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Review Article

Re-Print: New Perspectives in Immunotherapy: The importance of Dendritic Cells in Allergen-Specific Immunotherapy

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Abstract:

Allergen-specific immunotherapy is the only treatment capable of altering the natural course of the allergic disease. Clinical trials show that immunotherapy is safe and effective for many patients. However, it still faces problems related to efficacy, safety, long treatment duration and low patient adherence.

Contrary to what was imagined, the shift in immunity from Th2 to Th1 is not the key to successful treatment. Recent advances in the knowledge of Treg and Breg cells and tolerance mechanisms have been essential to explain the immunological changes resulting from immunotherapy.

In this context, there has been intense research into the development of adjuvants with the aim of increasing safety, optimizing treatment regimens and improving patient adherence. Allergens were modified (glycoconjugates) with carbohydrates derived from Saccharomyces Cerevisae to increase their uptake and presentation through carbohydrate receptors present in Dendritic Cells, benefiting from the ability to act in inducing tolerance to initiate immune responses.

Dendritic cells are the most professional antigen presenters of the APC system. They represent the bridge between innate and adaptive immunity and are capable of initiating and maintaining immune responses. In light of new evidence, they constitute a key therapeutic target to obtain an adequate response to allergen-specific immunotherapy with the potential to contribute to innovation in the field of immunotherapy.

Key words: paget's disease; breast, DCIS, eczema, ulceration, case report

Introduction

Although allergic diseases can be controlled by the administration of symptomatic medications or emergency medications, Allergen-specific immunotherapy is the only curative treatment option for allergic diseases with efficacy and safety described by several studies and meta-analyses [1,2].

Its limiting factors are the long duration of treatments, costs, low patient adherence and the risk of serious, life-threatening adverse reactions during allergen-specific immunotherapy.

The development of immunotherapy with modified allergens, with lower allergenicity and high immunogenicity, as well as in combination with new adjuvant molecules and through new routes can shorten the duration of treatment and possibly reduce these disadvantages [3].

Mechanisms of Allergen-Specific Immunotherapy

Contrary to what was previously imagined, the shift in immunity from Th2 to Th1 is not the key to successful treatment. Recent advances in the knowledge of Treg and Breg cells and peripheral tolerance mechanisms were essential to explain the immunological changes resulting from immunotherapy.

For many years it was believed that immunotherapy would induce a shift in immunity from Th2 to Th1, through the reduction of IL-4, IL-5 and IL-13 levels and a consequent increase in IFN-γ. However, this theory was unable to fully explain why individuals undergoing immunotherapy did not have a higher incidence of diseases related to the Th1 lymphocyte population [4].

In 2004, the first studies appeared demonstrating the participation of regulatory T cells in the mechanism of allergen-specific immunotherapy. Since then, the induction of immunological tolerance has become the main target in the prevention and treatment of diseases related to immune system dysfunction, such as allergies. [5]

Subsets of cells with regulatory capabilities are induced during Allergen-Specific Immunotherapy. IL-10 and TGF-beta factor are the main suppressive cytokines, in addition to surface molecules such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1). within the microenvironment. Modified T and B cell responses and antibody isotopes, increased activity thresholds for eosinophils, basophils and mast cells and the consequent limitation of inflammatory cascades induce and maintain a state of sustained allergen-specific unresponsiveness. Established tolerance is reflected in clinical perspectives as an improvement in allergic symptoms, along with a reduction in the need for medications and the evolution of disease severity. [5]

New adjuvants

Allergen-specific immunotherapy is the only treatment capable of altering the natural course of the allergic disease. Clinical trials show that immunotherapy is safe and effective for many patients; however, it still faces problems.

