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A Prime Time for Trained Immunity: Innate Immune Memory in Newborns & Infants

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Abstract

The newborn and infant periods of early life are associated with heightened vulnerability to infection. Limited antigen exposure and distinct adaptive immune function compared to the adult places a greater burden on innate immunity for host defense to microbial challenge during this time. *Trained immunity* describes the phenomenon of augmented innate immune function following a stimulus that is not specific to the original stimulus. We review the concept of trained immunity in the context of the newborn's unique innate immune system function, the preclinical and clinical evidence that support the tenet of innate immune memory in early life, and potential consequences of altered innate immune host responses.

Keywords

Newborn; neonate; infant; trained immunity; innate immunity

Introduction

Unlike the highly specific and long-lived memory responses associated with an effective adaptive immune system, the mammalian innate immune system has classically been described to manifest a rapid, short-lived "non-specific" response to foreign antigens. The concept whereby a prior exposure to an immune stimulus might result in augmentation of innate immune function upon subsequent exposure to the same or a different stimulus was described in humans nearly 50 years ago [1]. *Netea and colleagues* recently coined the term "trained immunity" to specifically describe enhancement of innate immune function with reinfection; the development of innate immune memory [2]. A *trained* innate immune response to a subsequent challenge has likely existed for millions of years in plants and invertebrates, both of which lack a classic adaptive immune system [3, 4].

In plants, the process by which protection against reinfection is mediated is termed systemic acquired resistance. Epigenetic reprogramming through specific histone acetylation (H3K9) is vital for this effect [5]. Because adaptive immunity is largely restricted to vertebrates, invertebrates represent excellent sources to look for the presence or absence of trained immunity [6]. Midgut barrier disruption by *Plasmodium* in *Anopheles gambiae* resulted in differentiation of hemocytes to an abundance of granulocytes associated with enhanced bacterial immunity that resulted in protection against reinfection with *Plasmodium [3]*. The

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mealworm beetle exhibited enhanced protection against antigenically unrelated secondary infection following lipopolysaccharide (LPS) or bacterial priming [7]. These are but a few examples of many investigations in organisms from plants to corals to shrimp to water fleas that demonstrate that trained innate immunity is prevalent. Recently, in-depth studies have also been performed in adult mammals aimed at uncovering the mechanisms that result in trained immunity among innate immune cellular populations including NK cells, monocytes, macrophages, DCs, and microglia. Discussions of each study's findings are beyond the scope of this mini review but the reader is directed to several recent outstanding reviews [2, 8, 9].

A more robust innate immune response on reinfection with the same pathogen may provide enhanced protection or have heterologous beneficial effects by providing protection against an unrelated pathogen. *Trained immunity* phenomena are demonstrable in both preclinical neonatal disease models and in human neonates (<28 days of life). Indeed, the development of trained immunity may be particularly important for host survival in early life and could potentially affect the risks of infection, allergy, and chronic inflammatory diseases later in life. In this mini review, we will review key functional distinctions of the newborn innate immune system, present evidence for early-life trained immunity in neonatal preclinical disease models and in neonatal humans, and discuss how trained immunity might be associated with negative effects on the host.

Distinct early-life innate immune function

Early life represents a period of dramatic stimulation of the relatively naïve newborn immune system. Exposure and colonization with commensal organisms harboring trillions of nucleic acid, carbohydrate, and protein antigens occurs shortly after birth. Sentinel cells of the innate immune system represent the first responders to this massive immune system exposure. Innate immune responses in turn stimulate the adaptive immune system and the development of classic immune memory responses. Thus, the response of the innate immune system is critical for the initiation and maintenance of host defense through effective immune surveillance, successful discrimination between pathogens and commensals, and development of immunologic memory.

Multiple lines of evidence now support that newborn and early-life innate immune function is not simply immature, but is distinct from that seen in older more mature populations well into the first year of life [10–12]. Furthermore, the newborn has a significant dependence on innate immune function due to distinct adaptive immune capabilities in early life [13]. Once innate immune epithelial barriers have been compromised, the first step towards the development of an immune response by local immune sentinel cells, including tissue macrophages, is the identification of invading pathogens. Pathogen-associated molecular patterns (PAMPs) are sensed via several pattern-recognition receptors (PRRs) including the *Toll*-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), retinoic-acid–inducible protein I (RIG-I)-like receptors, integrins and C-type lectins.

