The impact of early life nutrition on the immune system

ABSTRACT

The human immune system improves during fetal and postnatal growth, reaching full development in adolescents and young adults; therefore exposures and stimuli in early life have a strong influence on the development of the immune system and its programming in adult life. The initial stages of life, as compared to other stages, are points of strong regulation of gene expression: they present greater plasticity and, thus, greater capacity of adapting to stimuli. One of the conditions that can set up this epigenetic modulation of the immune system are nutritional factors present in pregnancy and lactation, such as nutritional status, diet, and microbiota, which stimulate—positively or negatively—the programming of the immune system of the progeny, to make them more or less susceptible to the development of diseases, such as allergies, inflammatory and infectious diseases. This review aims to present how the nutrition in early life can crucially influence the programming of the immune system development of one’s offspring.

Key words: Immunity, breastfeeding, diet, developmental origins of health and disease, gastrointestinal microbiome.

INTRODUCTION

Environmental conditions in early life can influence the long-term risks of the development of diseases in the offspring, known as 'developmental programming' (Fleming et al., 2018). The influence of early life experiences on an adult's health and diseases has been explored by the developmental origins of health and disease (DOHaD) hypothesis (Mulligan, 2016; Gluckman et al., 2008). It is proposed that stressors act via epigenetic mechanism -DNA methylation and gene expression. Due to nearly unlimited capacity to respond to the environmental triggers, the immune system has a decisive impact on the health. The mode of delivery, breastfeeding and diet on microbial colonization of the gut, was proved to be crucial for the programming of the immune system, the development of the tissues and the associated metabolism (Milani et al., 2017; Busslinger and Tarakhovsky, 2014; Pauwels et al., 2019; Stinson, 2019). In this review, we focus on the role of early life nutritional elements in the programming processes of the development of immune system, because they may lead to the protection or increased risk of diseases.

Key elements of immune system development

The immune system is a complex protection system that involves several organs and tissues—primarily, the thymus and bone marrow, and secondary lymphoid tissues of the spleen, lymph nodes, tonsils, and mucosa associated lymphoid tissue (Parkin and Cohen, 2001). The lymphoid organs are in constant communication aimed at maintaining the homeostasis of the organism through the recognition and elimination of exogenous or endogenous substances that interfere in the healthy physiological process. The immune system undergoes variations according to the development period. In human
development, the frequencies of monocytes and dendritic cells increase over gestation. However, at birth, neutrophils are the most prominent immune cell subtype (Sureshchandra et al., 2019). Subsequently, as cellular factors guide the neonatal immune response, the cord blood and neonatal serum levels of anti-inflammatory cytokines (including IL-4, IL-10, IL-13, and TGF-β) are higher than those observed in adults, but fetal skin and the mucosal layers present high levels of antimicrobial proteins and peptides such as defensins, lactoferrin and lysozyme that act as protectors against infections (Futata et al., 2012; Belderbos et al., 2013). A longitudinal study identified that during the first 3 months of life, occur intense changes in the immune components of children. The cell populations are more variable in newborns than in adults, and there is a gradual reduction in neutrophils from birth, with an increase in CD4+ and CD8+ T cell proportions (Olin et al., 2018).

Immune responses may change and are influenced, for example, by aging (Castelo-Branco and Soveral, 2014), physical activity (Song and Chan, 2018), nutrient intake (Maggini et al., 2018) and nutritional status (Alwarawrah et al., 2018). Studies demonstrated the fundamental importance of adequate nutrition for a competent immune system (Maggini et al., 2018; Alwarawrah et al., 2018). Adequate supply of energy, proteins, vitamins A, C, D, B2, B12, acid folic, iron, selenium, and zinc are essential to this process (Maggini et al., 2018; Alpert, 2017). Regarding nutritional status, both malnutrition and excess of nutrients, such as obesity, damage the working of the immune system. A nutritional imbalance brings physiological changes capable of intervening in the homeostatic system (Alwarawrah et al., 2018). Malnutrition, due to the scarcity of macronutrients and/or micronutrients, can weaken the immune response (Alpert, 2017). On the other hand, the excess of body fat, caused by storage of adipose cells in the tissues, influences mainly due to the exacerbated secretion of hormones and cytokines from the adipocyte itself that act in the immune signaling, modulating its response (Alwarawrah et al., 2018; Lehr et al., 2012; Blüher and Mantzoros, 2015; Frydrych et al., 2018; Russo and Lumeng, 2018; Cohen et al., 2017).

