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Influence of Maternal Antibodies on Neonatal Immunization against Respiratory Viruses

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Vaccines that successfully prevent severe infant respiratory virus diseases should induce protection at a very young age because of the low age of patients who are hospitalized owing to these viruses. Candidate respiratory virus vaccines are being tested in infants who are naïve to infection but seropositive to the viral agents because they possess maternal IgG antibodies (Abs). Transplacental maternal Abs may be partially protective against disease caused by respiratory virus infections. Carefully conducted studies have shown that these Abs can also profoundly suppress or enhance infant immune responses to immunization. The mechanisms underlying regulation of immune responses to viruses by maternal Abs are under investigation. This article explores the current knowledge regarding the effect of maternal Abs on respiratory virus and measles virus immunization, and it reviews the current approaches to overcoming Ab-mediated immunosuppression.

Immunization of infants and children against diseases caused by infection is perhaps the most effective medical intervention to date. Many infectious diseases are effectively controlled by immunization when immunization rates are high. Nevertheless, new vaccination efforts that aim to prevent the most common severe pediatric diseases of our time (principally viral respiratory and enteric diseases) face numerous obstacles. The peak age at incidence of many severe diseases targeted for immunization in current efforts is quite low. For instance, hospitalization rates for patients with lower respiratory tract disease caused by respiratory syncytial virus (RSV) peak at ≈2 months of age [1, 2]. Many of the previous successful efforts to immunize children against infectious diseases employ strategies that require multiple-dose immunizations starting at 2 months of age. Immunization against the bulk of severe RSV disease will require infants to be immune by this age. Therefore, vaccinologists are contemplating the immunization of persons at ever-younger ages.

NEONATAL IMMUNIZATION

The evidence to date is that immunization of neonates with many viral antigens is safe. The occurrence of unanticipated, serious, adverse reactions to primary immunization of infants with vaccine candidates, such as the formalin-inactivated RSV preparation and a high-titer measles virus vaccine, suggest that great caution is needed in studies of subjects in this age group. Immunization at this age does not often elicit vigorous immune responses. The low level of immune response to infection or immunization exhibited by neonates probably stems from multiple factors, including limited B cell repertoire, inefficient mechanisms of antigen (Ag) presentation and T cell help, and inhibition by passively acquired maternal Abs. In particular, I review the role of maternal Abs in Ab-mediated immunosuppression of the neonate. Young infants can become infected with respiratory viruses, such as RSV, even though they possess maternally derived RSV serum Abs. The need to understand the effect of passive Abs on the immune response to infection with such viruses as RSV has grown in recent years because of several clinical developments. First, present vaccine development efforts are focused on the testing of live attenuated
RSV vaccines for infants as young as 4 weeks of age who possess maternal Abs in their serum. Second, passive immunophylaxis, in the form of a parenterally administered humanized monoclonal antibody (mAb) directed to the RSV fusion (F) protein, is used in a significant proportion of the infants at high risk of severe disease. Third, maternal RSV immunization strategies are being tested clinically. The aim of maternal immunization is to boost maternal Ab levels and, thus, to transfer elevated levels of transplacental maternal Abs to fetuses prior to birth. Serum-neutralizing Abs, when present in high levels, protect the lower airways of a significant proportion of infants against RSV disease. Nevertheless, RSV can infect the upper, and sometimes the lower, respiratory tract of infants, even in the presence of passively acquired Abs. I will review what is known about the effect of passive Abs on the active immune response of neonates and young infants to infection with respiratory viruses and measles virus.

