

## Review Article

# Understanding the Importance of Mucosal Immunity in Mediating Protection against RSV Infection: A Role for Age and IgA Production

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**Abstract**

The infant immune response to respiratory syncytial virus (RSV) remains incompletely understood. A neonatal mouse model of RSV infection mimics severe infection in human infants and have shed light on key immunological distinctions that explain disease severity and impaired immune responses in the youngest. Early activation of innate immunity, type 1 interferon dominated pathways (e.g. IFN alpha), followed by pathways involved in B cell proliferation and maturation that lead to antibody production have gained interest in recent years. Here, we review the role for age-specific immune responses and IgA production in mediating protection against RSV infection and draw comparisons (when possible) to human infants.

**ABBREVIATIONS**

RSV: Respiratory Syncytial Virus; DC: Dendritic Cells; pDC: plasmacytoid Dendritic Cells; IgA: Immunoglobulin A; BAFF: B Cell Activating Factor; BAFF-R: B Cell Activating Factor-Receptor; IFN: Interferon

**INTRODUCTION**

Respiratory syncytial virus (RSV) is the leading viral respiratory pathogen in infants [1]. The global burden of this disease is estimated at 64 million cases and 160,000 deaths annually [2]. Yearly in the USA, it is responsible for 85,000 to 144,000 infant hospitalizations [2]. The highest risk of RSV-related hospitalization occurs in infants less than 3 months of life, while the majority of RSV-related hospitalizations will occur in the first year of life [3,4]. Healthcare costs are estimated at US\$365–585 million per year, and the economic impact, in relation to days lost from work, is greater than that of influenza [5]. Mortality rates from RSV in infants are 9 times higher than influenza in this age group [6].

Risk factors associated with severe RSV disease include preterm birth, immunodeficiency, and chronic lung or heart disease [7]. However, the most powerful risk factor for severe

RSV is young chronological age [8]. Most severe RSV disease is in infants (<1 year of age) [6,9]. Increased disease severity in young infants could be due to: 1) structural immaturity of the lung and/or smaller airway size of infants [10] and/or 2) immaturity of the immune system in infants [11,12].

There are numerous differences in the immune responses of infants and adults [13,14], including reduced numbers of innate and adaptive immune cells capable of responding to pathogens.

Evidence suggests that early inflammatory and immune events characteristic of the “innate” host response at the mucosal level are crucial in determining the outcome of acute RSV infection, as well as, its long-term consequences (asthma and recurrent wheezing) [15,16]. Approximately 60 RSV vaccine candidates are currently in development [17]. Adult host response to vaccination often appears to center on early activation of innate, type 1 interferon dominated pathways (e.g. IFN- $\alpha$ ), followed by pathways involved in B cell proliferation and maturation that leads to the production of protective antibodies [18]. For both of these pathways, substantial age-dependent differences appear to exist and very little is known about the mucosal immune response capabilities at young ages [18]. Understanding these key immunological pathways in the context of RSV natural

infection in an age relevant manner can immediately translate in vaccine design and future vaccination strategies by recognizing key mediators of the immune response against RSV. Here, we discuss the mucosal immune response against RSV infection and propose a mechanism that could explain, in part, the role of age in impaired mucosal immunity.

## Ontogeny of mucosal immune system

The mucosal immune system functions as a first line of physical and immunological defense against invading pathogens [19]. Components of the mucosal associated lymphoid tissue (MALT) include the gut associated lymphoid tissue (GALT; e.g. Peyer's patches), bronchus associated lymphoid tissue (BALT) and nasal associated lymphoid tissue (NALT). These tissues serve to protect mucosal epithelial surfaces from ingested or inhaled pathogens/antigens mainly through the secretion of IgA directly onto mucosal epithelial surfaces [19].

The structures of the mucosal immune system are fully developed in utero by 28 weeks gestation, but in the absence of intrauterine infection, activation does not occur until after birth [20]. Maternal and perinatal environmental factors have a profound influence on expression of local immunity at mucosal sites [21]. At birth, the mucosal immune system of a healthy neonate is naive, and is rapidly stimulated by bacterial colonization of the gut and external surfaces [21]. Thus, the predominant activities in MALT, and most likely but less studied NALT and BALT, after birth involve proliferative responses to environmental challenge rather than primary lymphopoiesis [20]. Maturation of the mucosal immune system and establishment of protective immunity varies between individuals but is usually fully developed in the first year of life, irrespective of gestational age at birth [20]. However, mucosal compartments achieve adult levels of effector activities more slowly than systemic compartments [21].

