Respiratory Viral Infection and Epithelial Immunity in Asthma

Subjects: Allergy | Respiratory System | Immunology
Contributor: So Ri Kim

Viral respiratory tract infections are associated with asthma development and exacerbation in children and adults. In the course of immune responses to viruses, airway epithelial cells are the initial platform of innate immunity against viral invasion. Patients with severe asthma are more vulnerable than those with mild to moderate asthma to viral infections.

Keywords: asthma ; viral infection ; acute exacerbation ; airway epithelium ; immunity

1. Introduction

In general, people with asthma are particularly susceptible to viral respiratory infections, which are a major cause of asthma exacerbation. Extensive basic and clinical studies in recent decades have contributed important insights about the role of viruses in asthma development and exacerbation and mediating factors related to those pathophysiologic processes. In addition, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has highlighted the need for more effective preventive and therapeutic approaches to viral infections in patients with asthma, which require a deeper understanding of the interactions between asthma and viral infections.

The respiratory viruses mainly involved in asthma inception and exacerbation include rhinovirus (RV), respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, adenovirus, and coronavirus [1][2][3]. Considerable epidemiological evidence supports the associations among RV infection, exposure, and sensitization to allergens with asthma onset and exacerbation [4][5]. Viral infections can cause asthma exacerbation via multiple mechanisms [2][3]: increased serum IgE levels, epithelial damage or activation, decreased antiviral responses (including the production of interferon (IFN)), alteration of host immune responses, promotion of inflammation in the respiratory tract, and direct infection of the lower respiratory tract.

In addition to their structural barrier function against allergens, infectious agents, and inhaled particulates, airway epithelial cells respond to various host and environmental stimuli by participating in diverse immune and inflammatory processes. In asthma, alterations in the airway epithelium are known to play critical roles in viral-infection-induced exacerbations, although contradictory results have been reported depending on the viral strain, cell type, experimental system (i.e., animal models vs. human subjects, in vivo vs. in vitro), and various host factors.

2. Role of Respiratory Viral Infection in Asthma Pathogenesis

2.1. Role of Viral Infection in the Development of Asthma

Although the hygiene hypothesis suggests that early childhood infections are protective against allergic diseases later in life, including asthma [6], respiratory viral infections associated with wheezing illness are known to contribute to the development of asthma. Viral-infection–related pathology is influenced by host factors such as age, previous infection or immunization, pre-existing respiratory or systemic disease, and immunosuppression or compromise [7]. Viral respiratory disease can be caused by a localized respiratory tract infection, such as RSV infant bronchiolitis, or can be part of a generalized systemic illness, such as measles [7]. Viral respiratory infections are a major cause of wheezing in infants and adult patients with asthma. In particular, RSV and RV are important causes of wheezing in early life, and wheezing illnesses with these viruses have been associated with increased asthma risk later in childhood. Each year, RSV is the leading contributor to hospitalization in children younger than 1 year of age, whereas RVs are the most frequently detected viruses in wheezing children older than 1 year and in children and adults with acute exacerbations of asthma [8][9]. Sigurs et al. explored the association between severe RSV bronchitis and the eventual development of asthma [10]. They assessed disease progression in infants hospitalized for RSV bronchitis until they were 13 years old. At 7.5 years of age, children with RSV bronchitis and a family history of asthma were found to have higher asthma morbidity than healthy

