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REVIEW

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From preschool wheezing to asthma: Immunological determinants

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Abstract

Asthma represents a chronic respiratory disease affecting millions of children worldwide. The transition from preschool wheezing to school-age asthma involves a multifaceted interplay of various factors, including immunological aspects in early childhood. These factors include complex cellular interactions among different immune cell subsets, induction of pro-inflammatory mediators and the molecular impact of environmental factors like allergens or viral infections on the developing immune system. Furthermore, the activation of specific genes and signalling pathways during this early phase plays a pivotal role in the manifestation of symptoms and subsequent development of asthma. Early identification of the propensity or risk for asthma development, for example by allergen sensitisation and viral infections during this critical period, is crucial for understanding the transition from wheeze to asthma. Favourable immune regulation during a critical 'window of opportunity' in early childhood can induce persistent changes in immune cell behaviour. In this context, trained immunity, including memory function of innate immune cells, has significant implications for understanding immune responses, potentially shaping long-term immunological outcomes based on early-life environmental exposures. Exploration of these underlying immune mechanisms that drive disease progression will provide valuable insights to understand childhood asthma development. This will be instrumental to develop preventive strategies at different stages of disease development for (i) inhibiting progression from wheeze to asthma or (ii) reducing disease severity and (iii) uncovering novel therapeutic strategies and contributing to more tailored and effective treatments for childhood asthma. In the long term, this shall empower healthcare professionals to develop evidence-based interventions that reduce the burden of asthma for children, families and society overall.

KEYWORDS
asthma, immunology, innate immune cells, polysensitisation, progression, viral infections, wheeze

1 | INTRODUCTION

The role of a number of immunological influences in early childhood as determinants for subsequent asthma is not completely understood. Whether underlying inflammation present in asthmatic children drives immune imbalance or whether immune imbalance at an early age sets the stage for progression from wheeze to asthma is not well determined.

The immune system consists of two main branches, innate and adaptive immunity and is a pivotal defence mechanism to distinguish between self and non-self components, protecting the host from the latter. This process involves several key steps, such as processing and recognition of non-self antigens, activation of immune cells and finally, initiation of inflammatory or cytotoxic responses as well as activation of multidirectional communication and signalling pathways. Therefore, healthy immune maturation and balanced interaction of innate and adaptive immune regulation are important for an evolving healthy immune system in childhood. In parallel, the respiratory system is not fully developed in early life and is still maturing until adolescence. As a result, changes in the lung environment during this 'window of opportunity' can lead to a modulated behaviour of immune cells and organs persisting long after the original trigger has vanished and may contribute to the progression from wheezing to asthma, along with other risk factors.

This section will focus on immunological processes in asthma, exploring key immune players, important signalling pathways, the role of allergens and immune cells, as well as cytokines and their contribution to the development of wheeze and asthma. Shedding light on these immunological aspects will enhance our understanding of the transition from preschool wheezing to asthma.

Key Message

The transition from preschool wheeze to asthma cannot be well predicted clinically and involves numerous immunological processes. These include responses to exposures/triggers in early childhood, executed by different subsets of immune cells producing pro- and anti-inflammatory mediators and inducing different signalling pathways, all of which may influence immune maturation at an early stage. Intervention at an early stage, the so-called 'window of opportunity' can promote immune tolerance, possibly reducing asthma risk, while identification of children with first signs of clinical allergy, allergic sensitisation, along with other risk factors such as early viral infection, can help predict early disease progression. Understanding the determinants of these immunologic mechanisms relevant for progression of wheezing to asthma is critical for developing targeted interventions and personalised approaches and ultimately reducing the burden of this global health problem.

2 | THE INVOLVEMENT OF DIFFERENT IMMUNE CELLS IN PROGRESSION FROM WHEEZE TO ASTHMA

The progression from preschool wheezing to asthma involves complex immunological interactions, encompassing various immune cells of adaptive and innate immunity, along with regulatory mechanisms. However, the exact mechanisms are still not well understood. There are many studies on molecular and cellular mechanisms in children with asthma. However, only a few investigated possible associations and involvements of immune cells in persistent wheeze progressing to subsequent asthma.

