**Immunity related to allergic response at the beginning of life**

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Abstract

Objective: given that the most common allergic manifestations (asthma, rhinitis, dermatitis, food allergies) occur during childhood, because the immune system can be induced into sensitization rather than into allergenic tolerance at the beginning of life, we analyzed the main immunological aspects of fetuses and infant in terms of allergic sensitization and response.

Methods: detailed bibliographic revision concerning nonspecific immune response (physical and chemical barriers, myeloid cells) and specific immune response (T and B lymphocytes, cytokines) of the fetus and infant, with special attention to studies carried out in the last fifteen years.

Results: various compartments of the immune system in fetuses and infants are different from those present in older children and adults. Thus, developmental aspects of nonspecific and specific immunity may contribute to atopic disease.

Conclusions: atopic predisposition is determined at the beginning of life and seems to originate not only from genetic factors, but also from intrauterine environment and initial stage of childhood, inducing the immune system to increase the synthesis of IgE.


Introduction

Allergic diseases result from the combination of genetic factors (production of cells, cytokines, and immunoglobulin E, for instance) and specific environmental factors (allergens) or nonspecific environmental factors (smoking, infections, exercises, psychosocial alterations, treatment, and others). This combination of factors provokes an inflammatory reaction that may be generalized (anaphylaxis) or localized (airways, skin, eyes, etc.), thus determining the allergic phenotype (asthma, rhinitis, conjunctivitis, etc.).¹,²

Allergic manifestations during the first year of life suggest that prenatal events, such as exposure to allergens or to other substances, cause changes to the development and maturation of the immune system, inducing an increased production of immunoglobulin E (IgE) in genetically predisposed individuals.³-⁷ (Figure 1).

Fetal immune response is often assessed in terms of gestational age, starting in the second term of development and reaching full maturity in adolescence.⁶,⁸,⁹

Considering antigenic stimuli, the (specific and nonspecific) immune system of newborns or young children...
shows some quantitative and functional differences in comparison with that of an adult, remarkably influencing the development of atopic disease, according to genetic features, cytokine profile, antigen-presenting cells, types of antigens, and access of antigens to the immune system.8,10-13

**Non-specific immune response**

**Physical and chemical barriers**

The physical and chemical barriers, represented by mucocutaneous surfaces, consist of enzymes and fatty acids between the inner and outer regions, with bacteriostatic action, and allow access to several types of antigens.8,9 Some authors observed that infants between their third week and twelfth month of life who developed atopic disease were those with higher rates of intestinal clostridia, and less incidence of bifidobacteria, when compared to healthy subjects. This led to the hypothesis that length and intensity of the exposure to commensal microflora may influence their protective effect on the immune system against atopic disease, inducing immunologic maturation.14

The normal regulation of the immune system to tolerance should occur at the beginning of life in order to avoid unfavorable immunological mechanisms, leading to allergic reaction or to autoimmunity. Although there is some evidence that both tolerance and sensitization may be transferred from one generation to the next at the beginning of childhood through antigenic exposure, the most important mechanism is presumably that of tolerance developed by the respiratory and gastrointestinal mucosa. Cutaneous antigen presentation tends to provoke sensitization with a higher frequency than mucosal presentation, which often tends to induce tolerance.15 On the other hand, since the permeability of the mucosa is enhanced during the first months of life, there is great vulnerability of the infant to several antigens,7,16 therefore, there is greater incidence of allergic manifestations if genetic predisposition is present.

**Myeloid cells and neutrophil chemotaxis**

When compared to healthy adults, phagocytes, chemotaxis, and the bactericidal activity of neutrophils in newborns, preterm or term infants show less quantitative and functional capacity. In this age group, however, the number of leukocytes is higher than in older children and in adults.16,17

According to recent studies, there is no significant difference in terms of absolute number, IL-3 and IL-5 cytokine receptors, as well as eosinophils with hematopoietic progenitor cells (CD34+) in the umbilical cord blood of infants born to atopic and nonatopic parents. The expression of granulocyte-macrophage colony-stimulating factors (GM-CSFRa) in these cells was significantly lower in infants born to atopic parents than in nonatopic ones. This reflects the association between genetic risk for atopic disease and alterations in the expression of these receptors during the perinatal period.19

Frenkel & Bryson20 have previously shown that macrophage culture of newborn infants with adult T cells resulted in reduced production of gamma interferon (INF-gamma); the opposite was observed in the macrophage culture of adults with newborn T cells, revealing the existence of functional phagocyte immaturity at this stage of life. The reduced production of this cytokine is one of the factors that favor the development of atopic disease, since INF-gamma inhibits the synthesis of IgE.11,21

**Specific immune response**

Lymphocytes are found in the fetal thymus after the eighth week of life. Lymphocytes in the liver and spleen increase in number after the fourteenth week, and migrate into the bloodstream after that,5,8,9,22 when they are activated in the presence of antigenic exposure.5,6,11,23

