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Modulation of Lung Allergic Inflammation and Malnutrition

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Abstract
Nutritional deficiency is commonly associated with a significantly impaired immune response, particularly in relation to cell-mediated immunity, the complement system, cytokine production and phagocyte function. However, there are few data on the consequences of nutritional deficiency in allergic diseases of the lung. In fact, malnutrition is the most common cause of immunodeficiency worldwide. Several studies have indicated that the incidence of alterations in lung functions can be associated with birth weight, specifically with maternal malnutrition, but data linking intrauterine undernutrition with allergic diseases of the lung are lacking. The purpose of this review is to associate malnutrition, including intrauterine malnutrition, with the establishment of immune responses and the development of lung allergic inflammation.

Immune System and Nutritional Deficiency

The immune system consists of organs and several cell types that recognize foreign antigens. The primary immunological organs are the bone marrow and the thymus, and the secondary organs include spleen, mesenteric lymph nodes and Peyer's patches. Immune cells can be grouped into two categories: lymphocytes and phagocytes. The latter group includes monocytes, macrophages and neutrophils [1]. In an immune response, the antigen is processed and presented to lymphocytes. Lymphocytes need to recognize the antigen via their receptors, as well as engage a co-stimulation molecule. This is followed by the activation of signaling molecules, which leads to the involvement of nuclear factor-κB (NF-κB), gene activation and mRNA transcription, followed by the synthesis and secretion of various cytokines. The secreted cytokines then bind to the appropriate receptors, leading to the clinical manifestations of various diseases [2].

Lymphocytes are a diverse population of cells that participate in both innate and adaptive immunity. Lymphocytes are white blood cells that are uniform in appearance but vary in function, and include T, B and natural killer (NK) cells. While T and B cells are the effectors of adaptive immunity, NK cells do not have recombined antigen receptors and are therefore innate immune lymphocytes [3].

When T cells recognize a foreign antigen presented to them, they initiate responses that precisely target that antigen. These responses include a direct attack by cytotoxic T cells against the antigen-bearing cell, the stimulation of antibody production by B cells and the induction of a local inflammatory response [4]. T cells can differentiate into at least two subtypes of T helper (Th) cells, Th1

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and Th2 cells. Th1 cells produce a number of cytokines including interferon-γ (IFN-γ), which plays a prominent role in coordinating the crosstalk between the innate and adaptive arms of the immune and inflammatory responses. IFN-γ stimulates macrophages to increase their production of a broad gamut of mediators, including autacoids, reactive oxygen species, lipid species and pro-inflammatory cytokines [5, 6]. Th2 cells can stimulate humoral immunity by producing a number of cytokines that stimulate the maturation of B cells into antibody-producing plasma cells, and promote B-cell class switching to increase the production of IgE antibodies. Th2 cells can also aid in the recruitment and activation of mast cells, additional effectors of allergic responses that contribute to chronic inflammation in a variety of tissues and disease states. In addition to these specialized pro-inflammatory responses, Th2 cells can dampen the inflammatory response by producing cytokines with anti-inflammatory properties, such as interleukin (IL)-10 [5].

It has long been accepted that immunity depends to some extent on nutrition. In fact, nutritional deficiency is commonly associated with impaired immune responses, particularly in relation to cell-mediated immunity, phagocyte function, cytokine production, the complement system, the secretory antibody response and antibody affinity [7–10].

Studies have pointed to the thymus as a potential mediator of the immunological consequences of undernutrition. Lymphoid tissues are acutely sensitive to undernutrition in infancy and early childhood, and severe malnutrition may lead to 'nutritional thymectomy', with lasting effects on immunity [11–14]. Besides atrophy of the lymphoid tissue, histologically, there is a loss of corticomedullary differentiation: there are fewer lymphoid cells, and Hassall bodies are enlarged, degenerated and occasionally calcified. In the spleen, there is loss of lymphoid cells around small blood vessels. In the lymph nodes, the thymus-dependent areas show lymphoid cell depletion [15]. The number of mature, fully differentiated T lymphocytes is decreased due, in part, to a reduction in serum thymic factor activity. In addition, lymphocyte proliferation and DNA synthesis are reduced [15].

Adverse factors that impair fetal growth can hinder immunological maturation, and this impairment causes prolonged effects on the immune response. Individuals born during the hungry season in the Gambia show immune system changes, e.g. lower thymic outputs, and decreased cellular and humoral responses [16, 17]. In Pakistani adults and Filipino adolescents, the antibody response to selected vaccines in those who were small at birth was lower than the response in those with a birth weight ≥2,500 g [18, 19].

