

Immunity in the Very Young: Challenges and Opportunities

Immunity in early life encompasses the delicate interphase at the maternal-fetal stage, as well as rapid development and adaptation that occur as the newborn transitions from the protected maternal environment to functioning in the outside world. Understanding the forces that shape immunity in the very young and that lay the groundwork for an effective adult immune system holds both questions and promise.

Vaccines for Immune Training



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Newborns have a developing immune system and face a high risk of infections, particularly in low-income countries where neonatal mortality remains high. BCG vaccine is recommended at birth to protect newborns against tuberculosis. Typically, BCG vaccination occurs at 6 weeks of age in low-weight newborns. Recent trials have shown that providing BCG vaccine at birth is associated with reductions in all-cause mortality; in a combined analysis of three trials in low-weight neonates, receiving BCG at birth was associated with a 38% reduction in neonatal mortality. Likewise, receiving oral polio vaccine within the first 2 days of life is associated with a 42% reduction in all-cause mortality. These effects are not explained by prevention of tuberculosis or polio; these infections very rarely kill neonates. Rather, these live vaccines broadly stimulate the neonatal immune system, fostering protection to other infectious challenges. In addition to promoting pathogen-specific immunity, these vaccines have beneficial non-specific effects. BCG challenge trains innate immune cells, increasing pro-inflammatory responses towards unrelated pathogens. Indeed, exposure to BCG was associated with reduced viremia after a yellow fever challenge. There is evidence that innate immune training occurs via epigenetic modifications, but the cellular and molecular mechanisms that underpin the beneficial immunity associated with early vaccination in the first days of life remain undefined. Intriguingly, the protective effects of early BCG vaccination are strongest in males, suggesting gender-specific differences in early life immunity. Understanding the biology that underlies these differences will be important in developing strategies to strengthen the general immunological competence of newborn boys and girls.

Right for the Time and Place



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Intriguing differences exist between cells and tissues of the neonate and the adult, and these differences are expected to significantly influence cell and organ function. Many of these differences suggest a less well-developed, immature phenotype in line with the myriad developmental processes that occur in the fetus and that continue, in part, after birth. Neonatal metabolism is unstable, and the immune system is less efficient in resolving infectious challenges. Yet, we should not forget that birth represents the single most dramatic transition that we experience during life. The newborn transits from the protected and supported situation *in utero* to an environmentally exposed, autonomous life. Within minutes, it has to cope with dramatic changes in blood circulation, the start of respiration and pulmonary gas exchange, and the requirement for an autonomous metabolic regulation. What if some neonate-specific features do not reflect developmental immaturity, but rather adaptation to this transition? Consider the context of the postnatal exposure to microorganisms. Clearly, the neonate's immune system has to be able to combat pathogens. On the other hand, it has to tolerate the rapid establishment of a dense and diverse enteric microbiota. Moreover, evidence suggests that microbial colonization guides immune development and the setting of the adult immune landscape, suggesting a complex interplay in early life. Thus, the neonatal immune system threads a thin line between response and tolerance. Investigating neonatal immunity with the mindset that many aspects of its cells and organ tissues might just be perfectly adapted to this delicate challenge will be revealing.

Elementary Education



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How the developing immune system integrates external cues with internal genetic programs to establish a baseline of immunity is unclear. Developmental plasticity may not only alter the penetrance of inborn errors in immunity, but could also have a significant impact on immune function early in life. Exploring this dimension of development from the lens of immunity is also necessary for linking early immune alterations to long-term health outcomes; for instance, susceptibility to inflammatory diseases that can be traced to early childhood perturbations. Developing faithful models to examine the impact of the environmental culprits uncovered by epidemiological studies on immune activity is essential. External influences may exert themselves at many distinct stages, including at the level of hematopoietic stem and progenitor cells (HSPCs), as well as in differentiated immune cells that seed tissues early in life. Owing to their longevity, alterations to HSPCs are of particular interest as they may have lasting consequences for health and disease. Indeed, inflammatory signals are known to epigenetically and metabolically entrain tissue stem cells, which pass along this memory to their progeny, consequently dictating their function. Environmentally dictated developmental alterations to HSPCs may be adaptive; for instance by setting lower threshold of activation to drive anti-pathogen responses. On the hand, these same features could be hijacked to promote autoimmune pathologies. Understanding whether and how such "education" takes place during development and the extra-genetic factors involved will illuminate the shaping of the immune system early in life and provide strategies to functionally tune immunity in young and old alike.



