Commentary

MOLECULAR METABOLISM

When gut fermentation controls satiety: A PYY story

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Gut microbiota is now considered to be an important regulator of body weight. With approximately 10 million genes [1], the gut metagenome is certainly hiding numerous mechanisms involved in the control of body weight and the consequent metabolic disease [2]. Among them, bacterial enzymes fermenting non-digestible dietary fibers into the short chain fatty acids (SCFA) acetate, propionate, and butyrate have garnered great attention over the last decade [3]. A major question remains about the identification of molecular targets of SCFA involved in the control of body weight and energy homeostasis. SCFA bind two receptors, FFAR2 (GPR43) and FFAR3 (GPR41), at the surface of numerous cells, which could explain the metabolic control. Among them are the intestinal enteroendocrine L cells. Specifically, FFAR2/3 are markers and sensors for SCFA for the majority of enteroendocrine cells, whereas FFAR3 apparently has this role alone in enteric neurons. It is therefore suggested that the secretion of the incretin glucagon-like peptide one (GLP-1) would be controlled by SCFA. This incretin triggers insulin secreting cells and the food intake axis, thereby regulating glycemia and body weight gain [4]. In addition to GLP-1, PYY is another enteroendocrine peptide secreted by the L cells and involved in the control of body weight gain [5]. However, the causal demonstration of the role of SCFA in controlling body weight gain through the activation of the FFARs remains to be demonstrated and is even considered controversial [6].

In this issue of *Molecular Metabolism*, Brooks and colleagues used mice with targeted deletion of FFAR2 to demonstrate its importance in SCFA controlling the secretion of the anorectic peptide PYY, and hence body weight gain [7]. Specifically, inulin, a non-digestible but highly fermenting fiber, was fed to mice. It has been shown that inulin promotes satiety through a mechanism involving GLP-1 [8], suggesting that it could control body weight. However, the impact of inulin on body weight is marginal and depends upon the animal model being used, suggesting that environmental and genetic factors are involved. Conversely, in a state of obesity induced by a fat-enriched diet, the impact of inulin on body weight is clear; it is due to decreased adiposity and liver triglyceride deposition, as shown by Brooks et al. and as previously described [7,9]. Importantly, inulin fermentation did not affect body weight through a change in energy expenditure, such as thermogenesis, but seemed specifically to affect food intake. This suggests that anorectic and orexigenic brain peptides could be under the control of SCFA since Brooks et al. found that mRNA expression of Agrp, but not of NPY and POMC, was reduced in the hypothalamus [7]. In FFAR2 ko mice, no such effect was observed; therefore, a specific gut Agrp FFAR2—dependent axis for the control of satiety could be suggested. The authors showed that FFAR2 signaling drives an expansion of the PYY cell population within the colon, leading to increased circulating PYY [7]. They previously demonstrated that inulin increased SCFA in the colon and suggested that these molecules could control PYY secretion to explain the reduced body weight gain. Their new data, therefore, confirms the role of gut microbiota in the control of obesity as the improved body weight was associated with an improved glycemic control showing a general beneficial impact of dietary fiber fermentation and, hence, gut microbiota.

The fact that inulin mostly controls body weight and glycemia in a fat-enriched diet suggested that besides the role of genetic factors, environmental factors such as dietary habits, pesticides, and exercise to cite a few, impact gut microbiota which could be involved in and fit with the SCFA hypothesis. Obesity and type 2 diabetes are characterized by gut microbiota dysbiosis. Therefore, one could suggest that inulin controls the dysbiotic microbiota, which then regulates SCFA production and impact obesity.

An important mechanism by which gut microbiota controls energy homeostasis is through its impact on low grade inflammation, which characterizes most dysmetabolic syndromes [2]. Obesity is characterized by an increased infiltration of innate and adaptive immune cells [10], which could be linked to increased intestinal permeability to bacterial proinflammatory determinants such as LPS and live bacteria [11]. However, Brooks et al. did not find any changes in tissue inflammation in FFAR2 ko mice, putting more focus on the role of SCFA fermentation on food intake rather than on inflammation [7].

An important observation from Brook et al. was that increased PYY secretion was linked to increased numbers of colonic L cells that express PYY but not GLP-1, and this preceded the change in body weight [7]. The increased number of L cells was blunted in FFAR2 ko

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mice suggesting that the differentiation process was SCFA dependent. An increase in Pax4, a transcription factor involved in terminal differentiation of enteroendocrine L cells, suggested an impact on stem cells.

Altogether, it appears that the gut microbiota from high-fat diet fed mice favors the fermentation of inulin into SCFA, which, through binding to FFAR2, controls the differentiation of enteric stem cells into PYY secreting cells. However, some data are available regarding the putative bacteria that could be responsible for fermentation, i.e. Bifidobacteriaceae and Lactobacteriaceae families. Numerous bacteria could still metabolize inulin and a precise sequencing of the 16SrDNA gene to identify precisely the ecology correlated with the fermentation of inulin would have helped. Similarly, the bacterial gene pathways involved can now be identified through metagenomics sequencing, which could provide hypotheses regarding the major bacterial metabolic pathways putatively involved and to be targeted. Such studies would clearly provide novel therapeutic avenues to treat obesity. Other enteroendocrine peptides are certainly controlled by gut microbiota; therefore, the study from Brooks et al. is a first proof of concept that needs to be further pursued in order to shed light on the next generation of tailored medicine based on gut microbiota characterization.

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