Early-Life Nutrition and Gut Immune Development

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Gut immune function conditions development of diseases that result from defects in immune regulation such as allergic and obesity-related disease [1]. As epidemiological studies support the developmental origin of health and disease, the deciphering of the critical factors modulating gut immune development should allow the advance of primary prevention strategies specifically adapted to the early-life immune system. Here, we will emphasize how nutrition can shape microbiota composition and metabolite production with immune-modulatory properties. We will also focus on the role of dietary compounds recently demonstrated to be essential in immune development and function such as dietary antigens, vitamin A, and aryl hydrocarbon receptor (AhR) ligands.

Microbiota is necessary for lymphoid tissue development and immune differentiation such as IgA secretion, regulation of IgE responses, and differentiation of T cells subsets [1]. Besides mode of delivery, nutrition is the key factor directing the early microbiota composition and function [2]. Breast milk contains viable bacteria that will contribute to the establishment of the neonatal microbiota, and maternal IgA will alter colonization patterns in the neonate. Breast milk also contains nutrients specific for the growth of commensals, i.e. human milk oligosaccharides (HMO), which stimulate the growth of bifidobacteria and affect their metabolic function. In animals fed solid food, Clostridia can metabolize dietary fibers into short-chain fatty acids (SCFA), while in breastfed neonates, SCFA are derived from HMO metabolized by bifidobacteria (Fig. 1a). The role of SCFA in gut immunity in preweaned mice has not been assessed yet. In young weaned mice, they were found to stimulate regulatory T cell expansion, IgA and mucus secretion, gut epithelium barrier function, ILC3 function, and induce resistance to food allergy and gut inflammatory disease [3] (Fig. 1a). Some commensals, such as Lactobacillus, metabolize tryptophan, an essential amino acid that is a common constituent of protein-based foods (Fig. 1b). The metabolites bind AhR expressed in ILC3 and stimulate the postnatal formation of isolated
lymphoid follicles and IL-22 secretion necessary for gut barrier function and protection from *Citrobacter* infection and colitis [3] (Fig. 1b). In breastfed infants, AhR ligands could originate from maternal microbiota or from maternal diet (Fig. 1b).

Mice studies have recently highlighted the regulatory function of diet-derived antigens in the small intestine [4] (Fig. 1c). In the human [5],
food diversification in the first year of life was associated with decreased risk of allergies. The shaping of immune reactivity by induction of oral tolerance to specific antigens during the period of immune ontogeny may be possible in the case of egg (OVA) and peanut antigen. Additional TGF-β, vitamin A, and IgG from maternal milk were critical for tolerance induction towards OVA transferred through breast milk in rodents [6] (Fig. 1c). TGF-β is a growth factor for epithelium, and both vitamin A and IgG acted on antigen transfer through epithelium. Vitamin A also increased the function of dendritic cells involved in tolerance and Th1 differentiation (Fig. 1c). Our recent data showed that not all the antigens in breast milk induce oral tolerance. Antigen from house dust mite, Der p 1, is present in human breast milk and its presence increased the risk of allergy both in mice and in the humans. This stresses the need to identify how maternal milk factors could be modulated to counteract deleterious action of some allergens [6].

In conclusion, before weaning, the physiological food for mammals is providing the neonate with the factors necessary for immune
maturation, which the neonate would otherwise miss due to the lack of a
diverse microbiota and solid food-derived molecules. Breast milk exposes
the infant to a variety of food antigens, and it contains ligands that are
critical for lymphoid tissue development and immune function such as
AhR ligands and vitamin A. It provides HMO, as surrogates to fibers
found in solid food, for commensals to produce SCFA. Breast milk also
delivers a microbiota and food for commensal growth in the sterile neo-
nate gut. After weaning, solid food-derived antigens and vitamins as well
as food metabolites produced by the microbiota will continue to shape the
immune system and dictate susceptibility to local and systemic immune-
mediated disease.

References
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