, Brazil; [2]Laboratory of Clinical Immunology, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro, RJ, Brazil.

Introduction

Allergy is the immune system's overreaction to certain antigens called allergens, making a specific class of immune response that produces skin, mucosal, or systemic inflammatory pathologies [1]. Allergy has a pandemic nature in the modern world, especially in countries with a high Human Development Index (HDI) [1, 2]. In this article, I shall discuss the current mechanistic view, comparing it to an alternative and testable hypothesis that may lead to more efficacious treatment.

The actual mechanistic view

Allergens are proteins that elicit a Th2, IgE-producing immune response [3]. The Th2 response depends on the differentiation of T cells that produce IL-4, IL-5, and IL-13, among other cytokines [3]. IL-4 is not produced by undifferentiated T cells (TH0) but is necessary for polarization to TH2. Alternatively, as recently shown, TH0 may differentiate into TH2 cells in the presence of IL-33 [3]. Interleukin-33 is an alarmin released upon damage to epithelial cells [4, 5]. ST2, the receptor for IL-33, is expressed in many cells, including eosinophils, basophils, NK, NKT, TH1, TH2, and Treg cells [4]. IL-33 is also essential for the maturation of type 2 innate lymphoid cells (ILC2) in the lungs and may act directly on dendritic cells to induce TH2 polarization and Treg generation [6-8]. Many allergens are proteases and may trigger IL-33 release directly from epithelial cells [9-11]. For instance, the honeybee venom phospholipase A2 elicits a TH2 immune response by disrupting the epithelial cell membrane and releasing IL-33, promoting a TH2 immune response [5]. Also, four (out of more than 20) aeroallergen groups from the dust mite *Dermatophagoides pteronyssinus* are proteases [9-11]. They may elicit a TH2 immune response by acting as described above for the bee venom phospholipase A2 or by directly inducing the release of another TH2 immune response-promoting cytokine, IL-4, from mast cells, as suggested by an *in vitro* study [12].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 November 2022 doi:10.20944/preprints202205.0345.v2

As pointed out above, unprimed T cells need an external source of IL-4 to develop the TH2 functional pattern [13]. Candidates such as ILC2, basophils, mast cells, and NK T lymphocytes may be a primary source of IL-4 [13-15]. Neonatal T cells or dendritic cells may also produce the initial IL-4 to polarize TH0 unprimed CD4 T cells [15-17]. The TH2 polarized response may induce the production of IgG1 and IgE by B cells [13, 18]. However, the amount of IL-4 necessary to cause IgE production is higher than the quantity required for IgG1 secretion [18]. Therefore, allergens must induce a robust TH2 response to generate IgE^+ plasmablasts. The strong, uncontrolled TH2 reaction could occur in allergic patients because they might not develop Tregs to allergens while having normal frequencies of Tregs to other antigens and, therefore, cannot control the allergen-induced immune response [19]. These findings open up at least three possibilities: 1- Allergy is due to Treg repertoire holes; 2- Treg proliferation or function is inhibited in the priming microenvironment; 3- Allergy could be accompanied by a lack of expansion of a particular set of Treg reactivities, implicated in the immune regulation of a given group of non-self molecules, contributing to make them, allergens.

