Paediatrica Indonesiana

VOLUME 45 September - October • 2005 NUMBER 9-10

Review Article

Child immune response and the role of nutrition

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The immune function is designed to defend the body in a safe and efficient way against a variety of dangerous materials including toxins and infectious organisms. Mechanical and biological barriers prevent the penetration of exogenous material into the body. Only after these barriers have been breached and cells have been directly attacked does the immune system come into play. By a variety of mechanisms, certain immune cells can directly phagocytose and destroy many pathogens. They require the close cooperation of somatic cells, which both alert the immune system through alarm signals and later participate in the effector phase. This first alarm signal can be grouped together as "stress signals", known as the innate immune response.[1]

The immune system

Host defense against pathogenic microbes requires different responses, depending on the character of the pathogen and on the tissue under attack. Central to the immune system's ability to mobilize a response to an invading pathogen is its ability to distinguish self from non-self. The host has evolved both innate and adaptive mechanisms to respond to and eliminate pathogenic microbes. Both of these mechanisms include self-non-self discrimination. The innate immune system includes all aspects of the host defense mechanisms that are encoded in the germ-line genes of the host. These include barrier mechanisms, such as epithelial cell layers that express tight cell-cell contacts (tight junctions, adherin mediated cell interactions, and others), the secreted mucus layer that overlays the epithelium in the respiratory, gastrointestinal, and genitourinary tracts, and the epithelial cilia that sweep away this mucus layer, permitting it to be constantly refreshed after it has been contaminated with inhaled or ingested particles.[2,3]

The innate response also includes soluble proteins and bioactive small molecules that are either constitutively present in biological fluids (such as the complement proteins and defensins) or are released from cells as they are activated (including cytokines that regulate the function of other cells, chemokines that attract inflammatory leukocytes, lipid mediators of inflammation, and bioactive amines and enzymes that also contribute to tissue inflammation). Lastly, the innate immune system includes cell surface receptors that bind molecular patterns expressed on the surfaces of invading microbes.[4]

In the response to stress signal, these cells respond with the release of variety of messenger that attract and activate phagocyte Antigen Presenting

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Cells (APC) and thus initiate the specific immune response. Once activated APC carry processed foreign antigens from the site of injury and migrate via the lymphatic to the regional lymph nodes, where they secrete the chemokines to attract naive CD4 and CD8 T cells. The APC present the foreign antigen peptide to these T cells. Those naive cells that recognize the foreign peptide on the basis of their receptor structure are in turn stimulated and differentiate in to blast cells. These activate T cell now express different surface antigens that make them capable of responding to growth factors, leaving the lymph notes and themselves secreting cytokines. Which mediators are involved and how the T cells in the end interact with their target cells and antigens is quite depending on how they are activated.[5]

The first important task for the activated T cells is a clonal proliferation to ensure that enough cells are available to react in a specific fashion against triggering noxious or infectious agent. Such specialized T cells can increase their number by factor of 10,000 over a period of a few days under the influence of cytokine interleukin 2 (IL-2). Activated T cells have many other tasks. They interact closely in the lymph nodes with B cells, giving them signals for immunoglobulin production. Finally, they leave the lymph nodes and return to initial site of injury. This return is made possible because the innate immune response has already started an inflammatory process at this site, leading to the production and expression of a variety of adhesion molecules. Certain adhesion molecules specifically allow the activated T cells to attach to the vessel wall, migrate through the wall, and then reach the inflamed tissue. There the activated T cells are stimulated again most likely by antigen-laden monocytes and macrophages to produce a wide variety of pro inflammatory mediators.[6]

Interferon gamma plays a major role at this stage. It triggers the macrophage to produce inflammatory mediators, which in turn further stimulate the neighboring cells to produce free radical, tumor necrosis factors and other factors with which they had initially triggered the immune response. Compared to the initiation phase, at this stage both magnitude responses and the spectrum of cytokines secreted is much greater. T and B-lymphocytes are the only components of the immune system that have antigen-specific recognition capabilities; they are responsible for adaptive immunity. Unlike the innate mechanisms of host defense, the adaptive immune system manifests exquisite specificity for its target antigens. Adaptive responses are based primarily on the antigen specific receptors expressed on the surfaces of T- and B-lymphocytes.[2,3]

