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Infant Immune Response to Respiratory Viral Infections

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INTRODUCTION

Respiratory viral infections, represent the leading cause of hospitalization in infants and young children worldwide, and the second cause of infant mortality[1]. Of all respiratory viruses that affect young children, respiratory syncytial virus (RSV), followed by rhinovirus (RV), represent the two leading pathogens, because of their implications with acute disease and also because of their association with the development of reactive airway disease (RAD)/asthma later in life[2–4]. By two years of age almost all children have been infected

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with RSV, and almost all infants develop at least one RV infection in the first year of life[5,6]. In addition, in a substantial proportion of children who develop asthma, the disease originates early in life with episodes of RSV or RV--specially RV-C-- induced wheezing[7,8]. One possible explanation for why respiratory viral infections early in life might drive RAD, including asthma, is that the antiviral immune response in infants is markedly different from that of adults, and even within the first months of life. Additionally, there is increasing evidence of the role of the microbiome in modulating the host infant immune response during the acute disease and long-term respiratory morbidity[9,10]. In this chapter, we will review the different components of the infant immune response to both RSV and RV, their differences according to age, and their possible influence in long-term lung morbidity.

THE INNATE IMMUNE RESPONSE

Innate immunity has a key role in orchestrating early responses to RSV and RV infections, providing an early, non-programmed first line of defense. The importance of innate immunity is critical in infants, in whom the immune system is still developing and often lack immunologic memory. Impaired or dysregulated innate immune responses may lead to slow and inadequate viral clearance, enhanced pathology and greater disease severity during the acute disease, with possible long-term consequences. Further, impaired innate immune responses lead to inadequate adaptive immune responses, poor immunological memory and recurrent infections. The different components of the innate immune response in response to RSV and RV infections are described below.

Respiratory epithelium and pathogen detection

The respiratory epithelium serves as the target for the infecting virus and has an important role at inhibiting RSV or RV infections. The respiratory epithelium not only acts as a protective barrier that prevents the direct contact between respiratory viruses and airway epithelial cells, but also has active anti-inflammatory and immunomodulatory properties releasing antimicrobial peptides and cytokines that contribute to the recruitment of inflammatory cells[11].

Respiratory viruses typically infect ciliated airway epithelial cells with different viruses having variable tropisms to the respiratory tract. Specifically, RSV infects human airway epithelia cells via the apical surface[12]. Different receptors have been identified for RSV --F or G proteins-- in epithelial cells including, TLR-4, CX3CR1, annexin or nucleolin[13,14]. RV also binds to respiratory epithelial cells using receptors that are different depending on the RV species. RV-A and RV-B bind to the ICAM-1 and LDLR receptor, while RV-C binds to the newly identified CDHR-3 receptor[15]. The attachment of RSV or RV to their receptors elicits an innate immune response that leads to airway inflammation and possibly remodeling. Thus, the airway epithelium along with the resident immune cells including macrophages, dendritic cells (DCs) and innate lymphoid cells (ILCs) have a critical role in pathogen detection and initiation of the immune response. These cells express pattern recognition receptors (PRRs) that bind to pathogen associated molecular patterns (PAMPs). Several PRRs are important in recognizing respiratory viruses including toll-like receptors (TLRs) TLR4, TLR3, TLR2/6, TLR7/8 or TLR9 that are expressed on the cell surface, or

RIG-I and MDA-5 that are soluble PRRs located in the cell cytoplasm[16]. Although with contradictory results, possibly due to differences in the patient populations studied, single nucleotide polymorphisms in TLR genes have been associated with increased risk and severity to both RSV (i.e, TLR-4, TLR-9) and RV (i.e TLR-8) respiratory infections in infants, emphasizing the importance of these receptors[17,18].

In addition, the nasopharyngeal microbiota seems to modulate both mucosal and systemic host responses to viral infections. In RSV infected infants, microbiota clusters enriched for *H. influenzae* and *Pneumococcus* were associated with increased disease severity, enhanced TLR signaling and overexpression of neutrophil and macrophage pathways[10].

Interferon responses

Of all cytokines and chemokines released during RSV or RV infection, interferons (IFNs) are one of the best characterized because of their antiviral properties. It is not surprising that viruses had developed ways to inhibit IFN production such as the non-structural (NS1/NS2) RSV proteins that inhibit the production of IFN-α/β[19]. The importance of IFN responses in the defense against respiratory viruses in infants are highlighted by several studies reporting associations between weaker IFN responses, in the mucosal and systemic compartments, and increased disease severity, mostly in RSV infected infants[20–23]. There are three types of IFNs:

1. Type-I IFNs, (IFN-α/β): have direct antiviral effects, inducing an antiviral state both in infected and uninfected cells through the expression of interferon induced genes (ISGs)[24]. IFN-α is produced by several cell types including airway epithelial cells, alveolar macrophages and monocytes, but at least in RSV infection, plasmacytoid dendritic cells (pDCs) appear to be their primary source. pDCs harvested ex-vivo from infants with RSV infection had lower IFN-α production capacity compared to adult pDCs[25]. In addition, a recent study showed that a predominant Th2, Th17 and Type-I IFN response in the respiratory mucosa in infants with acute RSV (but not RV) infection, was associated with recurrent wheezing during the first 2 years of life[26]. These data emphasize the important differences on immune responses to viral infections according to age and also to the specific virus.

2. Type-II IFN (IFN-γ), which early on is produced predominantly by natural killer (NK), NK T-cells (NKT) and type I innate lymphoid cells (ILCs). Later, after development of antigen specific immunity the main source of IFN-γ are T-cells including CD4+ Th1; and CD8+ cytotoxic T-cells. The association between IFN-γ responses and RSV disease severity has been shown in multiple studies. Initial data from studies in animal models and humans suggested that higher IFN-γ responses were directly associated with the severity of the disease[27,28]. However, a growing body of evidence has shown that the IFN response to RSV is dysregulated. Indeed, infants with more severe disease – oxygen administration, need for hospitalization or mechanical ventilation-- had lower concentrations of nasal IFN-γ and/or suboptimal expression of blood IFN-related genes, independent of their atopic status[20–23,29]. In children at risk for developing

asthma, lower RV-induced IFN-γ responses measured in cord blood samples were associated with recurrent wheezing during the first year of life[30].

3. Type-III IFN (IFN-λ) or mucosal IFNs, are structurally and functionally similar to type-I IFNs, although bind to a different receptor and control the infection locally, rather than systemically. The human airway epithelium mounts virus-specific immune responses that are likely to determine the subsequent immune responses. Specifically, studies suggest that absence of IL-28A/B, and IL-29—which belong to the Type-III IFN family-- from epithelial cells after RSV infection, may explain in part the inadequacy of the systemic immunity to the virus[31]. In addition, a recent study showed lower expression of the type-III IFN receptor IFNLR1 in respiratory samples from infants < 6 months of age hospitalized with RSV compared to RV bronchiolitis[32]. Nevertheless, deficient Type-I (IFN-β) and Type-III (IFN-λ) interferon responses have been implicated in the increased susceptibility to RV in patients with asthma[33,34].