The cellular immune response is impaired and lymphocyte subsets are altered in protein-calorie malnutrition (PCM) [20]. Tropical enteropathy often predates the onset of marasmus in Gambian children. This is characterized by a cell-mediated Th1 response, leading to chronic enteropathy characterized by crypt hyperplasia, villous stunting and high numbers of intraepithelial lymphocytes expressing CD25. T-cell numbers increase and B-cell numbers decrease with worsening nutrition, and mucosal cytokine production becomes biased toward a pro-inflammatory response [21]. These studies suggest that PCM is associated with a reduction in regulatory immune responses in the mucosal microenvironment, potentially impairing the normal mechanisms of immune regulation and tolerance [22].

In animal models of intrauterine nutritional deficiency, protein energy malnutrition as well as deprivation of selected nutrients results in reduced immune responses in the offspring [23]. Deficiencies in pyridoxine, folic acid, and vitamins A, C, and E result in impaired cell-mediated immunity and reduced antibody responses. Decreased lymphocyte stimulation in response to mitogens such as phytohemagglutinin is observed in vitamin B deficiency. Zinc deficiency is associated with lymphoid atrophy, decreased delayed cutaneous hypersensitivity responses and lower thymic hormone activity [9]. Fraker [24] suggested the effects of zinc restriction on lymphocyte glucocorticoid receptors in laboratory rodents as a mechanism for immunosuppression. In a mouse model, Beck et al. [25] showed that pulmonary damage due to the influenza virus was greater in selenium-deficient animals.

Although T and B lymphocytes represent effector cells of the immune system, the functional capacities of lymphocytes, especially in the induction and function of antigen-specific lymphocytes, are regulated by antigen-presenting dendritic cells (DC) [26]. Studies have demonstrated that impaired functional capacities of DC are related to the pathogenesis of a chronic viral carrier state and that the activation of DC in these subjects has therapeutic potential [27, 28]. Niiya et al. [29] demonstrated in PCM mice that there were decreases in the number of spleen DC, their T-lymphocyte-stimulatory capacities, and their production of IL-12p70 and IFN-γ. The authors suggested that chronic undernutrition disrupts antigen-specific immune responses, and that this disruption can be attributed at least in part to reduced numbers and impaired functions of DC.

Macrophages are a major component of the mononuclear phagocyte system and consist of closely related cells of bone marrow origin, including blood monocytes and tissue macrophages. From the blood, monocytes migrate to various tissues and transform into macrophages. Macrophages have three major functions in inflammation: antigen presentation, phagocytosis and immunomodulation through the production of various cytokines and growth factors. Macrophages play a critical role in the initiation, maintenance and resolution of inflammation. They are activated and deactivated in the inflammatory response. Activation signals include cytokines (IFN-γ, granulocyte-macrophage colony stimulating factor, GM-CSF, and TNF-α), bacterial lipopolysaccharide (LPS), extracellular matrix proteins and other chemical mediators. Inhibition of inflammation by the removal or deactivation of mediators and inflammatory effector cells permits the host to repair damaged tissues [30].

Depression of the cellular immune system predisposes the host to increased morbidity and mortality in experimental models and in human PCM [31, 32]. Significant impairments in global functions of the macrophages that are vital for regulating both the innate and adaptive immune systems have been demonstrated in PCM [33]. Macrophage dysfunction in PCM includes significantly diminished pro-inflammatory cytokine production, decreases in respiratory burst activity, impaired phagocyte activity and significant decreases in the cell yield of peritoneal macrophages [33, 34]. Additionally, malnutrition is associated with a significant increase in baseline and stimulated peritoneal macrophage apoptosis that contributes to an immunocompromised state [35]. Anstead et al. [36] demonstrated that macrophages from a murine model of multinutrient undernutrition showed increased IL-6 production (a potential immunosuppressive mediator) and decreased IL-10 and TNF-α production following stimulation with IFN-γ/LPS. Neutralization of TNF-α in macrophage cultures from control mice mimicked the effect of malnutrition on nitric oxide (NO) and IL-10 production (where these productions were reduced), whereas supplemental TNF-α added to cultures of macrophages from malnourished mice increased NO secretion. Redmond et al. [34] also demonstrated that superoxide anion production in resident and activated (LPS, IFN-γ and bacille Calmette-Guérin infection) peritoneal macrophages was significantly reduced in malnourished mice. Candida phagocytosis and killing was also suppressed [34].

