

The influence of the diet on the maturation of the immune system

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During fetal growth and development, there are periods of rapid cell division in various tissues of the body. During these periods, it is thought that the nutritional status of the fetus may alter expression of the fetal genome, the consequences of which may be lifelong. This phenomenon of "fetal programming" has been shown to have long-term effects on postnatal growth, relative organ size, and lipid metabolism of the offspring (1). The neonatal immune system is functionally immature and undergoes a period of extensive differentiation and maturation once exposed to foreign proteins and other dietary components. The vulnerability of neonates to infection is reflected in the poor proliferative and cytokine-secreting responses of lymphocytes from neonates to mitogenic stimulation in comparison with adults (2). Natural killer cells from neonates, present in smaller numbers than in adults, also appear to have a reduced functional response. As early as 1810, Menkell linked malnutrition with lymphoid-tissue atrophy (especially of the thymus), but information on the influence of diet on the developing immune system remains relatively sparse. This paper will briefly review three specific dietary influences on the maturation of the immune system during fetal development and early infancy: protein-energy malnutrition (PEM), maternal milk, and cow's milk allergy.

Protein-energy malnutrition

Although dietary factors can affect the structure and function of all cells in the body, the lymphoid tissues are particularly susceptible, due to their rapid turnover rate and synthesis of immunomodulating proteins. The thymus is the most vulnerable organ in this situation and the degree of atrophy can be used to gauge the severity of malnutrition. The absolute and relative numbers of total lymphocytes, and helper (CD4+) and suppressor (CD8+) T cells are also reduced in malnourished children (3). The proliferative responses of T cells to antigens and mitogens are reduced in malnourished individuals but can return to normal following dietary supplementation for 4 weeks (4). One possible mechanism for this is the decreased production of interleukin (IL)-1 by monocytes, a cytokine needed for the subsequent stimulation of IL-2 secretion and IL-2 receptor expression on lymphocytes, which is required for their proliferation, in malnourished children (5).

The consequences of nutritional deprivation during gestation can be very pervasive and may persist for many years, possibly compromising immune function permanently. In a 1-year follow-up of very low-birth-weight infants, serum IgG1 levels remained low and these low levels correlated with an increased susceptibility to bacterial infection

(6). The idea of an early, *in utero*, sensitivity of the immune system to malnutrition is supported by the observation that babies born up to 2–3 months after the peak of the hunger season in rural Gambia remain vulnerable in later life, having a greater incidence of premature mortality from the age of 15 years (7). There is also evidence, from animal models, that interuterine malnutrition can result in the persistence of a depressed cell-mediated immune response beyond the first-generation offspring (8, 9).

Maternal milk

Maternal milk is a complex fluid providing energy and essential nutrients for the growth and development of the neonate. The anti-infective properties of maternal milk are well established and depend in part upon the various cellular and soluble factors it contains, its buffering capacity, and several antigen nonspecific protective factors (10). It has been proposed that milk-borne cytokines and hormones may function as developmental regulators of the immune system in neonates (11). *In vitro* and *ex vivo* studies have shown that several components of cell-mediated immune responses differ between human neonates fed maternal milk and those fed substitutes without immunomodulatory activity (12). Although originally classified as an endocrine hormone, 23–24-kDa prolactin (PRL) and its several variants are increasingly regarded as immunomodulatory agents, since they appear to have cytokine-like actions on neonatal immune cells (13). Prolactin acts through the PRL receptor (PRL-R), which is a member of the IL-2 cytokine receptor superfamily, and influences natural killer cell activity, T-cell-dependent macrophage activation, and lymphocyte maturation and function (13). PRL present within the small intestine may modulate the differentiation of intraepithelial lymphocytes, which express PRL-R at a greater density than neonatal splenocytes. The expression of PRL-R in both the spleen and thymus of neonatal rats is downregulated by ingestion of maternal milk. Levels of PRL-R in the spleen decrease 7 h after birth in neonates ingesting milk compared with littermates not ingesting milk (11). This suppression of PRL-R expression may be one mechanism by which milk PRL regulates immune cell function and influences lymphocyte trafficking.

Cow's milk allergy

Many infants develop an intolerance of proteins present in their diet, and cow's milk protein intolerance occurs in 2–5% of infants, but the prevalence

declines with age, and up to 80% of infants lose their reactivity (14). The main proteins in cow's milk involved in causing reactions are β -lactoglobulin, α -lactoglobulin, and caseins, the first of which causes the highest rate of positive oral challenges. Oral tolerance, in which mature lymphocytes are rendered nonfunctional or hyporesponsive by prior oral administration of antigen (15), is known to function poorly during the preweaning period, so it is likely that allergen exposure in the very early period of infancy primes for subsequent T-cell reactivity (16). This gives rise to an early window of high risk for allergic sensitization, presumably due to the delayed postnatal maturation of the mucosal immune function that is rate-limiting in inducing tolerance (17). However, recent evidence suggests that the immune system may become sensitized to allergens before birth, by way of "intrauterine programming". Mononuclear cells in cord-blood samples from babies who subsequently developed atopic eczema, with positive allergy skin prick tests to cow's milk protein and egg at 1 year of age, showed a raised proliferative response and a reduced interferon-gamma production when stimulated with β -lactoglobulin when compared with cells from babies who did not develop atopic eczema or those with atopic eczema not associated with foods (18). A recent study suggests that *in utero* fetal exposure to food allergens (β -lactoglobulin and ovalbumin) from around 22 weeks' gestation may result in primary sensitization to that allergen, leading to a raised lymphocyte proliferative response at birth (19). In addition, the proportion of CD4⁺ cord-blood cells expressing the CD45RO phenotype (associated with T cells which have acquired memory of an antigen) was significantly higher when delivery was at >22 weeks than at <22 weeks (19), supporting the concept of intrauterine antigen priming. The unfortunate implication of these findings is that it might be necessary to move attempts to prevent the development of allergy back from early infancy into early pregnancy or even before conception.

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