Unlike the germ line encoded recognition molecules of the innate immune response, the antigen-specific receptors of the adaptive response are assembled by somatic rearrangement of germ line gene elements to form intact T-cell receptor (TCR) and Ig (B-cell antigen receptor) genes. The assembly of antigen receptors from a collection of a few hundred-germ line-encoded gene elements permits the formation of millions of different antigen receptors, each of with potentially unique specificity for a different antigen. NK cells are lymphocytes that are also derived from hematopoietic stem cells; they are thought to have a role in host defense against viral infections, in tumor surveillance, and in immune regulation. The proteins synthesized and secreted by T, B, and NK cells, and by the cells, with which they interact, are referred to as cytokines.[6]

The innate and adaptive immune systems are often described as contrasting, separate arms of the host response; however, they usually act together, with the innate response representing the first line of host defense and the adaptive response becoming prominent after several days, as antigen-specific T and B cells have undergone clonal expansion. Furthermore, the antigen-specific cells amplify their responses by recruiting innate effectors mechanisms to bring about the complete control of invading microbes. Thus, whereas the innate and adaptive immune responses are fundamentally different in their mechanisms of action, synergy between them is essential for an intact, fully effective immune response.[2,4,6]

Antibody-mediated immunity (AMI) and cell-mediated immunity (CMI)

Antibody-mediated immunity (AMI) is the type of immunity that is mediated by soluble host proteins called antibodies or immunoglobulin. Because it is largely due to the presence of circulating antibody

molecules in the serum, is also called circulating immunity or humoral immunity. Antibodies (Abs) are proteins (globulins) produced in response to an encounter with an antigen. There are several classes or types of antibodies (and subclasses of the types), but all of the classes of antibodies that are produced in response to a specific antigen react stereo chemically with that antigen and not with other (different) antigens. The host has the genetic capacity to produce specific antibodies to thousands of different antigens, but does not do until there is an appropriate (specific) antigenic stimulus. Due to clonal selection, the host produces only the homologous antibodies that will react with that antigen. These antibodies are found in the blood (plasma) and lymph and in many extra vascular tissues. They have a various roles in host defense against microbial and viral pathogens as discussed below. [2,3,6]

Cell-mediated immunity (CMI) is the type of immunity that is mediated by specific subpopulations of T-lymphocytes called effectors T cells. In non immune animal precursor T cells (pT cells) exist as "resting T cells". They bear receptors for specific antigens. Stimulation with Ag results in their activation. The cells enlarge, enter into a mitotic cycle, reproduce and develop into effectors T cells whose activities are responsible for this type of immunity. They also develop into clones of identical reactive T cells called memory T cells. The biological activities of the antibody-mediated and cell-mediated immune responses are different and vary from one type of infection to another. The AMI response involves interaction of B-lymphocytes with antigen and their differentiation into antibody-secreting plasma cells. The secreted antibody binds to the antigen and in some way leads to its neutralization or elimination from the body. The CMI response involves several subpopulations of T lymphocytes that recognize antigens on the surfaces of cells. TH cells responds to antigen with the production of lymphokines. The distinction between TH1 and TH2 is based on their lymphokine profiles. TH2 cells have previously been referred to as T helper cells because they provide lymphokines (e.g. IL-2 and IL-4), which activate T cells and B cells at the start of the immune response. TH1 cells were formerly known as delayed type hypersensitivity cells (TDTH) because of their role in this allergic process. TC cells or cytotoxic T lymphocytes (CTLs) are able to kill cells that are showing a new or foreign antigen on their surface (as virus-infected cells, or tumor cells, or transplanted tissue cells).[7]

