Published in final edited form as:

Expert Rev Anti Infect Ther. 2010 June ; 8(6): 617–621. doi:10.1586/eri.10.39.

Association of Interleukin- 13 in RSV induced pulmonary disease: Still a promising target

Sumanta Mukherjee and Nicholas W. Lukacs

RSV, a problem for the young and old

Respiratory syncytial virus (RSV) is a negative strand RNA virus and a member of the *Paramyxoviridae* family, genus *Pneumovirus*. It infects nearly all infants by age 2 and is the leading cause of bronchiolitis in children worldwide. It is estimated by the CDC that up to 125,000 pediatric hospitalizations in the United States each year are due to RSV, at an annual cost of over \$300,000,000 [1-3]. However, the elderly also succumb to RSV infections leading to pneumonia [4,5]. Thus, while RSV is especially detrimental in very young infants whose airways are small and easily occluded, it is still recognized as an important pathogen in patients with asthma, transplant recipients, patients with chronic obstructive pulmonary disease (COPD), the elderly, as well as other patients with chronic lung disease. During asthmatic exacerbations RSV can cause prolonged episodes of illness and recent data suggest that episodes of acute exacerbations of COPD (AECOPD) due to RSV cause ~10,000 deaths in persons over the age 65 in the US [3]. The combined annual average mortality due to RSV is predicted to be over 17,000 in the US. These numbers are likely grossly underestimated, as it has not been examined in adults in a consistent manner. Thus, RSV not only causes significant exacerbated lung disease in young and old, but also is associated with a significant amount of mortality directly.

One clinically relevant feature of RSV disease that may predispose children to later childhood pulmonary disease is the inability to acquire protective immunity due to an altered immune response [4,5]. Individuals previously infected with RSV can subsequently be reinfected with the same clinical isolate at a later time. This may be due to something inherently dysfunctional with the programming of the memory response to RSV. With repeated infections, protective immunity can develop but this may also come at a cost of profoundly altering the immune environment in the lung. Patient populations with compromised lung function (especially COPD patients) are at a high risk of severe complications due to RSV infection that is nearly as prevalent as those associated with influenza infections [6-10]. RSV compounds these complications further due to its ability to persist for long periods in the lung even after the acute disease has been resolved. This is thought to be associated with the development of an altered immune environment that less efficiently clears the virus.

Some approaches with antibodies and vaccines were attempted in the past to alleviate the RSV infection associated disease but has offered very limited success. Anti-RSV antibodies are available and appear to alleviate severe disease however; they perform best when given by a prophylactic protocol. On the contrary, Palivizumab prevents development of severe RSV illness in certain high-risk infants and children but is unable to prevent infection with RSV [11]. Importantly, the cost associated with the prophylaxis treatment with Palivizumab far exceeds the cost savings from reduced hospitalization [12,13]. Moreover, no safe and effective vaccine is available [14,15]. The repeated attempts for vaccine development against RSV have been hampered by the problems inherent in neonatal immunization [16] as well as a history of vaccine-enhanced illness upon reinfection with the virus. The latter incident occurred during the late 1960's when children were vaccinated with alum-precipitated formalin inactivated RSV

vaccine (FI-RSV) [17,18]. The clinical manifestations were a result of priming with FI-RSV that led to the enhanced Th2 lymphocyte response, mucus production and eosinophilia following challenge. Moreover, steroid treatment of children with severe RSV disease showed no difference in cytokine levels in tracheal aspirates [19]. Thus there is also a lack of clinical benefit of steroid treatment in children with severe RSV bronchiolitis.