Other cytokines

Other cytokines mediating early local innate immune responses to RSV and RV infections include TNF-α, IL-6, IL-9, IL-10, CXCL10 (IP-10), CXCL8 (IL-8), CCL2 (MCP1), CCL3 (MIP-1α) or CCL5 (RANTES) among others[35,36]. In addition to their direct cellular effect at the site of infection, these cytokines act as potent chemoattractants activating and recruiting circulating immune cells such as neutrophils, NK cells and cytotoxic T-cells to the airway mucosa.

Until recently, it was postulated that severe RSV infection was associated with an exaggerated inflammatory response. Similar to IFN responses, there is a growing body of evidence suggesting that some components of the host innate immune responses are actually inadequately activated or even suppressed in more severe cases[37–39]. Infants with severe RSV infection had lower production of blood TNF-α, IL-6 and CXCL8 after LPS stimulation compared with children with milder RSV infection and with age-matched healthy controls[40]. In another study concentrations of 29 cytokines in nasal wash samples were compared in young infants hospitalized with either RSV or RV bronchiolitis. The study showed that overall, infants with RSV infection mounted a more robust response and had higher cytokine concentrations than those with RV infection. Nevertheless, concentrations of MCP-1 and IL-1-α in infants with RV, and of PDG-Fββ, FGF-basic and also IFN-γ in those with RSV infection, inversely correlated with the clinical disease severity score[20]. In another study, of all cytokines measured in nasopharyngeal aspirates in young infants hospitalized with a first episode of wheezing, only MIP-1α demonstrated a strong and independent association with recurrent wheezing during the first two years of life[41].

Innate Immune cells

Neutrophils—The most abundant cell type in the airway from infants with RSV and RV bronchiolitis are neutrophils[42,43]. It still remains unclear whether neutrophils have a protective role or if they contribute to the immunopathogenesis of the disease. Neutrophils limit viral replication and spread by eliminating infected cells, but at the same time release

enzymes that may damage the surrounding tissues through neutrophil extracellular traps (NETs). It is possible that the damage induced by neutrophils during the vulnerable period of lung development in infants with acute RSV or RV infection, may play a role in asthma inception having long lasting consequences[44]. During acute RV infection, both blood and nasal neutrophils increase within the first 72 hours. The high presence of phagocytic cells and pro-inflammatory mediators involved in granulocyte regulation such as granulocyte colony stimulating factor (GCSF) and IL-8 correlate with the severity of RV symptoms, even during mild symptomatic illness[42]. In premature and full term infants with acute RSV infection, neutrophils seem to be the main source of IL-9[45], a pro-inflammatory cytokine associated with development of bronchial hyperresponsiveness and asthma[46].

Eosinophils—The role of eosinophils during RSV infection is still a matter of debate. Original studies suggested that eosinophilic degranulation in infants during RSV infection was associated with airway obstruction[47]. More recently, in vitro studies showed that eosinophils actually facilitated RSV clearance and infectivity[48]. On the other hand, RV infection may induce eosinophil infiltration and activation within the airway, which correlates with changes in airway hyperresponsiveness, especially in patients with asthma[49]. Some eosinophil-released products such as eosinophil-derived neurotoxin or eosinophilic cationic protein, have antiviral properties suggesting an innate antiviral role of these cells during RV infection[49].

Monocytes, NK, and DCs—Alveolar macrophages are thought to have both, immunoregulatory and antigen-presenting capabilities during respiratory viral infections. Macrophages can be infected by RSV and RV as demonstrated by ex-vivo viral replication in these cells[50]. In peripheral blood, the number of monocytes increase during acute RSV infection regardless of severity. However, in infants with severe RSV infection requiring hospitalization the proportion of monocytes expressing low levels of HLA-DR is increased, suggesting that monocyte function might be impaired in the most severe forms of the disease[51].

The numbers of DCs, NK cells and cytotoxic T-cells increase in the respiratory tract during RSV infection, as they have an important role in controlling viral replication[52]. A decrease in the number and/or function of these cells has been associated with worse clinical outcomes. In fact, lung tissue samples from infants that died with severe RSV infection showed absence of NK cells and CD8+ T cells, influx of neutrophils and macrophages in lung tissue, and extensive antigen load[38].

While pDCs are important producers of type-I IFN (IFN-α), conventional DCs have an important role as antigen presenting cells, regulating T-cell responses, and activating NK cells. NK cells contribute to early innate immune responses by providing an early source of IFN-γ, activating T-cells, and by direct cytotoxic killing of the infected cell[53]. Although the proportion of blood DC or NK cells with an activated phenotype increase during RSV infection, lower DC and NK cell numbers were observed in RSV infected children vs. healthy controls[39].

ADAPTIVE IMMUNE RESPONSES

Humoral Immune Responses

Infants have decreased antibody responses compared with adults, due in part to their immature/developing immune system with a limited B-cell repertoire and inefficient generation of somatic hypermutations. In addition, the presence of maternal antibodies may interfere with viral-induced immunogenicity[54,55]. These issues are especially challenging for RSV, which typically causes severe disease in infants at a very young age -- first 2–3 months of life. On the other hand, RV induces genotype-specific neutralizing antibodies, with little cross-neutralization among the >100 genotypes identified.

Antibody responses to RSV

In neonates, circulating RSV IgG antibodies, which are of maternal origin, decrease significantly by ~4 months of age, with an estimated half-life of 30–72 days[56–58]. The interference between pre-existing maternal antibodies and the infant humoral immune response after acute RSV infection has been shown in studies conducted in different patient populations[55,59]. In addition, antibody responses are possibly influenced by other factors, such as disease severity or age, both associated with impaired IFN responses, that must be activated to promote adequate T and B cell immunity[60]. The proof or principle that antibody responses are critical in preventing severe RSV disease has been demonstrated in different randomized clinical trials using monoclonal antibodies (mAb) against the RSV Fusion protein (palivizumab or motavizumab)[61–64]. In those studies, the use of mAb as prophylaxis was associated with a significant reduction in hospitalization rates for RSV lower respiratory tract infection (LRTI), indicating that enough concentrations of neutralizing antibodies could be protective. In addition, the prevention of acute RSV disease either by mAb or maternal vaccination in the future, may have implications for diminishing long-term pulmonary morbidity[65]. This has been shown in studies conducted in animal models and the infant population that showed a significant decreased in the incidence of subsequent wheezing/RAD in infants that received palivizumab[66–68].