**TRANSFER OF ABS FROM MOTHERS TO INFANTS**

The principal method of transfer of Abs from human mothers to infants is via the transplacental route. The IgG1 subclass of Abs is preferentially transferred, with little IgM, IgA, or IgE transferred. The placenta is not a simple permeable membrane; rather, it is a complex tissue with multiple cell layers and cell types that use regulated transport mechanisms. The transfer of Abs is not just leakage or passive diffusion across the placental barrier. Transfer is mediated by active transport using Fc receptors (FcRs). The placenta contains several known FcRs and also other proteins that bind Abs. Most important to Ab transfer is probably the human homologue of the neonatal rat FcR (FcRn), a heterodimer with pH-dependent IgG affinity, which is structurally similar to major histocompatibility complex (MHC) class I molecules [3]. The placental human FcRn heterodimer transports IgG to the fetus, probably by a mechanism in which maternal IgG is carried to fetal tissues by a pH gradient from acidic endosomes to the pH-neutral basolateral surface of the syncytiotrophoblast and possibly across the fetal blood vessel endothelium. The FcRn likely contributes broadly to the regulation of IgG concentrations in tissue and serum by controlling IgG transport and catabolism [3]. Other IgG binding FcRs, such as FcγRI, FcγRII, and FcγRIII, on Hofbauer cells in the stroma, and FcγRII, on endothelial cells, may also clear maternal Abs against fetal Ags, which are removed as immune complexes [4].

Transfer of Abs begins at ~28 weeks gestation in humans, and the quantity of maternal Abs in fetal circulation increases until the time of birth. Total and Ag-specific Ab levels, such as RSV-F or -G Ab titers, are lower in premature infants than they are in full-term infants [5]. Comparisons of Ag-specific IgG titers in mothers and their infants suggest that, on average, the term neonate’s serum possesses a level of Abs similar to that of the mother’s serum, and, in some cases, the level exceeds the mother’s titer of Abs to specific agents. All subclasses of IgG cross the human placenta [6], but carefully conducted studies have shown that placental transport of IgG Abs is related to their subclass composition, with IgG1 being preferentially transported across the placenta [7]. Some Ab specificities are relatively restricted to a particular subclass; therefore, the Ig subclass transfer bias may differentially affect the transport of Abs of some specificities. For example, streptococcal Abs associated with the IgG2 subclass are transported less efficiently than are antitetanus Abs, which are usually associated with IgG1 [7]. The highest titers of RSV-specific Abs are in the IgG1 and IgG2 subclasses [5]. The avidity of neonatal Abs for some Ags appears to differ from those of the mother, with some studies suggesting that high-avidity Abs preferentially cross the placenta, even in premature neonates [8].

**BREAST MILK ABS**

Human breast milk contains a large quantity of Abs, especially secretory IgA molecules, that have been transcytoposed into breast milk via the polymeric immunoglobulin receptor [10]. Some, but not all, epidemiological studies have suggested that breast feeding has a protective effect on the rate of respiratory illness caused by RSV [11, 12]. This effect is often attributed to Ab-mediated protection, although the mechanism and site of action of such Abs are unclear. Confounding variables, such as voluntary limitation of exposure to potentially infectious persons during the first 3 months of life, make these studies difficult to interpret. The relatively weak effect of breast feeding in the epidemiology studies suggests that breast milk Abs are not a principal mechanism of Ab-mediated protection against respiratory viruses in infants.

**CLINICAL STUDIES DEMONSTRATE THAT MATERNAL ABS ARE INHIBITORY**

Evidence of Ab-mediated immune suppression from human studies includes the response to naturally acquired infection with wild-type (wt) RSV, parainfluenza viruses (PIV), and influenza viruses and to experimental infection with live attenuated RSV, PIV, and candidate influenza vaccine viruses, which are reviewed elsewhere [13]. These pediatric respiratory viral pathogens infect via the mucosal epithelia and cause disease at the portal of entry. Many human studies also have demonstrated the inhibitory effect of passively acquired Abs on active immune responses to measles virus. Although measles virus also infects via respiratory mucosa, its pathogenesis differs from that of the classical respiratory viruses, because its spread...
through the body to sites of severe disease involves a viremic phase during which the virus is highly exposed to serum Abs. Immunization of children with live attenuated measles virus vaccine is currently performed by means of intramuscular immunization, a method of delivery in which vaccine virus is susceptible to serum Abs. The effect of serum Abs on systemic measles virus infection or immunization is more profound than that on the response to viruses that predominately cause severe disease limited to the airway.

