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REVIEW ARTICLE

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From trained immunity in allergy to trained immunity-based allergen vaccines

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Abstract

Innate immune cells experience long lasting metabolic and epigenetic changes after an encounter with specific stimuli. This facilitates enhanced immune responses upon secondary exposition to both the same and unrelated pathogens, a process termed trained immunity. Trained immunity-based vaccines (TIbV) are vaccines able to induce innate immune memory, thus conferring heterologous protection against a broad range of pathogens. While trained immunity has been well documented in the context of infections and multiple immune-mediated diseases, the role of innate immune memory and its contribution to the initiation and maintenance of chronic allergic diseases remains poorly understood. Over the last years, different studies attempting to uncover the role of trained immunity in allergy have emerged. Exposition to environmental factors impacting allergy development such as allergens or viruses induces the reprogramming of innate immune cells to acquire a more pro-inflammatory phenotype in the context of asthma or food allergy. Several studies have convincingly demonstrated that prevention of viral infections using TIbV contributes to reduce wheezing attacks in children, which represent a high-risk factor for asthma development later in life. Innate immune cells trained with specific stimuli might also acquire anti-inflammatory features and promote tolerance, which may have important implications for chronic inflammatory diseases such as allergies. Recent findings showed that allergoid-mannan conjugates, which are next generation vaccines for allergen-specific immunotherapy (AIT), are able to reprogram monocytes into tolerogenic dendritic cells by mechanisms depending on metabolic and epigenetic rewiring. A better understanding of the underlying mechanisms of trained immunity in allergy will pave the way for the design of novel trained immunity-based allergen vaccines as potential alternative strategies for the prevention and treatment of allergic diseases.

KEYWORDS
allergy, asthma, basic immunology, clinical immunology, food allergy, innate immunity, trained immunity, trained immunity-based allergen vaccines

Leticia Martín-Cruz and Carmen Sevilla-Ortega equally contributed to this work.

1 | INTRODUCTION

Although the immune memory has been classically associated with the adaptive immune system, in the recent years several studies convincingly demonstrated that innate immune cells also exhibit memory. Trained immunity was defined by Netea and colleagues in 2011 as the process by which innate immune cells display long-term functional reprogramming after an encounter with a primary stimulus, resulting in an enhanced immune response against a secondary challenge.[1] After recognition of the first stimulus, innate immune cells (monocytes, macrophages, NK cells, neutrophils, dendritic cells (DCs) and innate lymphoid cells (ILCs)) and bone marrow progenitors undergo metabolic and epigenetic reprogramming, two major molecular mechanisms responsible for the induction of trained immunity.[2] This process has also important applications in modern vaccinology. Trained immunity-based vaccines (TIbV) are defined as vaccines able to induce trained immunity, thus stimulating broader responses against both related and unrelated antigens contained in the vaccine formulation.[3,4]

Together with infections, allergic diseases are a major health problem whose prevalence is increasing around the world, mainly due to environmental factors, behavioural modifications or changes in lifestyle.[5,6] Induction of trained immunity could play a central role within the mechanisms involved in the initiation and chronification of allergy, but data related to the actual role of trained innate cells in allergy are scarce. Several studies reported that some allergens, virus, and other stimuli mediate training mechanisms that might contribute to the deleterious effects and aberrant innate immune responses reported in asthma and food allergy.[7–9] In contrast, some bacterial preparations promote trained immunity granting protection against respiratory viral infections and wheezing attacks in children, which represent a high-risk factor for later asthma development.[10,11] It has been suggested that allergen-specific immunotherapy (AIT) might induce trained immunity as a relevant mechanism contributing to the restoration of healthy immune responses to allergens.[12] In this regard, allergoid-mannan conjugates are able to reprogram monocytes into tolerogenic DCs through mechanisms depending on metabolic and epigenetic reprogramming. This suggests that this next generation AIT vaccine might have the potential to induce trained immunity.[13] However, the detailed molecular mechanisms by which trained immunity contributes to allergy development and to successful AIT remain largely unknown. In this article, we comprehensively review the most recent findings related to the role of trained immunity in the context of allergy, which might pave the way for the development of future novel TIbV for AIT as potential novel therapeutic strategies for allergic diseases.

Key messages

- Trained immunity-based vaccines induces innate immune memory providing heterologous protection against different pathogens.
- Environmental factors driving allergy promote training of innate cells enhancing type 2 inflammatory responses.
- Allergoid-mannan conjugates AIT vaccines reprogram monocytes into tolerogenic DCs by promoting metabolic and epigenetic rewiring.

