

# Analysis of Forkhead Box Protein-3 (Foxp3) in Allergic Rhinitis Patients

Bambang Suprayogi Resi Utomo<sup>1</sup>, Mochammad Hatta<sup>2</sup>,  
Sutji Pratiwi<sup>3</sup>, Muhammad Nasrum Massi<sup>4</sup>,  
Lina Marlina<sup>1</sup>, Erica Gilda Minawati Simanjuntak<sup>5</sup>

<sup>1</sup>Department of Ear Nose and Throat, Faculty of Medicine, Indonesia Christian University of Jakarta, Jakarta, Indonesia

<sup>2</sup>Molecular Biology and Immunology Laboratory for Infection Diseases, Faculty of Medicine, University of Hasanuddin, Makassar, Indonesia

<sup>3</sup>Department of Ear Nose and Throat, Faculty of Medicine, University of Hasanuddin, Makassar, Indonesia

<sup>4</sup>Department of Microbiology, Faculty of Medicine, University of Hasanuddin, Makassar, Indonesia

<sup>5</sup>Department of Anesthesiology, Faculty of Medicine, Indonesia Christian University of Jakarta, Jakarta, Indonesia

Email: \*hattaram@yahoo.com

**How to cite this paper:** Utomo, B.S.R., Hatta, M., Pratiwi, S., Massi, M.N., Marlina, L. and Simanjuntak, E.G.M. (2018) Analysis of Forkhead Box Protein-3 (Foxp3) in Allergic Rhinitis Patients. *International Journal of Otolaryngology and Head & Neck Surgery*, 7, 228-236.

<https://doi.org/10.4236/ijohns.2018.74024>

**Received:** July 2, 2018

**Accepted:** July 27, 2018

**Published:** July 30, 2018

Copyright © 2018 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

## Abstract

**Background:** A new concept in understanding allergic diseases is regulatory T cells (Tregs), which control the immune reaction caused by Th2 cytokine production. Forkhead Box Protein 3 (FoxP3) is a marker that has a critical role in the development and function of Tregs. Some studies found differences in FoxP3 level and in Tregs capacity to control immune reactions in allergic diseases. The aim of this study was to investigate FoxP3 level in Allergic rhinitis (AR) patients compared to atopic and healthy/normal persons in Jakarta. **Methodology:** This study used observation to analyze the level of FoxP3 in AR, atopic and healthy/normal persons, and used ELISA to measure the FoxP3 level. **Results:** The study had sixty participants divided into three groups: 21 in the Normal group, 16 in the Atopic group, and 23 in the AR group. The mean FoxP3 levels were  $0.81 \pm 0.35$  in the normal group,  $3.42 \pm 0.15$  in the atopic group, and  $3.40 \pm 0.13$  in the AR group. Statistical analysis with Mann-Whitney tests indicated significant differences, with AR and atopic groups having higher FoxP3 levels than the normal group, ( $p = 0.001$ ), and no statistically significant differences between the AR and atopic groups, ( $p = 0.92$ ). **Conclusion:** Our study results suggested that FoxP3 was active in the control of inflammatory processes due to allergies, and decrease level of FoxP3 indicated severe AR, but suggested another mechanism caused differences in the clinical phenotypes of AR and atopic patients, despite them having equally high levels of FoxP3.

## Keywords

Allergic Rhinitis, Atopic, Regulator T Cells, FoxP3, ELISA

## 1. Introduction

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposures by immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose. The symptoms of nasal reactions occurring in allergies are sneezing, nasal obstruction, mucous discharge (rhinorrhea) and/or itching. These symptoms occur for two or more consecutive days and for more than 1 hour most days [1].

The prevalence of allergic disease in the United States (US) is 20% and is still increasing [2]. The prevalence of AR in Asian-Pacific countries such as Australia, China, Hong Kong, Malaysia, Philippines, Taiwan, and Vietnam, ranges on average from 4.2% - 13.2% [3]. Allergic rhinitis is rarely found in people under the age of 5 years old, and occurrence peaks between the ages of 17 and 22 years old [4].