controls with a family history of asthma, suggesting that severe RSV infection with a family history of asthma increased the risk of developing asthma. In addition, some cohort studies have demonstrated an association between RSV-infection–induced wheezing illnesses in early life and the subsequent expression of persistent wheezing and asthma when a child begins school; the odds ratio (OR) for an asthma diagnosis in these studies was 2.6 (95% CI 1.0–6.3) [11][12]. In one of these studies, RV infection also turned out to be an important factor in the development of asthma in 6-year-old children who had experienced a related wheezing illness at age 3, with an OR for asthma of 9.8 (95% CI 4.3–22.0) [11]. These findings suggest that RV-induced bronchiolitis could be more strongly associated with the risk of developing wheeze and childhood asthma, which is also supported by a very recent meta-analysis [13]. The systemic review included 38 studies in the meta-analysis that directly compared between virus differences in the magnitude of virus-recurrent wheeze and virus–childhood asthma outcome. The analysis of the overall impact of RSV bronchiolitis on the development of recurrent wheezing or asthma in comparison to RV bronchiolitis showed that the RV bronchiolitis group was more likely to develop recurrent wheezing (OR 4.11; 95% CI 2.24–7.56) and asthma (OR 2.72; 95% CI 1.48–4.99) than the RSV group. More interestingly, an RV-infection–induced wheezing illness in infancy had a greater correlation with childhood asthma development than aeroallergen sensitization in infancy. Kusel et al. reported that the risk of asthma nearly doubled in children sensitized to common aeroallergens and increased by four times if more than two respiratory viral infections with wheezing were recorded during childhood. When the effects of allergic sensitization and a respiratory viral infection were evaluated together, their combination produced an approximately nine-fold increase in the risk of asthma, implying not only that atopy and viral infection are independent risk factors for developing asthma, but also that their combined effect seems to be synergistic [1][12]. Allergic sensitization and inflammation, particularly type 2 immune responses to allergens, are known to impair antiviral responses; however, the question of which comes first, type 2 inflammation or respiratory viral infections such as RSV- or RV-induced wheezing illness remains unanswered.

RV infections are very frequent at all ages in the general population, which begs the question of why only some of those infected with RV are at risk of developing asthma. In recent decades, many researchers have tried to answer that question by examining host genetic factors, viral strains, and environmental exposures. In terms of host genetics, polymorphisms in several antiviral and innate immune genes, including *STAT4*, *JAK2*, *MX1*, *VDR*, *DDX58*, and *EIF2AK2*, were linked to susceptibility to respiratory viruses, infection severity, and virus-induced asthma exacerbations [14]. In particular, variants in the 17q21 locus, including *ORMDL3* and *GSDMB*, were reportedly associated with an increased risk of RV-infection-induced wheezing in early life [15]. In children with an RV-infection-induced wheezing illness in the first 3 years of life, these variants were also associated with an increased risk of subsequent asthma. However, RSV-infection–induced wheezing was not linked to 17q21 variants in the same cohorts. Some environmental exposures, such as pets and farm materials, reduced the risk of asthma associated with the 17q21 genotype in children [16][17]. Meanwhile, RV-A and RV-C are more likely to show stronger virulence than RV-B, and thus, they are more likely to cause wheezing illnesses and lower respiratory infections [18]. A genome-wide association study of asthmatic children defined an association between asthma and a functional polymorphism in cadherin-related family member 3 (*CDHR3*) [19]. Considering that CDHR3 is a receptor that enables the binding and replication of RV-C, the link between CDHR3 and asthma risk might be mediated by RV-C infection [20]. In terms of the viral genome, the RSV A2, line 19, and Long strains have been used in experiments to define how the viral genome influences host immune responses to infections. The RSV A2 and Long strains produced similar immune responses in mice: predominant IFN-γ production, no production of IL-13 or airway mucus, and no airway hyperresponsiveness. However, RSV line 19 infection induced the production of IL-13 and airway mucus, reduced the production of IFN-γ, and produced exaggerated airway hyperresponsiveness [21][22]. When these strains were sequenced, differences were found in five amino acids in the fusion protein. Subsequently, a reverse genetic approach indicated that the fusion protein genes of the RSV line 19 strain were responsible for the lung production of IL-13 and airway mucus and airway hyperresponsiveness [22]. Throughout life, people are exposed to a variety of environmental factors, including respiratory pathogens, allergens, physicochemical irritants, and microbes. The influences of these exposures on human health, specifically in the development of asthma, remain the focus of research to define underlying pathogenic mechanisms and find new preventive and therapeutic interventions. From this point of view, epigenetics could be a promising approach to explaining the development of asthma associated with viral infection. Recent findings have shown that RV-induced alterations in DNA methylation are involved in the development and persistence of asthma [23][24]. In addition, several viral infections have been reported to contribute to the pathogenesis of asthma through the epigenetic expression of various non-coding RNAs (miRNAs). RV-infected asthmatic alveolar macrophages showed decreased TLR7 expression levels due to miR-150, miR-152, and miR-375 [25]. Mucus secretion was increased by a reduction in miR-34b/c-5p in RSV-infected human bronchial epithelial cells [26]. In epithelial cells from severe asthmatic patients, miR-22 was dysregulated by influenza A (IAV) infection, which could be one of the possible mechanisms of IAV-induced airway remodeling [27]. The microbiome, which is considered an endogenous environmental factor, may also contribute to respiratory viral infection. Teo et al. reported that the nasopharyngeal microbiome composition affected the infection severity and pathogen spread to lower airways, as well as the risk for future asthma