Antiviral Immune Responses to RSV

The innate immune system has evolved mechanisms to detect characteristics of viral nucleic acids that are either distinct in structure (dsRNA) or in subcellular location (ssRNA). Since RSV is an ssRNA negative sense virus both ssRNA and dsRNA species are formed and can be targets for the innate immune system. Recognition of the virus induces two distinct responses. First, the viral nucleic acids activate the innate immune system via Toll like receptors (TLRs) triggering the induction of type I interferons (IFNs). Type-I IFNs elicit an anti-viral state in virally infected cells and activate immunoregulatory functions in nearby cells. Second, TLR activation induces important early mediators such as chemokines and cytokines (Interleukin-12, IL-12), which tailor the adaptive immune T cell response to the invading pathogen. However RSV-specific T cells can be both protective and pathogenic. Studies in mice with depleted CD4 and CD8 T cells have shown that RSV persists for several weeks but no overt disease symptoms are observed suggesting a pathogenic role for T cells during the infectious disease response [20]. This latter observation rests on the fact that although individually, both CD4 and CD8 contribute to terminating RSV replication and increasing viral clearance it comes at a cost of significant immunopathology. However, CD8 T cell depletion studies have shown enhanced Th2 responses during RSV infection, demonstrating that CD8 T cells may also provide important regulatory and protective signals, such as IFN γ .

During RSV infection as mentioned above, the activation of TLRs on dendritic cells triggers IL-12 production and induces the differentiation of IFN γ producing Th1 cells. However, pathogen-induced Th2 (IL-4 and IL-13) responses tend to arise in the absence of TLRs leading some to suggest that Th2 differentiation is a pathway that is triggered in the absence of IL-12. Not all Th1-inducing stimuli default to Th2 responses in the absence of IL-12 indicating that other signals may exist on antigen-presenting cells to elicit a Th1 response. The strongest evidence for this possibility comes from recent studies showing that the expression of Notch ligands *delta*-like and *jagged* can provide these previously unknown instructional signals for the development of Th1 and Th2 cells, respectively [21]. Recently our lab has shown that RSV infection of DCs upregulates the expression of notch ligand Dll4 that modulates the Th2 response without affecting the Th1 response both *in vitro* and *in vivo* [22]. In addition neutralization of *Dll4*, enhanced Th2 responses with increased IL-4 and IL-13 in the presence of RSV resulting in mucus over production. Thus, it is likely that multiple mechanisms control the outcome of the immune responses during RSV infection.

Preliminary data from our lab also suggest that RSV infection induces IL-17 production (unpublished); a cytokine produced by another subset of helper T cells, Th17 cells. The intensity of IL-17 production during RSV infection may also depend upon Dll4 as under primary skewing conditions Dll4 augments IL-17 production [23]. Previous studies have demonstrated an association of RSV-induced IL-17 production during dysregulated exacerbation of allergic airway responses in mice, further supporting a role for IL-17 in the pathogenesis of RSV-induced disease [24]. Although IL-17 has been implicated in the induction of mucin genes, its role in mucus production during RSV disease pathogenesis is unclear but recent unpublished data from our laboratory indicate that IL-17 may contribute to mucus hypersecretion. Thus, it may be that the most devastating immune environment that can be elicited by RSV is one that has both IL-13 and IL-17 induced and leads to an intense mucus secretion profile. The overproduction of mucus, while in itself complicating, would greatly

exacerbate the disease condition in patients with underlying pulmonary problems, such as in asthma and COPD patients.

The different shades of IL-13 during RSV infection

IL-13 induced AHR

Several cytokines have been identified in the last decade that orchestrate the progression of lung damage by setting up the appropriate inflammatory milieu after RSV infection, leading to long term pulmonary problems. One of them in particular is IL-13. It has been associated with increased mucus production, goblet cell hypertrophy and airway hyperreactivity (AHR) in animal models [25,26]. These pathophysiologic outcomes and the augmented pulmonary dysfunction is the end result of increased IL-13 in the lung acting in concert with other interacting factors like tissue damage and airway remodeling response during the resolution phase of RSV infection [27-29]. IL-13-induced overproduction of mucus in itself can be a pathologically devastating event that can lead to airway congestion and lung dysfunction [30,31]. This observation was supported by studies utilizing IL-13-transgenic mice with targeted IL-13 overproduction in the lung that resulted in an overabundance of mucus production, severe AHR and end-stage fibrosis around the airway [32]. To further support the role IL-13 mediated devastating events locally within the lung, studies utilizing a neutralizing antibody of IL-13 showed that the mucus over production and AHR could be significantly abrogated post RSV infections. These data further demonstrate that IL-13 may be not only a contributing factor, but also the primary cytokine that initiates RSV-induced lung dysfunction. Although historically IL-4 is associated with severe Th-2 responses, during a primary RSV infection very little IL-4 is produced in the lung. Interestingly, physiological changes observed during RSV infection can also be independent of IL-4 [33]. An important characteristic of RSV is its strong propensity for inducing airway responses that exacerbate or may even promote asthma-like inflammation. To this end, IL-13 is also a major activating factor mediating exacerbation of allergic responses [34].