The role of micronutrients on phagocytosis functions has been demonstrated. Zinc deficiency results in decreased human monocyte phagocytosis [37], and zinc supplementation directly induces cytokine production (predominantly IL-1, IL-6 and TNF-α) by mononuclear cells in vitro [38].

In a recent study, Rodriguez et al. [39] showed that malnutrition in children severely impaired IL-2 and IFN-γ production, and increased IL-4 and IL-10 production by CD4+ and CD8+ cells. These findings demonstrate that malnutrition alters the balance of type 1 and type 2 responses. Th1 cells produce IL-2, IFN-γ and TNF-α, and mediate immunity to viral and bacterial pathogens, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-10 and IL-13, and are involved in allergic diseases and the defense against parasitic infections. In addition, the activation capability of CD4+ and CD8+ cells is considerably decreased. The authors concluded that these alterations contribute to the reduced immunological capacity and increased sensitivity to infections associated with malnutrition.

The complement system is composed of membrane-bound regulators and receptors as well as numerous plasma proteins that interact with various cells and mediators of the immune system [40]. This system plays an important role in anti-microbial defense, and in the clearance of immune complexes as well as apoptotic and necrotic cells. The role of complement is not restricted to the innate immune system and includes important functions in the regulation of adaptive immune responses. The complement system consists of three different pathways that all converge on the activation of the central complement molecule, C3 [41, 42]. Activation of C3 results in a variety of immunological reactions, such as immune adherence, phagocytosis, antibody response, cytolysis, inflammation and the killing of pathogenic microorganisms. In protein malnutrition, the concentrations and activity of most complement components are decreased. A reduction in C3, C5, factor B and total hemolytic activity has been well documented. A slight reduction in the opsonic activity of plasma and a reduction in the metabolic activation and intracellular destruction of bacteria have also been observed [7].

Chandra et al. [43] showed that PCM decreased the affinity of antibodies to tetanus toxoid, especially after primary immunization, which may explain the higher frequency of antigen-antibody complexes found in malnourished patients. As opposed to serum antibody responses, secretory IgA (sIgA) antibody concentrations were lower after immunization with viral vaccines; there was a selective reduction in sIgA concentrations with some compensatory increase in IgM concentrations in

secretions. This may have several clinical implications, including an increased frequency of septicemia commonly observed in undernourished children [7, 15]. IgG from the mother acquired through placental transfer is the principal immunoglobulin in cord blood. All four subclasses of IgG are detected in fetal sera as early as 16 weeks of gestation, with the bulk consisting of IgG1. In small-for-gestation infants, the cord blood levels of IgG1 are reduced much more than those of the other IgG subclasses; the number of immunoglobulin-producing cells and the amount of immunoglobulin secreted is decreased in small-for-gestation infants who are symptomatic (those with recurrent infections) [44].

Malnutrition and Lung Allergic Inflammation

Asthma is one of the most common allergic diseases in industrialized countries. In 1998, nearly 50% of school-aged children suffered from atopy or other types of hypersensitivity [45].

Asthma is a complex syndrome with many clinical phenotypes in both adults and children. Its major characteristics include a variable degree of airflow obstruction, bronchial hyperreactivity and airway inflammation [46]. The pathological process is linked to chronic inflammation and its role in the induction of hyperresponsiveness following infiltration and accumulation of inflammatory cells [47].

In asthma, the airway lumen is occluded by a tenacious mucus plug composed of plasma proteins exuded from airway vessels and mucus glycoproteins secreted from surface epithelial cells. The airway wall is edematous and infiltrated with inflammatory cells, which are predominantly eosinophils and lymphocytes. In fact, the inflammation that occurs in asthma is often described as eosinophilic [48]. The eosinophil number has been shown to correlate with the severity of the disease. This happens because eosinophils have the potential to cause damage to the airway mucosa and associated nerves through the release of granule-associated basic proteins (which damage nerves and epithelial cells), lipid mediators (which cause bronchoconstriction and mucus hypersecretion) and reactive oxygen species (potentially able to injure mucosal cells) [49].