development. Among the genera of bacteria in the nasopharyngeal microbiome, Streptococcus was a strong predictor, and antibiotic usage could disrupt the colonization patterns [28]. In a subsequent study, they revealed that viral-infection-associated respiratory illnesses were accompanied by a shift in the nasopharyngeal microbiome toward dominance by a small range of pathogenic bacteria genera. In addition, in conjunction with early allergic sensitization, the dominating presence of Streptococcus, Haemophilus, and Moraxella in the microbiome profiles of upper airways was a significant risk factor for persistent wheezing illness in school-age children, while these bacteria genera were associated with a transient wheeze that resolved in non-sensitized children [29].

2.2. Pathophysiological Effects of Viral Infection on Asthma Exacerbations

Respiratory viruses infect not only asthma patients but also healthy people. However, it is known that the pathological effects of respiratory viral infection in asthma patients are much more serious than those in healthy people. The clinical manifestations of viral infectious diseases are the results of both direct damage caused by the virus itself and damage caused by the host immune response to the virus. In an asthmatic patient, exacerbation can occur because of the functional interaction between the pathogenic effects of the virus and asthmatic inflammation [7]. Asthma exacerbation is characterized by an increase in fatal asthmatic symptoms, worse response to therapeutic controllers such as inhaled corticosteroids (ICS), and increased airway remodeling, which together can cause decreased lung function [30][31]. Viral respiratory infections are detected in about 85% of asthma exacerbations. Because asthma exacerbations are a major cause of morbidity in asthma patients of all ages, significant research efforts have been devoted to understanding the interaction between viral infection and asthmatic inflammation, particularly exacerbation [1]. Actually, the detailed immunological mechanisms associated with asthma exacerbation are currently unclear, although major advances in the research have improved people's understanding of many aspects of the interaction between respiratory viral infection and underlying allergic asthmatic inflammation. The effect that coronavirus disease 19 (COVID-19), which is caused by SARS-CoV-2, has on acute exacerbations of asthma appears to be complex [32]. Indeed, some studies have reported that, unlike other respiratory viruses, SARS-CoV-2 rarely induces asthma exacerbations during hospitalization for COVID-19, that COVID-19-related asthma exacerbations have been relatively rare during the outbreak, and that SARS-CoV-2 pneumonia does not induce severe asthma exacerbation [33][34][35]. A recently updated report demonstrated that COVID-19 could lead to the worsening of asthma symptoms and prolonged exacerbation in some asthma patients, but not in all of them, and that allergic asthma patients had a significantly lower asthma exacerbation rate than non-allergic asthma patients [36]. These findings seem to be completely opposite to the effect of previous respiratory viral infection on asthma exacerbation, implying that the relationship between SARS-CoV-2 infection and asthma is complex and possibly unique among the known pathologic effects of previous viral infection. Some interesting studies have provided mechanistic insights into these observations [37][38]. It is known that the host cell entry of SARS-CoV-2 depends on angiotensin-converting enzyme 2 (ACE2), and the cellular serine protease transmembrane protease serine 2 (TMPRSS2) is used by SARS-CoV-2 for S protein priming [39]. Type 2 inflammation, or type 2 cytokine IL-13, suppressed the expression of ACE2 and increased the expression of TMPRSS2 in airway epithelial cells [37][38]. In addition to the strong negative influence of T2 inflammation on ACE2 expression in the airway, Sajithi et al. revealed an equally strong positive influence of respiratory virus infections on ACE2 levels [38]. They suggest T2 inflammation and virus-induced IFN inflammation as the strongest determinants of ACE2 and TMPRSS2 expression in asthmatic airway epithelium, which could contribute to the complex manifestations and various severities of COVID-19 in patients with asthma. Therefore, more work and data on the interaction between SARS-CoV-2 and asthma are needed to fully understand these intriguing findings.

Among the respiratory viruses, RV is the major and most frequent determinant of asthma exacerbation [40][41][42], although until recently, RV infection was known to occur primarily in the upper respiratory tract. However, several experimental infection models have directly implicated RV in lower airway infections involved in the pathogenesis of asthma exacerbation [43][44][45][46][47]. The proposed mechanisms for RV-induced asthma exacerbation include the activation of the airway epithelium, which produces an innate immune response and antigen-specific Th2 pathways that combine with allergic inflammation to enhance the overall type 2 inflammatory response [42][48][49][50]. In addition, RV infection could induce asthma exacerbation through a non-Th2 immune response, increased airway hyperresponsiveness, mucus hypersecretion, airway remodeling, or respiratory failure [51].

