Nutritionally Mediated Programming of the Developing Immune System[1,2]

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ABSTRACT

A growing body of evidence highlights the importance of a mother's nutrition from preconception through lactation in programming the emerging organ systems and homeostatic pathways of her offspring. The developing immune system may be particularly vulnerable. Indeed, examples of nutrition-mediated immune programming can be found in the literature on intra-uterine growth retardation, maternal micronutrient deficiencies, and infant feeding. Current models of immune ontogeny depict a "layered" expansion of increasingly complex defenses, which may be permanently altered by maternal malnutrition. One programming mechanism involves activation of the maternal hypothalamic-pituitary-adrenal axis in response to nutritional stress. Fetal or neonatal exposure to elevated stress hormones is linked in animal studies to permanent changes in neuroendocrine-immune interactions, with diverse manifestations such as an attenuated inflammatory response or reduced resistance to tumor colonization. Maternal malnutrition may also have a direct influence, as evidenced by nutrient-driven epigenetic changes to developing T regulatory cells and subsequent risk of allergy or asthma. A 3rd programming pathway involves placental or breast milk transfer of maternal immune factors with immunomodulatory functions (e.g. cytokines). Maternal malnutrition can directly affect transfer mechanisms or influence the quality or quantity of transferred factors. The public health implications of nutrition-mediated immune programming are of particular importance in the developing world, where prevalent maternal undernutrition is coupled with persistent infectious challenges. However, early alterations to the immune system, resulting from either nutritional deficiencies or excesses, have broad relevance for immune-mediated diseases, such as asthma, and chronic inflammatory conditions like cardiovascular disease. *Adv. Nutr. 2: 377–395, 2011.*

Introduction

The "developmental origins of health and disease" paradigm maintains that nutritional or other environmental stimuli during critical periods of growth and development have the potential to permanently "program" the structure and/or function of cell populations, emerging organ systems, or homeostatic pathways (1). Although the immediate sensitivity of the embryo and fetus to external insults was well known, epidemiological studies carried out by Barker et al. (2,3) in the 1980s first revealed that events in fetal life could influence longer-term disease risk. Work in this field has primarily considered general nutritional conditions reflected by anthropometric measures (e.g. low birth weight) more so than micronutrient nutriture. It has also focused largely on chronic conditions resulting from alterations to the developing brain, kidney, and pancreas (4). A more limited set of studies has addressed plasticity in the immune system, including specific functional changes (5–9), disease susceptibility (10), and risk of mortality from infection (11–17).

Perturbations to the emerging immune system, particularly from nutritional imbalances, both deficiency and excess, can have considerable effects throughout life. Of primary public health concern is excess morbidity and mortality from infectious disease in infants and young children. However, the increased risk may continue throughout childhood, adolescence, and adult life. Moreover, alterations to the immune system's complex regulatory functions during early life can have consequences for autoimmune or allergic disorders, as well as chronic inflammatory conditions such as metabolic syndrome, cardiovascular disease, diabetes, and cancer (18–20).

Current status of knowledge

Ontogeny of the immune system

A modern understanding of the origins and development of the immune system is fundamental to studying its nutritional

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mediation in the fetus. In humans, immune cells and organs rapidly proliferate in the first trimester of pregnancy. Early cells undergo progressive waves of maturation, some unique to the fetal period, as they build the capacity to recognize and adapt defenses to specific pathogens (21). Although the immune system is qualitatively complete at birth, exposures during infancy and early childhood are essential for expansion and priming of adaptive cell populations. These critical periods of development are highly vulnerable to insult, which may permanently alter immune defenses. Ontogenesis of the immune organs, innate and adaptive defenses is discussed below (**Fig. 1**).

Organ development. Stem cells in the para-aortic splanchopleura, the yolk sac, and the liver sequentially generate lymphomyeloid precursors during the embryonic and early fetal periods (22). Although the liver remains the primary site of fetal hematopoiesis, circulating precursors home to the developing bone marrow as early as gestational wk 5 and this organ progressively assumes responsibility for lymphomyeloid progenitor activity (23). The thymus also emerges in wk 5 from the endoderm of the 3rd pharyngeal pouch (24). Although no lymphocytes are present, thymic epithelial cells differentiate and start secreting hormones at 5–6 wk gestation (25). Colonization by T cell precursors follows (26), with gestational wk 7–14 representing the critical period for thymic growth and development (27).

Secondary lymphoid organs appear during the late embryonic and early fetal periods (28), when liver-derived hematopoietic progenitors home to and cluster with mesenchymal cells at the sites of future organs (29). Lymphotoxin signaling by these clusters enables them to attract and capture additional hematopoietic cells, forming a primitive anlagen (30), and subsequently guides structural development, as in the segregation of B and T cells in the spleen (31). Development of the secondary lymphoid organs is highly ordered and largely complete by the time of birth (30,32). However, recent work indicates that these organs, and particularly the gut-associated ymphoid tissues, retain considerable plasticity to environmental stimuli throughout life (33).

Lymphopoiesis. As noted above, precursor cells migrate to the developing immune organs, which support their differentiation and maturation into lymphoid and myeloid immune cell populations (23). A growing body of evidence, largely based on murine models, suggests that these processes are developmentally programmed. Herzenberg (34) has referred to this as the "layered evolution" of adaptive immunity, whereby an early layer of broad defenses is followed by layers of increasingly complex mechanisms that recognize and control specific pathogens. The earliest immune layer is derived from pre-HSC[3], unique to the fetal and neonatal period. Pre-HSC are theoretically overtaken by mid-HSC around the time of weaning and finally the HSC of normal adults (35). Other models suggest a distinction only between pre-HSC and adult HSC (36). The concept of layered immune development is supported by the identification of phenotypically distinctive fetal progenitors in mice, which are derived from endothelial cells of the yolk sac and para-aortic splanchopleura (37,38). Recent research by Mold et al. (21) extends these findings to humans, revealing differences between fetal and adult HSC, as well as the lymphocyte lineages arising at different stages of development.

