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Review Article

New Perspectives in Immunotherapy: Dendritic Cell Training for Recurrent Respiratory Tract Infections

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Abstract:

Specific allergen immunotherapy (AIT) is the only treatment option currently available that has a disease-modifying effect which persists after treatment is stopped. Recent advancements involve using adjuvants with glycoconjugated allergens derived from Saccharomyces cerevisiae to enhance AIT by improving allergen immunogenicity and directing immune responses towards Th1 or regulatory profiles. Novel studies have also demonstrated that these glycoconjugates induce long-lasting epigenetic changes in dendritic cells (DCs), initiating a trained immunity effect that extends protection against subsequent microbial exposures in a process referred to as trained immunity. This process not only broadens the immune response to target antigens but also provides an enhanced response to subsequent microbial challenges, representing a significant breakthrough in the treatment of recurrent or multiple infections. Moreover, respiratory tract infections, among the most frequent causes of illness worldwide, often rely on antibiotics for management, despite many being of viral origin. The rampant abuse of antibiotics has led to an unstoppable growth in multidrug resistance, underscoring the urgent need for new strategies to provide an effective and safe alternative for managing recurrent respiratory tract infections (RRTIs).

Key words: specific allergen immunotherapy; recurrent respiratory tract infections; dendritic cells

Introduction

The immune system is traditionally divided into innate and adaptive responses, with the former providing rapid, non-specific defense mechanisms that do not confer long-term immunological memory, and the latter providing antigen-specific responses that do [1].

For a long time, it was thought that only adaptive immunity had immunological memory. The innate immune system is a coded system that is not capable of carrying genetic memory through cell division. Consequently, it was considered that the functions of the innate immune system were only associated with the acute non-specific elimination of pathogens, either by cellular mechanisms such as phagocytosis or by humoral processes such as the complement system. Recent discoveries in immunology have challenged this dichotomy, introducing the concept of "trained immunity" as a form of memory within the innate immune system [2].

However, the paradigm shift in recent years in the face of a series of discoveries has proven that the cells of the innate immune system are also capable of undergoing long-term adaptations and acquiring a greater capacity to respond to certain stimuli, a process that has been termed immune training, which is based on the long-term reprogramming that the cells of the innate immune system, such as monocytes, macrophages and NK cells, undergo after infection or immunostimulation [2,3].

This process involves epigenetic, transcriptional, and functional changes in innate immune cells upon their first encounter with a pathogen, enhancing their readiness and response to subsequent exposures.For example, training with b-glucan, a component of the walls, induces greater protection against bacterial infections caused by Staphylococcus aureus [4].

In this review, we will focus on the most recent and relevant advances that provide new insights on innovative strategies to exploit trained immunity in dendritic cells (DCs) responses to recurrent respiratory tract infections, a significant burden on global health.

Trained immunity and Pattern Recognition Receptors (PRRs)

Innate immunity is characterized by a rapid response to aggression regardless of the previous stimulus, which is non-specific and does not generate immunological memory. Adaptive immunity is characterized by

an antigen-specific immune response that generates immunological memory. It is known that both acts together, however, it has been observed that some organisms do not have adaptive immunity, although they do have immunological memory. [1]

"Trained immunity" is an immunological memory phenomenon linked to the innate immune system, given by the first encounter between a pathogen and classical innate immune cells, triggering cellular changes at an epigenetic, transcriptional and functional level that accelerate future defense against the same pathogen or an opportunistic pathogen. [2]

In the innate system, this recognition of pathogens can be done through pattern recognition receptors (PRRs) expressed in these cell types. Through this process, trained immunity can lead to greater protection by increasing the effectiveness of the non-specific response of innate immune cells against pathogens, especially monocytes and macrophages. Thus, taking advantage of the state of activation of dendritic cells to increase the adaptive responses of T cells to specific and unrelated pathogens, including the regulation of the intestinal microbiota. [4]

Pattern Recognition Receptors (PRRs) are proteins capable of recognizing molecules frequently found in pathogens (the so-called Pathogen-Associated Molecular Patterns-PAMPs), or molecules released by damaged cells (the Damage-Associated Molecular Patterns-DAMPs). They emerged phylogenetically prior to the appearance of the adaptive immunity and, therefore, are considered part of the innate immune system. Most described trained immunity inducers are microbial-derived products that stimulate innate immune cells via pattern recognition receptors (PRRs), such as C-type lectin receptors (CLRs) and Dectin-1. [5,6]

Saccharomyces cerevisiae

Mannose rich adjuvants derived from Saccharomyces cerevisiae cell walls for immunotherapy targeting APCs have shown to modulate immune responses towards both Th1 and Th2 responses by binding to both mannan- and C type lectin receptors (DC-SIGN) expressed e.g., by APCs, which leads to activation of complement pathways, the NLRP3 inflammasome, as well as increased phagocytosis and cytokine secretion in APCs. These types of adjuvants have both antigen carrier and immunostimulatory capabilities. [8,9]

Native Saccharomyces cerevisiae preserves macrostructures such as chitin, glucan, and mannan. The cell wall structure of Saccharomyces cerevisiae consists mainly of chains of glucose residues and mannoproteins. Saccharomyces cerevisiae Glucan fraction was reported to bind to either carbohydrate receptors or TLRs expressed on the surface of APCs, suggesting these molecules to have adjuvant potential. Their results showed that, as adjuvants, Saccharomyces cerevisiae b-glucans can also serve as both carriers and immune activators promoting immune responses in vitro and in vivo, which enhanced the delivery of antigens by binding to APCs, n to suppress specific IgE production and enforced antigen-specific antibody production [7,10,11].

