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Vaccine development for respiratory syncytial virus

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Respiratory syncytial virus (RSV) is an important and ubiquitous respiratory pathogen for which no vaccine is available notwithstanding more than 50 years of effort. It causes the most severe disease at the extremes of age and in settings of immunodeficiency. Although RSV is susceptible to neutralizing antibody, it has evolved multiple mechanisms of immune evasion allowing it to repeatedly infect people despite relatively little genetic diversity. Recent breakthroughs in determining the structure and antigenic content of the fusion (F) glycoprotein in its metastable untriggered prefusion form (pre-F) and the stable rearranged postfusion form (post-F) have yielded vaccine strategies that can induce potent neutralizing antibody responses and effectively boost pre-existing neutralizing activity. In parallel, novel live-attenuated and chimeric virus vaccine candidates and other novel approaches to deliver vaccine antigens have been developed. These events and activities have aroused optimism and a robust pipeline of potential vaccine products that promise to provide a means to reduce the public health burden of RSV infection.

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Epidemiology and vaccine target populations

Respiratory syncytial virus (RSV) is a pneumovirus in the paramyxoviridae family, and is the leading viral cause of severe respiratory disease and hospitalization in young children. The peak age of hospitalization is between 2 and 3 months of age, but risk of severe disease continues until about 5 years of age. In hospitalized children there is an increased frequency of childhood wheezing [1]. RSV infects nearly all people globally by the end of the 2nd year of life and everyone by 3 years of age [2]. People continue to be infected throughout life every 3–10 years [3]. In people over 5 years of age RSV infection rarely leads to hospitalization until they become susceptible through aging or immune deficiency. The frail elderly experience substantial increased mortality following RSV infection, in many years comparable to that of influenza [4], and it generally manifests as a complication of underlying heart and lung disease and a weakening constitution. People who have diminished CD8 T-cell function in lung because of severe combined immunodeficiency [5], allogenic bone marrow transplant [6], lung transplant [7], or aging [8,9] also experience severe disease from RSV infection. The goals for vaccination are to prevent severe disease and its subsequent complications. Therefore, the major target populations for protection by an RSV vaccine are children under 6 months of age and the frail elderly. While RSV infection is ubiquitous, the different population structure in high income (HIC) vs. low and middle income countries (LMIC), and the higher risk of infant mortality from RSV in LMIC [10], influences the emphasis on target populations. In LMIC the major focus is on protecting young infants and in HIC both young infants and the elderly have equivalent priority.

History

RSV was discovered in 1955 as Chimpanzee Coryza Agent [11], and associated with bronchiolitis in children in 1956 [11]. The first written description of the syndrome appears to be in 1826 [12], although it is likely RSV is an ancient disease and was not easily discriminated from other causes of acute respiratory disease in children. Goodpasture *et al.* described the pathology in 1939 [13] and Adams provided the first clinical description of the disease in the microbial era [14,15].

Why has RSV eluded vaccine development when the disease burden is so high; the identity of the virus has been known for 60 years; it is an acute self-limited infection; there is relatively little genetic variation; and there is no zoonotic reservoir? In addition, everyone is infected early in life so there is no 'antigen-naïve' population without pre-existing adaptive immunity other than the annual infant cohort which is no more than 2% of the total population. These features of an infectious disease would typically indicate that conventional intervention strategies are likely to be successful. Here I will describe the biological rationale for current RSV vaccine development efforts, and provide some thoughts on why RSV has been a successful pathogen when it occupies what seems to be a very vulnerable ecological niche.