Innate defenses. The epidermal and mucosal barriers that comprise the front line of innate defense appear early in gestation but rapidly mature in the 3rd trimester to provide adequate protection within a few weeks of birth (28,39). Complement proteins are also present in the first trimester and nearly all reach 50–75% of adult concentrations at term (40). Innate effector cells are detectable in emerging immune organs and fetal circulation by the end of the first trimester (41–43). Rapid DNA synthesis and mitotic division enable granulocytes to meet or surpass adult levels within 48–72 h; however, exhaustion of expansion capacity and surface protein expression limit innate effector cell functions during infancy (40,44,45). Tissue macrophages, NK cells, and natural killer cytolytic activity do not reach adult levels until later in childhood (46,47).

Adaptive-cellular defenses. Lymphoid progenitors are present in the thymus by approximately 8 wk of gestation. Maturing thymocytes produce CD3 mRNA by 10 wk and begin somatic recombination of TCR genes between 11 and 22 wk of gestation (26). Fetal T cells are capable of responding to challenge (48); however, most remain naïve due to reduced in utero antigen exposure (49). Early $CD4^+$ T cells also express CD45RA, limiting their helper activity and thereby suppressing $CD8^+$ cytolytic effector function (50). T lymphocytes that are activated in early life are typified by anti-inflammatory T-helper 2 responses and tolerance induction, whereas inflammatory T-helper 1 responses are developmentally delayed until ~1 y of age (51). In addition to classic $CD4^+$ and $CD8^+$ effector cells, a subset of $CD4^+$ cells expressing transcription factor FOXP3, i.e. natural T_{Reg} cells, are also present in the fetal thymus (52). Some work suggests that T_{Reg} production may be at its peak during fetal life (53) and that this subpopulation is largely responsible for tolerance induction in utero (54).

Recent research in humans demonstrates that fetal HSC give rise to T cells that differ both in functional properties and gene expression from adult T cells (21), supporting the hypothesis of layered immune development. Interestingly, fetal HSC-derived T cells exhibited a tolerogenic bias. Similar distinctions are well defined in mice, where early TCR gene rearrangements are highly ordered; bursts of $\gamma\delta$ T cells characterized by specific Vγ and Vδ gene segments are produced during fetal and neonatal life (55) but overtaken in infancy by the continuous production of cells with primarily (>95%) $\alpha\beta$ TCR (56). Thus, $\gamma\delta$ T cells may represent the earliest and most primitive cellular

[3] Abbreviations used: HPA, hypothalamic-pituitary-adrenal; HSC, hematopoietic stem cell; LBW, low birth weight; sIgA, secretory IgA; TCR, T cell receptor; T_{Reg}, regulatory T cell.

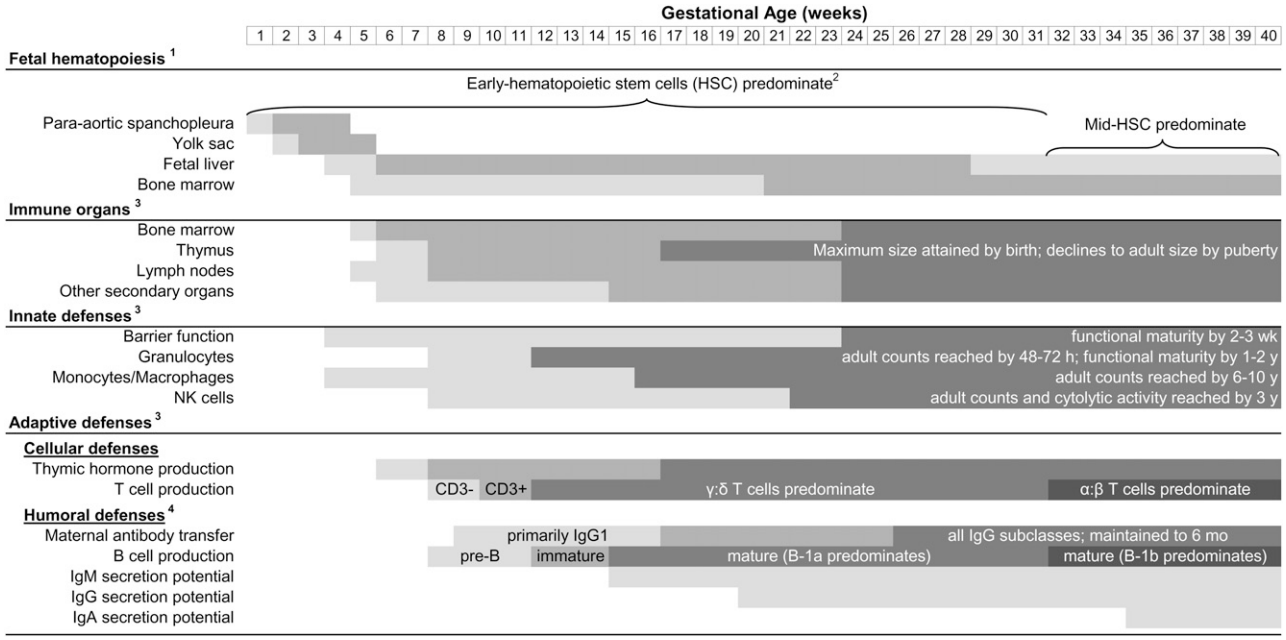

Figure 1 Developmental timeline of immune cells, organs, and effector functions. Lighter shading indicates stem cell homing to site; darker shading indicates primary site of hematopoiesis at given developmental stage. Timing of early-, middle-, and late-hematopoietic stem cells is not yet well defined in humans. Shading indicates relative maturation of organs (i.e. primordial, populated by progenitors, mature) and cell populations (i.e. cell counts and activity). For maternal antibodies, shading indicates increasing transfer efficiency; adult concentrations of IgM, IgG1, IgG3, and IgG4 are attained by 1–2 y, whereas IgG2 and IgA do not reach adult concentrations until puberty.

defenses derived from pre-HSC. Although relatively little is known about this population in humans, some extrapolations can be drawn from murine models. Cell populations expressing these specific receptors can be permanently deleted by injecting pregnant dams with anti-$\gamma\delta$ TCR antibodies (57). Furthermore, they cannot be replaced in irradiated mice by graft from adult bone marrow. Research in $\gamma\delta$ T cell-deficient mice has highlighted the importance of this population in controlling early and rapid multiplication of Listeria microorganisms and malaria parasites (58,59). Other postulated functions include an innate protective role in the mucosal immune system (56), acting as a bridge between innate and adaptive defenses (60), and downmodulating infection-induced inflammation (61,62). Natural ligands for human $\gamma\delta$ TCR have not been well characterized; however, evidence suggests that $\gamma\delta$ T cells differ from $\alpha\beta$ T cells primarily by how they are triggered rather than by effector functions (63).

