

Immunological Response to Respiratory Syncytial Virus Infection

Thyyar M Ravindranath*

***Corresponding Author:** Thyyar M Ravindranath, MBBS, MS (Gen Surg), MD (Pediatrics and Pediatric Critical Care Medicine), Senior Lecturer, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Irving Medical Center, Vagelos College of Physicians and Surgeons, 630 West 168th Street, New York, New York-10032, USA.

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Abstract

Immunological response to Respiratory Syncytial Virus (RSV) involves multiple entities such as cellular, antibody, cytokine, chemokine, and Pattern Recognizing Receptors (PRRs) that are mobilized to subdue the airway and pulmonary effects of the virus. RSV predominantly involves the respiratory tract including the bronchioles and the lungs in addition to the upper respiratory passage. Although RSV afflicts all age groups predominantly in winter, severe infection is more common in the very young and in older individuals, i.e., 60-65 years of age. Recently, vaccines and monoclonal antibodies have been developed as a preventive strategy for the vulnerable.

Keywords: RSV, T-cells, B-cells, cytokine, chemokine, PRRs.

Introduction

Respiratory Syncytial Virus (RSV) is a single-stranded, enveloped, RNA virus belonging to the Pneumoviridae family of the mononegavirales order. Infection occurs during the winter months in temperate climate. Infection is seen in children as well as in adults. Infection involves both upper, middle, and lower airways including the bronchioles and lung parenchyma. Reinfection is common because of a lack of natural immunity to RSV [1, 2]. Morbidity and mortality are more common in infants, young children, and adults older than 60-65 years of age. The body's immunological response determines the response to RSV infection. 58,000 to 80,000 children under age 5 are hospitalized with RSV each year and 1 to 2 of every 100 children younger than 6 months old with RSV may need to be hospitalized [3]. According to the U.S. Centers for Disease Control and Prevention, each year in the U.S., RSV leads to approximately 60,000-120,000 hospitalizations and 6,000-10,000 deaths among adults 65 years of age and older [4].

Immunological response: The immunological response involves cellular, antibody, type 1 and type 2 helper cells [Th1 and Th2], cytokine, chemokine, and Pattern Recognition Receptors (PRPs) that determine the outcome of RSV infection.

Cellular response includes neutrophils, natural killer cells (NK), dendritic cells (DC), macrophage and monocytes, eosinophils, and T-cells or Thymus derived cells.

Cellular response consisting of neutrophils and macrophages in RSV bronchiolitis were higher in term infants than in preterm infants due to the mature immune system of term infants [5]. However, lymphocyte count was similar in both groups.

Neutrophils: During lower respiratory tract infection (LRTI) with RSV, neutrophils are activated at the initial stages of infection with the production of elastase from neutrophils [6]. The maximal neutrophil infiltration in the lungs in LRTI is seen when symptoms peak at the highest viral load [7]. The lung shows heavy neutrophilic infiltration in non-survivors of LRTI [8].

NK cells: NK cells are involved in the regulation of inflammation and lower systemic levels associated with the severity of infection were observed [9]. NK cells that express granzyme B migrate to the lungs as evidenced by the presence of these cells from airway secretions in severe bronchiolitis [10].

DCs: DCs are the primary antigen presenting cells and are mobilized from the blood into the nasal mucosa during early infection and increase even more during recovery [11]. Blood plasmacytoid DCs (pDCs) are decreased during severe bronchiolitis [12]. Conventional DCs (cDCs), on the other hand, display a proinflammatory phenotype in infants with bronchiolitis on ventilator [13]. Following severe RSV bronchiolitis, preterm and infants over the age of 4 months show lower lung pDCs when compared to infants at term and infants less than 4-month. This suggests an ineffective immune response to severe RSV infection [13].

Macrophages and Monocytes: Alveolar macrophages exhibit antigen presentation and regulate the immune response. Blood monocytes reveal enhanced Toll-like receptor (TLR) 4 and decreased TLR 8 as well as Tumor Necrosis Factor- α [TNF- α] in acute RSV infection [14].

Eosinophils: Eosinophils help in the recovery process. Eosinophil counts are not increased in the early part of the infection but are elevated in the recovery phase [15]. Eosinophil may be associated with severe infection as a part of Th2 response.

T-cells: A transient T-cell lymphopenia is observed initially in RSV LRTI. T-cell subsets such as CD4⁺, CD8⁺, CD3, γ δ are reduced during infection compared to recovery phase [16]. T-cell lymphopenia is prominent in younger subjects. Low T-cell subsets are observed in more severe infection and are almost absent in fatal cases [17]. Circulating regulatory T-cells (Tregs) are decreased in hospitalized infants with RSV bronchiolitis for up to 3 weeks [18].

