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REVIEW

Neonatal vaccination against respiratory syncytial virus infection

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Abstract **Respiratory syncytial virus (RSV) is the leading cause of pneumonia and bronchiolitis in infants and is the most frequent cause of lower respiratory tract infections in children. Efficacious vaccination has been a longstanding goal in neonates. Due to immaturity of the neonatal immune system, vaccination has shown limited success in stimulating the neonatal endogenous immune system. Advances in the understanding of neonatal immunology have resulted in renewed development of neonatal vaccination. In this article, we review recent advances in neonatal anti-RSV vaccination strategies, including active and passive vaccination approaches, with emphasis on the effect of maternal neutralizing antibody and the role of maternal antibody in neonatal immune modulations. Recent reports in a variety of antiviral vaccine animal models have shown that maternal antibody, different from conventional vaccination, plays an immune modulatory role in the newborn immune system. Active immunization of the pregnant mother and the offspring can effectively stimulate and maintain potent neonatal immune responses, including an endogenous cytotoxic response and neutralizing antibody generation. The induced newborn endogenous antiviral immunity can last up to 6 months, and effectively blunt viral replication. Immune complexes, formed from the integral binding of the maternal neutralizing antibody and viral vaccine antigen, may play an important role in the maternal antibody-mediated neonatal immune response. The underlying mechanisms and future perspectives are discussed.**

Keywords respiratory syncytial virus, vaccination, neonates, maternal antibody, immune complex

Introduction

Respiratory syncytial virus (RSV) is one of the leading viruses infecting the neonatal respiratory system and a major cause of childhood hospitalization and health burden worldwide. Vaccination at early childhood emerges as a critical approach to prevent and ameliorate the disease. Because of the inefficient development of immunological memory in neonates, RSV vaccination in early life is not always successful, and often fails to prevent infection. RSV-specific protective T cells and B cells in local nasal-associated lymphoid tissue are usually not well activated to generate and maintain a robust local mucosal immune response (Singleton et al., 2003). Instead, early infant vaccination usually induces a dominant Th2-type immune response that increases the severity of respiratory tract inflammation and obstruction, associated with overexpression of IL-4 and IL-5. Current successful RSV vaccination is only achieved in young adult mice over 6-8 weeks old. There are limited successful reports of neonatal RSV vaccination. Neonates can be protected from RSV infection by phamacological monoclonal neutralizing anti-RSV antibody or mother-derived anti-RSV antibody via breastfeeding and placenta. However, the protection does not persist through the time until the neonatal immune system is developed enough to initiate endogenous adult-like anti-RSV immunity. Neonates risk infection after the passively transferred anti-RSV antibody disappears, therefore it is critical to be able to induce neonatal anti-RSV immunity. Recent reports observed that maternal antibody can promote neonatal endogenous cellular and humoral immune responses via formation of immune complexes (ICs) at the local immune system (Gros et al., 2005; Michaud et al., 2010). The immune modulatory property of maternal antibody provides a novel strategy in the development of neonatal vaccines against RSV.

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Th2 biased neonatal immune system

Exposure to high doses of antigen often skews neonatal immune responses toward induction of tolerance or development of immune suppressive Th2-type cells. Newborns as well as fetuses in utero face susceptibility to RSV and other microbial infections. During early days of life, dendritic cells (DCs) and other innate immune cells are poorly matured to process and present viral antigens. The delayed maturation of DCs is attributed to the poor Th1 immune responses, associated with low expression of costimulatory molecules and IL-12. The immature DCs induce $CD4^+$ and $CD8^+$ T cell apoptosis after TCR ligation in the absence of accessory cell costimulation. In contrast, IL-2 can rescue T cells from apoptosis *in vitro,* therefore, it can be used as a potent adjuvant in vaccination (Adkins et al., 1996). Different from adult Th1 cells, primary neonatal Th1 cells express high levels of IL-13 receptor α1 (IL-13Rα1), and heterodimerize with IL-4Rα. After secondary antigen challenge, high populations of Th2 cells produce IL-4 and IL-13, which bind to IL-4Rα/IL-13Rα1 and trigger the apoptosis of protective Th1 subtype cells. This may explain why the Th2 cell response becomes predominant after neonatal vaccination or viral infection (Zaghouani et al., 2009). However, after 6 days of age, murine DCs become more mature and express high levels of accessory costimulatory molecules and other maturation markers. Afterwards, $CD8\alpha^+$ $CD4^-$ DCs proliferate rapidly in the spleen, produce sufficient amount of IL-12, and subsequently induce rapid development of Th1 cell subtype after vaccination. Additionally, $CD8\alpha^+$ $CD4^-$ DCs downregulate IL-13Rα1 expressed on Th1 cells, protecting neonates from IL-4-driven Th1 cell apoptosis (Lee et al., 2008). This may explain why the Th1 cell response becomes predominant after vaccination or viral infection in adults.