Antibody responses to RV

Additional support of the importance of humoral immunity against RV is derived from patients with primary humoral immune deficiency who experience more frequent and severe RV infections[69]. Virus-specific antibodies, both mucosal IgA and serum IgG increase after one week of the acute infection and provide protection from homologous RV infections and disease[70]. It appears that mucosal antibodies have enhanced neutralizing activity compared with systemic antibody responses[71]. The latter also correlate with immunity and with reduced symptom severity[72].

Cellular Immune Responses

T cells participate in controlling RSV and RV infection through the recognition of viral antigens, facilitating both cytotoxic and antibody-mediated immune responses.

CD8 T-cell responses—After innate immune responses are activated, most of the cells that migrate to the respiratory tract are cytotoxic lymphocytes or CD8+ T-cells. Secretion of

RANTES and IP-10 (CXCL10) by RV-infected epithelial cells, neutrophils and phagocytes promote T-cell chemotaxis[70]. CD8+ T-cells play a key role in effective viral clearance, in fact T-cell immunodeficiencies are associated with prolonged viral shedding and therefore with more severe disease and even mortality[73]. In otherwise healthy infants, transient lymphopenia is common and occurs during the first days of RSV or RV infection, when T-cells are migrating to the respiratory tract[74]. CD8+ T cell kinetics inversely correlate with changes in bronchial hyper-responsiveness in the acute infection and revert to baseline during convalescence, suggesting that T-cells contribute to lower respiratory tract symptoms. In addition, it appears that T-cell differentiation into effector memory RA+ over resident memory T-cells (needed for long-term protection) predominates in young infants with RSV or RV infection, and is inverted as the infant immune system matures[75]. We found that symptomatic RV infection in young infants, was associated with marked under-expression of adaptive immunity genes, specifically those related to T-cells and cytotoxic/NK-cell pathways, which was more profound in patients with severe disease[76]. Whether this reflects a failure to mount an adequate response that leads to a more severe illness, or whether it represents a well-controlled early step in the host response that balances the excessive inflammation during the acute viral infection remains unclear.

CD4 T-cell responses—$CD4^+$ T-cells orchestrate the immune response against respiratory viruses. After T-cell receptors are activated, CD4+ T-cells differentiate into specific T-helper subsets including: Th1, Th2, Th17, regulatory T cells (T-regs) and T follicular helper (Tfh) cells, which are defined by their function and cytokine milieu (Fig 1).

- **Th1 cell responses:** are critical during the acute infection, and mediated mainly by IFN-γ. Other cytokines involved in Th1 immune responses include: IL1, IL-2, IL-12, IL-18 and TNF-α. As discussed previously, impaired type-II IFN responses in blood and respiratory samples have been associated with enhanced RSV disease severity[20,21,73]. Additionally, while IFN-γ can inhibit IL-4 mediated allergic responses, it may contribute to early wheeze after RV infection (but not RSV) in predisposed infants with atopy[77].
- **Th2 cell responses:** are defined by the production of IL-4, IL-5, IL-9, and IL-13 and involved in antibody production, class switching and also in eosinophilic responses. Studies suggest that a predominant infant Th2 response during acute RSV infection assessed by decreased IFN-γ/IL-4 ratios are associated with enhanced disease and also development of persistent wheezing[78–80]. There are several factors that could explain persistent wheezing after RSV or RV LRTI, including short and long-term remodeling of the airway physiology and certainly the airway immune response.
- **Th17 cells:** These cells are defined by the production of IL-17A/F and IL-22, playing an essential role in protection against extracellular pathogens, autoimmunity and also in the development of some forms of asthma[81]. These third type of CD4+ T-cells are considered a bridge between innate and adaptive immunity and have different functions during RSV or RV infections including: exaggerated mucus production, enhance Th2 responses, stimulate lung neutrophilic infiltration and modulate CD8+ T-cell responses[82,83]. Higher

concentrations of IL-17, but also IL-4 and IFN-γ, were associated with a decreased risk of hospitalization in infants with RSV or RV LRTI, suggesting that there is tremendous overlap on cytokines responses needed to control these viruses-induced lung disease in infants[29,84].

- **T-regulatory cells:** Tregs are responsible for maintaining tissue homeostasis during the acute infection by facilitating viral clearance and avoiding excessive innate (neutrophils/NK cells) and cellular immune responses of both CD4 and CD8 T-cells[82]. The main cytokines associated with Tregs are IL-10 and TGF-β, that play an important role in the delicate balance between Th1, Th2 and Th17 responses.[85,86] IL-10 has important regulatory functions during acute and convalescent RSV and RV infection in infants. Some studies showed the association between increased concentrations of serum IL-10 and acute RSV or RV severity, as assessed by the need for supplemental O2 or viral-induced wheeze, while others have shown a protective effect of mucosal IL-10 in regards to hypoxemia and severity[73]. While IL-12 favors the differentiation of CD4+ T-cells into a Th1 phenotype, IL-10 inhibits Th1 responses, thus favoring a Th2 phenotype and development of subsequent wheezing[87]. Moreover, increased serum monocyte derived IL-10 responses one month after acute RSV infection were associated with recurrent wheezing in the first year of life, emphasizing the important regulatory role of this cytokine[80].
- **T-follicular helper cells (Tfh):** These recently identified CD4 T-cells are characterized by the expression of CXCR5 (chemokine receptor), BCL6 (transcription factor) and PD-1 (inhibitory molecule). Tfh-cells help with B-cell class switching and are essential for affinity maturation and the development of memory B-cells[88]. There is limited information about their role during RSV or RV infection. A recent study in infants with bronchiolitis showed that activation of BCL6 pathways in blood or nasopharyngeal samples were associated with RSV, but not RV severity[89].

AGE SPECIFIC DIFFERENCES IN IMMUNE RESPONSES

The immune cell milieu in infants is immature and changes drastically in their composition and function after birth, especially during the first months of life[90]. Infant's immune response is geared towards T regulatory and CD4+ Th2 over Th1 responses. This balance may be beneficial in the development of tolerance to self and other antigens, but it may also increase the susceptibility to viral infections[91]. In addition, infants lack immunologic memory towards the invading pathogen, and maternal antibodies provide protection during the first months of life, but the protection is incomplete, especially against mucosal infections, and wanes after 4–6 months of age.

Environmental exposures seem to be key drivers in the development of the infant immune response. Thus, infancy represents a critical window that may shape the remodeling of the airway and the long-term function of the immune system, offering a potential explanation for the association between early life RSV and RV infections, and subsequent development of RAD/asthma. Studies have shown that immune responses are quantitatively and

qualitatively different in young infants compared with adults. Stimulation assays with different TLR agonists showed that cord blood derived white blood cells (WBCs) produced equal or greater amounts of Th2 and Th17 cytokines, but had weaker Th1 responses when compared with adult WBCs[92]. In addition, weaker responses to LPS and lower TLR4 expression were observed in cord blood derived monocytes compared with adult monocytes[93]. Thus, as pathogen detection is critical for the activation of the immune cascade, and as Th1 type responses and also memory are considered fundamental against respiratory viruses, these age specific differences could explain in part the increased susceptibility to viral respiratory tract infections in infants.

