Inhibition of Vaccine Responses by Maternal Antibodies

Aşı Yanıtlarının Maternal Antikorlarla Inhibisyonu

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Abstract

The inhibition of seroconversion by maternal antibodies after vaccination is a widely observed phenomenon in human and veterinary medicine. One of the best documented examples of this type of antibody interference is measles vaccination. Using the cotton rat (Sigmodon hispidus) model of measles virus pathogenesis, we have determined that maternal antibodies use a mechanism designed to prevent an overshooting immune (B cell) response. Maternal antibodies suppress B cell responses through cross-linking of the B-cell receptor (BCR) with FcγIIB receptor (CD32). CD32 is not expressed on T cells, and this explains why B cells are preferentially suppressed by maternal antibodies whereas T cell responses are usually detectable after vaccination. B cells can be stimulated through cross-linking of the BCR to the complement receptor 2 (CR2) via a complex of IgM, vaccine and C3d complement protein. During a successful primary immunization, children develop IgG as well as IgM antibodies, and this explains why they generate a B cell response after a second immunization in spite of IgG levels which would be inhibitory in children with maternal antibodies. For vaccine development, it is of importance to note that stimulation of B cell responses in the presence of maternal antibodies through type I interferon is successful because it activates two receptors (interferon receptor and CD21) on the B cell surface. These findings indicate that, for immunization in the presence of maternal antibodies, adjuvants should be used which stimulate type I interferon. In the presence of maternal antibodies, children can be immunized with vaccines which stimulate a protective T cell response. The only clinical solution to stimulating a protective B cell response in the presence of maternal antibodies is to immunize children repeatedly. *(J Pediatr Inf 2013; 7: 157-61)*

Key words: Maternal antibodies, measles virus, B cell response, type I interferon, cotton rat

Özet

Aşı sonrası serokonversiyonun maternal antikorlarla inhibisyonu insan ve veteriner hekimliğinde sıklıkla gözlenen bir olaydır. Bu tip antikor etkileşiminin en iyi dökümante edilmiş örneklerinden biri kızamık aşılamasıdır. Biz kızamık virüs patogenezinde, beyaz fare (cotton rat, Sigmodon hispidus) modeli kullanarak maternal antikorların hedeflenen yeterli immün (B hücre kaynaklı) yanıtını önleyen bir mekanizmayı kullandığını saptadık. Maternal antikorlar, B hücre reseptör (BCR) ile FcγIIB reseptörü (CD32)'nin karşılıklı bağlantısını etkileyerek B hücre yanıtlarını baskılar. CD32 T hücrelerinde eksprese edilmez, bu durum maternal antikorların aşı sonrası T hücre yanıtlarının genellikle saptanabilir olmasına rağmen niçin seçici olarak B hücre yanıtlarını baskıladığını açıklar. B hücreleri BCR ve kompleman reseptör 2 (CR2) karşılıklı bağlantısının, IgM, aşı ve C3d kompleman proteini kompleksi yoluyla uyarılabilir. Çocuklarda başarılı bir primer aşılama sırasında hem IgG hem de IgM antikorları gelişir, bu durum inhibitör etki gösterecek olan maternal antikorlu çocuklarda IgG düzeylerine rağmen 2. aşılama ile yeterli B hücre yanıtlarının oluşturulduğunu açıklar. Aşı geliştirilmesi için, maternal antikor varlığında, B hücre yüzeyindeki 2 reseptörü (interferon reseptörü ve CD21) aktive ettiği için tip I interferon yoluyla B hücre yanıtlarının uyarılmış olması gerektiğini akılda tutmak önemlidir ve bu bulgular maternal antikor varlığında aşılama için tip I interferonu uyaran adjuvanların gerektiğini gösterir. Maternal antikor varlığında çocuklar koruyucu T hücre yanıtını uyaran aşılarla aşılanabilirler. Halen maternal antikor varlığında koruyucu B hücre yanıtını uyarmanın tek klinik çözümü bu çocuklar mükerrer aşılamaktır.
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Anahtar kelimeler: Maternal antikorlar, kızamık virüsü, B hücre yanıtı, tip I interferon, beyaz fare (cotton rat).

