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DRUG ALLERGY. THE ROLE OF CYTOKINE GENES IN THE DEVELOPMENT OF A DRUG REACTION

Ирсалиева Фотима Хуснутдиновна
Доктор медицинских наук,Ташкент
E-mail: irsalieva73@mail.ru

Низомов Кутпидин Фатхулаевич
Старший преподаватель
E-mail: nimatxodjaevanasiba@gmail.com

Омонова Озода
Врач аллерголог,Ташкент
E-mail: 1995ozoda82@gmail.com

Ирсалиева Феруза Хуснутдиновна
Кандидат медицинских наук, Ташкент
E-mail: irsalieva73@mail.ru

F. Kh. Irsalieva
Candidate of Medical Sciences,Tashkent
E-mail: irsalieva73@mail.ru

ABSTRACT

Methods for early diagnosis of drug allergy are the gold standard for preventing adverse allergic reactions in patients in the future.
Recently, there is a theory according to which allergic diseases are caused by dysregulation in the immune system associated with increased activation of allergen-specific Th2 clones[1]. The allergic version of the immune system response is now called the type 2 immune response, and normally it ensures the development of humoral immunity. The immunological mechanisms of the formation of the type 2 immune response are associated with the activation of Th2 and ILC2, the synthesis of IgE by B-lymphocytes, the accumulation and activation of eosinophils, basophils and mast cells. All these processes are associated with an increase in the synthesis of cytokines of type 2 immune response by cells: IL-4, IL-5, IL-9, IL-13. Normally, the stimulation of the development of Th2 leads to the activation of the

KEYWORDS

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humoral link of immunity, without which the normal course of protective reactions against a number of pathogens is impossible, but in allergy such activation acquires the features of pathological inflammation.	

Introduction

Conduct

Approximately 15% of the population in developing countries first encounter adverse allergic reactions to drugs, mainly nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics[2-6]. Adverse drug reactions (ADRs) cause difficulties for patients and doctors in terms of accurate diagnosis, competent drug therapy, monetary costs for the management of adverse reactions, and patient mortality. 20-30% are considered preventable, the diseased part occurs during the administration of the drug to the patient[3,7,8].

The Government of the Republic of Uzbekistan has taken significant measures to improve the treatment and prevention of allergies, which includes improving the monitoring of allergic diseases and the establishment of specialized centers for advanced diagnosis and treatment. The government intends to provide allergy sufferers with free medicines and introduce a comprehensive allergen research system in various regions, especially in areas with a high prevalence of allergies.

The increase in drug allergy patients is drawing the government's attention to improving health care, with a focus on allergic and immunological diseases. The introduction of targeted screening and the development of an electronic registry of allergy patients are key components of this strategy.[9], [10].

Urticaria is diagnosed in 15-25% of the population, 1/4 of them are chronic urticaria (RC). The average duration of the disease in adults is from 3 to 5 years, but every 5th patient with CH notes the appearance of blisters over a longer period (up to 20 years). In addition, angioedema is recorded in every 2nd patient with urticaria [11].

Materials and methods of research:

Literature review. A comprehensive literature review was conducted to collect information on the etiology, pathogenesis and clinical treatment of drug allergy (LA). The search was carried out in the databases PubMed, Scopus and Google Scholar. Keywords such as "drug allergy", "etiology", "pathogenesis", "cytokines", "polymorphism", "adverse allergic reactions", "genetics" and "cellular and humoral immunity" were used for the analysis. the availability of clinical data or significant results related to LA.

Inclusion and exclusion criteria. The inclusion criteria included articles, various clinical trials, scientific studies, and review articles published in Russian and English over the past 20 years. Priority was given to articles addressing the etiological factors, pathogenetic mechanisms, and diagnostic findings of LA. Exclusion criteria included studies that were not peer-reviewed, articles in languages other than English and Russian, and articles not directly related to the the main topic of this review.

Data extraction

Key information on the etiology, genetic factors, epidemiology, pathogenesis, clinical manifestations, and strategies for the diagnosis and treatment of LA was collected. Particular attention was paid to the role of genetic predisposition, types of diagnostic tests.

Analysis of the collected data

The data obtained were analyzed in order to identify common themes and significant results. Various types of RA diagnostics have been studied. The pros and cons of early detection of LA were discussed.

Ethical considerations

As this study included a literature review, there were no direct ethical considerations regarding humans or animals. All sources have been appropriately cited to confirm authorship and preserve academic integrity.

Restrictions

The main limitation of this review is the reliance on existing literature, which may introduce biases based on the availability and quality of published studies. Future studies with primary data collection and longitudinal studies are recommended to complement the results of this review.