TLRs are key elements in the innate immune system's ability to recognize and respond to pathogens and are critically important for early life host immune responses [14]. Present on multiple cell types, TLRs recognize extracellular and intracellular pathogens by their respective microbial products. TLR agonist-receptor binding results in downstream production of cytokines and chemokines as well as antimicrobial effector mechanisms [15]. There are 10 known TLRs in humans, 12 in mice, and each receptor has a specific molecular activation trigger [15–17]. Microorganisms may stimulate multiple TLRs simultaneously akin to a 'molecular piano' playing 'chords' ultimately signaling the presence of particular

types of pathogens [16, 18]. Following PRR stimulation, production of cytokines and chemokines results in amplification of the innate response directed at the invading organisms.

Although multiple factors contribute to the altered innate immune response profile of the newborn as compared to the adult, key developmental age-related differences in TLR-mediated cytokine production as compared to adults have been recently reviewed [14]. Basal expression and cellular distribution of TLRs on term newborn monocytes is broadly similar to that of adult monocytes [19]. In contrast, TLR4 expression of preterm monocytes is reduced and increases with gestational age [20]. Interestingly, post-natal monocyte TLR expression increases early in life [21]. Despite similar basal TLR expression, the functional consequences of TLR engagement in neonates are distinct. For example, preterm infant mononuclear cells demonstrate robust interleukin (IL)-10 production but diminished production of pro-inflammatory cytokines [14]. In contrast, mononuclear cells of term infants demonstrate high levels of IL6 and IL23 production supporting T_H17 differentiation [14]. Diminished production of TNF-α, IFN-γ, IL-1β, and IL12p70 relative to adults are present for several weeks after birth and likely contribute to increased susceptibility to intracellular infection [14, 19, 20, 22, 23]. The decreased pro-inflammatory cytokine production is due in part to decreased production of important intracellular mediators of TLR signaling including Myeloid Differentiation Factor 88 (MyD88), Interferon Regulatory Factor 5 (IRF5), and p38, which exhibit gestational age-specific diminution [20]. Specifically, soluble newborn cord blood plasma factors, including high concentrations of adenosine, reduce monocytic production of TNF-α with preservation of IL-6 synthesis [24–27]. As IL6 has pro-resolution properties, including inhibition of neutrophil migration [28], this polarization may serve to reduce the risk of excessive pro-inflammatory/T_H1 response during the initial colonization of the skin and intestinal tract. Other potential teleologic explanations for the pattern of cytokine production in the newborn period include 1) the prevention preterm birth secondary to *in utero* inflammatory responses, 2) a reduction in the likelihood of fetal rejection by the mother and 3) developing fetal immunologic tolerance [29].

Laboratory and preclinical evidence of trained immunity in neonates

Our laboratories and others have reported on the effects of innate immune priming on subsequent cellular function in both *ex vivo* human and preclinical animal models of disease. For example, TLR4 is upregulated on monocytes and neutrophils from term neonates after labor and neutrophil migration is enhanced after exposure to a TLR4 agonist [30–32]. IL-8 priming of neutrophils that occurs during labor significantly improves neutrophil chemotaxis over that seen with Caesarian delivery and even adult controls [33]. *Zhang et al* showed newborns amplify the TLR2-MyD88 pathway in gram-positive bacterial infection and the TLR4/MD2/MyD88 pathway in gram-negative bacterial infection, suggesting infection-specific changes in innate immune signaling [34]. Rather than demonstrate a tolerance phenomena, these examples suggest the potential for enhanced innate immune function in human neonates following a stimulus.

Neonatal mice pretreated with low-dose specific TLR agonists such as lipopolysaccharide (LPS; TLR4) or the imidazoquinoline R-848 (TLR7/8) demonstrated a significant survival advantage over saline pretreated animals when later (24 hours after pretreatment) challenged with polymicrobial sepsis [35]. TLR-mediated immune priming induced multiple enhancements in subsequent innate immune function such as altered cytokine production, reactive oxygen species production, neutrophil phagocytosis, and improved bacterial clearance; all associated with improved survival. Importantly, the TLR-mediated survival enhancement was independent of the adaptive immune system (recombinase activating gene

1 −/−) and supports the premise of trained immunity in the neonate. Similar survival enhancements were seen in TLR-primed murine neonates with subsequent *Listeria* or neurotropic Tacaribe arena virus challenge [36, 37]. Cord blood monocytes harvested from fetal lambs exposed to a single dose of intra-amniotic endotoxin 7 and 14 days prior to delivery demonstrated augmented innate responses (IL6 & hydrogen peroxide) to subsequent *in vitro* endotoxin stimulation [38, 39].