**NEONATES ARE IMMUNOLOGICALLY IMMATURE**

Difficulties arise in defining the independent role of, and the mechanisms that cause, Ab-mediated immunosuppression in neonates. Neonates differ from older infants and children in ways other than simply the presence of maternal Abs. Neonates are immunologically immature and functionally deficient in their adaptive immune responses. Some studies have attempted to analyze independently the role of Abs in poor infant responses by statistical means that involve multivariate analysis, and these studies do suggest a profound inhibition of specific immune responses by passively acquired Ag-specific Abs [14]. Measles virus immunization can be studied in patients of an older age in the United States, because the incidence of the natural disease is extremely low in infants in the United States [15]. Such studies have revealed that young age has a significant independent effect on primary immune responses to measles virus vaccine that persists at least through the first 6 months of life, even in the absence of detectable levels of maternal Abs. The molecular and cellular basis for the functionally poor Ab responses of young infants to measles virus is not well defined.

**ANIMAL MODELS OF AB-MEDIATED IMMUNOSUPPRESSION**

Recent studies have focused on using experimental infections of laboratory animals with RSV to define the independent role of Abs in a definitive way. Rodent and primate models allow the study of the effect of passive Abs on immune responses independent of immunologic immaturity. It must be kept in mind, however, that most animal species used experimentally are only semipermissive hosts for human respiratory virus infection. Neonatal mice are particularly poor hosts for replication of RSV, and permissiveness of mice increases with advancing age. Also, caution must be exercised when modeling the transfer of Abs from human mothers to infants in animals. The placental mammals have evolved a variety of placental types that differ widely in their anatomy and function. There are marked differences among animals regarding whether Abs are transported across the placenta. In nonhuman primates and rodents, there is significant transfer of IgG from maternal to fetal circulations prior to birth. This process requires FcRs in the placenta. In contrast, there is no transplacental transfer of Abs in ruminants (i.e., cattle, sheep, goats, or deer) or horses or pigs. In these animals, the neonate lacks significant levels of serum Abs until it absorbs them from colostrum or breast milk via enteric Ab receptors. Furthermore, most of the studies of passive antibodies are conducted by parenteral administration of high-tiered Ab preparations rather than by transplacental transfer of Abs.

Despite these caveats, animal models of respiratory virus infection have clearly demonstrated the suppressive effect of passive Abs on primary immune responses. Passive Abs are particularly suppressive of responses to respiratory virus subunit vaccine candidates administered by means of the parenteral route [16]. Passive Abs also can inhibit responses to live virus vectors that express heterologous virus proteins, such as recombinant vaccinia virus or modified vaccinia virus Ankara recombinants that express the RSV or PIV surface glycoproteins [17, 18]. This inhibitory effect of serum Abs can be overcome partially through administration of such live vectored vaccines by the mucosal route [19]. Passive Abs also can inhibit the replication of live wild wt or attenuated viruses in rodents or nonhuman primates, such as chimpanzees [20, 21]. This inhibitory effect predominates in the lower respiratory tract, where IgG has greatest access to the epithelium. Virus neutralizing Abs in serum can inhibit respiratory virus replication in the nasopharynx when these titers are exceptionally high (>1:15,000), but such nonphysiologic levels are found only under experimental conditions [22]. Passive serum Abs inhibit both the quantitative level of serum Abs induced by infection (measured by ELISA binding to virus proteins) and the functional quality (virus neutralizing titer) of induced responses.

