



Advances in Targeting the Gut Microbiota for Obesity Therapy

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Obesity has been becoming a major threat for health globally with its effects on development of other metabolic disorders like type2 diabetes mellitus, hypertension, hyperlipidemia and some cancers. Earlier we have emphasized on the role of gut microbiota in contributing to the inflammation associated with obesity and how use of probiotics might help in treating it in one possible way, although still there are some controversial point that are to be resolved as reviewed in ref 4 [1-4]. Our body is colonized by an enormous number of organisms, both on its surface and inside. They account for >1kg of weight, and outnumber human eukaryotic cells by at least 10fold. Most of them live in our gut and thus constitute the so called "gut microbiota". In view of symbiosis existing between, the idea of a combined superorganism has been developed recently. With the development of culture independent tools, based on metagenomics technologies, further assessment of gut microbiota has been possible 4 major phyla represent >90% of bacterial component of gut namely, Firmicutes and Proteobacteria and Actinobacteria. Most of 'good' bacteria harbouring the human' gut microbiota are represented by Firmicutes and Cytophaga-Flavobacterium-Bacteroides (CFB). Firmicutes are subgrouped in coccoides (Clostridium cluster XIVa) and Clostridium leptum (Clostridium cluster IV), while CFB group are represented by Bacteroides phyla with a great number of Provotella and Porphyromonas [5,6].

Gut microbiota is characterized by an interindividual variability due to genetic and environmental factors. Of the environmental factors, dietary habits play a crucial role in the modulation of Gut microbiota composition. Subjects who are fed a western diet have markedly different microbiota from those fed prevalently diet rich in fibres. Specific changes in the composition of Gut microbiota have been shown among subjects as per different diet schedule. One particular diet might promote growth of specific bacterial strains, driving host to a consequent changes in the fermentative metabolism, with a direct effect on intestinal pH, that can be responsible for the development of a pathogenic flora. Further, a high fat diet can promote the development of a proinflammatory Gut microbiota, with a consequent increase of intestinal permeability

and subsequent increased levels of circulating lipopolysaccharides [7].

Probiotics like Lactobacillus and Bifidobacterium improve the balance of intestinal flora and have variety of physiological functions beneficial to human health. It has not been known whether ingested microbial cells are viable or killed. However even sterilized bacterial cells are functional. Bacterial cell functions are strain specific and their modes of action are still poorly understood. Thus Kikuchi, et al. tried to elucidate the roles of sterilized bifidobacteria in obesity and lipid metabolism. For this mice ingested sterilized bacteria. Male C57BL/6J mice aged 7wks were raised on a high fat diet (HFD) and received oral sterilized bifidobacteria for 4wks. Although the amount of food they ingested did not change in response to bifidobacteria administration, both weight gain and epididymal body fat mass were significantly reduced. Additionally, elevated blood glucose, triglyceride, and total cholesterol levels observed in mice on HFD decreased in response to bifidobacteria treatment. Hepatic triglyceride levels also decreased. Moreover oral glucose tolerance and insulin resistance (IR) tests indicated that sterilized bifidobacteria improved glucose tolerance and decreased IR. Sterilized bifidobacteria also reduced blood lipopolysaccharides and altered intestinal flora. Thus suggesting that in mice on HFD, sterilized bifidobacteria suppressed fat accumulation, improved IR, and lowered blood glucose levels [8].

Increasing interest in the effect of dietary polyphenols on the intestinal microbiota and the possible associations between this effect and development of obesity. But limited information is available regarding how these polyphenols affect the gut microbiota and lipid metabolism. The co-interaction of a HFD and tea polyphenol (TP) on gut microbiota and lipid metabolism using a human flora associated (HFA) C57BL/6J mice model was studied. TP reduced serum total cholesterol, triglyceride, low density lipoprotein, glucose and insulin levels of HFD mice in a dose dependent manner. TP also significantly increased acetic acid and butyric acid levels In HFA mice 16s RRNA V3 region polymerase chain reaction –denaturing

gradient gel electrophoresis (PCR-DGGE) profiles showed that HFD mice had significantly reduced microbial diversity. This reduction could be alleviated by TP, with a significant increase in the richness and diversity of colonic microbiota in the HFD and 0.2% TP (TPM) and HFD with 0.05% TP (TPL) groups ($p < 0.05$). 454 pyrosequencing analysis showed that the HFD group had a significant increase in the Bacteroides and Firmicutes (F/B) ratio, which could effectively be reversed by TP. Thus a HFD significantly impacted gut microbiota composition and lipid metabolism in human flora-associated mice, that was largely ameliorated by tea polyphenol. Therefore TP's might be effectively used in controlling or treating obesity, hyperlipidemia and other related metabolic diseases [9].

For investigating the modulatory effect of oolong tea phenol (OTP) on intestinal microbiota, OTP was prepared by column chromatography and its influence on the gut flora structure was analyzed by high throughput sequencing with a human-flora-associated HFD induced obesity mouse model. A robust increase in bacterial biodiversity and the abundance of genera known to be butyrate and acetate producing bacteria was observed. A large increase in Bacteroides with a decrease in Firmicutes was observed after the administration of OTP for 4 weeks and the corresponding decrease in the Firmicutes/Bacteroides ratio reflected the positive modulatory effect of OTP on the intestinal microbiota. Additionally KEGG pathways for the biosynthesis of amino acids, carbon metabolism, and the ribosome were among the most differentially expressed genes after OTP intervention. Thus this study of Cheng, *et al.* revealed that OTP rich in tea catechins, especially O-methylated derivatives, might have prebiotic like activity and can be used as a functional food component with potential therapeutic utility to prevent obesity-related metabolic disorders by manipulating the intestinal microbiota [10].

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