Host Transcriptional Profiling

Host transcriptional profiling has provided valuable insights into immune responses to respiratory viral infections. Our group and others have shown that the systemic immune response to RSV or RV respiratory tract infections is characterized by increased expression of neutrophil related genes and relative decreased expression of IFN, and B and T cell related genes according to severity[21,94,95]. Importantly, the magnitude of those responses was different according to the respiratory virus, and are greatly influenced by age and severity. Preliminary studies in healthy young infants (< 6 months) showed that IFN and inflammation genes were under-expressed compared with that of older infants, making infants in early life uniquely susceptible to respiratory viral infections. Recently, transcriptional profiling of nasopharyngeal and blood samples from infants with RSV or RV infection, showed similar strong innate and IFN responses in both compartments in RSV infected infants, while RV responses were not as strong and differed between nasopharyngeal and blood samples[95].

The authors showed that the immune transcriptional profile of infants <6 vs. 6–24 months old were significantly different in response to RSV or RV infection, adjusted for disease severity and other demographic characteristics[21]. Overall, the RSV immune profile in the younger age group was contracted and dominated by a greater proportion of under-expressed transcripts compared with older children (6–24 months). Using a number of analytic strategies, the authors found that despite these infants being equally ill as reflected by their similar clinical disease severity scores, those of younger age displayed significantly less expression of IFN, inflammation and neutrophil transcripts, lack of activation of plasma cell related genes, and greater under-expression of B-cell, NK-cell and T-cell related genes (Fig 2A)[21]. Further, when the authors analyzed the pathways activated or suppressed in infants with RV vs RSV LRTI, also stratified by age (<6 vs. 6–24 months), we found significant differences in the expression of a number of immune pathways. Infants with RV infection, independent of age, demonstrated mild activation of immune response related pathways, with more subtle differences according to age (Fig 2B). While younger RV infants showed less activation of IFN related genes, there were no differences in the overexpression of neutrophil, monocyte or inflammation genes. On the other hand, and similar to that from infants with RSV LRTI, adaptive immune response pathways were greatly suppressed in younger versus older children with RV LRTI[21]. These differences in the immune response were observed in symptomatic rhinovirus (RV) infection vs. with asymptomatic RV detection[76].

These data suggest that although there are pathways that are commonly activated upon infection with different respiratory viruses, the type and breadth of these responses are greatly influenced by age. Nevertheless, whether age at the time of the infection and/or the observed age-related changes in immune responses influence the subsequent development of asthma or atopy awaits further study.

SUMMARY

Infancy represents a critical window when environmental exposures, and in particular RSV and RV infections, may shape the remodeling of the airway and the function of a developing immune system. The immune response evolves during infancy and is characterized early on by lack of immunologic memory, and a biased tolerogenic immune response (Tregs & Th2 responses), while Th1 immunity is restrained and associated with disease severity. These specific nuances on the immune response, may explain the infant susceptibility to these infections and their association with the development of recurrent wheezing/asthma later in life.

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References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–2128. [PubMed: 23245604]
2. 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. [PubMed: 18565953]
3. 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. [PubMed: 20581410]
4. 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]
5. van der Zalm MM, Wilbrink B, van Ewijk BE, Overduin P, Wolfs TF, van der Ent CK. Highly frequent infections with human rhinovirus in healthy young children: a longitudinal cohort study. J Clin Virol. 2011;52(4):317–320. [PubMed: 21982210]
6. Mejias A, Ramilo O. New options in the treatment of respiratory syncytial virus disease. J Infect. 2015;71 Suppl 1:S80–87. [PubMed: 25922289]
7. Miller EK, Bugna J, Libster R, et al. Human rhinoviruses in severe respiratory disease in very low birth weight infants. Pediatrics. 2012;129(1):e60–67. [PubMed: 22201153]
8. Drysdale SB, Alcazar M, Wilson T, et al. Respiratory outcome of prematurely born infants following human rhinovirus A and C infections. Eur J Pediatr. 2014;173(7):913–919. [PubMed: 24493557]
9. Beigelman A, Bacharier LB. Early-life respiratory infections and asthma development: role in disease pathogenesis and potential targets for disease prevention. Curr Opin Allergy Clin Immunol. 2016;16(2):172–178. [PubMed: 26854761]

10. de Steenhuijsen Piters WA, Heinonen S, Hasrat R, et al. Nasopharyngeal Microbiota, Host Transcriptome, and Disease Severity in Children with Respiratory Syncytial Virus Infection. Am J Respir Crit Care Med. 2016;194(9):1104–1115. [PubMed: 27135599]
11. Zanin M, Baviskar P, Webster R, Webby R. The Interaction between Respiratory Pathogens and Mucus. Cell Host Microbe. 2016;19(2):159–168. [PubMed: 26867175]
12. Guo-Parke H, Canning P, Douglas I, et al. Relative respiratory syncytial virus cytopathogenesis in upper and lower respiratory tract epithelium. Am J Respir Crit Care Med. 2013;188(7):842–851. [PubMed: 23952745]
13. Johnson SM, McNally BA, Ioannidis I, et al. Respiratory Syncytial Virus Uses CX3CR1 as a Receptor on Primary Human Airway Epithelial Cultures. PLoS Pathog. 2015;11(12):e1005318. [PubMed: 26658574]
14. Tayyari F, Marchant D, Moraes TJ, Duan W, Mastrangelo P, Hegele RG. Identification of nucleolin as a cellular receptor for human respiratory syncytial virus. Nat Med. 2011;17(9):1132–1135. [PubMed: 21841784]
15. Bochkov YA, Watters K, Ashraf S, et al. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. Proc Natl Acad Sci U S A. 2015;112(17):5485–5490. [PubMed: 25848009]
16. Takeuchi O, Akira S. Innate immunity to virus infection. Immunol Rev. 2009;227(1):75–86. [PubMed: 19120477]
17. Toivonen L, Vuononvirta J, Mertsola J, Waris M, He Q, Peltola V. Polymorphisms of Mannose-binding Lectin and Toll-like Receptors 2, 3, 4, 7 and 8 and the Risk of Respiratory Infections and Acute Otitis Media in Children. Pediatr Infect Dis J. 2017;36(5):e114–e122. [PubMed: 28403045]
18. Alvarez AE, Marson FAL, Bertuzzo CS, et al. Association between single nucleotide polymorphisms in TLR4, TLR2, TLR9, VDR, NOS2 and CCL5 genes with acute viral bronchiolitis. Gene. 2018;645:7–17. [PubMed: 29253610]
19. Ramaswamy M, Shi L, Monick MM, Hunninghake GW, Look DC. Specific inhibition of type I interferon signal transduction by respiratory syncytial virus. Am J Respir Cell Mol Biol. 2004;30(6):893–900. [PubMed: 14722224]
20. Garcia C, Soriano-Fallas A, Lozano J, et al. Decreased innate immune cytokine responses correlate with disease severity in children with respiratory syncytial virus and human rhinovirus bronchiolitis. Pediatr Infect Dis J. 2012;31(1):86–89. [PubMed: 21829141]
21. Mejias A, Dimo B, Suarez NM, et al. Whole blood gene expression profiles to assess pathogenesis and disease severity in infants with respiratory syncytial virus infection. PLoS Med. 2013;10(11):e1001549. [PubMed: 24265599]
22. Bont L, Heijnen CJ, Kavelaars A, et al. Local interferon-gamma levels during respiratory syncytial virus lower respiratory tract infection are associated with disease severity. Journal of Infectious Diseases. 2001;184(3):355–358. [PubMed: 11443563]
23. Piedra FA, Mei M, Avadhanula V, et al. The interdependencies of viral load, the innate immune response, and clinical outcome in children presenting to the emergency department with respiratory syncytial virus-associated bronchiolitis. PLoS One. 2017;12(3):e0172953. [PubMed: 28267794]
24. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. Nat Rev Immunol. 2015;15(2):87–103. [PubMed: 25614319]
25. Marr N, Wang T-I, Kam SHY, et al. Attenuation of respiratory syncytial virus-induced and RIG-I dependent type I IFN responses in human neonates and very young children. J Immunol. 2014;192(3):948–957. [PubMed: 24391215]
26. Turi KN, Shankar J, Anderson LJ, et al. Infant Viral Respiratory Infection Nasal Immune-Response Patterns and Their Association with Subsequent Childhood Recurrent Wheeze. Am J Respir Crit Care Med. 2018;198(8):1064–1073. [PubMed: 29733679]
27. van Schaik SM, Tristram DA, Nagpal IS, Hintz KM, Welliver RC 2nd, Welliver RC. Increased production of IFN-gamma and cysteinyl leukotrienes in virus-induced wheezing. J Allergy Clin Immunol. 1999;103(4):630–636. [PubMed: 10200012]
28. Jafri HS, Chavez-Bueno S, Mejias A, et al. Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction, and chronic inflammatory infiltrates associated with long-