Immune system development

The human immune system arises in the embryo from gut-associated tissue. Pluripotential hematopoietic stem cells first appear in the yolk sac at 2.5-3 wk of gestational age and migrate to the fetal liver at 5 wk of gestation; they later reside in the bone marrow, where they remain throughout life. Lymphoid stem cells develop from such precursor cells and differentiate into T, B, or NK cells, depending on the organs or tissues to which the stem cells traffic. Primary lymphoid organ (thymus, bone marrow) development begins during the middle of the first trimester of gestation and proceeds rapidly; secondary lymphoid organ (spleen, lymph nodes, tonsils, Payer's patches, lamina propria) development soon follows. [5]

Neonates develop the capacity to respond foreign antigens before they are born. B and T cells are present by 14 weeks' gestation and express an enormous array of antigen-specific receptors.[8] Although the fetal immune system has the potential to respond to large numbers of foreign antigens, few foreign antigens are present in uteri, and cells of the immune system are primarily "naïve" at birth. The neonate is, in part, protected against disease by maternal immunoglobulin. Maternal IgG is transported across the placenta before birth and maternal secretory IgA is present in breast milk and colostrums. These passively acquired antibodies provide protection against pathogens to which the mother was immune. However, protection provided by passively transferred antibodies is short-lived. Passively acquired maternal IgG declines during the first few months of life,[9] and most infants are not breastfed beyond several months of age. More importantly, maternal antibodies offer limited immunologic protection when compared with protection afforded by an infant's active immune response.

Neonates are capable of generating both humoral and cellular immune responses to pathogens

at the time of birth.[10,11] Active immunity in the newborn includes the full range of B-cell responses including the production of IgM, IgG, and secretory and monomer IgA, as well as the development of helper T-cell (Th) and cytotoxic T-cell responses.[10,11] In addition, neonates can produce specific Th-cell subsets, including Th1-type cells that participate in cell-mediated immune responses and Th2-type cells that are primarily involved in promoting B-cell responses.[10,11]

The development of active humoral and cellular immune responses in the newborn is necessary to meet the tremendous number of environmental challenges encountered from the moment of birth. When children are born, they emerge from the relatively sterile environment of the uterus into a world teeming with bacteria and other microorganisms. Beginning with the birth process, the newborn is exposed to microbes from the mother's cervix and birth canal, then the surrounding environment. Within a matter of hours, the gastrointestinal tract of the newborn, initially relatively free of microbes, is heavily colonized with bacteria.[12] The most common of these colonizing bacteria include facultative anaerobic bacteria, such as *Escherichia coli* and streptococci, and strict anaerobic bacteria, such as *Bacteroides* and *Clostridium*.[12] Specific secretory IgA responses directed against these potentially harmful bacteria are produced by the neonate's intestinal lymphocytes within the first week of life.[13]

T-cell. Blood-borne T-cell precursors (pro-T) cells are identified by surface proteins designated as CD7 and CD34. At 8-8.5 wk gestation, $CD7^+$ cells are found intrathymically, and some cells also co express CD4, a protein present on the surfaces of mature T-helper (TH) cells, and CD8, a protein found on both mature cytotoxic cells and NK cells. Rearrangement of TCR genes signifies commitment of pro-T cells to T-lineage development-that is, to become pre-T cells. TCR gene rearrangement begins shortly after colonization of the thymus with stem cells, and the establishment of the T-cell repertoire begins at 8-10 wk of gestation. By 9.5-10 weeks, more than 95% of thymocytes are $CD7^+$, $CD2^+$, $CD4^+$, $CD8^+$, and c (cytoplasmic) $CD3^+$, and approximately 30% bear the CD1 inner cortical thymocyte antigen. By 10 wk, 25% of thymocytes bear ab TCRs. Ti ab+ cells gradually increase in number during embryonic life and represent more than 95% of thymocytes postnatal. As immature cortical thymocytes begin to express TCRs, the processes of positive and negative selection take place. Fetal cortical thymocytes are among the most rapidly dividing cells in the body; they increase in number by 100,000-fold within 2 wk after stem cells enter the thymus. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life and to the tonsils by 14-15 weeks. By 12 weeks gestation, T cells can proliferate in response to plant lectins (phytohemagglutinin [PHA] and concanavalin A [Con A]) and to allogeneic cells; antigen-binding T cells have been found by 20 weeks gestation. Hassall's bodies (swirls of terminally differentiated medullar epithelial cells) are first seen in the thymic medulla at 16-18 weeks of embryonic life.[5,14]

