International Journal of Infection
ISSN 1972-6945 / 2024 vol. 8, ISSUE N. 2, May-August

RESPIRATORY SYNCYTIAL VIRUS

Shadrokh Nabili[1] and Livio Giuliani[2*]

[1] Department of Ophthalmology, University Hospitals Of Morecambe Bay NHS Foundation Trust, United Kingdom;
[2] European Cancer and Environmental Institute (ECERI), Bruxelles, Belgium.

Correspondence to:
Livio Giuliani, PhD,
European Cancer and Environmental Institute (ECERI),
Bruxelles, Belgium.
e-mail: giuliani.livio@gmail.com

ABSTRACT

Respiratory syncytial virus (RSV) is a common and highly contagious virus that primarily affects the respiratory system, particularly in young children, older adults, and individuals with weakened immune systems. RSV causes lung and airway damage, resulting in the common respiratory disease. The virus enters the airways and creates epithelial inflammation with edema of the submucosa and adventitia. The infection involves the pulmonary alveoli and can cause epithelial necrosis and inflammation due to the accumulation of immune cells. RSV is known to induce alterations in the innate and adaptive immune system response. It activates the NF-κB pathway which leads to the transcription of pro-inflammatory cytokines. Infection triggers the innate immune response to the virus, involving pattern recognition receptors (PRRs) and Toll-like receptors (TLRs), particularly TLR3 and 4 that recognize RSV RNA. These receptors trigger signaling pathways that lead to the production of inflammatory cytokines, such as type I interferons (IFNs), IL-6, TNF, and IL-1β. Prophylaxis for RSV is performed either with monoclonal antibodies or with the recently developed vaccine.

KEYWORDS: *Respiratory syncytial virus, respiratory disease, inflammation, immune response, virus, infection*

INTRODUCTION

Respiratory syncytial virus (RSV) is a virus that primarily causes respiratory tract infections, especially in infants, young children, the elderly, and immunocompromised individuals (1). It is a major cause of hospitalization in infants. It usually causes mild cold-like symptoms but can also cause serious respiratory illnesses such as bronchiolitis and/or pneumonia (2). RSV is an RNA virus belonging to the Paramyxoviridae family that is divided into types A and B based on the antigenic differences of the membrane glycoproteins F and G, which are responsible for the adhesion and penetration of the microorganism into the membrane of the host cell (3).

Once it has penetrated the subject's airways, the virus localizes at the level of the smaller branches. Edema of the submucosa and adventitia appears simultaneously with epithelial inflammation (4). This results in obstruction of the small airways, with the appearance of areas of atelectasis, hyperinflation, and often, small areas of consolidation. RSV is a contagious virus and a common cause of respiratory disease worldwide (5). The virus can affect the lungs and airways of an infected individual, potentially causing severe disease or death (6).

The infection can cause necrosis of the epithelium followed by a process of regeneration of cells that accumulate inside the small lumen with inflammatory cells (7). This situation causes a substantial alteration of the normal gas exchange at the pulmonary level with consequent hypoxemia, associated with hypercapnia in the most severe forms (8). Alveoli are generally normal, except those immediately adjacent to the bronchioles. Extensive involvement of the alveoli may occur, with increased cellularity and formation of alveolar sweat.

Received: 03 April, 2024
Accepted: 10 August, 2024

1972-6945 (2024)

Specific anti-RSV antibodies play an important role in the pathogenesis of the disease (9). In this regard, it has been shown that the presence of specific IgE for RSV in nasopharyngeal secretions of individuals affected by bronchiolitis correlates with the severity of the disease and with possible development of respiratory sequelae.

Numerous studies demonstrate that there is an association between RSV bronchiolitis, recurrent wheezing, and asthma (10). Several analyses show that the highest frequency of asthma occurs when both a family history of atopy and RSV bronchiolitis are present as risk factors, although some cases have been described without a history of atopy (11). One of the most accredited hypotheses to describe this relationship considers the possibility that RSV can induce alterations in the response modalities of the innate immune system (12).

DISCUSSION

RSV infection activates both innate and adaptive immune responses (13). In the innate immune response to the virus, pattern recognition receptors (PRRs) are activated. Infection by RSV involves PRRs and Toll-like receptors (TLRs), particularly TLR3 and 4 that recognize RSV RNA (14). This recognition triggers signaling pathways that lead to the production of type I interferons (IFNs) and pro-inflammatory cytokines such as IL-6, TNF, and IL-1β (15).

