

Effect of Commensal and Pathogenic Bacteria on Programming of Neonatal Immune Response

Susanna Cunningham-Rundles, PhD
Weill Cornell Medical College, New York, New York 10065 USA
212 746 3414
scrundle@med.cornell.edu

The newborn infant encounters environmental antigens and colonizing microorganisms at a time when immune responses are still shaped by fetal life. Until recently infant susceptibility to infectious disease and propensity to allergies in early childhood was largely attributed to intrinsic developmental programming. Neonates were considered immune deficient compared to adults in having delayed and weaker B cell antibody responses, absence of memory T cells, low T cell helper type-1 (Th-1) cytokine responses, interleukin-2 (IL-2) and gamma interferon (IFN gamma), and dominant expression of T cell helper type-2 (Th-2) cytokines (IL-4, IL-13). Emerging studies now reveal a much high degree of T cell variability among human infants of the same gestational age than previously appreciated and have challenged this picture. T cell functional heterogeneity is an important source of individuated response and also reflects different conditions of antigen exposure. The influence of congenital infections such as HIV on developing T cell responses has been demonstrated. Much less is known about how HIV+ infants respond to commensal colonizing organisms and whether this exposure might have an immune modulatory effect. We have observed that administration of a probiotic bacteria influenced growth and immune development in children with HIV associated failure- to-thrive. Both nutrient and non-nutrient dietary immune modifiers exert strong regulatory effects on host microbial interactions. Enteric micronutrients derived from diet include minerals, vitamins, nucleotides and gangliosides, protein and non-protein N-containing compounds, lipids, carbohydrates, non-nutritional dietary compounds (flavonoids, carotenoids, phytoestrogens), and also substances such as oligo-saccharides and glycoconjugates. All influence colonization and establishment of the microbial ecosystem. The western style high fat diet with an increased proportion of omega-6 compared to omega -3 fatty acids has affected both the composition of the human microbiota and appears linked to an increase in inflammatory diseases. Neonatal response to potential microbial pathogens or bacterial lipopolysaccharide (LPS), the main component of the outer membrane of gram-negative bacteria, has impact on both the programming of immune response and brain development. We and others have observed that neonates do not upregulate TLR-4 as efficiently or as much as adults in response to LPS. Furthermore mode of delivery affects the pattern of cytokine responses to LPS at birth. Neonates appear to have a reduced compensatory anti-inflammatory response and therefore may be at greater risk for inflammatory damage. We reported that neonatal cytokine responses to physiological whole cell bacteria is regulated in a species-specific manner and has a tendency towards an uncompensated pro-inflammatory response. Although a lower percentage of neonatal monocytes produced cytokine responses to microbes than adults, the levels of some cytokines, specifically IL-6 and IL-8 secreted in response to the same microbes was actually higher. While T cell cytokine responses to microbes were remarkably similar among adults, the intracellular cytokine response of neonatal T cells to microbial activators was marked by wide individual variability especially in pre term infants. Introduction of omega-3 fatty acids into immune cell membranes prior to exposure to microbial activators, reduced cytokine response. Studies suggest that neonatal response to the specific bacterial components shapes immune response in early life according to gestational age, mode of delivery, micronutrient status and genetic factors, and is likely to affect the evolving pattern of microbial colonization. The implications may be particularly significant for infants struggling with congenital infection or exposed to enteric pathogens.