The first 12 months of life is a critical period in which mucosal immunity is required to ensure survival. It is paradoxical that mucosal immune maturation is delayed relative to systemic immunity. Although the cellular apparatus is in place at birth and mucosal antibodies [22] are detected within 1 month in 97% of the normal population [23], a functional deficit persists for some time. Longitudinal studies in children indicate that the switch from producing monomeric IgA to secretory IgA in saliva, an indicator of maturation of mucosal secretory immunity, occurs at widely varying times in the first 12 months [24]. Understanding the different factors that influence the mucosal immune system early in life and its response to infections is a critical step in moving forward with designing and implementing mucosal vaccines for pediatric patients. Animal models have proven valuable in understanding RSV pathogenesis; however, the majority of these studies have been performed using adult animal models and it is unclear how accurately data derived from these models reflect human disease [25]. A mouse model of neonatal RSV infection, which recapitulates many of the pathologies associated with RSV infection in infants, has gained interest. Mice infected as neonates (aged  $\leq 7$  days) develop long-term 'asthma' characterized by increased airway hypersensitivity, mucus hyperproduction, Th2 cytokine and cellular responses and airway remodeling [25]. Although it is unclear what Th2-biased immunopathologies upon

RSV reinfection mean, these models strengthen the importance of the age of initial infection of RSV, which is considered one of the greatest risk factors for severe RSV infection and long-term wheezing [26]. It is also important to take such comparisons between human and mouse with caution given that infants are defined by chronological age rather than immunology characteristics and that the mouse is not fully permissive for RSV. However, evidence suggest that overall, the first year of life can be considered a critical period where there is constant and dynamic interaction between the mucosal immune system and the environment that leads to a fully matured immune response.

## Role of maternal antibodies

RSV infections and hospitalization in children occur mainly during the first year of life in the presence of maternal antibodies. It is clear that maternal vaccination during pregnancy is a safe and effective strategy to protect infants against numerous infections including tetanus, diphtheria, and influenza [27]. However, recent data suggest that they may also interfere with the development of a systemic and humoral immune response to natural infections or even vaccination responses in the offspring [28-30]. Though the effect of maternal antibodies on mucosal immune responses to RSV has not been fully explored, we do know that maternal RSV-neutralizing antibodies are efficiently transferred transplacentally to the newborn [31,32]. Beyond this fact, the data appear to disagree. For example, there is evidence that higher cord blood RSV antibody titers protect against serologic infection [33] and other evidence that the presence of maternal IgG antibodies to RSV suppresses the infant serum IgA antibody response to RSV [28]. Since maternal vaccination to protect the infant against RSV is a realistic intervention that is currently being developed, it is clear that our understanding of the role of maternal antibodies on the infant immune response to RSV needs further exploration [34].

## Dendritic cell maturation and Type 1 interferon

Dendritic cells (DCs) represent a family of professional antigen presenting cells that have the capacity to induce antigen-specific T- and B-cell responses [35]. Efficient priming of T and B cell responses is dependent on full maturation of DCs, which is evoked by the recognition of specific pathogen-associated molecular patterns by pathogen recognition receptors including TLRs [36].

Two broad groups of DC subtypes can be distinguished: conventional DCs (cDCs) and plasmacytoid DCs (pDCs) [25,37]. The latter employ TLR7 and TLR9 to recognize single-stranded viral RNA, such as RSV [38]. Neonatal cDCs are approximately 50% as efficient as adult cDCs at producing TNF- in response LPS; and pDCs produce insufficient type I interferon (IFN) responses compared to adult pDCs [13,39]. The latter is critical, since type I IFN has antiviral activity and stimulates the innate and adaptive immune system by participating in antibody production at multiple stages, including modulation of plasma cell formation [40,41] and development of germinal centers during viral infection [42].

Two nonstructural proteins of RSV, NS1 and NS2, are known to suppress IFN production [43, 44]. On the other hand RSV induces high level expression of IFN- $\beta$  in cultures of various

human respiratory epithelial cells and fibroblasts [45,46]. RSV also induces high levels of IFN- $\alpha$  in different subsets of dendritic cells [47-49]. Interestingly, adult mice produce significantly higher amount of IFN- upon RSV infection when compared to neonates [50] suggesting that while RSV can suppress type I IFNs, there is something different in the IFN response between neonates/infants and adults.

IFN $\alpha$  treatment or adoptive transfer of adult pDCs, capable of inducing IFN $\alpha$ , prior to neonatal RSV infection decreases Th2-biased immunopathogenesis, reduces viral load and down regulates IL4R $\alpha$  on Th2 cells during RSV reinfection, highlighting an age dependent key role on mucosal immunity against RSV [50]. Remot et al., described two major deficiencies in neonatal lung innate responses of mouse infected with RSV: poor DC mobilization and weak engagement of the type I IFN pathway [51]. Administration of Flt3 ligand (Flt3-L), a growth factor that stimulates the proliferation of hematopoietic cells, to neonates before RSV-infection, resulted in increased lung DC number, and reconditioned the type I IFN pathway in neonates upon infection with RSV. Furthermore, these mice were protected from exacerbated airway disease upon adult reexposure to RSV by reorientation of RSV-specific responses toward Th1-mediated immunity [51].

### RSV and IgA class switching: T cell dependent IgA class switching (CD40/CD40L) and T cell independent (BAFF/APRIL)

IgA class-switch recombination (CSR) is induced by both T cell-dependent (TD) and independent (TI) pathways. DC-primed Th cells upregulate CD40L and differentiate to Th effector cells producing cytokines that define their Th subset (Th1, Th2, Th17, etc). In the TD pathway, CD40 ligand on Th cells stimulates CD40 on B cells. B-cell class switching to IgA also requires IL-10 and transformer growth factor beta (TGF- $\alpha$ ). In the TI pathway, B cells are activated through B cell-activating factor of the TNF family (BAFF), a proliferation-inducing ligand (APRIL), and cytokines such as IL-10 and cytokines such as IL-10 and TGF- $\alpha$ .