Asthmatic patients have increased susceptibility to viral respiratory infections, partly because they have deficient and delayed innate antiviral immune responses [52]. Many asthmatic patients tend to produce lower-than-average levels of type I IFN (i.e., IFN-α and IFN-β) and other cytokines in plasmacytoid dendritic cells (pDCs) and epithelial cells during viral respiratory infections [53][54][55][56]. This impaired antiviral immunity means that viral infections are associated with more severe airway damage in patients with asthma than in patients without asthma. Conversely, viral infection can increase the sensitivity of asthmatic airways to other triggers, such as allergens [7]. In addition, asthma is usually associated with pulmonary and extrapulmonary comorbidities, and these comorbidities are more common in severe asthma patients than

in patients with mild to moderate asthma or those in the general population [57][58]. Pulmonary comorbidities include allergic rhinitis, obstructive sleep apnea, chronic rhinosinusitis (CRS), nasal polyps, chronic obstructive pulmonary disease, and bronchiectasis [58][59]. In particular, the mean prevalence of bronchiectasis in asthma patients is 36.6%, and patients with severe asthma with bronchiectasis show a higher rate of infection [60][61]. Bronchiectasis is frequently considered to be a consequence of long-lasting, severe, uncontrolled asthma, while asthma could be overlapped in patients with bronchiectasis [62]. Considering the structural and functional changes of bronchiectasis, such as mucociliary defects and biofilm formation, bronchiectasis is one of the comorbidities associated with the recurrent infectious exacerbation of asthma. Moreover, a recent study reported that respiratory viruses contributed to about 25% of the acute exacerbation of bronchiectasis and that IAV and RV made up over 50% of the viruses [63].

Recent interesting studies have reported that the diverse and distinct airway microbiomes of asthmatic patients can also influence viral respiratory infection, which is linked to acute exacerbation. McCauley et al. demonstrated that RV infection was more likely to occur in asthmatic children with Streoptococcus-species-dominated nasal airway microbiomes and that nasal microbiomes dominated by Moraxella species were associated with increased exacerbation risk and eosinophil activation [64]. In addition, a recent study indicated that specific networks of upper airway microbes (those possessing Streptococcus, Haemophilus, Neisseria, Prevotella, and other genera or those lacking Staphylococcus) that interacted with host transcriptional responses significantly increased the risk of subsequent exacerbation and that this relationship was also strongly dependent on season [65].

Taken together, it appears that virus-induced asthma exacerbation is the final consequence of a complex interaction among a variety of pathogenic mechanisms in pre-existing asthmatic inflammation: epithelial disruption and dysfunction, impaired antiviral immunity, inflammatory mediator overproduction, the induction of inflammation, IgE dysregulation, airway remodeling, alterations in neural responses, airway microbiomes, and differences in asthma endotypes and phenotypes.