Active immunization with adjuvant in neonates

New knowledge in the field of neonatal DCs and their role in priming immune responses and antigen processing has facilitated the development of safe and effective novel vaccination strategies in children and neonates. Successful anti-RSV immunizations of Balb/c mice at 4 to 8 weeks of age are achieved with the assistance of a variety of adjuvants, which have been reported to promote and maintain potent anti-RSV Th1 subtype immune responses in young adult mice. For example, intranasal delivery of the formalin-inactivated RSV (FI-RSV) formulated with CpG oligodeoxynucleotide (ODN) and polyphosphazene (PP) effectively induces systemic and mucosal responses. RSV replication is significantly reduced after RSV challenge (Mapletoft et al., 2010). CpG ODN upregulates MHC class II and CD86 on DCs, and stimulates DCs to produce large amounts of IL-12 (Jakob et al., 1998). Cholera toxin is another potent mucosal adjuvant, stimulating class and subclass antibody responses to UV-inactivated RSV (Reuman et al., 1991). Recombinant BCG expressing RSV antigens can activate RSV-specific protective Th1 cells to produce IFN-γ and IL-2 and cause a significant reduction of inflammatory cell infiltration in the airways of immunized mice (Bueno et al., 2008). Bacterial outer membrane vesicle (OMV) is an effective adjuvant which can promote long-lasting balanced humoral and cellular immune responses and immunological memory. After intranasal immunization with recombinant G1F/M2, expressing a CTL epitope of RSV-M2 protein and a domain of RSV-G protein in the presence of OMV, the immune mice are protected against both virus replication and have diminished eosinophil infiltrate in the lung for more than 19 weeks (Etchart et al., 2006; Zeng et al., 2007).

Although active anti-RSV immunizations with the help of adjuvants have been successful in young adult mice, few successful immunizations have been reported in newborn and early age of children, and some have even exacerbated the disease after subsequent RSV infection. When formalin inactivated (FI) RSV vaccine (FIRSV) was administered to infants and children in the 1960s, serious incidents occurred, i.e. the death of two vaccinated recipients following a subsequent RSV infection. Additionally, there was increased frequency and severity of RSV infections and greater incidence of hospitalization after FIRSV-immunized children were exposed to RSV compared with non-immunized children (Kim et al., 1969). The increased incidence and severity were associated with production of high levels of non-protective anti-RSV antibodies. The underlying causes of ERD (enhanced RSV disease) have not been well clarified. Current accepted explanations are the imbalance of neonatal immune responses to RSV fusion (F) and attachment (G) proteins. The F protein epitope is highly antigenic and induces Th1 immune responses (Connors et al., 1992), but it is disrupted after formalin inactivation; the altered F epitope induces large amounts of low avidity and non-protective antibody, leading to immune complex deposition in the infected airways (Devey and Steward, 1980). In contrast, the G protein epitope is well preserved, but is predisposed to induce pathologic Th2 immune responses and an accumulation of pulmonary eosinophilia in the immunized individuals. High levels of IL-4 and pulmonary eosinophilia were observed in FIRSV-immunized BALB/c mice challenged with RSV (Hancock et al., 1996). CTLs are cytotoxic to virus-infected cells and downregulate the expression of Th2 cytokines, but FIRSV immunization fails to induce CTLs, leading to increased Th2 cytokine and pulmonary eosinophilia after RSV infection (Kim et al., 1969; Hussell et al., 1997; Srikiatkhachorn and Braciale, 1997a; Srikiatkhachorn and Braciale, 1997b; Anderson et al., 2007).

