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Title : MODULATION OF GUT MICROBIOME BY PROBIOTICS IN OBESITY AND RELATED METABOLIC ABNORMALITIES

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Accumulating evidence suggests that the aberrant taxonomic composition of gut microbiota is one of the etiological factor in the development of obesity. With the inherent plasticity of gut microbiota structure, it provides a new avenue for the application of biotherapeutics to modulate the shifted structure of microbiota in obesity. Lately, much attention has been focused on probiotic as a biotherapeutics candidate for obesity. In contrast, knowledge on the modulating effects of probiotic on the obese gut microbiota structure is still limited and should be evaluated. The present study aims to elucidate the inherent plasticity of gut microbiota and the dynamic response of the host metabolism during the induction of high-fat-diet-induced obesity and upon the amelioration of obesity by probiotics in obese rat models. Two probiotic candidates; (i) single strain *Lactobacillus casei* strain Shirota (LAB13) and (ii) probiotic cocktail LACTO-5™ (*L. rhamnosus, L. acidophilus, B. subtilis, B. longum* and *S. thermophilus*) were supplemented to the obese rats at doses of $1 \times 10_9$ CFU per/day/rat for 12 weeks. The probiotic treatment started after the induction of obesity using high fat diet (HFD, 60% fat). The heterogeneity of gut microbiota structure and its functional complement genes were profiled from the faecal samples of rats from each intervention group (n=3/group) using shotgun metagenomics sequencing. Phenotypically, the weight gain, energy intake, subcutaneous fat, total fat weights, total cholesterol, leptin, ratio of TC to HDL-c and leptin to adiponectin in obese rats were significantly reduced by the supplementation of both probiotics. These confirmed the anti-obesity, hypocholesterolemic and hypoleptinemia effects of both probiotics. The strain-specific salutary effect was noted in the reduction of TG and ratio of TG to HDL-c by LAB13. Both probiotics shifted the HFD-modulated gut microbiota towards the lean structure after the supplementation being given seven weeks after the induction of obesity. Comparative analysis revealed that the abundances of 68 bacterial genera were altered by HFD and probiotics. HFD uniquely modulated 21 genera, 17 of which were promoted and positively correlated with at least one of the obese phenotypes in obese control rats. Thus, these genera may be relevant to obesity. LAB13 modulated 32 genera, the enrichment of 16 genera of which were correlated positively with the ameliorated obese phenotypes. LACTO-5™ modulated five genera, of this, the enrichment of genus *Coxiella* was positively correlated with the ameliorated obese phenotypes. Out of this, three genera were also found reduced by LAB13. Theoccurrences of 13 out of 26 annotated functional categories were enriched in the HFD modulated gut microbiome; suggesting a relative higher metabolic capacity in the obese gut microbiome. Whereas both probiotic-modulated and STD-modulated gut microbiome had lower occurrences of several protein-coding genes for metabolism of carbohydrate, lipids, and nutrient transport; suggesting a relative lower energy harvesting capacity in comparison to the HFD microbiome. Metabolomics analysis showed increment in bile acid synthesis and reduction in glycerophospholipid and fatty acids metabolism after probiotic treatment. These had increased the lipid clearance in body which improved the obese phenotypes. Results from this study suggest the salutary effects of probiotic, in part, are mediated by the changes in the gut microbiota structure and its metabolic capacities in host metabolism particularly bile acid biosynthesis. This study proved the possible mechanistic links between gut microbial-host interactions and its role in obesity.