The ability of b-glucans in modulating immuneresponse has been well established, Furthermore, even with a high degree of purity, the beta-glucan fraction of yeast has a mannose-rich fraction, with short or long chains with a high concentration of mannose. Thus, glycoconjugates with this fraction of the Saccharomyces cerevisiae is able to maintain its structure (mannose, glucose) intact and its potentially associated tolerogenic properties, with adjuvant capacity for targeted delivery of allergens to dendritic cells.

Dendritic Cells Immunotherapy

Immunotherapy using glycoconjugate antigens based on Saccharomyces Cerevisiae antigen-mannose conjugation are defined as next-generation immunotherapy. The strategy involves conjugating allergens (from sources like dust mites or grass pollen) with a mannose—source derived from the cell wall of Saccharomyces cerevisiae. Targeting antigens to DCs to augment cellular uptake holds the promise of more effective and efficient immunotherapy, with mannan-coupled antigens from Saccharomyces cerevisiae proving particularly suitable due to the expression of CLR-binding receptors on these cells. These glycoconjugate antigens have been shown to be efficiently taken up by DCs in vivo, facilitating a shift from Ige to IgG production in response to allergens. [12-14]

While trained immunity increase uptake and presentation of pathogens through the carbohydrate receptors presented on dendritic cells, resulting in epigenetic changes from the reprogramming of chromatin marks in the progenitors of innate immune cells, the mechanism by which the adjuvant can strengthen these cells, while there is evidence of a more robust innate response of monocytes and macrophages against various pathogens following exposure to this substance, with improved antimicrobial and inflammatory properties derived from the activation of the dectin-1/toll-like receptor (TLR). Trained immunity takes advantage of the state of awareness of dendritic cells to promote host resistance against a wide spectrum of pathogens, increasing the nonspecific effector response of innate immune cells (e.g., monocyte/macrophages) to pathogens and to enhance adaptive T cell responses to both specific and non-related (bystander) antigens. [15,16]

Emerging Concept of Trained immunity

Trained immunity is revolutionizing our understanding of innate immunity by demonstrating its capability to be "educated" for enhanced responsiveness to subsequent infections. This paradigm shift is supported by studies on immunostimulants derived from trained immunity, which exploit dendritic cells' ability to offer broad and durable defense against various diseases. This concept is tied to the capacity of the innate immune system's immune memory to be trained. [3]

Through repeated exposure to pathogens, innate immune cells undergo epigenetic, transcriptional, and functional changes, speeding up their defense against recurring or new opportunistic pathogens. Trained immunity empowers the immune system to "remember" and prime cells via metabolic and transcriptional events, enabling a generalized defense against future pathogen encounters, leading to quicker, stronger, and more extensive responses. Regulating immune balance and modulating responses are crucial for maintaining equilibrium. Immunostimulant therapy based on trained immunity can act as powerful stimuli, clearing pathogens through various effects and providing broad protection against both non-specific and specific pathogens. trained immunity guides the development of immunostimulants aimed at enhancing host resistance to a wide array of pathogens. It seeks to induce a generalized effector response from innate immune cells, such as monocytes/macrophages, and to leverage dendritic cells' activated state to boost adaptive T cell reactions to both specific and unrelated antigens. Formulations inspired by trained immunity incorporate microbial structures containing appropriate pattern recognition receptor (PRR) ligands, including inactivated whole bacteria, bacterial lysates, and organelles, to trigger immune responses effectively. [5,17]

Dendritic Cell Training

Exposure to specific microbial stimuli can lead to enduring epigenetic alterations in innate immune cells, enhancing their reaction to subsequent exposures to the same or different microbial threats. This phenomenon, known as trained immunity, heralds a novel direction in immunotherapy—the creation of immunostimulants rooted in the trained immunity principle. These formulations are designed to prime innate immune cells, contrasting with vaccines that only target specific responses to particular antigens, immunostimulants for trained immunity are engineered to elicit a wider spectrum of immune responses. Triggered typically by pattern recognition receptors (PRRs), effective

immunostimulants must incorporate microbial structures rich in appropriate PRR ligands. This strategy underlines the development of immunostimulants aimed at bolstering host defenses against a broad array of pathogens. Leveraging trained immunity, extensive protection can be attained by enhancing the unspecific effector responses of innate immune cells, like monocytes/macrophages, and by utilizing the activation state of dendritic cells to amplify adaptive T cell responses towards both specific and unrelated antigens. This strategy's capacity to foster responses beyond direct antigens holds significant promise, especially in scenarios where traditional vaccines may be ineffective or absent, and in cases of multiple co-infections or recurrent infections in vulnerable populations. [5,17]

