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Asthma: An Undermined State of Immunodeficiency

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ABSTRACT

Asthma is a heterogeneous chronic respiratory disease characterized by an increased burden of infections. Respiratory tract infections associated with an increased risk for asthma especially when occurring in the first months of life, also represent the most common cause of asthma exacerbations. The association between asthma and the increased frequency of infections and microbiota dysbiosis might be explained by a common mechanism, such as an underlying immune system defect. Apart from the well-established association between primary immunodeficiencies and asthma, several alterations in the immune response following infection have also been observed in asthmatic patients. An impairment in lung epithelial barrier integrity exists and is associated with both an increased susceptibility to infections and the development of asthma. Asthmatic patients are also found to have a deficient interferon (IFN) response upon infection. Additionally, defects in Toll-like receptor (TLR) signaling are observed in asthma and are correlated with both recurrent infections and asthma development. In this review, we summarize the common pathophysiological background of asthma and infections, highlighting the importance of an underlying immune system defect that predispose individuals to recurrent infections and asthma.

Abbreviations: ADAM33: disintegrin and metalloprotease domain 33; BAL: bronchoalveolar lavage; ; BECs: bronchial epithelial cells; ; CVID: common variable immunodeficiency; ; EGF: epidermal growth factor; ; GSDMB: gasdermin B; ; HRV: human rhinovirus; ; IFN: interferon; ; IL-1R: interleukin-1 receptor; ; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; ; IRAK: interleukin 1 receptor associated kinase; ; HAART: highly active antiretroviral therapy; ; HIV: human immunodeficiency virus; ; mAb: monoclonal antibody; ; MD-1: myeloid differentiation-1; ; NF- κ B: nuclear factor- κ B; ; PBMCs: peripheral blood mononuclear cells; ; pDCs: plasmacytoid dendritic cells; ; RSV: respiratory syncytial virus; ; sIgAD: selective IgA deficiency; ; ORMDL3: sphingolipid biosynthesis regulator 3; ; SNPs: single nucleotide polymorphisms; ; SPINK: serine protease inhibitors of the Kazal type; ; SOCS: suppressor of cytokine signaling; ; TGF: transforming growth factor; ; Th1, 2: T-helper 1, 2; ; TLR: toll-like receptor

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Introduction

Asthma is a heterogeneous and genetically complex chronic respiratory disease characterized by variable symptoms of wheezing, shortness of breath, chest tightness, and cough that vary over time and intensity [1]. It affects approximately 300 million people worldwide, being one of the most common chronic diseases in both children and adults [2,3]. Asthma global prevalence is estimated to be 4.3%, affecting mostly developed countries [2]. Childhood-onset asthma is more common in boys than girls and is correlated with atopic sensitization. Adult-onset asthma, on the other hand is more common in female patients and does not seem to be associated with atopy [4].

The complex gene-environment interplay is responsible for the great heterogeneity in clinical presentations of asthma [2] in a degree that asthma is now considered as a syndrome consisting of different diseases with similar clinical presentation rather than a single disease [2,5]. Many researchers have tried to delineate the pathophysiology of asthma, with most of them focusing on the role of Th2 cytokines and the early-life allergen exposure and atopic sensitization [2], but the data are still scarce and our understanding remains poor [6].

There is a number of well described primary immunodeficiencies (Table 1) presenting with asthma in either childhood and/or adult life. However, even in presumed immunocompetent patients, respiratory tract

Table 1. Immune system defects associated with both an increased susceptibility to infections and asthma development.

	Mechanism	Reference
Several primary immunodeficiencies	All associated with asthma and recurrent infections	
CVID		7, 8
slgAD		7
Netherton syndrome		9, 10
IPEX		11
Hyper IgE syndromes		12
DiGeorge syndrome		13
HIV	Associated with asthma and infections. Increased prevalence with HAART.	14
Epithelial barrier defect		
ADAM33 & filaggrin	Involved in the lung epithelial barrier function and tissue remodeling and possibly increase the susceptibility to infections. Polymorphisms in <i>ADAM33</i> & <i>filaggrin</i> genes are associated with asthma.	15
<i>GSDMB</i> & <i>ORMDL3</i>	Both encoded in the 17q21 locus, which is associated with asthma and respiratory tract infections. Participate in the function of the lung epithelial barrier.	16
<i>SPINK5</i>	Contributes to the integrity of the lung epithelial barrier and is associated with chronic rhinosinusitis. Polymorphisms in <i>SPINK5</i> gene are associated with asthma.	17
IFN deficiency	Observed in asthmatic patients following viral infections and is associated with enhancement of respiratory tract infections and asthma exacerbations.	18–20
<i>SOC51</i> & <i>SOC53</i>	Increased in asthmatic patients and inhibits IFN production and enhances respiratory tract infection. Polymorphisms in <i>SOC51</i> and <i>SOC53</i> are associated with asthma.	21
TGF	Increased in BAL fluid and endobronchial biopsy specimens in asthmatic patients, inhibits IFN production and enhances respiratory tract viral infection. Polymorphisms in the <i>TGF-β</i> gene are associated with asthma.	22, 23
Vitamin A deficiency	Associated with an increased risk of asthma and wheezing, possibly caused by decreasing IFN-γ levels.	24
TLR polymorphisms	Polymorphisms in several <i>TLR</i> genes are associated with asthma and increased susceptibility to atopy and infections.	25, 26
<i>MD-1</i> polymorphisms	Polymorphism in the <i>MD-1</i> gene, which encodes a protein enhancing the TLR4 signaling upon LPS stimulation, is associated with asthma.	25
<i>IRAK-M</i>	Polymorphisms in <i>IRAK-M</i> , which is a negative regulator of TLR/IL-1R pathways, is associated with early-onset asthma. <i>IRAK-M</i> enhances respiratory tract HRV infection.	25, 27
IL-15 deficiency	Involved in asthma development and exacerbations. Polymorphisms in the <i>IL-15</i> gene are associated with pediatric asthma.	28