In addition, excess maternal body fat during pregnancy is associated with altered placental inflammatory responses (Sureshchandra et al., 2019; Challier et al., 2008; Gohir et al., 2019), which have been linked to harmful consequences from the development of the fetus to the susceptibility of diseases in adulthood (Challier et al., 2008; Edlow et al., 2019). The placenta is a transient organ formed during pregnancy, which acts as an interphase between mother and fetus. It has different functions, such as transporting nutrients, antibodies, gas exchange and hormone production, being fundamental for embryonic and fetal development (Maltepe and Fisher, 2015; Jennewein et al., 2017; Turco and Moffett, 2019), as it regulates several adaptive responses to the environment that impacts the mother and fetus link. Epigenetic mechanisms can cause morphological and functional changes in the placenta, that imply the modulation of several systems (Lester and Marsit, 2018; Maccani and Marsit, 2009). Research has shown that maternal obesity modulates placental function in the immune field by acting on mRNA levels of immune cell markers (Gohir et al., 2019) and causing macrophage accumulation in this tissue (Challier et al., 2008).

In this regard, it was identified that fetal mast cells phenotypically mature through pregnancy and can be sensitized by maternal IgE. IgE crosses the placental barrier, way dependent on the fetal neonatal Fc receptor, and sensitizes fetal mast cells for allergen-specific degranulation. Thus, fetal mast cells could lead to antigen-specific vertical transmission in allergic diseases. These results indicate that, in mice, prenatal exposure to maternal allergen-specific IgE may contribute to the immune response against the first exposure to the same allergen after birth, indicating that predisposition to allergic disease may be determined in part before conception (Msallem et al., 2020).

Another critical factor, the impact of vaginal delivery and elective cesarean section, was compared when counting leukocytes and lymphocyte subpopulations in umbilical cord blood. It was concluded that vaginal birth can be beneficial in the immunological scope for the newborn, as they have higher values of cells active (neutrophils, monocytes, and natural killers) compared to those born by elective cesarean section (Thilaganathan et al., 1994). In addition, labor was associated with a significant increase in IL-6 (Steinborn et al., 1999), higher polymorphonuclear leukocyte counts, complement system activation (Herson et al., 1992), and appears to have an effect on the activation of T cells in newborns (Thornton et al., 2003). This more functional activation of the immune system, resulting from labor, is impacted by exposure of the neonate to microorganisms at the moment of birth and seems to enable the newborn to develop an adequate immune response during development, associated with a reduction in susceptibility to infections or atopy (Francino, 2018).

Avery discussed point is related to the exposure of microorganisms during childbirth. Research shows that the type of delivery affects the diversity of colonization of intestinal microbiota in descendants. Babies born by elective caesarean section have a slower diversification of the microbiota (Salminen et al., 2004) with potential long-term consequences, such as increased propensity to develop allergies, asthma, type 2 diabetes and obesity (Bokulich et al., 2016). It is worth noting that caesarean sections after the beginning of labor (rupture of the membrane and contractions) show fewer changes in immunological terms (Francino, 2018). Vaginal delivery, on the other hand, seems to contribute to a greater total diversity of the microbiota during childhood, thus being an
important factor in promoting the maturation of the immune system and preventing infections, since microbial colonization is fundamental for the development and regulation of this system (Francino, 2018; Jakobsson et al., 2014; Rutayisire et al., 2016).

**Implications of epigenetic regulation in the programming**

Epigenetics investigates the mechanisms that determine the chromatin structure, which has a relevant function in the regulation of gene expression and genome stability (Putiri and Robertson, 2011). The main epigenetic mechanisms include DNA methylation and histone modifications, which are established during embryonic development and are transmitted by heritable information during mitosis, ensuring cell differentiation and function (Jasiulionis, 2018). During development, cells are subject to the influence of several factors that allow remodeling (Cantone and Fisher, 2013).