term airway hyperresponsiveness in mice. J Infect Dis. 2004;189(10):1856–1865. [PubMed: 15122522]

29. Nicholson EG, Schlegel C, Garofalo RP, et al. Robust Cytokine and Chemokine Response in Nasopharyngeal Secretions: Association With Decreased Severity in Children With Physician Diagnosed Bronchiolitis. J Infect Dis. 2016;214(4):649–655. [PubMed: 27190183]
30. Gern JE, Brooks GD, Meyer P, et al. Bidirectional interactions between viral respiratory illnesses and cytokine responses in the first year of life. J Allergy Clin Immunol. 2006;117(1):72–78. [PubMed: 16387587]
31. Ioannidis I, McNally B, Willette M, et al. Plasticity and virus specificity of the airway epithelial cell immune response during respiratory virus infection. J Virol. 2012;86(10):5422–5436. [PubMed: 22398282]
32. Pierangeli A, Statzu M, Nenna R, et al. Interferon lambda receptor 1 (IFNL1R) transcript is highly expressed in rhinovirus bronchiolitis and correlates with disease severity. J Clin Virol. 2018;102:101–109. [PubMed: 29549834]
33. 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. [PubMed: 15781584]
34. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nature medicine. 2006;12(9):1023–1026.
35. McNamara PS, Flanagan BF, Hart CA, Smyth RL. Production of chemokines in the lungs of infants with severe respiratory syncytial virus bronchiolitis. J Infect Dis. 2005;191(8):1225–1232. [PubMed: 15776367]
36. Sheeran P, Jafri H, Carubelli C, et al. Elevated cytokine concentrations in the nasopharyngeal and tracheal secretions of children with respiratory syncytial virus disease. Pediatr Infect Dis J. 1999;18(2):115–122. [PubMed: 10048682]
37. Bennett BL, Garofalo RP, Cron SG, et al. Immunopathogenesis of respiratory syncytial virus bronchiolitis. J Infect Dis. 2007;195(10):1532–1540. [PubMed: 17436234]
38. Welliver TP, Garofalo RP, Hosakote Y, et al. Severe human lower respiratory tract illness caused by respiratory syncytial virus and influenza virus is characterized by the absence of pulmonary cytotoxic lymphocyte responses. J Infect Dis. 2007;195(8):1126–1136. [PubMed: 17357048]
39. Larranaga CL, Ampuero SL, Luchsinger VF, et al. Impaired Immune Response in Severe Human Lower Tract Respiratory Infection by Respiratory Syncytial Virus. Pediatric Infectious Disease Journal. 2009;28(10):867–873. [PubMed: 19738511]
40. Mella C, Suarez-Arrabal MC, Lopez S, et al. Innate immune dysfunction is associated with enhanced disease severity in infants with severe respiratory syncytial virus bronchiolitis. J Infect Dis. 2013;207(4):564–573. [PubMed: 23204162]
41. Sugai K, Kimura H, Miyaji Y, et al. MIP-1alpha level in nasopharyngeal aspirates at the first wheezing episode predicts recurrent wheezing. J Allergy Clin Immunol. 2016;137(3):774–781. [PubMed: 26494023]
42. Turner RB, Weingand KW, Yeh CH, Leedy DW. Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. Clin Infect Dis. 1998;26(4):840–846. [PubMed: 9564459]
43. McNamara PS, Ritson P, Selby A, Hart CA, Smyth RL. Bronchoalveolar lavage cellularity in infants with severe respiratory syncytial virus bronchiolitis. Arch Dis Child. 2003;88(10):922–926. [PubMed: 14500316]
44. Geerdink RJ, Pillay J, Meyaard L, Bont L. Neutrophils in respiratory syncytial virus infection: A target for asthma prevention. J Allergy Clin Immunol. 2015;136(4):838–847. [PubMed: 26277597]
45. McNamara PS, Flanagan BF, Baldwin LM, Newland P, Hart CA, Smyth RL. Interleukin 9 production in the lungs of infants with severe respiratory syncytial virus bronchiolitis. Lancet. 2004;363(9414):1031–1037. [PubMed: 15051283]
46. Kearley J, Erjefalt JS, Andersson C, et al. IL-9 governs allergen-induced mast cell numbers in the lung and chronic remodeling of the airways. Am J Respir Crit Care Med. 2011;183(7):865–875. [PubMed: 20971830]

