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The role played by human microbiota in immune development, and its responses is nowadays better understood. Also, the contribution played by probiotics, prebiotics and synbiotics and their effects on the microbiota has gained much attention (32). Short-chain fructooligosaccharides (sc-FOS) are among the most researched non-digestible soluble prebiotic dietary fibers consumed by humans. A myriad of beneficial attributes has been documented for prebiotics. The ability of prebiotics like sc-FOS to affect our immune system is of great importance (2, 3-7, 17-19, 24, 27-30) and may play a safe strategy to sustain immune abilities. The immunomodulating action of prebiotics like sc-FOS is primarily mediated (but not only) via effects on the "innate immune system" by both direct and indirect mechanisms.

Mechanism by which prebiotics like sc-FOS act upon the immune system

Commensal microflora provides intrinsic protection against potential pathogenic bacteria by competing for both nutrients and controlling colonization of potential pathogens (i.e. by lowering colon pH). Human colon plays a central role in our immunity via mechanisms including mucosal barriers, and the GALT system (Gut Associated Lymphoid Tissue), which is the biggest human immune tissue. In mammals, intestinal immunity is largely maintained by interactions between gut microbiota and GALT (8). GALT stimulation may be mediated by the bifidogenic effect of prebiotics like sc-FOS, and its role is crucial to the digestive tract of newborns and infants by promoting maturation of B-type immune cells (13, 16). In animal models dietary sc-FOS increased intestinal IgA response in the small intestine as well as in the colon (9, 15). Most of the knowledge related to the understanding of mechanisms by which prebiotics such as sc-FOS affect the immune system are based on animal models, and GALT-associated responses (9,14,15,21,22).

Short oligosaccharide molecules components of sc-FOS (namely Kestose and Nystose) have been reported to be rapidly and preferably use by Bifidobacteria and certain Lactobacillus species due to unique enzymatic abilities innate to these bacteria. Indeed, sc-FOS is characterized by a relatively low threshold bifidogenic dose of only 2.5gr/day. The stimulatory action of prebiotics (like sc-FOS) on the immune system may occur via two mechanisms; [1] The bifidogenic effect, i.e. the ability of sc-FOS to induce the proliferation of Bifidobacteria and certain Lactobacillus species leading to inhibitory growth effects on potential pathogenic bacteria (competition for nutrients, acidification of colon lumen, increase release of short-chain fatty acids (SCFA) in the lumen), and [2] by direct or indirect activation of components of the immune system. Activation pathways by which sc-FOS positively affects components of the colonic immune system may include:

(1) Activation by contact with gut dendritic cells (DC) which are responsible for sampling immune active components from gut content, and intraepithelial lymphocytes (IEL) which can react while activated by food ingested component.
(2) Modulation of the innate immune barrier by improving the integrity of "Tight Junction" (the paracellular space between epithelial cells) or by creating signals from epithelial cells to the underlying immune cells layer preventing "leaky gut" phenomena (which induces inflammation).
(3) SCFA such as butyrate and propionate have been reported to induce the differentiation of T-regulatory cells, assisting in the control of intestinal

inflammation (reducing inflammation, and risk of bowel diseases/colorectal cancer (32).

Moreover, mucosal barrier (local immune system) separates and protects colonocytes facing the colon lumen and serves as a first line of defense reducing full systemic immunity. SCFA (mainly butyric acid) has been reported to induce mucin secretion enhancing physiological protection (17). SCFA's (like acetate) may also provide benefits to colon health by improving blood flow and oxygenation of colonic mucosa resulting in increased barrier integrity (10). Butyrate may increase mucosal depth by enhancing cell differentiation at the bottom level reducing apoptosis at the apex of the villi as demonstrated in a piglet study (26).

Sc-FOS and possible Immuno-protection against viral infections and diarrhea

Prebiotics like sc-FOS may also contribute immuno-protective activity in cases of respiratory infections like common flu which are often a result of viral agents such as Influenza (25). For example, in a human study, fructo-oligosaccharides have been included as a constituent of a nutritional formula (9% inclusion) for seniors (183-day follow-up, age >65). This study demonstrated positive enhancement of the immune function as measured by antibody and lymphocyte proliferation reducing day count with symptoms of upper respiratory tract infection following influenza vaccination (12). In an animal trial, addition of sc-FOS has been shown to bind "toxin A" alongside with changes in the composition of mucosal immune cells (increase numbers of macrophages in lamina propia). An important aspect of immunity enhancement by sc-FOS is the prevention of infectious diarrhea, and or alleviation of its symptoms. Juffrie M. (2002) showed that in children (1-14 years old) suffering from acute diarrhea sc-FOS dosed at 2.5-5g/day was able to reduce the duration of diarrhea events compared to control group (11).

Sc-FOS and Immuno-protection against carcinogenesis and oxidative stress

sc-FOS has been reported to reduce concentrations of potential procarcinogens produced in the colon. A 42-day human clinical study (12 healthy subjects, both genders, age 20-34) explored the effects of a sc-FOS supplementation of 4 gr./day (as chewable tablets and drink) on fecal flora and certain activities of reductive enzymes associated with conversion of procarcinogens to carcinogens (β-glucuronidase and glycocholic acid hydroxylase). Moreover, sc-FOS has been shown to neutralize the activity of ROS (reactive oxygen species) like hydroxyl radical. Pejin et al. (2014) demonstrated the capacity of sc-FOS components (1-kestose and nystose) to scavenge hydroxyl radicals •OH, suggesting their potential immuno-protective role (20). Therefore, sc-FOS may help reducing damages of oxidative stress and inflammation caused by improper nutrition (31).

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