D J Med Sci 2024;10(2):90-97
doi: 10.5606/fng.btd.2024.150

Review

Allergies and T-cell receptor signaling: Insights into immunological sensitivity

Buse Kaptan, Oytun Erbaş

Institute of Experimental Medicine, Kocaeli, Türkiye

ABSTRACT

An allergy occurs when the immune system reacts to substances that are typically harmless under normal circumstances. These reactions are triggered when antibodies respond specifically to these substances upon their entry into the body. Allergens such as pollen, dust, mites, and animal dander can be inhaled or ingested, such as food items. Symptoms of an allergic reaction may include hives, itching, allergic rhinitis, asthma, sneezing, runny nose, and nasal congestion. Removing or avoiding contact with the allergen can often resolve these symptoms. Allergies vary widely among individuals, manifesting differently in different age groups and affecting various parts of the body with varying severity. For instance, one person exposed to an allergen might experience nasal congestion, while another might suffer from sweating and itching. During an allergic response, T cells produced by our body come into play. T cells, a subset of lymphocytes, play a crucial role in the immune response by activating other immune system cells against foreign allergens. This review aims to provide an overview of the relationship between allergies and T cells.

Keywords: Allergy, immune system, immunity, T cells, T lymphocytes.

The primary goal of all living organisms is to ensure the continuation of their species. In striving to achieve this goal, they cannot always remain in safe environments and thus need to learn how to defend themselves against external factors perceived as threats. It is at this point that the immune system comes into play, responding to and combating foreign pathogens.[1] These globally widespread allergic reactions reduce the quality of life when the immune system is not sufficiently strong, which underscores their significance from a health perspective. Current treatment methods do not completely eliminate allergic reactions but aim to shorten the duration of symptoms and are not able to fully eradicate them.[2] T-cell receptors (TCRs) come into play to stimulate other immune systems against organisms present in the body that cause these allergic symptoms. Since the primary function of TCRs is to initiate immune responses to allergens, they are of significant importance in allergic diseases.[3] In the processes that form the cornerstone of allergic diseases, TCRs first recognize the allergen and, after differentiating in T helper (Th) cells, initiate the production of allergen-specific immunoglobulin E (IgE). When the system encounters the allergen again, it binds to the produced IgE.[4] Therefore, we can say that in allergic reactions, both the innate and adaptive immune systems play a role in a manner specific to the individual.

Allergy is a term that refers to one of the origins of human diseases and the different types of reactions resulting from their variations. Derived from the Greek word 'Allos,' this term has been defined as changes affecting the organism. Allergic reactions are quite common diseases that significantly impact both our physical and psychological health.[5] Allergies can begin at some point in life and persist for a long time, sometimes lasting a lifetime. A weakness in the immune system is known to be among the common causes of allergies. When faced with a weakened immune system, the intensity

Received: May 27, 2024
Accepted: June 02, 2024
Published online: October 01, 2024

Correspondence: Buse Kaptan.
E-mail: busekaptans@gmail.com

Cite this article as:
Kaptan B, Erbaş O. Allergies and T-cell receptor signaling: Insights into immunological sensitivity. D J Med Sci 2024;10(2):90-97. doi: 10.5606/fng.btd.2024.150.

and prevalence of allergens in our environment increase, making us more susceptible to frequent illnesses.[6] Allergic diseases, such as anaphylaxis, food allergies, asthma, rhinitis, conjunctivitis, hereditary angioedema, urticaria, eczema, and eosinophilic diseases, are the cause of many chronic conditions. This condition arises from the body's response to an allergen and requires treatment. Measures should be taken to avoid exposure to allergens that cause allergic reactions. Nutritional disorders, external factors, and genetic predisposition also play a role in the development of allergic changes. With allergy tests and appropriate treatment plans, it is possible to manage symptoms effectively. Additionally, providing the correct intervention against reactions is of vital importance.[7] It is crucial to accurately identify which foods individuals with specific food allergies are sensitive to. Despite the difficulty in abstaining from consuming these foods, it is necessary, and individuals should be prepared to administer adrenaline injections if needed. Although common allergenic products such as milk and eggs are widely used today, it is essential to read food packaging and labels carefully and, if necessary, avoid consuming them altogether.[8] Allergy symptoms typically include hives or itching, redness, sneezing, and nasal congestion or runny nose. If a person shows reactions to specific substances, avoiding these substances can help resolve the issue.[9]