One of the most important immune cells that play a significant role for asthma pathogenesis are dendritic cells (DCs), which act as antigen-presenting cells. They serve as key messengers between innate and adaptive immune regulation. For instance, deleting cluster of differentiation (CD)11c$^+$ cells, being the most widely used defining marker for DCs, prior to sensitisation resulted in the elimination of clinical asthma symptoms, whereas administration of CD11c$^+$ allergen-pulsed DCs induced asthma in naïve mice.[1] DCs can activate and prime naïve T cells, initiating adaptive immunity, contributing to the maintenance of T-helper 2 (TH2)-mediated responses and to the development of long-term immunity.[2] DCs have, therefore, facilitated the body's ability to defend against infections. Different subsets of DCs exist, including plasmacytoid (pDCs), myeloid/conventional (mDCs/cDCs) and monocyte-derived (moDCs) DCs, each playing distinct roles in the immune system. DCs can recognise foreign antigens and infectious agents at mucus sites, working closely with bronchial epithelial cells (ECs). In patients with allergic asthma, elevated numbers of mDCs and/or pDCs were observed in peripheral blood, sputum and bronchoalveolar lavage following allergen inhalation,[3–5] showing their crucial role as regulators of allergen-driven immune responses.[6]

Furthermore, DCs, for example pDCs, are involved in the maintenance of immune homeostasis by various tolerogenic mechanisms, including promoting regulatory T cells (Tregs) and regulatory cytokines like interleukin (IL)-10, IL-27 and transforming growth factor (TGF)-ß[7] or suppressing aberrant TH2 allergic responses, making them potential candidates for therapeutic use in controlling excessive TH2-driven allergic airway inflammation, particularly in experimental models.[8] Importantly, in children with a family history of atopy, a lower frequency of circulating pDCs until 1 year represents a risk factor for more frequent and more severe respiratory tract infections, the risk of subsequent wheezing and asthma diagnosis at 5 years of age, while a higher number of pDCs protected against these outcomes.[9] Furthermore, wheezy children with severe respiratory syncytial virus (RSV) bronchiolitis requiring hospitalisation until 1 year of age and who developed asthma by 6 years showed significantly less pDCs in peripheral blood than children who did not develop asthma.[10] These data indicate that pDCs play a role during wheeze and asthma development in children. However, their specific role in transition/progression from wheeze to

asthma remains to be determined. Therefore, further studies on pDC prior to asthma development may provide insights during this valuable 'window of opportunity' for future prevention of this common disease.

DCs have also been associated with environment-mediated protection against childhood asthma.[11–14] They induce tolerance mechanisms through unresponsiveness and directly downregulate inflammation to control harmful inflammation. For instance, the percentage of mDC2, a subset of mDCs associated with TH2 development and allergic asthma, was lower in farm-exposed children vs. non-farm children at age 6 years, while asthma in non-farm children was positively associated with mDC2s, reflecting TH2-skewed immunity.[14] Exposure to foreign antigens during this critical period of immune development may significantly influence the developmental programming of DCs, leading to the emergence of distinct DC phenotypes and functions. These changes can have both short-term and long-term effects on health, especially concerning the progression to childhood asthma.

Moreover, the communication between DCs and bronchial ECs is important in initiating asthma symptoms. Similar to DCs, ECs express various pathogen recognition receptors that recognise pathogen-associated molecular patterns. Upon activation (Figure 1), ECs secrete pro-inflammatory cytokines known as alarmins, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP). Additionally, they release chemokines such as CC-chemokine ligand (CCL)-5, CCL17, CCL11 and CCL22, leading to activation of the nuclear factor k-light-chain-enhancer (NF-κB) signalling pathway and promoting TH2 cell polarisation.[15] These epithelium-derived cytokines can activate various immune cells, including eosinophils, basophils, mast cells, type 2 innate lymphoid cells (ILC2), TH2 cells and cDC2s, thereby promoting a TH2 immune response that plays a central role in allergic asthma. Interestingly, recent research has also implicated TSLP and IL-33 in non-T2-type non-eosinophilic inflammation, suggesting their involvement with TH17 cells and associated cytokines like IL-17 and IL-23 in its pathogenesis. For instance, circulating TSLP was associated with a reduced incidence of recurrent wheeze in children not sensitised to aeroallergens,[16] indicating a complex interplay between various immune cells, atopy and asthma subtypes that may be important early in life.