Neutralizing antibody-based immunization

The limited success and potential risk of causing enhanced RSV disease encourage us to develop a novel, safe, and effective strategy in generating RSV neonatal vaccine. Passive infusion of anti-RSV neutralizing monoclonal antibody (mAb) is a safe and effective therapeutic approach. Pavilizumab, a pharmacological monoclonal anti-RSV antibody drug, was approved by the FDA in 1998 for treating infants infected by RSV (Mejías and Ramilo, 2008). This drug can effectively inhibit viral spread and replication, with a transient and rapid protection. Maternal-derived RSV neutralizing antibody has shown a similar extent of immune protection as mAb. Pregnant guinea-pigs immunized by RSV infections were able to transfer antibodies to their offspring prenatally via placenta and postnatally through breastfeeding. Immunization of pregnant guinea-pigs resulted in a significant reduction in viral replication in the lungs of their offspring when challenged intranasally with RSV. The viral titer of RSV was significantly reduced from 3.6 ± 1.5 pfu/g of lung in pups born to non-immunized mother to 2.3 ± 0.8 pfu/g in pups born to immunized mothers (Buraphacheep and Sullender, 1997). However, in human, it is not reported whether maternal anti-RSV antibody is protective in infants and has an impact on neonatal immune system. Not all vaccinated mothers can produce protective anti-viral antibody for infants. Mothers who are HIV carriers can transmit the virus to babies at birth, but do not produce protective neutralizing antibodies to HIV in infected mothers and infants. In some cases, the maternal neutralizing antibody may counteract active immunization in early life by neutralizing virus antigen load. Specifically, high levels of maternal anti-HA can suppress active neonatal vaccination, however, low levels of the antibody can improve normal newborn antibody responses. Thus, effective neonatal vaccine responses can be obtained earlier in the presence of maternal antibodies through the use of appropriate immunization strategies (Siegrist et al., 1998).

Immune modulation by maternal neutralizing antibody

As described above, active immunization in early age with formalin-inactivated RSV leads to production of non-neutralizing anti-RSV antibody and induces Th2-biased immune suppressive immune response, whereas passive infusion of pharmaceutical anti-RSV neutralizing monoclonal antibody and transmission of maternal neutralizing anti-RSV antibody are effective in blunting RSV propagation at early age of human beings and animal models. Therefore, passive immunization represents a safe and effective strategy in controlling RSV replication. However, because pharmaceutical mAbs are not able to initiate neonatal endogenous anti-RSV immunity, newborns lose protection after the mAbs disappear, and are again at risk of RSV re-infection. Thus, a new vaccination strategy with the ability to inhibit virus proliferation as well as to induce neonatal endogenous anti-RSV immunity is desirable. Recent studies in animal models suggest that, in addition to the direct antiviral effects of maternal-derived antibodies, the maternal-derived antibody also exerts an immune modulatory effect, and favors the mounting of neonatal endogenous Th1-biased antiviral immunity after pups are immunized with the same viral antigen. Importantly, the induced neonatal endogenous antiviral immunity can persist long after maternal antibody has been cleared. This is an encouraging observation because it provides a new strategy for the development of neonatal anti-RSV vaccines. Indeed, our preliminary data has provided strong evidences that pups born to RSV immunized mothers grow normally and are often less infected post nasal RSV challenge after birth than pups born to non-immunized mother. More importantly, the immunized mother-born pups developed significantly higher levels of endogenous IFN-γ in the lung and spleen, as well as higher levels of anti-RSV neutralizing total IgG and IgG2a antibodies in serum and lung tissue, compared with pups born to a non-immunized mother. Interestingly, active immunization of immunized mother-born pups with the same antigen at days 1, 3, 5 after birth induced significantly higher levels of anti-RSV neutralizing antibody than those of untreated pups born to an immunized mother, suggesting combinational active and passive immunization of pups has an additive or synergistic effect on anti-RSV antibody immune responses. The beneficial effects are correlated with low lung RSV load or undetectable RSV genomes in the double treated pups (unpublished data). Therefore, in neonatal vaccination against RSV, maternal anti-RSV did not interfere with neonatal endogenous anti-RSV immunity. In contrast, it promoted neonatal adult-like anti-RSV immune responses, particularly when neonates were actively immunized with the same antigen at early age.