Despite all the developments over more than 100 years, immunotherapy with allergen extracts is often not convenient for patients due to disadvantages such as multi-year treatment regimens, concerns about efficacy, treatment safety, and the longevity of induced effects. . For some allergies, immunotherapy is still only partially effective and may be hampered by unwanted side effects. Therefore, many research activities aim to improve immunotherapy by generating new vaccine candidates and adjuvants that increase efficacy while decreasing unwanted adverse effects. [6]

In recent publications, based on an extensive literature review, current innovative approaches were highlighted with the aim of increasing safety, maintaining or even increasing efficiency, improving treatment regimens in immunotherapy with allergens. To increase the effectiveness of immunotherapy, allergens were coupled to immunostimulating substances and new adjuvants were introduced. Allergens have been modified to increase their uptake and presentation. Hypoallergenic molecules have been developed to improve the safety profile of vaccines. Peptides derived from allergens, recombinant allergens, receptor agonists and other adjuvants, among which we highlight the new adjuvants obtained from Saccharomyces Cerevisae. [7,8].

Mannan from Saccharomyces Cerevisae is a polysaccharide consisting of mannose residues derived from the fungus. The potential of mannan as an adjuvant for the treatment of different diseases was presented by studies demonstrating greater maturation of DCs and antigen presentation, as well as immune responses obtained with the conjugation of the polysaccharide. [9,10] Conjugation of carbohydrates to allergens is a well-described approach to target antigen-presenting cells and render the conjugated allergen hypoallergenic. [11]

Mannan (Saccharomyces Cerevisae) has been used in several studies to target allergens to antigen-presenting cells. Weinberger and colleagues demonstrated that mannan conjugates were efficiently taken up by DCs in vivo, inducing a switch from IgE to IgG production. [11] The strategy conjugates antigens (from mites, grass pollens, etc.) with a carbohydrate source (mannose) extracted from the cell wall of a known yeast called Saccharomyces Cerevisae composed of 3 main structures (Mannan, Chitin and Glucan) and It is well described in current literature. [12]

Targeting antigens to dendritic cells to increase cellular uptake has the potential to result in more effective and efficient immunotherapy. Mannan-coupled antigens from Saccharomyces Cerevisae, as a source of mannose, are suitable for this purpose, since mannose-binding receptors are expressed on these cells. [12]

APC System - Dendritic Cells – CLRs

Glycoconjugate preparations, rich in mannose from Saccharomyces Cerevisae, target Dendritic Cells as a therapeutic target. These are formulations that benefit from the carbohydrate receptors present in DCs. They are aimed at CLR agonists, in which the adjuvant acts both as an immunostimulant and as an antigen delivery vector system – directing allergens to greater absorption by dendritic cells (DCs).

Described by 2011 Nobel Prize-winning immunologist Ralph Steinmen, dendritic cells are the most professional antigen-presenting cells of the APC system. They are located in all lymphoid tissue, primary and secondary lymphoid organs and in the blood. They are responsible for initiating and maintaining immune responses. [13]

Glycoconjugated antigens (Saccharomyces Cerevisae) represent vaccines suitable for Allergen-specific Immunotherapy with a growing number of relevant publications and may be of extreme relevance for the development of therapeutic interventions in other diseases related to immunological tolerance. [14] They induce potent blocking antibodies and are captured by human DCs much more efficiently than native antigens that depend on non-integrin-mediated internalization of the mannose receptor and specific dendritic cell. Activate human DCs to generate functional FOXP3 Treg cells through PD-L1. [14] These effects of the adjuvant can be explained by its ability to activate C-type Lectin receptors, pattern recognition receptors normally expressed on DCs. [14]

Glycoconjugated antigens form an antigen-mannose complex and these complexes are, therefore, more easily captured and internalized. From this moment on, dendritic cells, in the presence of IL-10, activate and transform into the tolerogenic phenotype towards the formation of a new population of tolerant Treg cells. [15] Glycoconjugation has been shown to promote a generation of tolerogenic DCs with the ability to induce FOXP3, functional Tregs both in vivo and in vitro. It is observed that the presence of alum impairs the tolerogenic properties of allergenic vaccines with glycoconjugated antigens (Saccharomyces Cerevisae).[16]