CVID: common variable immunodeficiency; HRV: human rhinovirus; IL-1R: interleukin-1 receptor; IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; MD-1: myeloid differentiation-1; RSV: respiratory syncytial virus; slgAD: selective IgA deficiency; ADAM33: disintegrin and metalloprotease domain 33; GSDMB: gasdermin B; ORMDL3: sphingolipid biosynthesis regulator 3; SPINK: serine protease inhibitors of the Kazal type; SOCS: suppressor of cytokine signaling; TGF: transforming growth factor; TLR: toll-like receptor; IRAK3 interleukin 1 receptor associated kinase 3.

infections have a central role in asthma constituting a major cause of asthma exacerbations and a significant risk factor for asthma development [29–31]. During infancy and childhood, recurrent infections are related to the immaturity of the immune system and may induce alterations of the developing lung, which can predispose to asthma [32]. However, although infections of the respiratory tract are very common during early life, only a minority of these affected children eventually develop asthma. In this context, we hypothesize that underlying immune system defects may predispose to recurrent respiratory tract infections and consequently to the development of asthma [32]. The aim of the present review is to summarize the evidence supporting the role of an impaired immune response to infectious agents in the development of asthma.

Infections and asthma

Viral infections and asthma

Infections of the respiratory tract play a major role in the pathogenesis of asthma as suggested by the

evidence that infants who experienced airway viral infections during the very first months of life are at a higher risk for developing asthma [33]. One wheezing episode or more during the first years of life are known risk factors for the development of asthma [29,32,34,35]. Similarly, an increased number of respiratory tract infections in adults represent a risk factor for the disease, especially in atopic individuals [30]. The atopic sensitization and the early-life wheezing episodes act synergistically in asthma pathogenesis [6,32,34,36].

Numerous birth cohort studies have assessed the association between viral respiratory tract infections in early-life and asthma risk [16,31,32,37–40]. Although this association is moderate for certain viruses [e.g. influenza and human metapneumovirus], the association is much stronger for respiratory syncytial virus (RSV) and human rhinovirus (HRV) [40]. HRV infection, for instance, has been associated with early-life and recurrent wheezing and is positively correlated with asthma development at school-age and atopy co-occurrence [41,42]. In mouse models, HRV has been found to trigger an immune response in the

intrapulmonary airways, leading to airway hyperresponsiveness and inflammation [43,44]. This finding could possibly explain the role of HRV in asthma exacerbation [6].

Moreover, HRV infection has been shown to promote the expression of several airway remodeling mediators, increase mucin production and upregulate the expression of genes involved in the interferon pathway [45]. HRV infection also causes overexpression of the epidermal growth factor (EGF), possibly leading to airway inflammation in asthmatic patients [46]. EGF acts synergistically with some matrix metalloproteinases [46], with the genes encoding for these matrix metalloproteinases also reported as candidate genes for asthma [46]. HRV infection has also been reported to break the tolerance to inhaled antigens in mouse models, inducing an increase in the production of TSLP, IL-33 and OX40 ligand [47]. However, these effects are transient and occur during the infection process, and thus their contribution in asthma pathogenesis remains to be determined [48].

Classic studies by Sigurs et al. showed that RSV bronchiolitis, severe enough to require hospitalization, is also a risk factor for asthma at the age of 7, 13, and 18 [35,49,50]. A recent study evaluating two large cohorts of infants (>80,000 and >180,000) found that the population-attributable risk for asthma contributed by infant bronchiolitis during the RSV season was 10% and 13%. However, in the subset of children with infant RSV-bronchiolitis, the attributable risk was 49% and 47% [40,51]. The relationship between RSV disease severity and subsequent asthma inception is dose-dependent lending support to a causal relationship [52,53]. However, Palivizumab, a monoclonal antibody (mAb) used as RSV-immunoprophylaxis, although found to decrease the number of wheezing days in the first year of life [30,44], has no effect in asthma prevention [54,55], suggesting a multifactorial cause of the disease.