**SUPPRESSION OF MUCOSAL RESPONSES**

In some aspects, the mucosal immune system can function independently of the systemic immune compartment. One might hope that the limited access of passive serum Abs to the mucosal surface would lessen their inhibitory effect on mucosal Ab responses. Data suggest, however, that passive Abs inhibit both mucosal and systemic Ab responses, whether measured by soluble Abs or numbers of Ag-specific mucosal Ab-secreting cells in both mice and humans [20, 23]. It has been difficult to determine whether maternally derived Ab suppresses mucosal responses in infants or children because of the technical challenges in reproducibly collecting mucosal antibody specimens. It is interesting that protective efficacy against wt RSV challenge can be induced in mice or chimpanzees by live attenuated RSV infection in the presence of serum RSV Abs even when primary Abs are profoundly suppressed [20, 21]. In mice,
CD4+ and CD8+ T cells are required for this protection [20]. Vigorous priming of the B cell repertoire for secondary Ab responses may occur during RSV passive/active immunization experiments, even when primary Ab responses are suppressed at levels that are lower than detectable limits. RSV passive/active immunized mice exhibited suppressed primary but normal secondary Ab responses. Remarkably, RSV passive/active immunized chimpanzees exhibited suppressed primary but substantially enhanced secondary Ab responses [21]. Measles virus immunization is even more susceptible to Ab-mediated suppression. In macaques, as little as 0.1 IU of monkey measles virus–neutralizing Ab per mL of serum abrogated the induction of specific serum IgM, IgG, and virus-neutralizing Abs after vaccination with live attenuated measles virus [24]. Unlike RSV Abs, however, low levels of measles virus Abs also can protect humans against severe measles virus disease [25]. Live attenuated measles virus vaccine induces protective immunity in seronegative individuals, but low levels of maternal Abs interfere with the induction of protective responses in humans [26, 27]. The age at which this inhibition is overcome varies, because different mothers possess differing levels of serum measles virus Abs. The mean levels of these Abs in the population are changing, because measles virus–neutralizing Ab titers are significantly lower in infants whose mothers were vaccinated than they are in infants whose mothers sustained natural measles virus infection [28]. Topical immunization may allow greater infectivity of the live attenuated measles viruses in the presence of serum maternal Abs, and this method of delivery was effective in early investigational trials conducted by Albert Sabin et al. [29] among others.

Mechanisms of enhancement or suppression. Recent studies of passive Ab-mediated regulation of active Ab responses have demonstrated that passive Abs can enhance or suppress immune responses dramatically. Despite a growing body of studies about this subject, the precise molecular mechanisms by which passive antiviral Abs mediate their effects in any particular respiratory virus experiment have remained largely unknown. Basic science studies with model antigens, however, are instructive in this regard.

Effect of Abs on presentation of T cell epitopes. Ag-specific Ab can affect Ag presentation to T cells. In most cases, viral Ag presentation at low concentrations is enhanced by the presence of Ab, which indicates that Ab contributes to FcR-mediated uptake by Ag-presenting cells (APCs) [30, 31]. In contrast, some Ag-Ab combinations yield lower responses than does Ag alone [32, 33], which suggests that Abs modulate the enzymatic processing of Ag that is required to generate the short peptides that serve as T cell epitopes when loaded onto class I MHC molecules. High-affinity Ag-Ab interactions are stable at endosomal/lysosomal pH, thus altering the substrate for Ag processing [34]. mAb studies have shown that bound Abs can modulate the capture of specific peptides by class II MHC, thus manipulating the T cell response toward or away from particular determinants [35]. The pattern of fragmentation observed for some proteins can experimentally vary from one laboratory B cell line to another, depending on the epitope through which the Ag is bound and endocytosed and whether additional epitopes in the Ag are complexed with the mAb [36]. Differential effects also are mediated by the use of different type II and III FcRs. These receptors use motifs that contain tyrosine to transduce cell-activation signals, with cytoplasmic domain heterogeneity determining the functions of different IgG FcRs in APCs, such as B cells [37–39]. FcγRIIB, an inhibitory receptor that probably usually plays a role in limiting immunogenic responses, may play an important role in passive Ab effects in neonates. Studies to date in mice with RSV, influenza, or measles virus do not demonstrate significant inhibition of cytolytic T lymphocyte (CTL) responses by passive Abs in vivo [20, 40, 41]. Studies to determine the role of CTL activity induced in infants by these viruses in the resolution of infection or protection against reinfection are underway in our laboratory.

**MOLECULAR AND CELLULAR MECHANISMS OF AB-MEDIATED INFLUENCE ON PRESENTATION OF B CELL EPITOPES**

Most of the fundamental work examining these mechanisms has centered on model Ags, such as the response in mice to injection of sheep erythrocytes. These studies were recently reviewed [42, 43]. IgG-mediated suppression is generally dose dependent, and all IgG subclasses have been reported to mediate suppression. In some cases, the suppressive ability of particular antibodies correlates with affinity of the antibodies. The necessity of the Fc region of the antibody for suppression is variable, but the Fc region is generally hypothesized to play an important role in suppression. Proposed mechanisms of suppression include elimination of immune complexes by receptor-mediated phagocytosis by FcγR+ cells, prevention of B cell recognition of Ag through epitope masking, and co–cross-linking of FcγRIIB and the B cell receptor (inhibiting B cell activation). Proposed mechanisms of enhancement include co–cross-linking the B cell receptor with the complement-receptor 2 complex (enhancing B cell activation), efficient receptor-mediated endocytosis by Ag-presenting cells followed by presentation to T cells, and increased localization of immune complexes in lymphoid follicles on follicular dendritic cells carrying complement receptors and FcRs.