Allergic rhinitis develops from environmental, immunological and genetic factors [5]. Immunological factors are important for understanding the pathophysiology, diagnosis, and treatment of the disease. Allergic rhinitis is a disease with symptoms that comes from immunologic abnormalities [6]. The latest concept in understanding the allergic disease is the role of regulatory T cells (Tregs). Tregs can control the immune reaction caused by Th2 cytokine production. Improvement in Tregs level can increase production of interleukin-10 and transform growth factor- $\beta$  (TGF- $\beta$ ), which can suppress specific Th2 immune responses [7].

FoxP3 is a primary transcription factor of Tregs and can be a specific marker for identifying the presence of Tregs [8] [9]. As a specific marker of Tregs, FoxP3 can be used to understand its function in allergic rhinitis [10]. The profile of FoxP3 levels in some research on allergic diseases has varied. Provoost *et al.*, notes that asthmatic patients had significantly decreased levels of FoxP3 compared to normal people [11]. Allergic rhinitis patients had decreased FoxP3 mRNA levels in nasal secretions compared to normal people [12], and levels of FoxP3 in people with AR were lower than in normal people [13]. However, there are some researchers who noted that patients with atopic asthma showed high Tregs numbers compared to normal controls [14] [15].

Differences result of the FoxP3 study can be explained by methodological differences. On the other hand, genetic disorders existence of FoxP3 genes can affect the results. The normal of Treg could rise at the time of inflammation due to immune reaction [16]. Treg could be induced by high or low dose inhaled allergen.

Up-regulated of Treg correlated to the increasing incidence of infection and confirmed to the understanding of the Hygiene hypothesis [17] [18] [19]. Persistent inflammation could rise the Treg and gave improvement of the AR symptoms [20]. Continuous exposure to small doses of the allergen throughout the year (perennial) such as Jakarta could allow the increasing level of the Tregs. Thus, environmental factors could regulate amount of the Tregs or FoxP3 level.

Allergic rhinitis developed from the state of the atopy. Atopy is a form of im-

munological abnormalities with the tendency of Th2 cytokine-producing and over-producing of IgE. People with atopy have a positive result with the skin prick test, they may not have a clinical symptom but have a history of allergies. The phenotype difference between atopy and AR indicates differences in FoxP3 level. Does Atopy have better FoxP3 level than AR?

Due to the differences in these results, we decided to study peripheral blood levels of FoxP3 in an allergic rhinitis, Atopic and healthy population.

## **2. Materials and Methods**

### **2.1. Participant**

Sixty participants including twenty-one Normal controls, sixteen Atopic and twenty-three AR patients participated in this study. A detailed clinical history and a complete physical examination were carried out for each participant diagnosis of rhinitis were made according to ARIA guidelines on the basis of history and skin prick test positivity for mite allergens (*i.e.*, *Dermatophagoides pteronyssinus*, *D. farinae*) or cockroaches only.

### **2.2. Study Design**

This study was an observational analytic study on individuals with AR symptoms whom came to the Ear, Nose and Throat Department at the Hospital in Jakarta in October 2017-March 2018. We used Wilcoxon table to determine number of the samples. The sample participants were recruited using consecutive sampling. All patients with AR were asked for their informed consent to be participants in this study. The inclusion criteria were a man or woman aged 15 - 66 years who had diagnosed with AR based on ARIA-WHO 2008 criteria: Exclusion criteria were individuals who are having an acute or chronic upper respiratory infection within 30 days prior before the start of the study, taking nasal or oral corticosteroids within 4 weeks prior before the start of the study, using antihistamines within one week prior before the start of the study, pregnant or currently undergoing immunotherapy. In the other hand, Atopic and normal control participants were recruited for this study. All participants with atopic symptoms or who were normal controls were asked for their informed consent before participating in this study. Atopic group criteria were not having symptoms of AR and a positive skin prick test and/or the presence of allergic history. Normal controls group criteria were not having symptoms of AR, a negative skin prick test and there were no history of allergies. One milliliter of the peripheral blood obtained from median cubital vein to measure the level of FoxP3 by using ELISA method was performed for all participants. This research has an ethical approval recommendation from the Institutional Ethics Committee with reference number 1343/H 4.8.4.5.31/PP36-KOMETIK/2016.