The ratio of $CD4^+$ to $CD8^+$ T cells is usually higher (3.5-4:1) in cord blood than in blood of children and adults (1.5-2:1). Virtually all T cells in cord blood bear the CD45RA (naive) isoform, and a dominance of $CD45RA^+$ over $CD45RO^+$ T cells persists during the first 2-3 years of life, after which time the numbers of cells bearing these two isoforms gradually equalize. TH cells can be further subdivided according to the cytokines they produce when activated. TH1 cells produce IL-2 and IFN-g, thereby promoting cytotoxic T-cell or delayed hypersensitivity types of responses, whereas TH2 cells produce IL-4, IL-5, IL-6, and IL-13, which promote B-cell responses and allergic sensitization.[15-18]

B-cells. In parallel with T-cell differentiation, B-cell development begins in the fetal liver before 7 weeks gestation. Pre-B cells can be found in fetal liver at 7 wk gestation, $sIgM^+$ and $sIgG^+$ B cells at between 7 and 11 weeks, and $sIgD^+$ and $sIgA^+$ B cells by 12-13 weeks. By 14 weeks of embryonic life, the percentage of circulating lymphocytes bearing sIgM and sIgD is the same as in cord blood and slightly higher than in the blood of adults. Secreted IgM and IgE have been found in abortuses as young as 10 wk, and IgG as early as 11-12 weeks.[19,20] Despite the capacity of fetal B lymphocytes to differentiate into immunoglobulin-synthesizing and -secreting cells, plasma cells are not usually found in lymphoid tissues of a fetus until about 20 weeks gestation, then only rarely, because of the sterile envi-

ronment of the uterus. Peyer's patches have been found in significant numbers by the 5th intrauterine month, and plasma cells have been seen in the lamina propria by 25 weeks gestation. Before birth there may be primary follicles in lymph nodes, but secondary follicles are usually not present. A human fetus begins to receive significant quantities of maternal IgG transplacentally at around 12 weeks gestation, and the quantities steadily increases until at birth cord serum contains a concentration of IgG comparable to or greater than that of maternal serum. IgG is the only class to cross the placenta to any significant degree; all four subclasses do this, but IgG2 does so least well. A small amount of IgM (10% of adult levels) and a few nanograms of IgA, IgD, and IgE are normally found in cord serum; because none of these proteins cross the placenta they are presumed to be of fetal origin.[21] These observations raise the possibility that certain antigenic stimuli normally cross the placenta to provoke responses, even in non-infected fetuses. Some atopic infants occasionally have reaginic antibodies to antigens (such as egg white) to which they have had no known exposure during postnatal life, suggesting that synthesis of these IgE antibodies could have been induced in the fetus by antigens ingested by the mother.[5]

Immunoglobulins. B-lymphocytes are present in cord blood in slightly higher percentages but considerably higher numbers than in the blood of children and adults because of higher absolute lymphocyte counts in all normal infants.[21] However, cord blood B cells do not synthesize the range of immunoglobulin isotypes made by B cells from children and adults when stimulated with pokeweed mitogen (PWM) or anti-CD40 plus IL-4 or IL-10, producing primarily IgM and at a much-reduced quantity. Neonates begin to synthesize antibodies of the IgM class at an increased rate very soon after birth in response to the immense antigenic stimulation of their new environment. Premature infants appear to be as capable of doing this as do full-term infants. At about 6 days after birth, the serum concentration of IgM rises sharply. It continues until adult levels are achieved by approximately 1 year of age. Cord serum from noninfected normal newborns does not contain detectable IgA. Serum IgA is normally first detected at around the 13th day of postnatal life; the level gradually increases during early childhood until adult levels are achieved and preserved between the 6th and 7th year of life. Cord serum contains an IgG concentration comparable to or greater than that of maternal serum.[22] Maternal IgG gradually disappears during the first 6-8 months of life, while the rate of infant IgG synthesis increases (IgG1 and IgG3 faster than IgG2 and IgG4 during the 1st year) until adult concentrations of total IgG are reached and maintained by 7-8 years of age. However, IgG1 and IgG4 reach adult levels first, followed by IgG3 at 10 years and IgG2 at 12 years of age. The total immunoglobulin level in infants usually reaches a low point at approximately 4-5 months of postnatal life.[5] The rate of development of IgE has generally been found to follow that of IgA. After adult concentrations of each of the three major immunoglobulins are reached, these levels remain remarkably constant for a normal individual. The capacity to produce specific antibodies to protein antigens is intact at the time of birth. However, normal infants cannot produce antibodies to polysaccharide antigens until usually after age 2 years unless the polysaccharide is conjugated to a protein carrier, as is the case for the conjugate *Haemophilus influenzae* type B (Hib) vaccines.[5]