2 | TRAINED IMMUNITY: DEFINITION, CELLS AND UNDERLYING MECHANISMS

The field of innate immune memory, also termed 'trained immunity', started one decade ago, when two studies respectively described the existence of enhanced responsiveness after sublethal *Candida* infection in mice, and the presence of increased cytokine production after the stimulation of peripheral blood mononuclear cells obtained from individuals vaccinated with the *Bacille Calmette-Guérin* (BCG).[14,15] In the last years, we have witnessed a quick expansion of this field, with multiple studies describing a variety of mechanisms, stimuli inducing trained immunity, development of experimental models, and potential applications, besides showing the existence of these processes in multiple cell models and organisms (for review, see Ref. [2]). In this rapidly expanding context, it is important to remind the definition of trained immunity and distinguish it from other related immunological processes such as priming or tolerance.[16] During trained immunity, an initial stimulus induces long-term epigenetic and metabolic changes that render the cells more responsive to secondary stimulation (Figure 1). Initially, trained immunity was described in differentiated innate immune cells such as monocytes, macrophages, and NK cells.[2] However, other cell types such as epithelial cells can also be trained.[17] Among the different cell subsets that can undergo this process, there is one that stands out: the haematopoietic stem cells of the bone marrow, which transmit their trained phenotype to their daughter cells allowing the long-term establishment of trained immunity responses that can last for weeks, months, and possible even years.[18,19] These mechanisms allow that those immune responses that initially occur locally are transmitted to the rest of the body and generate long-term systemic immunity.

Importantly, after the initial stimulation ceases, the immune response goes back to the steady state. Though the cells are trained, there is no maintained secretion of cytokines or chemokines (Figure 1). Nevertheless, trained cells undergo strong epigenetic and metabolic reprogramming, allowing them to present enhanced responsiveness upon secondary stimulation.[20,21] In contrast to adaptive immune responses, the secondary stimulus that triggers innate immune memory can be of the same or a different nature than the first one, so trained immunity induces heterologous, antigen-independent secondary enhanced responses (Figure 1).

As mentioned before, the induction and maintenance of trained immunity relies on two main pillars: the epigenetic and metabolic reprogramming of the cells. Trained cells increase their basal metabolic activities so they can use nutrients and energy faster and more efficiently.[22] In this regard, they quickly rewire their glycolytic and

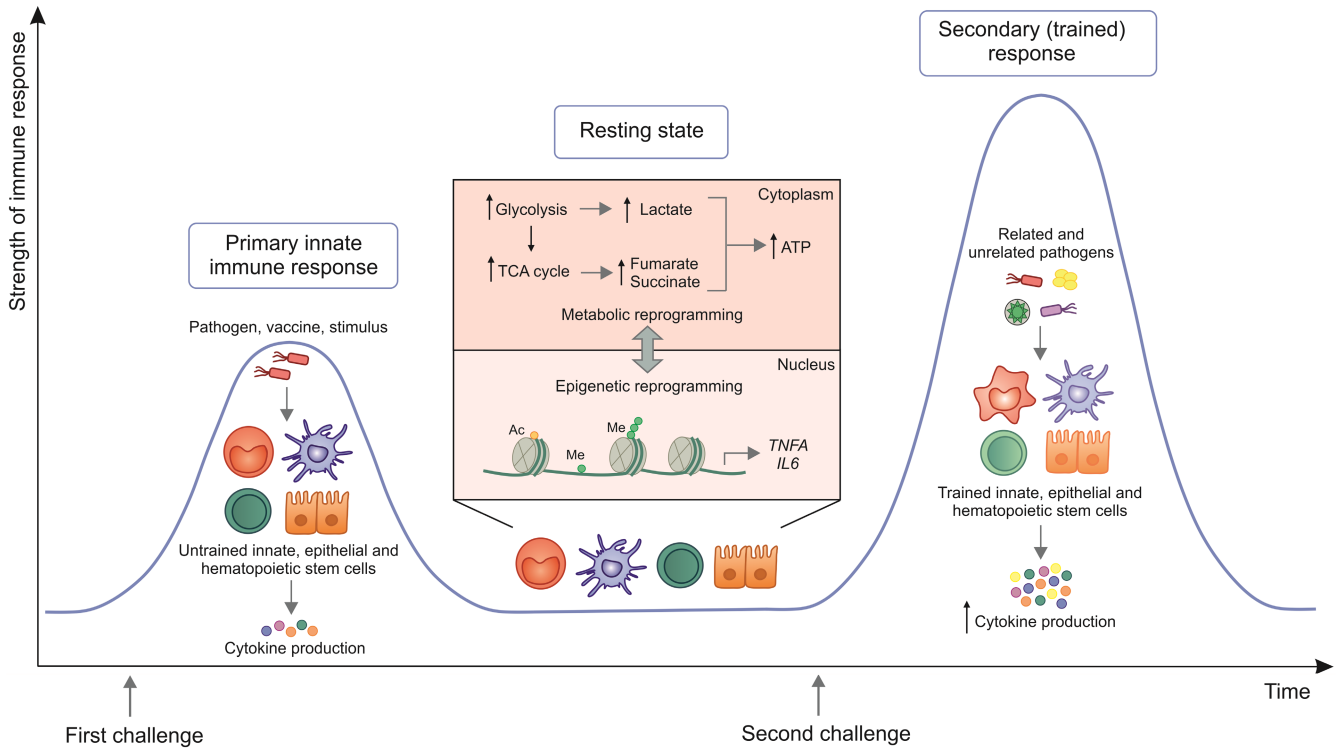

FIGURE 1 Induction of trained immunity. Different pathogens, vaccines and stimuli induce long-term functional, metabolic and epigenetic reprogramming of innate, epithelial and haematopoietic stem cells. Trained immunity facilitates enhanced responsiveness after a second challenge with related or unrelated pathogens conferring heterologous protection. TCA cycle, tricarboxylic acid cycle; ATP, adenosine triphosphate; Ac, acetylation; Me, methylation