47. Garofalo R, Kimpen JL, Welliver RC, Ogra PL. Eosinophil degranulation in the respiratory tract during naturally acquired respiratory syncytial virus infection. J Pediatr. 1992;120(1):28–32. [PubMed: 1731020]
48. Rosenberg HF, Dyer KD, Domachowske JB. Eosinophils and their interactions with respiratory virus pathogens. Immunol Res. 2009;43(1–3):128–137. [PubMed: 18818885]
49. Rosenberg HF, Domachowske JB. Eosinophils, eosinophil ribonucleases, and their role in host defense against respiratory virus pathogens. Journal of leukocyte biology. 2001;70(5):691–698. [PubMed: 11698487]
50. Midulla F, Villani A, Panuska JR, et al. Respiratory syncytial virus lung infection in infants: immunoregulatory role of infected alveolar macrophages. J Infect Dis. 1993;168(6):1515–1519. [PubMed: 8245538]
51. Ahout IM, Jans J, Haroutiounian L, et al. Reduced Expression of HLA-DR on Monocytes During Severe Respiratory Syncytial Virus Infections. Pediatr Infect Dis J. 2016;35(3):e89–96. [PubMed: 26658377]
52. Gill MA, Palucka AK, Barton T, et al. Mobilization of plasmacytoid and myeloid dendritic cells to mucosal sites in children with respiratory syncytial virus and other viral respiratory infections. J Infect Dis. 2005;191(7):1105–1115. [PubMed: 15747246]
53. Culley FJ. Natural killer cells in infection and inflammation of the lung. Immunology. 2009;128(2):151–163. [PubMed: 19740372]
54. Murphy BR, Alling DW, Snyder MH, et al. Effect of age and preexisting antibody on serum antibody response of infants and children to the F and G glycoproteins during respiratory syncytial virus infection. J Clin Microbiol. 1986;24(5):894–898. [PubMed: 3771779]
55. Trento A, Rodriguez-Fernandez R, Gonzalez-Sanchez MI, et al. The Complexity of Antibody Responses Elicited against the Respiratory Syncytial Virus Glycoproteins in Hospitalized Children Younger than 2 Years. Front Microbiol. 2017;8:2301. [PubMed: 29213258]
56. Capella C, Chaiwatpongsakorn S, Gorrell E, et al. Prefusion F, Postfusion F, G Antibodies, and Disease Severity in Infants and Young Children With Acute Respiratory Syncytial Virus Infection. J Infect Dis. 2017;216(11):1398–1406. [PubMed: 29029312]
57. Chu HY, Steinhoff MC, Magaret A, et al. Respiratory syncytial virus transplacental antibody transfer and kinetics in mother-infant pairs in Bangladesh. J Infect Dis. 2014;210(10):1582–1589. [PubMed: 24903663]
58. Ochola R, Sande C, Fegan G, et al. The level and duration of RSV-specific maternal IgG in infants in Kilifi Kenya. PLoS One. 2009;4(12):e8088. [PubMed: 19956576]
59. Shinoff JJ, O'Brien KL, Thumar B, et al. Young infants can develop protective levels of neutralizing antibody after infection with respiratory syncytial virus. J Infect Dis. 2008;198(7): 1007–1015. [PubMed: 18702606]
60. Swanson CL, Wilson TJ, Strauch P, Colonna M, Pelanda R, Torres RM. Type I IFN enhances follicular B cell contribution to the T cell-independent antibody response. J Exp Med. 2010;207(7):1485–1500. [PubMed: 20566717]
61. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. Pediatrics. 1998;102(3):531–537.
62. 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. J Pediatr. 2003;143(4):532–540. [PubMed: 14571236]
63. Carbonell-Estrany X, Simoes EA, Dagan R, et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. Pediatrics. 2010;125(1):e35–51. [PubMed: 20008423]
64. O'Brien KL, Chandran A, Weatherholtz R, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. Lancet Infect Dis. 2015;15(12):1398–1408. [PubMed: 26511956]

65. Mejias A, Garcia-Maurino C, Rodriguez-Fernandez R, Peeples ME, Ramilo O. Development and clinical applications of novel antibodies for prevention and treatment of respiratory syncytial virus infection. Vaccine. 2017;35(3):496–502. [PubMed: 27692523]
66. 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. [PubMed: 23656644]
67. Mejias A, Chavez-Bueno S, Rios AM, et al. Anti-respiratory syncytial virus (RSV) neutralizing antibody decreases lung inflammation, airway obstruction, and airway hyperresponsiveness in a murine RSV model. Antimicrob Agents Chemother. 2004;48(5):1811–1822. [PubMed: 15105140]
68. 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. [PubMed: 28152315]
69. Kainulainen L, Vuorinen T, Rantakokko-Jalava K, Osterback R, Ruuskanen O. Recurrent and persistent respiratory tract viral infections in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol. 2010;126(1):120–126. [PubMed: 20541246]
70. Jacobs SE, Lamson DM, St George K, Walsh TJ. Human rhinoviruses. Clinical microbiology reviews. 2013;26(1):135–162. [PubMed: 23297263]
71. Perkins JC, Tucker DN, Knopf HL, Wenzel RP, Kapikian AZ, Chanock RM. Comparison of protective effect of neutralizing antibody in serum and nasal secretions in experimental rhinovirus type 13 illness. American journal of epidemiology. 1969;90(6):519–526. [PubMed: 4312066]
72. Butler WT, Waldmann TA, Rossen RD, Douglas RG Jr., Couch RB. Changes in IgA and IgG concentrations in nasal secretions prior to the appearance of antibody during viral respiratory infection in man. J Immunol. 1970;105(3):584–591. [PubMed: 4318484]
73. Russell CD, Unger SA, Walton M, Schwarze J. The Human Immune Response to Respiratory Syncytial Virus Infection. Clin Microbiol Rev. 2017;30(2):481–502. [PubMed: 28179378]
74. Levandowski RA, Ou DW, Jackson GG. Acute-phase decrease of T lymphocyte subsets in rhinovirus infection. J Infect Dis. 1986;153(4):743–748. [PubMed: 2936833]
75. Connors TJ, Baird SJ, Yopes MC, et al. Developmental Regulation of Effector and Resident Memory T Cell Generation during Pediatric Viral Respiratory Tract Infection. J Immunol. 2018;201(2):432–439. [PubMed: 29848753]
76. Heinonen S, Jartti T, Garcia C, et al. Rhinovirus Detection in Symptomatic and Asymptomatic Children Value of Host Transcriptome Analysis. American Journal of Respiratory and Critical Care Medicine. 2016;193(7):772–782. [PubMed: 26571305]
77. Jartti T, Paul-Anttila M, Lehtinen P, et al. Systemic T-helper and T-regulatory cell type cytokine responses in rhinovirus vs. respiratory syncytial virus induced early wheezing: an observational study. Respir Res. 2009;10:85. [PubMed: 19781072]
78. Joshi P, Shaw A, Kakakios A, Isaacs D. Interferon-gamma levels in nasopharyngeal secretions of infants with respiratory syncytial virus and other respiratory viral infections. Clin Exp Immunol. 2003;131(1):143–147. [PubMed: 12519398]
79. Pinto RA, Arredondo SM, Bono MR, Gaggero AA, Diaz PV. T helper 1/T helper 2 cytokine imbalance in respiratory syncytial virus infection is associated with increased endogenous plasma cortisol. Pediatrics. 2006;117(5):e878–886. [PubMed: 16618789]
80. Bont L, Heijnen CJ, Kavelaars A, et al. Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. Am J Respir Crit Care Med. 2000;161(5):1518–1523. [PubMed: 10806148]
81. Mukherjee S, Lindell DM, Berlin AA, et al. IL-17-induced pulmonary pathogenesis during respiratory viral infection and exacerbation of allergic disease. Am J Pathol. 2011;179(1):248–258. [PubMed: 21703407]
82. Mangodt TC, Van Herck MA, Nullens S, et al. The role of Th17 and Treg responses in the pathogenesis of RSV infection. Pediatr Res. 2015;78(5):483–491. [PubMed: 26267154]
83. Wiehler S, Proud D. Interleukin-17A modulates human airway epithelial responses to human rhinovirus infection. Am J Physiol Lung Cell Mol Physiol. 2007;293(2):L505–515. [PubMed: 17545490]