Although they are relatively stable, epigenetic marks can change their dynamics due to cellular and environmental conditions. Some DNA regions appear to have their epigenetic marks more susceptible to environmental factors (Boyce et al., 2020). Lifestyle - including diet habits, physical exercises, stressors, smoke, and alcohol - could modify the epigenetic landscape, impacting the chromatin structure and function (Justice et al., 2020; Tavares et al., 2020). The environment can indeed affect the epigenotype and the phenotype, reflecting directly in health or disease states (Jasiulionis, 2018; Portela and Esteller, 2010). In this way, epigenetic marks act in the regulation of the immune system and contribute to the status of the health condition. An essential feature of the immune system is its capacity to recognize self from non-self, and the epigenetic mechanisms participate in the development and differentiation of immune cells (Busslinger and Tarakhovsky, 2014; Zhao et al., 2016).

The interaction between histones and effect or proteins could be used for selective interference with immune responses during health and disease. Several studies demonstrate the significant role of epigenetic reprogramming in innate immune memory, according to a review by Netea et al. (2016). The findings on molecular mechanisms reveal the ability of monocytes to integrate microenvironmental experiences into their programs of gene expression, a type of chromatin-based memory that highlights the potential reversibility of innate immune phenotypes (Heijden et al., 2018). In response to different environmental conditions, the cell may be able to adapt its phenotype through the epigenetic mechanisms, which is reflected in hematopoiesis and cellular activation (Placek et al., 2019). These changes are observed at different stages of development and act on multiple organs and tissues, with the maternal condition playing an essential role (Figure 1).
Nutritional status and dietary factors

**Calories and macronutrients**

Nutritional conditions in early life have an impact on health and disease in short- and long-term, and the immune system is vulnerable to these changes (Fleming et al., 2018). In this respect, maternal undernutrition during pregnancy resulted in increased expression of IL-1β and IL-6 (following LPS stimulation), and of IL-1R1, IL-6R and TLR4 in bone marrow macrophage in adult male offspring (Reynolds et al., 2013). In another study, mice were fed either a normal or calorically restricted or a high-fat diet (HFD) during pregnancy and a reduction in microbial richness was observed in mothers who received HFD, which was related to altered phenotypes of inflammation in plasma and intestine beyond peripheral leptin levels (Connor et al., 2018). Regarding the composition of breast milk, the consumption of fish oil by lactating women decreased secretory immunoglobulin (Ig) A, increased IL-10 production and eicosapentaenoic acid levels, and these results were associated with increased abundance of fecal *Bifidobacterium* and *Lactobacillus spp.* in the infants (Quin et al., 2020).

Pregnant mice were fed a protein restriction diet (8% protein) to establish an early-life undernutrition model. Protein restriction led to positive modulation in activation and proliferation of CD4 + T cells in the offspring, both in vitro and in vivo increasing the propensity of differentiation in Th2 cells and consequently to experimental asthma. The outcome of this process is the increase in the mechanistic target of glucose dependent on rapamycin 1, which is caused by maternal malnutrition and acts by inducing hypomethylation of the noncoding DNA sequence 1 in the Th2 cytokine locus of CD4 + T cells. When glycolysis is blocked, the Th2 distortion is impaired, relieving the experimental asthma of the offspring whose mother was in protein restriction during pregnancy (Chen et al., 2019). Following the investigation of the effects of parental (breeding, gestation and lactation) diet on offspring immunity, Myles et al. (2013) demonstrated that animals maintained on Western diet resulted in reduced expression of the vitamin D receptor and CYP27b1 (vitamin D activating enzyme). As result to ex vivo LPS stimulation, the colons of pups on Western diet produced enhanced levels of IL-6, IL-1β, and IL-17A, suggesting a hyperinflammatory milieu, and had reduced frequency of colonic T regulatory cells compared to low-fat pups, indicating a dysregulated gut immunity. This phenotype appears to be dependent on altered gut microbiota (Myles et al., 2013).