Inflammatory mediators such as prostaglandins, leukotrienes, platelet-activating factor (PAF) and NO are involved in the pathogenesis of asthma, where they contribute to early events such as inflammatory cell infiltration, bronchial hyperreactivity and mucus secretion [50].

The production of prostaglandins in the airways is well documented, but it is not clear whether these mediators play a deleterious or a beneficial role in airway diseases. Prostaglandin E_2 (PGE_2) has been shown to have a protective effect on allergen-induced [51] and aspirin-induced asthma [52]. An inverse correlation between eosinophilic airway inflammation and PGE_2 concentration in induced sputum from asthmatic subjects has also been shown, which supports the possible anti-inflammatory role of PGE_2 [53]. On the other hand, other studies suggested that PGE_2 may enhance eosinophil survival, supporting a potential pro-inflammatory role for PGE_2 [54, 55].

The cysteinyl-leukotrienes, LTC_4, LTD_4 and LTE_4, are potent inflammatory mediators that play an important role in the pathophysiology of asthma and are elevated in the airways in response to allergen challenge [56, 57]. In asthma, bronchoconstriction, bronchial hyperreactivity induction, increased vascular permeability, mucus secretion and smooth muscle cell proliferation are all related to leukotriene activity [58]. The inhibition of the cysteinyl-leukotrienes with selected receptor antagonists has marked anti-inflammatory effects, including inhibition of airway eosinophil influx and hyperreactivity, and secretion of mucus and cytokines [59, 60]. PAF is also released in several asthma models and has a number of effects, including the recruitment and activation of eosinophils [61], the release of mediators such as LTC_4 from eosinophils and the stimulation of mucus secretion [62]. However, previous studies with PAF receptor antagonists have failed to show significant beneficial effects on the allergen-induced response in asthmatic subjects, thus casting doubt on the importance of PAF as a major mediator in asthma [63, 64].

NO seems to play an important role in amplifying and perpetuating Th2-mediated inflammatory responses. It has been speculated that the large amount of NO generated in the asthmatic airways may result in the suppression of Th1 cells and that a concomitant reduction in IFN-γ levels may lead to the proliferation of Th2 cells [65]. The exhaled NO detected in asthmatics appears to be derived from inducible NO synthase (iNOS) expressed by bronchial epithelial cells or immuno-inflammatory cells following allergen exposure, as was shown in sensitized mice [66, 67]. It is also clear that pulmonary iNOS expression is up-regulated in the lungs of asthmatics [66, 68]. However, the role of iNOS in asthma as either a pro- or anti-inflammatory mediator remains unresolved. Experimental models of asthma in mice have shown that acute inhibition of iNOS activity either reduced the num-

ber of eosinophils and lymphocytes in the bronchoalveolar lavage fluid, reduced hyperreactivity and mucus production [69–71], or exacerbated airway inflammation and chemokine expression [72]. Controversial data were also found in studies with iNOS knockout mice. Xiong et al. [73] showed that iNOS knockout animals displayed diminished airway inflammation, while others showed that airway inflammation is fully expressed in iNOS knockout mice [70, 74].

In asthma, cytokines produced by activated Th2 lymphocytes are believed to play critical roles in regulating the inflammatory process. IL-4, IL-5, IL-13 and transforming growth factor-β (TGF-β) have been suggested to be key factors contributing to the chronic inflammatory state characterizing asthma [75].

In asthmatic patients, there is an increase in the number of CD4+ T cells in the airways, which are predominantly Th2 cells, whereas in normal airways, Th1 cells predominate [76].

IL-4 appears to be important in the early stages of Th2 cell development. The synthesis of IgE by B lymphocytes in immunoglobulin isotype switching occurs with the expression of IL-4 [49].

IL-5 may play an important part in eosinophil maturation, chemoattraction and activation in asthma, which may underlie bronchial hyperresponsiveness. It may also interact with other eosinophil chemoattractants and activators such as chemokines to activate and induce chemoattraction of eosinophils [75]. In addition, IL-5 is related to airway remodeling; in IL-5-deficient mice chronically challenged with allergens, peribronchial fibrosis and the thickness of the peribronchial smooth muscle layer are significantly reduced [77].

An increased expression of IL-13 mRNA has been reported in the airway mucosa of patients with atopic and non-atopic asthma. There is a significant correlation between eosinophil counts and IL-13 levels, since IL-13 administered to mice increases airway eosinophilia and bronchial hyperresponsiveness. IL-13 induces the expression of CD23 in purified human B cells and acts as a switch factor directing IgE synthesis, similarly to IL-4 [78].

