

Review Article

Dairy Products: Influence on Gut Microbiota

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Introduction

Since a century ago, scientists have demonstrated that diet can dramatically change the microbial composition of the microbiota associated to the gut; it has been demonstrated through animal models the importance of the microbiota for the development and maintenance of the mucosal immune system associated to the gut and the beneficial or negative effects on gut diseases [1]. The increase in the diffusion of antibiotics and drastic changes in the diet across years, in industrialized countries, have been linked to a surprising increase in the incidence of allergies. On the basis of previous concepts can we say that microbiota is a major regulator of the immune system? Therefore, microbiota could be considered as starter of inflammatory diseases, but it is also true that microbiota can be considered the main positive regulatory force for immune responses after development.

A normal microbiota plays a positive role in protecting the host against pathogenic microbial challenge excluding microbes from the mucosa. Thus, in the future, researchers should be able to win the challenge in order to identify the 'crossover points' where microbial signals regulate immune function. A possibility could be through the production of fatty acid metabolites, such as oxylipins and short-chain fatty acids, by the host and microbiota [2].

Dietary components can influence the response of gut, and changes in the diet can modify the relative abundance or dominance of several microorganism phyla [3,4] reported that a diet high in carbohydrate intake was associated with increase in the genera *Prevotella*-Type, protein and animal fat intake was associated with *Bacteroides*-Type, suggesting that food dietary intake might affect differently the community of microorganism of the gut. Every species of microbiota gut has a role [5]; their substrates, available to the microbiota, produce different outputs for the microorganism community [6]. The intestinal microbiota could be considered like a biomarker in relation to the consumption of healthy or unhealthy food intake; changes in the microbiota may encourage the consumer's choices towards a long term diet able to influence the production of beneficial microbial metabolites [7].

The Normal Microbiota: Characterization and Development

After birth the process of colonization of the GI tract leads to a series of ecological successions ending with the establishment of a stable microbiota ('Microflora') that is unique for each individual. At

birth, a complex community of microbes that reaches up to a density of 1×10^{12} bacterial cells per grams of content in the adult colon began to colonize the GI [1]. The stable adult microbiota is composed of autochthonous species (permanent members) and allochthonous species (colonizers that are briefly acquired from an external origin). The adult microbiota is composed of 400-1000 species, the major of them; about 60% are not culturable outside the GI environment. However, it is evaluated that 30-40 species predominate in this ecosystem [1]. Both prokaryotic and eukaryotic microbes are present, with bacterial species dominating. Main bacterial species are strict anaerobes (97%), whereas only 3% are aerobic (facultative anaerobes). The composition of the microbiota differs not only along the length of the GI tract, but also cross-sectionally, with different populations inhabiting the GI mucosa and lumen. The most common anaerobic genera in terms of concentration within the GI tract are *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Fusobacterium*, *Clostridium* and *Lactobacillus*. Among the aerobes are the Gram-negative enteric bacteria (*Escherichia coli* and *Salmonella spp.*) and the Gram-positive cocci (*Enterococcus*, *Staphylococcus* and *Streptococcus*). In addition, also aerobic fungal species, such as *Candida albicans*, are members of the normal microbiota [2]. These microbes live in a symbiotic relationship with the host and are key determinants of health and disease by influencing nutrient absorption, barrier functioning, and immune development [1].

Members of the normal microbiota, such as lactic acid bacteria, produce large quantities of biologically active Short-Chain Fatty Acids (SCFA). These fatty acids are byproducts of anaerobic fermentation and feature an anti-inflammatory function. Butyric acid is a well known short chain fatty acid holding immunomodulatory activities [8].