T-cell subsets: CD4⁺ T-cells (helper cells) dominate in comparison to CD8⁺ (suppressor/cytotoxic cells) in RSV LRTI [19]. However, as infection progresses, CD8⁺ becomes more predominant and exhibits an effector phenotype (antigen encountered cells). In bronchiolitis, blood cytotoxic T-cells predominate in mild cases, as opposed to the more severe cases [20]. RSV-specific lung CD 8⁺T-cells are inversely related to symptom severity and viral load in bronchiolar lavage fluid. T-cell apoptosis is used by RSV as an evasive strategy to the immune response of the host. T cell response is blunted through the expression of program death cell-1 (PD-1) protein and its interaction with its ligand on T cells in the lungs to control inflammation and mitigate lung injury [21]. Lymphopenia is associated with higher prolactin and lower leptin-1 levels suggesting the involvement of a neuroendocrine stress response in severe RSV infection [22].

Flawed T-cell response: Risk factors for susceptibility to severe RSV infection is found in elderly subjects [23], who have low RSV restricted CD4⁺ and CD8⁺ T cells, and in those on immunosuppressive drugs [24], and following bone marrow transplantation.

Antibody response via B-cells: Following RSV LRTI in infants, there is an enhanced circulating B cells with prominent plasma cells in pulmonary tissue in lethal cases of bronchiolitis. Type 1 Interferon- γ (IFN- γ) is suspected to be involved in early B cell response against RSV. B cell stimulating factors were also detected in pulmonary infected epithelial cells. RSV LRTI showed elevated immunoglobulins of A, G, and M types in the lungs. In adults with RSV infection, the presence of RSV specific circulating plasma cells over a prolonged period is associated with longer viral shedding [25]. Adults who have severe infection showed higher circulating levels of IgA and IgG post-infection which may be related to enhanced viral load.

Immunoglobulin E: IgE plays a deleterious role in RSV [26].

T helper cell responses: T helper cells consists of Th1, Th2 cells and their balance.

Th1 cells secrete IFN- γ , IL-1, IL-2, IL-12, IL-18, and TNF- α . Th 1 cell, through its proinflammatory effect, controls intracellular pathogens.

Th2 cells secrete IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and are important in generating antibody response. It counteracts the Th1 response and keeps inflammation under control.

There are changes seen in both types of cells in RSV infection which is beyond scope of this manuscript.

Cytokine: Proinflammatory IL-17A and IL-8 will be discussed.

IL-17 A: Circulating IL-17 levels and Th-17 cells counts are higher in infants with RSV bronchiolitis than in those infants with non-RSV LRTI. Nasal IL-17 A levels are elevated in infants on the ventilator [27]. In the acute phase, IL-17 A level may be deleterious since it is involved in the recruitment of neutrophils.

IL-8: In the acute phase of RSV LRTI, IL-8, a neutrophil chemoattractant level is increased in blood and respiratory tract. This is followed by a decline in circulating IL-8 in the recovery phase [28]. Elevated circulating and airway IL-8 levels are seen in infants who need ventilatory support and who are hypoxemic. RSV LRTI in term infants presents with higher nasal IL-8 and neutrophils, suggesting a robust inflammatory response.

Chemokine response: In RSV bronchiolitis and LRTI, increased levels of chemokine ligand 3 (CCL3) or Macrophage Inflammatory Protein (MIP-1 α), chemokine ligand 5 (CCL5) or Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), and eotaxin are found in the nasal mucosa and in the lungs [29].

Pattern Recognition Receptors (PRRs): These receptors are involved in the recognition of viral pathogens and in the production of cytokine and interferon. Increased expressions of TLR7, TLR8, Retinoic acid-inducible gene I (RIG-1), and Melanoma Differentiation-Associated gene 5 (MDA-5) are found in RSV bronchiolitis in infants [30].

Prevention

A new vaccine (GSK's Arexvy) has been approved by the Food and Drug Administration (FDA) against RSV LRTI as a preventive measure in adults over 60 years of age. The vaccine significantly reduced the risk of developing RSV-associated LRTI by 82.6% and reduced the risk of developing severe RSV-associated LRTI by 94.1% [4].

In a large study, when administered to the mother during the second or third trimester of pregnancy, Pfizer's RSVpreF or PF-06928316 showed an effectiveness of 82% for preventing severe RSV in babies from birth to 3 months of age, the efficacy was still high, at 69%, against severe RSV illness. However, there was a slight increase in preterm births in the RSV vaccine group that wasn't statistically significant. The rate of preterm births in women was 5.7% which is slightly higher than the 4.7% in the unvaccinated group. Also, the preterm births occurred later in the gestational period [3].

The FDA advisory panel has also recommended the approval of a monoclonal antibody Beyfortus (nirsevimab) aimed at preventing RSV in infants and vulnerable toddlers [31].

Conclusion

Immunological response to RSV infection is complex and involves multiple protein complexes which interact with each other to resolve infection that affects the airway and lung.

Conflict of Interest

None

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Ethical Approval

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