Central and peripheral regulatory T cells

It is widely accepted that a specialized regulatory T cell subpopulation controls several aspects of the immune system activity [20]. Treg cells are positively selected in the thymus by relatively high-affinity interactions with self-peptides in the context of MHC class II molecules. They mature as $CD4^+Foxp3^+$ T cells, expressing the high-affinity receptor for IL-2 (CD25) [20]. They remain activated after migration to peripheral lymphoid organs, supposedly by recognizing peripheral self-antigens [20]. The repertoire of Treg cells may suffer modifications by addition/deletion or expansion/contraction of different clones within the population [21]. These modifications of the Treg cell pool may involve continuous positive thymic selection, with the presentation of a different set of self or non-self peptides in the thymus [22], the activation of a precursor pool of thymic-derived $CD4^+Foxp3^+CD25^-$ peripheral T cells [23, 24] or the conversion of recent thymic emigrant $CD4^+Foxp3^-$ T cells into the regulatory pathway [21, 25]. Thymic and peripheral Treg generation complement each other to maintain tolerance [21]. Many cytokines are involved in Treg generation, differentiation, proliferation, and survival [26]. TGF-beta is essential for producing thymic and peripheral Tregs [26], whereas IL-2 is crucial in their expansion, maintenance, and functional activity [26]. Evidence suggests that IL-33 is vital in generating an IL-33 receptor-positive ($ST2^+$) Treg subpopulation in conjunction with IL-2 [8]. Tregs do not produce IL-2 but instead use the IL-2 produced by dendritic or effector T cells to grow [27]. Therefore, some degree of autoreactivity or response to non-self antigens might exist to stimulate the production of IL-2 by effector T cells [28]. For non-self antigens, other sources of IL-2 are being proposed to stimulate the corresponding Treg compartment, including effector T cells and even dendritic cells [27]. The increased IL-2

 doi:10.20944/preprints202205.0345.v2

production would promote the expansion and optimal function of Treg cells most appropriate for the antigen in question, adjusting the quality and quantity of recruited clones along time and setting up different plateaus of regulatory circuits defined by antigen reactivity/quantity/persistence [28, 29].

The need for an alternative view

As pointed out above, we have hypothesized three possible scenarios to explain the exaggerated TH2 response. Although possible in principle, holes in repertoires derived from a lack of Treg positive or excessive negative selection have not been demonstrated. Furthermore, the potential recruitment of other reactivities from peripheral $CD4^+$ T cell pools decreases the potential of having repertoire holes [23, 25]. Additionally, allergies would have to be linked to MHC/HLA alleles since negative or deficient positive thymic selection would determine the lack of antigen-reactive T cells [22]. Despite the relative importance of MHC/HLA alleles, no strong link has been reported for allergies, contrary to autoimmune conditions.

Furthermore, allergic patients have specific effector TH2 responses to the allergens, showing that allergen-reactive T cells can be positively selected [30]. The presence of effector $CD4^+$ T cells does not rule out the possibility of MHC/HLA playing a role since the selection rules for Treg cells and thymic emigrant $CD4^+$ T cells appear different [31]. Yet, I would prefer to call the readers' attention to the fact that environmental antigens are not abundant in the thymus during the selection process, which operates mostly based on self-peptides/MHC/HLA screening [31]. Therefore, the immune responses to environmental antigens must be based on degeneracy and crossreactivity of effector and regulatory T cells. In this case, one may hypothesize that a time gap must exist between the generation of effector T cells and the expansion of antigen-related regulatory T cells in peripheral lymphoid organs to allow immune responses and their subsequent control. Again, one should not expect a significant time gap for self-antigens as the players should be already balanced from the start by the continuous presence of self. Hence, the T cell repertoire has a high degree of degeneracy and crossreactivity, as first proposed by Don Mason [32]. Therefore, the hypothesis considering physical holes in repertoire does not fit the evidence.

Recently, a study supporting the functional inactivation of Treg cells was published [14]. It shows that IL-33-expanded ILC2, through the production of IL-4, could enhance mast cell activity, inhibiting the expansion and function of peripheral Treg precursors in food allergy [14]. However, IL-4 has been strongly linked to augmenting the functional activities of Treg cells in many models, including the intestinal microenvironment, upon helminth infection [33-35]. Furthermore, IL-33 and IL-4 increase Treg cell proliferation and aid in producing many regulatory cytokines, arguing against this possibility [34, 36].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 November 2022 doi:10.20944/preprints202205.0345.v2

Although the above theoretical framework explains the amplification of TH2 responses by a lack of control of their expansion, it cannot be responsible for both TH2 polarization and the absence of Treg cells simultaneously since IL-33 and IL-4 would be expected to promote regulatory T cell generation.