In asthma, the airway epithelium is frequently subject to damage, and current concepts suggest that TGF-β could play an important role in modulating repair of the airway in asthma [79]. TGF-β may contribute to epithelial repair by altering epithelial cell adhesion and modulating epithelial cell proliferation and differentiation as well as epithelial cell production of other mediators [80].

Although genetic factors play an important role in an individual's risk for asthma, there is strong evidence that nutrition also affects the development of lung allergic diseases.

Vitamin A, E and C are the vitamins most extensively investigated for their effects on asthma. All three are antioxidants, and vitamins C and E may also have other anti-inflammatory or anti-allergic effects [81] because supplementation with vitamins C and E improves lung function in asthmatic children exposed to high levels of air pollution [82].

Vitamin A is essential for cellular and subcellular membrane stability, and influences the growth and repair of epithelial cells [83]. Vitamin A may also modulate Th1/Th2 development with a shift toward Th2 [84]. Schuster et al. [84] showed that vitamin A deficiency produced by a strict diet deficient in vitamin A prevents the development of ovalbumin-induced allergic airway inflammation and hyperresponsiveness, which are the hallmarks of asthma. Vitamin A deficiency also reduced other markers of pulmonary inflammation, including pulmonary eosinophilia, the levels of IL-4 and IL-5 in bronchoalveolar lavage and the synthesis of plasma IgG.

Zinc deficiency in animals is associated with a wide range of immune impairments and has a marked impact on bone marrow, decreasing the number of nucleated cells, and the number and proportion of cells derived from lymphoid precursors [85]. Moderate or mild zinc deficiency in men results in decreased NK cell activity, a lowered CD4+:CD8+ ratio and decreased lymphocyte proliferation [86]. Richter et al. [87] demonstrated in a murine model that zinc deficiency increases allergic eosinophilic inflammation, whereas dietary zinc supplementation attenuates its intensity.

Minerals like selenium and magnesium have been linked to asthma development. Selenium is also involved in antioxidant defenses as a coenzyme for glutathione peroxidase. Early case-control studies demonstrated decreased selenium intakes and serum levels in patients with asthma in New Zealand [82, 88, 89] and the United Kingdom [90]. Magnesium has several biological effects of potential relevance to asthma, including bronchodilation when given intravenously in acute severe asthma [91]. There is also strong cross-sectional epidemiologic evidence for dietary magnesium as a protection against asthma [82, 88, 89].

Godfrey [92] reported that people in Africa presenting variable degrees of malnutrition have low incidences of allergic diseases despite having high IgE levels in the serum. In fact, Forte et al. [93] showed that children with

moderate primary PCM presented reduced serum IgE levels, which could correspond with reduced atopic reactions in malnourished patients.

Epidemiologic studies have indicated that in humans, the incidence of alterations in lung functions can be associated with birth weight and specifically with maternal malnutrition [94, 95]. However, with respect to lung allergic inflammation, the data are controversial.

Some authors have demonstrated no association between low birth weight and asthma. Hagstrom et al. [96], analyzing characteristics such as birth weight, birth height, head circumference, placental weight and gestational age, concluded that birth weight was not associated with a 'programming' factor for asthma, and other environmental factors in childhood seemed more important than fetal malnutrition for the development of asthma in adult life. Brooks et al. [97] evaluated the contribution of birth weight to asthma prevalence among children younger than 4 years in the United States, and observed a strong independent association between low birth weight and asthma.

On the other hand, some authors have demonstrated that asthma symptoms are inversely associated with birth weight. Kitchen et al. [98] concluded that increased bronchial responsiveness is common in school children who were born substantially preterm. Barker et al. [99] found that the level of forced expiratory volume in 1 s in elderly males and the mortality from chronic obstructive lung disease in males were both inversely associated with birth weight. The authors hypothesized that intrauterine conditions causing growth retardation might irreversibly constrain the development of the airways. A study in Israeli recruits showed an association between low birth weight and asthma in male adolescents [100], and in a study of British children aged 5–11 years, lung function was associated with birth weight, and respiratory illness was associated with prematurity [101]. Svanes et al. [102] analyzed a random sample of young adults in Norway, and concluded that asthma symptoms were strongly associated with low birth weights, and the risk for adult asthma partly established early in life. These results suggest that poor intrauterine growth is involved in the etiology of asthma.