In this context, studies with humans and animals have shown that the maternal BMI influences the programming of the descendants’ immune system. Children of obese mothers have fewer cells responsible for the defense of the organism, such as dendritic cells, CD4 T cells, lower response of monocytes, increased levels of IFN-α2, IL-6 (Wilson et al., 2015), erythropoietin (Ibrahim et al., 2017) and natural killer cells and CD8 T cells (Gonzalez-Espinosa et al., 2016) in cord plasma. It was evidenced by cord plasma transcriptome analysis that maternal obesity modulates the expression of genes that interfere in the inflammatory and immunological signaling pathways (Edlow et al., 2016). In addition, it was elucidated that newborns of obese women have an unbalanced macrophage polarization response, indicating the impact of maternal obesity on the programming of immune cells (Cifuentes-Zúñiga et al., 2017). These changes can lead to harmful outcomes in neurodevelopment and postnatal metabolism, contributing to the increase of complications in adulthood, such as the development of chronic inflammatory diseases (Sureshchandra et al., 2019).

A maternal HFD during pregnancy and lactation impacted the offspring with increase in production of inflammatory cytokines, reduction in the number of IgA-expressing cells in the small intestine, and changed the microbiota composition, being also responsible for the greater severity of DSS-induced colitis in mice (Xie et al., 2018). Maternal HFD was also responsible for microglia alterations in offspring and the maternal immune activation, with increase of circulating levels of IL-6 (Bordeleau et al., 2020). Animals whose mothers received stearidonic acid – substrate for synthesis of long-chain n-3 PUFAs – during part of pregnancy (5 days before parturition) and lactation (21 days) at 3rd week had a higher proportion of helper T (Th) cells (CD3+CD4+), and lower proportion of NK cells (CD3–CD161+) and macrophages (CD11+) when compared to the offspring of controlled diet mothers, thus enhancing the programming to better growth and immune system maturation (Patel et al., 2019). In a similar way, maternal malnutrition (pregnancy) decreased the expression levels of antimicrobial peptides genes (*Lyz2* and *Reg3g*) compared to controlled mice. For the fetus, there is an increased mRNA expression of gut transcription factor *Sox9* and a decrease in the mRNA expression levels of *Muc2* and *Cd62* versus controlled ones. Fetal gut mRNA expression in maternal malnutrition affects both sexes, but mucus layer maturity impacts only male fetuses (Srugo et al., 2019). These results reinforce the relationships between early life, gut, and immunity (Milani et al., 2017).

**Micronutrients**

The immune system requires several specific micronutrients in adequate quantitiesto ensure the proper function of immune cells. Some of these micronutrients are vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium, with specific and often synergistic functions at the immune response. Adequate amounts are essential to
ensure the proper function of physical barriers and immune cells; however, micronutrient demands vary according to different stages of development and health status. An inadequate micronutrient status contributes to the increased susceptibility to several infectious, inflammatory and metabolic conditions (Gombart et al., 2020).

Vitamin A is a critical micronutrient for regulating immunity (Brown and Noelle, 2015), and its deficiency during gestation or early life decreases the number of immune cells in offspring (Liu et al., 2014). When administered in deficient pregnant rats in early postnatal, it increases intestinal feces levels of secretory IgA with LPS challenge, as well as numbers of CD8+ intestinal intraepithelial lymphocytes and CD4+CD25+ T cells in the spleen (Liu et al., 2014). Following the investigation of how the vitamin status in maternal may affect the prenatal immune system development and allergic diseases, a cohort study analyzed concentrations of some micronutrients in the umbilical cord blood and the relation of prevalence of food allergy, allergic rhinitis, atopic dermatitis, and asthma in children aged 7-9 years old; a significant relationship has been demonstrated (Bobrowska-Korzeniowska et al., 2020). Thus, the study indicates that the maternal diet could modulate the immune tolerance and, consequently, the development of allergic diseases in the offspring.

When assessed cord blood samples from neonates born to mothers who ingested 4400 IU or 400 IU/day of vitamin D3, the supplementation during pregnancy with the high dose resulted in an enhanced broad-spectrum response of cord blood mononuclear cells to innate and mitogenic stimuli, with an increase in levels of cytokines (GM-CSF, IFN-γ, IL-1β, IL-6, and IL-8) of gene expression level of TLR2 and TLR9, and in IL-17A production after T-cell stimulation, and also in the response IL-10 of cord blood mononuclear cells. There was no significant effect on the relative proportions of the main immune cell types in cord blood (Hornsby et al., 2017). However, in a recent article, the cord blood samples showed not representative of postnatal immunity. Other research showed that maternal vitamin D supplementation during pregnancy and lactation alters DNA methylation in mothers and breastfed infants (4-6 week-old) (Anderson et al., 2018).