Adaptive-humoral defenses. Lymphocyte progenitors active during embryogenesis give rise to pre-B cells as early as gestational wk 7 and are actively producing immature B cells in the fetal liver and, to a lesser extent, bone marrow by wk 12 (64). Mature naïve B cells expressing membrane-bound M and D Ig and capable of antibody secretion are present shortly thereafter (65), although only negligible amounts of antibody are produced by the fetus in the absence of intrauterine infection (66). Neonatal humoral responses are generally considered "immature." Effector functions are limited by low Fc receptor expression and deficiencies in opsonizing complement proteins (51). Moreover, antigen exposure during infancy and early childhood is needed for the B cell priming, production of high affinity antibodies, and memory responses that characterize mature humoral defenses (56). Maturation of certain antibody classes is delayed as well (40); serum IgM reaches adult levels in early childhood, whereas IgA levels not until puberty and adult concentrations of the IgG2 subclass critical for T cell-independent responses to polysaccharides are acquired only by 10–12 y.

B1a cells represent the earliest layer of humoral development. Based on extrapolations from murine models, this population is produced exclusively by a pool of self-replenishing fetal progenitors and cannot be restored by bone marrow stem cells later in life (67,68). B1b cell progenitors predominantly develop from mid-HSC in the neonatal period, with some limited production by adult bone marrow (69). Although research on the B1 cells has been constrained by lack of exclusive phenotypic markers (70), their functions have been differentiated from conventional B2 cells. B1a cells serve as a first line of defense in the pleural and peritoneal cavities, where they constitutively secrete most of the body's polyreactive, low-affinity, natural IgM antibodies (71–74). These natural antibodies provide critical protection for infants who have not had prior exposure to common pathogens (75). Recent research is also elucidating the importance of these antibodies in responding to malignant cells (76) and in "housekeeping" after oxidative stress-induced tissue and cellular damage or conventional apoptosis (77–79),

suggesting life-long protective roles for B1a cells. Due to their ability to bind self antigens, natural antibodies derived from B1a cells have also been implicated in autoimmune disorders (80); however, their role may in fact be protective (81). Although less is known about B1b cells, some studies suggest their involvement in adaptive responses to T cell-independent antigens, including pneumococcal capsular polysaccharides (82–84).

Transfer of immunity

Although the immune system is qualitatively complete at the time of birth, there are significant delays in the maturation of specific defenses. These delays are necessary to conserve energy and nutrients for other complex organ systems (85). They may further provide a window for the development of tolerance, particularly to food antigens, and protect immature tissues and organs from potentially harmful inflammatory actions. Developmental delays are countered by the transfer of maternal immune factors via the placenta and in breast milk. Thus, maternal immune competence is relevant not only to the health of the pregnancy but also for continued protection of the infant after birth.

Immune transfer mechanisms. During intrauterine development, the placenta serves as an interface for transport of oxygen, nutrients, and waste and further acts in synthesizing and secreting hormones, growth factors, cytokines, and other bioactive molecules (86,87). In terms of the immune system, the placenta was initially perceived as a barrier to protect the developing fetal allograft from a maternal immune response (88,89). Although our understanding of the immune interface between mother and conceptus is still actively evolving (90), it is now well accepted that various immune factors can cross the placenta. To date, antibody transfer from mother to fetus has been the most widely studied; however, there is some evidence of maternal-fetal cell transfer (91–94).

An active mechanism for the transfer of maternal antibodies across the placenta was first proposed by Brambell (95) in the 1960s. As hypothesized, a placental Ig receptor, the Brambell receptor or FcRn, has since been localized to cells of the syncytiotrophoblast, with differential binding affinity for the various IgG subclasses (96). Maternal IgG complexes with the FcRn are shuttled across the syncytiotrophoblast and released at the cytotrophoblast. This placental layer is progressively degraded during pregnancy, enabling antibodies to cross and accounting for the observed rise in fetal IgG levels with increasing gestational age (97,98). An endothelial organelle containing FcγRIIb2 has recently been identified and is thought to transport IgG across the placenta's endothelial layer to the fetus (99). Although active transport mechanisms are specific for IgG, transfer of both IgA and IgM classes may occur in cases of moderate to severe uterine infections due to placental changes (100,101). Maternal antibody concentrations in the infant drop precipitously by 3 mo of age, primarily due to hemodilution, and antibodies are fully catabolized by $\sim$6 mo of age.

Mammals further rely on breast milk to transfer immune factors to their offspring, although the composition of that milk varies widely between species due to qualitative and quantitative differences in pathogen exposure (85). Numerous components of human breast milk are thought to have a primarily non-nutritional role. These include maternal antibodies, maternal leukocytes, cytokines, chemokines, and hormones. Components of breast milk initially considered for their nutritional value may also confer nonspecific protection against pathogens (102). For instance, PUFA released upon digestion of milk fat globules may also act in destabilizing the cell membranes of certain pathogens (103). In humans, sIgA is the primary defensive protein and has been most widely studied.

SIgA is a hallmark of the gut- and other mucosa-associated lymphoid tissues. It performs immune exclusion, preventing bacterial colonization and invasion, and neutralizes certain viruses (104). Maternal plasma cells primed in mucosal sites home to the lactating mammary gland during late pregnancy and lactation under the influences of the mucosal epithelial chemokine CCL28 (105). This enteromammary connection ensures that factors transferred in milk protect infants against pathogens specific to the maternal environment (49). Plasma cells secrete antibodies, which are recognized and taken up by the polymeric Ig receptor on the surface of mammary epithelial cells, into the interstitial space. At the apical cell surface, the external domain or secretory component of the receptor is cleaved with the bound antibody and released into milk (106). The secretory component may also be released free of bound antibody to perform immune exclusion (107). Although sIgA is the predominant antibody in milk, sIgM and sIgG are also present (108).

