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Commentary

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Functionally mature virus-specific CD8$^+$ T memory cells in congenitally infected newborns: proof of principle for neonatal vaccination?

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The presence in newborns of a mature and functional CD8$^+$ T cell response to congenital cytomegalovirus infection (see related article beginning on page 1747) suggests that the machinery necessary to prime such responses is present in utero and raises questions related to neonatal vaccination.

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In this issue of the *JCI*, Marchant et al. (1) report the presence of functionally mature cytolytic CD8$^+$ T lymphocytes in newborns with congenital cytomegalovirus (HCMV) infection. This finding adds to the growing body of evidence suggesting that intrauterine antigenic stimulation has the potential to elicit protective immunity in the fetus, which persists into the newborn period. This has important implications in relation to infant vaccine development, but significant questions remain to be answered before this potential can be fruitfully exploited.

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Nonstandard abbreviations used: human cytomegalovirus (HCMV); respiratory syncytial virus (RSV).

Susceptibility to infectious disease during infancy

Increased susceptibility to infectious diseases is an inescapable fact of neonatal life and is generally ascribed to developmentally related deficiencies in immune function, which are incompletely understood. Recent advances in developmental immunology have provided fresh insight into this issue. Of particular relevance are studies investigating the mechanisms that facilitate fetal survival in the face of continuous maternal immune surveillance. This body of research (reviewed in ref. 2) has demonstrated that Th1-type cytokines (especially IFN-γ) are exquisitely toxic to the placenta, and their release at the fetomaternal interface, triggered by antiallograft or antimicrobial responses, is an important cause of premature termination of pregnancy (2, 3).

In the face of these challenges to fetal survival, evolution has fashioned a range of overlapping control mechanisms to regulate expression of immunity at the fetomaternal interface. The most potent of these involve local placental production of tryptophan metabolites (4) and IL-10 (5), which inhibit T cell activation and proliferation, and expression of FasL, which eliminates activated T cells (6). A second tier of immunomodulatory mechanisms selectively dampens Th1 immunity via local production of a range of molecules that are Th2 trophic and/or Th1 inhibitory. These include production by placental trophoblasts of IL-10 and prostaglandin E2, which drive Th2 switching (5, 7), and progesterone, which inhibits IFN-γ gene transcription (8). Collectively, these mechanisms attenuate fetal capacity to develop active immunity and bias any responses that escape immunosuppression toward the Th2 phenotype.

Survival in the microbiologically hostile postnatal environment necessitates upregulation of immune (in particular Th1) functions, which is mediated via microbial pattern recognition receptors (9). However, the postnatal maturation of Th1 competence proceeds relatively slowly between birth and weaning, and this appears to underlie the generally attenuated capacity of infants to efficiently generate CD4$^+$ T cell memory to antigens in or on pathogens and in response to vaccines (10, 11). This may be attributable in part to deficient production of IL-12 (12), which is required for stabilization of the IFN-γ transcriptional machinery in T cells (13), and also to hypermethylation of the promoter of the IFN-γ gene in neonatal CD4$^+$ T cells, which directly inhibits transcription (14). Moreover, recent studies indicate that ≥90% of circulating CD4$^+$ CD45RO$^-$ naive T cells in neonates are

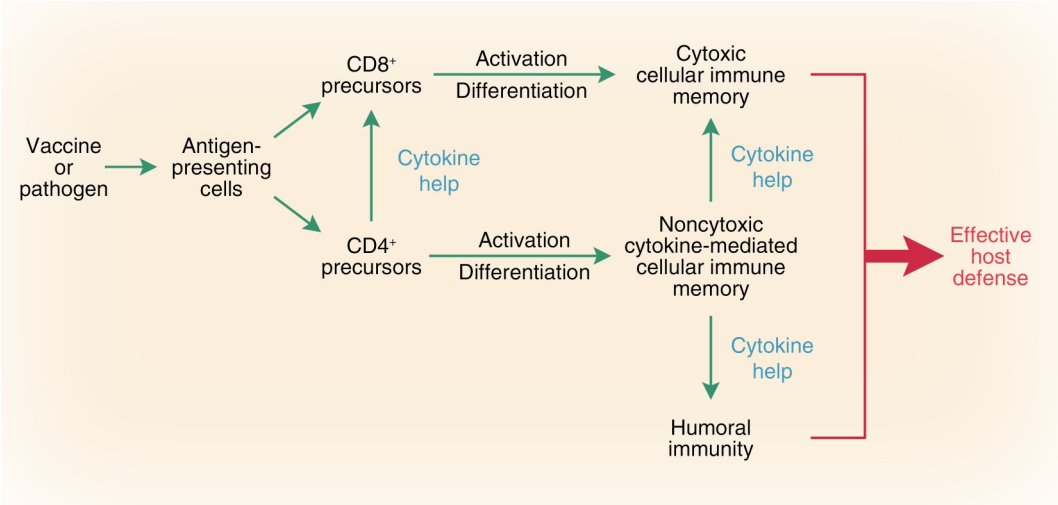

Figure 1
The central role of CD4+ T cell "help" in the development of acquired resistance to pathogens.

functionally immature recent thymic emigrants (15). In comparison to adult naive CD4+ T cells, these neonatal cells are deficient in activation-associated intracellular signalling and require higher levels of costimulation to achieve maximal activation.

