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A Review of the CD4+ T Cell Contribution to Lung Infection, Inflammation and Repair with a Focus on Wheeze and Asthma in the Pediatric Population

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Abstract

Childhood asthma and wheezing are very common, especially in those born preterm. Genetic and environmental factors are associated with developing asthma and wheezing. Respiratory syncytial virus and rhinovirus infections have been implicated in playing a causal role in the development of childhood asthma and wheezing, perhaps by altering the development of the immune system. Several subtypes of asthma and wheezing have been described which involve different mechanisms of pathophysiology. Much of the recent work in the field of asthma research has focused on describing unique aspects of these disease subtypes, which could lead to new drug targets. Alterations in CD4+ T cells have been described with alterations in the T helper 1, 2, 17 and regulatory cell balance could provide valuable targets for the development of new treatment strategies for the various subtypes of disease. This review article focuses on factors involved in childhood asthma and wheeze and potential drug targets.

Keywords: *Wheeze; Asthma; CD4+ T cells; Lower respiratory tract infection; Preterm birth; Treatment strategies*

Abbreviations: BPD: Bronchopulmonary Dysplasia; CD: Clusters of Differentiation; IL: Interleukin; LRTI: Lower Respiratory Tract Infection; NICU: Neonatal Intensive Care Unit; RSV: Respiratory Syncytial Virus; RV: Rhinovirus; TSLP: Thymic Stromal Lymphopoietin; Treg: T regulatory cell; Th: T helper

Introduction

Respiratory infections and wheezing are very common in young children. Recurrent wheezing has been associated with a decrease in the quality of life in children with asthma [1,2]. Given that infants who are born preterm face a higher risk of childhood wheezing and asthma [3], they represent a unique cohort to study the mechanisms behind what causes childhood wheezing. Understanding the causes of wheezing could lead to better treatments, thereby improving the quality of life in children who wheeze. Several subtypes of wheezing and asthma have been described in children [4], which likely have different pathophysiologies [5]. It is well established that exposure to inflammatory conditions in utero contribute to an increase in lung dysfunction and asthma later in life [6-8]. Epithelial cells and innate immune cells contribute to the pathogenesis of lung disease [9,10]. Furthermore, both a genetic predisposition and exposure to environmental factors, including infectious agents, likely contribute to the development of chronic lung disease [8-12]. This would then imply that early life alterations in immune function due to environmental exposure could contribute to later life respiratory diseases. While it is known that cells of the innate immune system, including eosinophils, neutrophils, and macrophages, contributes to the development and persistence of inflammatory lung disease [13-15], recent research has focused on a role for the adaptive immune system [16-20]. This review highlights the role that CD4+ T cells play in lung disease and repair, with a focus on the pediatric population.

The association of viral infections with development of wheezing in children

Infants who were born preterm exhibit impaired lung function, likely caused by incomplete lung development, which likely contributes to the development of wheezing. Incomplete lung development is an underlying cause of the lung disease bronchopulmonary dysplasia (BPD) [21-24]. However, increasing evidence also points to multiple viral infections at a young age and the immune system as playing a role in lung damage childhood wheezing [25-28]. An important study identifies that 50% of infants in the neonatal intensive care unit (NICU) were colonized with respiratory viruses, which illustrates the importance of understanding how viral infections affect these patients [29].

Many different viruses have been associated with childhood wheezing and/or impaired lung function. One such virus is respiratory syncytial virus (RSV), which has been shown to be a major cause of lower respiratory tract infection (LRTI) and is associated with high mortality rates globally [30]. Several studies show that children with high viral loads were more likely to have LRTI with symptoms, and that RSV infection was linked to LRTI and that could be associated with the initiation of asthma [31-33]. Additionally, children who were born preterm and develop BPD face an increased risk of being hospitalized due to RSV infection [34]. Furthermore, a recent study reports an inverse relationship between gestational age at birth and death between the ages of 1 and 5 due to respiratory disease, which obviates the need to understand how RSV mediates damage in the respiratory system [35]. Others studies indicate that RSV infection is more severe in children who were born preterm and that wheezing due to RSV infection is associated with a decrease in the health related quality of life in pediatric patients [36-39]. In fact, RSV infection in healthy preterm infants is associated with higher mortality [40]. Furthermore, preterm infants who were treated with an antibody directed against RSV in the first year of life wheezed at a lower rate in childhood versus those who did not receive the treatment [41]. The reduction in the rate of wheezing was seen only in children who were non-atopic. This would then imply that the subtypes of wheeze/asthma in children have different pathophysiologies. Additionally, the age at and the season in which children are exposed to RSV are related to the severity of infection and the development of wheezing [42,43]. Therefore, RSV infection is considered to be a contributor to childhood wheezing.