84. Faber TE, Groen H, Welfing M, Jansen KJ, Bont LJ. Specific increase in local IL-17 production during recovery from primary RSV bronchiolitis. J Med Virol. 2012;84(7):1084–1088. [PubMed: 22585726]

85. Durant LR, Makris S, Voorburg CM, Loebbermann J, Johansson C, Openshaw PJ. Regulatory T cells prevent Th2 immune responses and pulmonary eosinophilia during respiratory syncytial virus infection in mice. J Virol. 2013;87(20):10946–10954. [PubMed: 23926350]

86. Ruckwardt TJ, Morabito KM, Graham BS. Determinants of early life immune responses to RSV infection. Curr Opin Virol. 2016;16:151–157. [PubMed: 26986236]

87. Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. Pediatr Infect Dis J. 2003;22(2 Suppl):S76–82. [PubMed: 12671456]

88. Crotty S T follicular helper cell differentiation, function, and roles in disease. Immunity. 2014;41(4):529–542. [PubMed: 25367570]

89. Do LAH, Pellet J, van Doorn HR, et al. Host Transcription Profile in Nasal Epithelium and Whole Blood of Hospitalized Children Under 2 Years of Age With Respiratory Syncytial Virus Infection. J Infect Dis. 2017;217(1):134–146. [PubMed: 29029245]

90. Kollmann TR, Kampmann B, Mazmanian SK, Marchant A, Levy O. Protecting the Newborn and Young Infant from Infectious Diseases: Lessons from Immune Ontogeny. Immunity. 2017;46(3): 350–363. [PubMed: 28329702]

91. Restori KH, Srinivasa BT, Ward BJ, Fixman ED. Neonatal Immunity, Respiratory Virus Infections, and the Development of Asthma. Front Immunol. 2018;9:1249. [PubMed: 29915592]

92. Kollmann TR, Crabtree J, Rein-Weston A, et al. Neonatal innate TLR-mediated responses are distinct from those of adults. J Immunol. 2009;183(11):7150–7160. [PubMed: 19917677]

93. Pedraza-Sánchez S, Hise AG, Ramachandra L, Arechavaleta-Velasco F, King CL. Reduced frequency of a CD14+ CD16+ monocyte subset with high Toll-like receptor 4 expression in cord blood compared to adult blood contributes to lipopolysaccharide hyporesponsiveness in newborns. Clin Vaccine Immunol. 2013;20(7):962–971. [PubMed: 23595503]

94. Bucasas KL, Mian AI, Demmler-Harrison GJ, et al. Global gene expression profiling in infants with acute respiratory syncytial virus broncholitis demonstrates systemic activation of interferon signaling networks. Pediatr Infect Dis J. 2013;32(2):e68–76. [PubMed: 23190772]

95. Do LAH, Pellet J, van Doorn HR, et al. Host Transcription Profile in Nasal Epithelium and Whole Blood of Hospitalized Children Under 2 Years of Age With Respiratory Syncytial Virus Infection. J Infect Dis. 2017;217(1):134–146. [PubMed: 29029245]

Key points

- Infancy represents a critical window when environmental exposures, including viral respiratory infections, may shape the remodeling of the airway and the function of the immune system.
- Innate immune responses evolve during infancy and differs from that of adults, including weaker interferon responses that may explain their increased susceptibility to viral infections.
- Young infants lack immunologic memory towards the invading pathogen and their adaptive immune responses are biased towards tolerance promoting T regulatory and Th2 immune responses.
- Viral-induced changes in lung remodeling and the immune response during infancy may explain the association between early life RSV and RV infections and subsequent development of recurrent wheezing and asthma.

Synopsis

Of all respiratory viruses that affect infants, RSV and RV represent the leading pathogens causing acute disease (bronchiolitis) and are associated with the development of recurrent wheezing and asthma. The immune system in infants is still developing and several factors contribute to their increased susceptibility to viral infections. These factors include differences in pathogen detection, weaker interferon responses, lack of immunologic memory towards the invading pathogen and T helper cell responses balanced to promote tolerance and restrain inflammation. All these aspects are reviewed here with a focus on RSV and RV infections.