oxidative phosphorylation activities, by increasing their glucose consumption, leading to enhanced production of lactate and ATP.[23–25] This is paralleled by an increased amino acid and fatty acid consumption, so the cells extract the most of their available nutrients, using the necessary building blocks and energy to fuel and maintain the intracellular processes required for enhanced immune responsiveness.[24] This increased metabolic activity is accompanied by the remodelling of the epigenetic architecture of the cell (Figure 1). The modification of the acetylation and methylation marks in the histones and the DNA remodels the three-dimensional structure of the chromatin in the cell nucleus.[26] Through these mechanisms, the promoter regions of pro-inflammatory genes such as *TNFA* or *IL6* maintain an open conformation after the first stimulus ceases, so the transcriptional machinery of the cell has a facilitated access to these genome regions. Similar processes have been suggested to mediate long-term enhanced type 2 responses important in allergies in ILC2 cells.[27]

The combination of an increased metabolic activity and the enhanced accessibility to several pro-inflammatory regions of the genome promotes the quick and enhanced transcription, translation, processing and secretion of the necessary factors to mount an immune response. Moreover, rewiring the cell metabolism induces the production and accumulation of multiple metabolites with direct immunomodulatory activities, such as succinate, fumarate, or lactate.[22] Accumulation of these metabolites contributes to amplification or modulation of trained immunity through inhibiting or activating multiple enzymes and pathways fundamental for immune responses and epigenetic processes. Therefore, the interplay between the metabolic and epigenetic rewiring of the cells is fundamental for the induction, maintenance, and regulation of trained immunity (Figure 1).

Innate immune tolerance, as opposite to trained immunity, is defined as the process by which innate cells are unable to activate gene transcription, preventing them from carrying out their functions after restimulation, such as macrophages upon repeated or sustained stimulation with LPS.[16] In contrast, specific microbial products such as those derived from certain helminths might induce a so-called 'anti-inflammatory' trained immunity phenotype characterized by epigenetic and metabolic reprograming leading to the production of higher levels of anti-inflammatory cytokines such as IL-10 or IL-1RA. This might have important implications in the context of allergy as discussed in more detail in the following sections.[28]

3 | TRAINED IMMUNITY-BASED VACCINES (TIBV) AS A NEW PARADIGM IN VACCINOLOGY

The change in paradigm towards the recognition of innate immune memory as an important mechanism contributing to immunological memory has opened a new avenue in modern vaccinology.[29,30] While traditional vaccines promote adaptive immune responses acting on

antigen-specific memory B and T cells,[31] trained immunity-based vaccines (TIbV) are defined as vaccines able to induce trained immunity, thus stimulating broader responses against both related and unrelated antigens contained in the vaccine formulations.[3] Different vaccine preparations containing lived attenuated or inactivated pathogens might confer protection against target infections, but also exhibit heterologous effects by mechanisms combining enhanced innate and adaptive immune responses (Figure 2).[3,32]

The paradigmatic example of TIbV is the live attenuated *Mycobacterium bovis* BCG vaccine, which has been shown to enhance both antigen-specific T cell responses and non-specific innate immune responses.[33,34] BCG administration in healthy adults induced heterologous responses in monocytes and NK cells in response to mycobacteria and other unrelated pathogens such as *Staphylococcus aureus* or *Candida albicans* even 3 months after vaccination.[15,35] BCG vaccination also imprints trained immunity properties in bone marrow haematopoietic stem cells and multipotent progenitors, which are essential to maintain the memory of circulating innate immune cells in blood and tissues.[18] Epidemiological studies have convincingly demonstrated that BCG vaccination reduces all-cause mortality in children[36,37] and increases the time to the first infection in the elderly.[38] TIbV also provide protection against viral infections and, therefore, BCG has been suggested as a potential alternative for SARS-CoV-2 virus infection with several clinical trials already published and others still ongoing.[39,40] Other live attenuated formulations including measles-containing vaccines, oral polio, vaccinia virus and influenza vaccines provide protection against both homologous and heterologous diseases by promoting trained immunity. Therefore, could be also considered as conventional vaccines displaying features related to TIbV.[41–45]

