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COMMENTARY

Ready to benefit from training: heterologous effects of early life immunization

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Trained immunity reflects the ability of the innate immune system to adapt via epigenetic changes in monocytes, enhancing responses to a range of microbes, thereby potentially reducing infection in high-risk populations. Examples of trained immunity at birth include enhanced resistance to infection in TLR-simulated newborn mice, reduced risk of late onset sepsis with histologic chorioamnionitis and beneficial heterologous effects of neonatal bacille Calmette-Guérin administration in reducing diverse infections during infancy. Future efforts will assess leveraging trained immunity in early life by administering 'stand-alone' innate immune stimuli or (self-)adjuvanted vaccines to protect against a broad range of infections.

Keywords: Heterologous immunity, Infant, Newborn, Non-specific effect, Trained immunity, Vaccine

Approximately 2 million infants less than 6 months of age die every year due to infections.[1] In this context, early life immunization is attractive because: 1. many infections effect infants and thus reducing these infections requires intervention before this point in life, and 2. worldwide birth is a reliable point of healthcare contact such that vaccines given at birth tend to reach a large proportion of the population. However, the high susceptibility to infection in early life is partially due to distinct immunity, including suppressive soluble (plasma) and cellular factors,[2,3] which also result in sub-optimal vaccine responses.[4] Thus, while the neonatal immune system is adapted to early life needs, including avoidance of over-exuberant responses to initial colonization with the microbiome, it is distinct from the later in childhood and adulthood immunity. There is subsequent age-dependent maturation of immunity over the first years of life.[4]

A number of approaches suggest that safe and effective immunization at birth is possible despite distinct neonatal immunity. A key example of this approach is the administration of bacille Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, which is given at birth to reduce the risk of disseminated TB in infancy in TB-endemic countries.[5] It is the most commonly given vaccine worldwide and is part of the Expanded Program on Immunization. Because BCG is a live, whole microbe vaccine, it is 'self'- adjuvanted and activates multiple pattern recognition receptors, including Toll-like receptors (TLRs).

In addition to the example of the self-adjuvanted vaccine BCG, a number of novel candidate adjuvants have been identified as potentially active in early life by in vitro screening, such as TLR7/8 agonists.[6] In newborn mice, prior administration of a TLR7/8 agonist enhances innate cytokine and phagocytic responses to subsequent (24 hours later) polymicrobial peritonitis, reducing infection-induced mortality.[7] Moreover, in humans, histologic chorioamnionitis is associated with a lower risk of late onset sepsis due to coagulase-negative staphylococci and other bacteria,[8] suggesting that early inflammation/innate immune activation enhances host defense and reduces subsequent infection.

Against a backdrop of an unmet need for improved early life immunization and the potential of vaccine adjuvantation approaches, a recent development in immunology may offer yet another path to protect newborns. It has recently been appreciated that in addition to classic T and B cell memory, innate immunity also has the capacity for adaptive characteristics and memory, a phenomenon referred to as trained immunity, which is mediated via epigenetic changes (i.e., non-genetic modification of gene expression) to innate immune cells such as monocytes.[9] Thus, prior exposure to innate immune stimuli (e.g., self-adjuvanted vaccine or microbe) may enhance innate immunity by modifying gene expression thereby changing, and in particular enhancing, the set point of innate immune cells. Protection against reinfection is dependent on typical innate immune host response mechanisms such as macrophages.

A key example of trained immunity is the growing realization that vaccination with BCG protects mice not only against mycobacteria, but also against antigenically unrelated infections such as *Listeria monocytogenes*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Candida albicans* or *Schistosoma mansoni*.[10] In mice, BCG-induced epigenetic reprogramming of monocytes leads to

heightened function and protection against a broad range of infections in a tissue macrophage-dependent and T cell-independent manner conferring heterologous protective immunity. In adult humans, BCG administration is associated with enhanced monocyte expression of TLRs and increased innate cytokine responses to a range of bacteria and fungi.[10] Clinical studies in West Africa (Guinea-Bissau) demonstrate correlations between BCG administration to low birth weight newborns and decreased risk of non-TB infections, apparently resulting in decreased overall infant mortality.[11] BCG-induced epigenetic reprogramming of monocytes and other innate cells is thus a key feature of innate immune memory and is likely to be important after certain infections or certain self-adjuvanted vaccines, such as live attenuated vaccines. For example, a recent large retrospective study of the potential heterologous beneficial effects of measles mumps rubella immunization is associated with reduced risk of subsequent hospitalization with any infection.[12]

Growing understanding of immune ontogeny[4] coupled with the realization that a live attenuated self-adjuvanted vaccine can result in heterologous protection and clinical benefit[9,11] suggest that trained immunity may be leveraged to develop new approaches to reduce early life infection. Key areas for future investigation will include: 1. defining an optimal timeframe for early life heterologous immunization and induction of optimal epigenetic changes, taking into consideration immune ontogeny, and 2. defining the duration of beneficial heterologous effects, including their potential dependence on the continued viability in vivo of live attenuated vaccine strains. Overall, much remains to be learned regarding trained immunity, its underlying mechanisms, the range of stimuli that optimally induce it and any potential side effects its activation may produce. Moreover, as with all drug development, and particularly in the context of an agent (i.e., a vaccine to be given to young, healthy individuals) a large emphasis will appropriately be placed on safety. Although the challenges in developing such agents is a long-term prospect that should not be underestimated, the urgent need to reduce infection in early life coupled with the proof of concept of BCG will likely propel the biomedical development of this new concept forward.[13]

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