Therefore, allergy would be better explained by a theoretical framework that could accommodate both lack of Treg cell activity/expansion and polarization of TH0 to TH2 as one single mechanism.

The gluing role of IL-2: an alternative view

As discussed previously, the amplification of Treg frequencies depends on effector T cells that secrete IL-2, and in certain anatomical places, by IL-2 secreted by dendritic cells [27].

During natural development in mice and humans, neonatal T cells are polarized to the TH2 pathway without an apparent source of non-T cell IL-4 or ongoing immune responses to pathogens or self-antigens [16, 17]. Interestingly, in mice, splenic neonatal T cells do not produce IL-2 until a particular time after birth [37]. Also, in the mouse model, Tregs appear a little later after birth [20]. More intriguingly, IL-2 knockout mice have high levels of IgG1 and IgE accompanied by signs of autoimmunity [38-41]. Elevated serum IgG1 and IgE levels are diminished in the IL-2/IL-4 double-knockout mice, demonstrating that IL-4 was responsible for this phenotype [41]. These studies unequivocally show that TH2 cells can develop in the relative or total absence of IL-2 *in vivo*, even though IL-2 is essential to induce TH2 cells *in vitro* [42]. Therefore, we propose that the TH2 pathway would be the default response when a TH0 cell is activated without IL-2 *in vivo*.

Consequently, limited amounts of IL-2 could link the polarization of TH0 to TH2 and low numbers/activity of Tregs in the early allergic response. Hence, no cell lineages other than T cells would be necessary for the initial TH2 polarization [42]. This hypothesis, although not formally demonstrated, is completely amenable to experimentation.

Following this theoretical framework, allergens would be molecules that would not elicit enough IL-2 during their recognition, potentially generating TH2 cells without expanding regulatory T cells. However, one study shows an increased frequency of total $CD4^+CD25^+Foxp3^+$ T cells in patients with allergic asthma, thus contradicting a supposed Treg deficiency in this clinical condition [43]. Yet, this study did not consider antigen-related Tregs. Therefore, increased Treg percentages may be due to the associated inflammatory process and not the regulation of allergen-responsive TH2 effectors [44]. It should be noted that the indexation between IL-2 producers and Treg expansion/activity mentioned above must fail somehow in immune-related diseases so that homeostasis is lost. For instance, an increase in $CD4^+Foxp3^{+/low}$ $CD25^-$ T cells in human lupus correlates with a worsening condition, indicating that these cells may have a pathogenic role [45, 46]. It would be interesting to examine whether

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 November 2022 doi:10.20944/preprints202205.0345.v2

low-dose IL-2 treatment [47] would recruit these cells through the stimulation of CD122 instead of CD25, thus recovering their primordial regulatory function and demonstrating that lack of IL-2-producing T cells, rather than diminished Treg levels, contribute to this disease. Hence, this is a crucial point to investigate since IL-2 therapies have been developed to target the high-affinity IL-2 receptor (CD25). Therefore, these constructs might reinforce pathological conditions as they do not target $CD4^+CD25^-Foxp3^{+/low}$ cells. In addition, another experimental study has used IL-2/anti-IL-2 complexes to drive the IL-2 activity to regulatory cells already expressing the high-affinity CD25 molecules in an experimental model of allergic asthma [48]. In contrast to the expectation, the authors observed an increased inflammation that aggravated the allergic condition in mice treated with engineered IL-2 [48]. However, as the authors pointed out, previous contact with the allergen abolished the harmful effect of engineered IL-2 on their model, promoting regulation. An obvious interpretation of these results is that exposure to the allergen induces the expression of CD25 by TCR activation on an idle allergen-reactive Treg population, making them susceptible to the modified IL-2. Thus, IL-2 may be preferable in pathological conditions over modified forms that increase binding to CD25 unless the antigenic stimulation suffices.