Immunomodulatory role of IL-13

In addition to its role in causing a severe immune response to RSV, IL-13 also has an immunomodulatory role. In animal studies, neutralization of IL-13 using an IL-13 specific polyclonal antibody resulted in a concomitant increase in IL-12 production, suggesting a regulatory effect of IL-13 on IL-12 production. IL-12 has been linked to anti-viral responses to RSV and other viruses and is known to effect viral antigen clearance. Thus, a potential mechanism can be alteration of IL-12 production as a result of altered IL-13 production which in turn results in an alteration in viral antigen clearance and leading to prolonged persistence of viral antigens. This is specifically harmful to the host as the continued presence of RSV specific antigens can damage epithelial cell barrier in the airways resulting in AHR [35-37]. These observations were supported by studies demonstrating a decrease in IL-12 production in children who developed RSV induced bronchiolitis [38]. The function of IL-12 during RSV infection may be both direct for activation of NK cells and cytotoxic T cell responses as well as by indirect for induction of IFN- γ , which has been shown to directly activate anti-viral responses. Interestingly, while IL-13 neutralization in animal studies reduces several pathophysiologic parameters, it does not alter IFN- γ production and therefore IL-13 may not directly alter this aspect of anti-viral immunity. Together these data suggest that the IL-12/IL-13 axis may be critical in determining the severity of lung dysfunction associated with AHR, goblet cell hyperplasia and mucus production during RSV infections. In contrast, Zhou et al demonstrated that IL-13 is associated with reduced illness in terms of weight loss of mice that were infected with RSV during primary response and had favorable effects on viral clearance [39]. The differences in the results were attributed to the strains of virus that was utilized to induce RSV infections [39]. Later studies confirmed the detrimental role of IL-13 in RSV

disease [40]. A study using neonatal RSV infection followed by subsequent reinfection later in life with RSV demonstrated that early RSV infection exacerbates RSV induced disease in adult. The study further established the enhancement of AHR, pulmonary eosinophilia and mucus hyperproduction during reinfection were dependent on IL-13 [41].

IL-13: mouse to humans

In humans, two critical syndromes have been associated with RSV infections that suggest a role of type 2 cytokines in RSV pathogenesis, airway mucus and presence of eosinophilic cationic proteins in the nasal secretions. These disease-contributing parameters have been carefully studied using animal models of RSV disease. Studies in rodent models of RSV infections have established beyond doubt that there is increased IL-13 production during the development of the disease [26,34,42,43]. Focusing upon eosinophilia, Johnson et al demonstrated that IL-13 is causative for RSV-G glycoprotein induced eosinophilia after RSV infection [44]. It was further reaffirmed by Castilow et al that IL-13 is required for eosinophil entry into the lung during RSV vaccine-enhanced disease. These observations were extended to demonstrate that the recruitment of eosinophils into the lung parenchyma was shown to be dependent on IL-13-induced chemokines CCL22 and CCL11. The studies highlight the contribution of IL-13 during a secondary response to RSV in mice previously immunized with the G protein [45].

