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RESPIRATORY ALLERGIES AND IMMUNOTHERAPIES: THERAPEUTIC MECHANISM AND EFFICACY

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Abstract: Immune dysfunction in the body can trigger a wide range of pathological conditions, such as allergic reactions. Asthma and allergic rhinitis are the main respiratory allergies, affecting millions of people. Immunotherapy acts as an effective treatment against respiratory allergies, aiming to stimulate or suppress the immune system to treat specific diseases. The aim is to determine the theoretical basis for the current treatment of respiratory allergies with regard to the use of immunotherapies. This chapter uses an exploratory and descriptive qualitative research with an integrative literature review on immunological therapies. The inclusion criteria were original, peer-reviewed articles focusing on immunological therapies for respiratory allergies, published between 2015 and 2024, in Portuguese and English, with full access. Duplicate articles and those without clinical relevance were excluded; after screening, 14 articles were selected for final analysis. The studies analyzed show that asthma and allergic rhinitis are the main respiratory allergies in the world, with a strong relationship, since rhinitis can develop into asthma. These allergies are characterized by a type I hypersensitivity reaction mediated by IgE. Specific immunotherapy acts as an alternative to treating these diseases, as it reduces the sensitivity of the immune system to specific allergens, working like an allergen vaccine, promoting immune desensitization and reducing the inflammatory response. Its efficacy has been proven in reducing symptoms and preventing the progression of the disease, with a high potential for improving the quality of life of allergic patients.
Keywords: allergy; respiratory; immunotherapy; treatment

INTRODUCTION

The immune system is a complex and dynamic set of interconnected biological processes responsible for defending the body against pathogens and potentially harmful substances. It plays a crucial role in maintaining homeostasis and protecting the body against invading agents (Abbas, 2021).

Immune dysfunction in the body can trigger a wide range of pathological conditions, such as allergic reactions. In allergies, there is a hypersensitive and disproportionate response to harmless antigens, such as dust or pollen, mediated mainly by cells such as mast cells and eosinophils (Murphy; Weaver 2016).

Allergies are type I hypersensitivity reactions measured by immunoglobulin E (IgE). Around 30% of the world's population is affected by IgE-mediated allergies. Such allergies can affect the respiratory tract, skin and gastrointestinal tract, causing acute systemic reactions that can lead to death. Symptoms result from sensitization to a variety of allergens, and molecular diagnosis is a means of determining the allergens that cause the disease in order to contribute to prevention and treatment, with specific strategies aimed at non-exposure to the allergen, vaccination and tolerance induction (D'Souza *et al*., 2021).

In the context of respiratory allergies, asthma and rhinitis are the main ones. Asthma is characterized by inflammation, hyper-responsiveness and remodelling of the airways. It is a chronic inflammatory disease of the airways that affects millions of people worldwide and manifests itself with variable symptoms such as coughing, wheezing, chest tightness and difficulty breathing. Allergic rhinitis, on the other hand, can present as symptoms: nasal congestion, rhinorrhea, itching and sneezing. It has a high prevalence worldwide and is considered a risk factor for developing asthma (Segato, De Azeredo Coutinho and Da Rocha Sobrinho, 2024; Rosa, 2016).

In recent decades, immunopharmacology has evolved considerably, with the advent of immunotherapy, aimed at stimulating or suppressing the immune system to treat specific diseases. In this context, specific immunotherapy is defined as a treatment for allergic diseases using a vaccine of allergens, the same allergens that cause the allergy (Rosa, 2016).

This boosts human immunity, reducing sensitivity to certain substances. Immunotherapy is therefore characterized as a desensitization technique in special cases where there is no possibility of not being exposed to allergens and in situations where treatment is refractory (Blaiss *et al.,* 2024).

Therefore, this chapter will cover the main cutting-edge immunotherapies, reviewing their applications in relation to the treatment of allergies. Therefore, the aim of this chapter is to determine the theoretical basis for the current treatment of respiratory allergies with regard to the use of immunotherapies.