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A Clinical Problem: Immunization in the Presence of Maternal Antibodies

After birth the immune system of neonates and infants matures over time until it is capable of mounting a fast and protective immune response comparable to the one in adults, usually at the age of one year. During this sensitive period in which the infant's immune system matures, it is usually protected by maternal antibodies. Maternal antibodies of the IgG antibody class are transferred from mother to child through trans-placental transport mechanisms during pregnancy and via breast milk within the first 24 hours of life through intestinal uptake. As mothers share the same environment with their children, they have already encountered the pathogens that the children will be exposed to and their antibodies will protect the child. Over time, passively transferred maternal antibody titers decline to levels which no longer protect, but still interfere with successful vaccination. The inhibition of seroconversion after vaccination against infectious diseases of humans (1-7) and animals (8-17) by maternal antibodies has been well documented and is independent of the type of vaccine being used (i.e. whether it is live, attenuated or a (glyco) protein vaccine). Because maternally-derived antibodies are a major cause of vaccine failure, they should theoretically be measured to determine the time of vaccination. In practice, measuring antibodies and determining vaccination based on antibody levels is not cost-effective. Clinically, the problem is often dealt with by repeated immunizations so that an individual will eventually generate an immune response after maternal antibodies have been metabolized. However, this approach is problematic when the window of opportunity for the infecting pathogen should be as short as possible, or in developing countries where migrating populations preclude the application of repeated immunizations (18). For a number of infectious diseases (e.g. respiratory syncytial virus), it has been postulated that the gap in protection might be closed by increasing the amount of maternal antibodies (and thus length of protection) through immunization of the mothers. Although this would lead to protection early in life, the question of subsequent immunizations of the child is still unresolved.

Measles Vaccination: A Well Studied Example of Inhibition of Vaccination by Maternal Antibodies

To understand immunization in the presence of maternal antibodies, we may turn to the measles virus (MV) vaccine for which the interaction with maternal antibodies has been most thoroughly documented. During their first year of life, children are protected by neutralizing maternal antibodies against MV infection. Over time, these antibody titers wane and eventually do not protect against the wild type virus infection (for review (19)). However, even these low non-protective antibody titers inhibit the generation of neutralizing antibodies by B cells, although a MV-specific T cell response is induced (20). In measles virus infection, CD8 T cells help to clear virus-infected cells but do not protect against infection (21). CD4 T cells have no role in protecting or clearing the virus from the respiratory tract (22). Due to the inhibition of antibody generation after immunization in the presence of maternal antibodies, only seronegative children can be successfully immunized (reviewed in (23)). Since no current measles vaccine formulation is effective in the presence of maternal antibodies, two approaches have been used clinically to address the problem: 1) the use of a high titer measles vaccine, and 2) determination of the earliest possible time point for successful vaccination. The high titer vaccine ($>10^{4.7}$ pfu) had a 10- to 50-fold higher viral titer than the standard vaccine and induced some level of protection after immunization in the presence of maternal antibodies (24, 25). However, the use of this vaccine was associated with increased mortality (26-28), attributed to immune suppression by the vaccine, and its use was discontinued. In a second approach, children were immunized at different times after birth (in the face of declining maternal antibodies). These studies have shown that a low level of maternal antibody correlates best with vaccination success and the complete disappearance of antibody at the age of 12 months seems to be optimal for immunization (20, 29-31). In agreement with these findings, immunization is suggested to be scheduled at the age of 12 months.

Mechanism of Inhibition of Vaccination by Maternal Antibodies

In order to experimentally address the question of MV immunization, two animal models can be used: the rhesus/cynomolgus macaque and the cotton rat. In mice and rats (even after transgenesis with human MV receptor molecules) MV does not replicate in the respiratory tract. Infection of macaques very closely simulates the disease seen in humans but has obvious disadvantages in terms of costs, outbred status of animals and limitations in the availability of reagents. Cotton rats have been used for studies of MV pathogenesis including studies of immune suppression and vaccination by a number of laboratories (for review see (32). In cotton rats, maternal IgG inhibits seroconversion after MV vaccination, thus providing a valuable model to study the underlying mechanism (33).