### **2.3. Skin Prick Test**

Sensitization was assessed by performing a skin prick/ puncture testing proce-

dures as described in previous study [21]. The allergen panel was a mix of mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and cockroaches (ALK-Abello, Mississauga, Canada).

#### 2.4. FoxP3 Measurement

FoxP3 levels were measured with the enzyme-linked immunosorbent assay (ELISA) method (LifeSpanBioSciences/LSBio., Inc., Seattle, Washington, USA), according to the manufacturer's instructions.

#### 2.5. Statistical Analysis

The study data were collected, tabulated and processed using Statistical Product and Service Solution (SPSS) software version 15.0 (SPSS., Inc., South Wacker Drive, Chicago). The data were analyzed descriptively with means and standard deviations (SDs) and analyzed statistically as differences between groups using the Mann-Whitney test with p-values < 0.05 considered statistically significant. The data are presented in graphs and tables.

### 3. Results

This study investigated records from 60 participants, grouped into three groups as follows: 21 in the Normal group, 16 in the Atopic group and 23 in the AR group. The Normal group consisted of 6 men (28.6%) and 15 women (71.4%) with a mean age of  $25.04 \pm 1.19$  years and a mean FoxP3 level of  $0.80 \pm 0.35$ . The Atopic group consisted of 10 men (62.5%) and 6 women (37.5%) with a mean age of  $30.56 \pm 3.4$  years and a mean FoxP3 level of  $3.42 \pm 0.15$ . The AR group consisted of 7 men (30.4%) and 16 women (69.6%) with a mean age of  $27.69 \pm 2.52$  years and a mean FoxP3 level of  $3.40 \pm 0.13$ . Distributions in sex, age and level of FoxP3 for participants are presented in **Table 1**.

The data are presented as means and standard deviations. If the p-value of the Kruskal-Wallis test was <0.05, significant differences were considered between two groups.

To determine differences among groups, a post-hoc analysis using Mann-Whitney tests for the normal, atopic and allergic rhinitis groups was conducted, and the results are shown in **Figure 1**.

**Table 1.** Distributions in sex, age and level of FoxP3 for participants.

Variable	%, Mean (Standard Deviation)		
	Normal n = 21	Atopic n = 16	Allergic rhinitis n = 23
Sex			
Men	6 (28.6%)	10 (62.5%)	7 (30.4%)
women	15 (71.4%)	6 (37.5%)	16 (69.6%)
Age (years)	$25.04 \pm 1.19$	$30.56 \pm 3.40$	$27.69 \pm 2.52$
FoxP3	$0.81 \pm 0.35$	$3.42 \pm 0.15$	$3.40 \pm 0.13$

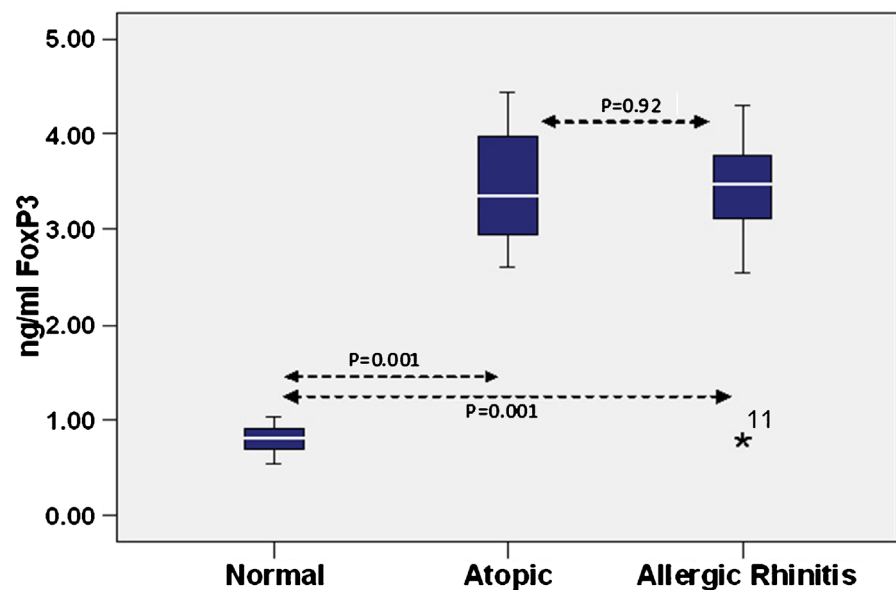
In **Figure 1**, there is a significant difference in mean levels of FoxP3 by Mann-Whitney tests between the Normal group and the Atopic/AR groups,  $p = 0.001$ , and no significant differences were found in mean levels of FoxP3 between the Atopic group and AR group, ( $p = 0.92$ ).