The mechanism by which several respiratory infections are associated with subsequent asthma is not fully understood but the different inflammatory responses released after viral infections seem to play a relevant role. The induction of a prevalent Th2-type response, with the production of IL-4, IL-5, and IL-13, results in a less robust and less efficient reaction to the infection, clinically presenting as increased disease severity and risk for future recurrent wheezing [56].

Recurrent airway infections in asthmatic patients also result in damage of the bronchial epithelial cells (BECs) which in turn leads to chronic airway alterations and hyperresponsiveness [44]. In asthmatic patients, during a viral infection, BECs express higher

levels of IL-25 and IL-33, which play an important role in the exacerbation of lung inflammation [21]. Moreover, IL-33 polymorphism is associated with both wheezing and allergic sensitization [57]. Consequently, recurrent lung infections may have a detrimental effect in impairing the architecture of the lungs, predisposing to asthma [45]. Passive or active smoking exacerbates the viral inflammation and lung remodeling, and might act synergistically with the catastrophic effect of the lung infection [46].

To conclude, the association between viral respiratory tract infections and asthma might be explained by the presence of common pathogenic mechanism [29,58]. An underlying immune defect could explain both the increased burden of respiratory tract infections and asthma.

Bacterial infections and asthma

Bacterial infections play an important role in the pathogenesis of asthma as well [59]. *Bordetella pertussis* and chronic *Chlamydomphila* infection have both been associated with asthma development [60]. *Mycoplasma pneumoniae*, *Haemophilus influenza*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis* have also been reported to cause asthma exacerbations [45]. *Chlamydia pneumonia* may increase virus-induced asthma exacerbations in addition to causing airway hyper-responsiveness and inflammation [39]. There are also reports of increased risk for invasive pneumococcal disease in asthmatic patients, indicating the possibility of an immune system defect of systemic nature [61].

Another link between bacterial infections and asthma is demonstrated by the beneficial use of the oral bacterial extract vaccine OM-85 in the protection from asthma [30,62]. The vaccine OM-85 has been shown to decrease the frequency and duration of the wheezing episodes in children and induce the production of Th1 IFNs and the activation of the inflammatory [30,62]. Moreover, azithromycin, possibly due to its anti-bacterial and anti-inflammatory role, has been shown to have a beneficial role in asthma in adulthood [63]. The pretreatment of BECs with azithromycin, for instance, has led to increased IFN release upon RV-1B and RV-16 infection [22].

Microbiota and asthma

The human microbiota indicates the entire content of the human body in microbes and plays a detrimental role in the human well-being and in the development

of human diseases [64]. Several studies demonstrate the key role of gut and lung microbiota in the pathogenesis of asthma.

Early-life gut microbiota dysbiosis has been described as a risk factor for asthma. Colonization with *Clostridium difficile* in the first month of life, for instance, as well as the increased proportion of certain fungi e.g. *Candida* and *Rhodotorula* spp. and the decreased amount of *Bifidobacteria*, *Akkermansia* and *Feacalibacterium* in neonates has been associated with an increased risk of asthma development [65]. A decreased maturation of gut microbiome in the first year of life also increases the risk for developing asthma, especially in children with asthmatic mothers [66]. Of importance, gut microbiota is found to shape lung immune responses, proposing a cross-talk between the two systems [67]. The use of prebiotic and probiotic supplements seems to protect preterm infants from rhinovirus infections while the administration of *Lactobacillus acidophilus* and *Bifidobacterium animalis* has been associated with reduction of the symptoms of viral respiratory tract infection in children [67].

The study of lung microbiome revealed that patients with asthma have a predominance of *Proteobacteria* phylum in the lower lungs and a lung colonization with pathogenic bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumonia* [67]. Moreover, colonization of the respiratory tract with *S. pneumoniae*, *H. influenza* and *M. catarrhalis* in the first month of life has been correlated with asthma development [65]. Patients with severe asthma are found to be colonized with *Klebsiella* spp. and in the case of obese asthmatics an increased proportion of *Bacteroides/Firmicutes* is observed [65]. The interplay between these pathogenic bacteria and viruses of the respiratory tract may also be of significance [45,59]. Of importance, the diversity of the respiratory tract microbiota is inversely correlated with sensitization to house dust mites early in life [65]. What remains to be elucidated is whether the observed microbial dysbiosis is a result of an underlying defect in the immune response, which promotes the growth of certain microbes possibly pathogenic for asthma, or whether the altered microbiota contributes to asthma development.