Many studies indicate low birth weight as a risk factor for asthma during childhood [97, 103, 104]. However, when only adult individuals were considered, the relationship between low weight presented at birth and asthma was controversial [105]. In fact, Landgraf et al. [106], investigating the development of asthma in intrauterine undernourished rats, observed that rats challenged with ovalbumin at 9 weeks of age presented significant decreases in the allergic inflammatory response compared with rats challenged with ovalbumin at 5 weeks of age. These data indicate that, in intrauterine undernourishment models, the intensity of the allergic inflammatory response depended on the age at which the organism was challenged.

Leptin and Glucocorticoids in Malnutrition

The obese *(ob)* gene product, named leptin from the Greek term *leptos* meaning thin, is a pleiotropic cytokine involved in different biologic systems. It shares structural similarities with some cytokines (including IL-6, IL-11, IL-12 and IL-15) as well as granulocyte colony-stimulating factor and leukemia-inhibitory factor. As an endocrine hormone, leptin is synthesized mainly by adipose tissue in proportion to the body mass index and the body fat mass [107–109]. It is present in nanogram concentrations in the systemic circulation to limit food intake, to promote the breakdown of fat and to increase energy expenditure [107].

The genetic defect in *ob/ob* mice was first described in the 1950s as a spontaneous mutation that causes a severe obese phenotype due to both overeating and decreased energy expenditure [110]. Studies on both leptin-deficient *(ob/ob)* and leptin receptor-deficient *(db/db)* mice have illustrated the diverse functions of leptin, as revealed by the findings of marked abnormalities in neuroendocrine function [111, 112].

Leptin plays a major role in modulating immune responses [113]. It has been shown to provide a proliferative signal in hematopoiesis and lymphopoiesis. Moreover, it can activate monocytes, DC and macrophages, and stimulate them to produce Th1-type cytokines [114]. Leptin also exerts activating effects on neutrophils and NK cells and stimulates their gene expression [115–117]. A modulatory role in adaptive immunity by enhancing T-cell survival and stimulating T-cell production of pro-inflammatory cytokines such as IFN-γ has also been demonstrated [118, 119].

Cytokines orchestrate the host response to infectious and inflammatory stimuli. The induction of a cytokine cascade, which includes TNF-α, IL-6 and IL-1, leads to pathophysiological changes such as hypoglycemia, induction of acute-phase response proteins and anorexia [120]. Leptin levels are acutely increased by inflammatory and infectious stimuli such as LPS, IL-1, TNF-α and ovalbumin [106, 121–123].

In macrophages/monocytes, leptin up-regulates phagocytic function [124] via phospholipase activation [125], as well as pro-inflammatory cytokine secretion, such as TNF-α (early), IL-6 (late) and IL-12 [119, 126, 127]. In macrophages, leptin can induce the production of factors involved in regulating the immune response, e.g. NO, LTB_4, cholesterol-acyl-transferases-1 and the cyclooxygenase COX-2 [124, 128–130]. Leptin deficiency exacerbates susceptibility to LPS- and TNF-α-induced lethality and liver injury [131]. These data support a pleiotropic role for leptin in maintaining immune homeostasis by regulating the survival and activity of immune cells and innate immune responses [132].

In addition to modulating phagocytosis and cytokine production by macrophages, leptin has been shown to regulate another aspect of the nonspecific immune response. Functional OB-R (leptin receptor) was detected on the membrane of polymorphonuclear neutrophils (PMN) and was shown to enhance oxidative species production by stimulated PMN [133]. This indicates that leptin can modulate PMN functions by regulating their oxidative capacity [108].

Other effects of leptin on lymphocytes include the alloproliferative enhancing response of human peripheral blood lymphocytes by acting on naïve T lymphocytes [113], phytohemagglutinin- and concanavalin A-induced proliferation in human T lymphocytes, which increases the expression of activation markers CD69, CD25 and CD71 in CD4+ and CD8+ cells [127], cytokine production by T lymphocytes, polarization of Th cells toward a Th1 phenotype by enhancing proliferation and IL-2 production of naïve T cells, the increase in IFN-γ production and the inhibition of IL-4 production in memory CD4+ T cells, and the up-regulation of the expression of adhesion molecules (e.g. VLA-2 and ICAM-1) on CD4+ T cells [113].