#### 4. Discussion

FoxP3 is a specific marker and has a critical role in the development and function of the Tregs to regulate (negative regulation) the immune responses [22]. FoxP3 is a specific marker for identifying the presence of Tregs [8] [9] [23].

The level of FoxP3 in the Atopic and AR groups were significantly higher compared to the normal controls. The high level of FoxP3 indicates the existence of a response to inflammatory processes. The high levels of FoxP3 in this study may be associated with a place like Jakarta as the location of current research. Jakarta in which area without pollen season has lighter symptoms due to exposure of small allergens concentration that occur throughout the year (perennial), allow an increasing of the FoxP3 level. Besides, Jakarta still has a high incidence of infection.

This result is consistent with previous research that noted high levels of Tregs and FoxP3 in people with atopic asthma compared to normal individuals [14] [15]. Readler *et al.* showed increased levels of FoxP3 in asthmatic patients has the capacity to control the immune response in an allergic reaction, despite the symptoms are still present. Another study showed that increased levels of FoxP3 in atopic patients were followed by good capacity control the immune response [24]. Despite an increase in FoxP3 levels, Tregs were not strong enough to suppress the cytokine-induced allergic reactions, at least for IL-5, IL-13 and IFN- $\gamma$  [15].



**P: Mann Whitney test**

**Figure 1.** Differences mean FoxP3 levels in the tree group with median in box plots.

Readler *et al.* concluded that there was the possibility of an additional mechanism, such as deficiency in innate immune regulation, might be relevant for persistent inflammation.

These results were different from those shown by Lin *et al.*, who found that a higher amount of Tregs was not accompanied by the ability to suppress specific T cells [14]. In the other research, persistent AR had higher levels of FoxP3 compared to intermittent AR [25]. Thus, an increasing number of Tregs was active in suppressing the inflammatory processes due to allergies.

In this study, we found no differences between the levels of FoxP3 in atopic and AR groups. This result indicates that another factor plays a role in the pathogenesis of allergies that was not observed in this study. This phenotype difference may be caused by the differences in dosage of exposure to allergens, differences in lifestyle, and the pollutants.

In this study, we measured FoxP3 level in patient no. 11, who was outside the Box Plot and has moderate-severe symptoms on the nasal blockage only, in **Figure 1**. Low levels of FoxP3 have been reported in another study [11]. Other studies have noted the levels of FoxP3 in people with AR were lower than normal controls, indicating a weakness in the function of FoxP3 to inhibit the pathogenesis of allergic processes in humans [13]. A decrease in the number and function of regulatory T cells can be caused by mutations in the FoxP3 gene, with syndromes including immune dysregulation, polyendocrinopathy, enteropathy and X-linked (IPEX) syndrome, which is a very rare disease in humans. IPEX syndrome has recessive, X-linked inheritance and can be detected within a few days of birth. IPEX syndrome is associated with autoimmune diseases, allergy, and failure to thrive. Chatilla *et al.* conducted a culture in peripheral blood mononuclear cells (PBMC) on autoimmune manifestations in child and conducted stimulation, which gave rise to the Th2 phenotype and produced cytokines such as IL-4, IL-5 and IL-13 [26]. The research indicates Tregs play an important role preventing sensitization in early life. The third case of IPEX syndrome did not have mutation of FoxP3 gene [27]. Some variations of IPEX syndrome showed IL-2 receptor alpha chain deficiency (CD25) and a normal FoxP3 gene [28] [29]. In a genetic study, there was an AR associated with FoxP3 genetic polymorphisms on homozygous alleles [30]. In this study, the presence of one case with low levels of FoxP3 was not included in the investigation.