Microbiome in environment and asthma

The environment seems to play an important role in the development of asthma as well. Amish people, for example, who exhibit a very low incidence of asthma,

live in an environment with increased microbiome diversity [68]. The opposite implies to Hutterine children, as the Hutterine environment is characterized by a decreased microbiome diversity and thus a much lower protection against asthma [69]. It has been demonstrated that Amish children express higher levels of *TNFAIP3*, which downregulates several inflammatory pathways that depend on nuclear factor- κ B (NF- κ B) [69]. On the other hand, Hutterine children express higher levels of *TRIM8*, which is a positive regulator of TNF- α and NF- κ B [69]. Moreover, Amish children have a decreased expression of *HLA-DR* on monocytes and an increased immature neutrophils from bone marrow, which might be the result of their increased microbial exposure [69]. Innate immune system responses might be associated with a protective role to asthma development. This is highlighted by the fact that *MyD88* and *Trif* deficiency, which are proteins important for the innate immune system signaling, constitutes no protection from asthma in a classic ovalbumin mouse model of allergic asthma, when Amish dust extracts was inhaled [69]. It is possible that the innate immune system protective role on asthma is mediated through the increased microbiome diversity of the environment, as the environment shapes the innate immune system responses towards an anti-inflammatory manner [69].

Asthma as an immunodeficiency

Epithelial barrier impairment

The importance of an impaired respiratory tract epithelial barrier in the pathogenesis of asthma has previously been highlighted in the literature [61]. Polymorphisms in genes involved in the lung epithelial barrier function and tissue remodeling, including *ADAM33* and *filaggrin*, may impact the interaction between the epithelial barrier and microbial pathogens, increasing the risk of developing asthma [15,68]. Single-nucleotide polymorphisms (SNPs) at chromosome 17q21 have been associated with susceptibility to respiratory tract infections in the first years of life and chronic inflammatory airway disease following a viral infection [70]. In particular, 17q21 variants have been linked to early-onset asthma and bronchial hyper-responsiveness, in patients with HRV-wheezing illness in the first years of life [16,71]. Moreover, 17q21 variants have been associated with both asthma and respiratory tract viral infections in children exposed to tobacco in the first years of life [16]. Of importance, the 17q21 variants are not associated with atopy [15], suggesting that the genetic and

environmental mechanisms that determine atopic asthma might be different.

The genes *ORMDL3* and *GSDMB*, both encoded in the 17q21 locus, are differentially expressed in asthmatic patients as compared to healthy individuals [4]. Although the function of *ORMDL3* is not yet fully described, this gene has been reported to be involved in lung epithelial secretory and stem cell proliferation pathways [15,16]. *GSDMB* is involved in the unfolded-protein response, which is a cellular mechanism triggered by a variety of stressful events such as infection, as well as in the function of the epithelial barrier [15]. HRV infections have been shown to increase *ORMDL3* expression, which in turn increases viral replication and decreases repair capacity [16]. *SPINK5* is another gene involved in the maintenance and repair of the epithelia [17,72]. Polymorphisms in *SPINK5* gene have been associated with atopy and asthma development [17]. Following a lung infection, *SPINK5* expression is downregulated in asthmatic patients compared to healthy individuals [17]. Of importance, loss-of-function mutations in *SPINK5* gene cause the Netherton syndrome, which is a rare autosomal recessive disorder that affects the skin and the hair, and causes immune dysfunction [9,73].

Interferon deficiency

BECs are the first line of defense against numerous agents. They produce type I and III IFNs, which constitute an early defensive mechanism against external pathogenic agents, including viruses [74,75]. These cells are able to inhibit the viral proliferation as well as the synthesis of viral proteins, and to induce apoptosis of the infected cell [75]. The function of BECs is impaired in asthmatic patients [18–20,76]. In particular, they have been observed to be resistant to early apoptosis following a HRV-16 infection [76]. Moreover, IFN synthesis in response to infections is decreased while the pro-inflammatory immune response to viral infection appears to be normal [76]. The production of IFN- α , IFN- β , IFN- γ , IFN λ 1, IFN λ 2/3, and IFN- κ s are decreased in asthmatic patients both in vitro and in vivo following RSV infection [18–20,77]. This alteration has been observed in both peripheral blood mononuclear cells (PBMCs) and in macrophages from bronchoalveolar lavage (BAL) [20]. Similar results were observed following HRV infections [19,77,78]. Studies show also a decrease of IFN production upon Newcastle disease virus infection from PBMCs and upon influenza virus infection from purified plasmacytoid dendritic cells

(pDCs) in asthmatic patients [20]. Of importance, the observed IFN deficiency is associated with an enhancement of respiratory tract infections and with asthma exacerbations [20]. However, it has not yet been clarified whether the IFN deficiency is a consequence of the infections or a defect in the host immune response associated with the pathogenesis of asthma [18].