Interestingly, different types of bacterial formulations for recurrent respiratory tract infections (RRTIs) confer protection against a broad range of infectious diseases. Clinical data showed that OM-85, a formulation of 21 bacterial strain lysates from five genera (*Moraxella*, *Haemophilus*, *Klebsiella*, *Staphylococcus* and *Streptococcus*), reduced the infection rates in children and adults with RRTIs.[46,47] In the same line, clinical studies demonstrated that MV130, a whole-heat inactivated polybacterial preparation containing 90% of Gram-positive (*Streptococcus pneumoniae*, *Staphylococcus aureus* and *Staphylococcus epidermidis*) and a 10% of Gram-negative (*Klebsiella pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*) bacteria, decreased the incidence and severity of RRTIs in adults.[48,49] A randomized, double-blind, placebo-controlled phase III clinical trial also demonstrated that sublingual MV130 prevents recurrent wheezing in children even after 6 months of treatment discontinuation.[50] MV140, a whole heat-inactivated formulation with 75% Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae and Proteus vulgaris*) and 25% Gram-positive (*Enterococcus faecalis*) bacteria, prevented recurrent urinary tract infections and promoted Th1/Th17 and IL-10 immune responses.[51–53] The combination of MV140 with heat-inactivated *Candida albicans* (V132) in a single preparation induced metabolic and epigenetic reprograming in human DCs and enhanced antigen specific T cell responses.[54]

Several studies have shown that TIbV may be also employed to treat cancer and some autoimmune diseases such as multiple sclerosis or type 1 diabetes.[55,56] In addition, BCG is a standard treatment for bladder cancer and the positive outcomes have been ascribed to the induction of trained immunity.[55] BCG vaccination has important clinical benefits for multiple sclerosis with decreased tissue damage reported even 5 years after BCG vaccination.[57,58] Mechanistically, BCG enhances glycolysis in conventional T cells, which in turn favours the generation of suppressive regulatory T cells (Tregs) that prevent neuronal damage.[55,59] BCG-mediated enhanced glycolysis also contributes to the control of blood sugar levels in type 1 diabetes.[56,60]

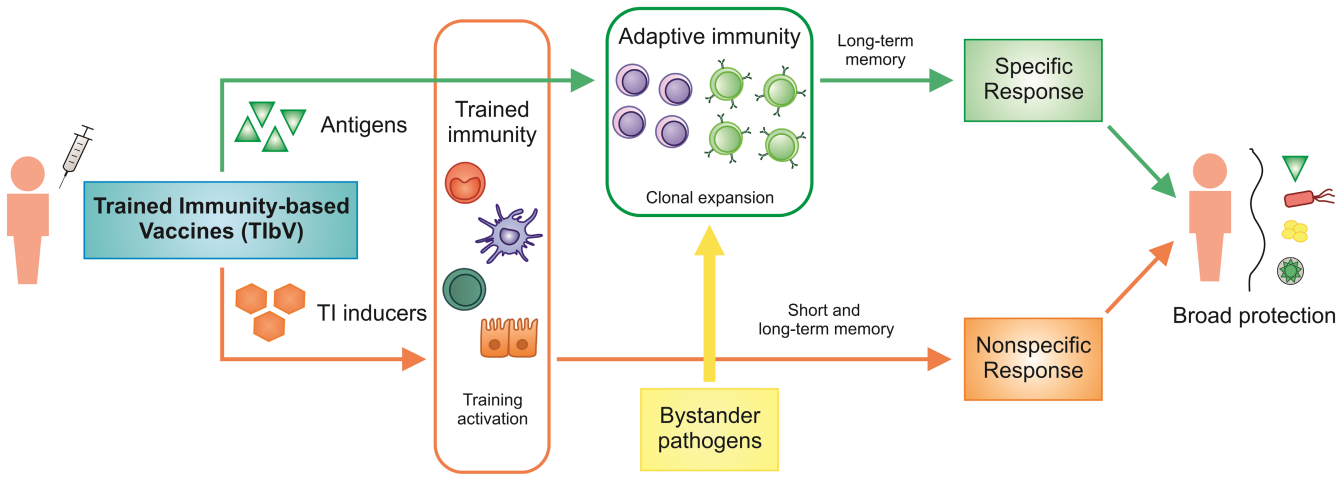

FIGURE 2 Mechanisms of trained immunity-based vaccines (TIbV) for infections. TIbV are formed by two essential components: Trained Immunity (TI) inducers and TIbV-related antigens. TI inducers reprogram innate, epithelial and haematopoietic stem cells so that they can respond in a much more efficient manner against bystander pathogens (both related and unrelated to those contained in the formulation), thus resulting in a short/long-lasting memory. Under TI conditions, more potent adaptive responses are orchestrated by T and B cells against both the antigens contained in the vaccine formulation but also against antigens contained in encountered bystander pathogens. TIbV are able to confer broad protection against both related and unrelated bystander pathogens.

While the concept of trained immunity is generally linked to higher responses after a secondary stimulation, trained innate immune cells might also acquire and promote anti-inflammatory and tolerogenic profiles depending on the type of stimuli, the concentration and duration of the stimulation, the type of TIbV or the specific pathological context.[16,56,61] The understanding of the potential role of trained immunity in the initiation and maintenance of inflammatory immune-mediated diseases such as asthma and allergy is improving over the last years, which might well pave the way for the development of novel interventions to prevent and/or restore proper immune responses.

