AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical and Vaccine Immunology

MINIREVIEW

Brief History and Characterization of Enhanced Respiratory Syncytial Virus Disease

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In 1967, infants and toddlers immunized with a formalin-inactivated vaccine against respiratory syncytial virus (RSV) experienced an enhanced form of RSV disease characterized by high fever, bronchopneumonia, and wheezing when they became infected with wild-type virus in the community. Hospitalizations were frequent, and two immunized toddlers died upon infection with wild-type RSV. The enhanced disease was initially characterized as a "peribronchiolar monocytic infiltration with some excess in eosinophils." Decades of research defined enhanced RSV disease (ERD) as the result of immunization with antigens not processed in the cytoplasm, resulting in a nonprotective antibody response and $CD4^+$ T helper priming in the absence of cytotoxic T lymphocytes. This response to vaccination led to a pathogenic Th2 memory response with eosinophil and immune complex deposition in the lungs after RSV infection. In recent years, the field of RSV experienced significant changes. Numerous vaccine candidates with novel designs and formulations are approaching clinical trials, defying our previous understanding of favorable parameters for ERD. This review provides a succinct analysis of these parameters and explores criteria for assessing the risk of ERD in new vaccine candidates.

Respiratory syncytial virus (RSV) is the leading respiratory cause of hospitalization in infants and young children in the United States and in the world (1, 2). Most severe infections occur in young infants, with the peak incidence of lower respiratory tract illness (LRTI) occurring between 2 and 4 months of age (3–5). In the United States, hospitalization rates have risen during the last decades (6), and while premature babies and infants with chronic lung disease and/or congenital heart disease are at increased risk for severe presentations, the majority of hospitalizations occur in previously healthy infants. Recent estimates of global mortality suggest that between 66,000 and 234,000 infants and young children die every year due to RSV (1, 2). Ninety-nine percent of deaths occur in the developing world (2). A significant proportion of these fatalities are thought to occur in the community. The need for preventive interventions against the virus is indisputable.

The virus. RSV is a member of the pneumovirus genus of the family *Paramyxoviridae*. The virus is a negative-sense RNA virus with a nonsegmented encapsidated genome and a lipid envelope (7). The envelope is a host plasma membrane-derived lipid bilayer containing three virally encoded transmembrane glycoproteins: the fusion (F) protein, the attachment (G) protein, and the small hydrophobic (SH) protein. RSV F is the main neutralizing antigen, highly conserved and essential for virus viability (7). The secondary protective antigen eliciting neutralizing antibodies is the RSV G protein. Both neutralizing antigens are the main candidates for novel vaccines and targets for monoclonal antibodies.

A new scenario. The world of RSV vaccines is experiencing important changes. In recent years, epidemiological studies highlighted the burden of RSV disease worldwide (2, 8), stressing the public health need for vaccine development against the pathogen. Strategies under evaluation in human subjects to prevent severe RSV LRTI include immunization of pregnant women and passive prophylaxis with long-lived monoclonal antibodies and inoculation of live attenuated RSV vaccines in young infants (9–11). Maternal immunization aims to elicit high levels of protective antibody in pregnant women, fostering transplacentally acquired antibody-mediated protection in infants during the first months of life (12–14). Passive prophylaxis with long-lived monoclonal antibodies against neutralizing epitopes in RSV and immunization with recombinant live, attenuated RSV vaccines target infants directly (11).

In addition, a variety of novel approaches to vaccination have emerged. Replication-defective gene-based single-cycle vectors (15, 16), subunit vaccines adjuvanted with various Toll-like receptor (TLR) agonists (17), viruslike particles (VLPs) with protective antigens (18–20), and new formulations with the prefusion conformation of RSV F (21–25) defy our traditional understanding of replicating and nonreplicating vaccines, posing new questions for the field and for human studies. This challenge is particularly significant for RSV because a vaccine designed to protect infants and toddlers against RSV in the 1960s primed for a severe form of respiratory illness upon RSV infection, known as enhanced RSV disease (ERD). Each of these novel formulations may present individual characteristics that theoretically affect the risk for ERD.

Brief history of enhanced RSV disease. In 1966, a formalin-inactivated vaccine against RSV (FIRSV) was administered to infants and children in four studies in the United States (26–29). The immunized children were exposed to RSV in the community, and those children who were seronegative for the virus before vaccination experienced a significant increase in the frequency and severity of RSV LRTI. This enhanced form of RSV disease presented with fever, wheezing, and bronchopneumonia and led to

Accepted manuscript posted online 16 December 2015

Citation Acosta PL, Caballero MT, Polack FP. 2016. Brief history and characterization of enhanced respiratory syncytial virus disease. Clin Vaccine Immunol 23:189–195. doi:10.1128/CVI.00609-15.