T-CELL RESPONSE TO ALLERGENS

T cells are a vital component of our immune system. T lymphocytes and TCRs are fundamental components of the immune response. They constitute a subset of lymphocytes and play a significant role in immune responses. The 'T' abbreviation comes from the thymus, where these cells undergo their final maturation stages. It plays a critical role in maintaining tolerance to harmless antigens. Type 1 allergies arise from IgE-mediated reactions to antigens. Allergy is known to be among the commonly occurring chronic diseases. It can manifest itself in formations such as allergic rhinitis, dermatitis, food allergies, and life-threatening anaphylaxis due to colony-associated IgE-mediated reactions. Therefore, the role of T lymphocytes is crucial in terms of the system's health, balance, and protective functionality.[10] All multicellular organisms are engaged in a battle against pathogenic bacteria, viruses, fungi, and parasites. The first line of defense against infectious pathogens consists of physical and chemical barriers. Overcoming these barriers allows pathogens to weaken, necessitating the activation of the system for the clearance of infection. The immune system is a host defense comprising numerous biological structures and processes that provide defense against foreign and also damaged and transformed entities within an organism.[11] The ability of the immune system to function optimally depends on its components' ability to distinguish between self and non-self and to respond to the non-self. In higher organisms, the system is classified as acquired or innate, with the former emerging later and the latter being present from birth.[12]

When an allergen enters the body, it triggers an immune response involving the production of antibodies such as IgE by B cells. It has been documented that IgE-mediated type 1 hypersensitivity reactions may be beneficial in defending against parasites, toxins, venoms, and various other harmful substances.[13] The presence of IgE-mediated products leads to the development of incompatible type 2 reactions and stimulates the synthesis of IgE antibodies against specific antigens known as allergens. Immunoglobulin E antibodies can trigger encounters with allergens by binding to high-affinity IgE receptors on mast cells and basophils, thereby initiating allergic reactions.[14] Immunoglobulin E-mediated allergic diseases arise from type 2 immune responses, which promote the synthesis of IgE antibodies directed against a specific class of antigens called allergens.[15] Immunoglobulin E antibodies bind to high-affinity IgE receptors on mast cells and basophils, rendering them sensitized for subsequent encounters with the same allergen. This triggers the release of various inflammatory mediators, including histamine, which are responsible for the sudden onset of hypersensitivity symptoms.[16] The development of type 2-mediated allergies is dependent on the complex interaction of genetic and environmental factors on barrier surfaces, including the host microbiome established early in life.[17] While IgE-mediated immediate hypersensitivity reactions undoubtedly underlie

the majority of allergies, it has become apparent that similar responses and symptoms can be triggered by other adaptive immune responses involving IgG or other immune cells and mediators, mediated through complement.[18] Similarly, it has been found that various innate triggers expressed through receptors on mast cells can either directly initiate a hypersensitivity reaction and/or enhance existing IgE-mediated responses.[19] Immunoglobulin G-dependent reactions typically diverge from Th2-mediated responses, which mediate the initiation and maintenance of the immune response due to antibody involvement. This divergence arises from changes in the reaction's dynamics. Along with the characteristics of cytokines such as interleukin (IL)-4, IL-5, and IL-9, eosinophils, basophils, and mast cells also become activated. These mechanisms play a significant role in the initiation and continuation of allergic events.[20] Although Th2-mediated immune responses are clearly beneficial for the host, they can also lead to uncontrolled or inappropriate inflammatory behaviors. In such cases, dysregulation can occur, and the individual may experience dissemination in various forms. Therefore, it is important to somehow control Th2-mediated immune responses and replicate them with appropriate treatment methods. This can prevent potential development and preserve the host's health.[21] These antibodies later bind to mast cells and basophils, which release histamine and other inflammatory mediators, leading to allergic symptoms such as sneezing, itching, and swelling.[22] T cells come in various types with different roles in the body, and T lymphocytes are functionally divided into two main subgroups: $CD4^+$ Th cells and $CD8^+$ cytotoxic T lymphocytes. Cytotoxic $CD8^+$ T cells are known as killer cells. They target and eliminate cells listed on the tumor list and those coming with organ transplants. T helper $CD4^+$ cells act as intermediary cells in the immune response. When activated, they rapidly proliferate and release numerous cytokines to help regulate effector lymphocyte functions. Regulatory T cells ($CD4^+CD25^+$), also known as suppressor T cells, suppress the activation of the immune system and maintain immune system homeostasis. Failure of regulatory T cells to function properly can lead to autoimmune diseases. Finally, T memory cells ensure rapid production of antibodies when encountering the same disease after having experienced it once.[23]