Increased level of Tregs in people with AR has indicated that they were effective in controlling inflammatory reaction [15] [24] and they provide a response to the severity of atopic diseases and allergies [18]. The decreased in level of Tregs indicated severe allergic diseases and asthma [13]. The increased level of Tregs was related to improvement in AR symptoms. Research has provided evidence for the hygiene hypothesis, indicating environmental factors can increase the level of Tregs [17] [18] [19]. Persistent sensitization can improve symptoms, as shown in the study by Bodtger and Linneberg that examined how allergic sensitization to house dust produced remission of symptoms amounting to 38%

over eight years [20]. It is possible that symptoms of RA decrease over time. FoxP3 expression increased significantly in patients with allergic rhinitis who received specific immunotherapy (SIT) sublingual pollen for 2 years, and there is a positive correlation between the increased expression of FoxP3 on increased IL-10 and TGF- $\beta$  in the study [10].

Finally, the purpose of this study is to investigate the level of FoxP3 in AR, atopic and healthy/normal persons. The results of this study increase our knowledge of the role of FoxP3 in AR, atopic and healthy/normal person. The limitation in this study is on its observational design against the FoxP3 level. The study was not accompanied by another parameter as a transcription factor networks that can explain the causes of high or low level of FoxP3.

## 5. Conclusion

In conclusion, high levels of FoxP3 indicated increasing control of inflammatory processes due to allergies, and decrease levels of FoxP3 indicated severe AR. It is possible other factors caused the differences in the clinical phenotypes between the Atopic and AR group, despite them having equally high levels of FoxP3.

## Acknowledgements

Thank to Prof. Asadul Islam for his advice. Thanks to Dr. Marwito, the Dean of Medical faculty of Christian University of Indonesia. The authors thanks to Listia D. Putrianti S.E. and Arlin D. C. Oktari S.Ked for editing this manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

- [1] Bausquet, J., Khaltaev, N., Cruz, A., Denburg, J., Fokkens, W.J., Togias, A., *et al.* (2008) Review Rhinitis Allergy Its Impact on Asthma (ARIA). *Journal of Allergy and Clinical Immunology*, **86**, 8-160.
- [2] Baroody, F.M. (2003) Allergic Rhinitis: Broader Disease Effects and Implications for Management. *Otolaryngology—Head and Neck Surgery*, **128**, 616-631. [https://doi.org/10.1016/S0194-5998\(03\)00257-2](https://doi.org/10.1016/S0194-5998(03)00257-2)
- [3] Wong, G.W.K., Leung, T.F. and Ko, F.W.S. (2013) Changing Prevalence of Allergic Diseases in the Asia-Pacific Region. *Allergy, Asthma & Immunology Research*, **5**, 251-257. <https://doi.org/10.4168/aaair.2013.5.5.251>
- [4] Huurre, T.M., Aro, H.M. and Jaakkola, J.J. (2004) Incidence and Prevalence of Asthma and Allergic Rhinitis: A Cohort Study of Finnish Adolescents. *Journal of Asthma*, **41**, 311-317. <https://doi.org/10.1081/JAS-120026088>
- [5] Kauffmann, F. and Demenais, F. (2012) Gene-Environment Interactions in Asthma and Allergic Diseases: Challenges and Perspectives. *Journal of Allergy and Clinical Immunology*, **130**, 1229-1242. <https://doi.org/10.1016/j.jaci.2012.10.038>
- [6] Chaaban, M.R. and Naclerio, R.M. (2014) *Head and Neck Surgery-Otolaryngology*. 5rd Edition, Lippincott-William and Wilkins, Philadelphia, 379-406.