It has been shown in rodents that zinc deficiency during pregnancy is related to the weakening of the offspring’s immune responses to certain types of vaccines, such as against tuberculosis (BCG and ESAT-6 / CFP-10), by decreasing the proliferation of T cells and negative regulation of the production of INF-γ and TNF-α (Shi et al., 2016). The same effect was seen in relation to the hepatitis B vaccine, caused by the decrease of the B cell count and the reduction in the proliferation and proportion of T cells (Zhao et al., 2013). Also, zinc deficiency was associated with changes in the intestinal microbiota and in the inflammatory response of pregnant mice (Sauer and Grabrucker, 2019), which may present a risk for the offspring, since these factors are known to influence the programming of their immune system (Ganal-Vonarburg et al., 2017; Vuillermin et al., 2017). The zinc deficiency during pregnancy in mice compromised the immune function in the second and third generations, even when they consume adequate amounts of this trace element (Beach et al., 1982). The excess of zinc in pregnancy also was detrimental to the immune function of the offspring (Sharkar et al., 2011). In humans, it was established that reduced levels of zinc in the umbilical cord of newborns with low weight at birth are correlated with the reduced size of the thymus, a key organ in the differentiation and maturation of T cells, indicating that the adequate zinc intake in pregnant women positively influences the size of their children’s thymus and consequently their immune activity (Kumar et al., 2014). Allergies are abnormal immune responses to antigens, usually due to hypersensitivity (Khan and Solensky, 2010; Sicherer, 2002). Research has shown that some maternal micronutrients at recommended levels act to prevent the appearance of allergies in the progeny. In humans, it was observed that the consumption of adequate food sources of vitamin C, copper (West et al., 2012) and vitamin E (Devereux et al., 2002) during pregnancy, but not the consumption of dietary supplements, reduced the allergen results of children prone to developing allergies. Also, vitamin E can act through different mechanisms in the immune response, such as in cell pathways, cell membrane functions, and also in the modulation of inflammatory mediators (Lewis et al., 2019). This deficiency is rare among adults; but in premature babies the reserves are relatively low, with a higher risk of deficiency. In cases of deficiency, neutrophils showed impairments in bactericidal and phagocytic activities (Miller, 1979).

Thus, further study of development programming is required to assess the effects of micronutrient intake involved in the immune response - both its deficiencies and excesses - at critical stages of development, in order to create an effective scientific foundation in this line of research. It is worth mentioning that a set of factors, including a diversified and balanced diet and not isolated nutrients is essential to promote health conditions for adequate immune function.

Breast milk

Breast milk is an essential factor to the development and constitution of the immune system at the beginning of life, acting through several mechanisms to be able to program for health or diseases related to the immune system (Verhasselt, 2020; World Health Organization, 2013). Its complete composition attends exclusively all the baby’s needs up to 6 months of life (Shah et al., 2020) (summarized in Table 1). Breastfeeding protects the newborns against infections, its components are produced
Table 1: Breast milk properties.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (Kcal/100mL) [Shah et al., 2020]</td>
<td>60-75</td>
</tr>
<tr>
<td>Water (World Health Organization, 2015)</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Macronutrients [Shah et al., 2020])</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>6.9 to 7.2%</td>
</tr>
<tr>
<td>Fats</td>
<td>3 to 5%</td>
</tr>
<tr>
<td>Proteins</td>
<td>0.8 to 0.9%</td>
</tr>
<tr>
<td>Micronutrients (Dror and Allen, 2018)</td>
<td></td>
</tr>
<tr>
<td>Vitamins</td>
<td>A, B1, B2, B6, B12 and E</td>
</tr>
<tr>
<td>Minerals</td>
<td>Sodium, potassium, magnesium and zinc</td>
</tr>
<tr>
<td>Human milk oligosaccharides [Coppa et al., 1999]</td>
<td></td>
</tr>
<tr>
<td>Colostrum</td>
<td>20-23 g/L</td>
</tr>
<tr>
<td>Mature milk</td>
<td>12-14 g/L</td>
</tr>
<tr>
<td>Breast milk microbiota [Zimmermann and Curtis, 2020]*</td>
<td>Staphylococcaceae (Staphylococcus), Streptococcaceae (Streptococcus), Lactobacilliaceae (Lactobacillus), Pseudomonadaceae (Pseudomonas), Bifidobacteriaceae (Bifidobacterium), Corynebacteriaceae (Corynebacterium).</td>
</tr>
</tbody>
</table>