T-cell receptors

T-cell receptors are essential components of the adaptive immune system. They circulate to the thymus gland, where they are activated upon binding to self-peptide-major histocompatibility complex (MHC) complexes with the TCR/CD3 complex. Simultaneously, they are maintained actively within cell compartments through stimulation by a cytokine called IL-7, in a recyclable manner. This process plays a significant role in T cell conditioning and functions, ensuring the smooth operation of the system's flexibility. Therefore, the proper maintenance and activation of pure T cells are critical structures with an expansive perspective on the defense system.[24] The activation of TCRs triggers cell division, clonal expansion, and differentiation. This process is initiated by three fundamental factors: stimulation of cell proliferation, nutrient availability, and oxygen levels. Increased cell proliferation allows T cells to interact with their surroundings and become activated. Nutrient availability supports T cell growth and proliferation by providing the diversity and nutritional options necessary for T cell survival. Oxygen levels regulate the activation process by influencing cellular metabolism. The convergence of these factors activates the T system, allowing it to begin performing its functions effectively.[25] When TCRs encounter single peptide-MHC (pMHC) complexes, they spread on the cell surface as individual proteins ready to initiate the signal. The CD4 and CD8 molecules interact with MHC II and MHC I molecules, respectively. This interaction determines the early mode of T-cell activation. Communication between the pMHC complex and CD4/CD8 co-receptors is recognized by the TCR.[26]

T-cell development

T-cell immunity plays a critical role in the body's defense mechanism. Secondary lymphoid organs serve as central hubs of this defense system. In these organs, mature T cells capable of defending against various foreign antigens encountered throughout life need to be present.[27] These cells having a broad TCR repertoire enables the body

to recognize a wide range of foreign antigens and develop an appropriate defense response to them. This diversity allows the body to be prepared for numerous foreign threats it may potentially encounter.[28] During the development and maturation of T cells, it is essential that only cells capable of mounting an effective response against foreign antigens are selected and distributed to the periphery, meaning various regions of the body. In this process, the elimination of T cells that mistakenly react to the body's own antigens is of great importance. This helps prevent undesired conditions like autoimmunity, where the body attacks its own tissues. This selective process is called central tolerance and enables the body to develop an immune system that is compatible with itself. Consequently, the effectiveness of T-cell immunity relies on mature T cells with a broad TCR repertoire found in secondary lymphoid organs.[29] Proper training of these cells plays a vital role in providing a fast and effective response against foreign antigens while preventing harm to the body's own antigens. This delicate balance is one of the cornerstones of a healthy immune system.[30] T cells play a critical role in the human body's immune system and develop in the thymus gland. The immune system works to protect the body from pathogens, or disease-causing microorganisms. There are various subtypes of T cells, with the most well-known being alpha/beta (α/β) T cells. These cells utilize antigen receptors to recognize antigens and defend the body against infections.[31]