Rhinovirus (RV) infection in infancy has been linked to an increased risk for childhood wheezing [44]. In addition to infection with RV, other factors including exposure to cigarette smoke, the presence of older siblings, and sensitization to food allergens increased the risk for developing wheezing in early childhood [45]. Another study shows that sensitization to aeroallergens increases RV-associated wheezing, with no association seen with RSV-infection [46]. Another study indicates that recurrent wheezing in 3 year olds was associated with eosinophilia and RV-infection [47]. The fact that sensitization to food- and aeroallergens and eosinophilia are associated with increased risk for developing wheezing indicates that increased systemic inflammation due to allergy likely plays a role in wheezing. The frequency of rhinovirus infection in infancy increased the risk of developing later wheezing, as did impaired neonatal lung function [44,48]. Additionally, children who wheeze and/or have asthma face an increased risk of hospitalization due to rhinovirus infection during young childhood [49]. Exposure of preterm infants to RV while in the NICU was associated with severe effects on the respiratory system [50]. Thus, rhinovirus infection is implicated in the development of childhood wheezing.

Other factors in addition to respiratory infection have been associated with childhood wheeze. Exposure to broad-spectrum antibiotics during infancy could be linked to the development of childhood wheezing [51]. This includes familial history of asthma and exposure to mold [52,53]. Additionally, bacterial infections have been linked to developing childhood asthma [54]. Mode of delivery and iron deficiency during pregnancy might also affect the risk of developing asthma or wheeze [55]. Low birth weight and high body mass index have also been associated with childhood wheeze at age 3 [56]. Thus, confounding factors should be taken into consideration when studying the relationship of infectious diseases with respect to developing childhood wheeze and/or asthma.

CD4+ T cells contribute to clearance of viral respiratory infections and lung repair upon resolution of infection

Anti-viral responses require many cell types from both the innate and adaptive immune systems [57-59]. Exaggerated immune responses, especially by T cells could lead to damage of the lung if sufficient immune restraint is not in place, which could contribute to the initiation and pathophysiology of asthma and other chronic inflammatory diseases [60-63].

While CD8+ T cells are known to play a critical role in anti-viral responses [64], CD4+ T cells also are critical for resolution of respiratory viral clearance and lung repair [65-67]. In fact, the first attempt to develop a vaccine against RSV in the 1960s failed and resulted in increased severity of infection in those vaccinated with a high rate of hospitalization and to death after infection with circulating RSV. The reasons for the failure remain unclear although animal models using the vaccine indicated that an aberrant antibody response, poor T cell priming, altered T helper (Th) 1/2 ratios and exaggerated lung inflammation were observed in vaccinated animals that were challenged [68].

CD4+ T cells take on highly specialized functions, depending on the activation signals received at the time of stimulation [69,70]. Each lineage of differentiation is associated with a network of gene expression pathways that include transcription factors, microRNA, cell surface effector molecules, and cytokines [71-74]. Th1 cells help to clear intracellular pathogens, produce high levels of IFN-γ and express the transcription factor T-bet [75]. Th2 cells produce IL-4, -5 and -13 and influence antibody class switching. Th17 cells produce IL-17A/F and IL-22, express RORγt, and are potent inducers of inflammation. T regulatory cells (Tregs) produce IL-10, express FoxP3, and dampen immune responses. Differentiation of CD4+ T cell lineages often occurs at the expense of another lineage. For instance, factors involved in Th1 differentiation inhibit Th2 differentiation and vice versa [73]. A similar reciprocal differentiation occurs between Th17 and Tregs [73,76]. Furthermore, the location and differentiation of CD4+ T cells during viral infections play a critical role in resolving the infection [77]. Thus, imbalance of the CD4+ T cells during a viral infection could lead to serious damage to the lung which could contribute to the development of later-life wheezing and asthma.

