Effects of fibers and gut microbiota on low-grade inflammatory human disease

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Obesity represents a major public health problem, as it leads to metabolic disorders involved in the development of type 2 diabetes, fatty liver diseases, cardiovascular diseases and cancer (1). The Western lifestyle, including over-feeding of highly refined diets and sedentary behavior, is associated with systemic low-grade inflammation, responsible for chronic degenerative disease. Moreover, animal and human data have demonstrated the impact of high-fat diet feeding on the onset of metabolic endotoxemia. This latter, being characterized by increase blood lipopolysaccharide (LPS) levels, triggers low-grade inflammation and contributes to the development of obesity. The gut microbiota are a candidate sources of plasma LPS. Indeed, LPS is a major component of the outer membrane in Gram-negative bacteria and its plasma levels are correlated with changes in intestinal microbiota where the Gram-negative to Gram-positive ratio is increased by high fat feeding (1). Not surprising that in humans, obesity is characterized by dysbiosis, i.e. imbalances in the composition and function of the intestinal microbes. Currently, many studies are being conducted to assess the contribution of intestinal microflora metabolites [mainly short-chain fatty acids (SCFAs)] to the organism's homeostasis. Dietary fibers have been promoted for their health benefits and high-fiber intake has been reported as beneficial in numerous chronic diseases (2). However, we have to keep in mind that consumption of dietary fiber significantly alters the composition of the gut microbiota. For instance, addition of fibers to the diet increases the abundance of butyrate-producing bacteria Roseburia species and *Eubacterium rectale*, whereas a low-fiber diet is associated to a major decrease in this group, with *Faecalibacterium prausnitzii* becoming the main

butyrate-producer. Hence, a greater understanding of the interaction between dietary fibers and the intestinal microbiota could represent a mean of maintaining or improving the community of gut microorganisms, particularly when dysbiosis exists. In addition, although various data indicate that increased SCFAs production positively affects the host by exerting antiobesity and antidiabetic effects, some *in vitro* and *in vivo* studies have indicated that overproduction or accumulation of SCFAs in the bowel may lead to obesity and cancer development, owing to increased energy accumulation and elevation of the inflammatory state. As correctly pointed out in the recent paper by Wen and Schwabe, more experimental and epidemiologic data are needed to completely elucidate the link among dietary fibers, gut microbiota and the onset of low-grade inflammatory diseases (3). However, the authors commented about the recent study by Singh *et al.* (4) and based only on these results stated that soluble fibers could be associated to liver disease and hepatocellular carcinoma. Specifically, it will be a great achievement to shed light on the influence that SCFAs exert on the intestinal environment as well as on distal tissues and organs. SCFAs, mainly acetate, propionate and butyrate, are organic acid produced by intestinal microbial fermentation of dietary fibers. Various mechanisms have been highlighted to justify the biological effects of butyrate: (I) inhibition of histone deacetylase (HDAC); (II) downregulation of neuropilin-1 (NRP-1); (III) activation of G-protein-coupled receptors, GPR41, GPR43 and GPR109A, and of the peroxisome proliferator-activated receptor γ (PPARγ); (IV) modulation of canonical Wnt signaling pathway; (V) activation of AIM2 and NLRP3 inflammasomes, enhancing production

of interleukin-18 (IL-18) and epithelial barrier function; (VI) differentiation of T lymphocytes into effector (Te) and regulatory (T reg) T cells; and (VII) modulation of T lymphocytes and dendritic cell functions (5). In the meantime, SCFAs can reach the liver through the portal vein and directly promote hepatic triglyceride accumulation and gluconeogenesis. In addition, various data have demonstrated that butyrate appears to have "paradoxical" effects on colonic epithelial proliferation due to the fact that the response of proliferative cells to butyrate are affected by the dose of butyrate, the physiological conditions under which the study was performed and the phenotype of the target cells (3). Butyrate can instead suppress proliferation in hyperproliferation situations (i.e., colon cancers cells), or stimulate proliferation in impaired energy status (i.e., atrophic colon) or having no effect in normal tissues. Similarly, butyrate can promote or inhibit apoptosis (1).

The concept of prebiotics is based on the possibility of favorable modulating the gut microbiota composition to maintain and/or promote health, using nutrients such as non-digestible, fermentable carbohydrates. Among these, the prebiotic effect of inulin-type fructans (ITF) and fructo-oligosaccharires (GOS) has been extensively studied *in vivo*, showing a selective stimulation of *Bifidobacteria* and *Lactobacilli* growth. Moreover, in 4 out of 13 randomized controlled trials dietary IFT was positively associated to decrease in serum glucose and fasting insulin concentrations. These effects were a consequence of the ability of IFT to increase the number of endocrine L cells in the jejunum and colon, enhancing the production and secretion of glucagon-like peptide-1 (GLP-1) and reducing glycemia. However, a recent meta-analysis of randomized controlled trials has shown that modulation of the gut microbiota via prebiotic supplementation may present modest effects on body weight and waist circumference in obese subjects. Conflicting results have been also obtained from cohort-based epidemiological studies that aimed at finding a link between fiber intake and colorectal cancer prevention (6). On the other hand, Donohoe *et al* using a mouse model demonstrated that dietary fiber could protect against colorectal cancer in a microbiota- and butyrate-dependent manner (7). In line with these data are the results published in a recent paper where butyrate was able to significantly abolish the neointimal formation in partially ligated carotid arteries of mice throughout NLRP3 inflammasome activation (8).

In conclusion, numerous studied have elucidated the complexity of the mechanisms responsible for the effects of SCFAs, mainly butyrate. However, more mechanistic and clinical studies to entirely clarify the role of dietary fibers on human health are needed.

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