Another important type of T cell is gamma/delta (γ/δ) T cells. Unlike α/β T cells, these cells carry characteristics of both natural killer (NK) cells and T cells through their antigen receptors. This unique combination enables γ/δ T cells to play a significant protective role in the body. Natural killer T cells, like γ/δ T cells, develop in the thymus and are a specialized type of T cell capable of providing a rapid and effective response to antigens. This diversity allows T cells to play a versatile role in the immune system.[32] Each type of T cell provides a broad range of defense against infections and diseases through different mechanisms, safeguarding the body in various ways. The development of these cells in the thymus is crucial for the proper programming of the immune system and maintaining the body's health. The entry of bone marrow-derived thymic progenitor cells into the thymus and the subsequent processes are of significant importance in immune system research. Originating from the bone marrow, these cells reach the thymus via the corticomedullary junction. The thymus, as one of the key organs of the immune system, facilitates the maturation and education of T cells. This process enables the body to effectively defend against pathogens without causing harm to itself.[33] After the entry of thymic progenitor cells into the thymus, these cells undergo various stages to differentiate into different subtypes of T cells. During this transformation, the differentiation process of Th1 cells becomes crucial. The Th1 cells play a critical role, particularly in cellular immune responses. They are at the forefront of defense against intracellular pathogens such as viruses and certain bacteria.[34]

T-CELL STRATEGIES IN THE TREATMENT OF ALLERGIC DISEASE

The fundamental mechanism of allergic reactions involves the exaggerated responses of the immune system to allergens. These responses are characterized by the activation of immune cells, particularly mast cells, basophils, and eosinophils. When these cells encounter allergens, they release inflammatory mediators. These mediators contribute to the occurrence of allergic reactions in the body. Additionally, during allergic reactions, cytokines such as IL-4 and IL-13 released from IgE-type antibodies and Th2 cells play a significant role. These molecules promote class switching of antibodies produced against allergens, making B cells more sensitive to the allergen.[35] Immunoglobulin E antibodies play a central role in allergic reactions and are part of the body's response to allergens. These antibodies are critically important in sensitizing to allergens found particularly on mucosal surfaces such as the respiratory tract and digestive system, as well as on the skin. Cytokines secreted by Th2 cells, such as IL-5, IL-3, granulocyte-macrophage colony-stimulating factor, IL-4, and IL-9, trigger cellular mechanisms that support IgE production and other key elements of the allergic response.[36] Interleukin-5 specifically promotes the release,

migration, and activation of eosinophils from the bone marrow. Eosinophils are white blood cells that play a significant role in fighting parasitic infections and allergic reactions. They are associated with conditions like allergic asthma and rhinitis and are critically important in sustaining inflammation.[37] T-cell epitope peptide therapy is an innovative approach developed based on the principles of our immune system's functioning. This treatment aims to modulate the functionality of our body's T cells, especially the effector and helper T cells that play a critical role in defense mechanisms against pathogens.[38] The use of peptides containing dominant T-cell epitopes is designed to target a specific immune response while inducing anergy (rendering unresponsive) or deletion (neutralization) of T cells. This process helps the body to control harmful T cell responses, thereby reducing excessive and detrimental immune reactions in conditions such as autoimmune diseases.[39]

The concept of specific anergy relies on the functional cytokine plasticity of T cells, particularly Th cells. T helper cells play a crucial regulatory role in the immune system, determining the direction of the immune response by controlling the release of various cytokines. T-cell epitope peptide therapy modulates cytokine production of these cells, thereby downregulating (reducing) pathogenic effector T cell responses. This process suppresses harmful reactions while preserving the healthy functioning of the immune system and the ability of naïve T cells to generate protective responses. Thus, while enhancing the body's self-defense capability, it also prevents detrimental autoimmune reactions.[40] This therapy holds promise, particularly in the treatment of autoimmune diseases, the management of allergic reactions, and potentially in cancer therapy. By targeting specific T-cell responses, this therapeutic approach aims to provide more precise control over the immune system. However, further research is needed to determine its efficacy and safety. Considering the complex nature of the immune system, T-cell epitope peptide therapy has the potential to revolutionize the treatment of immune-related diseases.[41]

