

Infant Immune Response to Respiratory Viral Infections



Santtu Heinonen, MD, PhD^a, Rosa Rodriguez-Fernandez, MD, PhD^{b,c},
Alejandro Diaz, MD^{d,e}, Silvia Oliva Rodriguez-Pastor, MD^{f,g}, Octavio Ramilo, MD^{d,e},
Asuncion Mejias, MD, PhD^{d,e,g,*}

KEYWORDS

• RSV • Rhinovirus • Innate immunity • Adaptive immune response

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 differ from that of adults, including weaker interferon responses that may explain their increased susceptibility to 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

Disclosures: A. Mejias and O. Ramilo have received research grants from Janssen. A. Mejias has received fees for participation in advisory boards from Janssen and lectures from Abbvie. O. Ramilo has received fees for participation in advisory boards from Abbvie, HuMabs, Janssen, Medimmune, Merck, and Regeneron and lectures from Abbvie. R. Rodriguez-Fernandez has received fees from participating in advisory boards and lectures from Abbvie. Those fees were not related to the research described in this article.

^a New Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, PO Box 347, Helsinki 00029 HUS, Finland; ^b Department of Pediatrics, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Hospital Materno-Infantil Gregorio Marañón, Madrid 28009, Spain; ^c Section of General Pediatrics, Hospital Gregorio Marañón, Madrid, Spain; ^d Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, The Ohio State College of Medicine, 700 Children's Drive, Columbus, OH 43205, USA; ^e Division of Infectious Diseases, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State College of Medicine, 700 Children's Drive, Columbus, OH 43205, USA; ^f Division of Pediatric Emergency Medicine and Critical Care, Hospital Regional Universitario de Malaga, Malaga 29001, Spain; ^g Department of Pharmacology and Pediatrics, Malaga Medical School, Malaga University (UMA), Malaga, Spain

* Corresponding author. Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, WA4022, 700 Children's Drive, Columbus, OH 43205.

E-mail address: Asuncion.Mejias@nationwidechildrens.org

Immunol Allergy Clin N Am 39 (2019) 361–376

<https://doi.org/10.1016/j.iac.2019.03.005>

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- Young infants lack immunologic memory toward the invading pathogen, and their adaptive immune responses are biased toward tolerance promoting T-regulatory and T-helper 2 immune responses.
- Viral-induced changes in lung remodeling and the immune response during infancy may explain the association between early life respiratory syncytial virus (RSV) and rhinovirus (RV) infections and subsequent development of recurrent wheezing and asthma.

respiratory viruses that affect young children, respiratory syncytial virus (RSV) and rhinovirus (RV) represent the 2 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 2 years of age, almost all children have been infected with RSV, and almost all infants develop at least 1 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, especially rhinovirus-C (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. In addition, 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 article, the authors 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, nonprogrammed first line of defense. The importance of innate immunity is critical in infants, in whom the immune system is still developing and who 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. Furthermore, impaired innate immune responses lead to inadequate adaptive immune responses, poor immunologic memory, and recurrent infections. The different components of the innate immune response to RSV and RV infections are described in this chapter.

Respiratory Epithelium and Pathogen Detection

The respiratory epithelium serves as the target for the infecting virus and has an important role in 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 RSV-G proteins, in epithelial cells, including toll-like receptor-4 (TLR-4),

CX3chemokine receptor 1 (CX3CR1), annexin, or nucleolin.^{13,14} RV also binds to respiratory epithelial cells using receptors that are different depending on the RV species. Rhinovirus-A (RV-A) and rhinovirus-B (RV-B) bind to ICAM-1 and LDLR receptor, whereas 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), has 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. Several PRRs are important in recognizing respiratory viruses, including TLR4, TLR3, TLR2/6, TLR7/8, or TLR9, that are expressed on the cell surface, or retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5), that are soluble PRRs located in the cell cytoplasm.¹⁶ Although the results are contradictory, possibly because of differences in the patient populations studied, single nucleotide polymorphisms in TLR genes have been associated with increased risk and severity to both RSV (ie, TLR-4, TLR-9) and RV (ie, 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 *Haemophilus 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 block IFN production, such as the nonstructural (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 is 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 3 types of IFNs:

1. Type I IFNs (IFN- α/β) have direct antiviral effects, inducing an antiviral state in both infected and uninfected cells through the expression of IFN-induced genes.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 with adult pDCs.²⁵ In addition, a recent study showed that a predominant T helper 2 (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) early on is produced predominantly by natural killer (NK), NK T cells, and type I ILCs. Later, after development of antigen-specific immunity, the main source of IFN- γ is 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 responses that are likely to determine the subsequent immune responses. Specifically, studies suggest that absence of interleukin-28A/B (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 less than 6 months of age hospitalized with RSV compared with RV bronchiolitis.³² Nevertheless, deficient type I (IFN- β) and type III (IFN- λ) IFN 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 tumor necrosis factor- α (TNF- α), IL-6, IL-9, IL-10, CXC chemokine ligand 10 (CXCL10; also known as interferon-gamma inducible protein 10 [IP-10]) (IP-10), CXCL8 (IL-8), CC chemokine ligand 2 (CCL2; monocyte chemoattractant protein-1 [MCP-1]), CCL3 (macrophage inflammatory protein [MIP-1 α]), or CCL5 (regulated on activation normal T expressed and secreted [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 response 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 lipopolysaccharide (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 platelet-derived growth factor beta [PDGF- $\beta\beta$], basic fibroblast growth factor (bFGF), 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-1 α demonstrated a strong and independent association with recurrent wheezing during the first 2 years of life.⁴¹

Innate Immune Cells

Neutrophils

The most abundant cell type in the airway from infants with RSV and RV bronchiolitis is 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. 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 proinflammatory mediators involved in granulocyte regulation, such as granulocyte colony stimulating factor 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 proinflammatory 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 reduced 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, Natural Killer, and Dendritic Cells

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 increases 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 also increase in the respiratory tract during RSV infection, because 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 who 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

Although 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 increases during RSV infection, lower DC and NK cell numbers were observed in RSV-infected children versus 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, their first 2 to 3 months of life. On the other hand, RV induce genotype-specific neutralizing antibodies, with little cross-neutralization among the greater than 100 genotypes identified.

Antibody responses to respiratory syncytial virus

In neonates, circulating RSV immunoglobulin G (IgG) antibodies, which are of maternal origin, decrease significantly by ~4 months of age, with an estimated half-life of 30 to 72 days.^{56–58} The interference between preexisting 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 of 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 by either mAb or maternal vaccination in the future may have implications for diminishing long-term pulmonary morbidity.⁶⁵ As an example, studies conducted in animal models and the infant population showed a significant decrease in the incidence of subsequent wheezing/RAD in infants who received palivizumab.^{66–68}

Antibody responses to rhinovirus

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 1 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 correlates 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 correlates with changes in bronchial hyperresponsiveness in the acute infection and reverts 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 A recent study showed that symptomatic RV infection in young infants was associated with marked underexpression 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 (Tregs), 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 are mediated mainly by IFN- γ . Other cytokines involved in Th1 immune responses include IL-1, 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} In addition, although 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

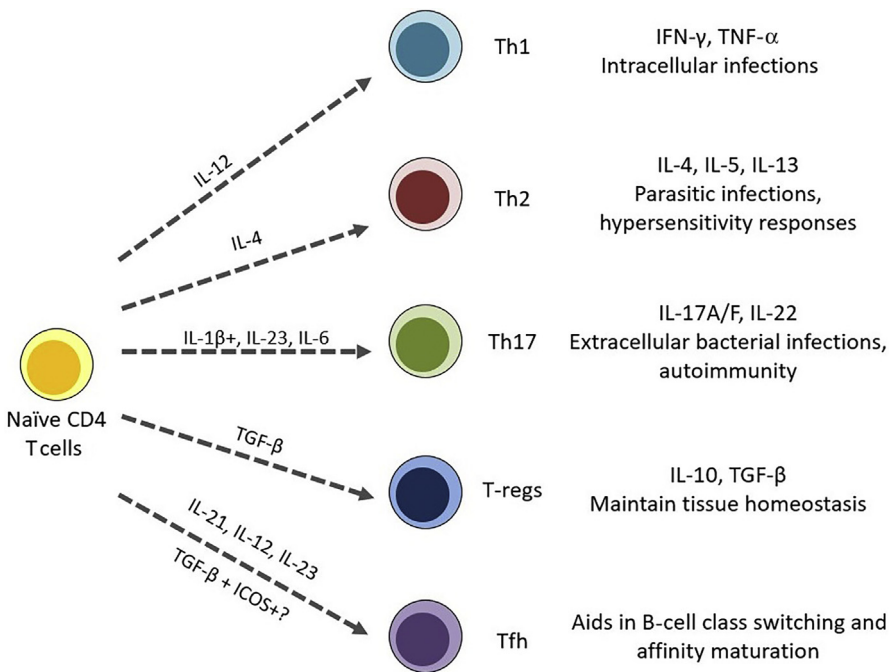


Fig. 1. CD4⁺ T-helper cell differentiation and signaling. CD4⁺ T cells differentiate into specific T-helper subsets upon activation of T-cell receptors, including Th1, Th2, Th17, Tregs, and Tfh cells, which are defined by their function and cytokine milieu. ICOS, Inducible T-cell costimulator; TGF- β , transforming growth factor- β .