This theoretical framework would support treatments where low doses of IL-2 may be employed to facilitate the development of Treg cells in association with low-dose allergenic stimulation, as demonstrated for experimental food allergy in mice [49]. A recent study shows that IL-2 is produced by a subpopulation of allergen-specific effector TH2 cells in the intestinal mucosa of allergic patients upon oral immunotherapy [50]. In successfully treated patients, an IL-2-dependent allergen-reactive Treg expansion could be observed, demonstrating for the first time that human oral tolerance is dependent on Treg cells and is mediated by antigen-related $CD4^+CD25^+Foxp3^+$ T cells peripherally expanded by IL-2 [50]. Other evidence in mice and humans has found that tolerance to allergens following allergen immunotherapy depends on $CD4^+$ $Foxp3^+$ Tregs [51, 52]. These studies indicate that Tregs are operative in ongoing immune responses. In addition, previous research shows a potentially interesting IL-2 and IL-4 combination effect, further potentiating Treg proliferation and functional activities, suggesting that active evolving TH2 immune responses may reinforce down-modulation by regulatory T cells [53]. $Foxp3^+$ Treg cells use many mechanisms to control settled immune responses, culminating with the global suppression of protein synthesis by effector $CD4^+$ T cells [54, 55]. Other indirect Treg activities remain to be explored. For instance, the function of allergen-specific Tregs may diminish the production of IL-4 and, therefore, the class switch from IgG to IgE [54, 56]. As previously suggested, the Treg activity may facilitate the production of regulatory, less mutated, low-affinity IgE directly from IgM^+ B cell precursors [57, 58]. In addition, whether or not IL-2 favors the appearance of $CD19^+CD25^+IL\text{-}10^+$ regulatory B cells

 doi:10.20944/preprints202205.0345.v2

and, consequently, the production of blocking allergen-specific IgG4 remains to be demonstrated [59, 60].

Allergen immunotherapy usually results in low clinical success, and its improvement is highly desired [61, 62]. Immunotherapy is traditionally applied in allergen-sensitized patients [61, 62]. Therefore, pre-clinical and clinical studies aiming to augment $Foxp3^+$ Treg generation by treatment with low-dose IL-2 administration during allergen immunotherapy are warranted.

 doi:10.20944/preprints202205.0345.v2

Acknowledgments
I thank Ana Caetano Faria, UFMG, Belo Horizonte, Brazil, and Owen Williams, UCL, London, UK, for their critical and constructive reading of the manuscript.

