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REVIEW ARTICLE

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Allergy, asthma, and proteomics: opportunities with immediate impact

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Abstract
Allergy is widely discussed by researchers due to its complex mechanism that leads to disorders and injuries, but the reason behind the allergic status remains unclear. Current treatments are insufficient to improve the patient's quality of life significantly. New technologies in scientific and technological development are emerging. For instance, the union between allergy and peptidomics and bioinformatics tools may help fill the gaps in this field, diagnosis, and treatment. In this review, we look at peptidomics and address some findings, such as target proteins or biomarkers that help better understand mechanisms that lead to inflammation, organ damage, and, consequently, poor quality of life or even death.

Introduction

Addressing immune hypersensitivity reflects a quote by Lao Tzu, *"Govern a great nation as you would cook a small fish. Do not overdo it."*

Before discussing allergies, it is essential to comment on the concept of immunology and allergology. Immunology is the study of cellular and molecular components of the immune system. It approaches health and disease as a balanced unit, in addition to the mechanisms that act in recognizing self and non-self-antigens.[1] Allergology is a branch of clinical immunology that evaluates the causes and treatments of allergic hypersensitivity.[1]

The immune response is composed of a complex interaction between cells and molecules generated due to an antigen. It is usually seen as a beneficial response to maintain the balance between the healthy and deleterious dimensions; therefore, the balance protects the organism against pathogens, thus preventing illness.[2] In most cases, it is an effective response, called a secondary response,

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in which T lymphocytes, B lymphocytes, and antibodies participate.[3]

However, in some cases, such as hypersensitivity, this response can damage tissues, causing a strong inflammatory reaction or excessive immune response to the antigen.

Four types of hypersensitivity are classified as I, II, III, and IV. Allergies are type I hypersensitivity, called IgE-mediated hypersensitivity or immediate hypersensitivity.[4]

Atopy is a genetic predisposition that can lead to allergy-related illnesses, such as allergic asthma, atopic dermatitis, food allergy, or allergic rhinitis.[5] These diseases are characterized by an exaggerated immune response to environmental allergens, which usually produce high titers of specific class E antibodies (IgE).[6,7]

Allergic diseases result from a complex interaction between genes and the environment,[8] with the effective participation of cells, cytokines, chemokines, and specific antibodies in this inflammatory response. The main cell involved in the allergy process is a subtype of the T helper lymphocyte (Th lymphocyte), called the Th2 lymphocyte.[9] The Th2 lymphocyte is associated with a change in class B lymphocytes, responsible for producing specific class E antibodies (IgE) against environmental allergens.[9]

However, allergic inflammation goes through some processes triggered after the allergen entry; it prepares the environment for the allergic inflammatory cascade. These processes are characterized as the sensitization phase and the effector phase.

The sensitization phase occurs minutes after the allergen enters through the mucosa or skin, reaching the subepithelial layer.[10,11] There are several populations of antigen-presenting cells (APCs) in this area. For example, immature dendritic cells (DCs) constantly search for an antigen.[12]When faced with the antigen, these cells are activated by receptors to capture and process it, initiating phagocytosis. During phagocytosis, the allergen is processed into small fragments, and DCs begin to mature, migrating to the nearest local lymph node.[13]

When DCs reach the lymph node, they start their presentation process through three signals. The degraded peptide is presented via MHC II to the T cell receptor (TCR), along with the costimulatory molecule (B7-1 or B7-2) for its CD28 ligand and cytokine secretion, for example, IL-2, IL-4, and IL-13, for clonal expansion of CD4+ T lymphocytes and differentiation of naive T lymphocytes into Th2 effector lymphocytes.[13]

IL-4 differentiates naive TCD4 lymphocytes into effector lymphocytes of Th2. At the same time, this population contributes to the activation of immature B lymphocytes in lymph nodes and matures when they capture the antigen and present it to Th2 lymphocytes. This binding increases cytokine secretion, activating B lymphocytes and producing antigen-specific IgE antibodies.

Th2 effector lymphocytes and B lymphocytes activated through the expression of specific receptors (homing) travel to the site of inflammation and the target tissue. Th2 effector lymphocytes are important cytokine secretors at this stage, such as IL-4, IL-5, and IL-13. They help differentiate B lymphocytes into plasma cells to secrete antibodies, which bind to high-affinity receptors, FcεRI, expressed on mast cells in the tissue, sensitizing them. Excessive IgE antibodies are captured by local lymph nodes, which enter the bloodstream and thus can travel to distant tissues. When IgE finds eosinophils and basophils in the blood, they bind to high-affinity receptors on these cells, sensitizing them as well.