METHODS

This chapter is a qualitative exploratory and descriptive study using an integrative review of the scientific literature. The exploratory approach seeks to map and clarify concepts related to new immunological therapies, while the descriptive approach details the mechanisms of action, efficacy and limitations of these therapies based on the theoretical analysis of relevant studies.

Secondary sources extracted from the PubMed scientific database were used for data collection. The keywords used in the Health Sciences Descriptors (DeCS) in English were: *"allergy," "respiratory," "immunotherapy," and "treatment."* In addition, a manual search was carried out on academic internet search engines using the same descriptors in Portuguese: "allergy," "respiratory," "immunotherapy" and "treatment." Only the Boolean operator "AND" was used.

The inclusion criteria considered original articles and peer-reviewed studies on immunological therapies for respiratory allergy that had full access to the content, published in the last ten years, from 2015 to 2024, in English and Portuguese.

Duplicate articles and those that did not show clinical therapeutic application or direct applicability to the understanding of new immunological therapies were excluded after analyzing the title and abstract.

Initially, a search was carried out in the selected databases, and 86 articles were found. After excluding duplicate articles and reading the titles and abstracts of the articles found, 53 were excluded that were not related to the subject matter, and after reading the full text, 14 articles were chosen.

In this way, the proposed methodology aims to offer a comprehensive and critical understanding of recent discoveries in immunopharmacology, contributing to the theoretical and practical foundation of this field of research.

RESULTS AND DISCUSSION

After reading in full and analyzing the immunotherapies available for the treatment of respiratory allergies, the following nuclei of meaning were identified: 1) Main respiratory allergies and their immunological mechanisms and 2) Specific immunotherapies: mechanism of action and benefits in the treatment of the main respiratory allergies.

