The gut-metabolism axis: Mechanistic understandings and new clinical directions

Gut microbes help regulate metabolic functions, affecting body weight, glucose control and overall health.

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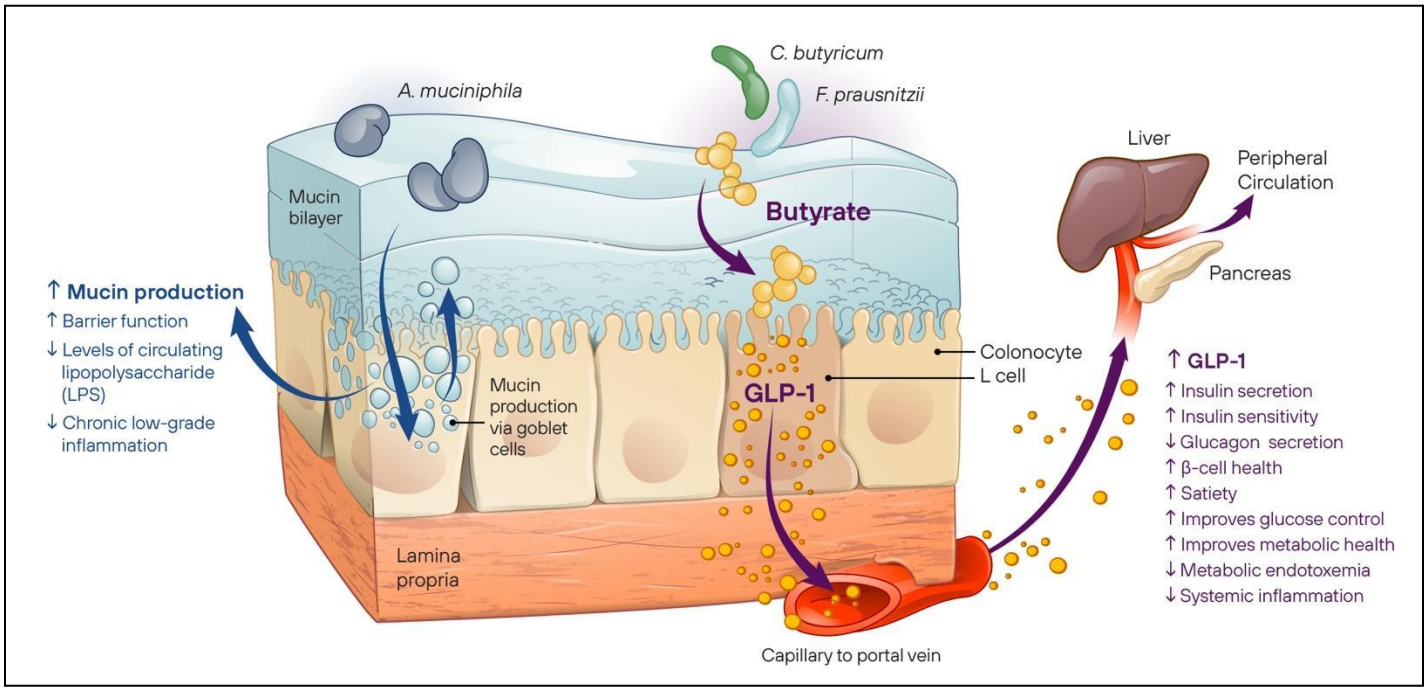

Poor metabolic health, encompassing elevated blood glucose, cholesterol and/or triglycerides (and most often, excess weight), is a global concern, placing significant burdens on healthcare systems and requiring urgent intervention. A 2022 report by the World Obesity Federation lists 30 countries projected to have 88 to 90% prevalence of overweight (BMI 25 to <30) and obesity (BMI 30 and above) by 2060. The global economic cost of overweight and obesity is predicted to be over US $3 trillion by 2030. Understanding the physiological mechanisms of metabolic health and obesity is essential for developing new and targeted approaches for clinical management. Cutting-edge science on the factors controlling human metabolic health and body weight highlights the significance of the “gut-metabolism axis”. This area of study concerns the connection between metabolic function and gut health—especially the gut microbiota, the collection of bacteria and other microorganisms inhabiting the digestive tract, with the greatest concentration in the colon. With growing evidence suggesting that gut microbiota contribute to many aspects of metabolism, the field is moving closer to specific gut-focused solutions for managing metabolic health and body weight (Fan and Pederson, 2021).

Evidence for the role of gut microbiota in metabolism

Metabolic functions include all the processes the body uses to convert food into energy. These highly complex functions can go awry in many ways, resulting in states of metabolic dysfunction such as insulin resistance, hyperglycemia, type 2 diabetes, hyperlipidemia, hypertension, inflammation, non-alcoholic fatty liver disease (NAFLD), obesity, and metabolic syndrome as defined by a combination of any three of the following: abdominal obesity, elevated fasting glucose, elevated triglycerides, low HDL cholesterol, and

increased blood pressure (Fändriks, 2017). Microbiome science over the past two decades has brought a new perspective on individuals with these metabolic disruptions: many studies show differing gut microbiota compositions associated with various metabolic diseases compared to the microbiomes of healthy individuals (Dabke et al, 2019). Additionally, the bacteria with higher abundance in multiple metabolic disorders compared to healthy subjects tend to be those associated with inflammation (Michels et al, 2022). This area of research underscores the relevance of gut microbiota to metabolic dysfunction and strongly suggests that restoring the microbiome in the gut represents a pathway for better clinical outcomes.