Once RSV has penetrated the lung, the virus can directly or indirectly damage the bronchial epithelium by downregulating the p53 gene responsible for cellular apoptosis (16). The resulting viral replication stimulates the expression of genes that regulate the cascade of pro-inflammatory chemokines such as CCL5, CCL2, CCL3, CXCL8, CXCL6, and CXCL10, and cytokines IL-1, 6, 11, GM-CSF, and TNF (17). In this way, the virus predisposes both children and adults to the onset of chronic respiratory disease.

Macrophages, dendritic cells (DCs), natural killer (NK) cells, and neutrophils also play a key role (18). Macrophages are activated when the RSV F protein binds to their wall through TLR-3 and -4 (18). Once recruited into the lungs, they activate the transcription factor NF-kB with the consequent production of pro-inflammatory cytokines, such as TNF, and the chemokines CXCL6 and CXCL12 (19).

Plasmacytoid DCs, a subset of DCs found in the blood and peripheral lymphatic tissue, produce IFN-α and β which are pro-inflammatory cytokines that inhibit viral replication (20). By way of its NS1 and NS2 proteins, RSV is able to inhibit the production of IFN-α and β persisting within the bronchial tree in its active form (21).

NK cells contain a serine protease called granzyme B that triggers the classic pathway of programmed cell death. In subjects affected by RSV bronchiolitis, NK cells cause a reduced expression of this enzyme, which triggers constant viral replication (22).

During RSV infection, 75% of recruited cells are neutrophils (23). Their role in the pathogenesis of the disease is clear; these cells produce large amounts of cytokines and have a long survival rate due to delayed apoptosis and are also the main cells involved in long-term exacerbations. The surfactant proteins SP-A, -B, and -D produced by the alveoli and airway epithelial cells also play a pathogenetic role (24). They bind the F and G proteins of the virus and help prevent RSV infection by promoting its clearance. Affected subjects show low levels of SP-A, -B, and -D, which results in prolonged persistence of the virus in the airways and poor viral clearance.

DCs and macrophages are also important in engulfing and processing the virus. These innate immune reactions induce the production of cytokines and present viral antigens to activate adaptive immune cells. NK cells recognize virus-infected cells, causing cell lysis and secreting antiviral cytokines such as IFN-γ to limit viral replication (25). Humoral or adaptive immunity involves B cells and plasma cells which produce neutralizing antibodies to the RSV fusion protein (F) and glycoprotein (G). Antibody neutralization prevents the virus from entering host cells, although this immune effect tends to wear off and lead to reinfection of the host. CD8+ cytotoxic T lymphocytes (CTLs) kill infected cells; while CD4+ helper T cells support both CTLs and B cell functions (26). However, T cell dysfunction can lead to increased inflammation.

RSV causes infection and activates inflammatory mechanisms that help control the infection, but excessive inflammation can lead to tissue damage and exacerbation of respiratory symptoms (10.1007/s12016-013-8368-9). The excess production of inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF, can cause a 'cytokine storm' characterized by the excessive release of immune mediators (27). TNF and IL-1β contribute to vascular permeability, which leads to fluid accumulation in the lungs and worsens inflammation. The IL-1 and TLR families share similar functions and are associated with innate immunity.

It has been reported that over 95% of organisms use the innate immune system for survival (28). IL-1 triggers inflammation through IL-1 receptors, while TLRs induce inflammation through microorganisms. IL-6 is involved in fever induction and acute phase responses, while IL-8 is an attractive chemokine that primarily recruits neutrophils to the site of inflammation. Reactive oxygen species (ROS) are produced by infected immune cells and are a defense mechanism

due to their capability to kill RSV, but they also cause oxidative stress and tissue damage (29). ROS can damage the lung epithelium causing leaks and altered permeability, which are serious symptoms.

The RSV F protein is involved in the entry of the virus into the host cell. The role of the F protein is to fuse the virus to the target cell, and it is the main target for neutralizing antibodies. In addition to mediating the attachment of the virus to the cell, the G protein modulates immune responses (30). This protein acts similarly to chemokines and can bind to host immune receptors, such as CX3CR1, inhibiting immune responses and promoting immune evasion (31). This allows the virus to carry out its pathogenic action and cause persistent inflammation.