The epitope-masking mechanism of B cell epitope suppression might spare uptake by APCs, thus accounting for relatively normal T cell responses, as described in the aforementioned animal experiments. Such sparing of T helper-cell responses would also suggest why complete suppression of memory and
secondary B cell responses is difficult even when antibodies are not detected after primary infection or immunization. In fact, we have documented the phenomenon of suppression of primary responses with marked enhancement of secondary responses to RSV vaccines by RSV Abs in primates [21]. It is currently not clear whether respiratory virus Ab-mediated suppression and enhancement is epitope-specific or nonspecific. Clinical studies suggest a broad suppression of responses to all epitopes on antigenic proteins, but the effect of polyclonal Ab immunosuppression is difficult to interpret in this regard. Careful mAb studies are needed to clarify this issue.

**AB-DEPENDENT CELL-MEDIATED CYTOTOXICITY (ADCC)**

Several of the FcRs bind Ag-Ab complexes and thereby induce a phagocytic cell-mediated mechanism of immunity termed “ADCC.” There is in vitro evidence that Abs in human serum can trigger ADCC activity. Abs that were mediating ADCC against influenza virus–infected cells were detected in serum samples obtained from young children after natural infection or after vaccination with inactivated and live attenuated viruses [44]. Both hemagglutinin (HA) and neuraminidase (NA) proteins are antigenic determinants for ADCC Abs. Cord blood lymphocytes, monocytes, and neutrophils from newborns can mediate ADCC against influenza virus–infected cells, and Abs mediating ADCC were detected in cord plasma [45]. Human ADCC Abs to RSV in serum have been detected in adults, including in colostrum, and in the serum of infants [46, 47]. Mucosal Abs that mediate ADCC can be measured in nasopharyngeal secretions collected after primary RSV infection [48, 49]. These data suggest that all of the components required to mediate ADCC against respiratory virus–infected cells are present in newborns; however, the role of ADCC in immunity or pathogenesis in vivo in human neonates is not clear.

**STRATEGIES USED TO OVERCOME AB-MEDIATED IMMUNOSUPPRESSION**

Most of the proposed methods for immunizing successfully in the presence of maternal Abs are based on an empiric approach.

**Dose.** The simplest method has been to increase the dose of vaccine. For purified subunit protein vaccine candidates, the cost of this approach is limiting. For live attenuated vaccines, increased dose is often easy to achieve, but results may be difficult to predict. In some cases, increasing the dose of live experimental vaccines increases the percentage of young vaccinees that become infected, without causing excess virus shedding or reactogenicity. Nevertheless, untoward effects can occur with this approach. High-titer measles virus vaccine (˃10⁶ pfu) was administered to infants at the age of 4–6 months, but it resulted in higher mortality rates because of infectious diseases in female recipients [50, 51].

**Mucosal immunization.** Serum Abs mediate a more profound suppressive effect on nonreplicating soluble Ags used for systemic immunization than on replicating viruses. A strategy that is successful in animal studies is the topical application of vaccines, especially live viruses. Live virus inoculation of the upper respiratory tract mucosa may allow the vaccine to escape the neutralizing effect of serum Abs. In some cases, however, profound inhibition of the primary Ab response has been observed even when virus replication in the upper respiratory tract is unaffected [20, 21, 52].

**NOVEL METHODS OF IMMUNIZATION**

New experimental methods of immunization may offer advantages for stimulating infant immune responses in the presence of maternal Abs. Three such strategies under investigation are vectored vaccines, plasmid DNA vaccination, and Ags in immunostimulating complexes (ISCOMs).