References

[1] R.J. Doll, N.I. Joseph, D. McGarry, D. Jhaveri, T. Sher, R. Hostoffer, Epidemiology of Allergic Diseases, Allergy and Asthma: The Basics to Best Practices, Springer International Publishing, Cham, 2019, pp. 31-51.
[2] J.F. Bach, Revisiting the Hygiene Hypothesis in the Context of Autoimmunity, Frontiers in immunology 11 (2020) 615192.
[3] P. Licona-Limon, L.K. Kim, N.W. Palm, R.A. Flavell, TH2, allergy and group 2 innate lymphoid cells, Nature immunology 14(6) (2013) 536-42.
[4] B. Griesenauer, S. Paczesny, The ST2/IL-33 Axis in Immune Cells during Inflammatory Diseases, Frontiers in immunology 8 (2017) 475.
[5] N.W. Palm, R.K. Rosenstein, S. Yu, D.D. Schenten, E. Florsheim, R. Medzhitov, Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity, Immunity 39(5) (2013) 976-85.
[6] M.T. Stier, J. Zhang, K. Goleniewska, J.Y. Cephus, M. Rusznak, L. Wu, L. Van Kaer, B. Zhou, D.C. Newcomb, R.S. Peebles, Jr., IL-33 promotes the egress of group 2 innate lymphoid cells from the bone marrow, The Journal of experimental medicine 215(1) (2018) 263-281.
[7] R.M. Maizels, Regulation of immunity and allergy by helminth parasites, Allergy 75(3) (2020) 524-534.
[8] B.M. Matta, J.M. Lott, L.R. Mathews, Q. Liu, B.R. Rosborough, B.R. Blazar, H.R. Turnquist, IL-33 is an unconventional Alarmin that stimulates IL-2 secretion by dendritic cells to selectively expand IL-33R/ST2+ regulatory T cells, Journal of immunology 193(8) (2014) 4010-20.
[9] W.R. Thomas, W.A. Smith, B.J. Hales, The allergenic specificities of the house dust mite, Chang Gung medical journal 27(8) (2004) 563-9.
[10] M. Weghofer, Y. Dall'Antonia, M. Grote, A. Stocklinger, M. Kneidinger, N. Balic, M.T. Krauth, E. Fernandez-Caldas, W.R. Thomas, M. van Hage, S. Vieths, S. Spitzauer, F. Horak, D.I. Svergun, P.V. Konarev, P. Valent, J. Thalhamer, W. Keller, R. Valenta, S. Vrtala, Characterization of Der p 21, a new important allergen derived from the gut of house dust mites, Allergy 63(6) (2008) 758-67.
[11] F. Shakib, A.M. Ghaemmaghami, H.F. Sewell, The molecular basis of allergenicity, Trends in immunology 29(12) (2008) 633-42.
[12] D.C. Machado, D. Horton, R. Harrop, P.T. Peachell, B.A. Helm, Potential allergens stimulate the release of mediators of the allergic response from cells of mast cell lineage in the absence of sensitization with antigen-specific IgE, European journal of immunology 26(12) (1996) 2972-80.
[13] T. Yoshimoto, The Hunt for the Source of Primary Interleukin-4: How We Discovered That Natural Killer T Cells and Basophils Determine T Helper Type 2 Cell Differentiation In Vivo, Frontiers in immunology 9 (2018) 716.
[14] M. Noval Rivas, O.T. Burton, H.C. Oettgen, T. Chatila, IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function, The Journal of allergy and clinical immunology 138(3) (2016) 801-811 e9.
[15] Y.L. Ma, F.J. Huang, L. Cong, W.C. Gong, H.M. Bai, J. Li, C.X. Chen, N.Y. Zhou, X.L. Jiang, L. Yin, X.P. Chen, IL-4-Producing Dendritic Cells Induced during Schistosoma japonica Infection Promote Th2 Cells via IL-4-Dependent Pathway, Journal of immunology 195(8) (2015) 3769-80.