It is perfectly clear that the induction of allergen-specific memory by T cells usually occurs in intrauterine life, and that maternal immunological pattern influences children’s immune system. The significantly elevated levels of immunoglobulin G (IgG) subclasses, especially IgG4, to food and/or inhalant allergens in umbilical cord blood in infants born to atopic mothers corroborate this fact.24,25 The transfer of this antibody class by the placenta suggests the existence of a probable extra mechanism for the regulation of the allergen-specific immune response in children, and also suggests maternal influence on the production of INF-gamma by T cells in children.25
T lymphocytes

Thymus-derived T lymphocytes play a crucial role in the mechanisms against allergic diseases as a source of interleukin-4 (IL-4) and also for they release one of the signals that tells B lymphocytes to synthesize IgE.26

At the final stage of T cell differentiation, there are three mature types of cells that influence the specific immune response: CD4+/CD8- (Th) or cluster of differentiation (CD), which act as helpers; CD4+/CD8- (Ts), which act as suppressors or have a cytotoxic function and, finally, CD4-/CD8, which protect against external attacks and act as natural killers (NK) of neoplastic or virus-infected cells.18,27,28 The CD4+/CD8+ T lymphocytes are qualitatively functional and quantitatively elevated at birth, decreasing in number up to the sixth month of life. Their number varies during childhood, gradually increasing until it reaches the same amount found in adults at the beginning of adolescence.18 In the last few years, some researchers have reported on the existence of an unbalance in the number of these cells by observing an abnormal predominance of CD4 or deficient CD8 in infants born to atopic parents.6,26,30

As the immune system is activated by the presence of antigens, nonactivated T cells (CD45RA+) are gradually replaced with TCD45RO+ (or CD45RA-) cells, which are markers for activated or memory T cells (CD4+/CD45+ or Th0), acting upon the regulation of T and B lymphocyte growth and proliferation.31-35 The placenta is an effective barrier against fetal invasion by microorganisms and antigens; that's why T CD45+ cell subsets in the circulatory system and fetal organs amount to 90%. Over time, CD45RA+ cells are gradually replaced with CD45RO+ cells, until they reach a plateau in adolescence. Thus, the disproportionate presence of CD45RO+ cells in newborns reflects the response to intrauterine antigenic stimuli.5,11,36 Recent studies have shown some similarity between adults and infants as to the response kinetics to the change from CD45RA+ phenotype to CD45RO+ phenotype on first stimulation by phytohemagglutinin A (PHA),35 and also in terms of the percentage increase of CD45RO+ cells in the umbilical cord blood of children who developed allergic disease by the end of their first year of life.37

Two cell subsets, using the activation of Th0 cell clones, were identified initially in mice and then in humans, according to their cytokine secretion pattern and functional activity: Th1 cells producing IL-2, INF-gamma and lymphotoxins; Th2 cells, producing IL-4, IL-5, IL-9 and IL-13 and, finally, Th1 and Th2 cells, producing IL-6, IL-10, tumor necrosis factor-beta (TNF-b) and GM-CSF.4,33,38

Th cells help B cells to respond to most antigens, significantly influencing the development of immunocompetence.5 T cells in lesser number in infants born to atopic parents in the neonatal period may mean suppressed activation of these cells, such as no antigenic sensitization or paucity of memory Th cells that produce cytokines with the Th0/Th1 pattern. The Th2-simile pattern predominates in newborns with predisposition to atopic disease.7,31,33,38,40

Th1 cells do not stimulate the secretion of antibodies by B lymphocytes, possibly due to the capacity of suppressing them through INF-gamma secretion. The expression of these cells is related to delayed-type hypersensitivity responses and macrophage activation. Autoimmune diseases and graft rejection occur when the differentiation between Th0 and Th1 cells is unbalanced.10,13

Th2 cells are abundantly found in atopic individuals.13 Their selective differentiation and proliferation are related to the induction of IgE synthesis and to the secretion of cytokines that act upon humoral immunity under the influence of IL-4, dislocating the immunoglobulin genes to the e locus, and eosinophilia by the action of IL-5 on these cell clones.7,10

B lymphocytes

After contact with the antigen, bursa equivalent lymphocytes (B) are differentiated through the primordial lymphoid cell into immunoglobulin-secreting plasmocytes (in this case, immunoglobulins are identified according to their structure and function.40 The production of B lymphocytes by the fetus and newborns is extremely low except when there is infectious or antigenic stimulus.5,23 Among the five classes of immunoglobulins known today (IgA, IgD, IgE, IgG and IgM), IgG is the only one that certainly crosses the placental barrier, representing nearly the totality of these antibodies in newborns.5,41