4 | TRAINED IMMUNITY IN ALLERGY

Allergic diseases represent a global health problem of increasing prevalence with huge socio-economic impact worldwide.[62,63] Allergic asthma, allergic rhinitis, food allergy, atopic eczema/dermatitis and anaphylaxis represent the most important chronic allergic diseases with a significant negative impact on patients' quality of life and health-associated costs. The immunological mechanisms underlying allergy can be divided into two phases: sensitization/memory and effector phase. Sensitization occurs during the first contact with the allergen and leads to the generation of allergen-specific $CD4^+$ Th2 cells and the production of allergen-specific IgE antibodies by B cells. Allergen-specific IgE binds to the high-affinity FcЄRI receptor on mast cells and basophils, thus leading to patient's sensitization.[64–66] New encounters with the allergen cause cross-linking of IgE-FcεRI complexes on sensitized mast cells and basophils, releasing a plethora of anaphylactic mediators that trigger the immediate clinical symptoms.[64–66] Accumulation of anaphylactic mediators and activation of allergen-specific memory Th2 cells via IgE-facilitated presentation by DC and B cells initiates late-phase reactions. IL-4, IL-5, IL-9 and IL-13 produced by Th2 cells in cooperation with ILC2s activated by epithelial alarmins (TSLP, IL-33 or IL-25) contribute to allergen-specific IgE levels, eosinophilia, mucus production, inflammatory cell recruitment and tissue inflammation. These effects are associated with the chronicity and more severe clinical manifestations.[64] Westernized lifestyle and exposome including all environmental exposures such as chemicals, pollutants as well as lifestyle factors, dietary habits, drugs and infections agents are important risk factors for allergic sensitization.[6,67,68] This association suggests the important role of gene-environmental interactions, supported by epigenetic and metabolic rewiring, in the development of allergic diseases.[69,70] Therefore, a better understanding of the potential role of trained immunity in the context of allergic diseases is of outmost importance for the development of future alternative interventions.

4.1 | Trained immunity in allergic asthma

Asthma is one of the most prevalent inflammatory airway diseases affecting more than 330 million people in the world.[71] Asthma is a heterogeneous syndrome characterized by reversible airway obstruction, bronchial hyperresponsiveness and inflammation, which progressively accelerate lung function decline and airway remodelling.[71,72] Allergic asthma constitutes one of the most common phenotypes and it is characterized by increased levels of total and allergen-specific serum IgE and type 2 immune responses.[64] Type 2 asthma onset is associated with early life exposure to allergens, pollutants, irritants or viral infections. Many children suffer from recurrent wheezing episodes triggered by rhinovirus or respiratory syncytial virus that can diminish with age, but for some individuals can mark the beginning of asthma.[73] As discussed above, the protective role of different bacterial preparations for preventing viral infections and wheezing attacks in children have been demonstrated in several clinical studies,[46,50] and the mechanisms underlying their mode of action are starting to be elucidated.[3,74] The bacterial lysate OM-85 increases protection against viral respiratory infections in murine models by enhancing mucosal antibody production.[10] Maternal oral OM-85 administration conferred protection to the offspring against neonatal respiratory viral infection by accelerating and enhancing innate immune responses.[75] In humans, oral OM-85 also prevented RRTI by mechanisms depending on immune training, but whether trained immunity is induced remains unknown.[76] Recently, it has been demonstrated that airway administration of OM-85 impairs asthma features by targeting DCs and IL-33-activated ILC2s.[77] The whole heat-inactivated polybacterial vaccine MV130 induced a robust activation of human DCs from healthy donors and patients suffering from RRTI, thus promoting the generation of potent Th1, Th17, and IL-10-producing T cells against both related and unrelated antigens contained in the vaccine formulation.[78] In mice models, it has been also demonstrated that intranasal administration of MV130 confers protection against viral infections by mechanisms depending on the induction of trained immunity via metabolic and epigenetic reprogramming of myeloid immune cells and bone marrow progenitor cells,[11] thus supporting the capacity of MV130 to prevent wheezing attacks in children previously reported in phase III clinical trials.[50]

Contrary to harmful effects widely associated with viral respiratory infections, it has been reported that murid gamma herpes virus (MuHV-4) infection prior to HDM experimental asthma induction, blocks asthma development.[79] MuHV-4 infection induces the death of lung resident alveolar macrophages and the subsequent repopulation of the lung niche by regulatory bone-marrow-derived monocytes. Locally differentiated monocyte-derived macrophages block type 2 HDM-induced specific response mediated by DCs, resulting in lower pro-asthmatic type 2 cytokines in both the lungs and mediastinal lymph nodes.[79] However, the mechanism by which MuHV-4 infection reprograms bone marrow-derived monocytes remains unknown.

