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Review Article

Development of child immunity in the context of COVID-19 pandemic

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ABSTRACT

Children, because of having an immature immune system, are usually more prone than the adults to the microbial infections and have more severe symptoms, which is especially true for the newborns, and very young children. However, the review of clinical data from the current COVID-19 pandemic indicates otherwise. We discuss here what are the main features and components of children's immune system, the role of maternal transmission of immunity, and what are the possible explanations for the seemingly lower infection rate and severity of COVI-19 in children.

1. Development of the immune system

During pregnancy, the developing fetus has to be tolerant of the maternal antigens, and the maternal immune system has to be fetotolerant. The reshaping of mother/fetus immune response, still not fully understood, relies on multiple mechanisms, including the emerging role of T regulatory cells (Tregs) in the achievement and maintenance of this tolerance [1]. After birth, the newborn becomes exposed to the enormous number of foreign antigens that require swift immune response. However, the immune system of the newborns is underdeveloped and subdued, fully maturing during the first 7–8 years of life. The first line immune responders present already in the fetus and newborn are the innate immune cells: monocytes, macrophages, dendritic cells, and neutrophils. The monocytes and macrophages in the newborn are immature and have lower cytokine response than in the adult. The mature neutrophils are already present at the 13th week of pregnancy and increase in number during consecutive weeks. After birth, the number of neutrophils stabilizes but they have only weak bactericidal activity [2]. Interestingly, the newborns' plasmacytoid dendritic cells (pDC) show very low production of alpha and beta interferon in response to different viruses, such as respiratory syncytial virus, herpes simplex virus and cytomegalovirus [2,3]. The NK cells of the fetus have low cytolytic activity, are hyperresponsive to the immunosuppressive activity of transforming growth factor-beta (TGF-β), and are hyporesponsive against cells lacking major histocompatibility complex (MHC) class I. At birth, the cytolytic activity of NK cells is only 50% of that in the adults, and they are hyporesponsive to IL-2 and IL-15 activation [2]. Such a muted innate immune system in newborns results in a higher than in the adults, susceptibility to bacterial and viral infection. Studies are indicating that in older children the innate and adaptive immune system develops the immunological (trained) memory of hemopoietic progenitors and NK cells, after the repeated exposure to the antigens and vaccinations, which may give cross-protection against reinfections [4–10].

Besides the innate immunity, the fetus, newborn, and developing child also have adaptive immunity. One of the cellular components of adaptive immunity are the T cells. Although the CD4- and CD8-positive T cells are established around the 15th week of pregnancy, and the mature T cells are already present in the newborn, they differ from the adult T cells by being more tolerogenic, and hyporesponsive to the antigens [2]. The newborns also have a special, recently discovered, a subpopulation of interleukin-8 (CXCL8)-producing T cells, which activate antimicrobial neutrophils (see above), and unconventional, γδT cells, which number decreases with age [2,11,12]. Other cells of the adaptive immunity are the B cells. In the newborn, and through the first few months of life, around 40% of the circulating B cells are the B1 cells

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that only produce low-affinity IgM, and later in life, they become replaced by the conventional B2 cells [2,13]. Because the newborns and young children have an underdeveloped and immature immune system they have to, at least partially, rely on the immune factors supplied by the mother. They are also theories that the immune system of the fetus is trained by maternal inflammation, which influences, and establishes a long-lasting immunologic memory in the fetal hematopoietic stem cells [14]. Below we summarize the components and routs of maternally derived immunity.

2. Maternal transmission of immunity

2.1. Placental transmission of immunity

The placenta develops from the trophectoderm of the blastocyst and serves as a protective barrier, and promotes the growth of the fetus. During pregnancy the placenta reciprocally exchanges gases, nutrients, and waste products between the mother and fetus [15]. The placenta is also crucial for providing fetal and newborn immunity. Because the placenta is continuously exposed to the pathogens present in the mother's blood, it has several mechanisms protecting the fetus from the infection. The surface of the placenta is built of a continuous layer of cells without cell junctions, and the brush border of the placental surface has a network of very dense actin filaments. These two biophysical barriers prevent the entry of pathogens from the mothernal blood. In addition, the unique composition of the membrane of placental cells prevents the attachment and penetration of some of the pathogens [16,17]. The placenta also secrets the antiviral compounds such as type III interferons, and, the enclosed within exosomes unique miRNAs, the trophomiRs, which prevent viral infection [18–20].