In humans, IL-13 and Th2 responses have also been closely linked to severity of disease. Sera of RSV-infected children have skewed Th2 cytokines with reported increases of IgE, IL-5, and IL-13 [46]. To this end, increased RSV-specific T-cell response in infants with severe RSV bronchiolitis causes episodes of wheezing and the development or exacerbation of asthma later in childhood, especially in infants with a family history of atopy [47,48]. A genetic abnormality due to functional IL-13 polymorphism can also contribute to the complications later on in life [49]. Studies with Gambian children at 5 years of age have shown that severe RSV infection in early life is associated with a higher production of type 2 cytokines [50]. In a cohort study of children with severe RSV infection during the first year of life with a 5-year follow-up reported that patients with severe RSV disease produced significantly higher IL-13 concentrations in response to tuberculin, had skin response to allergens, airway reactivity and increased serum IgE concentrations. In another study, Sigurs et al compared 47 children hospitalized with RSV bronchiolitis and 93 healthy children at the mean age of 1 and 3 years [47]. The same group of children was studied at age 7.5 years and concluded that RSV bronchiolitis had a higher risk for the development of asthma and also a significantly elevated risk ratio for allergic sensitization. Studies investigating age-related differences in cytokine responses to RSV infection have reported increased levels of IL-13 levels in children over 12 months of age compared to children aged below 6 months. Thus very early in life age-related difference in immune response to RSV infection can be observed and developmental changes in cytokine responses to RSV infection may be considered in the control of RSV bronchiolitis in young children [51]. To establish the course of the immune development the RBEL (RSV Bronchiolitis in Early Life) cohort study offered a unique opportunity to follow the changes in Th1 and Th2 cytokine production, during the first 6 years of life after severe RSV bronchiolitis, and to investigate the subsequent development of asthma, allergic sensitization, and eczema. The study found that Th1 cytokines in peripheral blood mononuclear cells (PBMCs) tend to decrease and Th2 cytokines tend to increase over time after initial severe RSV bronchiolitis [52]. Thus, while there are clearly multiple mediators that are involved in the generation of RSV-induced disease, evidence in both humans and animal models indicate that a major pathogenic factor in acute and longterm disease sequelae is IL-13.

Concluding remarks

The role of IL-13 during RSV disease progression in mouse models correlates with the presence of IL-13 in human disease phenotypes suggesting it as a putative target during disease. In addition to the association of IL-13 with AHR and mucus production in the airways, its immunomodulatory role during RSV infections may also compound the detrimental immune environment that develops further complicating long-term disease during RSV infection. It is also important to recognize that other mechanisms such as regulation of IL-13 by notch and the association of IL-13 with IL-17 during RSV infections are additional unexplored areas that will further define the pathogenic mechanisms involved in pulmonary disease. Thus the therapeutic potential of targeting IL-13 to alter the detrimental physiological and cytokine responses in the lung may help alleviate the long-term lung damage that initiates and/or maintains chronic lung problems following RSV infections.

References

1. Heilman CA. From the National Institute of Allergy and Infectious Diseases and the World Health Organization. Respiratory syncytial and parainfluenza viruses. *J Infect Dis* 1990;161(3):402–406. [PubMed: 2155971]
2. Openshaw PJ, Dean GS, Culley FJ. Links between respiratory syncytial virus bronchiolitis and childhood asthma: clinical and research approaches. *Pediatr Infect Dis J* 2003;22(2 Suppl):S58–64. discussion S64–55. [PubMed: 12671454]
3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289(2):179–186. [PubMed: 12517228]
4. Welliver RC. Respiratory syncytial virus and other respiratory viruses. *Pediatr Infect Dis J* 2003;22(2 Suppl):S6–10. discussion S10–12. [PubMed: 12671447]
5. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr* 2003;143(5 Suppl):S112–117. [PubMed: 14615709]
6. Beckham JD, Cadena A, Lin J, et al. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. *J Infect* 2005;50(4):322–330. [PubMed: 15845430]
7. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005;352(17):1749–1759. [PubMed: 15858184]
8. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;283(4):499–505. [PubMed: 10659876]
9. Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003;58(1):37–42. [PubMed: 12511718]
10. Sethi S, Murphy TF. RSV infection--not for kids only. *N Engl J Med* 2005;352(17):1810–1812. [PubMed: 15858191]
11. Meissner HC, Bocchini JA Jr, Brady MT, Hall CB, Kimberlin DW, Pickering LK. The role of immunoprophylaxis in the reduction of disease attributable to respiratory syncytial virus. *Pediatrics* 2009;124(6):1676–1679. [PubMed: 19948632]
12. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. *Pediatrics* 2004;114(6):1612–1619. [PubMed: 15574623]
13. Elhassan NO, Sorbero ME, Hall CB, Stevens TP, Dick AW. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. *Archives of pediatrics & adolescent medicine* 2006;160(10):1070–1076. [PubMed: 17018467]
14. Palivizumab a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMPact-RSV Study Group. *Pediatrics* 1998;102(3 Pt 1):531–537.
15. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *The Journal of pediatrics* 2003;143(4):532–540. [PubMed: 14571236]