The delayed reaction phase occurs approximately 4 to 6 hours after the initial reaction (sensitization) phase. Cells such as eosinophils, sensitized basophils, monocytes, and neutrophils leave the circulation via diapedesis in response to chemotactic factors released during the sensitization phase. Thus, these cells migrate to the target region–where there is a high concentration of allergens–and are activated to perform their destructive effector functions. Eosinophils release platelet-activating factors (PAF), leukotrienes, eosinophilic cationic protein, major basic protein, and cytokines. Basophils release serotonin, while proteases, histamine, macrophages, and neutrophils release leukotrienes, PAF, cytokines, and prostaglandins, leading to tissue damage.

Atopic march is widely discussed in the emergence of allergic diseases. In early life, children can develop clinical symptoms that lead to a gradual progression of atopic diseases. This progression happens classically in a sequence, beginning with the onset of atopic dermatitis, which progresses to food allergy, and eventually to the development of respiratory allergies, such as asthma and rhinitis.[14–16]

Allergic asthma is a complex disease triggered by the interaction between genetic and environmental factors, such as pollution, cigarettes, house dust mites, insect feces, fungal spores, tree pollen, etc. It happens in genetically predisposed individuals who develop strong allergic reactions after sensitization and subsequent contact with the allergen.[17]

Asthma, rhinitis, conjunctivitis, urticaria, atopic dermatitis, contact dermatitis, and food allergy have increased in developed and developing countries.[18] Asthma and other IgE-mediated diseases are significant health problems worldwide.[19]

The World Health Organization estimates that approximately 300 million people worldwide have asthma,[20] and the number of young people and adults affected by this disease continues to rise. The estimated number of asthmatic individuals can reach 400 million in 2025.[21]

The increase in the prevalence of allergic diseases implies a global health problem, as public health systems of all countries have suffered consequences not only at the economic level but also at the social level.[15] Besides having a high prevalence, allergies to aeroallergens also carry a significant economic burden, affecting health care systems and society.[22]

The consequences include many harmful effects, such as unexpected absences from work, low school performance, difficulties in leisure activities in open environments, low self-esteem, and decreased focus.[23]

Camilo-Nunes and Sole described how symptoms of nasal obstruction caused by allergic rhinitis affect adults and children. The obstruction of the air passage causes impacts on learning, cognitive deficit, lack of attention resulting in possible work accidents, and poor sleep quality, causing drowsiness during the day.[24]

Proteomics

Mass spectrometry-based proteomics has become a valuable tool in studying proteins in hypersensitivity with the rapid improvement in chromatography and mass spectrometry equipment and the development of more accurate algorithms for analyzing data. Proteomics helps understand biological processes, and in recent years it has helped researchers discover many potential biomarkers, even though few of them have reached the clinical stage. Important details for the feasibility of the clinical stage include the experimental design and the bottom-up methodology. In this approach, proteins are first digested, and resulting peptides are separated by multidimensional chromatography, then analyzed by mass spectrometry. The results of this process provide a wide proteome coverage. This technique has been successfully used to search for proteomic expression and investigate proteins and their associated interaction partners to verify the participation of T lymphocytes, B lymphocytes, and antibodies.

There are also several studies investigating endotypes to seek information through the characterization of the mechanisms that lead to asthma. Hannah Wangberg and Katherine Woessner studied asthma endotypes and phenotypes to understand their mechanisms for better management in clinical practice with the use of biological therapies.[25]

Some criteria are needed in the search for biological therapy, and it is important to consider the identification of endotypes and phenotypes. Phenotypes are observable characteristics resulting from the genotype expression plus the interaction with the environment. Endotypes are mechanisms in the pathophysiology of diseases. Asthma endotypes present two distinct characteristics, being called Th2-high and Th2-low.[25]

Th2-high is usually associated with eosinophilic airway inflammation, and about 50% of asthmatics have it.[26] It has Th2 lymphocytes, eosinophils, and mast cells, with cytokine profiles IL-4, IL-5, IL-9, and IL-13. Laboratory biomarkers include positive prick test and total IgE, and specific IgE. Current therapies are immunobiological agents targeting IL-5, effectively treating asthma.[25] Th2-low causes inflammation with neutrophilic infiltrate in the airways, usually associated with late manifestations of the disease and corticosteroid-resistant diseases.[27,28] It does not show eosinophils in the airway, and there is high activation of Th1 and Th17 lymphocytes. Cytokines include IFN, TNF-α, IL-1, IL-6, IL-8, IL-17, IL-25 and IL-33.[26-29] Even though there are several Th2-low endotypes, little is known about them. Thus, the treatment for this endotype is still a challenge. These two types of endotypes are often present in inflammatory crises. Th2-high has more control and treatment resources, while Th2-low still does not have an effective treatment that leads to control, thus causing patient suffering.

Researchers have searched for treatment for severe asthma, that is, an adequate biological therapy, to find the ideal treatment for each case. Currently, the most used treatment is anti-IL5 therapy, which targets IL-5 with immunobiological drugs, such as anti-IL5 monoclonal antibodies for the eosinophilic inflammatory pathway, like mepolizumab, reslizumab, or selective blocking antibody of the IL-5 receptor, benralizumab.[30,31] The treatment for severe asthma is still limited to anti-IL5, so broader knowledge is necessary to expand the range of tools and new strategies for the effective treatment of asthma. Researchers should explore the omic sciences, biomarkers to help understand the phenomena that worsen the disease, and more personalized treatments.