- [7] Akdis, M., Verhagen, J., Taylor, A., *et al.* (2004) Immune Responses in Healthy and Allergic Individuals Are Characterized by a Fine Balance between Allergen-Specific T Regulatory 1 and T Helper 2 cells. *Journal of Experimental Medicine*, **199**, 1567-1575. <https://doi.org/10.1084/jem.20032058>
- [8] Hori, S., Nomura, T. and Sakaguchi, S. (2003) Control of Regulatory T Cell Development by the Transcription Factor FoxP3. *Science*, **299**, 1057-1061. <https://doi.org/10.1126/science.1079490>
- [9] Fontenot, J.D., Gavin, M.A. and Rudensky, A.Y. (2003) Foxp3 Programs the Development and Function of CD4+CD25+ Regulatory T Cells. *Nature Immunology*, **4**, 330-336. <https://doi.org/10.1038/ni904>
- [10] Nieminen, K., Valovirta, E. and Savolainen, J. (2010) Clinical Outcome and IL-17, IL-23, IL-27 and FoxP3 Expression in Peripheral Blood Mononuclear Cells of Pollen-Allergic Children during Sublingual Immunotherapy. *Pediatric Allergy & Immunology*, **21**, e174-e184. <https://doi.org/10.1111/j.1399-3038.2009.00920.x>
- [11] Provoost, S., Maes, T., van Durme, Y.M., Gavaert, P., Bachert, C., Shmidt-Weber, C.B., *et al.* (2009) Decreased FoxP3 Protein Expression in Patients with Asthma. *Allergy*, **63**, 1539-1546. <https://doi.org/10.1111/j.1398-9995.2009.02056.x>
- [12] Lee, S.M., Gao, B., Dahl, M., Calhoun, K. and Fang, D. (2009) Decreased FoxP3 Gene Expression in the Nasal Secretions from Patients with Allergic Rhinitis. *Otolaryngology—Head and Neck Surgery*, **140**, 197-201. <https://doi.org/10.1016/j.otohns.2008.08.016>
- [13] Zheng, R., Wu, X., Huang, X., Chen, Y., Yang, Q., Li, Y., *et al.* (2014) Gene Expression Pattern of Treg and TCR V $\gamma$  Subfamily T Cells before and after Specific Immunotherapy in Allergic Rhinitis. *Journal of Translational Medicine*, **12**, 24. <https://doi.org/10.1186/1479-5876-12-24>
- [14] Lin, Y.L., Shieh, C.C. and Wang, J.Y. (2008) The Functional Insufficiency of Human CD4+CD25 High T Regulatory Cells in Allergic Asthma Is Subjected to TNF-Alpha Modulation. *Allergy*, **63**, 67-75. <https://doi.org/10.1111/j.1398-9995.2007.01526.x>
- [15] Readler, D., Ballenberger, N., Klucker, E., Bock, A., Otto, R., Prazeres, da Costa, O., *et al.* (2015) Identification of Novel Immune Phenotype for Allergic Childhood Asthma. *The Journal of Allergy and Clinical Immunology*, **135**, 81-91. <https://doi.org/10.1016/j.jaci.2014.07.046>
- [16] Abbas, A.K., Lichtman, A.H. and Pillai, S. (2015) Cellular and Molecular Immunology. Eighth Edition, Elsevier Saunder, Philadelphia, 199-212, 137-169, 315-337.
- [17] Wilson, M.S., Taylor, M.D., Balic, A., Finney, C.A.M., Lamb, J.R. and Maizels, R.M. (2005) Suppression of Allergic Airway Inflammation by Helminth-Induced Regulatory T Cells. *The Journal of Experimental Medicine*, **202**, 1199-1212. <https://doi.org/10.1084/jem.20042572>
- [18] Maizels, R.M. and Yazdanbakhsh, M. (2003) Immune Regulation by Helminth Parasites: Cellular and Molecular Mechanisms. *Nature Reviews Immunology*, **3**, 733-744. <https://doi.org/10.1038/nri1183>
- [19] Figueiredo, C.A., Alcantra-Neves, N.M., Amorim, L.D., Silva, N.B., Pontes de Carvalho, L.C., Cooper, P.J., *et al.* (2010) Evidence for a Modulatory Effect of IL-10 on both Th1 and Th2 Cytokine Production: The Role of the Environment. *Clinical Immunology*, **139**, 57-64. <https://doi.org/10.1016/j.clim.2010.12.019>
- [20] Bodtger, U. and Linneberg, A. (2004) Remission of Allergic Rhinitis: An 8-Year Observational Study. *Journal of Allergy and Clinical Immunology*, **114**, 1384-1388. <https://doi.org/10.1016/j.jaci.2004.08.039>