In humans, starting from the 16th week of gestation, until birth, the placenta is also involved in the continuous transfer of passive immunity from the mother to the fetus. The surface cells of the placenta express neonatal receptors for immunoglobulin G (IgG), which bind and pass maternal antibodies to the fetus. In consequence, at birth, the fetus has more maternal IgGs than the mother [15,17,21], which can protect infant during first months of life, until the maturation of their own immune system. Thus, the preterm infants, with a lower level of maternally derived antibodies, are more vulnerable to the infection.

2.2. Vaginal delivery shapes infant's immunity

The vaginal delivery shapes, through the contact with mother's microorganisms, the composition of a child's gut microbiota, which, in turn, affects the development of the newborn's immune system [22]. The recent analysis, using the 16S rRNA gene amplicon sequencing and high-resolution metagenomics of the microorganisms present in the neonatal gut after vaginal and caesarian section delivery, indicates that the vaginal birth enriches the gram-negative bacteria, including 23 enteric taxa of Bacteroidetes and Actinobacteria, in the newborns. This stimulates, via lipopolysaccharide (LPS) pathway, the production of pro-inflammatory cytokines TNF-a and IL-18, increases the immunostimulatory potentials of the gut microbiome, and primes immune system of neonates born by vaginal delivery [22].

2.3. Breast milk immune factors

Breast milk contains not only the basic nutrients (proteins, carbohydrates, and fats) but also a multitude of factors that drive development and maturation of the immune system and protect newborns from the environmental pathogens. Milk contains not only antibacterial compounds, chemokines, cytokines, immunoglobulins, hormones, and growth factors [23] but also the immune cells including lymphocytes, neutrophils, and macrophages.

The composition and the level of these compounds change during the different phases of lactation in response to the changing needs of the growing and developing infant. Recent studies of the milk proteome [24] showed that between the first 72 h and 3 days postpartum the colostrum milk has the highest level of the immunoregulatory factors. The transitional milk produced between the 3rd and 15th day is very rich in proteins, and the mature, produced from day 16th, milk is enriched in fatty acids, and its overall composition becomes less variable. The antimicrobial compounds in the milk include among others: lactoferrin, haptocorrin, lysozyme, defensins, cathelicidins, proteins of the complement system, components of the lactoperoxidase system (LP-s), and various glycans. The lactoferrin and haptocorrin are bacteriostatic through the binding of free ions, and vitamin B_{12}, respectively, which are required for bacterial growth [25]. The lysozyme, defensins, and cathelicidins disrupt or puncture the wall of the bacteria, leading to their lysis [26]. The proteins of the complement system opsonize pathogen to promote phagocytosis, act as the chemoattractants recruiting and activating phagocytes, and/or puncture bacterial membrane [27]. The lactoperoxidase catalyzes (from the thiocyanate ions in the presence of hydrogen peroxide) production of the antibacterial substance, and glycans reduce proliferation and virulence of some pathogens [28].

Human early colostrum milk contains around 5 million leukocytes/ml. Among them, 10% are B cells, T cells, and NK cells. The remaining leukocytes are mainly neutrophils and macrophages. The number of leukocytes decreases with time, and mature milk has approximately 10 times fewer leukocytes than the colostrum [29,30]. The breast milk also contains a high number of recently discovered innate lymphoid cells (ILCs), which had been divided into 3 subgroups: ILC1s, ILC2s, and ILC3s, with different cytokine and gene expression profiles [31,32]. The ILCs do not have receptors for the antigens but, instead, rapidly respond to infection and produce the same array of inflammatory mediators like the T cells [32]. The immune cells present in breast milk are resistant to the child digestive enzymes and can mount a vigorous immune response by directly destroying pathogens they encounter and shape the infant's gut microbiota, and immunity [29–33].

