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Review

Neonatal autoimmune diseases: A critical review

Christopher Chang*

1600 Rockland Road, Division of Allergy, Asthma and Immunology, Thomas Jefferson University, Nemours/A.I. duPont Hospital for Children, Wilmington, DE 19803, USA

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ABSTRACT

Neonatal autoimmune diseases are distinctly rare. Most neonatal autoimmune diseases result from the transplacental transfer of maternal antibodies directed against fetal or neonatal antigens in various tissues. In neonatal lupus, the heart seems to be particularly susceptible. Primary autoimmunity in newborns, with the exception of familial autoinflammatory diseases, is virtually non-existent. The pathophysiologic basis for the development of neonatal autoimmunity is not entirely clear, but differences in the neonatal immune system compared with the adult immune system, as well as unique characteristics of target antigens in the newborn period may be important factors. Neonatal lupus is the most common presentation of autoimmunity in the newborn. But the characteristics defining neonatal lupus are not well defined and the presentation of neonatal lupus differs from that of classical lupus. Other neonatal autoimmune diseases involving the interaction between maternal antibodies and fetal/neonatal antigens include neonatal anti-phospholipid syndrome, Behcet's disease, neonatal autoimmune thyroid disease, neonatal polymyositis and dermatomyositis, neonatal scleroderma and neonatal type I diabetes mellitus. While autoantibodies have been detected in patients with neonatal autoimmune disease, the pathogenic role of autoantibodies has not been well defined. Other mechanisms may play a role in the development of neonatal autoimmunity, including fetal/maternal microchimerism and aberrant apoptosis of fetal cells. The autoinflammatory syndromes are a completely different category, but are also included in discussion of neonatal autoimmune diseases. The autoinflammatory syndromes include the cryopyrin associated periodic syndromes (CAPS) – familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID) and Muckle–Wells syndrome, which all share a common pathophysiologic mechanism.

1. Introduction

The neonatal immune system is an immature system that is undergoing constant change. The development of the immune system starts in utero, and the response of the immune system to self or foreign antigens, or alternatively, dangerous or non-dangerous entities is an evolving process that changes with age and development. This response is influenced by not only genetic or host factors, but also by epigenetic regulation and environmental modulation of our immune system, a process that leads to a functioning system that ultimately serves the purpose of preserving our viability as an organism in the face of countless external dangers.

Autoimmunity is a result of an immune system that has become inappropriately over-reactive, with different humoral and cellular components of the immune system responding to self-tissues, causing tissue inflammation and destruction. One might argue that autoimmune diseases in the neonate and in the fetus are unlikely to occur, because the "immature" immune system at that stage of development is in a state of relative immunodeficiency, and incapable of becoming over-reactive to self-tissues. Indeed, almost all neonatal autoimmune diseases result from transplacental transfer of maternal antibodies that target fetal or neonatal antigens. Primary neonatal autoimmunity has almost never been described. The prototypic neonatal autoimmune disease is neonatal lupus, involving the transfer of maternal anti-Ro or anti-La antibodies across the placenta, which are directed against heart tissues of the neonate, leading to heart block. This is a passive immune response, a function of the maternal immune system directed against the fetus, rather than a true *de novo* response of the neonatal immune system. The mechanism of action of other neonatal autoimmune diseases is also believed to be through this same process. But is there in fact an active role of the neonatal immune system in the pathogenesis of neonatal autoimmunity?

* Tel.: +1 302 651 4321; fax: +1 302 651 6558.
E-mail address: cchang@nemours.org.

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2. The neonatal immune system

Developmentally, the earliest event in the development of the human immune system can be traced to the appearance of blood cells. Initially, these are early progenitors of hematopoietic stem cells, which eventually populate the fetal liver and bone marrow and provide the basis for future differentiate into a variety of immune and non-immune cells [1]. How hematopoietic stem cells get into the bone marrow is a complex process, but appears to be mediated by the chemokine CXCL12 which is secreted by bone marrow stromal cells. The interaction between CXCL12 and its ligand, CXCR4, is a crucial step in populating the bone marrow with progenitors of immune cells. A mutation in the CXCR4 gene leads to an immunodeficiency known as WHIM syndrome [2].

Another organ that is developing simultaneously, the thymus, also receives hematopoietic stem cells at around 8 weeks of gestation in the human. Organogenesis of the thymus occurs by a gestational age of 20 weeks, and T cells populate the thymus by 16 weeks gestation [3]. Mediated by the interaction between stromal cells and hematopoietic stem cells, secondary lymphoid tissue is also being generated at this time in the form of spleen, lymph nodes and the mucosal immune system of the gut [4]. This occurs around a gestational age of 12 weeks and T cells can be detected in peripheral lymph nodes by 14 weeks of gestation [5]. Subsequently, lymph nodes are populated by B cells by about 17 weeks of gestation. The populating of lymphoid tissue by immune cells and the concurrent development into organized tissues continues through birth into infancy.