Several recent studies focus on identifying factors associated with subtypes of asthma. One recent study provides evidence that CD4+ T cell skewing toward Th2 or Th1 is different in pediatric patients with allergic asthma versus nonallergic asthma, respectively [78]. In another study, allergic asthmatics were challenged with dust mite antigen, which lead to an increase in systemic Th17 cells and increased neutrophil survival in those subjects who had a prolonged asthmatic response [15,79]. Several other studies present data showing that adults and pediatric asthmatics with atopy exhibited a skewed Th2 status and increased IL-17 production by CD4+ T cells along with decreased Tregs correlated to more severe disease [80,83]. Thus, IL-17 appears to be an indicator of disease severity. It is interesting to note that increased IL-17 production has been seen in tracheal aspirates from infants with severe RSV infection [84]. It will be of great value to determine whether IL-17 is related to the pathophysiology of both RSV infection and asthma.

Another series of related studies indicates that Th1 skewing also relates to asthma disease severity. For example, a study following young adults reported that nonallergic asthmatics showed signs of Th1 skewing [85]. Another study shows that pediatric asthmatics exhibit a higher ratio of expression of GATA3/T-bet and ROR-γ/FoxP3 expression in peripheral blood CD4+ T cells, indicating a Th2 and Th17 skewing in pediatric asthmatics [82]. Additionally, enhanced proliferation and defective activation-induced cell death of CD4+ T cells in childhood asthma [86,87], which suggests poor resolution of an immune response. Since neonatal CD4+ T cell function tends to differentiate toward the regulatory and Th2 pathway, it is possible that a misguided CD4+ T cell response could contribute to the development of childhood wheezing and asthma in the pediatric population [88-90]. It is possible that Treg function is impaired, which would prevent resolution of an inflammatory response. By understanding how the factors involved in this imbalance of T cell differentiation and the function of Tregs, it might be possible to devise new strategies for treating this disease.

Many studies to understand how CD4+ T cells help guide the immune system to mount an appropriate immune response have been completed. It is well known that the BALB/c strain of mouse is skewed toward a Th2 phenotype and exhibits respiratory pathology in response to RSV infection, whereas the Th1-skewed C57BL/6 develops a less severe disease [91]. Mouse models of infection have identified a critical developmental window for the ability of RSV infection to cause lung damage. In one study, neonatal mice were infected with RSV and the same mice were challenged as adults with high-dose RSV [92]. Mice that experienced neonatal RSV infection and were challenged as adults experienced severe weight loss plus lung damage, which could be prevented if CD4+ T cell depletion prior to challenge.

When mice were infected only as adults, severe lung pathology was not observed, indicating that T cell priming as neonates leads to a reprogramming of the immune response. Another study demonstrates that depletion of Tregs prior to RSV infection leads to increased lung damage [93]. Other studies demonstrate that Tregs can rescue antigen-specific CD8+ T cell function in the lung of mice that are chronically infected with lymphocytic choriomeningitis virus and that depletion of Tregs leads to an increased viral load and accumulation of defective viral-specific CD8+ T cells [94,95]. Thus, CD4+ T cells can improve the function of chronically stimulated CD8+ T cells *in vivo.*

In addition to inhibiting T cell activation, they have also been shown to promote lung repair in mouse models of infection and lung inflammation. Tregs have been shown to play an important role in the resolution of lung inflammation following influenza infection [96]. Tregs have been shown to inhibit fibroblast and enhance epithelial cell proliferation in a model of acute lung injury, which could limit fibrosis formation and promote repair in a TGF-β-dependent manner [97-99]. The repair was dependent on extracellular adenosine and CD73 [100]. Treatment of Tregs with a DNA methyltransferase inhibitor enhanced their ability to repair lung following acute lung inflammation [101]. Further evidence for Tregs playing a role in lung repair can be found in models of pulmonary ischemia by promoting angiogenesis [102]. Thus, recent evidence points to a direct role for Tregs in lung repair and factors that impair Treg differentiation or function could contribute to lack of lung repair and the development of wheeze.