Shaping Immunity In Utero

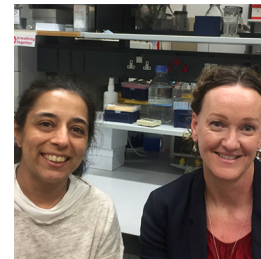
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Our current appreciation that the human immune system is shaped by events that occur during its development in utero provides new opportunities for promoting immunity in the very young. For example, it is now clear that the developing immune system will only be able to attain its genetically determined potential in the presence of good maternal nutrition and the absence of obstetrical complications such as intrauterine growth restriction and preterm delivery. But the expected efficacy of such preventative measures in turn suggests that the fetal immune system could be further bolstered by more direct interventions. These interventions would complement the passive immunity provided by maternal antibodies but would also foster a newborn's ability to actively mount its own defenses. Accordingly, what aspects of immune system development should we target to best protect against the pathogens of early childhood? How would this be accomplished without risking allergic or autoimmune predisposition in later life? And can we stimulate the fetal immune system without provoking adverse maternal immune reactions that themselves might cause obstetrical complications? Unfortunately, given that the murine immune system develops much later than the human immune system (relative to birth timing), experiments in mice might be unable to answer these questions despite the mouse having admirably modeled the human immune system in so many other ways. We may need other model organisms to investigate this critical aspect of human immunity.

All Neuro-Immune Connections

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Understanding how the maternal immune system changes during pregnancy and how it affects the developing offspring's nervous system and immune system are relatively unexplored areas of research. New studies in this field have ignited key questions. For instance, how does the maternal gut microbiota change during pregnancy and what is the impact of these changes on the maternal immune system and vice versa? In turn, how do these changes affect the immune system and early bacterial colonization in the intestines of newborns? Studies have suggested that the placental/trophoblast barrier acts as a selective gateway for the exchange of maternally derived, life-supporting molecules, while preventing the transfer of harmful maternal immune cells and cytokines. However, the mechanisms underlying this selectivity and, more broadly, the tolerance program that is deployed to protect an immunologically distinct fetus from the maternal immune response are not well understood. Furthermore, maternal inflammation during pregnancy affects fetal brain development and behavior; the mechanisms underlying these effects are only beginning to be unraveled. Beyond this, how maternal immunity relates to normal neurological development in the fetus is unclear. Making inroads into these questions will require identifying the cells and tissues in both mother and fetus that mediate these interactions, as well as the relevant bacterial strains, and will involve leveraging tools such as single-cell RNA sequencing and gnotobiotic mice. Understanding the basis for how the maternal microbiota, maternal immunity system, and the development of the neuro-immune system interact during pregnancy may lead to the identification of immunomodulatory mechanisms with potentially translatable clinical implications.

Every Little Breath

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Respiratory diseases are common in children and although for the majority they do not present as a clinical problem, a significant proportion develop wheeze following exposure to common viruses. All babies will encounter respiratory viruses, but only approximately a third will wheeze when infected, and only a proportion of these will go on to develop asthma at school age. However, we cannot predict which babies will wheeze or which will progress to asthma, nor do we have any interventions to prevent progression. This is important because asthma is predominantly a childhood onset disease and affects over 300 million people worldwide. Asthmatic children have significant deficits in lung function by age 6 years, which are sustained into adulthood. The first 6 years of life are therefore critical in determining adult lung function. Although interactions between structural airway abnormalities, infantile viral and bacterial infections, and atopy/allergy are key influences, it is vital to gain a greater understanding of roles played by the immune cells within the pulmonary environment during early life, and determine how these maintain a balance between promoting tolerance to environmental antigens and commensal bacteria, and mounting rapid immune responses to pathogens. The mechanisms that enable tolerance must be in place early on, as post-natal colonization with commensal bacterial begins with a neonate's first breath; what these tolerance mechanisms are and how they change as children age is unclear. For us to make a step change, we must recognize age as a key influence on disease mechanisms and translate in vivo findings into pediatric cohorts.