Pathogenesis

What is associated with susceptibility to severe disease? Only about 2–3% of infants develop severe disease requiring hospitalization. The rest either have mild or subclinical disease sometimes with complications of otitis media or sinusitis. Factors most associated with infant hospitalization include prematurity especially with bronchopulmonary dysplasia, congenital heart disease, family history or genetic predisposition to allergic inflammation, being male, and environmental factors like smoke exposure. Disease severity is highest in some ethnic populations like Native Americans [16,17]. These individuals are also highly susceptible to encapsulated bacteria, but it is not known whether the immunological basis for this vulnerability is the same. Another factor that complicates RSV vaccine development is the history of vaccine-enhanced disease that occurred when a heat and formalin-inactivated whole virus vaccine was administered to children in the 1960s. During the season subsequent to vaccination, infection was not prevented, and disease was more severe with 80% hospitalization rate among vaccinees and 2 deaths in the youngest age cohort immunized between 2 and 7 months of age [18]. Pre-existing host factors including prior antigen exposure contribute to disease severity for different reasons. In thinking about how vaccine-induced immunity might reduce disease it is helpful to separate disease of the upper respiratory tract, lower airways, and the lung. It is also, useful to consider the role of viral cytopathology, lung and airway physiology, and immune response patterns in each compartment, and the special circumstances relevant to infants and the elderly (Table 1).

Immunity

Antibody is the principle immune mediator associated with protection from viral infections. The best evidence that antibody plays an important role in RSV immunity are studies showing that passively administered antibody (either polyclonal or monoclonal) can protect infants from severe disease [19–21]. The irony is that people with immunoglobulin deficiency do not experience more frequent or severe RSV infections. It is the children and adults with diminished CD8 T-cell function because of SCID, allogenic bone marrow transplantation, or lung transplantation that have the most lethal RSV disease. These are conditions in which the CD8 T-cells cannot be produced at all or where the antigen presenting cells in the lung are not perfectly matched to the effector T cells. Therefore antibody neutralizing activity can diminish the number of infected cells from the initial inoculum and delay spread of virus into the lower airway, but once infection has been established, T cells are critical for viral clearance and bringing the infection to a close. There are some antibody Fc-mediated antibody functions that could contribute to viral clearance, but in most settings they likely play an ancillary role to CD8 T-cells. We are learning more about the role of local mucosal induction of intraepithelial T cells and their role in viral clearance [22] and about the selection of effector cells with the optimal phenotype for accomplishing viral clearance without undue pathology [22,23], but we do not yet have enough basic knowledge to rationally design a T-cell based vaccine that can rapidly respond and clear infection without risk of disease. It is possible that knowledge will come from other vaccine development programs on HIV, malaria, or tuberculosis, and it would be valuable to include CD8 T-cell immunity in a vaccine especially if one of the goals is to interrupt transmission by preventing or reducing the period of viral shedding in infected people.

Mechanisms of immune escape

RSV has multiple mechanisms of evading immunity, which may explain how it can be a ubiquitous pathogen that reinfects people throughout life, yet has relatively little genetic variation compared to other RNA viruses. There are three major categories of evasion that include anatomical, conformational evasion of neutralizing antibody, and direct modulation of immune function. RSV is the HPV of the respiratory tract. It infects superficial epithelium of the airway and is even more superficial and protected from systemic immunity that than HPV because its tropism does not include basal epithelium. In the airway the virus enters and buds apically almost exclusively from highly differentiated, polarized, ciliated epithelium [24,25], and RSV antigen is not displayed basolaterally. Occasionally, dendritic cells must be infected or otherwise carry antigens to local lymph nodes to initiate immune responses. Therefore, the virus evades much of the systemic immune mechanisms by residing primarily outside the body.

The virus itself, while easily transmitted by aerosol, is susceptible to high temperatures and dies in a few hours on fomites at room temperature [26]. In part this is due to instability of the F glycoprotein that spontaneously rearranges and transitions from the prefusion conformation of the trimer (pre-F) to the postfusion form (post-F) [27]. The pre-F conformation is required for viral entry and mediates membrane fusion between virus and cell or between an infected cell and an uninfected cell. In shed virus that is no longer part of the budding filament from the infected cell, the matrix eventually becomes fragmented and the virus assumes a pleomorphic and eventually a round shape. As this happens, the pre-F flips into the post-F conformation. The post-F is taller (~16 nm) than the functional pre-F (~11 nm) and can shield pre-F from neutralizing antibodies (Figure 1). Thus, the virus has to make a calculation of how easily triggered the F protein should be. Being easily triggered may make the virus more fusogenic and potentially better suited for cell-to-cell spread, and may provide some cover for pre-F and inhibit access of neutralizing antibodies. However, if it is too easily triggered, rearrangement may occur before the