RSV encodes the NS1 and NS2 proteins, which antagonize the response to IFN. They block the signaling pathways that induce the production of antiviral IFN, weakening the host's ability to control viral replication. RSV infection recruits large numbers of granulocytes to the lungs. These immune cells release proteolytic enzymes, ROS, and inflammatory mediators, which can cause tissue injury and worsen airway inflammation, a hallmark of severe RSV disease (32).

RSV activates the NF-κB pathway, which leads to the transcription of pro-inflammatory cytokines. NF-κB activation is a major contributor to lung inflammation and exacerbation of respiratory symptoms in RSV infections (33). The JAK-STAT pathway is involved in mediating IFN signaling. RSV uses its NS proteins to interfere with JAK-STAT signaling, reducing host antiviral defenses and contributing to immune dysregulation (34).

When RSV infection is severe, a pathological immune response occurs that is harmful to the body. If the severe immune reaction involves adaptive immunity with Th2 lymphocytes, there may be excess production of some cytokines such as IL-4, IL-5, and IL-13, with airway inflammation and mucus production. In addition, excessive infiltration of immune cells, such as granulocytes, can cause bronchial blockage and alter respiratory function (10.1128/JVI.73.10.8485-8495.1999).

Prophylaxis

Prophylaxis is necessary to avoid or prevent the spread of RSV. It is the passive protection of the lower respiratory tract (36). Currently, the main form of prophylaxis, which aims to prevent or reduce RSV infection, is with the use of monoclonal antibodies such as palivizumab (synagis) and nirsevimab (beyfortus) (37). The monoclonal antibody palivizumab is given to high-risk infants, such as premature infants, and those with chronic lung disease or congenital heart disease (38). Nirsevimab is a newer generation monoclonal antibody approved by the FDA in July 2023, that provides broader and longer-lasting protection than palivizumab and is aimed at preventing severe RSV disease in infants and children (37). Active immunization with a recombinant bivalent vaccine is now available in Europe and the United States to protect infants and the elderly, but also adults at risk.

CONCLUSIONS

RSV infection triggers an immune response that can lead to a pathological state mediated by inflammation. RSV infection causes a complex immune response involving both protective and pathological mechanisms. While innate and adaptive immune responses are critical for viral clearance, they can also drive inflammation, causing lung damage and worsening respiratory conditions. Understanding the biochemical mechanisms of immunity and inflammation at play in RSV infection can guide vaccine development and targeted therapies that won’t trigger excessive inflammation.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Meissner HC. Viral Bronchiolitis in Children. Ingelfinger JR, ed. *New England Journal of Medicine*. 2016;374(1):62-72. doi:https://doi.org/10.1056/nejmra1413456
2. Hall CB. Respiratory Syncytial Virus and Parainfluenza Virus. *New England Journal of Medicine*. 2001;344(25):1917-1928. doi:https://doi.org/10.1056/nejm200106213442507
3. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. *BMJ*. 2019;366:l5021. doi:https://doi.org/10.1136/bmj.l5021
4. Talukdar SN, McGregor B, Osan JK, Hur J, Masfique Mehedi. Respiratory Syncytial Virus Infection Does Not Induce Epithelial-Mesenchymal Transition. *Journal of Virology*. 2023;97(7). doi:https://doi.org/10.1128/jvi.00394-23
5. Baraldi E, Checcucci Lisi G, Costantino C, et al. RSV disease in infants and young children: Can we see a brighter future? *Human Vaccines & Immunotherapeutics*. 2022;18(4). doi:https://doi.org/10.1080/21645515.2022.2079322