Outcomes

A drug allergy is a hypersensitivity reaction in which the immune system mistakenly identifies a drug as a harmful substance, triggering an allergic immune response. This in turn is characterized by a range of cellular and molecular interactions.

Allergens enter the body through the respiratory tract, digestive tract, drug administration, or skin using dendritic cells, B cells, or macrophages. After phagocytosis, allergen fragments are presented to allergen-specific T cells. As a result of this process, allergen-reactive T cells are induced, which are of the Th2 type and secrete the cytokines IL-4, IL-5 and IL-10. Direct contact of Th2 cells with B cells leads to the activation of these cells. The cytokine Th2 IL-4 instructs B cells to switch from the production of IgM to the production of IgE antibodies. IgE antibodies play a major role in the occurrence of allergic diseases. IgE antibodies are taken up by basophils and mast cells due to high-affinity receptors for IgE on these cells. Contact with the allergen results in the activation of such IgE-sensitized cells, resulting in the release of various mediators such as histamine, leukotrienes, and prostaglandins; Together, they cause clinical manifestations of allergic reactions.

In drug allergies, the immune system reacts abnormally to the drug, leading to allergic symptoms. Cytokines, which are signaling molecules that modulate immune responses, play a crucial role in these responses.

Here are some key cytokines involved in the development of drug allergies:

1. Interleukin-4 (IL-4) plays an important role in the differentiation of naïve T cells into Th2 cells, which are associated with allergic reactions. It also stimulates the production of immunoglobulin E (IgE) by B cells, which is a hallmark of allergic reactions.

2. Interleukin-5 (IL-5) is essential for the growth and activation of eosinophils, a type of white blood cell that promotes inflammation and tissue damage in allergic reactions, including drug-induced allergies.
3. Interleukin-6 (IL-6) is an anti-inflammatory cytokine that can enhance the immune response, leading to symptoms seen in drug allergies, such as fever, rash, and more severe systemic reactions.
4. Interleukin-10 (IL-10) is also an anti-inflammatory cytokine that can regulate and suppress the immune response, potentially limiting the severity of allergic reactions.
5. Interleukin-13 (IL-13) Like IL-4, IL-13 is involved in the production of IgE and is also implicated in the hyperreactivity of the airways seen in allergic asthma, which can be triggered by drug allergies.
6. Interferon-gamma (IFN-γ) is commonly associated with Th1 immune responses, but may play a role in drug allergies by promoting inflammation and modulating the activity of other immune cells.
7. Tumor necrosis factor-alpha (TNF-α) is a potent anti-inflammatory cytokine that contributes to the inflammation and tissue damage seen in drug allergies.
8. Interleukin-17 (IL-17) is involved in the recruitment and activation of neutrophils and may promote an inflammatory response in drug-induced hypersensitivity reactions.
9. Transforming growth factor-beta (TGF-β) has a dual role, potentially promoting tolerance and suppressing the immune response, but it can also promote fibrosis and tissue remodeling in chronic allergic diseases. [12,13]

These cytokines interact in complex ways to exacerbate or attenuate the allergic response to medications. Understanding their role is critical to developing effective treatments for drug allergies. [14]

Genetic variations, such as single nucleotide polymorphisms (SNPs) in cytokine genes, can influence the response of the human immune system to drugs. These variations can lead to overproduction or underproduction of cytokines, affecting the severity of the allergic reaction.

Understanding these genetic variations can help predict the risk of developing a drug allergy, leading to more personalized and safe drug prescribing.

Measuring cytokine levels can provide insight into the immune response to allergic reactions. [15]

Methods for determining cytokines:

1. ELISA (enzyme-linked immunosorbent assay): This method uses antibodies that are specific to the cytokine you are interested in. When a cytokine binds to an antibody, the secondary antibody bound to the enzyme produces a measurable signal, usually a change in color. Pros: High sensitivity and specificity; suitable for the determination of individual cytokines. Cons: Only one cytokine is measured in a single assay, so multiple tests are required to obtain a complete profile.
2. Multiplex assays (e.g., Luminex): This technology uses beads labeled with different antibodies, allowing multiple cytokines to be measured simultaneously in a single sample. Pros: Ability to measure many cytokines simultaneously; faster and uses a smaller sample volume. Cons: More expensive and requires specialized equipment.
3. Flow Cytometry (Cytokine Bead Array): Similar to multiplex assays, flow cytometry allows the simultaneous measurement of multiple cytokines using fluorescently labeled antibodies. Pros: Allows for a detailed immune profile, including cellular sources of cytokines. Cons: Requires specialized equipment and technical knowledge.

