Review Article

Immune Response to Respiratory Syncytial Virus

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Abstract

Respiratory syncytial virus (RSV) is an important cause of respiratory infection among children and infants globally. The first line of the immune response against this virus is neutrophils, macrophages, and innate lymphoid cells. Antigen-presenting cells such as dendritic cells which present the viral antigen to T lymphocytes that mediate viral clearance by T cytotoxic cells and initiate systemic lymphopenia. Humoral immunity will also be stimulated through B-cell-stimulating factors derived from epithelial cells of the respiratory tract that play an important factor in antibody production and induction memory to reinfection through IgG and IgA protective antibodies that are useful in vaccine production.

Keywords: Immunity, respiratory, respiratory syncytial virus

Introduction

One of the common causes of lower respiratory tract infection (pneumonia and bronchiolitis) during infancy (lower than 2 years of age), early childhood, and young adults is infection with respiratory syncytial virus (RSV) which is a common highly contagious seasonal virus that required hospitalization.[1] Considering the recent COVID-19 pandemic over all the world, there is growing alertness and fear of the morbidity and mortality related with upper and lower respiratory viruses. This virus had a significant health-care concern and burden due to high death rate of about 1 death in 50 deaths among patients their ages below 5 years are due to RSV infection. Patients who survive will had chronic recurrent dyspnea and asthma later in their life. The main factor that determines the progress of the disease is the immune response of the patient which is important in determination the magnitude and the severity of the infection. In addition to that, alteration in microbiota in the digestive tract can affect the severity of the disease.[2]

Immune Response to Respiratory Syncytial Virus

The mode of transmission of this virus is through respiratory droplets and the first replication of this virus was nasopharynx then spread from the upper respiratory tract to lower airways from one cell to another cell without emerging into the extracellular environment through binding with specific receptors (Cx3CR1 and nucleolin) mediating attachment and internalization inside the cell then inducing cell fusion and syncytium establishment.[3,4] Additional mechanism for the spread of RSV to the lower respiratory tract is through infection of macrophages which is the first line of defense innate immune mechanism and there are two types of alveolar macrophages (M1 and M2) and the communication between the M1 and M2 macrophages is important in limit inflammatory damage to the tissues that lined the mucosa of the respiratory tract.[5,6] In addition to that, natural killer cells with interferon-γ (IFN-γ) production which is the cellular barrier against viral infection and later on showed memory-like response.[7] The main target cells for this virus are epithelial cells of the respiratory system which act as a barrier and inducing immune response through stimulation group 2 innate lymphoid cells, and epithelial-derived alarmin proteins that activate interleukin (IL)-33, IL-25, thymic stromal lymphopoietin, high mobility group box 1, IL-4, IL-5 (eosinophil growth and differentiation), and IL-13 (induce

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mucus secretion and metaplasia) secretion that induce a type 2 innate immune response.[8,9] The imbalance of Type-1, Type-2, and Type-17 cytokines secretion by different immune cells (Tc1, Tc2, Th, and Th17, respectively) is responsible for disease severity and other chemokines will also secreted mainly CCL-5 and CCL-3.[10] Other local innate immune factors such as cathelicidins and IFN-λ which contribute in the pathogenesis of the disease. Then, the second line of defense mechanism will be activated which is the adaptive immune response. The host immune response includes the production of virus-neutralizing antibodies and T-cell-specific immunity such as RSV-epitope-specific $CD8^+$ T cytotoxic cell-mediated viral clearance. There is an increase in both $CD4^+$ and $CD8^+$ T cells with the $CD8^+$:$CD4^+$ ratio (Th1/Th2) being altered in acute lung injury toward Th2.[11] There is also stimulation of Th2 and secretion of IL-4, IL-5, IL-10, and IL-13 in the blood that caused an increased in nonneutralizing IgE levels suggesting allergy such as infection occurs during the course of the disease.[12] IL-5-activated eosinophils in the respiratory tract of the lungs of the patient. Hence, initially, the F glycoprotein antigen of the virus stimulates Th1 cells through different antigen-presenting cells in the lung that secrete different cytokines such as IL-2, IL-12, and IFN-γ to activate precursors Tc lymphocytes to become anti-RSV Tc cells. Other viral soluble G glycoprotein superantigens that bind to the variable heavy chain 3 domain of IgE that attached to Fc epsilon receptor on hematopoietic cells, basophils, mast cells, and monocytes leading to degranulate and release large amounts mediators. This superantigen is also attached to fractalkine receptors on ciliary respiratory epithelial cells, eosinophils of the lung that activate these eosinophils to the lungs of the patient.[13] This inflammation is regulated through T regulatory (T_{reg})(CD4+CD25+) cells and B regulatory cells (B_{reg}) which are the main cells in immunosuppressive response that secrets IL-10 and IL-35 and express FoxP3 transcription factor and inhibit NF-KB and pro-inflammatory cytokines.[14]

Prevention Strategies for Respiratory Syncytial Virus

Protection against this RSV could be achieved through vaccination that was first trials performed in the 1950s and continue using different types of vaccines such as recombinant vector, subunit of the virus, particle-based vaccine, live-attenuated virus, chimeric type of vaccine, nucleic acid vaccines, and monoclonal antibodies type of vaccine that given to high-risk infants in many developed countries to reduce disease severity and hospital admission.[15] The bivalent RSV prefusion F glycoprotein antigen from RSV A and RSV B that prevent respiratory tract infection in adults more than 60 years of age.[16,17] [Figure 1].