Recently, mouse studies showed that ILC2s, critical players in type 2 asthma development, might also acquire memory in an IL-33 dependent manner.[80–82] Different stimuli such as IL-33, *Aspergillus* protease, rhinovirus infection or papain allergen drives IL-33 production by the epithelial cells, and consequently, this IL-33 leads to

the activation and proliferation of lung ILC2s. Following activation, a resting phase takes place with a decrease in ILC2 numbers in the lungs and a subsequent reduction of cytokine production. However, the re-stimulation with a second unrelated stimulus significantly enhances cytokine production by IL-33-trained ILC2s, which could be associated with an enhancement of allergic asthmatic inflammation (Figure 3).[7,8,27]

4.2 | Trained Immunity in food allergy

The prevalence of food allergy is rising in westernized countries, affecting approximately 6% of children and 4% of adults.[83,84] Food allergy arises from a breakdown of oral tolerance to ingested antigens in people genetically and possibly also environmentally predisposed to atopic disease.[83] Therefore, the association of food allergy prevalence with lifestyles suggests that trained immunity mechanisms could be also involved in the development and persistence of food allergy.[6]

Regarding the potential role of innate immune memory in food allergy, some studies have reported excessive innate immune responses at birth in cord blood-derived mononuclear cells from allergic children compared to non-allergic donors.[85,86] These responses were characterized by large amounts of IL-6, IL-1β and TNF-α production following in vitro Toll-like receptor stimulation. This study has reported that the predisposition for allergen-specific type 2 responses is associated with the hyperinflammatory reaction in the perinatal period.[85] To further confirm the hypothesis, naive $CD4^+$ T cells from cord blood were stimulated with IL-1β and TNF-α (in combination with TGF-β), which resulted in an enhanced type 2 immune response.[86] Recent studies have confirmed the enhancement of innate immune responses in egg- and peanut-allergic 1-year-old infants compared to healthy donors.[9,87,88] Egg-allergic paediatric patients showed a higher frequency of circulating monocytes and DCs. Moreover, monocytes stimulated with LPS produced higher amount of IL-6, IL-1β, IL-8 and TNF-α compared with non-allergic patients. However, levels of IL-12p70 were higher in non-allergic donors than in allergic children (before and after LPS stimulation).[87] Egg-allergic infants also displayed a lower number of $CD4^+$ Tregs and increased monocye:$CD4^+$ T cell ratio.[9] On the other hand, other study with peanut allergic infants demonstrated an increase in TNF-α production after non-specific stimulation of total peripheral blood mononuclear cells from one-year peanut-allergic donors compared to healthy infants.[88] To confirm whether the enhanced innate immune response remains with ageing, the same parameters were evaluated in single peanut or multi-food allergic adolescences.[89] Both single peanut and multi-food allergic adolescence displayed an increase in circulating levels of DCs and monocytes. A higher pro-inflammatory cytokine production after LPS stimulation of monocytes than in healthy donors was observed.[89] Collectively, all these results suggest an increase in innate immune response displaying trained immunity features, which might favour DC and T cell interaction favouring type 2 immune responses early in life in food-allergic patients that might persist through adolescence (Figure 4).[9,85–89]

4.3 | Trained Immunity in allergen-specific immunotherapy (AIT)

AIT is currently the only causative treatment for allergic diseases with potential disease-modifying capacity.[90] AIT consists of the administration of high doses of the causative allergens to induce patient's desensitization and allergen tolerance after treatment cessation. Research on the mechanisms of action of AIT has been traditionally focused on the regulation of adaptive immune responses, however, recent findings suggest that innate immune responses might also be regulated during successful AIT.[91] It has been shown that AIT restores the frequencies of different innate immune cell populations (ILCs, monocytes and DCs) to those observed in non-allergic individuals.[12] Whether metabolic and epigenetic reprogramming driving trained immunity was also induced by AIT in these restored innate immune cell populations was not reported in this study. At this regard, subcutaneous and sublingual AIT as well as grass pollen-induced seasonal allergic rhinitis changed the chromatin landscape in circulating follicular helper T cells (T_{FH}) and follicular Tregs (T_{FR}) compared with non-atopic patients and between groups.[92] T_{FH} from pollen allergic patients displayed more accessible chromatin regions associated with cell growth, differentiation,