Therapeutic targets for treating wheezing and/or asthma in pediatric populations

Currently, most episodes of childhood wheezing are treated using corticosteroids and bronchodilators [103]. However, given the complex nature of pediatric asthma and wheezing, new more targeted treatments could help to target specific pathways [104,105]. Developing new drug targets in pediatric patients who wheeze and/or are asthmatic will be challenging due to their being many subtypes of disease, which are likely caused by different factors. Despite the challenges of the heterogeneity of disease, many drugs are being developed to treat childhood wheeze and/or asthma [106]. Targets include Th2 cytokines including IL-4, -5 and -13, including Suplatast Tosilate, which has been in use for over 20 years in Japan and inhibits eosinophil function [106,107]. Targeting IgE has also been shown to be an effective treatment for atopic asthma and has been used clinically for over a decade in the US. Other drugs in development are targeting the granulocyte-macrophage colony-stimulating factor, which is key to eosinophil trafficking to the lung and mast cell activation [106].

Other drugs being developed are aimed at modulating CD4+ T cell skewing. For instance, an antibody targeting the receptor for a potent Th2 inducer, Thymic Stromal Lymphopoietin (TSLP), has been shown to improve disease in a monkey model of asthma [108-110] and in a murine model of airway inflammation [111]. A recent clinical trial in humans also gave positive results [112]. The OX40/OX40L pathway, which is a potent inducer of Th2 responses, has also been identified as druggable targets [113,114]. Given that Tregs are decreased in some asthmatics and play a role in lung repair, boosting these cells in asthmatics could be beneficial. In a recent study, sublingual administration of house dust mite antigen to allergic pediatric asthmatics led to a decrease in circulating Th17 cells and an increase in Tregs [115]. Blockade of IL-6 in patients with another inflammatory disease, rheumatoid arthritis, increased Treg production without changing Th17 frequencies [116]. Targeting the IL-17 pathway has also been identified as a potential drug target for treating inflammatory diseases [117-119]. Other methods of desensitizing patients to allergens are also being developed [120]. A recent study targeted the T cell co-stimulatory molecule, CD86, in a mouse model of airway hypersensitivity, which decreased lung inflammation [121]. Promising results have been seen in reducing IL-17 production in rheumatoid arthritis patients who were treated with an antibody that targets the T cell co-stimulatory molecule CD28 [122]. Additional targets of antigen presenting cell maturation, such as the Toll-Like Rectors are also being developed [123]. Overall, many treatment strategies are focused on resetting the cytokine production by CD4+ T cells in order to better treat childhood asthma and wheeze.

Discussion

Asthma and wheezing is a major concern in pediatric patients. While lower respiratory tract infections play a substantial role in pediatric asthma and wheeze, alterations in lung structure likely contribute to the development of these conditions. Given that infants born preterm have lungs that are not fully developed, and that their immune systems are skewed toward a regulatory/Th2 phenotype, they face a higher risk of developing asthma and/or wheeze versus those born full term. However, other alterations in immune function are well described in the literature, including changes in the Th17 CD4+ T cell population and in cells of the innate immune system. Many of the changes in the immune result from chronic inflammation that is not resolved properly. T regulatory cells are capable of resolving inflammation and participate in lung repair. By increasing the relative number and function of T regulatory cells, it might be possible to decrease inflammation while concurrently promoting lung healing, thereby effectively treating pediatric asthma and/or wheeze. Future treatments will likely be highly targeted to treat specific subtypes of asthma and/or wheeze.

Conclusion

Given that childhood asthma and wheeze is so heterogeneous, continuing research to a better understanding of which factors are associated with the various subtypes is necessary. The use of drugs to treat other inflammatory diseases could provide potential therapeutic options to be tested in pediatric patients with asthma and/or wheeze. The most effective treatments will likely control inflammation, while at the same time promote lung repair.

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