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# **The gut microbiota: stable bioreactor of variable composition?**

**Gilles Mithieux**

Institut National de la Santé et de la Recherche Médicale U1213 "Nutrition, Diabetes and the Brain", Université Claude Bernard Lyon 1, Université de Lyon, France.

Contact:

Inserm U1213

Faculté de Médecine Lyon-Est, 7 Rue Guillaume Paradin, Lyon 69372, France.

gilles.mithieux@inserm.fr

+33 4 78 77 87 88

## **Keywords**

Gut microbiota; microbial metabolites, short chain fatty acids, intestinal gluconeogenesis

## **Abstract**

The gut microbiota plays a crucial role in host health, providing energy and vitamins from food undigested by the host's gut enzymes. Bacterial metabolites, such as short chain fatty acids, are essentially metabolized by the gut mucosa. The importance in metabolic health of gut microbiota composition versus function is discussed.

## **I. Essential role of gut microbiota in host's health**

The intestinal microbiota first plays a major role in the recovery of energy from food. Nutrients that resist to hydrolysis by host enzymes traverse the proximal intestine to reach more distal portions, which contain the bulk of the resident bacteria forming the intestinal microbiota. The most studied case is that of soluble dietary fiber, that are fermented by the microbiota in low molecular weight metabolites, such as lactate, pyruvate or succinate, and short-chain fatty acids (SCFAs): acetate (2 carbons), propionate (3 carbons), butyrate (4 carbons) and, to a lesser extent, valerate (5 carbons) and caproate (6 carbons) (Flint et al., 2012). These small metabolites penetrate the cells of the intestinal mucosa and are metabolized to provide energy or 3-carbon building blocks for the synthesis of essential metabolites.

This contribution of the microbiota function to the host's metabolism is major. Louis Pasteur predicted that the life of complex organisms should not be possible without germs (Pasteur, 1885). He was partially right, since germ-free hamsters were later shown viable (Nuttall and Thierfelder, 1896). However, prolonged survival in this case requires quantitative and qualitative supplementation of the diet to compensate for energy (caloric) and vitamin (vitamin A, B12, folic acid, produced owing to the microbiota) deficiencies. Moreover, germ-free animals present immaturity of vascularization and innervation of the gastrointestinal tract and impaired gut barrier permeability. The liver, lungs and heart are smaller than normal, and immune system is also markedly deficient (Macpherson and Harris, 2004).

These data have emphasized the essentiality of the intestinal microbiota for the host's health. What is more, the benefits of bacterial fermentation in the context of metabolic diseases in humans have also been documented by an extensive literature (Blaak et al, 2020; Koh et al, 2016 for reviews). Recently, a hypothesis has emerged from novel genomic sequencing approaches that allow large-scale analyses of the genetic composition of the intestinal microbiota, i.e. that the genetic composition of the microbiota in itself could play a role on host metabolic health. It is a purpose of this review to discuss the role of the composition *versus* the function of the gut microbiota in host's metabolic health.

## **II. Integration of bacterial metabolites into host's metabolism**

### *II.1 In the intestinal metabolism*

It is intuitive that a metabolite like pyruvate penetrates the mucosa and is immediately integrated into the mucosal glucose metabolism. Pyruvate is extremely important in intestinal cells. As a co-substrate with glutamate of glutamate-pyruvate transaminase (GPT), it allows the integration into the Krebs cycle of the carbons of glutamine (Gln) and glutamate (Glu) at the level of  $\alpha$ -ketoglutarate, a crucial metabolic process in this organ (Mithieux, 2001). Succinate has a special place in microbial metabolism. As a precursor of propionate, it was thought that its luminal concentration should not increase under conditions of production of SCFAs. Contrary to this view, succinate accumulates more than SCFAs in the cecum of mice fed a high-fiber diet (De Vadder et al., 2016). Basically, succinate is actively incorporated into the Krebs cycle (of which it is

a component) of mucosal cells, thanks to dicarboxylic acid transporters in the mucosa membranes (Figure 1). Like Gln or Glu, it is one of the precursors of glucose produced by intestinal gluconeogenesis (IGN) (De Vadder et al., 2016).

The metabolism of SCFAs differs according to their carbon number. Bacterial metabolites with even carbon number, such as acetate (acylated to acetyl-CoA in the colonocyte), integrate into the Krebs cycle by combining with oxaloacetate to form citrate and provide energy under the form of ATP. The same applies to butyrate (after acylation to butyryl-CoA), which will be converted to acetyl-CoA to be incorporated in the Krebs cycle (Figure 1). Butyrate is thus a major source of ATP for the intestinal mucosa (Blaak et al. 2020). This production of ATP is such that it is capable of activating adenylate cyclase and cAMP production, which will then activate the expression of IGN genes, targets of cAMP (De Vadder et al., 2014; Gautier-Stein et al., 2006).