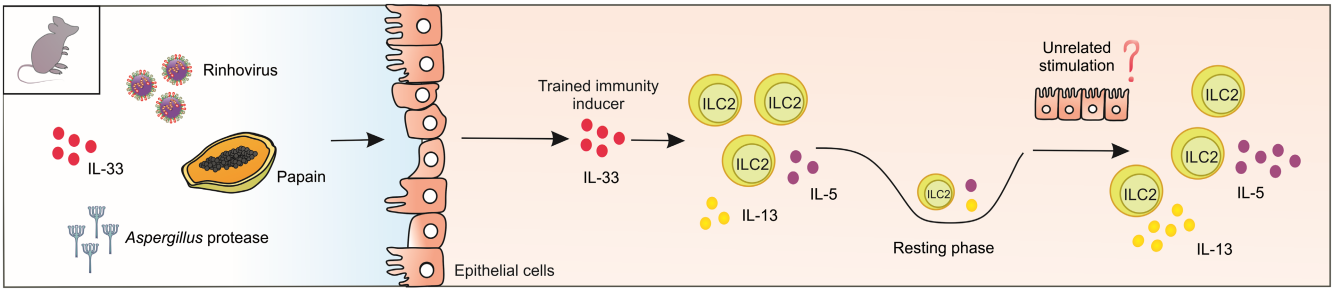

FIGURE 3 Induction of trained immunity in ILC2 under allergy conditions. Different stimuli (IL-33, papain, *Aspergillus* protease and rhinovirus) induce IL-33 production by epithelial cells, which stimulate type 2 innate lymphoid cells (ILC2) activation and cytokine production. After stimulation a resting phase takes place with less ILC2 that also produce less IL-13 and IL-5. Second unrelated stimulation of ILC2 results in an enhanced response that could be associated with a worst asthmatic reaction

and proliferation than T_{FR}. Remarkably, AIT modified this chromatin landscape and generated a more regulatory profile characterized by the induction of T_{FR} and IL10$^+$ T_{FH}.[92] Moreover, another clinical trial shows that sublingual AIT induces IL-10-producting ILCs in patients with grass-pollen allergy.[93] It has been also demonstrated that ILC2 can be converted into IL-10-producing ILC2, which plays a critical role in the restoration of epithelial cell integrity, suppression of type 2 responses and promotion of tolerance to aeroallergens.[94] This plasticity might be linked to epigenetic reviewing, but further research is needed to fully confirm it. The concept of trained immunity has been enlarged with reports showing that myeloid cells can be also trained in vitro or in vivo to be more anti-inflammatory following helminth exposure, which might confer protection against T cell-mediated autoimmunity.[28] Macrophages in vitro trained with *Fasciola hepatica* total extracts or *F. hepatica* excretory products (FHES) showed an increase in the anti-inflammatory cytokines IL-1RA and IL-10 and lower production of pro-inflammatory cytokines TNF-α and IL-12p70. In vivo administration of FHES resulted in hyporesponsive monocytes due to alterations of the haematopoietic stem cell niche in the bone marrow.[28] The administration of helminth products produced an 'anti-inflammatory' trained immunity associated with reduced Th1 and Th17 responses.[28] Whether such helminth products could be also exploited in the field of AIT to restore healthy immune responses to allergens remains unknown. Up to date, the data related to allergen vaccines able to induce 'anti-inflammatory' trained immunity are still scarce. In this regard, allergoid-mannan conjugates, next generation AIT vaccines targeting DCs and promoting the generation of functional Tregs,[95] are able to reprogram monocytes from allergic and healthy donors into tolerogenic DCs with higher capacity to prime functional FOXP3$^+$ Tregs.[13] Allergoid-mannan conjugates imprint epigenetic and metabolic rewiring in monocyte-derived DCs that ensures an open chromatin status in tolerogenic genes and shifts metabolism into mitochondrial oxidative phosphorylation, thus suggesting that training immunity mechanisms might also take place and contribute to the beneficial reported effects of this next generation AIT vaccine.[13]

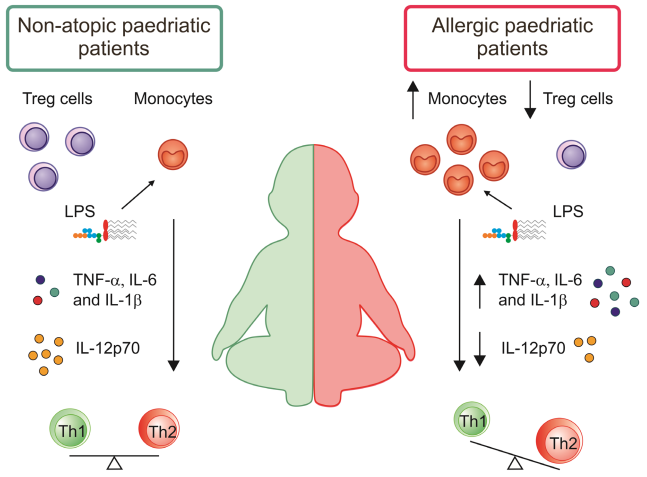

FIGURE 4 Food allergic paediatric patients display early hyperinflammatory innate immune responses that are associated with type 2 immunity. Allergic patients show less baseline Treg frequency and IL-12p70 production than healthy children. Children with food allergy also display larger number of monocytes producing higher amounts of IL-6, IL-1β and TNF-α after LPS stimulation than monocytes from non-allergic children. Those differences between groups skew the balance in favour to type 2 responses in allergic patients while maintaining a Th1:Th2 balance in healthy children. Treg cells, regulatory T cells; LPS, lipopolysaccharide; TNF-α, tumour necrosis factor alpha