Most of the synthesized vaccines against RSV were directed toward surface glycoproteins that include the fusion (F) protein antigens and attachment (G) proteins antigens. The variations in G antigens will lead to had two subtypes of RSV (A and B) while F antigen had a conserved structure in both types which made it suitable target for the synthesis of a vaccine.[19] F proteins had two forms named prefusion and postfusion and later had more antigenicity than preferred in synthesis vaccines.[20] The current vaccines are as follows:[21]

a. Recombinant-vector-based vaccines
   - This type of vaccine uses a modified defective virus such as adenovirus or vaccinia virus that delivers genes that code for RSV proteins or antigens leads to stimulate the immune response whether the humoral through antibody production especially sIgAor cellular through via CD4 and CD8 stimulation.[22,23] This type of vaccination will protect against this virus by many arms of adaptive immunity.

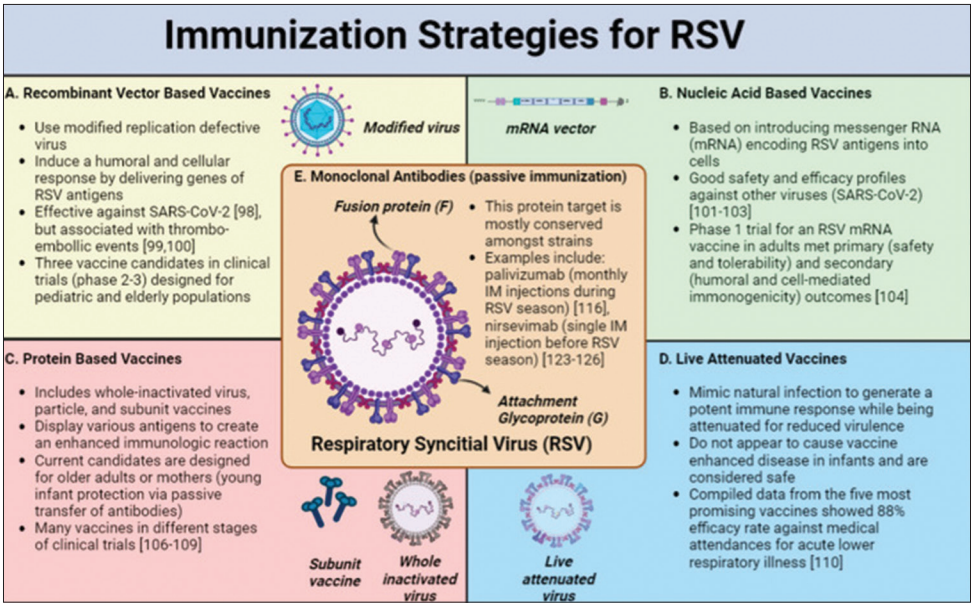

Figure 1: Common types of vaccines used for respiratory syncytial virus.[18] RSV: Respiratory syncytial virus, mRNA: Messenger RNA

b. Nucleic acid vaccines
   - The principle of this type of vaccine is introducing messenger RNA (mRNA) inside the cell that encodes viral antigens.[24,25]

c. Protein-based vaccine
   - This type of vaccine uses the whole killed virus or part of it that expressed more potent antigens (F and non-F antigens) that enhance the immune response in young infants and older adults.[26]

d. Live-attenuated vaccines (Chimeric)
   - The most used virus in this type of vaccine is recombinant live-attenuated influenza viruses which are known as chimeric vaccines that encode T-cell epitopes of RSV M2 protein in the neuraminidase genes. This will stimulate the immune response against two viruses: first influenza-specific and second RSV-specific CD4 and CD8 T-cell responses in the lungs with the formation of memory T-cell subsets to both viruses.[27]

e. Monoclonal antibodies
   - The first approach established to offer passive immunization for the inhibition of severe RSV infection was a combination of human intravenous immunoglobulin encompassing high concentrations of RSV defensive antibodies which is most useful in infants with mild side effects.[28] Other type of passive immunization was using palivizumab and motavizumab for prophylaxis of RSV in high-risk children intramuscularly which is a humanized monoclonal antibodies against the RSV fusion (F) glycoprotein, inhibiting RSV entry and infection that reduced the infection and hospitalization in most of the children.[29]

Hence, this virus had an inadequate type of therapy, and the cornerstone of treatment focuses on prevention through vaccinations and monoclonal antibodies such as the worldwide COVID-19 pandemic. Moreover, social isolation reduced the respiratory infection but led to subjects had little immune response or no immunity against these viruses, and later winter season led to increased respiratory tract infections. Hence, prevention should be linked with vaccinations to build immunity and decrease mortality and morbidity.

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Conflicts of interest
There are no conflicts of interest.

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