Furthermore, an increased permeability of the EC barrier, probably due to the loss of tight junction and adherent junction proteins, allows allergens to cleave these intercellular junctions, leading to the loss of cell–cell contacts, EC damage and promotion of this inflammatory response.[17] These changes in EC function are already observable at a very young age,[18] suggesting their potential contribution to wheeze and early onset of asthma. For instance, this defect in airway EC repair was strongly associated with young children with wheezing, potentially mediated via dysregulations in phosphoinositide-3-kinase (PI3K)-Akt-integrin α5β1 axis[19] and Notch-integrin α5β1 axis,[20] a process also identified in children who developed asthma later in life.[21] In addition, the role of changes in the sub-epithelial membrane thickness seems to be important at an early age. An increasing thickness of the reticular basement membrane was already present in very young children with asthma risk factors before a symptom-based diagnosis of asthma,[22] proposing that airway remodelling starts at a very early age, even before the first clinical onset. Hence, regulating airway epithelial barrier function is gaining significance as a crucial checkpoint during early wheeze manifestation.

Other important immune cells comprise Tregs, which play a critical role in maintaining immune balance. A deficiency or inefficient function of Tregs contributes to an exaggerated inflammatory response early in life and subsequent asthma progression. Tregs suppress effector T cells, maintaining immune balance and preventing excessive inflammation. However, Treg dysfunction or reduced frequency may disrupt this delicate balance, leading to enhanced allergic responses and asthma exacerbations. Findings in cord blood from offspring of atopic mothers showed lower Treg number expression and impaired function,[23] while farm-exposed neonates showed the opposite. Furthermore, in asthma-protected farm-exposed 4.5-year-old children, increased Treg numbers upon stimulation were identified, which was not present any more at age 6 years. This suggests a 'window of opportunity' during which the environment influences the immune system, potentially contributing to protective effects against asthma development.[24–27] Also, impaired Treg function can lead to dysregulated immune responses, contributing to the initiation and persistence of asthma.[28] Due to heterogeneous findings of Tregs with reduced and increased numbers in children with asthma, the study context seems relevant to how they exert their healthy biological function.[27,29,30] Moreover, their role in early wheeze is barely described. Notably, the interplay between Tregs and other immune cells, such as TH2 and DCs, significantly impacts asthma pathogenesis. Tregs regulate the differentiation and activation of TH2 cells, which drive allergic responses and can modulate DC function, influencing allergen presentation and shaping subsequent immune responses.

Recent studies have highlighted the significant role of innate immune cells, mainly ILC2s, in type 2 asthma inflammation alongside the well-known TH2-mediated response. Upon activation by alarmins, ILC2s produce type 2 cytokines (IL-4, IL-5, IL-9 and IL-13) as well as prostaglandin (Figure 1), similar to TH2-cells but with a quicker response time,[31] further promoting TH2-driven allergic response. For instance, a study showed that depletion of ILC2s in papain-sensitised mice reduced IL-4-producing memory TH2 cells in the airways.[32] Another study showed an interaction between ECs and ILC2s that play a major role in maintaining chronic asthma.[33] Moreover, a cord blood ILC2 subpopulation was associated with lower infant lung function,[34] and recent studies showed that increased ILC2 numbers were associated with RSV-induced bronchiolitis and recurrent wheezing,[35] potentially involved in increased susceptibility to asthma. However, as ILCs are a quite newly studied immune cell population, not many data report on the impact of ILC2s during wheeze and progression to asthma. Nevertheless, recent data show that ILCs can be trained by inflammatory stimuli, exhibiting a similar gene expression profile to memory T cells, which might explain why patients with asthma are often sensitised to multiple allergens as the recall response is nonspecific to allergen types and induce TH2