Mannose Antigen - Internalization and Activation

Although there is evidence for the conjugation of carbohydrates to allergens (glycoconjugation) and the source of Saccharomyces Cerevisae is easily found in Brazil, the use of the adjuvant rich in mannose Mannan (Saccharomyces Cerevisae) is linked to an international patent (INMUNOTEK - Spain). However, there are other carbohydrate structures in the cell wall of Saccharomyces Cerevisae as a source of obtaining mannose, through which the general principle of glycoconjugation of antigens to mannose (Saccharomyces Cerevisae) can be transferred.

Saccharomyces Cerevisae (native) preserves its macrostructures (Chitin, Glucan and Mannan). The cell wall structure of Saccaromyces Cerevisae consists mainly of chains of glucose residues and mannoproteins. Even with a high degree of purity, the yeast Betaglucan fraction presents a fraction rich in mannose with short or long chains with a high concentration of mannose. In this way, glycoconjugation with this fraction of Saccaromyces Cerevisae is capable of maintaining its carbohydrate structure (mannose, glucose) intact and its potentially associated tolerogenic properties, with adjuvant capacity for targeted delivery of the allergen to dendritic cells (DCs).

Differences, safety and effects in immunotherapy

In the past, the scheme of polysaccharides in immunotherapy using one of the fractions of Saccaromyces Cerevisae rich in mannose was the subject of study in a publication by Revista ASBAI (Polysaccharides application in immunotherapy methods - Rev. bras. alerg. immunopatol. 2002). In the article, it was described as experimental, although the authors considered the practice promising.

Currently, studies demonstrate that glycoconjugates (Saccharomyces Cerevisae) target DCs via the mannose receptor and DC-SIGN, increasing allergen uptake, increasing IL-10 production and PD-L1 expression and promoting the generation of FOXP3 functional allergen-specific Treg cells, both in vitro and in vivo, which is impaired by conventional alum adjuvant.[16]

In a recent review, it was also demonstrated that these conjugates reprogram monocyte differentiation and generate tolerogenic DCs through epigenetic and metabolic rewiring. Overall, unprecedented molecular mechanisms by which these glycoconjugates can restore allergen tolerance during Allergen-Specific Immunotherapy have been discovered. [17]

Conclusion and future perspectives

Although schemes using polysaccharides, currently best described as glycoconjugated antigens with mannose from Saccharomyces Cerevisae, in immunotherapy have been poorly understood in the past, today there are several international studies that support their use in immunotherapy with allergens and a new and important evolution in the field of immunotherapy. , with benefits superior to native antigens.

The fundamental role of dendritic cells stands out from the current literature, which, after capturing and internalizing antigens, activate the tolerogenic phenotype towards T cells – a fundamental mechanism of specific allergen immunotherapy. Studies demonstrate benefits in improving safety and optimizing the therapeutic regimen, as well as in greater promotion of tolerant cells (Treg). [15]

All this absorption of DCs increases bioavailability and absorption, improving the dosage schedule, with suppression of the induction phase and more spaced applications, with intervals every 5 weeks. Vaccines for pollen and dust mite allergies have already been developed, but the same concept is also being studied for other allergens, including peanuts. [15]

Glycoconjugated antigens (Saccharomyces Cerevisae), represent, according to their authors, a new generation of allergen vaccines, optimize the uptake of allergens by Dcs, increase the bioavailability of the doses administered while promoting safe immune responses. [15]

In light of this new evidence, we understand the immunostimulating action and the vector system for delivering allergens to DCs enhanced by the glycoconjugation of antigens to the mannose-rich adjuvant from Saccaromyces Cerevisae and its potential contribution to innovation in the field of immunotherapy.

Conflict of interest and Author's notes.

Dr Maria Angela Vigoritto – No conflict of interest.

Gustavo Pradez declares conflict of interest.

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