CellPress

Gut Microbes Controlling Blood Sugar: No Fire Required!

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https://doi.org/10.1016/j.cmet.2020.02.007

The gut microbiota plays an important role for the absorption of nutrients and the maintenance of metabolism, potentially impacting the development of human metabolic disorders such as obesity and type 2 diabetes. In this issue of *Cell Metabolism*, Krisko et al. (2020) demonstrate that the gut microbiota regulates glucose homeostasis solely via hepatic gluconeogenesis and not via thermogenic adipose tissue as suggested previously.

Metabolic disorders have become one of the most challenging burdens of our society, hampering the quality of life while deeply impacting the healthcare system. Thus, it is of utmost importance that the scientific community continues to invest major efforts preventing and treating metabolic diseases. The fundamental understanding of metabolic mechanisms usually starts with investigations in laboratory mice before this knowledge is translated to humans. A complex interaction of cellular and molecular pathways enables the organism to maintain metabolic homeostasis, influenced by genetics, age, and environmental factors. We have barely started to understand the role of various organs in the pathogenesis and progression of metabolic disease, though it has become appreciated that the gut microbiota significantly impacts these processes. The gut microbiome consists of a diverse community of microorganisms in our digestive system that interacts with host metabolism and thereby dramatically increases the complexity of metabolic regulation. In healthy individuals, the gut microbial ecosystem is in balance with metabolic demands of the host. Environmental stressors, such as changes in nutrition and ambient temperature, have a significant impact on the interaction between microbial and host metabolism, affecting body weight, thermoregulation, and glucose homeostasis (Bäckhed et al., 2004; Ziętak et al., 2016). Vice versa, metabolic disorders such as obesity, as well as host genetics, have a tremendous effect on the composition of the gut microbiome (Ley et al., 2005; Ussar et al., 2015).

Given such complexity, it is not surprising that scientists observe diverse, often conflicting, results on the interaction between the gut microbiota and host metabolism. In experiments using laboratory mice, this may be due to differences in the genetics of the mouse strain, hygienic status, differences in food and water supply, and housing temperatures: all contributing factors that influence the biology of the gut microbial community and thus, the host. It is likely that investigators cannot control for all confounding factors, despite the desire of the scientific community to perform standardized experiments and thus provide a single, unambiguous conclusion. Although this limitation might make it difficult to confidently compare results between different laboratories, we can also consider these circumstances as a positive; that is, it's a chance to discover the entire diversity of interactions and metabolic effects. In this respect, we should not forget that humans, more than laboratory mice, display substantial variation in their genetics, do not live in standardized, sterile environments, and their lifestyle exposes them to continuously changing environmental conditions.

But, how does the gut microbiota communicate with distant organs? How does this link influence the progression of obesity and type 2 diabetes? To date, the details of this communication are hardly understood. Important approaches to investigate the metabolic effects aim to deplete microbiota using a mix of antibiotics, or maintain mice in a germ-free environment, or transplant microbiota between mice. Using these methods, previous studies claim that the microbiome impacts adipose tissue thermogenesis and energy metabolism, thereby indirectly controlling glucose homeostasis through enhanced glucose combustion (Chevalier et al., 2015; Suárez-Zamorano et al., 2015; Li et al., 2019). These claims remain contradictory, as some studies imply a positive impact of the gut microbiota on brown and beige adipose tissue to increase thermogenesis and energy expenditure in the cold (Chevalier et al., 2015; Li et al., 2019), whereas others show the emergence of beige adipose tissue when mice are microbiome depleted (Suárez-Zamorano et al., 2015). All studies to date, however, suggest that the effect on thermogenic adipose tissue in turn affects glucose homeostasis.

In this issue, Krisko et al. (2020) delineate the relation between the gut microbiota, thermogenesis, and glucose homeostasis (Figure 1) by elegantly excluding the requirement for increased energy metabolism and thermogenic adipose tissue and instead demonstrate that the gut microbiota regulates glucose homeostasis through hepatic gluconeogenesis. Important for their conclusions, the authors did not ignore the massive cecum dilation and intestinal elongation in their two complimentary mouse models of microbial depletion, antibiotic-mediated microbiota-depletion and germ-free mice. In their detailed analyses, they appreciate for the first time that the additional mass of inert watery stool confounds the calculation of energy expenditure, which should solely rely on the total weight of metabolically active organs. Removing the confounding

mass difference, either from calculations or experimentally by cecectomy, eliminates differences in energy expenditure, calling into question claims that the microbiota affects energy expenditure. Coherent with the energy expenditure data, Krisko and colleagues do not observe changes within thermogenic adipose tissue.