Proteomic Tools and Work Strategy

Biochemical techniques provide rich information about the physiology of individual cells regarding individual proteins, their structure, function, location within a cell, and their participation in protein complexes and functions. Combining this knowledge with information from systems biology can broaden the perspective of cell physiology under specific conditions. Furthermore, systems biology approaches include several techniques that investigate the average population of proteins within a cell as well as their possible modifications and functions.

The most studied techniques in hypersensitivity are expression proteome and functional proteome. The expression proteome consists of cells' entire set of proteins, while the functional proteome examines protein-protein interactions to uncover all the functional pathways expressed.[32] Based on these definitions, proteomics studies and identifies the total number of proteins expressed in a given sample under certain physiological conditions. Mass spectrometry has emerged as a powerful experimental tool for investigating proteomes in hypersensitivity due to its high sensitivity and ability to identify a large percentage of proteins present in complex mixtures, such as blood.

However, even though there are ample possibilities for analysis by different proteomics techniques, the most used technique for hypersensitivity is the shotgun technique through the bottom-up methodology. This term derives from shotgun DNA sequencing,[33] a method in which proteins in a complex mixture are digested with proteases to produce a mixture of peptides for sample injection. Peptides within this mixture are separated, allowing the precise identification of the corresponding proteins from which they were derived after bioinformatics analysis.[34-36] Individual peptide sequences can be derived by comparing the peptide ion fragmentation pattern with theoretical spectra from a database available.[37,38]

Database search algorithms such as SEQUEST[34] and MASCOT[33] can then compare raw spectra with theoretical spectra derived from *in silico* to different digest protein sequences, providing scores for each match available. Next, programs such as DTASelect[39] filter and sort the output from the search algorithm's data, gathering the final protein lists in an easy-to-read format. Regardless of the type of experiment performed, the quality of the raw data collected affects the ability of search algorithms to make accurate identifications. When searching an entire proteome, such as blood samples, a large amount of data is acquired, and the possibility of false positives is high. Studies have been conducted to address the issues of quality optimization of data inserted into search algorithms,[40-44] and filter level optimization to ensure quality data output after searches.[45]

Peptidomics for Allergy

"Omics" projects aim to study a given biological sample's complete characteristics through experiments. Although genomics has affected molecular biology[46,47] and medicine,[48] the information encoded by the genome fails to describe the dynamics of important processes that occur in cells and organisms.

The combination of data from large peptidomics projects and sophisticated bioinformatics tools offer great perspectives for the rapid discovery of diagnostic and therapeutic targets and for understanding the pathophysiological mechanisms involved in any disease.[49,50]

In the field of allergy and asthma, cytokines and chemokines,[51,52] small peptide mediators released from effector cells,[53] and peptides bound to MHC I and II[54] play a central role in pathogenesis. Peptidomics has great potential for analyzing the concentration of known peptides in biological samples[55] and discovering new immunogenic peptides for celiac disease and wheat allergy.[56]

The discovery of peptidomics biomarkers in body fluids, cell cultures, and animal models[57-59] shows the power of technology, which is particularly suited for investigations in the field of immunology.[57,60,61] The first reports of quantitative profiles of plasma peptides were made in mice with asthma.[62] These results identified disease-associated humoral antigens[63] and pathways of activated platelet-derived growth factors in human asthmatic lung-derived mesenchymal cells,[64] indicating the peptidomics potential for allergy and asthma research. The most significant advances in treatment were observed only for celiac disease, regardless of the wheat genotype.[65] Thus, making predictions about future developments in the field of peptidomics is an imperative task.

Conclusions

The technology for gene sequencing has reached a high level of maturity, allowing the obtention of entire genomes in a short time.[66] However, genome information alone is insufficient to understand the relationship between phenotype and genotype since approximately 100,000 proteins are expressed by about 20,235 genes in humans, showing the complexity of the proteome study.[67,68] The identification and analysis of proteins using methods based on mass spectrometry have become an interesting approach in hypersensitivity, complementing traditional techniques in biochemical and molecular biology research.[67,68] Proteomics has also been used to search for new biomarkers of allergic diseases. However, its use in clinical diagnosis is still limited, given the difficulty of validating these methods in a significant sample population.[68,69]

Given all the concepts and research in allergy, further studies are necessary to understand the mechanism of allergic crises resulting in disease development. From this perspective, we propose using proteomics to help understand this mechanism in the face of a more in-depth study of the analyses of proteins and peptides. There is a lot to be discovered regarding the mechanisms that trigger allergy. Above all, it is important to add proteomic techniques to this analysis, which can contribute to the discovery of biomarkers, the search for target molecules, a more accurate diagnosis, and the development of treatment options.

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