During the first year of life, the immune system is exposed to a wide variety of antigens, especially those found in foods, which may activate the immune response mediated by IgG. IgA, IgM and IgE.42,43 On top of that, the lack of protective action of secreting IgA, although transient, increases the risk of exposure to such antigens, leaving room for subsequent atopic disease.16

B lymphocytes in newborns and young children have a twofold expression of low-affinity IgE receptors (CD23 or FceRII) when compared to adult individuals. Therefore, the levels of soluble fragments of these receptors (sCD23) are higher at birth and decline with age, differently from IgE, possibly due to negative feedback mechanisms of the immune system.11,44 Allergic diseases are related to an increase in CD23 expression in the activated cells that have these antigens (B and T cells, macrophages, eosinophils and platelets), reflecting to some extent an increase in IL-4 synthesis in these diseases and the capacity of this cytokine to produce hyperactivation of these receptors.45

Cytokines

Cytokines, also known as lymphokines, monokines, interleukins, hematopoietic growth factors or peptides and
neuropeptides - depending on the order in which they were discovered and/or their mechanisms of action- are soluble molecules that mediate intercellular immune response. Due to these characteristics, cytokines allow for uniformity, diversity, and specificity of cellular responses and of physiological and pathological processes, such as allergic inflammation, because of their capacity to regulate nonspecific immunity (IL-1, TNF, IL-6, chemokines), promote activation, growth, and regulation of lymphocytes (IL-2, IL-4, transformation and growth factor-beta - TGF-b), activate inflammatory cells (INF-gamma, IL-5, macrophage migration inhibitory factor- MIF, lymphotoxin, IL-10, IL-12) or induce growth and differentiation of cell colonies (IL-3, IL-7, IL-9, IL-11, GM-CSF, granulocyte colony stimulating factor- G-CSF, macrophage colony stimulating factor- M-CSF).46

Cytokine production during pregnancy probably results from the immune response to the antigen pattern that the fetus represents to the pregnant woman, Thus, IL-1b and M-CSF are necessary for blastocyst implantation, and IL-3, M-CSF and GM-CSF, for trophoblast growth. Placental hormones also use cytokines in their synthesis, and IL-1, IL-2 and IL-6 induce an increase in the production of prostaglandins, which act upon labor.15

Natural killer cells at the mother-fetus interface are activated by Th1-derived interleukins, and may lead to reduced growth or fetal death. On the other hand, IL-4, IL-5, IL-6, IL-10 and IL-13, which derive from Th2 cells, act contrariwise, showing that carrying pregnancy to term must be a Th2-related phenomenon.5,15

After 22 weeks’ gestation, there is antigenic proliferative response after stimulation by PHA, which results in the production of cytokines from Th2 cells. The quality pattern of IL-4, IL-6, IL-13, INF-gamma and GM-CSF response of in vitro newborns under proper stimulation is the same as that observed in adults, although it is different in terms of quantity, thus favoring the susceptibility to allergic sensitization.5,11 During the same gestational period, we also have spontaneous and nonspecific production of INF-gamma by mononuclear cells in the fetal peripheral blood, with the probable aim of neutralizing the effects of IL-4 and IL-10, which are produced by the placenta and/or mother as protection against allergic phenotype via Th2.5 However, the quantitative production of INF-gamma in newborns corresponds to 10% of that found in adults, possibly due to the intrinsic deficiency in its synthesis by T cells or by inefficient accessory activity of mononuclear cells and, certainly because of the low exposure of fetuses’ and newborns’ gastrointestinal and respiratory tracts to environmental antigens.11,47 Even so, Early & Reen could find some similarity between newborns and adults in terms of kinetic profile of production of IL-2, IL-4 and INF-gamma after additional stimulation by PHA. The production of IL-4 and NK cells are also remarkably lower in newborns than in adults, and their number gradually increases with age.11 The presence of IL-4 in human amniotic epithelial cells has been recently observed after the first trimester of gestation.48 Allergen-induced IL-4, IL-5 and IL-13 could be recently observed in higher quantity in umbilical cord blood of newborns that developed allergic disease up to their first year of life than in the cord blood of nonallergic infants, who just presented IL-10 in response to allergen stimulation, suggesting the existence of a flaw in the regulating mechanism of INF-gamma production.37 No INF-gamma was observed in the umbilical cord blood of newborns.

Predisposition to atopic disease seems to be determined at the beginning of life by intrauterine and early childhood events, causing the immune system to increase the synthesis of IgE.49,50 Since immune response is heterogeneous and involves a wide variety of antibodies and cytokines and interactions with other systems regarding antigen stimulation, the whole set serves as early (genetic, immunologic, and biochemical) indicators of allergic sensitization.50-54 Therefore, it is necessary to further investigate the participation of these indicators (markers) in allergic diseases, especially in pediatric patients, given that their immunologic profile has different quantitative and functional characteristics during the developmental stage. By doing this, predictive, preventive, and therapeutic strategies to address allergic diseases can be better outlined.

References
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