NK-cells. NK-cells can be detected as early as six weeks of gestation, and the number increases progressively until birth. In cord blood, 10 to 15 percent of all lymphocytes are NK cells, which is comparable to the percentage in adult peripheral blood.[23,24] The phenotype of fetal NK cells, however, is different from that of adults' cells. Fifty to 80 percent fetal NK cells express CD3 gamma, epsilon, delta, and sigma proteins, unlike a much smaller number in term infants, or in adults where only CD3 sigma is expressed.[24] NK-cell activity has been found in human fetal liver cells at 8-11 weeks of gestation. After release from bone marrow, NK cells enter the circulation or migrate to the spleen; there are very few NK cells in lymph nodes. In normal individuals, NK cells represent 10% of lymphocytes; this percentage is often slightly lower in cord blood. The percentage of NK cells in cord blood is usually lower than in the blood of children and adults, but the absolute number of NK cells is approximately the same owing to the higher lymphocyte count. The capacity of cord blood NK cells to mediate target

lysis in either NK-cell assays or ADCC assays is roughly two-thirds that of adults.

Lymphoid organs. Lymphoid tissue is proportionally small but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during fetal life and at birth is ordinarily two thirds of its mature weight, which it attains during the 1st year of life. It reaches its peak mass, however, just before puberty, and then gradually involutes thereafter. By 1 year of age, all lymphoid structures are mature histologically. Absolute lymphocyte counts in the peripheral blood also reach a peak during the 1st year of life. Peripheral lymphoid tissue increases rapidly in mass during infancy and early childhood. It reaches adult size by approximately 6 years of age, exceeds those dimensions during the prepubertal years, and then undergoes involution coincident with puberty. The spleen gradually accrues its mass during maturation and does not reach full weight until adulthood. The mean number of Payer's patches at birth is one half the adult numbers and gradually increases until the adult mean number is exceeded during adolescent years.[5]

Monocytes and macrophages. Embryonic macrophages are first observed in the yolk sac at three to four weeks of gestation.[25,26] conventionally, macrophages were believed to be progeny of bone marrow-derived monocytes. However, more recent observations suggest that the macrophage ontogeny in early embryos may be different, arising instead from yolk sac-derived primitive macrophages before the development of adult monocytes.[27] Furthermore, during the second month, as hematopoiesis is established in the fetal liver and the yolk sac is open to fetal circulation, monocytes are seen in high proportions, and constitute nearly 70 percent of all hematopoietic cells.[28] Over the next six weeks, as erythroid cells predominate, this proportion falls to 1 to 2 percent.[29] At five weeks, there are two distinct cell populations with a dendrite/macrophage structure in the yolk sac, mesenchyme, and the fetal liver. Although monocytes and promonocytes are present in the fetal liver, intravascular monocytes are not observed until about the fifth month of gestation.[30] Circulating monocytes remain rare until the bone marrow becomes the predominant site of hematopoiesis. At 30 weeks, monocytes comprise 3 to 7 percent of hematopoietic cells.[31] Term cord blood studies show a relative monocytosis, which persists during the neonatal period. The absolute monocyte counts tend to decline gradually from 1340 to 2200/μL in the first week of life to about 700 by the third week. Most studies on monocyte/macrophage cell function have been done on cord blood, and fetal cells have not been evaluated to the same extent thus far. Term cord-blood monocytes produce IL-1, IFN-α, and TNF-α in concentrations that are comparable to those of adults, but the levels of IFN-γ, IL-8, IL-10, and GM-CSF are lower. These cells also produce lower concentrations of extra cellular proteins (such as fibronectin), and bioreactive lipids (such as leukotriene B4).[32] Impaired monocyte function in neonates may be partially responsible for poorer cytokine responses of neonatal T cells. Although cord-blood mononuclear cells can phagocytes at a level comparable to that seen in the adult, chemo taxis is reduced.[32,33]