Evidence supporting trained immunity in human neonates following early life exposures

An early life immune stimulus may transform the host defense status of the preterm infant from a relative state of tolerance, as required to prevent maternal rejection, to a state of immunocompetence to provide effective defense against the many microbes in the extrauterine environment. In line with this hypothesis, *Strunk et al*. demonstrated that histologic chorioamnionitis (HCA) exposure (inflammation of the placental chorionic disk and the extraplacental membranes) reduced the risk of late onset sepsis (LOS) in preterm neonates [40]. Analyses of whole blood genome-wide expression profiling revealed >2-fold upregulation of C5aR, C-LEC7A/12A, IL8RA/B, TLR4, TREM1, SIRPB1, and TNFAI6 in those with HCA exposure but without the development of early-life infection as compared to control preterm infants without HCA exposure/early life infection [41]. Retrospective analyses of two large independent cohorts of very-low birth weight (<1500g at birth, VLBW) infants (n = 136,713) showed that early (≤ 3 days after birth) blood culture-positive sepsis in preterm infants was not associated with an increased risk of subsequent infection during the hospitalization (late sepsis) [42] and was associated with a reduced risk of late sepsis in the smallest most immature infants [43].

Additional precedents for potentially beneficial trained immunity exist in neonatal humans in the form of heterologous vaccination benefits that may lead to a reduction in subsequent infection-related mortality [44]. Low birth weight neonates given *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccination (has TLR2/4/8/9 agonist activity [45]) at birth experienced a heterologous (so called “non-specific”) reduction in neonatal mortality over neonates who did not receive BCG [46, 47]. In line with the hygiene hypothesis based on epidemiologic studies of those exposed to microbes and microbial products early in life, the risk of asthma/atopy may be reduced with early life immune stimulation via infection [45] or breast feeding [49]. Much remains to be learned regarding both the mechanisms and ontogeny of trained immunity in humans, including whether this phenomenon demonstrates distinct features in preterm neonates.

Potential negative effects of trained immunity

There may also be potential negative effects of early-life trained immunity. Preterm neonates are at high risk of inflammatory sequelae of prematurity including retinopathy, chronic lung disease (CLD), and white matter injury [50]. There are clear relationships between chorioamnionitis exposure and a variety of untoward neonatal morbidities including CLD, cystic periventricular leukomalacia, intraventricular hemorrhage and cerebral palsy [51–53]. Early immune exposures might result in enhanced innate immune responses that contribute negatively to these and other sequelae of preterm birth [54].

Though beyond the scope of this review, preterm and/or low birth weight infants demonstrate an increased risk for adult cardiovascular and renal disease [55], raising the possibility that trained immunity may potentially contribute to the risks of developing chronic inflammatory conditions in later life. Others have suggested that neonatal exposure may eventually lead to development of disease as an adult [56], including Barker’s fetal

origins of adult disease [57]. Early-life innate immune system exposures such as severe infection or enhanced innate immune responses in young adulthood following innate immune training with low-grade chronic inflammatory conditions such as gingivitis or bacterial vaginosis could potentially contribute to the greater risk of preterm labor, stroke, diabetes, or myocardial infarction associated with these conditions. This phenomena, if relevant to preterm birth (PTB), would shed light on why treatment of these conditions has not modified PTB risk [58, 59], may partially explain racial disparities in PTB risk [60], and may lead to the development and testing of immunomodulation strategies. Indeed, recent global surveys suggest a worldwide incidence of preterm birth of ~11% [61]. In a recent report, it was stated "*preterm births will remain a major public health issue, from which no country in the world is immune*" [62]. Perhaps what is needed is a re-training of innate immunity.

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Summary

Trained immunity is apparent in the newborn and may be an important and necessary process to protect the vulnerable newborn while adaptive responses are limited. At this early stage of our understanding of trained immunity in newborns, there are far more questions than answers. What are the limits of the triggers and duration of the innate immune augmentation effect? Are the effects permanent? Are the modifications transmitted to offspring as they can be in plants? How are innate immune modifications mediated? Do post-translational epigenetic changes such as histone protein modification including methylation, acetylation, phosphorylation, ubiquitination, and sumoylation play a role? Much remains to be learned about the immunology behind the transition from intrauterine to extrauterine life, the factors that modify this transition, and the duration and clinical consequences of the modifications that occur.