4. RT-PCR (Real-Time Polymerase Chain Reaction): Measures the levels of cytokine mRNA that correlate with protein levels. This is done by amplifying mRNA of specific cytokines from blood cells or tissues. Pros: Very sensitive and detects low levels of cytokine expression. Cons: mRNA is measured, which is not always directly correlated with protein levels; requires careful processing of samples.
5. Western blot: Detection of cytokine proteins by separating them by gel electrophoresis, followed by transfer to the membrane and testing with specific antibodies. Pros: Allows you to confirm the presence of specific cytokine proteins. Cons: Time-consuming and less quantitative than other methods.
6. Immunohistochemistry: Detects cytokines in tissue sections using antibodies, providing spatial information about cytokine production. Pros: Allows you to localize cytokines in tissues. Cons: Less quantitative method; More useful for research or confirmation of specific results. [18,21]

Interpretation of the results

Normal and elevated levels of specific cytokines (e.g., IL-4, IL-5, IL-13) compared to baseline or non-allergic control may indicate an allergic reaction.
Cytokine patterns, different cytokine profiles can be observed in different allergic reactions. For example, Th2-associated cytokines (such as IL-4 and IL-13) are often elevated in allergic reactions.
Over time, cytokine levels can change during an allergic reaction, so it is important to determine when to take a sample relative to the onset of symptoms.
Of course, there are several levels of control in the body to over-activate inflammation both in response to pathogens and in the development of allergic reactions to prevent damage to one's own tissues. In the system of cytokine regulation, immunoregulatory and immunosuppressive cytokines, including TGF-β, IL-10, IL-27, IL-35, and IL-37, are responsible for this [4]. They are synthesized mainly by Treg lymphocyte clones and partly by Th2 clones, as well as by some other cells. The role of immunoregulatory cytokines is to maintain a balance in the development of allergic reactions and limit their pathological manifestations leading to tissue damage and severe clinical manifestations. Perhaps it is the violation of this balance that causes the formation of allergies. [19,21]
Cytokine measurements play an important role in research aimed at understanding the mechanisms of allergic reactions and developing new therapies, as well as providing valuable information about the immune response in allergic reactions and can help in diagnosis and treatment.
Advances in genetic and immunological research allow for more detailed profiling of cytokine reactions in patients with drug allergies. This can lead to the development of more advanced diagnostic tools and treatments.
Modern methods of treating allergic diseases are directed against histamine and IgE. Approaches are currently being developed to block Th2 cytokines, including IL-4, IL-13, and IL-31, as well as epithelial cell cytokines, especially IL-33 and thymic stromal lymphopoietin. Other novel targets include histamine-4 receptor, JAK, κ-opioid receptor, neurokinin-1 receptor, and phosphodiesterase-4. [20-21]

Conclusion

Cytokine genes play a central role in the development and progression of drug allergies. They affect the immune system's response to drugs, and genetic variations in these genes can influence a person's susceptibility to allergic reactions. Understanding the role of cytokine genes in the development of drug allergies could lead to better diagnostic tools, personalized medicine, and targeted therapies to prevent or mitigate these side effects Reactions. Different clones of Th2 can contribute to the development of allergies, but the main mediators of the formation and further progression of allergic inflammation in tissues are still Th2. The choice of the direction of differentiation towards Th2 is determined by two main factors: 1) the nature of the antigen belonging to the group of allergens (molecules that are heterogeneous in structure, but common in terms of allergy induction), 2) the genetic characteristics of the individual. Studying how genetic factors, including cytokine gene polymorphisms, affect drug response is a growing field. It aims to reduce adverse drug reactions by tailoring treatments to individual genetic profiles. Common mechanisms of allergic diseases include an increase in the production of IL-4, IL-5, and IL-13, high frequencies of mixed allergic diseases, and the possibility of therapeutic suppression of these ILs by recombinant receptors or humanized monoclonal antibodies.

References

[1] Cytokines in the immunopathogenesis of allergies26 April 2021 Gos.NII OCHB FMBA of Russia, St. Petersburg, Russia The original article was published on the website of the Russian Medical Journal:https://www.rmj.ru/articles/allergologiya/Citokiny_v_immunopatogeneze_allergii/#ixzz8jW 3J6l00 Under Creative Commons License: Attribution

[2] L.L. Leape, T.A. Brennan, N. Laird, A.G. Lawthers, A.R. Localio, B.A. Barnes, et al., The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II, N. Engl. J. Med. 324 (1991 Feb) 377–384.

[3] D.W. Bates, D.J. Cullen, N. Laird, L.A. Petersen, S.D. Small, D. Servi, et al., Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group, JAMA 274 (1995 Jul) 29–34.