Recent studies leveraging high-throughput DNA sequencing and analysis of big data have demonstrated that complex interactions between an individual's genome and their existing microbiome genome impact responses to the composition of meals. This approach, while complex and still unrefined, holds promise to favorably impact glucose control, especially during the immediate postprandial period (Zeevi et al, 2015).

Uncovering Gut Microbial Mechanisms

The critical importance of gut microbiota for regulating host metabolism has become clear from scientific work in animal models. Mice with an absent or depleted gut microbiota, for example, show improved glucose tolerance compared to mice with intact gut microbiota (Molinaro et al., 2017). Scientists also found that transferring fecal samples from obese or lean humans into germ-free mice caused the mice to take on the metabolic phenotype of the human, (e.g., the same propensity for weight gain on a high-fat diet) (Ridaura et al, 2013).

The currently existing body of scientific work in this area has revealed some important mechanisms by which gut microbiota influences metabolic function and body weight. Although these complex mechanisms are still under investigation, broad strokes have been established.

- Enteroendocrine cells within the mucosal lining of the gut secrete different hormones and signaling molecules—CCK, PYY, GLP-1, GIP, and 5-HT—that help regulate key metabolic processes such as insulin sensitivity, glucose tolerance, fat storage, and appetite (Martin et al., 2019). Gut microbes send signals to these enteroendocrine cells, thus serving as master regulators of some of these hormones. As one example, when fermentable carbohydrates (in other words, dietary fibers) are digested by certain bacteria in the gut, the bacteria release metabolites (e.g. short-chain fatty acids, or SCFAs) that trigger the secretion of GLP-1 and PYY, helping regulate energy balance and glucose homeostasis (Everard & Cani, 2014). Butyrate is a key SCFA that is mechanistically linked with metabolic benefits in numerous pre-clinical studies; bacterial strains such as *Clostridium butyricum* and *Faecalibacterium prausnitzii*, which possess genes to specifically increase butyrate production, can be of use to trigger host secretion of GLP-1 and PYY.

- Another important mechanism by which the gut drives metabolic dysfunction is through low-grade inflammation. This inflammation occurs due to activation of the immune system that stems, at least in part, from an increase in permeability of the gut barrier, which normally separates contents of the gut lumen from peripheral circulation. Increased gut permeability appears to be one of the consequences of a high-fat diet. When the gut barrier becomes too permeable, levels of circulating lipopolysaccharide (LPS), a component of the external coat of Gram-negative bacteria, increase. The LPS circulating throughout the body activates pro-inflammatory cytokines, leading to chronic low-grade inflammation (Cani et al, 2008). This causes both weight gain and higher fasting glucose levels (Cani et al, 2007). A major protective factor against gut barrier permeability is the layer of mucus coating the inner wall of the digestive tract, which provides a home for certain mucin-loving bacteria such as *Akkermansia muciniphila*. When *A. muciniphila* consumes mucins, the host compensates by continuing to produce more mucins, helping replenish this protective layer and thus

enhancing the integrity of the intestinal barrier (Liu et al, 2022). This constitutes one way in which specific bacteria help regulate immune responses and work against low-grade inflammation.

Through these mechanisms and others, the gut microbiota contributes to the regulation of host metabolic functions.

Toward New Strategies in Clinical Practice

Armed with the knowledge of the gut microbiota's contributions to metabolic function, scientists have explored various approaches to manipulating gut microbes for better clinical outcomes. Trials studying fecal transplants from lean donors to individuals with metabolic dysfunction have shown positive results similar to those found in rodent models of obesity and type 2 diabetes, with modest, short-term improvements in insulin sensitivity, but ultimately the broad approach of fecal transplant serves as a proof of concept for further development of more targeted approaches (Vrieze et al, 2012; de Groot et al, 2020; Kootte et al, 2017).

Evidence indicates that lifestyle interventions (i.e. diet and exercise) for weight loss and metabolic health may depend on the baseline gut microbiota. A real-world challenge is that the gut microbiomes of individuals in developed countries tend to be depleted through many factors such as frequent antibiotic use, a Western diet, physical inactivity, and chronic stress. A promising clinical approach is thus to normalize an individual's gut microbiota so it is more like that found in healthy subjects. Compared to the exploratory fecal transplant studies cited above, more precise approaches can be envisioned: namely, using precise probiotic strains with relevant mechanisms of action to target metabolic health improvements. Targeting replenishment of specific microbes repeatedly shown to be diminished in patients with metabolic disorders, e.g., *Akkermansia* and butyrate producers, has the potential to support and amplify the beneficial effects of lifestyle interventions.

The challenge of the current moment is to translate all of the scientific knowledge on the role of the gut microbiota into new tools for managing metabolic health and weight management in clinical practice. The gut-metabolism axis is an exciting area of ongoing scientific development that will surely yield results and bring hope for patients in the years ahead—helping address the urgent global problem of metabolic health and obesity.

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