- 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 eosinophilic responses. Studies suggest that a predominant infant Th2 response during acute RSV infection assessed by decreased IFN- γ /IL-4 ratios is 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.
- We are discussing the functions of Th17 cells that include: a) more mucus production, b) enhance Th2 responses, c) modulate CD8 T cells, etc. Th17 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 This third type of CD4⁺ T cells is considered a bridge between innate and adaptive immunity and has different functions during RSV or RV infections, including favoring an 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 cytokine responses needed to control these virus-induced lung diseases in infants.^{29,84}
- Treg cells 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 transforming growth factor- β , which 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, whereas others have shown a protective effect of mucosal IL-10 in regards to hypoxemia and severity.⁷³ Although 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 1 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
- Tfh cells, recently identified as 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 was 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 The infant's immune response is geared toward Treg 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 toward 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 to 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, because pathogen detection is critical for the activation of the immune cascade, and because 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. Different studies 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.^{21,89,94} Importantly, the magnitude of those responses was different according to the respiratory virus and were greatly influenced by age and severity. Preliminary studies in healthy young infants (<6 months) showed that IFN and inflammation genes were underexpressed 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, whereas RV responses were not as strong and differed between nasopharyngeal and blood samples.⁸⁹

A recent study showed that the immune transcriptional profile of infants less than 6 months old versus 6 to 24 months old was 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 underexpressed transcripts compared with older children (6–24 months). Using several analytical strategies, the study showed 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 underexpression of B-cell-, NK-cell-, and T-cell-related genes (Fig 2A).²¹ Furthermore, when the pathways activated or suppressed in infants with RV versus RSV LRTI were analyzed, also stratified by age (<6 vs 6–24 months), significant differences in the expression of several immune pathways were identified. Infants with RV infection, independent of age, demonstrated mild activation of immune response-related pathways, with more subtle differences according to age (Fig 2B). Although 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

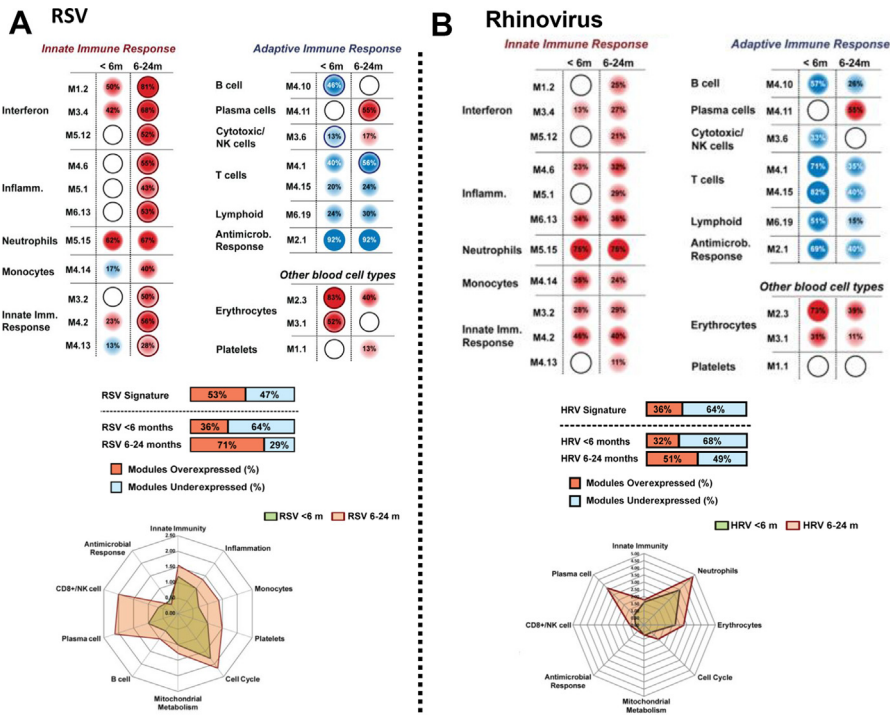


Fig. 2. Age at the time of infection influences the host immune response to RSV and RV infection. (A) Immune pathways activated or suppressed during RSV LRTI were compared between 20 infants less than 6 months of age and 17 children with RSV LRTI 6 to 24 months of age (*upper panel*). Both groups had similar clinical disease severity scores. Colored spots represent the percentage of significantly overexpressed (*red*) or underexpressed (*blue*) transcripts within a module, and the number included in the dots is the percentage of overexpressed or underexpressed transcripts. Blank modules demonstrate no significant differences in expression. The middle panel summarizes the percentage of overexpressed and underexpressed transcripts according to the 2 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 2 age groups. (B) Infants with RV LRTI (<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 overexpressed and underexpressed modules in infants (<6 months) and children 6 to 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 2 age groups. Antimicrob, antimicrobial; HRV, human rhinovirus; Imm, Immune; Inflamm, Inflammation. (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.)

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 RV infection versus 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 or the observed age-related changes in immune responses influence the subsequent development of asthma or atopy await 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 and Th2 responses), whereas 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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