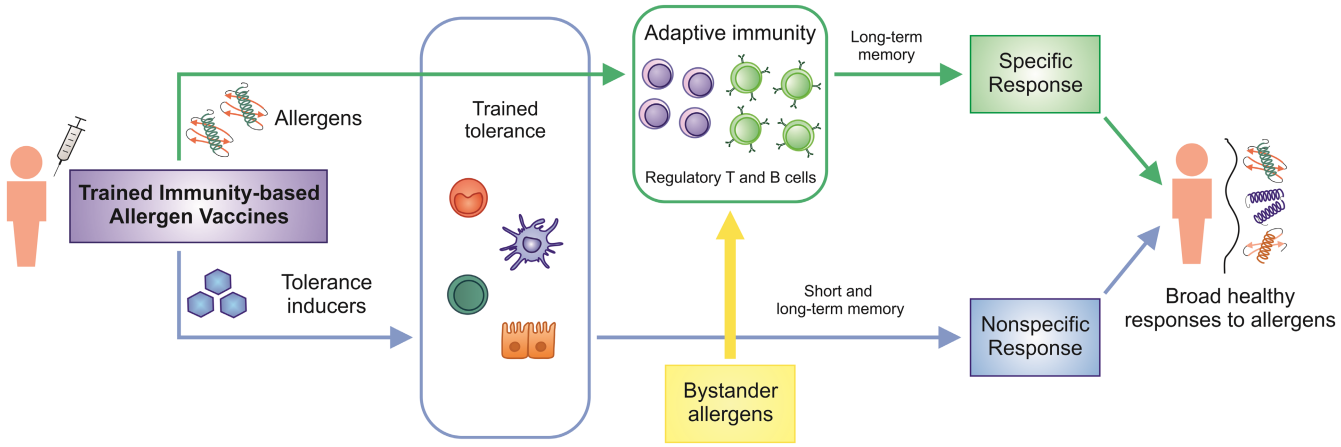

FIGURE 5 Proposed mode of action of trained immunity-based allergen vaccines. Trained immunity-based allergen vaccines should contain two essential components: Tolerance inducers and specific allergens to which the patients are sensitized to. These components will reprogram innate, epithelial, and haematopoietic stem cells so that they can mount anti-inflammatory and tolerogenic responses against bystander allergens (both related and unrelated to those contained the formulation), thus resulting in a short/long-lasting memory. Under these conditions, more potent tolerogenic adaptive responses are orchestrated by T and B cells against both the allergens contained in the vaccine formulation but also against encountered bystander allergens. Trained immunity-based allergen vaccines can induce broad healthy immune responses to allergens in a non-specific and allergen-specific manner, thus conferring broad tolerance against related and bystander allergens

5 | CONCLUSION AND FUTURE PERSPECTIVES

Our knowledge of the molecular mechanisms underlying trained immunity has significantly improved over the last decade. Nowadays it is widely accepted that innate immune cells also contribute to immunological memory. This change in paradigm has opened new alternatives in modern vaccinology. The use of TIbV has emerged as a useful approach to treating recurrent infections caused by related and heterologous pathogens. Different studies convincingly demonstrate that TIbV can be also successfully employed in other immune-mediated diseases such as cancer or autoimmunity. Recent findings showed that innate immune cells trained with a specific stimulus, such as helminth- and other specific bacterial- or yeast-derived products, might also acquire anti-inflammatory features and promote tolerance, which may have important implications for chronic inflammatory diseases such as allergies. Although the potential contribution of trained immunity to the development and chronification of allergic diseases such as asthma or food allergy is starting to be elucidated, the actual role of trained innate immune cells, epithelial cells or haematopoietic stem cell precursors in these processes still remains largely unknown. From a preventive and therapeutic point of view, TIbV formulated with certain polybacterial components showed efficacy in preventing RRTI, including viral-induced wheezing attacks in children, which represent a risk factor for asthma development. The restoration of proper innate immune responses might be also of great relevance during successful AIT. To date, allergen vaccines have not convincingly demonstrated yet capacity to induce trained immunity during AIT. In this regard, it has been previously shown that next generation allergoid-mannan conjugates reprogram monocytes into tolerogenic DCs by mechanisms depending on metabolic and epigenetic reprogramming, suggesting that this next generation AIT vaccine might well promote additional trained tolerance mechanisms associated with the reported clinical effects. However, further research is still needed to firmly demonstrate this capacity for allergoid-mannan conjugates. The better understanding of the potential role of trained immunity in the initiation and maintenance of allergy is of utmost importance as it will help to pave the way for the development of future novel TIbV for AIT (Figure 5), which might well contribute to improving preventive and/or therapeutic strategies for allergic diseases.

AUTHOR CONTRIBUTIONS

O.P. conceptualized and designed the scope of the review. L.M.-C., C.S.-O., A.A., J.D.-A., M.G.N., J.L.S. and O.P. wrote the manuscript. All the authors approved the final version of the paper.

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CONFLICT OF INTEREST

O.P. has received fee for lectures or participation in Advisory Boards from Allergy Therapeutics, Amgen, AstraZeneca, Diater, GSK, Pfizer, Inmunotek SL, Novartis, Sanofi Genzyme, Stallergenes and Regeneron. O.P. has received research grants from Inmunotek SL, Novartis SL, MINECO, MICINNIN and CAM. JLS is the founder and CEO of Inmunotek SL. The rest of the authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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