References

1. Busse, W.W.; Lemanske, R.F., Jr.; Gern, J.E. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010, 376, 826–834.
2. Adeli, M.; El-Shareif, T.; Hendaus, M.A. Asthma exacerbation related to viral infections: An up to date summary. J. Fam. Med. Prim. Care 2019, 8, 2753–2759.
3. Novak, N.; Cabanillas, B. Viruses and asthma: The role of common respiratory viruses in asthma and its potential meaning for SARS-CoV-2. Immunology 2020, 161, 83–93.
4. Rubner, F.J.; Jackson, D.J.; Evans, M.D.; Gangnon, R.E.; Tisler, C.J.; Pappas, T.E.; Gern, J.E.; Lemanske, R.F., Jr. Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. J. Allergy Clin. Immunol. 2017, 139, 501–507.
5. Soto-Quiros, M.; Avila, L.; Platts-Mills, T.A.; Hunt, J.F.; Erdman, D.D.; Carper, H.; Murphy, D.D.; Odio, S.; James, H.R.; Patrie, J.T.; et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. J. Allergy Clin. Immunol. 2012, 129, 1499–1505.e5.
6. Pfefferle, P.I.; Keber, C.U.; Cohen, R.M.; Garn, H. The Hygiene Hypothesis—Learning from but Not Living in the Past. Front. Immunol. 2021, 12, 632.
7. Message, S.D.; Johnston, S.L. The immunology of virus infection in asthma. Eur. Respir. J. 2001, 18, 1013–1025.
8. Stier, M.T.; Peebles, R.S., Jr. Host and Viral Determinants of Respiratory Syncytial Virus-Induced Airway Mucus. Ann. Am. Thorac. Soc. 2018, 15 (Suppl. S3), S205–S209.
9. Papadopoulos, N.G.; Christodoulou, I.; Rohde, G.; Agache, I.; Almqvist, C.; Bruno, A.; Bonini, S.; Bont, L.; Bossios, A.; Bousquet, J.; et al. Viruses and bacteria in acute asthma exacerbations—A GA2 LEN-DARE systematic review. Allergy 2011, 66, 458–468.
10. 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, 1501–1507.
11. Jackson, D.J.; Gangnon, R.E.; Evans, M.D.; Roberg, K.A.; Anderson, E.L.; Pappas, T.E.; Printz, M.C.; Lee, W.M.; Shult, P.A.; Reisdorf, E.; et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am. J. Respir. Crit. Care Med. 2008, 178, 667–672.
12. Kusel, M.M.; de Klerk, N.H.; Kebadze, T.; Vohma, V.; Holt, P.G.; Johnston, S.L.; Sly, P.D. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J. Allergy Clin. Immunol.

2007, 119, 1105–1110.