6. Griffiths C, Drews SJ, Marchant DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. *Clinical Microbiology Reviews*. 2016;30(1):277-319. doi:https://doi.org/10.1128/cmr.00010-16
7. Rossi GA, Silvestri M, Colin AA. Respiratory syncytial virus infection of airway cells: Role of microRNAs. *Pediatric Pulmonology*. 2015;50(7):727-732. doi:https://doi.org/10.1002/ppul.23193
8. Maitre G, Schaffner D, Natterer J, et al. Leukemoid Reaction in Infant Pertussis: Is There a Place for Hydroxyurea? A Case Report. *Frontiers in Pediatrics*. 2018;6. doi:https://doi.org/10.3389/fped.2018.00261
9. Tesari Crnković H, Bendelja K, Drkulec V, Gjergja Juraški R, Turkalj M. Respiratory Syncytial Virus-Specific Antibodies and Atopic Diseases in Children: A 10-Year Follow-Up. *Pathogens*. 2023;12(4):546-546. doi:https://doi.org/10.3390/pathogens12040546
10. Binns E, Tuckerman J, Licciardi PV, Wurzel D. Respiratory syncytial virus, recurrent wheeze and asthma: A narrative review of pathophysiology, prevention and future directions. *Journal of Paediatrics and Child Health*. 2022;58(10). doi:https://doi.org/10.1111/jpc.16197
11. Relic T, Ilic N, Kostic G, Jovanovic D, Tambur Z, Lazarevic I. Respiratory syncytial virus infection and bronchial hyperreactivity in children up to two years of age in correlation with atopy. *Vojnosanitetski pregled*. 2015;73(1):59-65. doi:https://doi.org/10.2298/vsp140930030r
12. Russell CD, Unger SA, Walton M, Schwarze J. The Human Immune Response to Respiratory Syncytial Virus Infection. *Clinical Microbiology Reviews*. 2017;30(2):481-502. doi:https://doi.org/10.1128/cmr.00090-16
13. Agac A, Kolbe S, Ludlow M, Albert, Meineke R, Rimmelzwaan GF. Host Responses to Respiratory Syncytial Virus Infection. *Viruses*. 2023;15(10):1999-1999. doi:https://doi.org/10.3390/v15101999
14. Zeng R, Cui Y, Hai Y, Liu Y. Pattern recognition receptors for respiratory syncytial virus infection and design of vaccines. *Virus Research*. 2012;167(2):138-145. doi:https://doi.org/10.1016/j.virusres.2012.06.003
15. Bohmwald K, Gálvez NMS, Canedo-Marroquín G, et al. Contribution of Cytokines to Tissue Damage During Human Respiratory Syncytial Virus Infection. *Frontiers in Immunology*. 2019;10. doi:https://doi.org/10.3389/fimmu.2019.00452
16. Dapat C, Kumaki S, Sakurai H, et al. Gene signature of children with severe respiratory syncytial virus infection. *Pediatric Research*. 2021;89(7):1664-1672. doi:https://doi.org/10.1038/s41390-020-01347-9
17. Glaser L, Coulter PJ, Shields M, Touzelet O, Power UF, Broadbent L. Airway Epithelial Derived Cytokines and Chemokines and Their Role in the Immune Response to Respiratory Syncytial Virus Infection. *Pathogens*. 2019;8(3):106. doi:https://doi.org/10.3390/pathogens8030106
18. Qi F, Wang D, Liu J, et al. Respiratory macrophages and dendritic cells mediate respiratory syncytial virus-induced IL-33 production in TLR3- or TLR7-dependent manner. *International Immunopharmacology*. 2015;29(2):408-415. doi:https://doi.org/10.1016/j.intimp.2015.10.022
19. Carpenter LR, Moy JN, Roebuck KA. Respiratory syncytial virus and TNFalpha induction of chemokine gene expression involves differential activation of Rel A and NF-kappaB1. *BMC Infectious Diseases*. 2002;2(1). doi:https://doi.org/10.1186/1471-2334-2-5
20. Qin S, Huang X, Qu S. Baicalin Induces a Potent Innate Immune Response to Inhibit Respiratory Syncytial Virus Replication via Regulating Viral Non-Structural 1 and Matrix RNA. *Frontiers in Immunology*. 2022;13. doi:https://doi.org/10.3389/fimmu.2022.907047
21. Evans JE, Cane PA, Pringle CR. Expression and characterisation of the NS1 and NS2 proteins of respiratory syncytial virus. *Virus Research*. 1996;43(2):155-161. doi:https://doi.org/10.1016/0168-1702(96)01327-5
22. van Erp EA, Lakerveld AJ, de Graaf E, et al. Natural killer cell activation by respiratory syncytial virus-specific antibodies is decreased in infants with severe respiratory infections and correlates with Fc-glycosylation. *Clinical & Translational Immunology*. 2020;9(2). doi:https://doi.org/10.1002/cti2.1112
23. Tahamtan A, Besteman S, Samadizadeh S, Rastegar M, Bont L, Salimi V. Neutrophils in respiratory syncytial virus infection: from harmful effects to therapeutic opportunities. *British Journal of Pharmacology*. 2020;178(3):515-530. doi:https://doi.org/10.1111/bph.15318
24. Watson A, Madsen J, Clark HW. SP-A and SP-D: Dual Functioning Immune Molecules With Antiviral and Immunomodulatory Properties. *Frontiers in Immunology*. 2021;11. doi:https://doi.org/10.3389/fimmu.2020.622598