Three possible mechanisms have been postulated to explain the inhibition of vaccination by maternal antibodies: neutralization of the vaccine virus, epitope masking and B cell inhibition. Against the neutralization theory

speaks the fact that both inactivated and live-attenuated vaccines are inhibited by maternal antibodies. We have also shown in the cotton rat model that non-neutralizing antibodies block vaccination with a live-attenuated vaccine (34). The idea of epitope masking predicts that B cell epitopes on a vaccine will be covered by the antibody and therefore will not be recognized by B cells. In consequence, this effect is dependent on the concentration of antibody present in the circulation, and should be seen with both a complete IgG antibody and an IgG antibody lacking its constant region (so-called $F(ab)_2$ fragment). However, we could demonstrate experimentally that a number of antibodies at low concentration are more effective than one antibody at a high concentration in inhibiting vaccination and that only complete IgG antibody can block vaccination. The real mechanism of inhibition depends on complex formation of the vaccine with IgG antibodies (34). This complex cross-links the B cell receptor (which recognizes the vaccine) to the FcγIIB receptor (which binds the constant region of the IgG antibody) on the surface of B cells. The cross-link results in a negative signal which inhibits both the proliferation of B cells and the secretion of antibodies (Figure 1). In evolutionary terms, this mechanism developed to avoid an overshooting B cell response. If IgG antibodies are already present in an organism after infection or vaccination, it is not necessary to produce more antibodies. In essence, maternal antibodies signal that there is no need to produce more antibodies. In contrast to antibody production after an active immune response, however, the passively transferred maternal antibodies decline and the infant is left without an immune response.

After immunization, children often have IgG antibody levels similar to children with maternal antibodies. In contrast to the latter, however, they will generate additional antibodies after re-immunization. The increase is not twice the original level, and with increasing numbers of immunizations the increase in amount of antibody is getting smaller and smaller. This phenomenon can (at least partially) be explained by the presence of IgM which is being generated after active immunization. IgM forms a complex with the vaccine and a complement component (C3d). This complex cross-links the B cell receptor with the complement receptor 2 on the surface of B cells. The cross-link results in activation of B cells and can partially overcome the inhibition by the cross-link of the B cell receptor and CD32 (34). In consequence, some IgG antibody is produced. Another way to stimulate B cells experimentally is the induction of type I interferon. B cells use both the interferon receptor and CD21 (which is a chain of the complement receptor 2) as a functional interferon receptor to stimulate antibody secretion (35). Because of the dual receptor usage, the induction of type I interferon in vivo strongly stimulates B cell responses and restores antibody levels after immunization in the presence of maternal antibodies. In neonates, immunization is not only impaired by the inhibitory action of maternal antibodies, but also by the overall immature immune system. It could be demonstrated that type I interferon induction not only stimulates antibody responses in the presence of maternal antibodies but also stimulates immature B cells in neonatal cotton rats (36).