DETERMINATION OF ALLERGENS BY T-CELL RECEPTORS

Immunotherapy holds a significant place in the treatment of diseases ranging from cancer to autoimmune disorders. The success of these therapies largely depends on effectively mobilizing the immune system to combat the targeted disease. The selection of peptides used in immunotherapy is a critical part of this process. Recognition of peptides by T cells is crucial for the effectiveness of these treatments. In this context, the ability of peptides to be presented by different human leukocyte antigen (HLA) class 2 molecules is of great importance in terms of addressing a wide range of populations.[42] The HLA class 2 molecules play a central role in the human immune system, particularly in the activation of $CD4^+$ T cells. The ability of a peptide to form a complex with HLA class 2 molecules encoded by any of the HLA-DR, HLA-DP, or HLA-DQ loci allows recognition of this peptide by $CD4^+$ T cells and thus initiates the immune response. Therefore, in the selection of potential therapeutic peptides, consideration should be given to their ability to interact with a broad repertoire of HLA molecules.[43] T-cell epitope prediction algorithms are crucial tools in this process. These algorithms can predict how a peptide may interact with different HLA types, enabling the evaluation of the potential effectiveness of candidate peptides for therapy across genetically diverse human populations. Success in immunotherapy thus relies on the development of treatments that can be applied to a broad patient base. The selection and optimization of peptides are at the core of this comprehensive approach, and the future of immunotherapy is directly linked to the development and implementation of these scientific strategies.[44] The differences between allergic diseases and autoimmune conditions provide profound insights into how the immune system responds. In autoimmune diseases, the body's immune system erroneously attacks its own tissues, whereas allergic reactions typically develop in response to specific external factors, known as allergens. Interestingly, while some autoimmune diseases show a strong association with specific HLA types, such a connection is generally weaker in allergic diseases.[45] The underlying mechanisms behind allergic reactions

can be better understood through the role of T cells. Allergens can function as T-cell epitopes, and these epitopes often exhibit broad tolerance in binding to HLA molecules. This means that an allergen can interact with many different HLA class 2 molecules. Consequently, allergen-specific $CD4^+$ T cells can recognize a specific epitope complexed with various HLA class 2 molecules. This broad recognition capacity may be one reason why allergic diseases are not tightly associated with specific HLA types.[46] These insights point to important avenues in the treatment and understanding of allergic reactions. Better understanding how allergens trigger T cell responses and interact with HLA class 2 molecules can aid in more effectively managing allergic diseases. The complex nature of allergic reactions and the broad range of interactions with HLA molecules underscore the importance of developing personalized approaches to treating these diseases.[47] The immune system in the human body employs various mechanisms to combat diseases. One of these mechanisms involves antigen presentation and T cell responses. T cells recognize foreign substances (antigens) that enter the body and develop a response against them. This process occurs primarily on molecules called HLA molecules. Human leukocyte antigen molecules are responsible for enabling the immune system to recognize antigens.[48] Research indicates that nominal antigens are most commonly presented on HLA-DR molecules. However, it has been discovered that the T-cell epitopes of allergens and other antigens can also be presented on HLA-DQ and HLA-DP molecules.[49] These molecules exhibit more conserved features among populations compared to HLA-DR. This means that there are fewer variations in the structure of these molecules across different human groups. This situation provides a significant advantage for therapeutic approaches related to the immune system.[50] From a therapeutic perspective, the similarity of HLA-DQ and HLA-DP across a broader population allows for the development of general strategies that can be utilized in areas such as vaccine development and the treatment of autoimmune diseases. Additionally, it suggests that epitopes presented on these molecules may be effective in a wider range of patient groups. This is particularly promising in today's context, where personalized medicine and targeted therapies are gaining importance, spanning a broad spectrum of applications from allergies to autoimmune diseases.[51]

