

Sidestepping maternal antibody: a lesson from measles virus vaccination

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A fundamental unresolved issue in vaccinology is the inhibition of vaccination against infectious diseases of humans and animals by maternal antibodies. To understand this issue, 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 wild-type virus infection (for review [1]). However, even these low nonprotective antibody titers inhibit the generation of neutralizing antibodies by B cells, although a MV-specific T-cell response is induced [2]. In MV infection, CD8⁺ T cells help to clear virus-infected cells but do not protect against infection [3]. CD4⁺ T cells have no role in protecting or clearing virus from the respiratory tract [4]. Owing to the inhibition of antibody generation after immunization in the presence of maternal antibodies, only seronegative children can be successfully immunized (reviewed in [5]). Since no current measles vaccine formulation is effective in the presence of maternal antibodies, two approaches have been used clinically to address the problem: the use of a high titer measles vaccine, and determining the earliest time point possible for successful vaccination. The high titer vaccine ($>10^{4.7}$ pfu) had a 10–50-fold higher viral titer than the standard vaccine and induced some level of protection after

immunization in the presence of maternal antibodies [6,7]. However, the use of this vaccine was associated with increased mortality [8–10], 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 demonstrated that low levels of maternal antibody correlates best with vaccination success and the complete disappearance of antibody at the age of 12 months appears to be optimal for immunization [2,11–13]. In agreement with these findings, immunization is suggested to be scheduled at the age of 12 months. However, given the fact that many children in Africa and parts of Asia are exposed to infection prior to 12 months of age, immunization is not able to close this window of susceptibility.

Mechanism of inhibition by maternal antibodies

Although the inhibition of vaccination by maternal IgG antibodies in medicine and veterinary medicine has been known for a long time, no effective vaccination strategy could be developed because the underlying mechanism was not understood. In the absence of experimental data, it has been assumed that epitope masking (i.e., blocking of epitope recognition by B cells due to maternal antibody) is the mechanism responsible for inhibition of vaccination by maternal antibodies [14]. This assumption was based on data from antibody feedback

mechanism studies in which sheep red blood cell-specific IgG antibodies inhibit the B-cell response against sheep red blood cell (for review see [15]). As a consequence, the only possible intervention would be to increase the amount of vaccine in order to saturate existing antibody. This solution appears to be impossible to achieve in the presence of high levels of maternal antibody and an increase in vaccine dose would probably be harmful (as in the case of measles vaccination [8–10]). Using the cotton rat model of MV vaccination [16], we have now established that inhibition by maternal antibody is due to cross-linking of the B-cell receptor (BCR) and FcγIIB receptor by a measles virus–antibody (IgG) complex [17]. Thus, maternal antibodies trigger a regulatory mechanism of B-cell responses similar to that used by IgG antibodies after active immunization. Biologically, limited generation of antibodies in the presence of already existing antibodies is a means to avoid an overshooting antibody response. However, in the case of maternal antibodies, passively transferred maternal antibodies are being metabolized and the organism is left with no antibodies. In order to improve immunization, the balance between inhibitory maternal antibody and stimulatory signals needs to be shifted towards activation of B cells and the secretion of neutralizing antibodies.

Improving vaccination in the presence of maternal antibodies

B-cell responses are thought to be activated by a three-signal sequence: interaction of BCR with antigen (first signal), interaction with T cells through CD40–CD40 ligand (second signal) and soluble mediators (e.g., IL-6, type I interferon; third signal). MV-specific T cells (second signal) are easily detectable in humans and cotton rats after immunization in the presence of maternal antibodies. Experimentally, the stimulation of the first signal can be improved by cross-linking BCR to complement receptor 2 through an MV–IgM–C3d complement protein complex. In an enzyme-linked immunosorbent spot assay, MV-specific IgM stimulates B cells to secrete antibody even in the presence of inhibitory IgG. After coimmunization of MV vaccine and a monoclonal

IgM antibody specific for MV hemagglutinin in the presence of maternal antibodies, neutralizing antibodies were restored to approximately 20–40% of antibody levels after immunization in the absence of maternal antibodies [17]. Another approach has focused on the induction of a third signal because MV vaccine virus does not induce type I interferon secretion by dendritic cells in tissue culture, or in the bronchoalveolar lavage in cotton rats [18]. If MV hemagglutinin is expressed by a Newcastle disease virus vector which induces IFN-α secretion *in vitro* and *in vivo*, the neutralizing antibody response can be partially restored after immunization in the presence of maternal IgG [18].

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Although these studies did not lead to complete restoration of the immune response, the approach to focus on first and third signals of B-cell activation provides us with a conceptual framework for the rational development of vaccines in the presence of maternal antibodies. Improvements in vaccination in the presence of maternal antibodies will have direct relevance for measles vaccination, but also for the use of numerous vaccines for which maternal antibody interference has been documented.

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