Consistent with the proliferative activity of leptin on T cells, thymic atrophy is present in leptin-deficient mice *(ob/ob)* and leptin receptor-deficient *(db/db)* mice [134, 135]. Indeed, leptin-deficient mice *(ob/ob)* and leptin receptor-deficient *(db/db)* mice develop a complex syndrome characterized by abnormal reproductive function, hormonal imbalance, and alterations in the hematopoietic and immune systems. Similar alterations have been described in leptin-deficient-humans [136].

The mechanism for the presumed anti-inflammatory effect of leptin deficiency is unknown [137], but an imbalance between pro- and anti-inflammatory cytokines has been noted [131, 138]. Mancuso et al. [124, 125] showed that leptin augments leukotriene synthesis of alveolar macrophages, and leptin-deficient mice present reduced leukotriene synthesis. In nourished rats submitted to allergic lung inflammation, leptin levels were increased, while no increase was observed in intrauterinely undernourished rats. Coincidently, reduced levels of LTB_4 and LTC_4 were also found [106].

Malnutrition is known to induce a state of immunodeficiency and a predisposition to death by infectious diseases [139]. During fasting or starvation, leptin levels drop disproportionately to the decrease in adipose tissue mass, and the correlation between leptin levels and fat stores is lost [140]. The adaptation of the organism to starvation is characterized by metabolic, endocrine and immunological changes. Suppression of immune, reproductive and thyroid functions, and stimulation of the hypothalamus-pituitary-adrenal (HPA) axis are among the changes induced by starvation, as well as reduced immunity, particularly the T-lymphocyte response [141, 142]. Leptin levels fall sharply with the onset of starvation. Conversely, the administration of leptin effectively prevents neuroendocrine alterations, which include changes in gonadal, adrenal and thyroid hormones in male mice, and the delay in ovulation in female mice [140]. In humans, Canavan et al. [143] observed that physiological leptin administration stimulates inflammatory and platelet responses during caloric deprivation.

Leptin is hypothesized to promote the Th1 immune response with secretion of the pro-inflammatory cytokine IFN-γ [144], and malnutrition-related hypoleptinemia is associated with a reduced Th1 response [145].

Glucocorticoids, specifically cortisol in humans and corticosterone in rodents, are potent anti-inflammatory agents, and the HPA axis functions to modulate susceptibility or resistance to inflammatory disease [146].

Glucocorticoids bind to glucocorticoid receptors in the cytoplasm which then dimerize and translocate to the nucleus, where they bind to glucocorticoid response elements on glucocorticoid-responsive genes, resulting in increased transcription. The most striking effect of glucocorticoids is to inhibit the expression of multiple inflammatory genes (cytokines, enzymes, receptors and adhesion molecules). This is likely to be due to a direct inhibitory interaction between activated glucocorticoid receptors and activated transcription factors, such as NF-κB and activator protein-1, which regulate inflammatory gene expression [147, 148].

Glucocorticoids may control inflammation by inhibiting many aspects of the inflammatory process via an increase in the transcription of anti-inflammatory genes and a decrease in the transcription of inflammatory genes [147, 149, 150].

Glucocorticoids can suppress inflammation by increasing the synthesis of several anti-inflammatory proteins, such as:

- lipocortin-1, a protein that has an inhibitory effect on phospholipase A_2 (PLA_2) and therefore may inhibit the production of lipid mediators [151];
- IL-1 receptor antagonist, a cytokine that blocks the binding of IL-1 to its receptors, whose synthesis is increased by glucocorticoids, thus counteracting the effect of the pro-inflammatory cytokine IL-1 [152, 153];
- IL-10, which inhibits the transcription of many pro-inflammatory cytokines, chemokines and inflammatory enzymes [154, 155];
- IκB, the inhibitory protein that regulates NF-κB; glucocorticoids can increase the synthesis and transcription of IκB-α, the predominant form of IκB, in mononuclear cells and T lymphocytes, inhibiting NF-κB activity [148, 156].

Glucocorticoids also exert inhibitory effects on the transcription of several pro-inflammatory cytokines such as IL-1β, IL-2, IL-3, IL-6, TNF-α, GM-CSF and chemokines including IL-8, RANTES, MCP-1, MCP-3, MCP-4, MIP-1α and eotaxin [157–162].