In conclusion, from birth onwards, the human body is in constant interaction with both self-antigens and foreign pathogens from the environment. In this dynamic environment, our immune system develops an effective defense mechanism against foreign pathogens while also establishing a tolerance mechanism to prevent harm to our own cells. Maintaining this balance is of vital importance; otherwise, we may become vulnerable to foreign threats or develop autoimmune diseases that harm ourselves. T cells play a central role in this complex process of maintaining balance within the immune system. Initially thought to primarily trigger the immune response to antigens, recent research has revealed that effector T cells have a much broader range of functions. Effector T cells assume negative regulatory roles within the adaptive and innate immune systems, preventing immune responses from becoming excessive and aiding in the establishment of immune tolerance. With these characteristics, effector T cells have become a critical balancing factor for the body to mount an effective defense against pathogens without harming its own cells. Understanding the various functions and regulatory mechanisms of these cells may contribute to the development of new immunotherapies and vaccines. The differentiation of T cells enables the body to develop a more effective response to these pathogens. The migration and differentiation of thymic progenitor cells are crucial for understanding the complex regulation and dynamics of the immune system. A better understanding of these processes may open new doors for the treatment of various diseases such as allergies, autoimmune diseases, infections, and cancer. Furthermore, enhancing Th1 cell responses may assist in the development of therapeutic strategies in some cases, indicating that this area is highly promising for research. Additionally, it may lead to innovative approaches in the treatment of many diseases such as autoimmune diseases, allergies, and cancer. Therefore, research on these important players of the immune system is a great source of hope for the health sciences.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equallyto this article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Janeway CA Jr, Medzhitov R. Innate immune recognition. Annu Rev Immunol 2002;20:197-216. doi: 10.1146/annurev.immunol.20.083001.084359.
2. Agache I, Akdis CA. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases. J Clin Invest 2019;129:1493-503. doi: 10.1172/JCI124611.
3. Sušac L, Vuong MT, Thomas C, von Bülow S, O'Brien-Ball C, Santos AM, et al. Structure of a fully assembled tumor-specific T cell receptor ligated by pMHC. Cell 2022;185:3201-13.e19. doi: 10.1016/j.cell.2022.07.010.
4. Akbulut E, Üzümcü İ, Kayaaltı, Erbaş O. Fecal microbiota transplantation: Impacts on neurological disorders, allergies, and cancer. JEB Med Sci 2021;2:420-9. doi: 10.5606/jebms.2021.75685.
5. Simon D. Recent advances in clinical allergy and immunology. Int Arch Allergy Immunol 2018;177:324-33. doi: 10.1159/000494931.
6. Brodin P, Davis MM. Human immune system variation. Nat Rev Immunol 2017;17:21-9. doi: 10.1038/nri.2016.125.