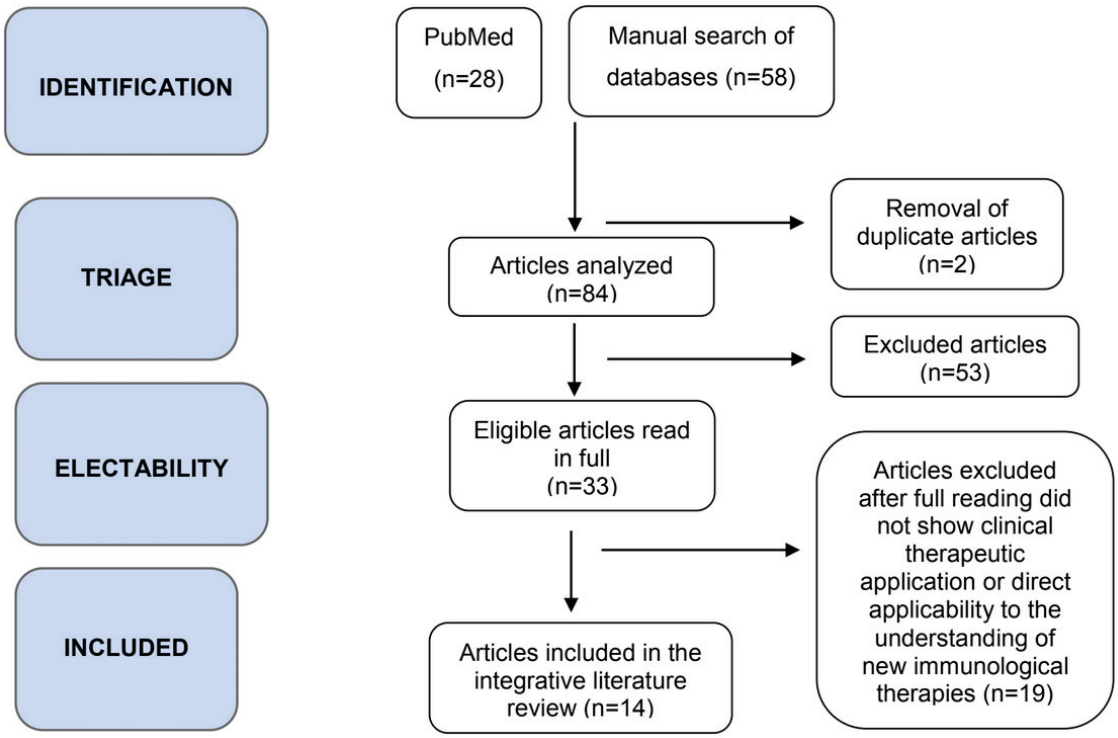

Figure 1. Flowchart for selecting studies for the integrative review.

Source: Own authorship.

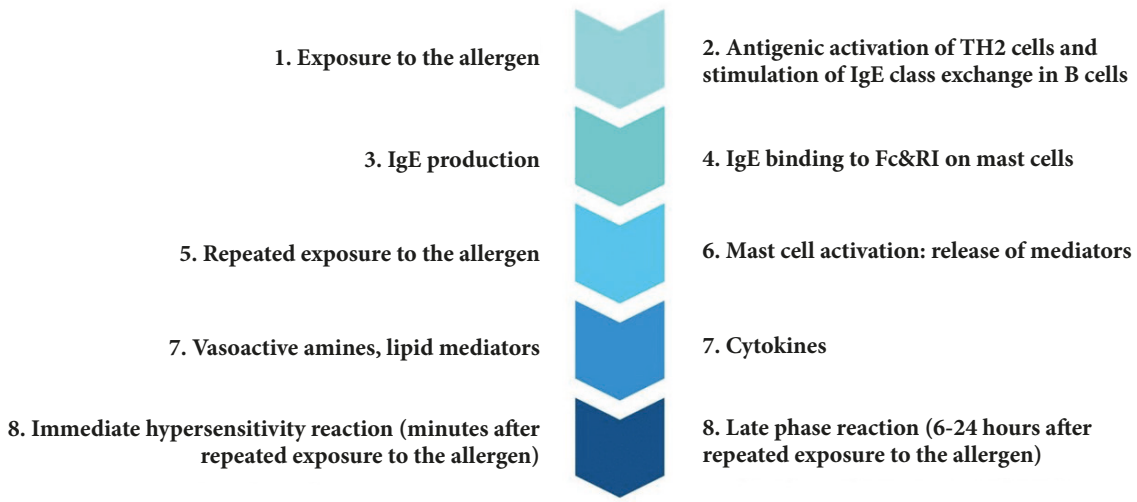

Figure 2: Type I hypersensitivity reaction mechanism.

Source: (Abbas, 2021)

MAIN RESPIRATORY ALLERGIES AND THEIR IMMUNOLOGICAL MECHANISMS

The most common form of immunological hypersensitivity is allergy mediated by immunoglobulin E (IgE), also known as type 1 hypersensitivity, which affects more than 30% of the world's population and has a variety of symptoms, such as rhinitis, asthma, atopic dermatitis, gastrointestinal allergy and, in severe cases, anaphylactic shock (D'souza *et al*., 2021).

According to D'Souza *et al.* (2021), allergic sensitization begins in childhood and, due to genetic factors and exposure to the allergen, can evolve from asymptomatic sensitization to mild symptoms and, eventually, to serious conditions. Generally, allergies begin silently and the main types are respiratory allergies such as asthma and rhinitis.

Asthma is characterized by inflammation, hyper-responsiveness and remodelling of the airways. It is a chronic inflammatory disease of the airways that affects millions of people worldwide and manifests itself with variable symptoms such as coughing, wheezing, chest tightness and difficulty breathing (Segato, De Azeredo Coutinho and Da Rocha Sobrinho, 2024).