Passive protection. The primary function of maternal immune transfer is to protect the developing fetus and breastfeeding infant from early-life infections (49). Protective effects, particularly against gastrointestinal and respiratory tract infections, of both immediate and exclusive breastfeeding have been demonstrated in numerous epidemiologic studies (109–112). Much of this is thought to be mediated by maternal antibodies (49), primed by the mother's immune system against pathogens in her environment. Maternal vaccination to drive the production of specific antibodies is, in fact, viewed as a potentially important strategy to reduce the burden of neonatal and infant infection (113). Beyond antibodies, other factors with known protective properties are synthesized by mammary epithelial cells and secreted into milk. Lactoferrin and lysozyme, e.g., are capable of degrading certain bacterial cell walls and have unexplained antiviral and antifungal activities (114). Milk oligosaccharides have antimicrobial activity; they act as receptor analogs, mimicking surface carbohydrates on the gut mucosa, thereby confounding bacterial binding and invasion (115). As noted, fatty acids in milk can weaken the cell membranes of pathogens (103). Immune factors often act synergistically to withhold nutrients from, inhibit binding of, or directly lyse pathogens without necessitating

activation of a potentially dangerous inflammatory immune response (49).

Immune modulation. In addition to the passive protection afforded by factors transferred across the placenta or in breast milk, maternal-fetal transfer may modulate the developmental trajectory of the immune system. Cytokines and chemokines, produced and secreted mainly by mammary epithelial cells, are thought to be the primary immunoregulatory factors in milk (116). For example, cytokines such as TGF-β2, IL-10, and, more recently, thymic stromal lymphopoietin are the focus of numerous studies regarding the protective effects of breastfeeding on the development of allergic or atopic diseases (117–120). The actions of maternal antibodies may also extend beyond passive protection. Antibodies directed at the antigen-binding variable regions of B and T cell receptors, i.e. anti-idiotypic antibodies, have long been recognized and are thought to play a role in sustaining and regulating immune cell populations (121). Findings from both animal (122–126) and human studies (127–130) support the notion that transfer of maternal antiidiotypic antibodies can prime fetal and neonatal cells and may be irreplaceable for the selection of B cell repertoires that recognize common pathogens (131).

Although research on other transferred immune factors is more limited, these may also influence the developing immune system. There is some evidence that activated maternal immune cells may have the ability to migrate into infant tissues and interact with fetal or neonatal cells (132,133). Hormones and growth factors are present at relatively high concentrations in human milk (134,135). Although they are thought important for mammary tissue growth and secretory function, they may further influence the maturation of the infant gut and associated lymphoid tissues (134,136,137). Other nutritional or defensive factors with established immunomodulatory properties include: PUFA (115), nucleotides (138), glycoproteins (139), oligosaccharides (140), and microRNA (141).

Programming pathways

Insults during critical developmental windows may program the structure and/or function of distinct cell populations, organ systems, or homeostatic pathways. Accepting that the immune system develops in layers, with ontogeny of the most basic defenses limited to early life, it is plausible that nutritional insults during this period can permanently alter specific cell populations and/or organogenesis. Early-life nutritional exposures may also have a lasting impact on the development of protective regulatory mechanisms.

The pathways by which maternal malnutrition may exert an influence on the emerging immune system are discussed below (**Fig. 2**). These include: *1*) alterations to the HPA axis; *2*) limiting nutrients available for embryonic and fetal development; and *3*) altering the transfer of immunity from mother to child.

HPA axis. Malnutrition is perceived by the organism as a threat to homeostasis (i.e. stressor), driving activation of the HPA axis and yielding elevated levels of glucocorticoids (142,143). This is evident, e.g., in cases of zinc deficiency (144,145) or protein-energy malnutrition (146). Although fetal exposure to maternal glucocorticoids is usually tightly

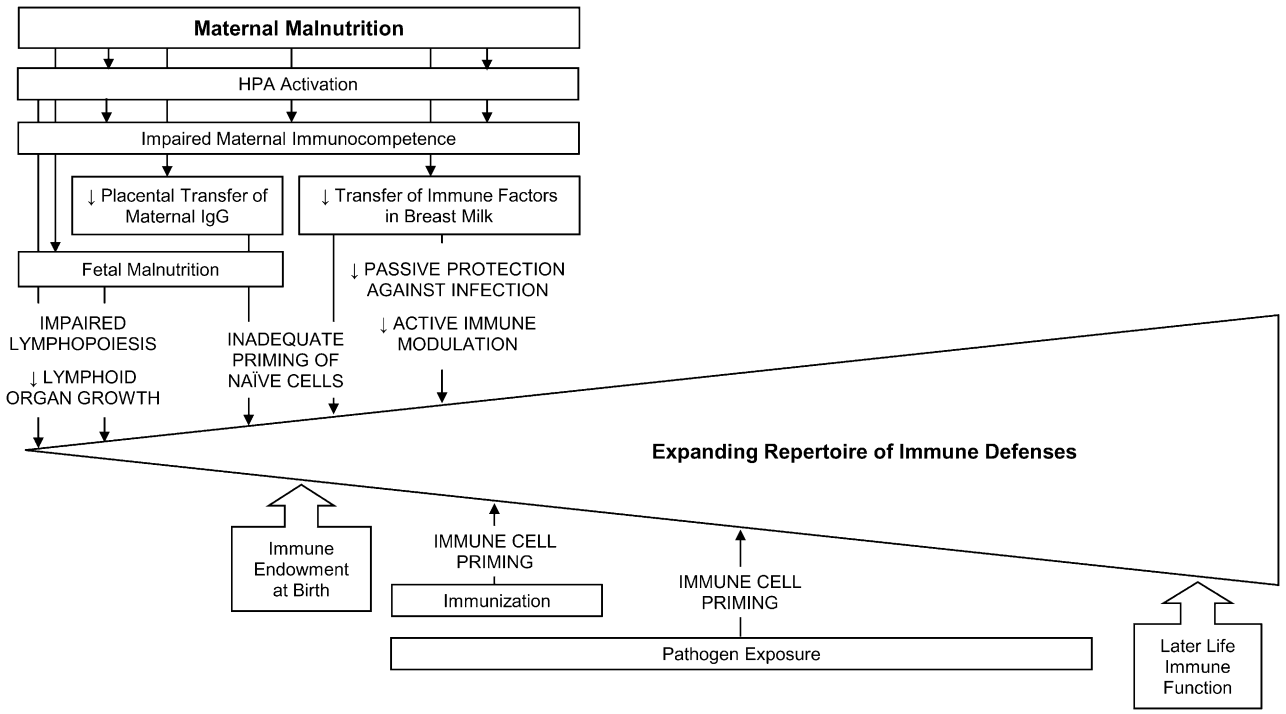

Figure 2 Hypothesized associations between maternal malnutrition and the emerging immune system.