The functional status of CD8+ T cells in neonates is less well characterized. While the diminished resistance of neonates to viral infections is widely interpreted as a deficiency in cytolytic CD8+ T effectors, there is little functional data upon which to draw. Indeed, limiting dilution studies indicate that unlike the situation for CD4+ Th cells, the precursor frequency of CD8+ cytolytic T cells in neonates is comparable to that in adults (16). Moreover, our recent studies on the IFN-γ promoter indicate that the hypermethylation characteristic of neonatal CD4+ T cells is not mirrored in CD8+ cells, and this is reflected in much higher neonatal CD8+ IFN-γ responses (14). These findings collectively suggest that the developmental constraints on expression of Th1-associated functions may be targeted principally at CD4+ Th cells, potentially preserving capacity for expression of efficient CD8+ effector function during infancy, at least in primary responses. In this context, the demonstration of functionally mature neonatal CD8+ cytotoxic responses is not restricted to congenital HCMV and has also been documented in infants during primary infections with respiratory syncytial virus (RSV) (17); however, the situation with respect to the stability of these putative CD8+ T memory responses is unclear. In this regard, it is noteworthy that, as illustrated in Figure 1, cytokine "help" from CD4+ T cells plays an essential role in promoting the activation and terminal differentiation of CD8+ T cell precursors and in reactivation of CD8+ memory cells. Hence the attenuation of CD4+ T cell function in infancy discussed above may be a significant factor in determining the overall efficiency of expression of CD8+-dependent T cell immunity during this life phase.

The intriguing findings reported by Marchant et al. (1) add an additional dimension to this discussion. The authors report the presence of mature CD8+ HCMV–specific T memory cells in congenitally infected newborns, indicating that under appropriate conditions of stimulation, any underlying developmental deficiencies intrinsic to the fetal T cell compartment, which potentially limit CD8+ T cell memory development, can be overcome. Moreover, this is not restricted to HCMV, as newborns with congenital *Trypanosoma cruzi* infection also develop potent CD8+ T cell memory responses (18). This may reflect a situation similar to that described above for neonatal CD4+ T cells, which require very high levels of stimulation to achieve optimal activation but express vigorous activity once the stimulation threshold is achieved. In the case of congenital HCMV, a feature of the disease is persistent viral excretion, which corresponds to prolonged antigen exposure, as opposed to transient exposure in the case of viruses such as RSV. The presence of mature CD8+ T memory cells implies that this prolonged HCMV exposure provides sufficiently intense stimulation to elicit not only acute CD8+ T cell activation but also activation of the CD4+ Th cells that are required to provide cytokine help for differentiation of CD8+ primary effectors into long-lived memory cells.

Protection of infants via neonatal vaccination

Infectious diseases represent the major cause of infant mortality internationally, and vaccines that are effective in the high-risk period of the first three to six months of life remain an increasingly urgent unmet need. It is becoming clear that a series of partially defined developmental factors associated with late-stage maturation of immune function constitute the basis for the poor performance of conventional vaccines in neonates. However, it is not clear which of these factors are truly rate limiting and which represent epiphenomena. The report by Marchant et al. (1) describes an "experiment of nature" in which the developmental constraints that limit virus-specific Th memory development are overcome as a result of intrauterine infection. More detailed definition of the immune response to congenital HCMV may resolve many of the outstanding mechanistic questions relating to priming of protective immunity during the neonatal period.

In this context, one of the most rapidly growing areas of research in vaccinology is maternal immunization, aimed at transplacental protection via maternal antibodies. The report by Marchant (1) suggests that under appropriate conditions of prenatal stimulation, this protective net can potentially be broadened to include the generation of protective cellular immunity in the neonate. Further research into the underlying mechanism(s) of prenatal T cell priming in this and other congenital infections may provide important new clues to guide the development of safe vaccines that aim to achieve a comparable end.

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New insights into a persistent problem — chlamydial infections

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Tissue tropism of clinical ocular and genital *Chlamydia trachomatis* strains is shown to be linked to the tryptophan synthase genotype (see related article beginning on page 1757). It is suggested that, in the presence of IFN-γ, which depletes available tryptophan, there exist unique host-parasite interactions that may contribute to persistent chlamydial infection.

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Chlamydial infections are noted for the broad array of clinically distinct manifestations that they produce, ranging from acute self-limiting ocular and genital infections to chronic inflammatory diseases that result in blindness or infertility. Trachoma, an ocular infection, is caused by *Chlamydia trachomatis* serovars A–C and is a primary cause of preventable blindness. The majority of *C. trachomatis* serovars (D–K) cause urogenital infection, which can progress to serious genital tract disease in men and women. A genetic basis for the remarkable tissue tropism of the various chlamydial serovars (i.e., ocular vs. urogenital strains) was first proposed by Fehlner-Gardiner et al., based upon their analysis of the tryptophan synthase gene cluster (*trp*RBA) of laboratory strains of chlamydiae (1). They found that the tryptophan synthase genotype is closely linked to the tissue tropism of ocular and genital chlamydial strains; urogenital serovars possess a functional tryptophan synthase and are capable of utilizing indole as a substrate for tryptophan synthesis, whereas ocular isolates possess a nonfunctional tryptophan synthase. In this issue of the *JCI*, Caldwell et al. have extended that earlier work to include the characterization of tryptophan synthase genes from hundreds of clinical isolates, thereby confirming the correlation between chlamydial tryptophan synthase genotype and tissue tropism (2).

Between the extremes of acute self-limiting infection and chronic inflammatory disease lies the notion of persistent and/or chronic states of chlamydial infection. Cell culture systems have been used for a number of years to demonstrate and study chlamydial persistence in vitro (3). However, the experimental documentation of persistent infection in the human host and of the mechanisms of in vivo persistence has been a much greater challenge. A particularly intriguing hypothesis put forth by the authors is that tryptophan synthase genes function as chlamydial virulence factors and may be involved in the maintenance of persistent/chronic chlamydial infection. That hypoth-

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Nonstandard abbreviations used: elementary body (EB); reticulate body (RB); indoleamine 2,3-dioxygenase (IDO).