Asthma is differentiated into two main phenotypes: allergic asthma, which usually begins in childhood, is IgE-mediated and associated with eosinophilic inflammation; and non-allergic asthma, which often begins in adulthood and is associated with immunosenescence and factors such as viral infections and obesity. The diagnosis is usually confirmed by spirometry with bronchodilators, which assesses the reversibility of airway obstruction (Segato, De Azeredo Coutinho and Da Rocha Sobrinho, 2024; Zhao *et al.*, 2021).

Allergic rhinitis is another clinically important respiratory allergy, characterized as inflammation of the nasal lining mucosa, caused by an inflammatory reaction mediated by IgE, eosinophils, the Th2 response and inflammatory cytokines (IL-4, IL-5 and IL-13). Symptoms include nasal congestion, rhinorrhea, itching and sneezing. The high prevalence of rhinitis worldwide designates it as a risk factor for developing asthma, impacting on the quality of life of those affected (Rosa, 2016).

In this sense, it is understood that both asthma and rhinitis have an inflammatory process as their pathophysiological mechanism, which is the result of a hypersensitivity reaction. The immunological mechanism of this reaction begins with the sensitization of the individual, initially there is exposure to the allergen (dust mites, pollen, dander and others), this allergen is presented to the immune system by the antigen presenting cells (APCs). With this, Th2 lymphocytes are activated and produce cytokines, which activate B lymphocytes that produce specific IgE for a specific allergen (Medeiros *et al.*, 2021).

Allergen-specific IgE is associated with high-affinity IgE receptors located on mast cells. Upon a second exposure to the allergen, molecules bind to the IgE present on the mast cells of the nasal mucosa, resulting in degranulation and the release of chemical mediators such as histamine, which causes the cardinal symptoms of allergic rhinitis: sneezing, obstruction, rhinorrhea and nasal itching. This is because histamine stimulates vasodilation, gland secretion and increased blood vessel permeability (Li and Luo, 2020; Medeiros *et al.*, 2021).

In asthma, this increase in epithelial permeability leads to greater access of particles to the submucosal compartment and the systemic circulation, which allows the entry of internal or external components that access the submucosal innate immune cells and blood vessels, promoting sensitization and pro-inflammatory response of the mucosa, with abnormal repair of the bronchial airways, hyperreactivity and remodeling (Segato, De Azeredo Coutinho and Da Rocha Sobrinho, 2024).

Thus, given the global problem, advances in immunopharmacology have been necessary, the main one being the advent of immunotherapy, aimed at stimulating or suppressing the immune system to treat specific diseases, such as asthma and rhinitis.

SPECIFIC IMMUNOTHERAPIES: MECHANISM OF ACTION AND BENEFITS IN THE TREATMENT OF THE MAIN RESPIRATORY ALLERGIES

Immunotherapies aim to reduce the sensitivity of the immune system to specific allergens. Before understanding the main immunotherapies developed for the management of asthma and allergic rhinitis, it is necessary to understand the therapeutic management of these diseases (Dhami *et al.*, 2017).

Currently, standard asthma treatment includes the use of inhaled medications, such as β2-agonist bronchodilators and corticosteroids. This treatment aims to relieve muscle constriction and inflammation in the airways, mainly with the use of short- and long-acting beta 2 agonists (SABA and LABA), inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) (Fosrtescue, Kew and Leung, 2020; Santini *et al.*, 2023).

For severe allergic asthma, biological therapies such as omalizumab (anti-IgE) are already widely used and new therapies that block IL-5 and IL-4/IL-13 receptors have shown promise in reducing exacerbations and improving patients' quality of life (Segato, De Azeredo Coutinho and Da Rocha Sobrinho, 2024).