13. Makrinioti, H.; Hasegawa, K.; Lakoumentas, J.; Xepapadaki, P.; Tsolia, M.; Castro-Rodriguez, J.A.; Feleszko, W.; Jartti, T.; Johnston, S.L.; Bush, A.; et al. The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma-A systematic review and meta-analysis. Pediatr. Allergy Immunol. 2022, 33, e13741.
14. Loisel, D.A.; Du, G.; Ahluwalia, T.S.; Tisler, C.J.; Evans, M.D.; Myers, R.A.; Gangnon, R.E.; Kreiner-Møller, E.; Bønnelykke, K.; Bisgaard, H.; et al. Genetic associations with viral respiratory illnesses and asthma control in children. Clin. Exp. Allergy 2016, 46, 112–124.
15. Çalışkan, M.; Bochkov, Y.A.; Kreiner-Møller, E.; Bønnelykke, K.; Stein, M.M.; Du, G.; Bisgaard, H.; Jackson, D.J.; Gern, J.E.; Lemanske, R.F., Jr. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N. Engl. J. Med. 2013, 368, 1398–1407.
16. Loss, G.J.; Depner, M.; Hose, A.J.; Genuneit, J.; Karvonen, A.M.; Hyvärinen, A.; Roduit, C.; Kabesch, M.; Lauener, R.; Pfefferle, P.I.; et al. The Early Development of Wheeze. Environmental Determinants and Genetic Susceptibility at 17q21. Am. J. Respir. Crit. Care Med. 2016, 193, 889–897.
17. Stokholm, J.; Chawes, B.L.; Vissing, N.; Bønnelykke, K.; Bisgaard, H. Cat exposure in early life decreases asthma risk from the 17q21 high-risk variant. J. Allergy Clin. Immunol. 2018, 141, 1598–1606.
18. Lee, W.M.; Lemanske, R.F., Jr.; Evans, M.D.; Vang, F.; Pappas, T.; Gangnon, R.; Jackson, D.J.; Gern, J.E. Human rhinovirus species and season of infection determine illness severity. Am. J. Respir. Crit. Care Med. 2012, 186, 886–891.
19. Bønnelykke, K.; Sleiman, P.; Nielsen, K.; Kreiner-Møller, E.; Mercader, J.M.; Belgrave, D.; den Dekker, H.T.; Husby, A.; Sevelsted, A.; Faura-Tellez, G.; et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat. Genet. 2014, 46, 51–55.
20. Bochkov, Y.A.; Watters, K.; Ashraf, S.; Griggs, T.F.; Devries, M.K.; Jackson, D.J.; Palmenberg, A.C.; Gern, J.E. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. Proc. Natl. Acad. Sci. USA 2015, 112, 5485–5490.
21. Lukacs, N.W.; Moore, M.L.; Rudd, B.D.; Berlin, A.A.; Collins, R.D.; Olson, S.J.; Ho, S.B.; Peebles, R.S. Differential Immune Responses and Pulmonary Pathophysiology Are Induced by Two Different Strains of Respiratory Syncytial Virus. Am. J. Pathol. 2006, 169, 977–986.
22. Moore, M.L.; Chi, M.H.; Luongo, C.; Lukacs, N.W.; Polosukhin, V.V.; Huckabee, M.M.; Newcomb, D.C.; Buchholz, U.J.; Crowe, J.E., Jr.; Goleniewska, K.; et al. A chimeric A2 strain of respiratory syncytial virus (RSV) with the fusion protein of RSV strain line 19 exhibits enhanced viral load, mucus, and airway dysfunction. J. Virol. 2009, 83, 4185–4194.
23. Pech, M.; Weckmann, M.; König, I.R.; Franke, A.; Heinsen, F.A.; Oliver, B.; Ricklefs, I.; Fuchs, O.; Rabe, K.; Hansen, G.; et al. Rhinovirus infections change DNA methylation and mRNA expression in children with asthma. PLoS ONE 2018, 13, e0205275.
24. Lund, R.J.; Osmala, M.; Malonzo, M.; Lukkarinen, M.; Leino, A.; Salmi, J.; Vuorikoski, S.; Turunen, R.; Vuorinen, T.; Akdis, C.; et al. Atopic asthma after rhinovirus-induced wheezing is associated with DNA methylation change in the SMAD3 gene promoter. Allergy 2018, 73, 1735–1740.
25. Rupani, H.; Martinez-Nunez, R.T.; Dennison, P.; Lau, L.C.; Jayasekera, N.; Havelock, T.; Francisco-Garcia, A.S.; Grainge, C.; Howarth, P.H.; Sanchez-Elsner, T. Toll-like Receptor 7 Is Reduced in Severe Asthma and Linked to an Altered MicroRNA Profile. Am. J. Respir. Crit. Care Med. 2016, 194, 26–37.
26. Du, X.; Yang, Y.; Xiao, G.; Yang, M.; Yuan, L.; Qin, L.; He, R.; Wang, L.; Wu, M.; Wu, S.; et al. Respiratory syncytial virus infection-induced mucus secretion by down-regulation of miR-34b/c-5p expression in airway epithelial cells. J. Cell. Mol. Med. 2020, 24, 12694–12705.
27. Moheimani, F.; Koops, J.; Williams, T.; Reid, A.T.; Hansbro, P.M.; Wark, P.A.; Knight, D.A. Influenza A virus infection dysregulates the expression of microRNA-22 and its targets; CD147 and HDAC4, in epithelium of asthmatics. Respir. Res. 2018, 19, 145.
28. Teo, S.M.; Mok, D.; Pham, K.; Kusel, M.; Serralha, M.; Troy, N.; Holt, B.J.; Hales, B.J.; Walker, M.L.; Hollams, E.; et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe 2015, 17, 704–715.
29. Teo, S.M.; Tang, H.H.F.; Mok, D.; Judd, L.M.; Watts, S.C.; Pham, K.; Holt, B.J.; Kusel, M.; Serralha, M.; Troy, N.; et al. Airway Microbiota Dynamics Uncover a Critical Window for Interplay of Pathogenic Bacteria and Allergy in Childhood Respiratory Disease. Cell Host Microbe 2018, 24, 341–352.e5.
30. Anderson, G.P. Endotyping asthma: New insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 2008, 372, 1107–1119.

31. Hossain, F.M.A.; Choi, J.Y.; Uyangaa, E.; Park, S.O.; Eo, S.K. The Interplay between Host Immunity and Respiratory Viral Infection in Asthma Exacerbation. Immune Netw. 2019, 19, e31.

32. Lombardi, C.; Gani, F.; Berti, A.; Comberiati, P.; Peroni, D.; Cottini, M. Asthma and COVID-19: A dangerous liaison? Asthma Res. Pract. 2021, 7, 9.

33. Beurnier, A.; Jutant, E.M.; Jevnikar, M.; Boucly, A.; Pichon, J.; Preda, M.; Frank, M.; Laurent, J.; Richard, C.; Monnet, X.; et al. Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalisation. Eur. Respir. J. 2020, 56, 2001875.