**Vectored vaccines.** Scientists have developed a variety of vectored vaccines, which are recombinant viruses that accommodate and express the protective genes of heterologous viruses. The vectors used are often large DNA viruses, such as adenoviruses or vaccinia and related poxviruses. Routine vaccinia immunization was discontinued in the United States in 1971; therefore, it is reasoned that infants born to mothers ≤30 years of age will not possess vaccinia virus–neutralizing Abs. A large number of studies in rodents and monkeys that have evaluated the immunogenicity of poxvirus recombinants in the presence of passive respiratory virus Abs have been performed. Recombinants that have been tested in this manner include vaccinia virus or modified vaccinia Ankara recombinants encoding the measles virus F or HA glycoproteins [53–55], the RSV F or attachment (G) glycoproteins [17, 19], the PIV hemagglutinin-neuraminidase (HN) or F glycoproteins of human PIV-3 [56], and the HA of influenza [57, 58]. Most of these studies, however, show that the Ab response to the respiratory virus protein is inhibited by passive Abs to those proteins, especially when the immunization is given systemically. Smaller viruses, such as vesicular stomatitis virus, have been used as the recombinant vector for expression of measles virus HA [59] or RSV F or G glycoproteins [60], but the safety of this vector in humans is questionable. An interesting variation on the use of vectored vaccines is the use of 1 recombinant live attenuated respiratory virus to express the protective Ag of another, such as a recombinant attenuated human PIV3 virus that expresses the HA glycoprotein of measles virus [61]. Such viruses might be used as bivalent vaccine viruses that could be administered intranasally to protect against both the vector and the heterologous virus.
ISCOMs. The ISCOM method is a vaccine formulation that incorporates multimeric presentation of an Ag with adjuvant molecules in a symmetrical particle composed of Quillaja saponins, cholesterol, phospholipids, and protein [62]. The adjuvant activity of ISCOMs is due to the Quillaja glycosides. ISCOM vaccines incorporating protective Ags of measles virus or RSV induce protection in the presence of passive Abs in animal models [63]. The feasibility of this approach in human neonates is unclear.

Plasmid DNA vaccines. DNA vaccines offer an interesting strategy for immunizing neonates in the presence of maternal Abs. Plasmid DNAs encoding protective viral Ags are injected, and these DNAs can transfect cells in vivo directly without displaying the protective protein Ags on the immunizing material itself. This method avoids complex formation between the vaccine and maternal Abs. Also, some plasmids express viral Ags in vivo for a prolonged period of time, thus enhancing the likelihood that sufficient immunizing protein Ag will be present at the optimal time during the physiologic waning of inhibitory maternal Ab levels that occurs during the first months of life. Neonatal DNA immunization in the presence of maternal Abs has been shown to be effective in priming or inducing immunity in several animal species, using protective Ags from influenza [40] and measles virus [41, 64] as well as other viruses, such as herpes viruses [65–67], rabies virus [68], lymphocytic choriomeningitis virus [69], and pseudorabies virus [70, 71]. To date, however, there is little evidence that DNA vaccines are significantly immunogenic in humans, so the utility of this strategy for immunizing human neonates is unclear at this time.

Maternal immunization. Maternal immunization is an alternate strategy to neonatal immunization for protection against infectious diseases at an early age. The principle of maternal immunization is to boost the level of protective Abs to higher levels in pregnant women, thus delivering a higher level of transplacental Abs to the infant. Trials with influenza and tetanus vaccines have demonstrated that maternal immunization with these vaccines is safe and immunogenic and results in the transfer of elevated quantities of vaccine-specific Abs [72]. Maternal immunization studies with a subunit RSV vaccine candidate are underway. Most current clinical applications of this strategy do not intend to deliver Ag across the placenta (i.e., the immunizations are intended as active immunizations of the mother but passive immunization of the infant). Nevertheless, evidence is accumulating that some Ags can cross the placental barrier in animals before birth. The significance of transplacental Ag transfer will be a topic of intense interest in coming years. Some researchers have postulated that exposure to transplacental Ags in utero predisposes to allergic responses because the fetal cytokine milieu exhibits a predominant TH2-like bias associated with allergic responses. Further work is needed to clarify whether such sensitization occurs in humans. In animals, priming of the fetus has also been demonstrated by induction of anti-idiotypic antibodies. Again, the relevance of such antibodies to human neonatal immune responses is not clear at this time.

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