The discrepancy with previous observations in adipose tissue remains puzzling (Suárez-Zamorano et al., 2015; Li et al., 2019). Is there a possibility to decode the data for a unifying explanation? Microbiota depletion potentially exposes the mice to various states of energy deprivation, depending on their condition. If the microbial energy supply to the host is insufficient in the cold, the microbial-free mouse may show repressed brown adipose tissue thermogenesis (Li et al., 2019) (Figure 1), and transplantation of cold-adapted microbiota may assist in recruiting additional thermogenic capacity via beige adipose tissue (Chevalier et al., 2015) (Figure 1). However, beige adipose tissue is also seen in response to microbial depletion (Suárez-Zamorano et al., 2015). Here, adipose browning may be primarily associated with enhanced endogenous fat mobilization rather than with increased energy expenditure (Keipert and Jastroch, 2014) (Figure 1). In other experimental mice, the impact of microbial depletion may not even require beige fat recruitment (Krisko et al., 2020). Laboratory-to-laboratory differences in experimental results can to some extent be attributed to differences in mouse facility standards and mouse strains (Ussar et al., 2015). Importantly, however, the observed reduction in blood glucose levels in microbiome-deficient mice reported by Krisko et al. (2020) was in line with previous findings that others related to changes in insulin sensitivity (Bäckhed et al., 2004) and thermogenic activity (Suárez-Zamorano et al., 2015). Thus, it is credible to conclude that the blood glucose control can act independently of energy expenditure and thermogenic adipose tissue, shifting the focus to other organs. The authors in this new report discover that the microbiota modulates gluconeogenesis in the liver to maintain blood glucose levels. Krisko and colleagues, furthermore, identified metabolites enhancing gluconeogenesis by performing comprehensive metabolomics analyses, thereby providing an important resource of potentially bioactive microbial molecules. Additional studies will be required to establish causality, possibly involving selective microbiota transfer or genetic manipulation of liver-specific transporters.

Collectively, the novel work by Krisko et al. (2020) delivers new paradigms with importance for the metabolic field: first, the appreciation of inert mass in the intestinal tract to accurately determine metabolic rates, and second, the microbiome-liver axis in control of gluconeogenesis, fostering deeper explorations of molecular mechanisms residing in the liver to unravel paths toward moving these observations into clinical intervention strategies.

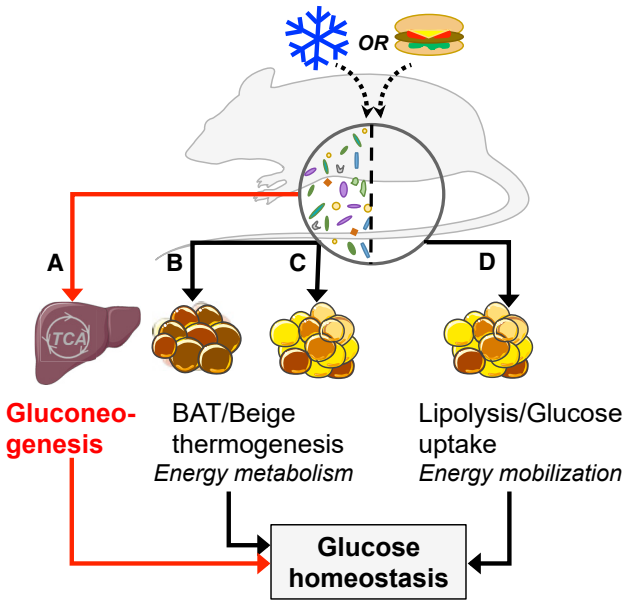

Figure 1. The Gut Microbiota and Its Relation to Glucose Homeostasis and Energy Metabolism

(A) Microbial metabolites control hepatic gluconeogenesis, shown by Krisko et al. (2020) in this issue of *Cell Metabolism*.

(B and C) (B) Gut microbiota positively support brown adipose tissue (BAT) thermogenesis and (C) additionally recruit beige adipose tissue, both contributing to energy metabolism.

(D) Beige adipose tissue is also recruited in microbiota-depleted mice, possibly relating to endogenous energy mobilization, as also seen under fasting conditions. All mechanisms would potentially impact systemic glucose homeostasis of the mouse.

ACKNOWLEDGMENTS

M.J. and S.K. are supported by the Swedish Research Council (2018-02150 to S.K. and 2018-03472 to M.J.). S.U. is supported by the project Aging and Metabolic Programming (AMPro) and the BMBF within the framework of the European ERA-NET Marine Biotechnology project CYANOBESITY (cyanobacteria as a source of bioactive compounds with effects on obesity and obesity-related co-morbidities).

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