25. Zhang Y, Luo J, Wu H, Wang H, Sun X. Changes in T-Cell Subsets and Serum IFN-γ, IL-17, and IgE Levels in Children with Respiratory Syncytial Virus Capillary Bronchitis and Their Clinical Significance. *Disease Markers*. 2022;2022:1-5. doi:https://doi.org/10.1155/2022/2549845
26. Schmidt ME, Varga SM. Cytokines and CD8 T cell immunity during respiratory syncytial virus infection. *Cytokine*. 2020;133:154481. doi:https://doi.org/10.1016/j.cyto.2018.07.012
27. Walsh KB, Teijaro JR, Brock LG, et al. Animal Model of Respiratory Syncytial Virus: CD8 $^{+}$ T Cells Cause a Cytokine Storm That Is Chemically Tractable by Sphingosine-1-Phosphate 1 Receptor Agonist Therapy. García-Sastre A, ed. *Journal of Virology*. 2014;88(11):6281-6293. doi:https://doi.org/10.1128/jvi.00464-14
28. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*. 2017;281(1):8-27. doi:https://doi.org/10.1111/imr.12621
29. Dumont P. Increasing the complexity of respiratory syncytial virus infection: Reactive oxygen species, DNA damage, and premature senescence. *Virulence*. 2016;7(4):372-375. doi:https://doi.org/10.1080/21505594.2016.1162370
30. Anderson L, Jadhao S, Paden C, Tong S. Functional Features of the Respiratory Syncytial Virus G Protein. *Viruses*. 2021;13(7):1214. doi:https://doi.org/10.3390/v13071214
31. Anderson CS, Chu CY, Wang Q, et al. CX3CR1 as a respiratory syncytial virus receptor in pediatric human lung. *Pediatric Research*. 2019;87(5):862-867. doi:https://doi.org/10.1038/s41390-019-0677-0
32. Muraro SP, De Souza GF, Gallo SW, et al. Respiratory Syncytial Virus induces the classical ROS-dependent NETosis through PAD-4 and necroptosis pathways activation. *Scientific Reports*. 2018;8(1). doi:https://doi.org/10.1038/s41598-018-32576-y
33. Jin Y, Zhang D, Deng K, et al. Role of the cAMP-PKA-NF-κB pathway in Mucin1 over-expression in A549 cells during Respiratory syncytial virus infection. *BMC infectious diseases*. 2023;23(1). doi:https://doi.org/10.1186/s12879-023-08837-1
34. Kong X, Juan HS, Kumar M, et al. Respiratory syncytial virus infection activates STAT signaling in human epithelial cells. *Biochemical and Biophysical Research Communications*. 2003;306(2):616-622. doi:https://doi.org/10.1016/s0006-291x(03)01008-8
35. Johnson TR, Graham BS. Secreted Respiratory Syncytial Virus G Glycoprotein Induces Interleukin-5 (IL-5), IL-13, and Eosinophilia by an IL-4-Independent Mechanism. *Journal of Virology*. 1999;73(10):8485-8495. doi:https://doi.org/10.1128/jvi.73.10.8485-8495.1999
36. Quinn LA, Shields MD, Sinha I, Groves HE. Respiratory syncytial virus prophylaxis for prevention of recurrent childhood wheeze and asthma: a systematic review. *Systematic Reviews*. 2020;9(1). doi:https://doi.org/10.1186/s13643-020-01527-y
37. Simões EAF, Madhi SA, Muller WJ, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. *The Lancet Child & Adolescent Health*. 2023;7(3):180-189. doi:https://doi.org/10.1016/S2352-4642(22)00321-2
38. Garegnani L, Styrmisdóttir L, Roson Rodriguez P, Escobar Liquitay CM, Esteban I, Franco JV. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. *Cochrane Database of Systematic Reviews*. 2021;2021(11). doi:https://doi.org/10.1002/14651858.cd013757.pub2