Propionate, with 3 carbons, is acylated to propionyl-CoA, but does not enter directly into the Krebs cycle. It is first carboxylated by propionyl-CoA carboxylase in methylmalonyl-CoA and then converted to succinyl-CoA by methyl-malonyl-CoA mutase. It can so enter the Krebs cycle and contribute to IGN like succinate or Gln (Figure 1).

## *II.2 In the host metabolism downstream of the intestine?*

SCFAs cross cell membranes very easily and exert various metabolic effects in cultured cells. Thus, the idea is widespread that they could exert *in vivo* their effects directly on organs, after transport in blood (Blaak et al., 2020). However, it is difficult to imagine that molecules so easily integrated into the energy metabolism could escape the particularly active metabolism of the intestinal mucosa. In fact, comparative studies of the concentration of SCFAs in the colonic lumen and the portal vein in humans have shown that while this concentration can reach several tens of mmol/L in the colon, it is only a few tens of  $\mu\text{mol/L}$  in the portal vein for propionate and butyrate. Thus, it has been estimated in humans that 99.9% of luminal butyrate and propionate are absorbed by the metabolism of the intestinal mucosa, the remaining being used by the liver (Blaak et al., 2020). In line with this massive use of SCFAs by the intestinal mucosa, the concentration of SCFAs in mice under a fiber-enriched diet increases only slightly in the portal vein and not at all in the peripheral blood (De Vadder et al., 2014). Thus, the intestinal mucosa metabolizes almost the totality of SCFAs; the very small amount that escapes is metabolized by the liver and does not reach the organs downstream. It must

be mentioned that this is less true of acetate that can reach around 200  $\mu\text{mol/L}$  in the portal vein and in peripheral blood. Thus, it cannot be excluded that acetate could exert peripheral effects. Accordingly, mice deficient in acetyl-CoA synthase exhibit altered lipid metabolism (Huang et al, 2018). In all cases, the numerous *in vitro* studies evaluating the effect of SCFAs on isolated cells must be analyzed with caution, taking into account the physiologically relevant circulating concentrations.

### *II.3 Regulation of energy homeostasis*

Beyond their role in energetic metabolism, SCFAs exert multiple benefits in glucose and energy homeostasis. They are long considered as the relay of the anti-obesity and anti-diabetes effects of dietary fibers (Blaak et al, 2020). This has long been misunderstood in terms of the mechanisms involved. Finally, from experiments in rats and mice, it was shown that SCFAs activate IGN and its associated metabolic benefits (Text Box 1) (De Vadder et al., 2014).

That a signal generated by the intestinal mucosa and detected at the portal vein level mediates the anti-obesity and anti-diabetes effects of fiber/SCFAs was supported by the observation that no effect of fiber takes place after denervation of the gastrointestinal nervous system (De Vadder et al., 2014). That IGN is a link was formally established by the fact that no anti-obesity/diabetes effects of fiber, SCFAs or succinate are observed in mice whose IGN was inactivated by genetic manipulation (De Vadder et al., 2014, 2016). It is noteworthy that SCFAs to brain *via* IGN mainly takes place during post-absorptive periods, notably involving the binding of propionate to neuronal free fatty acids receptor 3 (FFAR) (Text Box 1). Numerous FFARs in addition to FFAR3 are present in various mucosal cells (Kimura et al, 2020). Therefore, SCFAs could modulate other metabolic pathways of interest in energy homeostasis, such as the secretion of the hunger-curbing intestinal hormones cholecystokinin and glucagon-like peptide during the postprandial period (Kimura et al, 2020).

## **III. Metabolic health and gut microbiota: composition or function?**

That changes in the genetic composition of the microbiota in itself could play a role on host metabolic health has today been supported by a large number of studies in reputable journals, reporting that particular compositions of the intestinal microbiota

are associated with metabolic diseases such as obesity or diabetes (also called "dysbiosis"). A possible causal role of the microbiota composition was also supported by experiments of transfer of human "dysbiotic" microbiota to axenic mice, which generally confers the disease phenotype on transferred mice. Another argument supporting this notion was that some bacteria provided as probiotics, like *Akkermansia muciniphila* or *Prevotella copri*, counter the deleterious effects of high-fat diets in mice ( Everard et al., 2013; De Vadder et al., 2016).