At about the same stage of gestation that T and B cells in the thymus and bone marrow respectively begin to develop, maternal antibodies, primarily of the IgG1 and IgG3 subclasses, are able to cross the placenta into the fetal circulation. This starts at about 12 weeks of gestation, but it is not until about the 22nd week of gestation, or mid to late 2nd trimester, that one sees acceleration of transfer.

The fetal and neonatal immune system, like that of the elderly, is considered to be relatively immunodeficient, when compared to that in younger adults. Several observations support this viewpoint. With regard to the innate immune system, development of monocyte function and maturation, as well as phagocytosis occurs during gestation, but neonatal monocytes still end up with less functionality than adult cells, and production of cytokines is limited [6]. Higher levels of superoxide and IL8 production are accompanied by a lower production of proinflammatory cytokines such as TNF-α and IL-6. The capacity to produce these cytokines does not reach adult levels until three years of age [7]. Achievement of adult levels of other cytokines may be even further delayed.

Antigen producing cells, which have a role in both innate and adaptive immunity, are similarly affected. Lower levels of IL-12 from myeloid dendritic cells and INF-α from plasmacytoid dendritic cells have been observed [8]. Again, with this cell type, adult levels may not be reached for several years after birth. Neutrophils are also affected, as they only appear at about 31 weeks of gestation, and then levels increase rapidly [9,10]. But functionally, the neonatal neutrophil has defective adherence [11,12] and less ability to home to sites of infection. They are also less able to produce natural antibacterials that are important in innate immunity, such as lactoferrin [11].

NK cells numbers are at their maximum at birth, but there is impaired functionality, which is believed to be a result of low levels of stimulatory cytokines in the blood and/or tissues. Addition of cytokines will restore functionality of NK cells *in vitro* [13,14]. Levels of complement components are decreased and complement function is also defective in the neonate [14].

With regard to the adaptive immune system, the pertinent cell types are T and B lymphocytes. Other important considerations include the production of antibodies. In the fetus, T cells levels are proportionally associated with gestation age. The exposure of the neonate after birth, whereby there is removal from a "sterile" environment, and the beginning of a life surrounded by foreign antigens, whether dangerous or not, leads to a rapid response in adaptive immunity. T cell levels increase rapidly after birth, and then decrease during the first few years after birth. However, T cells in the fetus and neonate are functionally deficient, which may be related to the low levels of T cell stimulatory cytokines such as IL-2 [15]. With regard to the different T cell types. CD8+ cytotoxic T lymphocytes (CTL) responses appear to be attenuated in the fetus and neonate, which translates to a predominantly Th2 paradigm at this stage of life. Regulatory T cells are found in high levels in human cord blood at birth [16], suggesting that the neonatal immune system is predominantly tolerogenic.

B cells also suffer from deficient functionality, even though numbers tend to be high by the time of delivery of the fetus. Most B cells are naïve at birth (about 95% compared to 20% in the first decade of life and 10% in adults) [17]. The lack of danger signals in the fetus is postulated to the reason for the relative naivety of fetal and neonatal B cells. There is limited antigenic stimulation to trigger B cell responses. Class switching is therefore also delayed and IgM is the predominant antibody in the fetus and at birth, again reflecting the lack of antigenic stimulation in the fetal environment [18]. In the neonate, class switching rapidly increases, but it takes time for the neonatal B cells to acquire the diversity of the adult adaptive immune system [19]. In general, IgA and IgG levels do not reach adult levels until well after the first year of life. A summary of the development of the immune system in early life is illustrated in Fig. 1.

It should be clear from the descriptions of the fetal and neonatal immune systems that this stage of life is associated with a relative degree of immunodeficiency (Table 1). This renders the neonate particularly susceptible to infections. Some of the early aspects of immunodeficiency can persist into later years, such as responses to polysaccharide antigens. The "handicapped" immune system of the neonate is somewhat compensated by maternal transfer of protective antibodies, which allows for the neonate to remain protected from foreign pathogens while allowing for the neonatal immune system to develop. It has been postulated that maternal antibodies not only protect the neonate from infection, but may also play a role in ongoing immunomodulation of the immune system by a process called genetic imprinting [20].

In general, the fetal and neonatal immune system appears to be more skewed towards a tolerogenic system. This is logical when one takes into consideration that there are numerous foreign antigens that we will be exposed to early on in life, and many are not dangerous. The initial immune system needs to learn to recognize non-harmful antigens, whether self or foreign. However, this tolerogenic system is associated with a concomitant immunodeficiency, thus neonates are more highly susceptible to infection. On the other hand, the greater tolerogenicity means that there may be a lower risk of autoimmune disease, although the exact pathogenic mechanisms determining the pathways for developing such autoimmunity are not entirely clear. An understanding of fetal and neonatal immunity is the first step towards solving the mystery of neonatal autoimmunity.

3. Neonatal autoinflammatory diseases

Neonatal autoimmunity is defined as an aberrant immune response to self-tissues in the first few months of life, leading to diseases that are closely related to autoimmune diseases in older