[16] S. Rose, M. Lichtenheld, M.R. Foote, B. Adkins, Murine neonatal CD4+ cells are poised for rapid Th2 effector-like function, Journal of immunology 178(5) (2007) 2667-78.
[17] K. Hebel, S. Weinert, B. Kuropka, J. Knolle, B. Kosak, G. Jorch, C. Arens, E. Krause, R.C. Braun-Dullaeus, M.C. Brunner-Weinzierl, CD4+ T cells from human neonates and infants are poised spontaneously to run a nonclassical IL-4 program, Journal of immunology 192(11) (2014) 5160-70.
[18] C.M. Snapper, F.D. Finkelman, W.E. Paul, Differential regulation of IgG1 and IgE synthesis by interleukin 4, The Journal of experimental medicine 167(1) (1988) 183-96.
[19] P. Bacher, F. Heinrich, U. Stervbo, M. Nienen, M. Vahldieck, C. Iwert, K. Vogt, J. Kollet, N. Babel, B. Sawitzki, C. Schwarz, S. Bereswill, M.M. Heimesaat, G. Heine, G. Gadermaier, C. Asam, M. Assenmacher, O. Kniemeyer, A.A. Brakhage, F. Ferreira, M. Wallner, M. Worm, A. Scheffold, Regulatory T Cell Specificity Directs Tolerance versus Allergy against Aeroantigens in Humans, Cell 167(4) (2016) 1067-1078 e16.
[20] O. Annacker, R. Pimenta-Araujo, O. Burlen-Defranoux, A. Bandeira, On the ontogeny and physiology of regulatory T cells, Immunological reviews 182 (2001) 5-17.
[21] R. Pacholczyk, J. Kern, The T-cell receptor repertoire of regulatory T cells, Immunology 125(4) (2008) 450-8.
[22] L. Klein, B. Kyewski, P.M. Allen, K.A. Hogquist, Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see), Nature reviews. Immunology 14(6) (2014) 377-91.
[23] S. Zelenay, T. Lopes-Carvalho, I. Caramalho, M.F. Moraes-Fontes, M. Rebelo, J. Demengeot, Foxp3+ CD25- CD4 T cells constitute a reservoir of committed regulatory cells that regain CD25 expression upon homeostatic expansion, Proceedings of the National Academy of Sciences of the United States of America 102(11) (2005) 4091-6.
[24] S. Schallenberg, P.Y. Tsai, J. Riewaldt, K. Kretschmer, Identification of an immediate Foxp3(-) precursor to Foxp3(+) regulatory T cells in peripheral lymphoid organs of nonmanipulated mice, The Journal of experimental medicine 207(7) (2010) 1393-407.
[25] R.S. Paiva, A.C. Lino, M.L. Bergman, I. Caramalho, A.E. Sousa, S. Zelenay, J. Demengeot, Recent thymic emigrants are the preferential precursors of regulatory T cells differentiated in the periphery, Proceedings of the National Academy of Sciences of the United States of America 110(16) (2013) 6494-9.
[26] E.M. Dons, G. Raimondi, D.K. Cooper, A.W. Thomson, Induced regulatory T cells: mechanisms of conversion and suppressive potential, Human immunology 73(4) (2012) 328-34.
[27] D.L. Owen, S.A. Mahmud, K.B. Vang, R.M. Kelly, B.R. Blazar, K.A. Smith, M.A. Farrar, Identification of Cellular Sources of IL-2 Needed for Regulatory T Cell Development and Homeostasis, Journal of immunology 200(12) (2018) 3926-3933.
[28] I.F. Amado, J. Berges, R.J. Luther, M.P. Mailhe, S. Garcia, A. Bandeira, C. Weaver, A. Liston, A.A. Freitas, IL-2 coordinates IL-2-producing and regulatory T cell interplay, The Journal of experimental medicine 210(12) (2013) 2707-20.
[29] H.S. Wong, K. Park, A. Gola, A.P. Baptista, C.H. Miller, D. Deep, M. Lou, L.F. Boyd, A.Y. Rudensky, P.A. Savage, G. Altan-Bonnet, J.S. Tsang, R.N. Germain, A local regulatory T cell feedback circuit maintains immune homeostasis by pruning self-activated T cells, Cell 184(15) (2021) 3981-3997 e22.