Dendritic Cell Training in Recurrent Respiratory Tract Infections

Immunity Training has been shown to confer innate immune cells with a quite long-term nonspecific protection against a broad spectrum of pathogens. Inducers of immunity training include some bacterial immunostimulants. Trained immunity immunotherapy of bacterial origin has the capability to induce nonspecific responses to a variety of pathogens, including respiratory viruses, in addition to their nominal bacterial antigens. [5]

Prominent examples of successful immunostimulant formulations for upper respiratory tract infections (URTI) include antigens from S. pneumoniae, S. aureus, S. epidermidis, Klebsiella pneumoniae, Moraxella catarrhalis, and Haemophiles influenzae. These have been effectively incorporated into an immunity Training immunostimulant. This novel approach involves inactivated whole-cell bacteria aimed at preventing recurrent respiratory tract infections (RRTIs) by inducing immunity training. A retrospective multicenter study assessed the impact of the administration on both children and adults suffering from RRTIs. The study encompassed 186 children aged 6 months to 17 years and 413 adults, evaluating the number of infectious episodes and antibiotic courses 12 months before and after immunization. Results indicated a significant reduction in infections and antibiotic use across all age groups. In children, infections in upper airways decreased from a median of 5 to 1, and in lower airways from 5 to 2 In adults, upper respiratory infections reduced from a median of 5 to 1.0, and lower respiratory infections from 4 to 1. Antibiotic consumption in upper respiratory tract infections dropped from a median of 4 courses to zero, confirming it as an effective strategy in preventing RRTIs and reducing antibiotic intake, with the additional benefit of having a disease-modifying effect that persists after treatment is stopped. [18]

Conclusions and future perspectives

It has become evident that cells of the innate immunity may be primed upon encounter with certain pathogens or molecular patterns associated to pathogens (PAMPs), acquiring a higher resistance to a second infection against the same or unrelated pathogens (cross-protection) for a relatively long time [15, 16].

Dendritic Cell immunity Training marks a groundbreaking shift in therapeutic strategies, offering a state-of-the-art approach to reprogramming immune responses. This revolutionary method significantly impacts scenarios lacking conventional vaccines or facing recurrent infections in vulnerable populations by enabling responses beyond specific antigens. Given the prevalence of recurrent respiratory tract infections as a major source of both community-acquired and nosocomial infections, and the growing concern over antibiotic resistance due to antibiotic dependency, there's a pressing need for novel preventative and therapeutic alternatives. Training immunity offers a solution by equipping innate immune cells with the ability to provide nonspecific, long-term defense against a diverse array of pathogens. This has been evidenced by the effectiveness of some bacterial vaccines and formulations derived from bacterial origins, which have shown promise in eliciting broad responses, including against respiratory viruses beyond their initial bacterial targets. Clinical evidence, from epidemiological studies to randomized trials, supports that such immunostimulants can prevent viral respiratory infections, potentially reducing incidences of conditions like recurrent wheezing or asthma exacerbations in children. trained immunity is paving the way for innovative directions in immunotherapy beyond specific allergen immunotherapy. This approach focuses on creating immunostimulant formulations that leverage the concept of trained immunity, offering a broader spectrum of protective measures against infectious diseases. The ability of these formulations to elicit responses that extend beyond their target antigens highlights their remarkable potential within the field of immunotherapy. This is particularly significant for addressing co-existing multiple infections or managing recurrent infections among vulnerable populations. Clinical data indicates that trained immunity is also effective in treating recurrent infections, such as Candida infections and urinary tract infections. [22]

In summary, the identification and development of new protective tools mark a promising strategy for enhancing immunotherapy. This novel approach holds particular promise for the prevention of respiratory viral infections, including recurrent wheezing in children, and opens new avenues for more effectively addressing complex immune challenges. Moreover, in recent years, research has been exploring the influence of trained immunity on allergies. Exposure to environmental factors like allergens or viruses can lead to the reprogramming of innate immune cells, often resulting in a more pro-inflammatory profile, particularly in cases of asthma or food allergies. Studies have shown that preventing viral infections can decrease wheezing episodes in children, a significant marker for the future development of asthma. Additionally, immune cells trained with specific stimuli might develop anti-inflammatory characteristics, promoting tolerance and potentially impacting the treatment of chronic inflammatory diseases like allergies. [23]

Recent findings have demonstrated that neo glycoconjugates, next-generation vaccines for allergen-specific immunotherapy, can reprogram monocytes into tolerogenic dendritic cells through metabolic and epigenetic changes. A deeper understanding of the mechanisms of trained immunity in allergies could lead to the development of innovative trained immunity-based allergen vaccines, presenting alternative strategies for the prevention and treatment of allergic diseases. Looking to the future, ongoing research into trained immunity could revolutionize our approach to managing allergies, potentially leading to more personalized and effective therapeutic options that harness the body's innate immune responses.

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