16. Siegrist CA. Vaccination in the neonatal period and early infancy. *Int Rev Immunol* 2000;19(2-3): 195–219. [PubMed: 10763709]
17. Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. *Am J Epidemiol* 1969;89(4):449–463. [PubMed: 4305200]
18. Fulginiti VA, Eller JJ, Sieber OF, Joyner JW, Minamitani M, Meiklejohn G. Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. *Am J Epidemiol* 1969;89(4):435–448. [PubMed: 4305199]
19. Somers CC, Ahmad N, Mejias A, et al. Effect of dexamethasone on respiratory syncytial virus-induced lung inflammation in children: results of a randomized, placebo controlled clinical trial. *Pediatr Allergy Immunol* 2009;20(5):477–485. [PubMed: 19397752]
20. Graham BS, Bunton LA, Wright PF, Karzon DT. Role of T lymphocyte subsets in the pathogenesis of primary infection and rechallenge with respiratory syncytial virus in mice. *J Clin Invest* 1991;88(3):1026–1033. [PubMed: 1909350]
21. Dallman MJ, Smith E, Benson RA, Lamb JR. Notch: control of lymphocyte differentiation in the periphery. *Curr Opin Immunol* 2005;17(3):259–266. [PubMed: 15886115]
22. Schaller MA, Neupane R, Rudd BD, et al. Notch ligand Delta-like 4 regulates disease pathogenesis during respiratory viral infections by modulating Th2 cytokines. *J Exp Med* 2007;204(12):2925–2934. [PubMed: 17998388]
23. Mukherjee S, Schaller MA, Neupane R, Kunkel SL, Lukacs NW. Regulation of T cell activation by Notch ligand, DLL4, promotes IL-17 production and Rorc activation. *J Immunol* 2009;182(12): 7381–7388. [PubMed: 19494260]
24. Hashimoto K, Durbin JE, Zhou W, et al. Respiratory syncytial virus infection in the absence of STAT 1 results in airway dysfunction, airway mucus, and augmented IL-17 levels. *J Allergy Clin Immunol* 2005;116(3):550–557. [PubMed: 16159623]
25. Welliver RC. RSV and chronic asthma. *Lancet* 1995;346(8978):789–790. [PubMed: 7674741]
26. Grunig G, Warnock M, Wakil AE, et al. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* 1998;282(5397):2261–2263. [PubMed: 9856950]
27. Corne JM, Holgate ST. Mechanisms of virus induced exacerbations of asthma. *Thorax* 1997;52(4): 380–389. [PubMed: 9196525]
28. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *Bmj* 1993;307(6910):982–986. [PubMed: 8241910]
29. Sly PD, Hibbert ME. Childhood asthma following hospitalization with acute viral bronchiolitis in infancy. *Pediatr Pulmonol* 1989;7(3):153–158. [PubMed: 2797929]
30. Oehling A, Antepara I, Baena Cagnani CE. The viral factor in the etiology of acute asthma attacks in children. *Allergol Immunopathol (Madr)* 1981;9(1):29–36. [PubMed: 6266242]
31. Peebles RS Jr, Sheller JR, Collins RD, et al. Respiratory syncytial virus infection does not increase allergen-induced type 2 cytokine production, yet increases airway hyperresponsiveness in mice. *J Med Virol* 2001;63(2):178–188. [PubMed: 11170055]
32. Schwarze J, Hamelmann E, Bradley KL, Takeda K, Gelfand EW. Respiratory syncytial virus infection results in airway hyperresponsiveness and enhanced airway sensitization to allergen. *J Clin Invest* 1997;100(1):226–233. [PubMed: 9202075]
33. Schwarze J, Cieslewicz G, Hamelmann E, et al. IL-5 and eosinophils are essential for the development of airway hyperresponsiveness following acute respiratory syncytial virus infection. *J Immunol* 1999;162(5):2997–3004. [PubMed: 10072551]
34. Lukacs NW, Tekkanat KK, Berlin A, et al. Respiratory syncytial virus predisposes mice to augmented allergic airway responses via IL-13-mediated mechanisms. *J Immunol* 2001;167(2):1060–1065. [PubMed: 11441116]
35. Andrew DP, Chang MS, McNinch J, et al. STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. *J Immunol* 1998;161(9):5027–5038. [PubMed: 9794440]