*most frequently found bacterial family and respective genera.

individually by the mother for her baby's immunological imprinting, including specific antibodies and human milk oligosaccharides (HMO) that has lasting effects on the health of the infant and the adult individual (Ayechu-Muruzabal et al., 2018; Šuligoj et al., 2020; Walsh et al., 2020). It has already evidenced that the maternal diet (during lactation) may change the composition of breast milk and that it programs the lipid profile in adult male rat offspring (Vieira et al., 2018).

In proximity of the partum, the cell population of breast milk becomes enriched with CD8+ T cells, which are effector memory cells responsible for immunologic memory that provides long-term protection. These cells appear in different magnitude and quality in breast milk when compared with the peripheral blood compartment. This may represent a mechanism for passive transfer of cellular immunity from mother to child (Myles and Datta, 2020). At the same time, in murine model it was demonstrated that maternal immunization and foster pup suckling resulted not only in transfer of passive cellular immunity to the pup, but also in the development of Ag-specific T cells in foster pups. This evidences the existence of two complementary mechanisms for ensuring early cell-mediated immune protection against intracellular pathogens to which the mother has been exposed (Ghosh et al., 2016).

The breast milk is a substrate for the synthesis of short-chain fatty acids (SCFA), where obligate anaerobes bacteria, mainly *Bifidobacterium*, digest HMO to produce SCFAs (Gopalakrishna and Hand, 2020). The oligosaccharides are a group of complex multifunctional glycans that are present in relevant quantities in the human milk (Wiciński et al., 2020). The SCFAs have the potential to inhibit histone deacetylase, which affects the expression of genes such as Foxp3. The expression of Foxp3 is involved in the development and functions of Treg cells, inhibiting inflammation and maintaining homeostasis (Nakajima et al., 2020). Butyrate, for example, increases tight-junction and mucus genes; however, the inhibition of these genes leads to a partial loss of the anti-inflammatory effect (Gao et al., 2020). In addition, the food allergic response in animals that received butyrate (30 mg/kg/day) is reduced, with inhibition of Th2 cytokines, increase in the IFN-γ and IL-10, and modulation of oxidative stress (Paparo et al., 2020).

HMOs support the growth of the microbiota and exert several immune functions, such as the prevention of microbial adhesion and invasion of the mucosa; it is a growth factor for *Bifidobacterium*; it reduces the levels of cytokine IL-8, IL-6, and IL-1β (Plaza-Díaz et al., 2018). A longitudinal study estimated that breast milk is responsible for 27.7% of the gut bacteria in infants during the first month of life, while areolar skin account for 10.4%. Milk has a predominance of the phylum Proteobacteria and kept the alpha diversity constant throughout the first year (Pannaraj...
et al., 2017). This establishment of the microbiota in early life is critical since it impacts health and immunity during childhood and throughout life. Galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) are not hydrolyzed by digestive enzymes and seem to be a key factor for the development of the intestinal microbiota of breast-fed infants, showing prebiotic effect (Zuurveld et al., 2020). Maternal microbiota and its metabolites during prenatal and early postnatal may protect against infection (Zheng et al., 2020), immune status (Mulligan and Friedman, 2017), and offspring obesity development (Li, 2018).

**Gut microbiota**

Complementarily, breast milk has been crucially associated the establishment and development of the early gut microbiota. Conditions that cause changes in this microbiota, in its diversity or/and composition can lead to the occurrence of alterations in the gastrointestinal and immunological function, which can manifest themselves both in babies and later in life as manifestations of diseases: asthma, inflammatory bowel disease and even metabolic disorders (Milani et al., 2017; Zheng et al., 2020). It was observed that in wild-type C57BL/6 mice, the colonization of *E. coli* HA107 only during pregnancy altered the number of innate leukocytes in the offspring’s intestine in the postnatal period, and several bacteria-derived metabolites were also passed from mother to offspring. In addition, it was noted that maternal antibodies affect the fetus and newborn, increasing the microbial molecular levels of both (Agüero et al., 2016).