controlled by placental 11 β-hydroxysteroid dehydrogenase, the activity of this enzyme is reduced by undernutrition (147). Resultant high concentrations of maternal cortisol can directly impact the developing immune system. Early research regarding the potential side effects of corticosteroid administration during pregnancy revealed a reduction in thymic weight (148) as well as morphological changes and a decreased cortical lymphocyte count (149). These observations have since been explained by glucocorticoid activation of an endogenous endonuclease, which results in thymocyte apoptosis (150). Lymphopoiesis, specifically at the pre- and immature stages of B and T cells development, has proven similarly susceptible to endocrine perturbations (151–155). Controlled animal studies suggest that these effects are at least partially reversible (156–158). Indeed, the immediate safety of early-life exposure to corticosteroid drugs in human infants is well accepted (159). However, some concerns have been cited regarding longer term implications for the immune system (160).

Maternal stress hormones also influence the developing and highly sensitive fetal HPA axis (161), with potential consequences for neuroendocrine-immune interactions throughout life. Experimental animal studies of prenatal and neonatal HPA activation have revealed numerous alterations to the immune response later in life. These include differences in the febrile response (162–172), cytokine expression (162,164,165,173–181), antibody production (182), lymphocyte proliferation (183–185), and NK cell activity (186); resistance to tumor colonization (186); intestinal microflora (187); and pain sensation (188). Consequentially, early HPA activation affected longer term risk of both infectious (173) and chronic disease outcomes (175,186,189). Some researchers have suggested that these alterations are driven by a potentiated HPA response upon stress later in life, perhaps due to epigenetic changes in the expression of glucocorticoid receptors (190). Support for this hypothesis includes the increased production of corticosteroids or adrenocorticotropin hormone production following acute stress in later life observed in some studies (165–167,177,186,189,191–194) and, more compellingly, the reversal of observed effects on fever, cytokines, and COX-2 expression by either adrenalectomy or administration of a glucocorticoid receptor-blocking drug (165,166,192).

There are some inconsistencies in this literature as to the effects of early-life HPA activation on later life immune responses. For instance, most studies have reported a reduction in the inflammatory response later in life, indicated by lower plasma concentrations of inflammatory cytokines or diminished production of these cytokines upon stimulation (164,165,174,176,178–180). In contrast, other groups have noted an amplified inflammatory response (173,175,181) as well as heightened susceptibility to inflammatory periodontal disease (175). These inconsistencies may be explained in part by differences in animal models (195). The timing of the initial stressor may also be critical; research in rhesus monkeys has demonstrated that exposure to stress hormones during early pregnancy increased the proliferative response of lymphocytes to a foreign antigenic protein, whereas HPA activation in late pregnancy decreased the proliferative response (184). Finally, long-term effects may vary depending on the nature of the early-life stressor (i.e. psychological, nutritional, immune) studied (172). Although differences in study design make it difficult to predict the consequences of early-life exposures, this large body of research underscores the vulnerability of the neuroendocrine-immune axis to developmental programming.

Direct nutritional effects. Nutritional deficiencies can affect immune ontogeny independently of HPA activation. Murine studies conducted by Beach et al. (196,197) in the early 1980s indicated that even moderate gestational zinc deprivation can lead to long-term impairments in thymic and spleen size, decreased antibody concentrations, and impaired lymphocyte activity. Although these effects may have been mediated in part by deficiency-related rises in glucocorticoids (144,198), research from adrenalectomized animals supports an alternate pathway by which deficiency may affect the immune system (145). For example, deficient adrenalectomized mice still exhibited atrophy of the thymic cortex, enlargement of the thymic medulla, and a loss of functional lymphocytes (145). Further support for an alternate pathway is offered by the studies by Beach et al. (199,200); offspring of mice exposed in utero to zinc deficiency also had lower antibody levels and lymphocyte activity than their peers, suggesting an intergenerational epigenetic effect.

Specific molecular mechanisms underlying this type of direct nutritional pathway are an active area of research. Deficiencies during critical periods of tissue growth and differentiation do have the potential to permanently alter structural characteristics. For example, the development of a wide range of tissues and organs is controlled by retinoid receptor signaling (201). This includes the correct patterning of the pharyngeal endoderm (202–204), which comprises the primordial thymus. Restriction of vitamin A by genetic, pharmacologic, or dietary means thus precludes development of the thymus (203,205–208). Retinoids are also critical for hematopoiesis (209). Although much of the research in this area has focused on the myeloid lineage, investigations of B cell precursors suggest that physiologic levels of retinoic acid may regulate the balance between B lymphocyte growth and apoptosis (210). In more recent work, all-*trans* retinoic acid treatment of cultured adult B lymphoid progenitors from healthy mice shortened the time required for differentiation into $CD19^+$ cells (211). Cultured fetal progenitors did not respond in a similar manner; however, when mice were exposed to vitamin A deficiency in utero and early life, the researchers noted a stark reduction in both B1a and B1b lymphocyte subsets, which could be corrected by all-*trans* retinoic acid (212). Although there are currently no published data regarding the actions of retinoids on fetal T lymphocytes, it is possible that the earliest wave of T cells could be similarly affected.