36. Goebeler M, Schnarr B, Toksoy A, et al. Interleukin-13 selectively induces monocyte chemoattractant protein-1 synthesis and secretion by human endothelial cells. Involvement of IL-4R alpha and Stat6 phosphorylation. *Immunology* 1997;91(3):450–457. [PubMed: 9301536]
37. Yamaguchi Y, Suda T, Suda J, et al. Purified interleukin 5 supports the terminal differentiation and proliferation of murine eosinophilic precursors. *J Exp Med* 1988;167(1):43–56. [PubMed: 3257253]
38. Li L, Xia Y, Nguyen A, et al. Effects of Th2 cytokines on chemokine expression in the lung: IL-13 potently induces eotaxin expression by airway epithelial cells. *J Immunol* 1999;162(5):2477–2487. [PubMed: 10072486]
39. Zhou W, Hashimoto K, Moore ML, et al. IL-13 is associated with reduced illness and replication in primary respiratory syncytial virus infection in the mouse. *Microbes Infect* 2006;8(14-15):2880–2889. [PubMed: 17110149]
40. You D, Becnel D, Wang K, Ripple M, Daly M, Cormier SA. Exposure of neonates to respiratory syncytial virus is critical in determining subsequent airway response in adults. *Respir Res* 2006;7:107. [PubMed: 16893457]
41. Dakhama A, Park JW, Taube C, et al. The enhancement or prevention of airway hyperresponsiveness during reinfection with respiratory syncytial virus is critically dependent on the age at first infection and IL-13 production. *J Immunol* 2005;175(3):1876–1883. [PubMed: 16034131]
42. Wills-Karp M, Luyimbazi J, Xu X, et al. Interleukin-13: central mediator of allergic asthma. *Science* 1998;282(5397):2258–2261. [PubMed: 9856949]
43. Zhu Z, Homer RJ, Wang Z, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest* 1999;103(6):779–788. [PubMed: 10079098]
44. Johnson TR, Parker RA, Johnson JE, Graham BS. IL-13 is sufficient for respiratory syncytial virus G glycoprotein-induced eosinophilia after respiratory syncytial virus challenge. *J Immunol* 2003;170(4):2037–2045. [PubMed: 12574374]
45. Castilow EM, Meyerholz DK, Varga SM. IL-13 is required for eosinophil entry into the lung during respiratory syncytial virus vaccine-enhanced disease. *J Immunol* 2008;180(4):2376–2384. [PubMed: 18250447]
46. Becker Y. Respiratory syncytial virus (RSV) evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines and IgE, markers of allergy--a review. *Virus Genes* 2006;33(2):235–252. [PubMed: 16972040]
47. 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. [PubMed: 10806145]
48. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354(9178):541–545. [PubMed: 10470697]
49. Ermers MJ, Hoebee B, Hodemaekers HM, Kimman TG, Kimpfen JL, Bont L. IL-13 genetic polymorphism identifies children with late wheezing after respiratory syncytial virus infection. *J Allergy Clin Immunol* 2007;119(5):1086–1091. [PubMed: 17313976]
50. van der Sande MA, Kidd IM, Goetghebuer T, et al. Severe respiratory syncytial virus infection in early life is associated with increased type 2 cytokine production in Gambian children. *Clin Exp Allergy* 2002;32(10):1430–1435. [PubMed: 12372121]
51. Chung HL, Park HJ, Kim SY, Kim SG. Age-related difference in immune responses to respiratory syncytial virus infection in young children. *Pediatr Allergy Immunol* 2007;18(2):94–99. [PubMed: 17338780]
52. Castro M, Schweiger T, Yin-Declue H, et al. Cytokine response after severe respiratory syncytial virus bronchiolitis in early life. *J Allergy Clin Immunol* 2008;122(4):726–733. e723. [PubMed: 18760461]