Dendrite cells. Dendrite cells (DCs) with a macrophage/macrophage structure are present in the yolk sac, mesenchyme, and the liver at four to six weeks of age. DCs are detectable in the skin by six to seven weeks of gestation.[21,34] DCs initially derived their name from their distinctive morphology, with numerous fine macrophage cytoplasm processes. However, phenotype alone is not sufficient to identify these cells in view of functional differences between the subpopulations. A working definition requires DCs to be capable of stimulating T cells, home to T cell dependent lymph node areas, be able to pinocytose, and have characteristic cell surface antigens.[35]

Functional differences between the infant and adult immune responses

Despite the fact that infants can generate all functional T-cells (i.e., Th1, Th2, and cytotoxic T-cells),[10,11] infant B-cell responses are deficient when compared with those of older children and adults. Infants respond well to antigens (such as proteins) that require T-cell help for development. However, until about 2 years of age, the B-cell response to T-cell-independent antigens (such as polysaccharides) is considerably weaker than that found in adults.[3]

For this reason, infants are uniquely susceptible to bacteria that are coated with polysaccharides (such as *Haemophilus influenzae* type B and *Streptococcus pneumoniae*).

The role of nutrition in immunity

Immunodepression is an accepted risk factor in the infection-related morbidity and mortality of childhood protein-energy malnutrition (PEM). In childhood protein-energy malnutrition (PEM), diverse innate and adaptive defenses are affected. With regard to innate defenses, influences on epithelial mucus are consistent with childhood protein-energy malnutrition (PEM)–associated risk of mucosal infection and bacterial translocation. Extensive information documents the phagocyte barriers.[36] Mononuclear phagocyte numbers are depressed, whereas the blood neutrophil count is generally unaffected even in the most severe PEM. Likewise, macrophage microbicidal capacity appears intact, but information is limited to the rat, a species unlike humans in terms of microbicide-related biochemical pathways.[36] In contrast, the microbicidal activity of neutrophil usually depressed in childhood PEM, particularly when overt infection is apparent, and a spare database demonstrates depressed NK-cell lytic capacity. Blood concentration of complement proteins and complement-dependent lytic activity are much depressed by PEM, at least during infection, and the acute phase response in frequently attenuated. Although this has been linked to reduce synthesis of macrophage cytokines,[36] measurements of blood cytokine levels[37] suggest that target cell responsiveness is a factor. The ability to sustain an acute-phase-protein response in childhood PEM has been emphasized recently. Cell-mediated immunity competence is consistently depressed in PEM, whereas the influence on humoral adaptive immunity is unpredictable. Recent evidence suggests that mucosal and systemic antibody production may show similar sensitivity to PEM, and that the polymeric immunoglobulin receptor is a point of impact the disease.[36] Lymphoid atrophy, although profound, provides only a superficial explanation of adaptive immunodepression in PEM. Imbalance among regulatory T cell subsets maybe important and over abundance of the sluggish naïve-phenotype T-cell has recently been identified in experimental PEM.[36] However, the low CD4/CD8 ratio that often occurs in blood is almost certainly irrelevant to PEM-associated immune depression.[36] T-cell cytokine studies are beginning to contribute toward an understanding of thymus dependent immuno-depression in PEM,[36,37] and recent results highlight the requiring study cytokine networks.