Editor: C. J. Papasian

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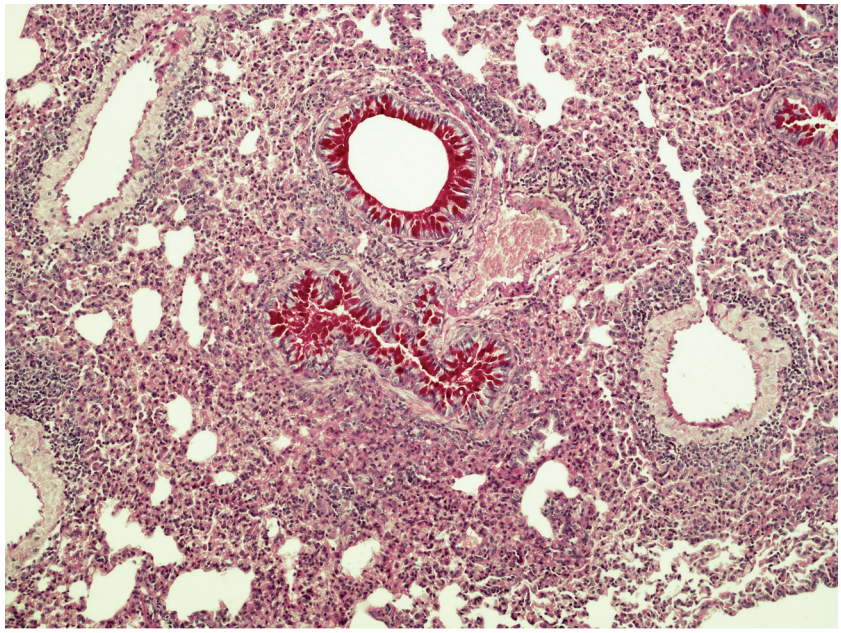

FIG 1 Photomicrograph of lung section from BALB/c mouse with enhanced RSV disease. Hematoxylin and periodic acid-Schiff stain shows peribronchiolar, perialveolar, and perivascular inflammation with abundant mucus production.

frequent hospitalizations (80% in FIRSV recipients versus 5% in controls among RSV-infected children in one study) (26). In fact, two immunized infants died as toddlers as a consequence of subsequent RSV infection (26).

In the last 3 decades, much effort has been devoted to clarifying the pathogenesis of ERD. For many years, the consensus was that nothing but live, attenuated vaccines against RSV would ever be used to immunize infants. Therefore, the characterization of ERD phenotypes was of academic interest but had limited regulatory implications. The need for identifying clear biomarkers of disease enhancement is now particularly important, because novel vaccine formulations challenging our old safety parameters are emerging and may be ready for human studies in the near future. While not all candidate vaccines present similar risks of eliciting ERD, identifying safety parameters for the evaluation of certain new formulations will be critical. Importantly, these evaluations will have to be conducted in animal models, because ERD never occurred in children who were seropositive for RSV before immunization with FIRSV (26–29). Therefore, only animal models may be able to identify vaccines that prime for ERD before they reach seronegative infants (26–29).

Numerous cell types, cytokines, and chemokines have been reported to promote or mitigate ERD in the last decades (30–40). The studies used a variety of animal models, immunogens, and immunization strategies (31, 32, 41–51). We have chosen to focus on the most widely accepted and arguably best-studied characteristics of ERD to provide a concise and critical review of disease pathogenesis and discuss the potential value of selected biomarkers in the evaluation of novel RSV vaccine candidates.

Eosinophils in ERD. Autopsy material from both toddlers killed by ERD showed bronchopneumonia with atelectases and pneumothoraces. The pulmonary histopathology was reported in the literature as a "peribronchiolar monocytic infiltration with some excess in eosinophils" (26), but rereview of the autopsy reports (42) revealed a pulmonary neutrophilia with abundant macrophages and lymphocytes and excess eosinophils (Fig. 1). Given the overwhelming predominance of neutrophils and mononuclear cells in ERD, the reason why these cells were ignored in the original manuscript is unclear (26). Perhaps the postmortem recovery in culture of *Klebsiella* and *Escherichia coli* bacteria from autopsy specimens of both children (26) raised suspicion that a bacterial superinfection had triggered the pulmonary neutrophilia. However, high RSV titers were recovered from the lungs of the affected children (26), the lung histopathology in both cases was not entirely consistent with bacterial pneumonia (52, 53), and recovery of Gram-negative bacilli from the respiratory tracts of ill, hospitalized patients is exceedingly common (54–56).

