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Mini Review Article

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Microbiota Innovative Management Modalities in Mastering a Healthy Gut … Feeding Update …!

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Abstract

Introduction: *Our mini review aims to state the evidence-based effect of the implementation of newborn infant nutrition with prebiotics and probiotics has been demonstrated in changing microflora composition toward the desired breast-feeding pattern and stimulating immune response*

Considerable efforts have been made to mimic the composition of human milk by the addition to formula feeding of living bacteria (probiotics), non-digestible fibers, nucleotides and oligosaccharides (prebiotics), and bovine lactoferrin in order to induce a breast-fed-similar microbiota colonization in formula-fed infants, with the final aim to stimulate the maturation and proper function of the immune system

Several studies performed in the past decades have clearly demonstrated the complexity of gut microbiota composition and the modulatory effect played by several endogenous and exogenous factors on it. Type of feeding in the first months of life appears as one of the most important determinants of the child and adult well-being, and its protective action seems to rely mainly on its ability to modulate intestinal microflora composition at early stages of life. Diet has a dominant role over other possible variables such ethnicity, sanitation, hygiene, geography, and climate, in shaping the gut microbiota. In recent years, the implementation of milk formula with prebiotics, probiotics, and lactoferrin has been demonstrated to change newborns' microflora composition toward breast-feeding pattern and stimulate immune response

Conclusions: *The aim of this Mini Review is to elucidate the specific immunologic role of the human milk-associated microbiota and its impact on the newborn's health and life, highlighting the importance to properly study the biological interactions in a bacterial population and between the microbiota and the host. This mini review discusses the composition of human milk and its biological benefit for infants. Additionally, we also discuss how these beneficial effects can be mimicked if breastfeeding is not possible. And to highlight the specific and fundamental role of human milk-associated bacteria in modulating and influencing the newborns' immune system during their life.*

Keywords: Human Milk, Milk Microbiota, Colostrum, Immunomodulation, Newborn's Immune System

Introduction

According to the recommendations of the World Health Organization, infants must be exclusively breastfed during the first six months of life. Human breast milk provides more than half of the child's nutritional needs during the second year of life [1]. World Health Organization. 2018. The infants who are formula-fed are more prone to infectious diseases, such as gastroenteritis and acute otitis media, and immune-mediated diseases such as allergy, when compared to the infants who are exclusively breastfed [2]. ESPGHAN Committee on Nutrition, Agostoni C, Braegger C2009. The first milk produced by mothers after the delivery is called colostrum, it is biochemically, and functionally different from the mature milk [3].

The human milk is a rich and complete nourishment that is essential for the correct development of the infant's organism [4]. Colostrum, indeed, contains high concentration of lactoferrin, Immunoglobulin A (IgA), leukocytes and specific developmental factors, and a low amount of lactose, potassium and calcium, underlying its immunological functions rather than nutritional [5, 6]. From 5 days

to 2 weeks postpartum, there is the production of transitional milk which shares some characteristics of colostrum, although its main function is to support newborn at nutritional level [7, 8].

Bacteria located in both colostrum and mature milk can stimulate the anti inflammatory response, by stimulating the production of specific cytokines, reducing the risk of developing a broad range of inflammatory diseases and preventing the expression of immune-mediated pathologies, such as asthma and atopic dermatitis. This mini review discusses the composition of human milk and its biological benefit for infants. Additionally, we also discuss how these beneficial effects can be mimicked if breastfeeding is not possible

Discussion

Microbiota and the rule in the early newborn immunity

The specific mechanisms that lead to the formation of the human milk microbiota are still unknown; however, there are different hypothesis that can explain the origin of milk associated bacteria. Indeed, some skin or infant's oral cavity may become an integral component of the milk microbiota by means of a milk flow back into mammary ducts during lactation [9]. This mechanism may justify the presence of cutaneous and oral bacteria that are recovered in the milk microbiota, such as Streptococcus spp. and Staphylococcus spp [10, 11]. Interestingly microorganisms belonging to the maternal, human milk contained also a great number of intestinal bacteria, which may spread from the maternal intestinal environment by a mechanism involving dendritic cells (DCs) and CD18+ cells; these cellular types would be able to capture intestinal microorganisms from the gut lumen and transfer them to lactating mammary glands by means of translocation, which results to be increased during late pregnancy and lactation [9]. Consequently, the milk microbiota can shape the initial intestinal microbiome of newborns, together with the maternal intestinal and vaginal microorganisms that are ingested by the neonate during the passage through the birth canal [11].