Nutritional factors may also exert an influence on the emerging immune system via epigenetic mechanisms. This has recently been established in studies of allergic, atopic,

and autoimmune diseases. One example illustrated that feeding pregnant mice a diet rich in methyl donors had a direct impact on DNA methylation, gene expression, and T lymphocyte development (213). Ultimately, these phenotypic changes to T_{Reg} cells increased the severity of allergic airway disease among the offspring of supplemented animals. A similar relationship was reported based on data from a prospective cohort in Norway, in this case showing an association between first trimester folic acid supplementation and increased risk of wheeze in infants and young children (214).

Impaired transfer of immunity. Maternal immune factors transferred across the placenta or in breast milk can actively modulate immune development. Thus, any impairment to immune transfer may alter the system's developmental trajectory. Of primary concern is the impact of maternal malnutrition on the quality or quantity of immune factors available for transfer. Interactions between protein-energy or micronutrient deficiencies and immune function are supported by decades of research and are reviewed elsewhere (215–218). The unique immunological state of pregnancy adds yet another dimension. For example, vitamin A deficiency is associated with cytokine dysregulation (219). One human study, conducted among pregnant women in Ghana, suggested that the Type 2 cytokine bias of pregnancy may be exacerbated by vitamin A deficiency (220). In addition to a direct effect on maternal immune factors, malnutrition during pregnancy and lactation may alter the mechanisms of transfer to the fetus or breastfeeding infant.

Placental transfer. Maternal malnutrition can alter placental development, evidenced by differences in size and morphology, modifications to nutrient transporters, and changes in vascular development and blood flow (221–223). The extent to which these specific alterations may influence maternal transfer of immune factors to the developing fetus is not known. However, both animal and human studies indicate substantial variability in placental transfer, again, with a specific focus on antibodies. Some animal studies have shown differing levels of IgG in neonates, presumably due to altered transfer, with maternal HPA activation, as seen in nutritional stress, during pregnancy (224–226). These effects may depend on the timing and nature of the stressor (225,227,228) as well as the sex of the offspring (225).

In healthy human pregnancies, antibody transfer is highly efficient and the concentration of maternal IgG in cord blood exceeds that of IgG in the mother's serum (229). However, several studies have reported transfer efficiency ratios of <1. Because the majority of maternal IgG is transferred in the last 4–6 wk of pregnancy, preterm delivery is a well-known cause of IgG deficiency in early infancy (98). Placental anomalies associated with the preterm delivery may compound this problem by limiting transfer efficiency, as has been reported in cases of placental malaria (230–233) and HIV infection (233–235). Maternal hypergammaglobulinemia, frequently observed in areas with a high burden of infections, also results in a transfer efficiency ratio < 1 (232,236,237), because high levels of maternal antibody exceed the number of placental FcRn (95). Few studies have investigated nutritional influences on placental IgG transfer. Cavalcante et al. (238) reported a 14% reduction in antibody transfer among women with low compared to normal weight-for-height in early pregnancy. Total and pathogen-specific IgG appear to be limited also in small-for-gestational age infants (239–241). Transfer of IgG1 and IgG2 are particularly affected (242). Other work illustrates a role for micronutrients; antenatal zinc supplementation increased cord blood concentrations of all IgG subclasses (243) and, although observational, maternal anemia has been associated with reduced transfer efficiency (239).

Breast milk transfer. Several studies have also explored variability in breast milk immune factors. Again, animal studies showed an impact of maternal HPA activation on milk sIgA concentrations (244,245). Human breast milk composition is determined by stage of lactation (246,247), maternal age, parity (247,248), and infant's sex (249). Maternal systemic infection, indicated by elevated serum levels of C-reactive protein, does not appear to alter overall milk volume or immune protein concentrations (250,251). However, both clinical and subclinical mastitis have an effect on various immune factors (252–254), reflecting their joint actions in protecting both mother and infant. Seasonal variations in breast milk immune factors have also been reported, independent of their impact on maternal and/or infant infection (255,256). Recent work has pointed to variability in breast milk immune factors by maternal country of birth (comparing immigrants from developing countries to indigenous population) and parity (257,258).

Some research groups have investigated the role of maternal nutritional status on breast milk immune factors. To our knowledge, only one study has considered nutrition-related variability in breast milk immune factors in the context of a randomized trial. It found that postpartum vitamin A or β-carotene supplementation had no effect on sIgA, lactoferrin, lysozyme, or IL-8 at 3 mo postpartum (252); however, concentrations of these factors were within normal ranges in all treatment groups. With a few exceptions (259,260), observational studies have not detected any association between maternal nutritional status and breast milk immune factors (246,261–263). However, there has been little standardization with regard to: *1*) nutritional assessment and classification; *2*) breast milk collection, processing, and storage; *3*) laboratory techniques; and *4*) sampling and statistical analyses.

Evidence of nutritionally mediated immune programming

Evidence from human studies, both experimental and epidemiological, suggests that early-life nutritional exposures may influence the developing immune system, with consequences extending even into adulthood.

Intra-uterine growth retardation. Although intra-uterine growth retardation has multiple etiologies, maternal malnutrition is a major determinant of poor fetal growth. Substantial epidemiological evidence links LBW, a rough indicator of intra-uterine growth retardation, with increased risk of infectious morbidity and mortality later in life. Often-cited studies using data from the United States have highlighted LBW and even moderately LBW as strong determinants of infant mortality and morbidity during infancy and childhood (264–266). However, LBW in developed countries is predominantly due to preterm delivery rather than intra-uterine growth retardation. In Scandinavia, researchers have noted more frequent hospitalization for infectious morbidity throughout childhood and mortality through 15 y of age among children born LBW, even after controlling for gestational age (267,268). Data from the Dutch Famine also suggest a link between early- and mid-gestation exposure to famine, resulting in lower birth weight and excess mortality up to the age of 18 y (15).