In the case of allergic rhinitis, effective prevention or symptom relief is the proposed treatment. For prevention, it is necessary to avoid contact with allergens, in addition to which pharmacological measures can be used. This pharmacological management consists of nasal lavage with saline solution or topical or oral anti histamine in association, sometimes, with low doses of corticosteroids. Antihistamines are effective in relieving the clinical manifestations: nasal itching, sneezing, rhinorrhea and associated eye symptoms, as well as nasal blockage (Luz *et al.*, 2022; Medeiros *et al.*, 2021).

In this context, specific immunotherapies have emerged as an alternative to traditional treatment. Defined as an allergen vaccine, they aim to increase the patient's immunity through desensitization. It is effective for the prophylaxis of IgE atopy, acting to decrease IgE antibodies and reducing immediate symptoms. In addition, it interferes with the inflammatory process, making it useful for treating rhinitis and asthma (Rosa, 2016; Blaiss *et al.*, 2024).

The therapy consists of administering various, gradual and increasingly concentrated doses of allergen extracts, which are applied regularly over a long pre-established period of time, ranging from one to five years. This is done until the patient develops clinical tolerability to the allergy triggers (Rosa, 2016; Blaiss *et al.*, 2024).

The main mechanism of action of immunotherapy is to increase the production of IgG antibodies specific to the allergen, especially igG4 antibodies. These antibodies bind to the allergen and have a blocking action, preventing it from binding to IgE in mast cells and basophils, preventing the release of inflammatory mediators and, consequently, the allergic cascade (Fosrtescue, Kew and Leung, 2020).

In addition, immunotherapy also reduces the expression of IgE receptors on effector cells, reducing mast cell and basophil reactivity and increasing the amount of IgA, which strengthens respiratory defense. Another important mechanism is the change from a Th2 to a Th1 profile, which leads to an increase in anti-inflammatory cytokines such as IL-2, IL-12 and INF-γ and a decrease in pro-inflammatory cytokines such as IL-4, IL-5 and IL-13. With treatment, there is a significant decrease in mast cells, basophils and eosinophils in the inflamed areas, reducing the inflammatory response and allergic symptoms in the airways (Rosa, 2016).

One of the main obstacles to the therapeutic success of immunotherapy is that patients generally have hypersensitivity to several allergens, making it difficult to identify the allergen for the vaccine. The preferred route of administration is subcutaneous (Kristiansen *et al.*, 2016).

Currently, some studies have emerged on sublingual immunotherapy (SLIT), which is a therapy that aims to reduce asthma symptoms by administering progressively higher doses of an allergen (such as house dust mite or pollen extract) under the tongue in order to induce immunological tolerance. However, due to the scarcity of evidence on its effectiveness in important outcomes, as well as the limited and inconclusive evidence, it is not usually recommended as a stand-alone treatment for asthma, proving to be relatively safe only for people with well-controlled mild to moderate asthma and other respiratory allergies (Fosrtescue, Kew and Leung, 2020).

Thus, allergen-specific immunotherapy is an effective treatment capable of altering the natural history of allergies, and in some situations, it can even promote a cure. It prevents the progression of rhinitis to asthma, reduces sensitization to new allergens and reduces the symptoms of rhinitis and asthma, promoting a better quality of life for the allergic patient (Li and Luo, 2020).

CONCLUSION

The studies analyzed show that asthma and allergic rhinitis are the main respiratory allergies in the world, with a strong relationship, since rhinitis can develop into asthma. These allergies are characterized by a type I hypersensitivity reaction mediated by IgE.

Asthma is managed with bronchodilators and inhaled corticosteroids, as well as biological therapies such as omalizumab for severe cases. In allergic rhinitis, treatment involves abstaining from allergens and using antihistamines and corticosteroids to control symptoms.

Specific immunotherapy acts as an alternative to treating these diseases, as it reduces the sensitivity of the immune system to specific allergens, working like an allergen vaccine, promoting immune desensitization and reducing the inflammatory response. Its efficacy has been proven in reducing symptoms and preventing the progression of the disease, with a high potential for improving the quality of life of allergic patients.

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