7. Colilla S, Nicolae D, Pluzhnikov A, Blumenthal MN, Beaty TH, Bleecker ER, et al. Evidence for gene-environment interactions in a linkage study of asthma and smoking exposure. J Allergy Clin Immunol 2003;111:840-6. doi: 10.1067/mai.2003.170.
8. Liu G, Liu M, Wang J, Mou Y, Che H. The role of regulatory T cells in epicutaneous immunotherapy for food allergy. Front Immunol 2021;12:660974. doi: 10.3389/fimmu.2021.660974.
9. Duru S, Kurt EB. Astım, çevre ve epigenetic. Tuberk Toraks 2014;62:165-9. doi: 10.5578/tt.6818.
10. Suhrkamp I, Scheffold A, Heine G. T-cell subsets in allergy and tolerance induction. Eur J Immunol 2023;53:e2249983. doi: 10.1002/eji.202249983.
11. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature 2007;449:819-26. doi: 10.1038/nature06246.
12. Coates M, Lee MJ, Norton D, MacLeod AS. The skin and intestinal microbiota and their specific innate immune systems. Front Immunol 2019;10:2950. doi: 10.3389/fimmu.2019.02950.
13. Finkelman FD, Khodoun MV, Strait R. Human IgE-independent systemic anaphylaxis. J Allergy Clin Immunol 2016;137:1674-80. doi: 10.1016/j.jaci.2016.02.015.
14. Peters RL, Krawiec M, Koplin JJ, Santos AF. Update on food allergy. Pediatr Allergy Immunol 2021;32:647-57. doi: 10.1111/pai.13443.
15. Arda M, Minbay A, Aydın N, Akay Ö, Özgür M, Diker KS. İmmunoloji. 1. Baskı. Ankara: Medisan Yayınevi; 1994.
16. Geginat J, Paroni M, Maglie S, Alfen JS, Kastirr I, Gruarin P, et al. Plasticity of human CD4 T cell subsets. Front Immunol 2014;5:630. doi: 10.3389/fimmu.2014.00630.
17. Tabarkiewicz J, Pogoda K, Karczmarczyk A, Pozarowski P, Giannopoulos K. The role of IL-17 and Th17 lymphocytes in autoimmune diseases. Arch Immunol Ther Exp (Warsz) 2015;63:435-49. doi: 10.1007/s00005-015-0344-z.
18. Capone A, Volpe E. Transcriptional regulators of T helper 17 cell differentiation in health and autoimmune diseases. Front Immunol 2020;11:348. doi: 10.3389/fimmu.2020.00348.
19. Booth JS, Toapanta FR. B and T cell immunity in tissues and across the ages. Vaccines (Basel) 2021;9:24. doi: 10.3390/vaccines9010024.
20. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. Nature 2008;454:445-54. doi: 10.1038/nature07204.
21. Oliveria JP, Agayby R, Gauvreau GM. Regulatory and IgE+ B cells in allergic asthma. Methods Mol Biol 2021;2270:375-418. doi: 10.1007/978-1-0716-1237-8_21.
22. Rahman RS, Wesemann DR. Immunology of allergen immunotherapy. Immunother Adv 2022;2:ltac022. doi: 10.1093/immadv/ltac022.
23. Natalini A, Simonetti S, Favaretto G, Peruzzi G, Antonangeli F, Santoni A, et al. OMIP-079: Cell cycle of CD4+ and CD8+ naïve/memory T cell subsets, and of Treg cells from mouse spleen. Cytometry A 2021;99:1171-5. doi: 10.1002/cyto.a.24509.
24. Ankathatti Munegowda M, Xu S, Freywald A, Xiang J. CD4+ Th2 cells function alike effector Tr1 and Th1 cells through the deletion of a single cytokine IL-6 and IL-10 gene. Mol Immunol 2012;51:143-9. doi: 10.1016/j.molimm.2012.02.120.
25. Mosmann TR, Coffman RL. TH1 and TH2 cells: Different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol 1989;7:145-73. doi: 10.1146/annurev.iy.07.040189.001045.
26. Yamagata T, Skepner J, Yang J. Targeting Th17 effector cytokines for the treatment of autoimmune diseases. Arch Immunol Ther Exp (Warsz) 2015;63:405-14. doi: 10.1007/s00005-015-0362-x.
27. Salomon B, Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. Annu Rev