Microbiota

The survival advantage of breastfed infants over non-breastfed infants is known since the 1900s. The stool bacterial composition of breastfed infants was reported to be different from that of the formula-fed infants. Additionally, the presence of an unidentified carbohydrate fraction was also reported in human breast milk. The amount and composition of microbiota vary among women, and during the lactation period. Generally, the total microbiota concentration is higher during the early stages of lactation and decreases within the first three months [12-14]. Xu G, Davis, 2017J Thurl S, Munzert M, 2010. The microbiota content of breast milk after term delivery is higher than that after preterm delivery. The HMO fraction is the third most abundant component in human milk after lactose and lipids, excluding water. The HMO content usually varies between 10–15 grams per liter (g/L) of mature milk (or 1.5–2.3 g/100 kcal, assuming an energy density of human milk of 64 kcal/100 mL) and 20–25 g/L of colostrum [15-17]. Bode L. 2012, Kunz C, Kuntz S 2014 Zivkovic AM, 2011The HMO content in the human breast milk is more abundant than the protein content, which is typically around 10 g/L or 1.5 g/100 kcal.

Health Benefits of the Microbiota

Several studies have reported the beneficial effects of microbiota that include modification of the intestinal microbiota, anti-adhesive effect against pathogens, modulation of the intestinal epithelial cell response, and development of the immune system. We will discuss each of these effects further.

Modulation of intestinal microbiota

Human milk oligosaccharides (HMO) are intrinsic components that affect the gut microbiota by providing an energy source for the beneficial intestinal bacteria. Additionally, HMOs affect the health of the host by serving as a decoy receptor for the opportunistic pathogens in the mucosal surface [18]. Salminen S. 2017 One study reported that none of the selected Enterobacteriaceae strains exhibited growth on a medium containing 2′-FL, 6′-sialyllactose or LNnT as a carbohydrate source. However, several strains were capable of utilizing galacto-oligosaccharides (GOS), maltodextrin, and monosaccharide and disaccharide components of HMOs for their growth [19, 20]. The enriched fecal consortia also did not exhibit growth on a medium containing 2′-FL or 6′-sialyllactose, but exhibited limited growth on a medium containing LNnT [19].

Several in vitro studies have demonstrated that HMOs promote the growth of certain but not all Bifidobacterium [15]. Bode L 2012Bifidobacterium longum subsp. Bifidobacterium infantis exhibit good growth on medium supplemented with HMOs, including 2′-FL, as the sole source of carbohydrate [20]. LoCascio RG, 2007 over time, B. infantis consumes all HMOs including its monosaccharide and disaccharide metabolites [21]. Asakuma S, 2011. The growth of Bifidobacterium bifidum is slower than that of B. infantis in the presence of HMOs. Additionally, certain B. longum strains metabolize fucosylated HMOs [15, 21, 22]. Bode L. 2012 Asakuma S, 2011 Garrido D, 2016 ,The Bifidobacterium kashiwanohense strain exhibits growth in the presence of 2′-FL and 3′-FL [23-25]. HMOs are a preferred substrate for B. infantis. Other bifidobacteria may reduce the nutrients available for potentially harmful bacteria and limit their growth. Additionally, B. infantis produces short-chain fatty acids (SCFAs), which favor the growth of commensal bacteria and not pathogenic bacteria [23]. Gibson GR, 1994A study reported that among the 24-probiotic strains, only B. longum subsp. B. infantis ATCC 15697 and B. infantis M-63 were able to ferment 3′-sialyllactose, 6′-sialyllactose, 2′-FL, and 3′-FL [24].

When infants are fed with a formula supplemented with 2′-FL and LNnT, they develop a distinctive stool bacterial profile that is more similar to that of the breastfed infants compared to the infants that are fed with a formula not supplemented with prebiotics. The bacterial diversity of infants at the age of 3 months exhibited increased colonization with beneficial bifidobacteria and decreased colonization with pathogenic bacteria [25]. Puccio G2017. Antiadhesive properties HMOs improve the host defense mechanism by strengthening the gut barrier function [26]. Angeloni S2005 the HMO, 2′-FL inhibits Campylobacter jejuni infection and C. jejuni -associated mucosal inflammation [27].

An in vitro study demonstrated that 2′-FL attenuates C. jejuni invasion by 80% and inhibits the release of mucosal pro-inflammatory signals. A study on mouse model revealed that the ingestion of 2′-FL inhibits the C. jejuni colonization by 80%, weight loss by 5%, intestinal inflammation, and induction of inflammatory signaling molecules [28]. Ruiz-Palacios GM, A2003. Prospective study on infants suggested that the beneficial effect of 2′-FL includes a reduction in the number of episodes of C. jejuni -associated diarrhea [29]. Morrow AL, Ruiz-Palacios GM, 2005 LNnT was reported to reduce the abundance of Streptococcus pneumoniae in the lungs of an animal model Idänpään-Heikkilä I, 1997 HMOs may function as a

decoy receptor for group B Streptococcus [30, 31].