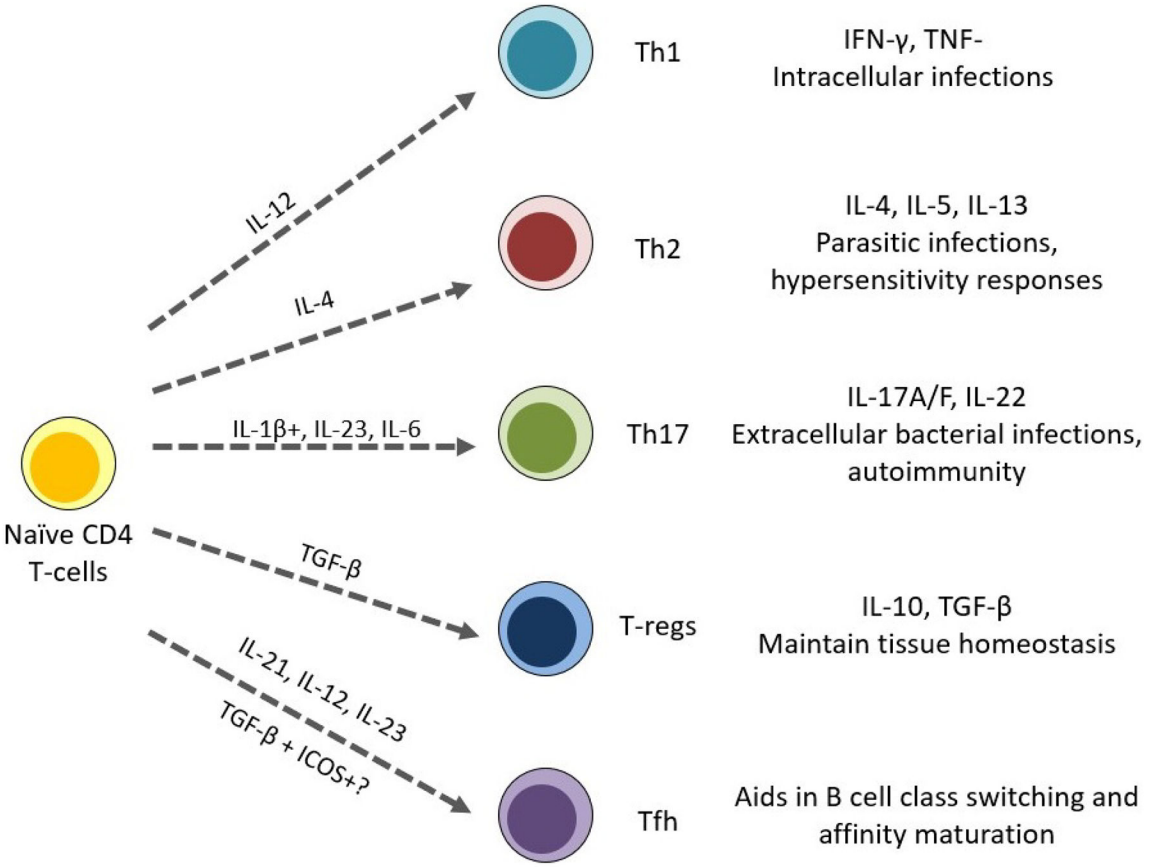

Figure 1. CD4+ T helper cell differentiation and signaling.

CD4+ T-cells differentiate into specific T-helper subsets upon activation of T-cell receptors including: Th1, Th2, Th17, T-regs and T follicular helper (Tfh) cells, which are defined by their function and cytokine milieu.

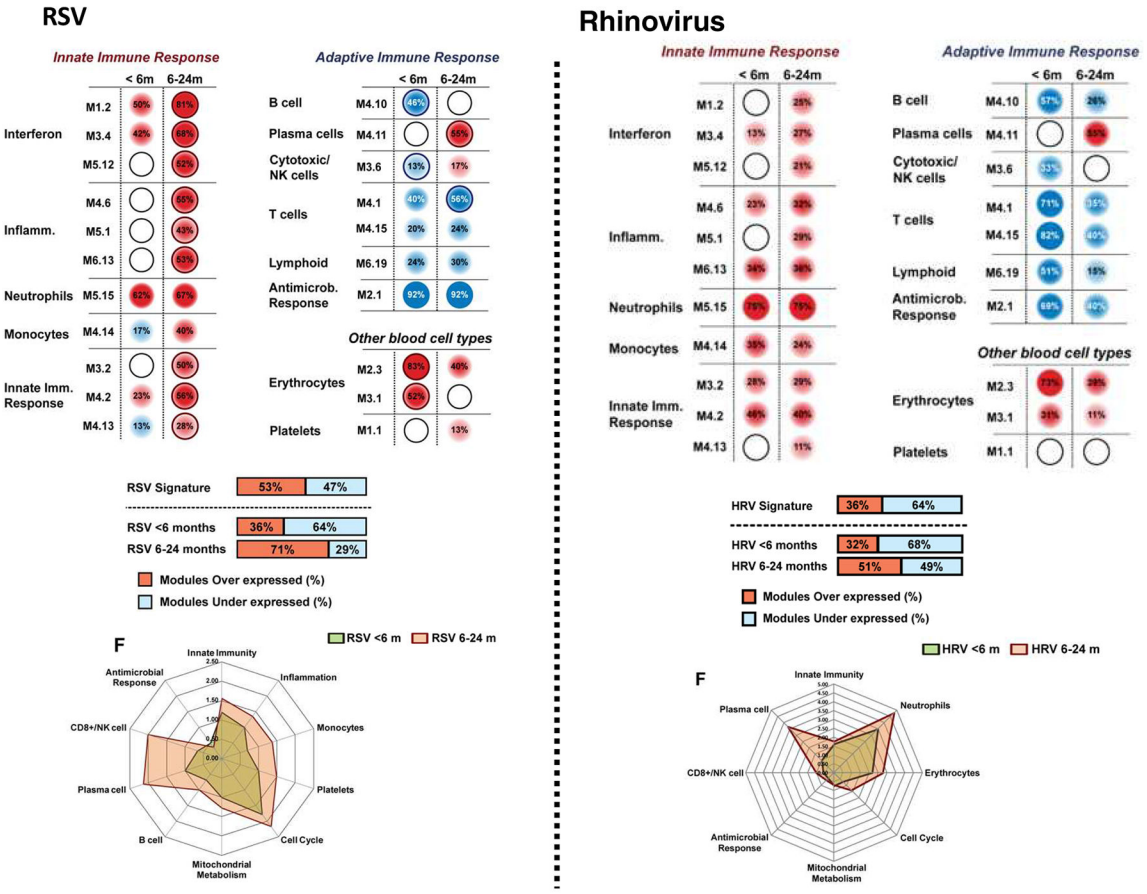

Figure 2. Age at the time of infection influences the host immune response to respiratory syncytial virus (RSV) and rhinovirus (RV) infection.

(A) Immune pathways activated or suppressed during RSV lower respiratory tract infection (LRTI) were compared between 20 infants < 6 months of age and 17 children with RSV LRTI 6–24 months of age (upper panel). Both groups had similar clinical disease severity scores (CDSS). Colored spots represent the percentage of significantly over-expressed (red) or under-expressed (blue) transcripts within a module, and the number included in the dots are the percentage of over or underexpressed transcripts. Blank modules demonstrate no significant differences in expression. The middle panel summarizes the percentage of over and underexpressed transcripts according to the two age groups and in relation to the overall RSV signature. The lower panel further illustrates in a spider graph format the differences in immune responses between the two age groups. **(B)** Infants with RV LRTI (less than 6 months; n=12 and 6–24 months: n=8) revealed fewer differences in host responses according to age. Horizontal bars illustrate the proportion of over-and under-expressed modules in infants (less than 6 months) and children 6–24 months of age in relation to the global influenza and RV signature. These differences are further illustrated in a spider graph format representing the per-module median expression values of the significant different modules between the two age groups.

Adapted from Mejias A, Dimo B, Suarez NM, et al. Whole blood gene expression profiles to assess pathogenesis and disease severity in infants with respiratory syncytial virus infection. PLoS Med 2013;10(11):e1001549; with permission.