The original report emphasizing eosinophils in the lung pathology made these cells a critical endpoint of ERD models. In fact, FIRSV was often replaced in ERD models by vaccines with significant differences in design and properties, namely, vaccinia virus expressing RSV G (vvG) (31, 32, 49–51). These alternative vaccines were chosen based on their ability to promote eosinophilia upon RSV challenge (35, 38–40, 57–90). Notably, more than half of all mouse studies of ERD pathogenesis used vvG immunization instead of FIRSV. And while vvG primed for an undesirable pulmonary eosinophilia after challenge, this replicating immunogen differed significantly from FIRSV. Consequently, its disease-priming mechanisms were not necessarily those of inactivated vaccines leading to ERD. Moreover, the strong emphasis on lung eosinophilia in mouse models of ERD often translated into considering the presence of other inflammatory cells irrelevant (26–32, 35, 45, 49–51, 91–99). This is paradoxical, as eosinophils were not always the dominant infiltrating cells even in Th2-biased mouse models of ERD (31, 32, 34, 38–40, 49–51, 57–90, 100), and they are absent in cotton rats and several cattle models of enhanced illness (42, 43). Recently, new evidence revealed that eosinophils do not play a critical role in ERD pathogenesis (37).

Their role in illness, like that of neutrophils, remains unclear. However, the presence of eosinophils in lung sections of immunized and challenged BALB/c mice may serve as a warning sign and prompt caution against any vaccine candidate targeting RSV. Conversely, the absence of eosinophils in other disease models should not be interpreted as solid reassurance against the risk of ERD.

T helper bias in ERD. Twenty-four years ago, the first evaluation of ERD pathogenesis showed increased production of interleukin 4 (IL-4) in lungs of affected BALB/c mice by using Northern blot analyses (30). Subsequent depletion of $CD4^+$ T lymphocytes and codepletion of IL-4 and IL-10 down-modulated ERD lung pathology, suggesting that the disease was due to an exacerbated Th2 response (34, 35). These observations were further supported by reports of increased numbers of eosinophils and $CD4^+$ (but not $CD8^+$) T cells in mice with ERD and high levels of both IL-5 and IL-13 type 2 cytokines in murine models (38). Finally, recent studies in BALB/c mice confirmed a critical role for Th2 bias (but not eosinophils) in airway hyperreactivity and mucus hypersecretion (37). Formaldehyde, used for virus inactivation in FIRSV, may have contributed to Th2 polarization during ERD by generating carbonyl groups on viral antigens (96).

The activation and/or suppression of other T lymphocyte populations may contribute to ERD. Recent work associated ERD with marked suppression of T regulatory cell (Treg) activity (an observation that aligns with earlier evidence of modulation by IL-10 [35]), exacerbating the Th2 bias in recipients of inactivated RSV vaccines (36). Th1 responses may also be suppressed during acute illness (101), while exacerbated Th17 responses may associate with lung neutrophilia and synergize with Th2 cytokines (102–104).

In summary, ERD pathogenesis is associated with Th2 polarization of the immune response in the lungs after RSV challenge. RSV vaccines eliciting high levels of IL-4 and/or IL-13 in animal models (compared to the levels in control animals protected by prior wild-type [wt] RSV infection) should be considered prone to priming for ERD and excluded as potential candidates for infant immunization.

Cytotoxic T lymphocytes in ERD. A critical element in ERD pathogenesis is the inability of FIRSV and other vaccine antigens not processed in the cytoplasm to elicit cytotoxic T lymphocytes (CTL) in immunized subjects (39). The absence of a CTL response during immunization is associated with virus replication in the lungs and Th2 polarization of the anamnestic $CD4^+$ T lymphocyte response during RSV infection (38, 39, 92). Correcting this deficit led to Th1 protective responses, abrogating the pathogenic phenotype (39). These manifestations were first evidenced using vvG immunization in mice as a surrogate for FIRSV (31, 32, 49–51). In summary, the absence of CTLs and nonprotective antibodies (discussed below) allows RSV replication after challenge and, in the context of primed $CD4^+$ T lymphocytes, sets the stage for an aberrant anamnestic response that results in ERD.

Antibodies in ERD. Two mysterious observations defied our understanding of ERD susceptibility for decades: ERD never occurred in those infants who were seropositive for RSV at the time of FIRSV administration, and no child ever experienced ERD twice (26). The answer to these two enigmas also explains why FIRSV elicited antibodies that failed to protect against RSV infection (26). The mechanism responsible for the absence of a protective antibody response against RSV remained unclear for decades, hampering the development of new vaccines against the virus.