[30] B. Leon, A. Ballesteros-Tato, Modulating Th2 Cell Immunity for the Treatment of Asthma, Frontiers in immunology 12 (2021) 637948.
[31] P. Kraj, L. Ignatowicz, The mechanisms shaping the repertoire of CD4(+) Foxp3(+) regulatory T cells, Immunology 153(3) (2018) 290-296.
[32] D. Mason, A very high level of crossreactivity is an essential feature of the T-cell receptor, Immunology today 19(9) (1998) 395-404.
[33] P. Maerten, C. Shen, D.M. Bullens, G. Van Assche, S. Van Gool, K. Geboes, P. Rutgeerts, J.L. Ceuppens, Effects of interleukin 4 on CD25+CD4+ regulatory T cell function, Journal of autoimmunity 25(2) (2005) 112-20.
[34] M.B. Jones, C.A. Alvarez, J.L. Johnson, J.Y. Zhou, N. Morris, B.A. Cobb, CD45Rb-low effector T cells require IL-4 to induce IL-10 in FoxP3 Tregs and to protect mice from inflammation, PloS one 14(5) (2019) e0216893.
[35] N. Abdel Aziz, J.K. Nono, T. Mpotje, F. Brombacher, The Foxp3+ regulatory T-cell population requires IL-4Ralpha signaling to control inflammation during helminth infections, PLoS biology 16(10) (2018) e2005850.
[36] F. Alvarez, J.H. Fritz, C.A. Piccirillo, Pleiotropic Effects of IL-33 on CD4(+) T Cell Differentiation and Effector Functions, Frontiers in immunology 10 (2019) 522.
[37] S.T. Ishizaka, O. Stutman, Analysis by limiting dilution of interleukin 2-producing T cells in murine ontogeny, European journal of immunology 13(11) (1983) 936-42.
[38] I. Horak, Immunodeficiency in IL-2-knockout mice, Clinical immunology and immunopathology 76(3 Pt 2) (1995) S172-3.
[39] H. Schorle, T. Holtschke, T. Hunig, A. Schimpl, I. Horak, Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting, Nature 352(6336) (1991) 621-4.
[40] I. Horak, J. Lohler, A. Ma, K.A. Smith, Interleukin-2 deficient mice: a new model to study autoimmunity and self-tolerance, Immunological reviews 148 (1995) 35-44.
[41] B. Sadlack, R. Kuhn, H. Schorle, K. Rajewsky, W. Muller, I. Horak, Development and proliferation of lymphocytes in mice deficient for both interleukins-2 and -4, European journal of immunology 24(1) (1994) 281-4.
[42] J. Zhu, H. Yamane, W.E. Paul, Differentiation of effector CD4 T cell populations (*), Annual review of immunology 28 (2010) 445-89.
[43] D. Raedler, N. Ballenberger, E. Klucker, A. Bock, R. Otto, O. Prazeres da Costa, O. Holst, T. Illig, T. Buch, E. von Mutius, B. Schaub, Identification of novel immune phenotypes for allergic and nonallergic childhood asthma, The Journal of allergy and clinical immunology 135(1) (2015) 81-91.
[44] T. Schmid, L. Falter, S. Weber, N. Muller, K. Molitor, D. Zeller, D. Weber-Steffens, T. Hehlgans, H. Wajant, S. Mostbock, D.N. Mannel, Chronic Inflammation Increases the Sensitivity of Mouse Treg for TNFR2 Costimulation, Frontiers in immunology 8 (2017) 1471.
[45] D.A. Horwitz, The clinical significance of decreased T cell interleukin-2 production in systemic lupus erythematosus: connecting historical dots, Arthritis and rheumatism 62(8) (2010) 2185-7.
[46] M. Bonelli, A. Savitskaya, C.W. Steiner, E. Rath, J.S. Smolen, C. Scheinecker, Phenotypic and functional analysis of CD4+ CD25- Foxp3+ T cells in patients with systemic lupus erythematosus, Journal of immunology 182(3) (2009) 1689-95.