The immune modulatory property of maternal antibody has also been observed in other antiviral and allergic animal models (Haigwood et al., 2004; Gros et al., 2005; Victor et al., 2010). Treatment of neonatal mice at 5 days of age with anti-FrCasE murine retrovirus neutralizing mAb 667 accelerated pup survival and mounted long-lasting protective Th1 and CTL responses following challenge with a lethal dose (5×10^4 PFU/mL) of FrCasE murine retrovirus. Neonatal mice treated with mAb 667 showed neither neurodegeneration nor leukemia; whereas mAb 667 untreated mice developed rapid non-inflammatory spongiform degenerative disease, leading to the death of all mice within 1 to 2 months. The virus propagated rapidly in peripheral lymphoid organs and penetrated into the central nervous system (CNS). Following mAb 667 treatment and virus infection, neonatal endogenous anti-FrCas(E) IgG2a antibody was developed, persisted up to 16 months, and provided long-term protective effects (Gros et al., 2005). Meanwhile, the double treatment stimulated neonatal endogenous antiviral $CD8^+$ CTL responses, which

are essential in eliminating virus-infected cells. Mice deficient in $CD8^+$ cells cannot prevent death from erythroleukemia after FrCas(E) infection, even with a high titer of neonatal endogenous anti-FrCas(E) IgG2a antibody (Gros et al., 2005; Gros et al., 2006; Gros et al., 2008).

As described above, not only does the double immunization of the pregnant mother and neonate provide passive protection to the newborn, but it also initiates the newborn's own anti-RSV and anti-FrCas(E) immunity. The strategy could be useful in protecting neonates against a variety of life-threatening viruses. However, maternal antibody may counteract the development of newborn's own antiviral immunity in some animal models, ultimately inducing chronic infections (Pinschewer et al., 2004). Pups born to mother immunized to Sendai virus (SV) envelope proteins only developed low levels of endogenous anti-Sendai virus SV IgG2a antibody, IFN-γ, and IL-5 after immunization with the same vaccine proteins at 2 days of age, but the interfering effect did not persist at adult age when maternal antibody disappeared (Blomqvist et al., 2003).

Immune complexes in the immune modulatory role of maternal neutralizing antibody

How does maternal neutralizing antibody initiate endogenous protective antiviral immunity in virus-infected mice? Several mechanisms may explain the consequences of neutralizing antibody (Ab) treatment on neonatal endogenous immunity. Abs can stall viral propagation before the neonatal adaptive immune response emerges; this immediate effect might provide time for the neonatal immune system to mount a protective antiviral response before being overwhelmed. In addition, Abs exert cytolytic activity against virus-infected cells through antibody-dependent cytotoxicity (ADCC) and complement-dependent (CDC) mechanisms mediated by natural killer cells. Animals treated with variant neutralizing antibodies with $F(ab)_2$ fragment alone or mutations in the complement binding and FcR binding sites were not protected after virus infection (Mozdzanowska et al., 2003; Hessell et al., 2007). The ADCC and CDC-mediated cytotoxicity creates an inflammatory environment favoring uptake, processing, and presentation of viral antigens by DCs to naïve T cells, leading to potent antiviral antibody and CTL responses directed at infected cells.

FrCasE-infected/667 mAb treated mice mount stronger humoral and CTL anti-FrCasE immune responses than infected/non-667 mAb treated mice. The stronger antiviral immunity is associated with enhanced antigen uptake by infected cells and more efficient activation of DCs and subsequent virus-specific $CD8^+$ T cell responses in neonates (Michaud et al., 2010). ICs play an important role in the process. After pups were nasally or orally immunized using the same antigen as their immunized mother, ICs formed as maternal antibody reacted with administered vaccine antigen at mucosal surfaces of the respiratory and digestive systems. The ICs may effectively bind to APCs (macrophages and dendritic cells) residing in respiratory and digestive tracts via Fc receptors (FcRs), causing increased uptake, processing, and MHC presentation of antigens by APCs (Schuurhuis et al., 2006).