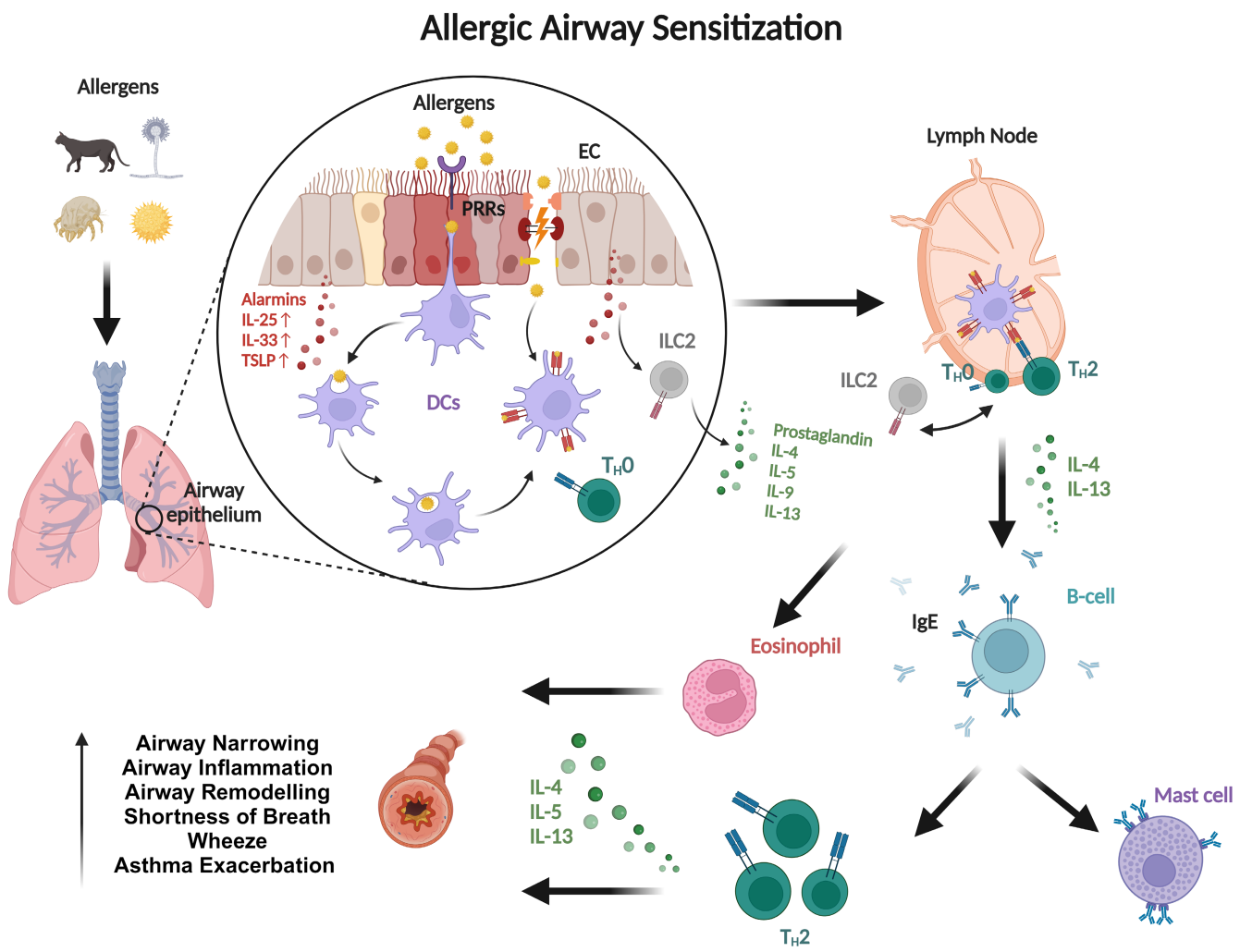

FIGURE 1 Immunological mechanisms of allergic sensitisation. Early childhood allergen exposure triggers immune responses that produce allergen-specific immunoglobulin E (IgE) antibodies, resulting in increased epithelial cell (EC) barrier permeability and promotion of inflammatory responses. Bronchial epithelial cells and dendritic cells (DCs) interact during allergic responses. The airway epithelium releases cytokines (alarmins) like IL-25, IL-33 and TSLP, promoting TH2 cell polarisation in response to allergens, pollutants and pathogens. Upon encountering airborne allergens, DCs process them into peptides, presenting allergen components to naïve $CD4^+$ helper T cells (TH0) in lymph nodes. Group 2 innate lymphoid cells (ILC2s) play a vital role in type 2 immunity and asthma, activated by TSLP, IL-25 and IL-33 to produce type 2 cytokines (IL-4, IL-5, IL-9 and IL-13) and prostaglandin. ILC2s may also act as antigen-presenting cells, influencing T cell activity and promoting eosinophil activity. Additionally, IgE production, mainly from memory IgG^+ B-cells and cytokines secreted by TH2 and ILC2 cells during sensitisation, is critical for the immune system's recognition and memory of the allergen. The cross-linking of these allergen-specific IgE antibodies to the high-affinity FcεR on the surface of mast cells leads to the activation and the release of several inflammatory mediators, such as histamine, prostaglandins and leukotrienes, promoting further the allergic reactions and with that asthma-associated symptoms (created with BioRender.com).

