Trends in Immunology

CellPress

Series: Lifetime Immunity

Review

Impact of Early-Life Exposures on Immune Maturation and Susceptibility to Disease

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Exiting from the largely sterile environment of the womb, the neonatal immune system is not fully mature, and thus neonatal immune cells must simultaneously mount responses against environmental stimuli while maturing. This dynamic process of immune maturation is driven by a variety of cell-intrinsic and extrinsic factors. Recent studies have focused on some of these factors and have shed light on the mechanisms by which they drive immune maturation. We review the interactions and consequences of immune maturation during the pre- and perinatal period. We discuss environmental signals in early life that are needed for healthy immune homeostasis, and highlight detrimental factors that can set an individual on a path towards disease. This early-life period of immune maturation could hold the key to strategies for setting individuals on trajectories towards health and reduced disease susceptibility.

Trends

A convergence in the timing of environmental stimuli and maturation of the immune system influences disease susceptibility. Factors that might be innocuous at one stage of development could be detrimental or beneficial at other stages.

The majority of previously described environmental signals that influence disease development are linked to changes in the microbiota. Microbes provide crucial signals for immune maturation.

Early life interventions, particularly by shaping the microbiota, could be the key to disease prevention in the future.

Introduction

Chronic inflammatory disorders, including inflammatory bowel disease (IBD), type 1 diabetes, asthma, and allergy are fundamentally linked with immune dysfunction, and therefore strategies that can shape appropriate immune development have the potential to impact upon disease burden. Epidemiologically it is well established that the pre- and perinatal environment can have profound effects on the development of chronic inflammatory and metabolic diseases [1–3]; however, mechanistic insight into how the early-life environment can impact on the development of the immune system is still emerging. In recent years, early-life events and exposures, particularly mode of delivery [4], diet [5,6], and lifestyle [7–9], have been shown to influence immune cell phenotypes and maturation. One common denominator influenced by all of those factors is the microbiota [10–12], and early-life signals for appropriate immune function have been directly linked with the formation of the microbiota [13–17].

We provide an overview of the leading early-life environmental factors that can shape immune maturation during this key period. We focus on findings examining the impact of pre- and perinatal exposures, and discuss the current understanding of how they shape immune function and the role of the microbiota in this process.

Pre- and Perinatal Immune Development and Function

Fetal Immune Programming

Innate and adaptive immune cells are present in the fetus early during gestation. Most of the immune cell types appear during the first trimester and then expand significantly until birth [6,18]. The first innate cells are monocytes/macrophages and can be found in very low numbers as early as gestational week (GW) 4 in humans [6]. They are followed by granulocytes (especially

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neutrophils) and natural killer (NK) cells which start to appear by GW8 and then undergo a massive expansion to reach their peak levels around birth [18–21]. B and T cell precursors can also be found from GW8 onwards. Naïve T cells can be detected in low numbers in GW12; however, the fetal T cell pool is predominated by γδ T cells until approximately GW32, when αβ T cells become the majority [6]. Immature B cells also appear at GW12, followed by the first mature fetal B1 cells by GW14 [22]. Although innate and adaptive immune cells are already present early during fetal development, their effector functions are considered to be poorly developed during the entire fetal period [6,18,23]. One influence is the nature of the antigens the fetus is exposed to during a healthy pregnancy – namely self and maternal antigens. Both types of antigens need to be tolerated [24] to ensure the viability of the fetus during pregnancy, and postnatally to avoid autoimmunity. Hence, the fetal immune system by nature is tolerogenic so as to avoid deleterious inflammatory responses. In line with this, it has been reported that fetal $CD4^+$ T cells have a tendency to differentiate into regulatory T (T_{REG}) cells upon stimulation, aiding peripheral tolerance of fetal self-antigens and non-self maternal antigens during development [25]. Furthermore, fetal proinflammatory pathways, such as the induction of type 1 T helper cell (T_H1) immune responses, are thought to be less responsive and weaker in magnitude compared to the same pathways in adults [18] (Figure 1). Whether the tolerogenic bias of fetal T cells is simply due to a lack of strong antigen stimulation, poor costimulation and low or absent microbial stimuli, or at least in part also due to intrinsic cellular immaturity is not entirely clear. It is however important to note that there are very limited data available concerning fetal, as opposed to neonatal, immune maturation profiles. Moreover, it has yet to be studied in great detail how *in utero* exposures influence discrete immune cell activation/maturation pathways, as is starting to be revealed in neonatal studies (discussed below).

Immune Function in the Newborn

The neonatal immune system initially resembles that of the fetus and has therefore been described as being immature and not able to mount strong immune responses [26,27]. Recent reports have revealed the situation is not as clear-cut as originally thought. In fact, strong stimuli, such as that provided by the Bacillus Calmette–Guérin (BCG) vaccine, can induce efficient T_H1 responses that are comparable to those of adult cells [28,29]. It has also been shown that, during the first postnatal days, DCs in neonatal mouse lungs exhibit a high expression of a variety of cell

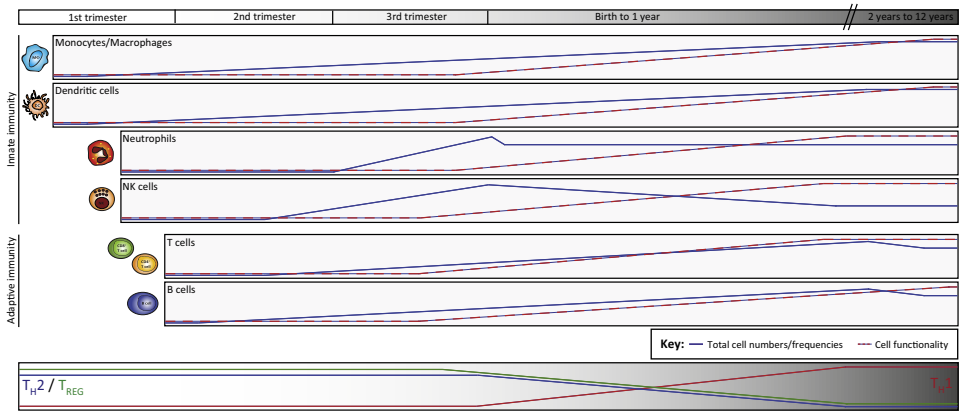

Figure 1. Pre- and Perinatal Development of Immune Cells. Dynamics of innate [monocytes/macrophages, dendritic cells, neutrophils, and natural killer (NK) cells] and adaptive (T and B cells) immune cells during cell maturation from early gestation until adolescence. Shown are changes in total cell numbers/frequencies (blue line) over time and the increase in cell functionality (red broken line). Adult-like cell numbers and functionality for all cell types depicted is reached by the end of the time-line. The switch from anti-inflammatory type 2 T helper cell (T_H2) immunity (green/blue) to T_H1 immunity (red) is illustrated in the lower panel. Full potential to mount T_H1-type immune responses is reached at around 1 year.