Influence of Maternal Antibodies on Early-Life Antibody Responses

It has long been recognized that residual maternal IgG antibodies (MatAb) passively transferred during gestation may inhibit infant vaccine responses to measles and oral poliomyelitis vaccines, and more recently that they may also affect responses to non-live vaccines (reviewed in Ref. 14). The main determinant of MatAb-mediated inhibition of antibody responses was identified as the titer of MatAb present at the time of immunization, or rather as the ratio between vaccine antigen and MatAb (30–32). Indeed, reducing MatAb titer at time of immunization or enhancing the dose of vaccine antigen may both circumvent the inhibition of infant antibody responses in human and murine infants. This is best explained by the fact that following introduction of a vaccine antigen into a host with preexisting passive antibodies, MatAb readily bind to specific B cell vaccine epitopes, preventing access of infant B cells to the same determinants. If the vaccine antigen/MatAb ratio is low, this prevents access of infant B cells to B-cell epitopes, and therefore inhibits their differentiation into antibody-secreting cells. At a higher ratio, some B-cell epitopes may remain unmasked by MatAb, and thus available for binding by infant B cells and priming of B-cell responses. Thus, strategies to circumvent MatAb inhibition of vaccine antibody responses currently mainly include delayed vaccine administration, awaiting decline of MatAb or use of higher vaccine doses. Whether slow-release vaccines or certain delivery systems could better shield B-cell epitopes from MatAb is an interesting possibility, which awaits confirmation. In theory, mucosal vaccines should prove better able at escaping from MatAb inhibition, as concentrations of MatAb reaching infant mucosae are significantly lower than those reaching their serum. However, this may only be the case for immune responses elicited directly at the mucosal surface and not into the draining lymph nodes where MatAb concentration is higher.

Perspectives for Enhancing Early-Life Antibody Responses

In neonatal and infant murine models of immunization, certain adjuvant formulations are able to significantly enhance early-life vaccine responses, whereas others fail to do so despite their strong adjuvanticity in adult animals (reviewed in Ref. 14). In infants, coadministration of BCG at time of neonatal hepatitis B immunization strongly enhanced (50-fold) HBsAg antibody titers after the third vaccine dose compared with control infants (33), an influence likely to reflect the known maturation influence exerted by BCG on dendritic cells (DCs). Enhancing DC/T cells/B cells interaction, for example, through adjuvantation, may thus have a positive influence on the magnitude of antibody responses elicited in neonates. Whether this will enhance responses to the first vaccine dose remains to be tested. Indeed, observations gathered with a large panel of adjuvants in murine models (reviewed in Ref. 34) suggest that some limiting factors may not be corrected by enhanced DC/T cells/B cells activation.

Novel antigen delivery systems, such as DNA vaccines, have not yet been tested in human neonates but were extensively studied in neonatal animal models. DNA vaccines induced similar antibody responses in newborn and adult mice (reviewed in Ref. 34) but failed to induce stronger early-life antibody responses than those elicited by conventional protein/, subunit, or live attenuated vaccines. Accordingly, DNA immunization of newborn or infant nonhuman primates against hepatitis B, HIV, or influenza also resulted in weak antibody responses (35), and sequential bleeding indicated lack of antibody responses prior to four or eight weeks of age, after two or three vaccine doses (36). Thus, vaccine formulations/delivery systems capable of rapidly inducing strong antibody responses in early life have not yet been identified. This calls for a better understanding of the limiting factors, so that strategies can be designed to circumvent them. Indeed, although early priming–later boosting strategies are currently the most promising for enhancing early-life antibody responses, the time required for completion of such strategies is likely to be a limiting factor against pathogens for which exposure occurs very early in life. Alternative strategies include maternal immunization, as recently demonstrated efficient against infant influenza (37).

CHALLENGES TO THE INDUCTION OF STRONG T-CELL RESPONSES IN EARLY LIFE

Characteristics of Early-Life $CD4^+$ and $CD8^+$ T-Cell Responses

In contrast to the slow maturation of antibody responses, acquisition of antigen-specific T-cell responses is an early event. The age-dependent maturation and differentiation of Th1 (IFN-γ secreting) and Th2 (IL-4, IL-5, IL-13 secreting) T-cell responses is, however, yet poorly characterized (Table 1). T-cell proliferative responses following BCG were stronger when administration was delayed from birth until two to six months of age in some studies, whereas adultlike IFN-γ responses to neonatal BCG were reported in The Gambia (38). In contrast, Gambian infants showed defective IFN-γ responses during the primary phase of the response to oral polio vaccine (39), as compared to adults. Analyses of T-cell responses to measles and mumps vaccines indicated similar antigen-specific T-cell proliferative and IFN-γ responses in infants immunized at 6, 9, or 12 months of age, but lower infant responses than those of adult controls (13,40). Infant T cells also showed a limited capacity to increase their IFN-γ release in response to IL-12 supplementation (40), which required both IL-12 and IL-15 (41). BCG vaccination of human newborns induces T cells with complex cytokine and phenotypic profiles (42), and CD154 is not expressed at adult levels prior to the second year of life (43). A limitation of these MMR/OPV/BCG studies is that they cannot include previously unprimed naive adult controls. To precisely define the influence of immune immaturity on T cell differentiation thus awaits additional clinical evidence.

Little is yet known of the maturation of human infant $CD8^+$ cytotoxic T lymphocyte (CTL) responses. Although infection-induced CTLs may be detected within the first weeks of life, CTL responses could also be age and vaccine dependent (44–46). As an example, CTLs were recovered in infants following influenza infection, but not following immunization with a live influenza vaccine, suggesting that a certain immunogenicity threshold had only been reached in infected infants (45). Thus, it seemed likely that the maturation of $CD8^+$ cytotoxic responses will prove age- and vaccine type–dependent in human as in mice, as supported by recent studies (47,48).

Which Are the Factors Limiting Early-Life T-Cell Responses?

Studies assessing the determinants of early-life T-cell responses were long limited to murine models of early-life immunization. They indicated that antigen-specific T-cell responses may be