The Relation between Microbiota and Gut Immune System

Recent reviews have evidenced that the microbiota arouses innate and adaptive immune mechanisms collaborating to protect the host and maintain intestinal homeostasis [9,10]. The central components in the immune system of the gut are epithelial cells. Like immune cells, epithelial cells express receptors for Microbial-Associated Molecular Patterns (MAMPs). These receptors are able to activate signaling cascades that accurately tuned epithelial cell production of antimicrobial products and chemokines, on the basis on the signals that are provided by the microbiota. Thus, gut epithelial cells form a potent and inducible physico-chemical barrier, limiting microbial growth and access to the gut surface. They can also induce leukocytes to strengthen their barrier function or to participate in the activation of gut adaptive immune responses. Gut-associated Lymphoid Tissues (GALT) consist of the Peyer's Patches (PP) and Small Intestinal Lymphoid Tissue (SILT) in the small intestine, lymphoid aggregates in the large intestine, and diffusely distributed immune cells in the lamina of the gastrointestinal tract. In addition to the immune cells, the intestinal epithelium also plays a role in the generation of immune

responses through sampling of foreign antigens thanks to Toll-Like Receptors (TLR) and NOD-Like Receptors (NLR). In mammals, the developments of GALT begin before birth by a genetic program [11]. However, the maturation of GALT and the recruitment of IgA-secreting plasma cells, and activated T cells to mucosal sites, take place only after birth and it is strictly dependent on microbiota-derived signals. Furthermore, microbiota-derived signals influence the crosstalk between epithelial cells and gut Dendritic Cells (DCs), modulating the nature and intensity of intestinal B and T cell responses [12]. In trials on immune-competent mice, intestinal colonization stimulates the production of secretory IgA, the differentiation of effect or T helper 1 (Th1), Th2 and Th17 cells, and the development of regulatory T (TReg) cells that are involved in the homeostasis of gut. Clearly, these adaptive immune elements cooperate with innate immune cells to improve the gut barrier and protect the host from invading pathogens [13].

It has been known that alterations in the gut microbiota can influence mucosal immunity [14]. Gut microbiota has a central role in the development of mucosal immunity considering that the intestinal mucosa represents the largest surface area in contact with the antigens of the external environment. In addition, the surface of the gut microbiota covering the mucosa normally represents the main proportion of the antigens presented to the resident immune cells and those stimulating the pattern recognition receptors as TLR and NLRs of the intestinal epithelial cells [15]. It is still unclear how individual members of the microbiota or their derived products can affect the balance between pro-inflammatory and regulatory immune responses; moreover, it is unclear if the composition of the microbiota can influence the development of inflammatory diseases in the gut. Before considering the possible role of the microbiota in disease, it should be necessary to understand how the different colonization strategies of individual members of the microbiota could influence the development and functioning of the gut immune system and to prove that is the host immune system that determines if a bacterium is a possible friend or an enemy.

The mucosal immune system needs to comply two, apparently conflicting, functions. It needs to be tolerant of the overlying microbiota to prevent the induction of an excessive systemic immune response, but it needs to control the gut microbiota to prevent its overgrowth and translocation to systemic sites.

The Microbiota Evolution

Particular dietary components should be carefully controlled human dietary studies, because they could have opposite effects on gut. Many studies have documented the response of selected groups to prebiotics, but only few studies have examined temporal changes in the gut microbial community in response to dietary food intake and changing in diet [16]. It should also be noted that many dominant groups of bacteria, perhaps those that possess a greater degree of nutritional diversity or flexibility, remained unaffected by dietary changes [3]. Infants born naturally become inoculated by the mother's vaginal and faecal microbiota during delivers [17]. Babies that are breastfed have a more stable, less diverse, bacterial community than not breastfed babies [18,19].

After the introduction of solid food, gut microbiota composition develops towards the adult pattern with increased diversity [20] and

increased abundance of anaerobic Firmicutes [21].

Early colonization of the gut has been shown to influence maturation of the immune system [22]. In old age a decline in microbiota diversity has been reported [23], with reduced numbers of Bifidobacteria and an increase in Enterobacteriaceae. At the moment is not yet clear how these changes correspond to changes in health status, as well as the extent to which they are linked with alterations in dietary intake, physical activity or changes in immune function.