Work in Brazil confirms the association between LBW and both neonatal and post-neonatal mortality (269). Preterm infants had a 2.5-fold higher mortality risk than small-for-gestational age infants during the neonatal period, although these differences were less pronounced afterwards. Further analysis also revealed that infants with both low birth length and low ponderal index were at greatest risk of hospitalization and mortality in the first year of life regardless of gestational age (270). Using datasets from multiple countries, Ashworth (271) found increased risk of neonatal and postneonatal morality among infants born LBW due to intra-uterine growth retardation. Even though RR for small–for-gestational age infants were less consistent across studies than for preterm infants, their mortality risk was elevated even beyond infancy. Similar findings emerged from analysis of long-standing demographic surveillance in the Gambia. Moore et al. (12) reported increased infectious mortality among adults born during the hungry season, characterized by an elevated incidence of nutritionally mediated LBW. This seasonal pattern was not apparent in adult mortality trends from Bangladesh (13), Senegal (16), or Burkina Faso (17). Neither was mortality after the age of 18 y affected by in utero exposure to the Dutch Famine (15). Yet the authors of this latter work stressed the small number of deaths in this cohort, to date, and their limited power to detect survival differences.

Findings from the case-control study by Moore et al. (12) led to the exploration of immune function in Gambian primary school children. Participants were challenged with human diploid cell rabies and 23 valent pneumococcal capsular polysaccharide vaccines, and both a delayed-type hypersensitivity skin reaction and mucosal antibodies were measured (5). This study found no differences between children born in the hungry compared to harvest seasons. Addressing these same questions in an older Pakistani population for whom birth weights were available, researchers reported a less robust response to the Vi polysaccharide typhoid vaccine among those born at a LBW (7). A typhoid vaccine challenge yielded similar results among LBW infants in the Philippines in their teenage years at the time of the study (8). This lack of effect among Gambian individuals compared to study participants in both Pakistan and Bangladesh may be due to their younger age, i.e. differences may not become apparent until later in life (272).

Although differential response to predominantly T cell-independent vaccine responses would suggest otherwise, subsequent work has focused on altered thymic development. In the Gambian children, researchers noted significant seasonal variation in thymic size and function; hungry season babies had a lower thymic index and impaired thymic function, indicated by lower serum TCR excision circles (6). Similar work in Bangladesh confirmed this seasonal pattern and further demonstrated a direct association between thymic size and infant weight (273). In the Philippines, researchers noted that serum thymopoietin concentrations were indeed lower among those who had been born small for gestational age compared to their appropriate for gestational age peers (9). If these differences in the smaller thymus were not due to nutrient restriction in early pregnancy, it has been suggested that they could be mediated by seasonal variations in breast milk IL-7 (274). Subsequent explorations of T lymphocyte kinetics in these populations have yielded conflicting results (275,276).

Maternal micronutrient deficiencies. The impact of maternal micronutrient deficiencies on the emerging immune system is a relatively new area of inquiry. Trials of single or multiple micronutrient deficiencies conducted in developing countries have focused primarily on outcomes of infectious morbidity and mortality. In rural Nepal, maternal supplementation with either vitamin A or β-carotene failed to improve fetal or infant survival (277). However, after restricting the analysis to infants whose mothers reported night blindness during pregnancy, supplementation substantially reduced, but did not eliminate, the increased risk of early infant mortality (278). Subsequent work in the same population demonstrated that maternal folic acid supplementation, delivered alone or with iron, reduced early infant mortality among those delivered preterm (279). Similar findings were recently reported from China, where early neonatal deaths were reduced by 54% in the iron-folic acid arm of the trial compared to folic acid alone (280). Trials of antenatal zinc supplementation have also documented significant reductions in infectious morbidity among infants (281–283).

To date, only the antenatal zinc supplementation trials have directly assessed any aspects of infant immune function. The trial conducted in Bangladesh reported fewer anergic delayed-type hypersensitivity responses to purified protein derivative among LBW infants born to supplemented mothers (284). No similar effect was apparent among normal birth weight infants. The authors found no impact on immune response to *Haemophilus influenzae* type b vaccine, although they noted that high natural

infection rates may have masked any beneficial effect. Data from a separate trial in Indonesia showed an impact of antenatal zinc supplementation on ex vivo cytokine response among infants (282). Taken together, the findings of maternal supplementation trials with regard to infant mortality, morbidity, and immune function are suggestive of immune programming. However, any effects may be modified by the severity of maternal deficiency, size at birth, and/or gestational age at delivery.

In addition to studies in developing countries, there is an increasing focus on the importance of maternal micronutrient status in the literature on allergic and atopic diseases (285). Much of this work has concentrated on vitamin E, which is important for promoting a tolerogenic response upon initial allergen exposure (286). Although no randomized trials are yet available, evidence from prospective cohort studies links low maternal vitamin E intake during pregnancy with increased peripheral blood mononuclear cell responsiveness, wheezing/asthma, and markers of airway inflammation (287–290). Vitamin D also plays a role in tolerance induction and the promotion of a regulatory phenotype (291). The impact of vitamin D status during pregnancy on development of immune-mediated diseases is thus a growing area of investigation (292). For example, investigators from a multi-country prospective cohort study reported that vitamin D supplement use during pregnancy increased tolerogenic antigen-presenting cells in cord blood (293). Additional research is needed to expand these findings, both to clarify mechanisms of action and to test prophylactic efficacy in randomized trials (285).

Infant feeding. Infants exposed to human milk are characterized by an antiinflammatory and tolerance-inducing gut environment (49) as well as immunophenotypic differences in lymphocyte populations (294). Improved mucosal (295) and systemic immune function (296) have also been reported after exposure to breast milk, although the latter may be modified by gestational age (297). Furthermore, breast-fed infants have a larger thymic size than formula-fed infants (298,299), which correlates well both with thymic function (300) and infant survival (301).

To assess changes in immune function related to breast milk exposure, many groups have relied on vaccine response as an accepted indicator of immune function (302). There have been reports of improved antibody response to the *Hemophilus influenzae B* conjugate (303,304), oral polio (305,306), diphtheria (305), and tetanus toxoid vaccines (305). However, most studies have found little difference in antibody responses between breast- and formula-fed infants for common vaccine antigens (307–312). Findings regarding cellular responses are similarly inconclusive. Although Pabst et al. (313,314) noted an increased T cell proliferative response to BCG vaccination in breastfed infants (313), they also reported lower responses for both measles hemagglutinin (314) and a recall tetanus toxoid challenge (313).