Differences in T cells between neonates and adults may contribute to defects in TD pathways of IgA production. T cells from infant umbilical cord blood express lower levels of CD40L than adult peripheral blood [52]. Reduced CD40/CD40L interactions in RSV infection of infants could contribute to poor antibody responses. In fact, an RSV vaccine achieved higher IgA titers in serum and increased frequency of antibody-producing cells when CD40L was added [53]. There is evidence that infants can mount TI responses to RSV. Human airway epithelial cells (AEC) produce BAFF in response to RSV infection *in vitro*, suggesting a role for TI antibody responses to RSV in the lung [54]. Additionally, BAFF localize to infected respiratory epithelium of lungs from infants with fatal bronchiolitis [55]. However, this may not be enough to induce long lasting mucosal immune response, because when compared to adults the BAFF/BAFF-R systems is severely impaired. BAFF-R is expressed at reduced levels in the very young and reduced expression of BAFF-R is associated with decreased B cell survival [56]. B cells from human preterm neonates expressed less BAFF-R compared with adult B cells and had significantly less proliferation compared with adult

B cells after stimulation with human recombinant BAFF [57]. Furthermore, BAFF or APRIL was unable to induce IgA/IgG/IgM secretion from newborn B lymphocytes *in vitro* [56].

### Mucosal IgA antibodies and RSV protection

Human IgA (IgA1 and IgA2) is found predominantly in blood and mucosal secretions. At birth, the frequency of IgA1- and IgA2-bearing B cells is equivalent [13]. Subsequently, a preferential expansion of the IgA1-bearing cell population occurs [13]. Serum concentrations remain <35 % of those in adults for the first two years of life [13]. Despite relative antigenic stability, infections with RSV occur throughout life. Substantial effort has focused on determining correlates and/or mediators of protection against RSV disease. Current vaccine candidates seek to induce high levels of RSV-specific serum neutralizing antibodies, which are associated with reduced RSV-related hospitalization rates. However, these may not actually prevent infection. In fact, both mucosal IgA and IgG have been shown to correlate better with RSV protection than serum antibodies in both infants and adults implying that mucosal and serum antibodies are independent co-correlates of protection against RSV infection [58,59] and highlighting the importance of mucosal humoral response against RSV. In the adult human challenge model, the level of virus replication and the magnitude of the subsequent antibody response are inversely correlated with the level of nasal secretory neutralizing antibody prior to infection [60]. RSV-specific nasal IgA correlates significantly more strongly with protection from polymerase chain reaction-confirmed infection than serum neutralizing antibody [61] and higher nasal immunoglobulin (Ig) A predicts lower infectivity and lower measures of viral replication [58]. Furthermore, low RSV-specific nasal IgA is an independently significant risk factor for RSV infection [62].

Age-related differences in mucosal IgA concentrations have not been extensively measured, but it is likely critical as a first line of defense against RSV at its point-of-entry in the human nasal respiratory epithelial tissues [63-65]. McIntosh et al showed a role of age in the capacity to develop antibody in secretions while studying the the immunologic response to infection with RSV in infants [66]. They noticed a significant difference in the IgA antibody response to RSV between infants younger or older than two months. Scott et al found that IgA was the only immunoglobulin consistently present at a detectable concentration in respiratory secretions of infants after RSV primary infection and that the neutralizing activity against RSV was shown to be due to specific IgA antibody [67]. Murphy et al analyzed the serum and secretory immune responses of 18 infants and children, 4 to 21 months of age, who underwent primary infection with RSV [68] and found that younger infants failed to develop a rise in serum or nasal-wash neutralizing antibody. This failure to achieve high titers of antibodies following primary infection likely plays some role in their subsequent susceptibility to reinfection.

### DISCUSSION & CONCLUSION

Although there is comprehensive data on the role of age and immune responses against RSV, many questions remain unanswered: First, what are the mechanisms responsible for protection against RSV? Are mucosal antibodies, specifically IgA, protective? Are mucosal IgA antibody responses affected

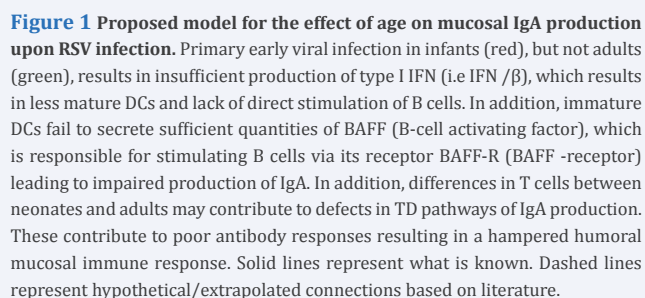


differences may account, in part, for the age dependent immune response against RSV and the increased susceptibility of the youngest to severe infection.

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