Toll-like receptors

Toll-like receptors (TLRs) constitute a family of innate immunity receptors expressed on antigen-presenting and epithelial cells, that recognize conserved microbial molecules as ligands [79,80]. Following recognition, TLRs primarily activate the innate immune system and initiate an inflammatory response [81]. Polymorphisms in *TLR2*, *TLR7* and *TLR8* have been linked with an increased risk for asthma [25]. SNPs in *CD14*, *TLR2*, *TLR4* and *TLR9* genes have also been found to modify the risk of asthma in children exposed to country living compared to those living in urban environment [26]. TLRs polymorphisms associated with asthma have also been associated with susceptibility to infections and atopy [25]. Polymorphism in the *Myeloid differentiation-1 (MD-1)* gene which encodes a protein enhancing the TLR4 signaling upon LPS stimulation, has been associated with both pediatric- and adult-onset asthma [25]. Moreover, SNPs in *IRAK-M*, which is a negative regulator of TLR/IL-1R pathways, is correlated with early-onset asthma [25]. More studies are needed to shed light on the functional impact of these polymorphisms to the pathogenesis of asthma.

Concluding remarks

Asthma is a chronic heterogeneous disease, resulting from a complex interplay between genetic and environmental factors [16]. Both viral and bacterial infections of the respiratory tract constitute a major risk factor for asthma development and exacerbations, having a causal role in the pathogenesis of the disease (Figure 1). Several defects in the respiratory tract epithelial function as well as in the interferon and TLR response have been associated with asthma. A common denominator of these immune system defects is the increased susceptibility to infections, possibly explaining the increased infectious burden in asthma. Whether the reported immune system defects are causally related to the pathogenesis of asthma or rather a consequence of the disease remains to be

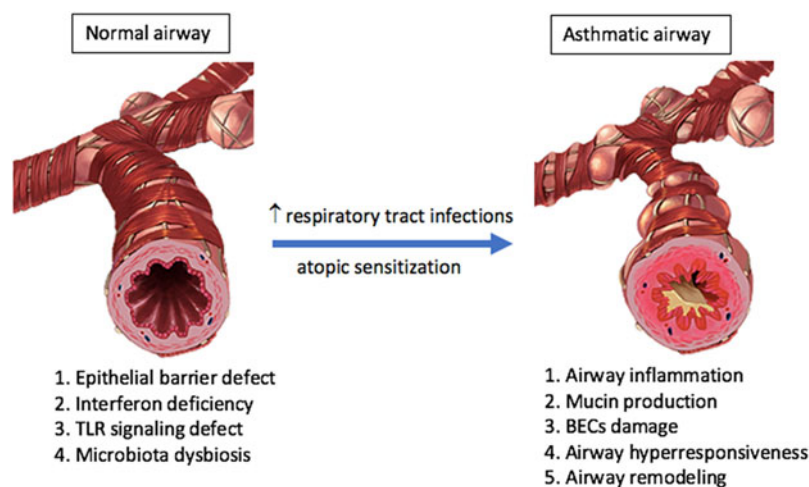


Figure 1. The effect of recurrent respiratory tract infections in the airway. Several factors affecting the immune response following a respiratory tract infection are associated with asthma development. Recurrent respiratory tract infections, which act synergistically with the atopic sensitization, alter airway architecture and predispose individuals to asthma. BECs: bronchial epithelial cells; TLR: toll-like receptor.

elucidated. Further studies are required to investigate the role of immunodeficiency on asthma development and to explore additional pathogenic pathways for the implementation of asthma prevention and targeted treatment.

Declaration statement

The authors declare no conflicts of interest with respect to the research, authorship and publication of this article.