differentiation.[36] This process, known as 'trained immunity' may influence long-term immune responses to subsequent exposures, suggesting that early-life exposure to environmental factors may play a crucial role in shaping an individual's immune system. For instance, long-lasting functional changes through reprogramming processes involving epigenetic modifications and metabolic shifts may lead to an enhanced and rapid response upon subsequent encounters with the same pathogen or even unrelated infections.[37] On the contrary, individuals raised in rural or farm environments, where diverse microbial exposures are common, have shown reduced rates of allergic diseases due to the protective effects of trained immunity.[38] This growing understanding of the potential impact of trained immunity on immune function depending on the environment may pave the way for a deeper understanding of the development of wheeze and asthma and possible prevention strategies.

3 | THE IMPACT OF EARLY-LIFE SENSITISATION

A fully functional immune system has three main functions: (i) defending against foreign substances, (ii) eliminating worn-out

self-components and mutant cells and (iii) enabling the host to tolerate the presence of both non-pathogenic and pathogenic microorganisms.[39] Consequently, a healthy immune system balances attack and tolerance mechanisms, developing regulatory pathways to prevent excessive immune responses to self or harmless antigens. However, deficient immunological tolerance mechanisms may lead to an inappropriate immune response to harmless substances. This may manifest clinically as wheeze in the first years of life or subsequently as asthma in childhood. Allergen exposure during early childhood triggers complex immune responses, leading to the production of allergen-specific immunoglobulin E (IgE) antibodies. These IgE antibodies bind to high-affinity (FcεRI) and the low-affinity CD23 (FcεRII) receptors, expressed on various immune cells (basophils, mast cells, eosinophils, monocytes and dendritic cells) and airway cells (airway smooth muscle cells, endothelial cells and epithelial cells).[40] Expression of the FcεRI receptor is directly correlated with IgE serum levels.[41] This priming phase, known as sensitisation (Figure 1), is crucial as it enables the immune system to recognise and 'remember' the allergen for future encounters, setting the stage for subsequent allergic reactions and asthma development. The link between allergic sensitisation and progression from wheeze to asthma has been suggested in several studies (Figure 2).[42,43] Even elevated cord blood IgE levels were suggested as early markers to predict newborns at risk for allergies later in childhood.[44,45]

Furthermore, the early and augmented degree of specific (s) IgEs may reflect an early-life origin of a T2 high phenotype (high blood eosinophilia and atopy), associated with children with wheeze that were more likely to develop asthma at the age of 6 years.[46] Moreover, early-life persistent polysensitisation was a strong predictor of preschool wheeze, playing an important role in the progression to school-age asthma.[47] The pattern of interaction between molecule-specific IgE responses to several allergen molecules appears to hold a better predictive value for asthma development than a single specific IgE response.[48] Moreover, certain allergenic molecules (e.g. Bet v 1, Ara h 2, Ara h 6 and Fel d 1) have been identified as initiators, triggering an immune (IgE-) response towards different, non-cross-reactive molecules of the same allergen source. The process from sensitisation to one allergen, that is a mono- or oligomolecular stage, to polymolecular sensitisation has been named 'molecular spreading' and contributes to asthma development.[47] In addition, the time course, type of allergen exposure and strength of sensitisation during critical developmental periods significantly influence the risk of subsequent asthma development. For instance, children with high sIgE levels to seasonal allergens (e.g. grass pollen and birch pollen) were associated with low lung function at a young age without established asthma diagnosis,[49] indicating the first symptoms of the atopic late-onset wheeze phenotype. However, not all sensitised children will develop asthma later in life, and several studies suggest that a positive parental history of atopy is important for the increased risk of developing asthma.[50] Furthermore, it is important to note that asthma and other atopic diseases can also occur independently of allergic sensitisation, for example induced by other triggers such as viral infections. The strength of the association between atopy and asthma varies among different populations based on factors such as socioeconomic status, urbanisation, ethnical origin and geographic region, reflecting the crucial role of genetic