The longer term effects of breastfeeding are also widely debated (315). Several studies have reported a reduced incidence of allergic diseases (316–318), presumably through an early influence on regulatory mechanisms. Similar work has emerged for other diseases of the immune system including rheumatoid arthritis (319,320), Type 1 diabetes mellitus (321,322), Crohn's disease (323,324), and certain lymphomas (325). However, these findings are countered by a number of studies showing little to no effect (326–334). Whether assessing the response to vaccination or long-term effects on immune-mediated disease, the observational evidence thus far is open to doubt. An impact of infant feeding on the developing immune system is biologically plausible and likely to remain an active area of research (335). However, an experimental design, such as long-term follow-up of participants from the Promotion of Breastfeeding Intervention Trial (336), is needed to further guide this debate.

Conclusions

The emerging immune system is vulnerable to insult, particularly during embryonic and early fetal life. Even once the system is qualitatively complete, the fetus and infant requires continued input from its mother in the form of immune factors transferred across the placenta and in breast milk. Maternal nutritional status may affect both of these pathways. Initial work on nutritional programming of the immune system employed a vaccine challenge as a broad indicator of the body's ability to respond to infection (5,7,8). Although the implications of an altered vaccine response would be easily translatable, the lack of consistency across these studies has been difficult to explain (272). Rather than considering overall immune function, it might be more revealing to focus on those aspects of the immune system that are most plausibly affected by early-life nutritional insults.

Early lymphopoiesis

As discussed above, distinct waves of progenitor cells produce diverse lymphocyte populations with progressively complex functions. The earliest wave of progenitors, a long-lived and self-sustaining population generated only by fetal stem cells, gives rise to the innate-like B1a cells and specialized T cells (67). Little research exists into the influence of early-life nutrition on lymphopoiesis. As noted above, researchers have reported reduced lymphocyte counts and altered cell function in animals exposed to prenatal/neonatal stressors or glucocorticoids (158,178,182,184,185). These findings may reflect glucocorticoid-mediated changes in the number or function of lymphocyte precursors (151–154). Altered lymphocyte counts or function have also been reported in the animal literature regarding in utero exposure to nutrient deficiencies (337–339). One recent study indicated that fetal exposure to vitamin A deficiency can affect early progenitors, resulting in smaller B1a and B1b lymphocyte populations (212). Given that the earliest wave of progenitors is produced solely by fetal stem cells, any insults during this critical period could have a permanent effect. Future research should closely monitor lymphopoietic

trajectories, specifically the earliest progenitors and their innate-like progeny, and investigate any longer term functional consequences that may result from B1a and early T cell deficits.

Immune organ development

Primary and secondary lymphoid organs (e.g. gut-associated lymphoid tissue) undergo rapid expansion during the late fetal and early neonatal periods, during which time they may be uniquely sensitive to nutritional insults. The thymus has been most widely studied to date. Indeed, researchers have long recognized the sensitivity of the thymus to nutritional status (340,341). Protein-energy malnutrition (342–344) and various single nutrient deficiencies (345–348) are associated with thymic atrophy, attributed both to thymocyte depletion by apoptosis (342,343,349) and decreased cell proliferation (350). Morphological changes and decreased hormone production have also been reported for thymic epithelial cells (351). These alterations are mediated at least in part by concomitant hormonal changes (152,352) and are thought to be reversible. Based on ultrasound images, the thymus recovers in size within 2 mo of nutrition rehabilitation (353,354). Recovery has not been well studied at the cellular level.

The thymus emerges early in pregnancy, undergoing a critical period of development from 7 to 14 wk of gestation and reaches its maximum size relative to body weight by the time of birth (24,27). The period of "thymic education" in mid-pregnancy, at which point $CD4^+CD8^+$ thymocytes undergo both positive and negative selection, is also considered a period of susceptibility (355). Given the organ's sensitivity to malnutrition, exposures during these critical periods may be particularly important. Indeed, animal studies support a link between protein-energy and/or micronutrient deficiencies during pregnancy and thymic size/function among offspring (196,356–359). There is some evidence that these in utero effects on the thymus are not fully reversible (196). As discussed above, epidemiologic studies also support the notion that early-life nutritional exposures can have a lasting impact on thymic size and function (6,9,274,276). Additional research on nutritional programming of immune organ development is clearly warranted, with future studies including both primary and secondary lymphoid organs.

Regulatory mechanisms

Exposures during pregnancy and early life may further influence the development of protective regulatory mechanisms, i.e. how the immune system maintains a balance between mounting an effective immune response against pathogens and preventing inflammatory damage to host tissues. As previously described, there are several examples from the animal literature regarding the lasting impact of in utero or neonatal exposure to stressors on inflammatory processes later in life (162,164,165,173–181). These changes have largely been attributed to programming of the fetal HPA axis, which can permanently alter interactions between the neuroendocrine and immune systems (161,190). Early-life influences on immunoregulatory mechanisms are also evident from the literature on allergic, atopic, and autoimmune disorders (360,361). Adequate maternal intake of vitamins E and D in particular appear important for emerging regulatory mechanisms and protection against airway inflammation (285,287–290,293). Recent reports also indicate the sensitivity of T_{Reg} cell populations to epigenetic programming (213,362).

The highly complex nature of immune regulation makes it difficult to predict how early nutritional exposures may influence regulatory development. In the HPA programming literature, long-term effects have varied widely depending on the timing of the stressor (184), the nature of the stressor (172), and the choice of animal model (195). The allergy/atopy literature also stresses the complex and often confusing interplay between "a host's immune response, characteristics of the invading microorganisms, the level and variety of the environmental microbial exposure and a genetic background (363)." Although prior research offers some basis for future studies, there is also ample justification for exploratory work in this field as scientists continue to unravel the mechanisms of immune regulation.

Summary

Maternal malnutrition, including both nutritional deficiencies and excesses, is highly prevalent and can have lasting consequences for the health of offspring. Here we have highlighted several plausible pathways by which in utero nutrient deprivation may influence the nascent immune system. Indeed, considerable evidence exists in the literature of associations between early-life nutritional exposures and immune alterations extending throughout childhood and, in some cases, adult life. Perturbations to the emerging immune system resulting from early nutritional imbalances may have immediate consequences for susceptibility to infection during infancy as well as implications for later-life risk of immune-mediated and/or inflammatory disease.

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