It has been demonstrated that mice fed with high fiber diet have a distinctive gut microbiota, which increases SCFA levels. The diet rich in fiber or acetate was able to increase the number and function of regulatory T cells and Foxp3 acetylation, which acts as a promoter, probably because it inhibits HDAC9, since SCFAs are natural inhibitors of histone deacetylases (HDACs). This cascade of effects significantly influenced the suppression of allergic airway disease (a model compatible with human asthma). Therefore, a maternal diet rich in fibers/acetate during pregnancy can be program protection in the adult offspring against the development of robust asthma in an epigenetic way, by reducing the expression of pulmonary genes that modulate the development of human asthma and allergic diseases of the airways in mice (Thorburn et al., 2015). Type 1 diabetes, also has been associated to dysbiosis of the gut microbiota, including alterations in abundance and diversity. It has been proven that a dietary intervention (eg. with prebiotics and probiotics) during early life, is capable of modulating epigenetic changes related to type 1 diabetes, modifying the expression of standard genes for this disease by means of epigenetic mechanisms (Thayab et al., 2020). The diet, as one of the main factors of modulating the composition of the intestinal microbiota, has potential to serve as a preventive and therapeutic strategy for several diseases.

Early-life microbial exposure elicits long-lasting effects on invariant natural killer T (iNKT) cells, an innate-like T cell subset that expresses an invariant T cell receptor-(Crosby and Kronenberg, 2018). In this context, the quantity and function of iNKT cells in the colon and lungs are modulated by CXCL16, a factor that is microbially regulated (Olszek et al., 2012). The development of mucosal-associated invariant T (MAIT) cells relies on a specific period of time, which is closely related to exposures to specific microbes in early life, which are responsible for synthesizing riboflavin-derived antigens. In adults, cutaneous MAIT cells are a dominant population of IL-17A-producing lymphocytes, which display a unique transcriptional signature and can subsequently respond to skin commensals in an IL-17A-, IL-18-, and antigen-dependent manner. As consequence, local activation of cutaneous MAIT cells promotes tissue repair. Constantinides et al. (2019) propose a central strategy utilized by the immune system to interact with the microbiota, which is due to the recognition of canonical microbially derived antigens by unconventional T cells. Among others cells, including MAIT cells, this seems to play an important role in controlling the physiology of the host (Constantinides et al., 2019).

Infants exposed to bifidobacteria-supplemented formula (10² colony-forming units (CFU)/g) showed decreased occurrence of *Bacteroides* and *Blautia* spp. associated with changes in lipids and metabolites at first month. The mode of feeding (breast milk or formula) and type of delivery (vaginal or cesarean) were also factors associated with the modulation of the microbiota and metabolites of babies. It is worth pointing out that the strains failed to persistently colonize beyond intervention, despite the high prevalence of other bifidobacteria in all feeding groups even after 2 years old (Bazanella et al., 2017).

A randomized, controlled clinical trial demonstrated that consumption by babies of formula fermented with *Lactobacillus paracasei* CBA L74 caused an increase in secretory IgA compared to standard formula feeding. It is important to point out that, formula-fed infants demonstrated a differentiation in fecal metabolites compared with breastfed infants, even when was added probiotic. Similar result was observed for the mode of delivery (Roggero et al., 2020).

**Conclusion**

There is a set of evidence from human and animal studies that indicate that altered epigenetic states may contribute to immune development from the beginning of life. Nonetheless, many questions remain unanswered, including if these epigenetic changes are reversible, as well as how long the immune plasticity window remains open. An improved understanding of the epigenetic pathways and immune development, including the potential of nutrition,
Figure 2: Role of the nutrition in immune system regulation of offspring. During critical periods of development, the diet and nutritional status can contribute to reduces the inflammatory and increases the anti-inflammatory response of the innate and adaptive immunity. However, under nutrition and a high-fat diet can result in disruption of the immune system, affecting gut microbiota, inflammatory cytokines, and immune cells.

may represent a strategy for using the modulation factors as a target for preventive and therapeutic approaches to address immune disorders (summarized in Figure 2). Although the scientific literature has advanced in research with animals, conducting long follow-up human studies in different populations has proved to be a challenge in the context of programming, which make to define practical approaches and clinical applications based on the present findings difficult.

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