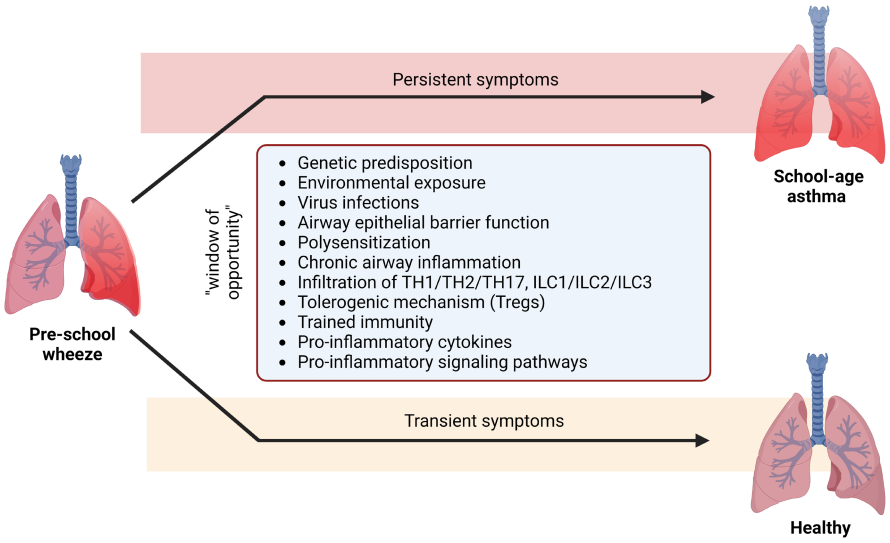

FIGURE 2 Early 'window of opportunity' and determinants of asthma progression. Asthma is a complex chronic respiratory disease affecting millions of children worldwide, starting already at an early age. The progression from preschool wheezing to school-age asthma involves complex immunological interactions like activation proliferation of specific innate and adaptive immune cells, pro-inflammatory cytokines and genes and downstream activation of certain signalling pathways. Identifying specific allergens and viral antigens, as well as their interactions with the immune system during this critical period, is crucial for understanding the immunological basis of the transition from wheeze to asthma. On the other side, some factors like early exposure to diverse microbial environments and allergens, trained immunity and activation of tolerogenic mechanisms can influence immune maturation and homeostasis, protecting against atopic diseases later on. Hence, immune regulation during the critical 'window of opportunity' in early childhood can induce lasting changes in immune cell behaviour, influencing asthma development (progression/remission) and shaping disease trajectories (created with BioRender.com).

predisposition and environmental factors in the development of wheeze and the progression to asthma.[51]

4 | THE IMPACT OF VIRAL INFECTIONS

Approximately half of all children experience at least one episode of wheezing before the age of six, mainly due to RSV or rhinovirus (RV) infection during childhood.[52,53] These early viral infections can cause significant—yet currently not completely understood—changes in immune and lung development, potentially affecting respiratory health in the long term by, for example the development of asthma (Figure 2). Respiratory viruses like RV typically enter epithelial cells through intercellular adhesion molecule (ICAM)-1, disrupt tight junctions, impair epithelial barrier function and trigger the proliferation of inflammatory cells and cytokines in the airway, constituting a nonspecific immune response.[54] Moreover, viral antigens can induce IgE production, leading to sustained FcεRI activation, which could exacerbate viral-induced airway damage.[55] During viral infection, FcεRI activation may inhibit the release of type I interferons (IFNs) by pDCs, influencing severity and duration of viral-induced airway damage. The production of viral-induced IgE may also involve the release of TSLP by the airway epithelium, further triggering TH2 and TH9-related immune response, potentially contributing to wheeze and asthma onset or exacerbation early in life. Indeed, recent epidemiological evidence supports a synergistic interaction between virus infection and allergen exposure.[56] For instance, RV-induced wheezing together with sensitisation by age 3 years showed the highest risk of subsequent asthma until 13 years.[57] Moreover, recent studies have observed that certain viruses can induce TH2-type immunity, which may lead to a persistent asthma-like pathology even after the resolution of the infection, including mucous hyperplasia, eosinophilic inflammation and AHR.[58] For instance, a substantial proportion of children hospitalised with RSV bronchiolitis mostly have a skewed TH2 response, an increased prevalence of atopy later in life, and develop more frequent recurrent wheeze that may progress to asthma.[53,59] However, the detailed immunological mechanisms underlying the interaction between airway virus infection and chronic airway inflammation in wheeze and/or asthma remain unclear.