HMOs reduce preterm mortality and morbidity by modulating the gut microbiome to protect against necrotizing enterocolitis, candidiasis, and several immune-related diseases [32]. Moukarzel S, 2017LNnT reduces the risk of developing necrotizing enterocolitis in preterm infants [33]. Autran CA 2018Similarly, 2′-FL has also been reported to exhibit beneficial effect against necrotizing enterocolitis [34].

Modulators of intestinal cell response

HMOs are able to directly affect the intestinal cell response by reducing the cell growth and by inducing differentiation and apoptosis [35]. Kuntz S, Kunz C, 2009 Intestinal health and barrier function are considered the first line of defense in innate immunity. HMOs have been reported to increase the intestinal cell maturation [36].

Immune modulators

One of the important properties of HMOs is the immunomodulation. HMOs directly modulate the gene expression of intestinal cells, leading to changes in the expression of cell surface glycans and other cell responses [37]. Kulinich A, 2016 HMOs modulate lymphocyte cytokine production and enable a more balanced TH1/TH2 response. An increasing number of in vitro.

Studies suggest that HMOs exert microbiota-independent effects by directly modulating the immune response and by regulating the immune cell population and cytokine secretion [38]. Donovan SM, 2016HMOs may either act locally on the mucosa-associated lymphoid tissue or act at a systemic level [15].

The plasma concentration of inflammatory cytokines in the breastfed infants and infants fed with experimental formula supplemented with 2′-FL was markedly lower than that in the infants fed with control formula supplemented with galacto-oligosaccharides [39]. Goehring KC, 2016 these data indicate that infants fed with a formula supplemented with 2′-FL exhibit lower plasma inflammatory cytokine profiles, which is similar to those of a breastfed reference group [39]. Goehring KC, 2016 HMOs were more effective than non-human prebiotic oligosaccharides in modulating the systemic and gastrointestinal immune cell responses in pigs [40]. Comstock SS, 2017 these altered immune cell populations may mediate the rotavirus infection susceptibility [40]. Comstock SS, 2017 the symptoms of food allergy are reduced by 2′-FL through induction of interleukin-10+ T-regulatory cells and through indirect stabilization of mast cells [41].

HMOs, especially 2′-FL, directly inhibit the lipopolysaccharide-mediated inflammation during enter toxigenic Escherichia coli invasion of T84 and H4 intestinal epithelial cells through attenuation of CD14 induction [42]. He Y, Liu S, 2016, CD14 expression mediates the lipopolysaccharide-Toll-like receptor 4 stimulation of a part of the macrophage migration inhibitory factors inflammatory pathway by suppressing the cytokine signaling 2/signal transducer and by activating the transcription factor 3/nuclear factor-κB. The direct inhibition of inflammation supports the role of HMOs as a stimulator of the innate immune system [42]. He Y, Liu S, 2016 Two-year-old children who were born through C-section and fed on an infant formula supplemented with 2′-FL had a lower risk of developing immunoglobulin E-associated allergies compared to those fed unsupplemented formula [43].

New insight into the microbial ecology

The study of microbial interactions within a bacterial population is of extreme importance to clearly understand the specific role of microbiome. Indeed, microorganisms compete for nutrients, exchange genetic material and metabolites, being responsible of influencing the microbiota composition and the host's health [44]. Due to its dynamic nature and high heterogeneity, the microbiota can be considered a complex and variable ecosystem not often well understandable. For this reason, in the last years a novel approach has been developed to study the microbiota, by using graph theoretical, systems-oriented method able to facilitate the understanding of evolutionary and complex ecological processes [44]. Bacterial network is becoming essential to study microbial relationships and clarify the impact of various interactions on the host by identifying the main "hubs" that may represent the most influential member in a bacterial community [44]. Moreover, a central node is thought to have more links with other hubs, having a pivotal role in the stability of the whole microbial network.

Conclusion

This Mini Review is to elucidate the specific immunologic role of the microbiota and its impact on the newborn's health and life, highlighting the importance to properly study the biological interactions in a bacterial population and between the microbiota and the host. Microbiota can serve as soluble decoy receptors that block the attachment of viral, bacterial, or protozoan parasitic pathogens to the epithelial cell surface receptors, which may aid in preventing infectious diseases. HMOs are also antimicrobials that act as bacteriostatic or bactericidal agents. Additionally, microbiota enhance host epithelial and immune cell responses in the neonate.

However, further studies are needed to highlight the direct and strong connection between the human milk microbiota and the stimulation of newborns' immune system, as to date there are no clear and specific evidence about this association. Application of network biology will significantly improve our knowledge on bacterial interactions among the milk microbiota, with important applications for eventual targeted modification of bacterial composition, aimed to enhance the abundance of those microorganisms that may be essential not only for the modulation of the infants' immune system, but also for improving the whole host's health

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