Influence of Fatty Acids of Dairy Products on Gut Microbiota

Polyunsaturated Fatty Acids (PUFA) contain two or more double bonds and are categorized on the basis of location of the double bond relative to the last methyl at the end of the molecule. Linoleic acid (C18:2 ω -6) and α -linolenic acid (C18:3 ω -3) are essential fatty acids belonging to PUFA family. Although the adult microbiome is not particularly enriched in genes involved in fatty acid metabolism [24] some interactions between PUFAs and some probiotics in microbiota have been reported, which could be able to affect the biological roles of both. Studies in vitro demonstrate that some PUFAs as linoleic, gamma-linolenic, arachidonic, alphinolenic and docosahexaenoic acids have effects on the growth and adhesion of different Lactobacillus strains [25]. CLA is a mixture of positional and geometric isomers of octadecadienoic acid (predominantly at position 9 and 11, or 10 and 12) and appear in a conjugated double bond system (two double bonds separated by a single bond). Several health benefits are associated with their consumption. Several CLA isomers, including cis-9, trans-11 CLA, are naturally found in milk, cheese and ruminant food products [26]. However, since CLA can also modulate the production of arachidonic acid metabolites [27,28], it could be speculated that the reduced production of inflammatory lipid mediators could have a role to CLA's beneficial actions in Inflammatory Bowel Disease (IBD) that is a group of disorders characterized by different levels of intestinal inflammation. Moreover, PUFA in general have beneficial effects on health; they are involved in the formation of prostacyclins and thromboxanes, pro-inflammatory cytokine production, and induction of the release of acetylcholine [29]. In different studies it has been showed that diets rich in PUFAs positively influence immune function, blood pressure, cholesterol and triglycerides levels, and cardiovascular function in animals and humans [30]. In cheese, CLA content ranges depends on CLA content of raw milk. The transfer of fatty acids from milk to dairy products is influenced by their content in the milk. During cheese ripening CLA concentration is subjected to a decrement. This bioactive compound is adsorbed from gastrointestinal tract and could give beneficial effects on human health.

Microbiota community can alter and modify ω -3 PUFA metabolism to generate an increasing of long-chain PUFA metabolites that are able to produce CLA and an increase production of SCFA [31]. SCFA are the last products of anaerobic gut microbial fermentation and they play an important role in prevention of metabolic disorders interacting with the intestinal microbiota [32]. Bacterial products like short-chain fatty acids (SCFAs: Acetic acid, Propionic acid and Butyric acid) have also been shown to induce TREG cells [33,34,35]. Tregs play an essential role in immune tolerance and in their absence both humans and mice spontaneously develop autoimmune disorders

at a young age [36]. Natural Tregs develop in the thymus and induced Tregs development at sites of inflammation in the presence of IL-2 and TGF- β [37]. SCFAs are showed to induce IL-18 production from epithelial cells and promote tolerogenic dendritic cells, which produce IL-10 and retinoic acid [38].

Besides, SCFAs have a number of important functions, such as the regulation of the balance between fatty acids synthesis, fatty acid oxidation and lypolysis in human body. Other studies reported that SCFAs, especially butyrate, have anti-inflammatory properties [39] and changes in gut motility [40] and energy consumption [41]. Thus SCFAs production changing may determine important physiological consequences.

Future Perspectives and Conclusions

The gut microbiota has a great impact on the nutritional and health status of the host, modulating the immune and metabolic functions. The bacterial community of gut is involved in the transformation of dietary compounds that could have beneficial effects. Thus, some kind of food compounds also exerts significant effects on the intestinal environment, changing the gut microbiota composition and probably its functional effects on human organism.

Further knowledge and research on interactions between bioactive food compounds and specific intestinal bacteria could contribute to a better understanding of both positive and negative interactions in human health and it could be interesting to investigate how milk and dairy products can influence the gut microbiota and subsequently outputs.

Investigate how milk and dairy products can influence the gut microbiota and subsequently outputs.

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