[4] J. Lazarou, B.H. Pomeranz, P.N. Corey, Incidence of Adverse Drug Reactions in Hospitalized Patients: a meta-analysis of prospective studies, JAMA 279 (1998)1200–1205.

[5] D.W. Bates, L.L. Leape, D.J. Cullen, N. Laird, L.A. Petersen, J.M. Teich, et al., Effect of computerized physician order entry and a team intervention on prevention of serious medication errors, JAMA 280 (1998 Oct) 1311–1316.

[6] D.C. Classen, S.L. Pestotnik, R.S. Evans, J.F. Lloyd, J.P. Burke, Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality, JAMA 277 (1997 Jan) 301–306.

[7] T. Morimoto, T.K. Gandhi, A.C. Seger, T.C. Hsieh, D.W. Bates, Adverse drug events and medication errors: detection and classification methods, Qual. Saf. Health Care. 13 (2004) 306–314.

[8] E.K. Genco, J.E. Forster, H. Flaten, F. Goss, K.J. Heard, J. Hoppe, et al., Clinically inconsequential alerts: the characteristics of opioid drug alerts and their utility in preventing adverse drug events in the emergency department, Ann. Emerg. Med. 67 (2016) 240–248.

[9] Uzbekistan implements comprehensive measures for allergy prevention and care. https://daryo.uz/en/2023/11/26/uzbekistan-implements-comprehensive-measures-for-allergy-prevention-and-care
[10] Uzbekistan improves the system of providing allergy care to the population. https://www.uzdaily.uz/en/uzbekistan-improves-the-system-of-providing-allergy-care-to-the-population/
[11] Feng H., Feng J., Zhang Z., Xu Q., Hu M., Wu Y., Lu Y. Role of IL-9 and IL-10 in the pathogenesis of chronic spontaneous urticarial through the JAK/STAT signalling pathway. Cell Biochem Funct. 2020; 38 (4): 480–9. DOI: 10.1002/cbf.3481.
[12] Ospelnikova T.P., Morozova O.V. Comparative analysis of cytokines in acute respiratory infections and allergic bronchial asthma. Review. Immunopathology, allergology, infectology. 2019; 4: 28–36. DOI: 10.14427/jipai.2019.4.28
[13] Tetereva V.V., Ospelnikova T.P. Cytokines in chronic urticaria. In the book: "New approaches in the field of microbiology, virology and immunology" within the framework of the international student schools of Sechenov University. Collection of abstracts of young scientists with international participation. Ed. by V.V. Zverev. 2020; 26.
[14] Immune response and pathophysiology of the allergic reaction, Article in German, C H Heusser 1, V Brinkmann https://pubmed.ncbi.nlm.nih.gov/8146808/
[15] Modern assessment of the cytokine status of children with atopic dermatitis by T.V. Vinogradova, A.A. Chuslyaeva, E.E. Varlamov, E.A. Ruzhitskaya, V.S. Sukhorukov, A.N. Pampura https://www.ped-perinatology.ru/jour/article/download/38/71
[16] Branchett W., Lloyd C. Regulatory cytokine function in the respiratory tract. Mucosal Immunol. 2019; 12(3):589–600. DOI: 10.1038/s41385-019-0158-0
[17] Alieva V.Sh., Nazarov A.A., Arifov S.S., Karimov Kh.Ya., Boboev K.T. Analysis of anti-inflammatory cytokine genes associated with the risk of development of atopic allergic rhinitis. // Medical Journal of Uzbekistan - Tashkent. - 2009.- No3 - p.29-31.
[18] Alimkhodjaeva P.R., Karimov Kh.Ya., Muminova S.R., et al. Development of molecular testing systems and analysis of the relationship between the -590C>T polymorphism of the IL4 gene and atopic dermatitis.// Uzbekistan Tibbiyot Journal.- No1.-2012. – pp. 19-21.
[19] Roan F., Obata-Ninomiya K., Ziegler S. Epithelial cell-derived cytokines: more than just signaling the alarm. J Clin Invest. 2019; 129(4):1441–1451. DOI: 10.1172/JCI124606.
[20] Rochman Y., Dienger-Stambaugh K., Richgels P. et al. TSLP signaling in CD4+ T cells programs a pathogenic T helper 2 cell state. Sci. Signal. 2018; 11(521): eaam8858. DOI: 10.1126/scisignal.aam8858.
[21] O.V. Morozova, T.P. Ospelnikova, "CYTOKINES IN ALLERGIC DISEASES" 2022https://doi.org/10.29296/24999490-2022-02-01 file:///C:/Users/User/Downloads/tsitokiny-pri-allergicheskih-zabolevaniyah.pdf