- [21] Fatteh, S., Rekkerth, D.J. and Hadley, J. (2012) Skin Prick/Puncture Testing in North America: A Call for Standards and Consistency. *Allergy, Asthma & Clinical Immunology*, **10**, 44. <https://doi.org/10.1186/1710-1492-10-44>
- [22] Beissert, S., Schwarz, A. and Schwarz, T. (2006) Regulatory T Cells. *Journal of Investigative Dermatology*, **126**, 15-24. <https://doi.org/10.1038/sj.jid.5700004>  
[https://www.jidonline.org/article/S0022-202X\(15\)32594-X/fulltext](https://www.jidonline.org/article/S0022-202X(15)32594-X/fulltext)
- [23] Yagi, H., Nomura, T., Nakamura, K., Yamazaki, S., Kitawaki, T., Hori, S., *et al.* (2004) Crucial Role of FOXP3 in the Development and Function of Human CD4+ CD25+ Regulatory T Cells. *International Immunology*, **16**, 1643-1656. <https://doi.org/10.1093/intimm/dxh165>
- [24] Maggi, L., Sanatrlasci, V., Liotta, F., *et al.* (2007) Demonstration of Circulating Allergen-Specific CD41CD251Foxp3 T-Regulatory Cells in both Nonatopic and Atopic Individuals. *Journal of Allergy and Clinical Immunology*, **120**, 429-436. <https://doi.org/10.1016/j.jaci.2007.05.002>
- [25] Lee, J.-H., Yu, H.-H., Wang, L.-C., Yang, Y.-H., Lin, Y.-T. and Chiang, B.-L. (2007) The Levels of CD4+ CD25+ Regulatory T Cells in Paediatric Patients with Allergic Rhinitis and Bronchial Asthma. *Clinical and Experimental Immunology*, **148**, 53-63. <https://doi.org/10.1111/j.1365-2249.2007.03329.x>
- [26] Chatila, T.A., Blaeser, F., Ho, N., Lederman, H.M., Vaulgaropoulos, C., Helms, C. and Bowcock, A.M. (2002) *JM2*, Encoding a Fork Head-Related Protein, Is Mutated in x-Linked Autoimmunity-Allergic Disregulation Syndrome. *Journal of Clinical Investigation*, **106**, R75-R81. <https://www.jci.org/articles/view/11679>  
<https://doi.org/10.1172/JCI11679>
- [27] Gambineri, E., Torgerson, T.R. and Ochs, H.D. (2003) Immune Dysregulation Polyendocrinopathy, Enteropathy, and x-Linked Inheritance (IPEX), a Syndrome of Systemic Autoimmunity Caused by Mutations of FOXP3, a Critical Regulator of T-Cell Homeostasis. *Current Opinion in Rheumatology*, **15**, 430-435. <https://www.ncbi.nlm.nih.gov/pubmed/12819471>  
<https://doi.org/10.1097/00002281-200307000-00010>
- [28] Roifman, C.M. (2000) Human IL-2 Receptor Alpha Chain Deficiency. *Pediatric Research*, **48**, 6-11. <https://doi.org/10.1203/00006450-200007000-00004>
- [29] Caudy, A.A., Reddy, S.T., Chatila, T., Atkinson, J.P. and Verbsky, J.W. (2007) CD25 Deficiency Causes an Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked Syndrome, and Defective IL-10 Expression from CD4 Lymphocytes. *Journal of Allergy and Clinical Immunology*, **119**, 482-487. [https://www.jacionline.org/article/S0091-6749\(06\)02119-1/fulltext](https://www.jacionline.org/article/S0091-6749(06)02119-1/fulltext)  
<https://doi.org/10.1016/j.jaci.2006.10.007>
- [30] Zhang, L., Zhang, Y., Desrosiers, M., Wang, C., Zhao, Y. and Han, D. (2009) Genetic Association Study of FOXP3 Polymorphisms in Allergic Rhinitis in a Chinese Population. *Human Immunology*, **70**, 930-934.