5 | THE IMPACT OF PHENOTYPES AND ENDOTYPES

Numerous studies indicate that the developmental trajectory of distinct asthma phenotypes into clinical allergic asthma (AA) and non-allergic asthma (NAA) is determined during early childhood events. As asthma is a heterogeneous condition with various clinical and immunological profiles, emerging evidence underscores the critical role of early-life events, suggesting different clinical characteristics and distinct pathophysiological entities in these two phenotypes. For instance, it was shown that preschool children with elevated levels of sIgE and multiple wheezing triggers, including allergens and viruses, are often at increased risk of developing asthma.[60,61] This pattern, already observed early in childhood, is similar to the AA phenotype. On the contrary, children with viral-induced wheeze were suggested to show shared underlying characteristics of the NAA phenotype, for example viral infections as a trigger and lower/no sensitisation.[62,63] However, the underlying mechanisms of different wheeze phenotypes and the progression to asthma sub-phenotypes still require further research.

Many studies have shown that gene expression patterns in at-risk children at birth were similar to those with wheeze and asthma later in life. For example, a study detected decreased Toll-like receptor 2 (*TLR2*) expression in unstimulated cord blood samples of allergic mothers,[64] while *TLR2* expression was upregulated following stimulation in another study.[65] Additionally, another study in PBMCs reported reduced *TLR2* expression under unstimulated conditions but increased expression upon stimulation in asthmatics in comparison with controls.[66] Interestingly, higher *TLR2* expression upon mitogen stimulation at birth was associated with subsequent multitrigger wheeze and was found to act as a mediator between the 17q12-21 risk variant and multitrigger wheeze.[67] Of note, unstimulated and stimulated *TLR2* expression was increased in cord blood mononuclear cells (CBMCs) from farm-exposed mothers, suggesting that early exposure to a rich microbial environment induces a robust and long-lasting upregulation of innate immunity receptors.[68] This phenomenon might play a crucial role in immune maturation and protection against atopic diseases later in childhood. Additionally, the expression of the anti-inflammatory gene TNF alpha-induced protein 3 (*TNFAIP3*) at birth was decreased in children with asthma at school-age and even in children with manifested asthma, reflecting an increased inflammatory status that is already visible at birth.[12] Moreover, differences in gene expression between the allergic and non-allergic asthma phenotype were observed, showing, for example decreased expression of chloride intracellular channel 4 (*CLIC4*), tuberous sclerosis 1 (*TSC1*) in allergic asthma, and increased expression of neutrophilic genes *CD93*, triggering receptor expressed on myeloid cells 1 (*TREM1*), and regulator of G-protein signalling 13 (*RGS13*) in non-allergic asthma.[29]

Molecular endotyping and multi-omics strategies can also be useful to identify endotypes, for example by applying clustering algorithms. Recent research utilising a proteomics dataset successfully revealed three distinct endotypes, whereby one of these endotypes was associated with a higher risk of asthma diagnosis at 6 years.[69] This cluster was characterised by atopy and upregulation of NF-κB and PI3K signalling pathways. As mentioned above, the PI3K-Akt pathway was also identified as the top upstream transcriptional regulator mainly associated with viral-induced wheeze exacerbation. These findings underscore the potential of proteomics data in identifying distinct endotypes and predicting future asthma outcomes early in children.[19] Furthermore, Janus kinase (JAK) signal transducer and activator of transcription proteins (STAT) pathway has been linked to both the eosinophilic[70] and neutrophilic asthma subtype.[71] For instance, type I IFN may activate the JAK–STAT1/2 pathway and a series of IFN-stimulatory genes that produce potent

antiviral proteins for eliminating virus infections, possibly playing a role early in life. Targeting the JAK–STAT pathway has emerged as a potential therapeutic strategy for T2-high asthma, with JAK inhibitors being investigated in clinical trials to control airway inflammation and improve asthma symptoms.[72] However, no direct association between JAK–STAT and wheeze progression to asthma has been identified yet.