[47] H. Grasshoff, S. Comduhr, L.R. Monne, A. Muller, P. Lamprecht, G. Riemekasten, J.Y. Humrich, Low-Dose IL-2 Therapy in Autoimmune and Rheumatic Diseases, Frontiers in immunology 12 (2021) 648408.
[48] S.W. Hong, E. O, J.Y. Lee, J. Yi, K. Cho, J. Kim, D. Kim, C.D. Surh, K.S. Kim, Interleukin-2/antibody complex expanding Foxp3() regulatory T cells exacerbates Th2-mediated allergic airway inflammation, BMB reports 52(4) (2019) 283-288.
[49] P.L. Smaldini, F. Trejo, J.L. Cohen, E. Piaggio, G.H. Docena, Systemic IL-2/anti-IL-2Ab complex combined with sublingual immunotherapy suppresses experimental food allergy in mice through induction of mucosal regulatory T cells, Allergy 73(4) (2018) 885-895.
[50] D. Lozano-Ojalvo, S.R. Tyler, C.J. Aranda, J. Wang, S. Sicherer, H.A. Sampson, R.A. Wood, A.W. Burks, S.M. Jones, D.Y.M. Leung, M.C. de Lafaille, M.C. Berin, Allergen recognition by specific effector Th2 cells enables IL-2-dependent activation of regulatory T-cell responses in humans, Allergy (2022).
[51] L. Bohm, J. Maxeiner, H. Meyer-Martin, S. Reuter, S. Finotto, M. Klein, H. Schild, E. Schmitt, T. Bopp, C. Taube, IL-10 and regulatory T cells cooperate in allergen-specific immunotherapy to ameliorate allergic asthma, Journal of immunology 194(3) (2015) 887-97.
[52] J.F. Ryan, R. Hovde, J. Glanville, S.C. Lyu, X. Ji, S. Gupta, R.J. Tibshirani, D.C. Jay, S.D. Boyd, R.S. Chinthrajah, M.M. Davis, S.J. Galli, H.T. Maecker, K.C. Nadeau, Successful immunotherapy induces previously unidentified allergen-specific CD4+ T-cell subsets, Proceedings of the National Academy of Sciences of the United States of America 113(9) (2016) E1286-95.
[53] J.Y. Zhou, C.A. Alvarez, B.A. Cobb, Integration of IL-2 and IL-4 signals coordinates divergent regulatory T cell responses and drives therapeutic efficacy, eLife 10 (2021).
[54] M. Noval Rivas, T.A. Chatila, Regulatory T cells in allergic diseases, The Journal of allergy and clinical immunology 138(3) (2016) 639-652.
[55] L. So, K. Obata-Ninomiya, A. Hu, V. Muir, A. Takamori, J. Song, J.H. Buckner, R. Savan, S.F. Ziegler, Active Translation Control of CD4 T Cell Activation by Regulatory T Cells, bioRxiv (2022) 2021.09.23.461566.
[56] A. Erazo, N. Kutchukhidze, M. Leung, A.P. Christ, J.F. Urban, Jr., M.A. Curotto de Lafaille, J.J. Lafaille, Unique maturation program of the IgE response in vivo, Immunity 26(2) (2007) 191-203.
[57] L. Pontes-de-Carvalho, J. Mengel, A Question of Nature: Some Antigens are Bound to be Allergens, Frontiers in immunology 5 (2014) 373.
[58] M.T. Koning, I.J.M. Trollmann, C.A.M. van Bergen, D. Alvarez Saravia, M.A. Navarrete, S.M. Kielbasa, H. Veelken, Peripheral IgE Repertoires of Healthy Donors Carry Moderate Mutation Loads and Do Not Overlap With Other Isotypes, Frontiers in immunology 10 (2019) 1543.
[59] D. Catalan, M.A. Mansilla, A. Ferrier, L. Soto, K. Oleinika, J.C. Aguillon, O. Aravena, Immunosuppressive Mechanisms of Regulatory B Cells, Frontiers in immunology 12 (2021) 611795.
[60] 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, The Journal of allergy and clinical immunology 131(4) (2013) 1204-12.

 doi:10.20944/preprints202205.0345.v2

[61] R. Valenta, R. Campana, K. Marth, M. van Hage, Allergen-specific immunotherapy: from therapeutic vaccines to prophylactic approaches, Journal of internal medicine 272(2) (2012) 144-57.
[62] B. Linhart, R. Valenta, Vaccines for allergy, Current opinion in immunology 24(3) (2012) 354-60.