3. Incidence rate and severity of COVID-19 in children

Over the years, the research and clinical data have shown that because children have an immature immune system, they are more prone than the adults to microbial infections, and have higher severity of symptoms, which is especially true for the newborns and very young children. The analyses of clinical data from the current COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are conflicting in this respect. Some data indicate that children are rarely infected and have less severe symptoms, and other show otherwise [4]. Analysis of clinical data of 2135, 2–13 years old children in China, between January 16, 2020, and February 8, 2020, showed that more than 90% of children were either asymptomatic or had less severe symptoms than the adults and that children are no less susceptible than adults to SARS-CoV-2 infection, and the infants are more vulnerable (10.6%) to the infection than older children [34]. Some studies showed that the frequency and severity of infection in 0–19 years old children are much lower than in adults. Analysis from China showed 0.9% infection in children 0–9 years old, 1.2% in children 10–19 years old, and 0.2% fatality [35]. Similar results were reported from Italy with 0.5% cases in 0–9 years old children, 0.7% in 10–19 years old children, and no fatalities (www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_23-marzo%202020.pdf, cited in 4). If the older children are really less vulnerable to COVID-19, what would be a plausible explanation for this phenomenon? One explanation is that the child's immune system has been trained by the maternal respiratory inflammations to develop a long-lasting immunologic memory against respiratory viruses [4,14]. Also, frequent exposure of children to respiratory viruses in daycare, kindergarten, and school may lead to the development of partial protection against the SARS-CoV-2 virus. Another explanation may lie in the difference between children and adults in the expression level of the SARS-CoV-2 receptor. The entry of the SARS-CoV-2 to the host cells relies on the angiotensin-converting enzyme 2 (ACE2) receptors present in

various tissues, and also in lung epithelial cells, and alveolar macrophages [36,37]. Recently, Bunyavanich et al. [38] showed that in the cohort of 305 individuals (4 to 60 years old) the expression of ACE2 in the nasal epithelium, which serves as a virus' point of entry, increased with age: ACE2 expression was lowest in younger children (below 10 years old), and successively higher in older children (10–17 years old), young adults (1–24 years old), and highest in the adults (above 25 years old). The authors suggest that the lower expression of ACE2 receptor in children may explain why children are less prone to SARS-CoV-2 infection. However, Cristiani et al. [4] and Chen et al. [39] present a completely opposite, and more convoluted, theory of the effect of ACE2 expression on the vulnerability to and severity of the infection. They argue that because the ACE2 has also a role, especially prominent in the lungs, in the conversion of the angiotensin II to angiotensin- [1–7] (Ang1–7), and balancing the ratio and level of Ang II/Ang1–7, which affects inflammation, the higher number of ACE2 receptors in children lung pneumocytes would protect against COVID-19 lung inflammation. Theoretically, both of these contradictory theories may be valid. It is possible that the lower number of ACE2 receptors in the children's nasal epithelium limits the virus entry, while the higher level of ACE2 receptors in the children's lungs protects against the virus. Another issue worth of pursuing would be the difference, if any, between children and adult lung macrophage response to SARS-CoV-2 infection. One of the reasons for the severity of COVID-19 infection is the overdrive of the inflammatory response in alveolar macrophages, which also have ACE2 receptors, become infected with SARS-CoV-2, and drive the so-called cytokine storm [36,40]. The ongoing clinical trials with the Anakinra, the drug which inhibits pro-inflammatory cytokines interleukin (IL)-1α and IL-1β, which act in the monocyte/macrophage-driven cytokine storm in the COVID-19 patients, can be a novel therapy for the ARDS (41).Thus, it would be very interesting to study if the less severe symptoms of COVID-19 in children are related to the decreased response and downregulation of cytokine storm of their lung macrophages.

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