Inflammatory enzymes can be negatively modulated by glucocorticoids, resulting in a reduced inflammatory response. It has been shown that inhibition of COX-2 by glucocorticoids results in the reduced formation of prostaglandins and tromboxanes [163, 164], as well as inhibition of gene transcription of a cytosolic form of PLA_2 induced by cytokines [165]. Glucocorticoids can also inhibit the induction of the inducible form of NO synthase (iNOS).

Glucocorticoids can reduce the survival of some inflammatory cells such as eosinophils and T lymphocytes. Eosinophil survival is dependent on the presence of cytokines such as IL-5 and GM-CSF, and exposure to glucocorticoids blocks the effects of these cytokines and leads to eosinophil apoptosis [147, 166, 167].

Adhesion molecules play an important role in the trafficking of inflammatory cells to sites of inflammation. The expression of adhesion molecules on endothelial, epithelial or inflammatory cells can be induced by cytokines, and glucocorticoids may indirectly reduce the expression of these molecules. Inhibitory effects on the production of cytokines (e.g. IL-1β and TNF-α) or a direct inhibitory effect on adhesion molecules such as ICAM-1 and E-selectin at the level of gene transcription can account for the indirect effects of glucocorticoids [168–170].

Animal models [171, 172] and clinical studies [173–175] have associated maternal protein-calorie undernutrition with higher glucocorticoid levels. In intrauterine undernourished rats, along with increased glucocorticoid levels, downregulation of L- and P-selectin and ICAM-1 expression have been observed. This may contribute to the decreased leukocyte migration presented by these rats [176]. In addition, impaired L-selectin expression was found in bone marrow cells [177].

It is well established that food availability influences the rhythmicity of the HPA axis. Indeed, starvation and food restriction increase the activity of the HPA axis both in humans [178, 179] and in rats [180, 181]. This can lead to adrenal hypertrophy and increased circulating glucocorticoid levels. This alteration, in addition to affecting the metabolic homeostasis, can compromise innate defense mechanisms [182].

In prenatal undernutrition, this is not well established. Lesage et al. [183] verified that rat fetuses from undernourished dams during the last week of gestation presented higher plasma corticosterone levels than did fetuses from nourished dams. Landgraf et al. [106] observed that an increase in glucocorticoid levels probably contributes to attenuated allergic lung inflammation in intrauterine undernourished rats. On the other hand, Langley-Evans et al. [184] observed unaltered basal corticosterone concentrations, but increased hippocampal glucocorticoid receptor binding, in the progeny of protein-restricted rats, a result that suggests increased glucocorticoid feedback sensitivity.

Low leptin levels and hypercortisolemia are prominent features of starvation, and both leptin and glucocorticoids have been shown to have immunomodulating properties. Furthermore, a regulatory loop exists between the HPA axis and circulating leptin. In *ob/ob* mice, leptin deficiency results in chronic HPA axis activation, which is reversed by leptin treatment [185]. Fasting leads to low leptin levels and HPA axis activation. Leptin administration during fasting substantially prevents the activation of the HPA axis [185, 186], and the reduction of hypercortisolemia might mediate some of the immunosuppression due to the low levels of leptin during starvation. It is therefore likely that the effects of leptin on the immune system are both direct and mediated by the leptin-induced modulation of glucocorticoid levels [108].

Combined with a decrease in leptin levels that may mediate the glucocorticoid response [149], the increase in blood glucocorticoid levels is part of the early endocrinologic response to acute deficits in protein and energy [187].

Concluding Remarks

The data presented in this article indicate that inadequate nutrition affects immune responses. Adverse factors that impair fetal growth can hinder immunological maturation, and this impairment causes prolonged effects on immune responses. The nutritional deficiency is associated with depression of immune responses, in relation to cell-mediated immunity, phagocyte function, cytokine production, the complement system, the secretory antibody response and antibody affinity. Epidemiologic studies have indicated that in humans the incidence of alterations in lung functions can be associated with birth weight and specifically with maternal malnutrition. Whereas some authors demonstrated no association between low birth weight and asthma, others demonstrated that asthma symptoms are inversely associated with birth weight. Intrauterine nutrition is fundamental for the development and functioning of organs and tissues, and intrauterine undernourishment reduced allergic lung inflammation in the offspring. In an intrauterine undernourishment model, the intensity of the allergic inflammatory response depends on the age at which the organism is challenged. It is likely that leptin affected the immune system (i.e. the decrease in allergic inflammatory responses) both via a direct effect and via interference on glucocorticoid levels.

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