References

1. (GINA) GIfA. <https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/> (accessed 01/08/2018). 2018.
2. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2017;391(10122):783–800.
3. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015;16(1):45–56. doi:10.1038/ni.3049.
4. Moffatt MF, Gut IG, Demenais F. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363(13):1211–1221. doi:10.1056/NEJMoa0906312.
5. Belgrave DC, Custovic A, Simpson A. Characterizing wheeze phenotypes to identify endotypes of childhood asthma, and the implications for future management. *Expert Rev Clin Immunol* 2013;9(10):921–936. doi:10.1586/1744666X.2013.836450.
6. Busse WW, Lemanske RF, Jr., Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010;376(9743):826–834. doi:10.1016/S0140-6736(10)61380-3.
7. Urm SH, Yun HD, Fenta YA, et al. Asthma and risk of selective IgA deficiency or common variable immunodeficiency: a population-based case-control study. *Mayo Clin Proc* 2013;88(8):813–821. doi:10.1016/j.mayocp.2013.05.021.
8. Yazdani R, Heydari A, Azizi G, et al. Asthma and allergic diseases in a selected group of patients with common variable immunodeficiency. *J Invest Allergol Clin Immunol* 2016;26(3):209–211. doi:10.18176/jiaci.0062.
9. Renner ED, Hartl D, Rylaarsdam S, et al. Comèl-Netherton syndrome defined as primary immunodeficiency. *J Allergy Clin Immunol* 2009;124(3):536–543. doi:10.1016/j.jaci.2009.06.009.
10. Chavanas S, Garner C, Bodemer C, et al. Localization of the Netherton syndrome gene to chromosome 5q32, by linkage analysis and homozygosity mapping. *Am J Hum Genet* 2000;66(3):914–921.
11. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. *Front Immunol* 2012;3:211.
12. Freeman AF, Holland SM. Clinical manifestations of hyper IgE syndromes. *Dis Markers* 2010;29(3-4):123–130. doi:10.3233/DMA-2010-0734.
13. Staple L, Andrews T, McDonald-McGinn D, et al. Allergies in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) and patients with chronic granulomatous disease. *Pediatr Allergy Immunol* 2005;16(3):226–230. doi:10.1111/j.1399-3038.2005.00259.x.
14. Kynk JA, Parsons JP, Para MF, et al. HIV and asthma, is there an association? *Respir Med* 2012;106(4):493–499. doi:10.1016/j.rmed.2011.12.017.
15. Raedler D, Schaub B. Immune mechanisms and development of childhood asthma. *Lancet Respir Med* 2014;2(8):647–656. doi:10.1016/S2213-2600(14)70129-8.
16. Calışkan M, Bochkov YA, Kreiner-Møller E, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013;368(15):1398–1407. doi:10.1056/NEJMoa1211592.

17. Heymann PW, Nguyen H-T, Steinke JW, et al. Rhinovirus infection results in stronger and more persistent genomic dysregulation: evidence for altered innate immune response in asthmatics at baseline, early in infection, and during convalescence. *PLoS One* 2017;12(5):e0178096. doi:10.1371/journal.pone.0178096.
18. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006;12(9):1023–1026. doi:10.1038/nm1462.
19. Durrani SR, Montville DJ, Pratt AS, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. *J Allergy Clin Immunol* 2012;130(2):489–495. doi:10.1016/j.jaci.2012.05.023.
20. Edwards MR, Regamey N, Vareille M, et al. Impaired innate interferon induction in severe therapy resistant atopic asthmatic children. *Mucosal Immunol* 2013; 6(4):797–806. doi:10.1038/mi.2012.118.
21. Ritchie AI, Farne HA, Singanayagam A, et al. Pathogenesis of viral infection in exacerbations of airway disease. *Ann Am Thorac Soc* 2015;12(Suppl 2): S115–S132. doi:10.1513/AnnalsATS.201503-151AW.
22. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010; 125(6):1178–1187; quiz 1188–1179. doi:10.1016/j.jaci.2010.04.021.
23. Li H, Romieu I, Wu H, et al. Genetic polymorphisms in transforming growth factor beta-1 (TGFB1) and childhood asthma and atopy. *Hum Genet* 2007;121(5): 529–538. doi:10.1007/s00439-007-0337-z.
24. Elenius V, Palomares O, Waris M, et al. The relationship of serum vitamins A, D, E and LL-37 levels with allergic status, tonsillar virus detection and immune response. *PLoS One* 2017;12(2):e0172350. doi:10.1371/journal.pone.0172350.
25. Bartlett NW, McLean GR, Chang YS, Johnston SL. Genetics and epidemiology: asthma and infection. *Curr Opin Allergy Clin Immunol* 2009;9(5):395–400. doi:10.1097/ACI.0b013e32833066fa.
26. Smit LA, Siroux V, Bouzigon E, et al. CD14 and toll-like receptor gene polymorphisms, country living, and asthma in adults. *Am J Respir Crit Care Med* 2009; 179(5):363–368. doi:10.1164/rccm.200810-1533OC.
27. Wu Q, van Dyk LF, Jiang D, et al. Interleukin-1 receptor-associated kinase M (IRAK-M) promotes human rhinovirus infection in lung epithelial cells via the autophagic pathway. *Virology* 2013;446(1-2): 199–206. doi:10.1016/j.virol.2013.08.005.
28. Laza-Stanca V, Message SD, Edwards MR, et al. The role of IL-15 deficiency in the pathogenesis of virus-induced asthma exacerbations. *PLoS Pathog* 2011;7(7): e1002114. doi:10.1371/journal.ppat.1002114.
29. Thomsen SF, van der Sluis S, Stensballe LG. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. *Am J Respir Crit Care Med* 2009;179(12): 1091–1097. doi:10.1164/rccm.200809-1471OC.
30. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet* 2015;386(9998): 1075–1085. doi:10.1016/S0140-6736(15)00156-7.
31. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *Br Med J* 1995;310(6989):1225–1229.
32. Oliver BG, Robinson P, Peters M, Black J. Viral infections and asthma: an inflammatory interface? *Eur Respir J* 2014;44(6):1666–1681. doi:10.1183/09031936.00047714.
33. Saglani S. Viral infections and the development of asthma in children. *Ther Adv Infect Dis* 2013;1(4): 139–150. doi:10.1177/2049936113497202.
34. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178(7):667–672. doi:10.1164/rccm.200802-309OC.
35. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010;65(12): 1045–1052. doi:10.1136/thx.2009.121582.
36. Kusel MM, de Klerk NH, Keadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119(5):1105–1110. doi: 10.1016/j.jaci.2006.12.669.
37. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *Br Med J* 1993;307(6910):982–986.
38. Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002;359(9309):831–834. doi: 10.1016/S0140-6736(02)07953-9.
39. Sykes A, Johnston SL. Etiology of asthma exacerbations. *J Allergy Clin Immunol* 2008;122(4):685–688. doi:10.1016/j.jaci.2008.08.017.
40. Lynch JP, Sikder MA, Curren BF, et al. The influence of the microbiome on early-life severe viral lower respiratory infections and asthma—food for thought? *Front Immunol* 2017;8:156.
41. Jartti T, Korppi M, Ruuskanen O. The clinical importance of rhinovirus-associated early wheezing. *Eur Respir J* 2009;33(3):706–707; author reply 707–708. doi:10.1183/09031936.00155808.
42. Jartti T, Lehtinen P, Vanto T, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006;25(6):482–488. doi:10.1097/01.inf.0000215226.69696.0c.
43. de Kluijver J, Grunberg K, Sont JK, et al. Rhinovirus infection in nonasthmatic subjects: effects on intrapulmonary airways. *Eur Respir J* 2002;20(2):274–279. doi: 10.1183/09031936.02.00247202.
44. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013;368(19): 1791–1799. doi:10.1056/NEJMoa1211917.
45. Smits HH, Hiemstra PS, Prazeres da Costa C, et al. Microbes and asthma: Opportunities for intervention. *J Allergy Clin Immunol* 2016;137(3):690–697. doi: 10.1016/j.jaci.2016.01.004.

46. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet* 2008;372(9643):1107–1119. doi:10.1016/S0140-6736(08)61452-X.
47. Mehta AK, Duan W, Doerner AM, et al. Rhinovirus infection interferes with induction of tolerance to aeroantigens through OX40 ligand, thymic stromal lymphopoietin, and IL-33. *J Allergy Clin Immunol* 2016;137(1):278–288 e276. doi:10.1016/j.jaci.2015.05.007.
48. Durant LR, Makris S, Voorburg CM, et al. Regulatory T cells prevent Th2 immune responses and pulmonary eosinophilia during respiratory syncytial virus infection in mice. *J Virol* 2013;87(20):10946–10954. doi:10.1128/JVI.01295-13.
49. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161(5):1501–1507. doi:10.1164/ajrccm.161.5.9906076.
50. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171(2):137–141. doi:10.1164/rccm.200406-730OC.
51. James KM, Gebretsadik T, Escobar GJ, et al. Risk of childhood asthma following infant bronchiolitis during the respiratory syncytial virus season. *J Allergy Clin Immunol* 2013;132(1):227–229. doi:10.1016/j.jaci.2013.01.009.
52. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, et al. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111(1):66–71.
53. Escobar GJ, Ragins A, Li SX, et al. Recurrent wheezing in the third year of life among children born at 32 weeks' gestation or later: relationship to laboratory-confirmed, medically attended infection with respiratory syncytial virus during the first year of life. *Arch Pediatr Adolesc Med* 2010;164(10):915–922. doi:10.1001/archpediatrics.2010.177.
54. Haerskjold A, Stokholm L, Linder M, et al. Palivizumab exposure and the risk of atopic dermatitis, asthma and allergic rhinoconjunctivitis: a cross-national, population-based cohort study. *Pediatr Drugs* 2017;19(2):155–164. doi:10.1007/s40272-017-0215-7.
55. Mochizuki H, Kusuda S, Okada K, et al. Palivizumab prophylaxis in preterm infants and subsequent recurrent wheezing. Six-year follow-up study. *Am J Respir Crit Care Med* 2017;196(1):29–38. doi:10.1164/rccm.201609-1812OC.
56. Garcia-Garcia ML, Calvo C, Ruiz S, et al. Role of viral coinfections in asthma development. *PLoS One* 2017;12(12):e0189083. doi:10.1371/journal.pone.0189083.
57. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol* 2017;140(4):895–906. doi:10.1016/j.jaci.2017.08.003.
58. Kuehni CE, Spycher BD, Silverman M. Causal links between RSV infection and asthma: no clear answers to an old question. *Am J Respir Crit Care Med* 2009;179(12):1079–1080. doi:10.1164/rccm.200904-0567ED.
59. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2017;391(10118):350–400.
60. Wu P, Dupont WD, Griffin MR, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am J Respir Crit Care Med* 2008;178(11):1123–1129. doi:10.1164/rccm.200804-579OC.
61. Martinez FD, Vercelli D. Asthma. *Lancet* 2013;382(9901):1360–1372. doi:10.1016/S0140-6736(13)61536-6.
62. Dang AT, Pasquali C, Ludigs K, Guarda G. OM-85 is an immunomodulator of interferon- β production and inflammasome activity. *Sci Rep* 2017;7:43844. doi:10.1038/srep43844.
63. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390(10095):659–668. doi:10.1016/S0140-6736(17)31281-3.
64. Sanchez B, Hevia A, Gonzalez S, Margolles A. Interaction of intestinal microorganisms with the human host in the framework of autoimmune diseases. *Front Immunol* 2015;6:594.
65. Sokolowska M, Frei R, Lunjani N, et al. Microbiome and asthma. *Asthma Res Pract* 2018;4:1. doi:10.1186/s40733-017-0037-y.
66. Stokholm J, Blaser MJ, Thorsen J, et al. Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun* 2018;9(1):141.
67. Huang YJ, Boushey HA. The microbiome in asthma. *J Allergy Clin Immunol* 2015;135(1):25–30. doi:10.1016/j.jaci.2014.11.011.
68. Holgate ST, Roberts G, Arshad HS, et al. The role of the airway epithelium and its interaction with environmental factors in asthma pathogenesis. *Proc Am Thorac Soc* 2009;6(8):655–659. doi:10.1513/pats.200907-072DP.
69. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in amish and hutterite farm children. *N Engl J Med* 2016;375(5):411–421. doi:10.1056/NEJMoa1508749.
70. Smit LA, Bouzigon E, Pin I, et al. 17q21 variants modify the association between early respiratory infections and asthma. *Eur Respir J* 2010;36(1):57–64. doi:10.1183/09031936.00154509.
71. Ono JG, Worgall TS, Worgall S. 17q21 locus and ORMDL3: an increased risk for childhood asthma. *Pediatr Res* 2014;75(1-2):165–170. doi:10.1038/pr.2013.186.
72. Birben E, Sackesen C, Turgutoglu N, Kalayci O. The role of SPINK5 in asthma related physiological events in the airway epithelium. *Respir Med* 2012;106(3):349–355. doi:10.1016/j.rmed.2011.11.007.
73. Yalcin AD. A case of Netherton syndrome: successful treatment with omalizumab and pulse prednisolone and its effects on cytokines and immunoglobulin levels. *Immunopharmacol Immunotoxicol* 2016;38(2):162–166. doi:10.3109/08923973.2015.1115518.