The role of micronutrient deficiency as a conditioning factor in host response to infection widely recognized. Vitamin A deficiency causes keratinization of the respiratory epithelium, leading to a decrease in mucus production and diminished clearance capacity of the respiratory epithelium to bacterial pathogens. Deficiency of other minerals, including iron and zinc, are recognized to impair immune function in experimental animals, as well as in humans. One postulated mechanism is that both of these metals are essential for the function of a number of metalloenzymes required for nucleic acid synthesis and cell replication. This is an important barrier to an effective immune response to infectious diseases that is based on the rapid reproduction of antigen-specific responsive clones of stimulated lymphocytes and the capacity of bone marrow to produce increasing numbers of neutrophils and monocytes. Alterations in certain specific nucleotide positions also correlate with increases or decreases in viral virulence. Study in selenium-deficient mice infected with virulent virus also causes disease, and when the progeny virus is reinfected into normal mice, severe disease results, indicating that nutrition deficient cause virulence in virus.[38]

Vitamin A. In an animal study supplementation of 0.3 mg of retinyl acetate daily to protein-deficient mice for 2 weeks resulted in the increase the plasma retinol level to the value in protein sufficient mice. However, to prevent the decline of the IgA level caused by the protein deficiency1 mg/day of retinyl acetate was required. Profile of Th2 cytokines in this case IL-4 and IL-5 decreased in the small intestinal mucosa in mice fed with low-protein diet, and fewer IL-4 and IL-5-containing cells in the lamina propria were observed. The optimal dose of retinyl acetate seem likely was 1 mg/day, which significantly restored the IL-5 level and the number of IL-4- and IL-5-containing cells. The

same dose of retinyl acetate prevented the decline of anti-CT IgA level in the protein-deficient mice, improving their survival rate after an exposure to 0.1 mg of CT. High dose of oral vitamin A may improve mucosal IgA level during protein malnutrition, possibly by stimulating Th2 cytokine production and thereby, inducing resistance against infection.[39]

Vitamin E. Vitamin E is an efficient antioxidant and a modulator of the immune system. The study to investigate the immunology and antioxidant effects of vitamin E in healthy ethnic Chinese men and women found that the antioxidant properties of vitamin E were established by the elevation of plasma vitamin E, together with depression in both plasma malondialdehyde and urinary DNA adduct 8-hydroxy-29-deoxyguanosine after supplementation. This data suggest a specific requirement for vitamin E in total-T and T-helper cell proliferation. This study presents the first evidence of the beneficial effects of supplemental vitamin E in healthy Chinese individuals on cell-mediated immunity and oxidative stress.[40]

Zinc. Previous studies of more than thirty years yield that zinc deficiency rapidly diminishes both antibody- and cell-mediated responses in humans and animals. Increases in opportunistic infections and mortality rates were found in moderate deficiencies of zinc in sickle cell anemia, renal disease, chronic gastrointestinal disorders and acrodermatitis enteropathica; subjects with human immunodeficiency virus; children with diarrhea; and elderly persons can greatly alter host defense systems. Studies providing short periods of zinc supplementation fundamentally improve immune defense in individuals with these diseases. In animal models demonstrate that sub-optimal intake of zinc for 30 days can lead to 30–80% losses in defense capacity. Taken together, immune integrity is tightly associated with zinc status. Lymphopenia and thymic atrophy, which were early main features of zinc deficiency, are now known to be caused by high losses of precursor T and B cells in the bone marrow. This ultimately leads to lymphopenia or a failure to replenish the lymphocyte system. Glucocorticoid mediated apoptosis induced by zinc deficiency causes down-regulation of lymphopoiesis. Zinc itself can modulate death processes in precursor lymphocytes. There is substantial evidence that zinc supplementation may well reduce the impact of many of the aforementioned diseases by preventing the dismantling of the immune system. [41]