Immunol 2001;19:225-52. doi: 10.1146/annurev.immunol.19.1.225.
28. Williams MA, Bevan MJ. Effector and memory CTL differentiation. Annu Rev Immunol 2007;25:171-92. doi: 10.1146/annurev.immunol.25.022106.141548.
29. Wan YY, Flavell RA. How diverse--CD4 effector T cells and their functions. J Mol Cell Biol 2009;1:20-36. doi: 10.1093/jmcb/mjp001.
30. Zhu J, Paul WE. Peripheral CD4+ T-cell differentiation regulated by networks of cytokines and transcription factors. Immunol Rev 2010;238:247-62. doi: 10.1111/j.1600-065X.2010.00951.x.
31. Soerens AG, Künzli M, Quarnstrom CF, Scott MC, Swanson L, Locquiao JJ, et al. Functional T cells are capable of supernumerary cell division and longevity. Nature 2023;614:762-6. doi: 10.1038/s41586-022-05626-9.
32. Ribot JC, Lopes N, Silva-Santos B. γδ T cells in tissue physiology and surveillance. Nat Rev Immunol 2021;21:221-32. doi: 10.1038/s41577-020-00452-4.
33. Thapa P, Farber DL. The role of the thymus in the immune response. Thorac Surg Clin 2019;29:123-31. doi: 10.1016/j.thorsurg.2018.12.001.
34. Seet CS, He C, Bethune MT, Li S, Chick B, Gschweng EH, et al. Generation of mature T cells from human hematopoietic stem and progenitor cells in artificial thymic organoids. Nat Methods 2017;14:521-30. doi: 10.1038/nmeth.4237.
35. Kay AB. Allergy and allergic diseases. Second of two parts. N Engl J Med 2001;344:109-13. doi: 10.1056/NEJM200101113440206.
36. Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med 2001;344:30-7. doi: 10.1056/NEJM200101043440106.
37. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 2014;133:621-31. doi: 10.1016/j.jaci.2013.12.1088.
38. O'Hehir RE, Prickett SR, Rolland JM. T cell epitope peptide therapy for allergic diseases. Curr Allergy Asthma Rep 2016;16:14. doi: 10.1007/s11882-015-0587-0.
39. Woodfolk JA. Epitope-specific T-cell responses and allergic phenotypes: Implications for T-cell peptide therapy. Expert Rev Clin Immunol 2006;2:309-18. doi: 10.1586/1744666X.2.2.309. PMID: 20477080.
40. Murphy KM, Stockinger B. Effector T cell plasticity: Flexibility in the face of changing circumstances. Nat Immunol 2010;11:674-80. doi: 10.1038/ni.1899.
41 Zhu J, Paul WE. Heterogeneity and plasticity of T helper cells. Cell Res 2010;20:4-12. doi: 10.1038/cr.2009.138.
42. Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. Cancer Cell 2020;37:443-55. doi: 10.1016/j.ccell.2020.03.017.
43. Schulten V, Oseroff C, Alam R, Broide D, Vijayanand P, Peters B, et al. The identification of potentially pathogenic and therapeutic epitopes from common human allergens. Ann Allergy Asthma Immunol 2013;110:7-10. doi: 10.1016/j.anai.2012.10.015.
44. Verhoef A, Higgins JA, Thorpe CJ, Marsh SG, Hayball JD, Lamb JR, et al. Clonal analysis of the atopic immune response to the group 2 allergen of Dermatophagoides spp.: Identification of HLA-DR and -DQ restricted T cell epitopes. Int Immunol 1993;5:1589-97. doi: 10.1093/intimm/5.12.1589.
45. Bateman EA, Ardern-Jones MR, Ogg GS. Identification of an immunodominant region of Fel d 1 and characterization of constituent epitopes. Clin Exp Allergy 2008;38:1760-8. doi: 10.1111/j.1365-2222.2008.03098.x.
46. Oseroff C, Sidney J, Kotturi MF, Kolla R, Alam R, Broide DH, et al. Molecular determinants of T cell epitope recognition to the common Timothy grass allergen. J Immunol 2010;185:943-55. doi: 10.4049/jimmunol.1000405.
47. Jahn-Schmid B, Pickl WF, Bohle B. Interaction of allergens, major histocompatibility complex molecules, and T cell receptors: A 'ménage à trois' that opens new avenues for therapeutic intervention in type I allergy. Int Arch Allergy Immunol 2011;156:27-42. doi: 10.1159/000321904.
48. Yssel H, Johnson KE, Schneider PV, Wideman J, Terr A, Kastelein R, et al. T cell activation-inducing epitopes of the house dust mite allergen Der p I. Proliferation and lymphokine production patterns by Der p I-specific CD4+ T cell clones. J Immunol 1992;148:738-45.
49. Prickett SR, Voskamp AL, Phan T, Dacumos-Hill A, Mannering SI, Rolland JM, et al. Ara h 1 CD4+ T cell epitope-based peptides: Candidates for a peanut allergy therapeutic. Clin Exp Allergy 2013;43:684-97. doi: 10.1111/cea.12113.
50. Prickett SR, Voskamp AL, Dacumos-Hill A, Symons K, Rolland JM, O'Hehir RE. Ara h 2 peptides containing dominant CD4+ T-cell epitopes: Candidates for a peanut allergy therapeutic. J Allergy Clin Immunol 2011;127:608-15.e1-5. doi: 10.1016/j.jaci.2010.09.027.
51. Higgins JA, Lamb JR, Marsh SG, Tonks S, Hayball JD, Rosen-Bronson S, et al. Peptide-induced nonresponsiveness of HLA-DP restricted human T cells reactive with Dermatophagoides spp. (house dust mite). J Allergy Clin Immunol 1992;90:749-56. doi: 10.1016/0091-6749(92)90098-m.