Similarly, the mitogen-activated protein kinase (MAPK) pathway is activated in response to allergens, pollutants and other environmental triggers and was shown to be important in asthma development. In particular, the p38 MAPK and extracellular signal-regulated kinases 1/2 (ERK1/2) pathways have been implicated in asthma pathogenesis.[73] For instance, lower levels of dual-specificity phosphatase (*DUSP1*) expression were observed in asthmatic children. Interestingly, *DUSP1* expression levels could be restored to healthy levels upon farm-dust stimulation, leading to the downregulation of inflammatory MAPKs on gene and protein levels.[11] As *DUSP1* serves as a crucial regulator of MAPK and a suppressor of pro-inflammatory processes involving key players such as ERK1/2 and p38,[74] these results contribute to understanding the underlying mechanisms of asthma pathogenesis. Moreover, decreased expression of *JUNB*, *TNFAIP3*, *DUSP2*, leukocyte immunoglobulin-like receptor subfamily B member 2 (*LILRB2*) and TNF superfamily member 13 (*TNSF13B*) in peripheral $CD4^+$ T cells, all involved in stress responses either via the MAPK/ERK-pathway or via the NF-kB-pathway, were already found in children with wheeze but without active disease,[75] showing further potential pathways involved in early life. However, the literature on the pathogenesis of MAPK signalling pathway in preschool wheeze is also limited and further studies on this topic are urgently needed as understanding of the molecular signatures and immunological pathways associated with asthma may be critical for the transition from a healthy state to wheezing and ultimately to asthma manifestation. Using family history, clinical symptoms, proteomic and transcriptomic data and unbiased data-driven phenotyping through hypothesis-free analyses could provide a powerful tool that could enable significant advances in asthma research.

6 | CONCLUSION

The underlying immunological mechanisms for why some children with preschool wheeze develop asthma, and others do not, even with similar genetic predisposition and initial clinical symptoms, remain unclear. This raises two central questions: (i) How can we more precisely predict which children will develop severe wheezing episodes requiring hospitalisation? and (ii) What strategies can we employ to prevent the progression of preschool wheezing to asthma? If both questions are causally related, a promising solution may lie in identifying genes and immune cells that exhibit distinct regulatory patterns in children during early wheeze and can predict subsequent asthma.

Although this comprehensive review provides insights into determinants and underlying mechanisms that can drive disease progression from preschool wheezing to asthma, the precise mechanisms that initiate this progression still require longitudinal, well-powered studies in early life with very thorough clinical characterisation. The multifaceted interplay of immune sequelae following allergen exposure and/or viral infections involving numerous immune cell subsets, mRNA and protein expression of multiple networks measurable as gene and cytokine expression is critical in shaping the trajectory from early childhood wheezing to asthma development. Particularly, the propensity for healthy immune regulation during critical developmental stages, often labelled as a 'window of opportunity' (Figure 2), can lead to permanent changes in immune cell behaviour and organ response, even after the initial trigger has subsided. Therefore, understanding and assessing immunological mechanisms key to asthma development during early childhood is crucial for (i) early preventative options and (ii) reducing disease burden and developing targeted interventions and personalised approaches to manage asthma in children effectively. Distinguishing between wheezing prospectively in childhood (e.g. between transient and persistent wheezing phenotypes, which have similar onset) may facilitate appropriate treatment selection. While longitudinal wheeze trajectories overlap with asthma, patterns of symptom heterogeneity over time may further delineate the dynamics of disease progression and/or remittance of asthma and may reveal phenotypes of airway disease that are distinct from clinically diagnosed asthma.

AUTHOR CONTRIBUTIONS

Kristina Laubhahn: Writing – original draft; visualization; conceptualization. **Bianca Schaub:** Supervision; writing – review and editing; conceptualization.

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