Iron. Although it is difficult to demonstrate the severity and relevance of these in observational studies, iron deficiency is associated with reversible abnormalities of immune function. Recent studies indicated iron treatment has been associated with acute exacerbations of infection, especially malaria. Five of 9 studies of oral iron supplementation have been associated with increased rates of clinical malaria, and 4 of 8 studies increased morbidity from other infectious disease. No studies of oral iron supplementation clearly show deleterious effects in non-malarias areas. However iron fortification milk reduced morbidity due to respiratory disease in two very early studies in non-malarias regions, but this was not confirmed in three later fortification studies, surprisingly breast-feeding alone resulted better morbidity rates. A study from Indonesia in a non-malarial area showed reduction infectious outcome after oral iron supplementation of anemic school children. No evidence of oral iron supplementation and infectious morbidity in breast-fed infants in non-malarial regions.[42]

Lipids. Nutritional status is generally believed as an essential factor involved in the modulation of immune response, which may be determinant in the development of the clinical effects derived from a malnutrition process. In recent years the effects that different dietary lipids exert upon immune functions have paid a special attention, since dietary lipid administration usually followed by alteration of different functions of immune system. Furthermore, in both animals and humans studies lymphocyte proliferation, cytokine production, phagocyte activity, adhesion molecule expression, and NK cell activity is susceptible to modification by the action of certain lipids. Modification of in these processes have been proposed to be involved, such as lipid peroxidation, changes in the plasma membrane, eicosanoid production, or alteration of gene expression. Both epidemiological and experimental studies have applied the beneficial properties associated with modulation of the immune functions. The immunosuppressant role associated with dietary polyunsaturated fatty acids containing fish oil may pro-

duce adverse effects because they reduce the host's natural resistance against pathogenic agents. Therefore, on the basis of recent experimental observations, the benefits of administering these dietary lipids should be considered before they are applied as immunosuppression factors, to prevent detrimental or adverse effects caused by an excessive suppression of immune functions.[43]

Summary

The host defense against pathogenic microbes requires dramatically different responses, depending on the character of the pathogen and on the tissue under attack. The host has evolved both innate and adaptive mechanisms to respond and eliminate pathogenic microbes. Both of these mechanisms include self-non-self discrimination.

Neonates, in part, protected against disease by maternal immunoglobulin (Ig). Maternal IgG is transported across the placenta before birth and maternal secretory IgA is present in breast milk and colostrums. These passively acquired antibodies provide protection against pathogens to which the mother was immune. Protection provided by passively transferred antibodies is short-lived. Maternal antibodies offer limited immunologic protection when compared with protection afforded by an infant's active immune response. Neonates are capable of generating both humoral and cellular immune responses to pathogens at the time of birth. Neonates can produce specific Th-cell subsets, including Th1-type cells that participate in cell-mediated immune responses and Th2-type cells that are primarily involved in promoting B-cell responses. The development of active humoral and cellular immune responses in the newborn is necessary environmental challenges.

In childhood protein-energy malnutrition (PEM), diverse innate and adaptive defenses are affected. With regard to innate defenses, influences on epithelial mucus are consistent with childhood protein-energy malnutrition (PEM)–associated risk of mucosal infection and bacterial translocation. Extensive information documents the phagocyte barriers. Cell-mediated immunity competence is consistently depressed in PEM, whereas the influence on humoral adaptive immunity is unpredictable.

Vitamin A deficiency is known to result in keratinization of the respiratory epithelium, leading to decrease in mucus production and diminished capacity of the respiratory epithelium to clear bacterial pathogens. Deficiency of other minerals, including iron and zinc, are well documented to impair immune function in experimental animals and in humans as well. The Vitamin E study found that there were specific requirement for vitamin E in total-T and T-helper cell proliferation and the beneficial effects of supplemental vitamin E in healthy individuals on cell-mediated immunity and oxidative stress. Zinc supplementation may reduce the impact of many of the aforementioned diseases by preventing the dismantling of the immune system. Milk with iron fortification reduced morbidity due to respiratory and infectious disease in anemic schoolchildren. Epidemiological and experimental studies have applied the beneficial lipid properties associated to a modulation of the immune functions.

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