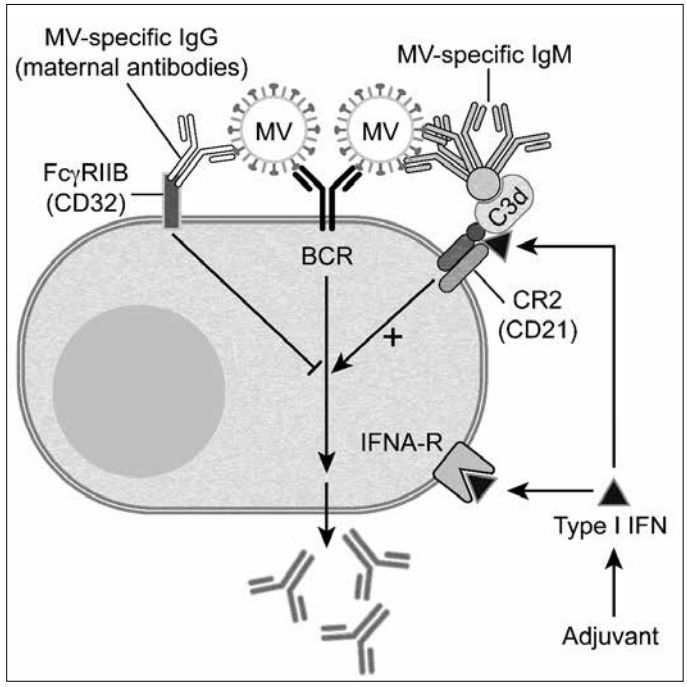

Figure 1. Model of B cell activation in the presence of maternal IgG
B cells are being activated by binding of the vaccine antigen (e.g. measles virus (MV)) to the B cell receptor (BCR) to secrete antibodies. Maternal antibodies (IgG) bind the vaccine virus and form a complex. This complex cross-links the FcγIIB receptor (FcγRIIB or CD32) with the BCR and inhibits B cell activation. IgM binds to the vaccine virus and complement protein C3d. This complex cross-links the BCR to the complement receptor 2 (CR 2) which contains the CD21 molecule. This cross-link leads to the activation of B cells with subsequent release of antibodies. Adjuvants with the ability to induce type I interferon activate B cells in the presence of maternal antibodies. Type I interferon is a very potent stimulator of B cells because it can bind and act through two receptors, interferon receptor (IFNA-R) and CD21.

What Is the Efficacy of Existing or Experimental Vaccines in the Presence of Maternal Antibodies?

A number of studies claim vaccine efficacy after immunization in the presence of maternal antibodies for both approved vaccines and vaccine candidates. To evaluate these studies, it is important to ensure that the following points were addressed. 1. Was the level of maternal antibodies determined in the test population? 2. Was the immunological response measured as a T cell response or as a B cell/antibody response? What measure of pro-

tection was used? A vaccine can most easily be proven to be successful if it is used in the presence of low titers of maternal antibodies, if T cell responses are measured and if surrogate markers like histological changes are used for protective efficacy. To prove the efficacy of vaccination in the presence of maternal antibodies convincingly, levels of maternal antibodies at the time of vaccination have to be high, neutralizing antibodies should be measured as immunological parameter and protection should be measured as the absence of clinical symptoms or significant reduction in viral/bacterial titers. By these standards very few examples of successful immunization in the presence of maternal antibodies exist.

What Is the Prospect for Developing Vaccines Effective in the Presence of Maternal Antibodies?

Progress in the development of vaccines effective in the presence of maternal antibodies seems to be possible through three different avenues. The use of time-release mechanisms should enable a vaccine to stimulate the immune system as maternal antibodies are being metabolized. Alternately, adjuvants with the ability to stimulate type I interferon secretion might be used. Over recent years, a number of new adjuvants has been approved worldwide which have novel features of immune stimulation including induction of type I interferon (37). Based on our studies, we would expect that some of these adjuvants will provide an advantage for vaccination in the presence of maternal antibodies. Last but not least, the use of peptide vaccines is a promising approach (38) although protection is relatively short-lived. The experimental success of these vaccines might be explained by a lack of cross-linking of B cell receptor and FcγRIIB due to the small size of the antigen.

What are the Consequences of These Studies for Immunization?

Clinically and experimentally, it has been shown that immunization in the presence of maternal antibodies fails to induce an appropriate B cell response. The good news, however, is that immunization in the presence of maternal antibodies has no negative effect on the immune system (e.g. induction of (unresoponsiveness of immune cells)). After the disappearance of maternal antibodies, the immune system is fully responsive to vaccination. Clinically, repeated immunizations offer the best chance to keep the window of opportunity for infection with small pathogens. Depending on the situation, it might be practical to vary the time point of the first immunization depending on the level of maternal antibodies present in the population and the risk of infection by a particular pathogen. Immunization early in life is particularly promising if protection depends on T cell responses rather than the generation of neutralizing antibodies (e.g. hepatitis B virus). Another concept which is seriously discussed is the immunization of mothers to induce high levels of maternal antibodies which, in areas with high infection pressure, will prolong protection of the neonate/infant and allows the child's immune system to mature.

Conflict of Interest
No conflict of interest was declared by the author.

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