34. Garg, S.; Kim, L.; Whitaker, M.; O'Halloran, A.; Cummings, C.; Holstein, R.; Prill, M.; Chai, S.J.; Kirley, P.D.; Alden, N.B.; et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019—COVID-NET, 14 States, 1–30 March 2020. Morb. Mortal. Wkly. Rep. 2020, 69, 458–464.

35. Grandbastien, M.; Piotin, A.; Godet, J.; Abessolo-Amougou, I.; Ederlé, C.; Enache, I.; Fraisse, P.; Hoang, T.C.T.; Kassegne, L.; Labani, A.; et al. SARS-CoV-2 Pneumonia in Hospitalized Asthmatic Patients Did Not Induce Severe Exacerbation. J. Allergy Clin. Immunol. Pract. 2020, 8, 2600–2607.

36. Jaswaney, R.; Foster, K.; Moore, D.; Andy-Nweye, A.; Mahdavinia, M. Allergic Asthma Patients Experience Lower Rates of Asthma Exacerbation Compared to Non-Allergic Asthma Patients Following COVID-19 Infection. J. Allergy Clin. Immunol. 2022, 149 (Suppl. S2), AB58.

37. Kimura, H.; Francisco, D.; Conway, M.; Martinez, F.D.; Vercelli, D.; Polverino, F.; Billheimer, D.; Kraft, M. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. J. Allergy Clin. Immunol. 2020, 146, 80–88.e8.

38. Sajuthi, S.P.; DeFord, P.; Li, Y.; Jackson, N.D.; Montgomery, M.T.; Everman, J.L.; Rios, C.L.; Pruesse, E.; Nolin, J.D.; Plender, E.G.; et al. Type 2 and interferon inflammation regulate SARS-CoV-2 entry factor expression in the airway epithelium. Nat. Commun. 2020, 11, 5139.

39. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020, 181, 271–280.e8.

40. Wark, P.A.; Johnston, S.L.; Moric, I.; Simpson, J.L.; Hensley, M.J.; Gibson, P.G. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. Eur. Respir. J. 2002, 19, 68–75.

41. Grissell, T.V.; Powell, H.; Shafren, D.R.; Boyle, M.J.; Hensley, M.J.; Jones, P.D.; Whitehead, B.F.; Gibson, P.G. Interleukin-10 gene expression in acute virus-induced asthma. Am. J. Respir. Crit. Care Med. 2005, 172, 433–439.

42. Jackson, D.J.; Johnston, S.L. The role of viruses in acute exacerbations of asthma. J. Allergy Clin. Immunol. 2010, 125, 1178–1187.

43. Hayden, F.G. Rhinovirus and the lower respiratory tract. Rev. Med. Virol. 2004, 14, 17–31.

44. Schroth, M.K.; Grimm, E.; Frindt, P.; Galagan, D.M.; Konno, S.I.; Love, R.; Gern, J.E. Rhinovirus replication causes RANTES production in primary bronchial epithelial cells. Am. J. Respir. Cell Mol. Biol. 1999, 20, 1220–1228.

45. Papadopoulos, N.G.; Bates, P.J.; Bardin, P.G.; Papi, A.; Leir, S.H.; Fraenkel, D.J.; Meyer, J.; Lackie, P.M.; Sanderson, G.; Holgate, S.T.; et al. Rhinoviruses infect the lower airways. J. Infect. Dis. 2000, 181, 1875–1884.

46. Subauste, M.C.; Jacoby, D.B.; Richards, S.M.; Proud, D. Infection of a human respiratory epithelial cell line with rhinovirus. Induction of cytokine release and modulation of susceptibility to infection by cytokine exposure. J. Clin. Investig. 1995, 96, 549–557.

47. Gern, J.E.; Galagan, D.M.; Jarjour, N.N.; Dick, E.C.; Busse, W.W. Detection of rhinovirus RNA in lower airway cells during experimentally induced infection. Am. J. Respir. Crit. Care Med. 1997, 155, 1159–1161.

48. Bartlett, N.W.; Walton, R.P.; Edwards, M.R.; Aniscenko, J.; Caramori, G.; Zhu, J.; Glanville, N.; Choy, K.J.; Jourdan, P.; Burnet, J.; et al. Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. Nat. Med. 2008, 14, 199–204.