74. Chawla-Sarkar M, Lindner DJ, Liu YF, et al. Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. *Apoptosis* 2003; 8(3):237–249.
75. De Andrea M, Ravera R, Gioia D, et al. The interferon system: an overview. *Eur J Paediatr Neurol* 2002;6 (Suppl A):A41–A46; discussion A55–48.
76. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005;201(6):937–947. doi:[10.1084/jem.20041901](https://doi.org/10.1084/jem.20041901).
77. Semic-Jusufagic A, Belgrave D, Pickles A, et al. Assessing the association of early life antibiotic prescription with asthma exacerbations, impaired antiviral immunity, and genetic variants in 17q21: a population-based birth cohort study. *Lancet Respir Med* 2014;2(8): 621–630. doi:[10.1016/S2213-2600\(14\)70096-7](https://doi.org/10.1016/S2213-2600(14)70096-7).
78. Uller L, Leino M, Bedke N, et al. Double-stranded RNA induces disproportionate expression of thymic stromal lymphopoietin versus interferon-beta in bronchial epithelial cells from donors with asthma. *Thorax* 2010;65(7):626–632. doi:[10.1136/thx.2009.125930](https://doi.org/10.1136/thx.2009.125930).
79. Adamczak DM. The role of toll-like receptors and vitamin D in cardiovascular diseases-a review. *Int J Mol Sci* 2017;18(11):pii:E2252.
80. Medzhitov R. Toll-like receptors and innate immunity. *Nat Rev Immunol* 2001;1(2):135–145. doi:[10.1038/35100529](https://doi.org/10.1038/35100529).
81. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell* 2010;140(6):805–820. doi:[10.1016/j.cell.2010.01.022](https://doi.org/10.1016/j.cell.2010.01.022).