The nonprotective antibody response elicited by RSV vaccines encoding antigens not processed in the cytoplasm is the result of lack of affinity maturation in B cells (33). This low-avidity response to FIRSV stems from poor TLR activation during immunization and, upon RSV infection, triggers immune complex formation and complement activation, potentiating Th2-mediated bronchoconstriction, pneumonia, and mucus production through anaphylotoxin C3a (33, 105).

The importance of antibody avidity for protection against respiratory viruses is also observed in responses against measles virus (MV) (106, 107). A formalin-inactivated vaccine against MV (FIMV) also elicited low-avidity, nonprotective antibodies followed by an atypical and severe illness (i.e., atypical measles) in individuals exposed to wild-type virus (106). In the case of MV, low-avidity antibody did not neutralize viral infection through the CD150 high-affinity MV receptor and—as observed in ERD (105)—promoted immune complex-mediated illness (106). In RSV, differences in affinity between the antibodies elicited by FIRSV and viral attachment proteins versus these proteins and their receptors may explain the nonprotective responses and pathogenic immune complexes associated with disease enhancement (108–110).

Affinity maturation also explains why children who were seropositive for RSV before immunization with FIRSV never developed ERD. Preexisting high-avidity antibody against wt RSV probably outcompeted low-avidity B cell clones elicited by FIRSV, eliminating pathogenic B cell priming against the virus. After ERD, B cells elicited by RSV infection also outcompeted preexistent pathogenic B cells and reestablished a healthy response against subsequent reinfections. In fact, a similar process was inadvertently elicited by corrective subcutaneous inoculation of live, attenuated MV vaccine in individuals immunized with FIMV in the 1960s. Live MV vaccine recipients developed localized atypical measles at the injection site (111, 112) but eliminated pathogenic B cell clones, preventing future systemic exacerbations. Whether other factors in RSV protective antigens, such as the RSV F pre- or postfusion conformation in vaccine candidates (23, 25), also contribute to antibody quality and disease enhancement requires further study.

In summary, vaccines eliciting nonneutralizing antibody against RSV in seronegative individuals may prime for ERD and should not be administered to infants (at least until effective nonneutralizing mechanisms of antibody-mediated protection are demonstrated).

Current vaccine candidates. Fortunately, concerns for ERD are minimal for immunization of pregnant women, administration of monoclonal antibodies to susceptible populations, and infant intranasal immunization with live, attenuated RSV vaccines (11, 113, 114). However, novel RSV vaccine candidates in preclinical and clinical development potentially targeted to naive infants confront the field with new challenges. Understanding ERD pathogenesis and the mechanisms of illness associated with candidate biomarkers is critical to evaluate these immunogens in animal models. Some of these candidates, using antigens not processed in the cytoplasm, may present excessive risks for further testing. Others will demand careful evaluation in small and large animal models. Cotton rats have proven useful in characterizing ERD based on lung histopathology, particularly in studies focus-

ing on alveolitis (42), RSV replication, neutrophilia, and inflammation. Alveolitis in rodents replicates findings in lung sections from children with ERD and may serve as an indicator of illness (42). Cattle ERD models have certain limitations but may also provide useful information (43). Bovine RSV is related to human RSV in numerous aspects, including epidemiology and pathology (115–117). The clinical forms mimic those observed in humans (ranging from subclinical to severe bronchiolitis and pneumonia). Furthermore, most affected animals are younger than 6 months of age (115, 117). However, while some studies reported complete protection using the inactivated vaccine (118, 119), others described nonprotective responses (120, 121) and, in other cases, partial reproduction of the human ERD phenotype (43, 122, 123).

Conclusion. To summarize, in the 1960s, ERD was a severe complication of infant immunization against RSV using vaccine antigens not processed in the cytoplasm. The illness was characterized by failure to elicit protective antibody and CTLs after immunization, followed by Th2 polarization, an excess of lung eosinophils (accompanying robust lung neutrophilia and mononuclear cell infiltration), and pulmonary immune complex deposition after wt RSV infection.

ACKNOWLEDGMENTS

The work was supported by a Director's Challenge award from NIEHS and a grant from the Bill & Melinda Gates Foundation.

FUNDING INFORMATION

BMGF provided funding to Fernando P Polack under grant number OPP1084347. HHS | NIH | National Institute of Environmental Health Sciences (NIEHS) provided funding to Fernando P Polack under grant number Director's Challenge.

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