Neonatal intestinal epithelial cell surfaces express abundant FcRs, which are responsible for transporting IgG across the intestinal epithelial barrier into the lamina propria where the IgG can bind to viral vaccine antigens, resulting in highly concentrated viral antigen uptake by residing APCs. After capture of ICs, DCs more efficiently process and present viral antigens to $CD4^+$ T cells in regional organized lymphoid structures than after capture of antigen alone (Abrahamson et al., 1979; Yoshida et al., 2004), and DCs rapidly increase expression of CD40 and CD86, and migrate to lymphoid organs (Franki et al., 2007; Hamano et al., 2000), leading to both enhanced humoral (Heyman, 2000; Wu et al., 2008) and stronger $CD4^+$ and $CD8^+$ T cell responses. Our preliminary studies indicate that *in vitro* stimulation of splenocytes from RSV-vaccinated adult mice with RSV immune complexes leads to more efficient cell activation than RSV antigen stimulation alone, producing significant amounts of IFN-γ and total anti-RSV neutralizing IgG antibody in cell culture supernatants (unpublished data). The beneficial effects of ICs were observed in an anti-SIV macaque vaccine model in which ICs induced more potent stimulation of anti-SIV CTL than p55 gag antigen alone (Villinger et al., 2003). When vaccine antigen is fused to the Fc region of IgG, transportation and antigen presentation are facilitated significantly. For example, chimeric proteins composed of HIV Gag p24 peptide fused to the Fc region of IgG (Gag-Fc) can efficiently bind to airway mucosa and improve transportation across epithelial surfaces and processing by APCs. Intranasal immunization of mice with Gag-Fc led to the development of durable memory B and T cells, and protected against an intravaginal challenge with recombinant vaccinia virus expressing the HIV Gag protein (Lu et al., 2011). Immunization of FcR transgenic mice with OVA resulted in a 3- to 10-fold increase of serum antigen-specific IgG, with a large amount of phagocytosed IgG ICs in local neutrophils, macrophages, and follicular DCs in mesenteric lymph nodes (Cervenak et al., 2011; Hazenbos et al., 1998). ICs trigger and maintain potent *in vitro* and *in vivo* endogenous immune effector functions until adult age. The endogenous immune response is sufficient to takeover maternal Abs to blunt viral propagation. Residential infected cells can persistently stimulate and proliferate CTLs, leading to long-lasting antiviral effects. IC-containing cells induce development and maintenance of the memory antiviral CTLs (Bachmann et al., 2004). when mice were virus challenged, strong memory antiviral CTL responses were developed (Bachmann et al., 2004; Elrefaei et al., 2004;Aiuti and Mezzaroma, 2006).

Conclusions and future perspectives

RSV infection is the leading cause of bronchiolitis and viral pneumonia in infants and young children. Active RSV immunization in 4–8 week-old female BALB/c mice usually leads to some level of immune protection, but there is limited success in neonatal mice and humans, frequently leading to re-infection. Monoclonal neutralizing antibody alone can provide efficient short-term protection, but is unable to induce neonatal endogenous antiviral immune responses. Our unpublished preliminary data and current reports show that active immunization of pups born to the same viral antigen immunized mother not only protects newborns from infection at early life, but also induces potent neonatal endogenous antiviral CTL and antibody responses. These immune responses persist after disappearance of the maternal antibody. Maternal antibody may enhance vaccine antigen uptake, increase DC activation, and priming of neonatal naïve T cells when neonates are actively vaccinated nasally or orally with the same antigen. ICs may play a critical role in stimulating beneficial adult-like Th1 antiviral immunity in the vaccinated neonates. Further investigation of underlying mechanisms will contribute to improving the designs of safe and effective anti-RSV vaccines for neonates.

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