49. Yılmaz, İ. Is Asthma-COPD overlap an asthma phenotype or a COPD phenotype? Tuberk. Toraks 2018, 66, 78–79.

50. Muehling, L.M.; Heymann, P.W.; Wright, P.W.; Eccles, J.D.; Agrawal, R.; Carper, H.T.; Murphy, D.D.; Workman, L.J.; Word, C.R.; Ratcliffe, S.J.; et al. Human TH1 and TH2 cells targeting rhinovirus and allergen coordinately promote allergic asthma. J. Allergy Clin. Immunol. 2020, 146, 555–570.

51. Agache, I. Non-Eosinophilic Asthma Endotypes. Curr. Treat. Options Allergy 2015, 2, 257–267.

52. James, K.M.; Peebles, R.S., Jr.; Hartert, T.V. Response to infections in patients with asthma and atopic disease: An epiphenomenon or reflection of host susceptibility? J. Allergy Clin. Immunol. 2012, 130, 343–351.

53. Lebre, M.C.; van Capel, T.M.; Bos, J.D.; Knol, E.F.; Kapsenberg, M.L.; de Jong, E.C. Aberrant function of peripheral blood myeloid and plasmacytoid dendritic cells in atopic dermatitis patients. J. Allergy Clin. Immunol. 2008, 122, 969–

976.e5.

54. Wark, P.A.; Johnston, S.L.; Bucchieri, F.; Powell, R.; Puddicombe, S.; Laza-Stanca, V.; Holgate, S.T.; Davies, D.E. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J. Exp. Med. 2005, 201, 937–947.
55. Durrani, S.R.; Montville, D.J.; Pratt, A.S.; Sahu, S.; DeVries, M.K.; Rajamanickam, V.; Gangnon, R.E.; Gill, M.A.; Gern, J.E.; Lemanske, R.F., Jr.; 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, 489–495.
56. Channappanavar, R.; Fehr, A.R.; Vijay, R.; Mack, M.; Zhao, J.; Meyerholz, D.K.; Perlman, S. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. Cell Host Microbe 2016, 19, 181–193.
57. Gaffin, J.M.; Castro, M.; Bacharier, L.B.; Fuhlbrigge, A.L. The Role of Comorbidities in Difficult-to-Control Asthma in Adults and Children. J. Allergy Clin. Immunol. Pract. 2022, 10, 397–408.
58. Rogliani, P.; Sforza, M.; Calzetta, L. The impact of comorbidities on severe asthma. Curr. Opin. Pulm. Med. 2020, 26, 47–55.
59. Gibson, P.G.; McDonald, V.M.; Granchelli, A.; Olin, J.T. Asthma and Comorbid Conditions-Pulmonary Comorbidity. J. Allergy Clin. Immunol. Pract. 2021, 9, 3868–3875.
60. Zhang, S.-Q.; Xiong, X.-F.; Wu, Z.-H.; Huang, T.-T.; Cheng, D.-Y. Clinical features of asthma with comorbid bronchiectasis: A systematic review and meta-analysis. Medicine 2021, 100, e23858.
61. Porsbjerg, C.; Menzies-Gow, A. Co-morbidities in severe asthma: Clinical impact and management. Respirology 2017, 22, 651–661.
62. Polverino, E.; Dimakou, K.; Hurst, J.; Martinez-Garcia, M.A.; Miravitlles, M.; Paggiaro, P.; Shteinberg, M.; Aliberti, S.; Chalmers, J.D. The overlap between bronchiectasis and chronic airway diseases: State of the art and future directions. Eur. Respir. J. 2018, 52, 1800328.
63. Park, Y.E.; Sung, H.; Oh, Y.M. Respiratory Viruses in Acute Exacerbations of Bronchiectasis. J. Korean Med. Sci. 2021, 36, e217.
64. McCauley, K.; Durack, J.; Valladares, R.; Fadrosh, D.W.; Lin, D.L.; Calatroni, A.; LeBeau, P.K.; Tran, H.T.; Fujimura, K.E.; LaMere, B.; et al. Distinct nasal airway bacterial microbiotas differentially relate to exacerbation in pediatric patients with asthma. J. Allergy Clin. Immunol. 2019, 144, 1187–1197.
65. McCauley, K.E.; Flynn, K.; Calatroni, A.; DiMassa, V.; LaMere, B.; Fadrosh, D.W.; Lynch, K.V.; Gill, M.A.; Pongracic, J.A.; Hershey, G.K.K.; et al. Seasonal airway microbiome and transcriptome interactions promote childhood asthma exacerbations. J. Allergy Clin. Immunol. 2022, 150, 204–213.