With regard to prebiotics like fermentable fibers, it is established that they induce a wide diversification of the gut microbiota (David et al., 2014; De Vadder et al., 2016; Mithieux, 2018), associated in mice with a marked change in the balance between the two main bacterial phylums (*Bacteroidetes* and *Firmicutes*) (De Vadder et al., 2014, 2016). However, relating to prebiotics, the proposition that there is no need of a change in the composition of the gut microbiota to promote their metabolic benefits on host metabolism is tenable. Indeed, no metabolic benefit of fiber was observed in mice genetically devoid of IGN, which nevertheless benefited from the same fiber-induced change in the microbiota composition as wild type mice (De Vadder et al., 2014, 2016). These studies have suggested that the "function" of the microbiota (the production of SCFAs), rather than its "composition", is essential in the metabolic benefits of fiber. This is also consistent with the observation that SCFA-producing bacteria are widely distributed among all major phyla (Reichardt et al., 2014). That the microbiota composition may vary according to nutritional conditions is therefore not mechanically accompanied by a change in its overall function, with regards to the production of SCFAs. Moreover, the beneficial effects of fiber take place both in mice fed a standard diet and in mice fed a high-calorie diet, exhibiting strongly diverging microbiota compositions (De Vadder et al., 2014).

Arguing in the same direction, high-protein diets are also associated with the production of SCFAs from the fermentation of amino acids (Koh et al., 2016) and with metabolic benefits comparable to fiber-rich diets (Soty et al., 2017). However, the two types of diet rapidly induce very different changes in the composition of the intestinal microbiota (David et al., 2014). Thus, as for energy metabolism in relation to the quality of food, one could propose that the "function" of the intestinal microbiota, rather than its "composition", is essential for metabolic health. It is noteworthy that this is in line with the observation that strong variations in the gut microbiota composition among families

of mothers and twins were not associated with significant changes in the categories of genes across each sampled microbiomes (Turnbaugh et al., 2009). One should nevertheless take the precaution of mentioning that one cannot formally rule out that an eventual strong enrichment of the gut microbiota in SCFA-producing bacterial species could result in an increased SCFA production and associated benefits.

#### **IV. Concluding comments**

From the paragraph above, it appears that the intestinal microbiota might finally be regarded as a metabolic bioreactor, where the microbes, independently of specific genetic composition, provide the specific enzymes absent from the body, but vital to carry out metabolic reactions permitting to supply metabolites essential to the host. Thus, the symbiosis between hosts and microbes allows any living organism to get the most out of the food eaten, irrespective of food content, in a given enzymatic equipment of the host for food digestion.

It is probable that the continuous co-evolution of the hosts and their microbes has been a key to make that “biologically” resembling animals as ruminants and carnivores can live and feed from so different food sources like herb or meat, respectively. Since microbes most often depend on one unique nutrient type, they grow or regress depending on whether they find or not with this nutrient in the host’s food. Continuing with ruminants and carnivores, this may explain, e.g. why the gut microbiota of herbivores markedly differs from that of carnivores as for genetic composition (David et al., 2014). This may explain as well that some hours only after a given meal, the human gut microbiota turns to a pattern characteristic of herbivorous or carnivorous animals, depending on whether the preceding meals were composed of vegetables or meat, respectively (David et al., 2014). This could also explain the variations in gut microbiota observed in obesity versus leanness, both conditions are associated with very different food habits.

In conclusion, whatever the respective roles of the composition and function of the microbiota in metabolic health, much remains to be understood in this fascinating field of research.

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### **Declaration of interests**

The author has no conflict of interest to disclose relating to this article.

### **Text box 1: Metabolic benefits of intestinal gluconeogenesis**

Glucose is released by IGN in the portal vein and is sensed by gastrointestinal nerves in the vein walls, which takes place during post-absorptive periods. IGN thus signals to the main areas of the hypothalamus regulating energy homeostasis. This promotes multiple brain-driven benefits in energy homeostasis, including satiety, decreased lipid storage, decreased hepatic glucose production, improved hepatic insulin sensitivity and glucose control. The activation of IGN has explained the anti-diabetic and anti-obesity effects of protein- and fiber-enriched diets and of gastric bypass surgery of obesity (for a review Soty et al, 2017).

As for fiber, bacterial metabolites activate IGN via several complementary mechanisms. Propionate plays a dual role in this activation. Through binding to its receptor in the periportal nervous system (free fatty acids receptor 3), it activates a reflex arc resulting in the release of vasoactive intestinal peptide in the intestinal mucosa, which activates adenylate cyclase and the expression of IGN genes (De Vadder et al., 2015; Gautier-Stein et al., 2006). Butyrate concurs to activation of IGN gene expression via cAMP production. The second major role of propionate is to contribute to IGN through the incorporation of its carbons into intestinal glucose, which is also the case for succinate (De Vadder et al., 2014, 2016).

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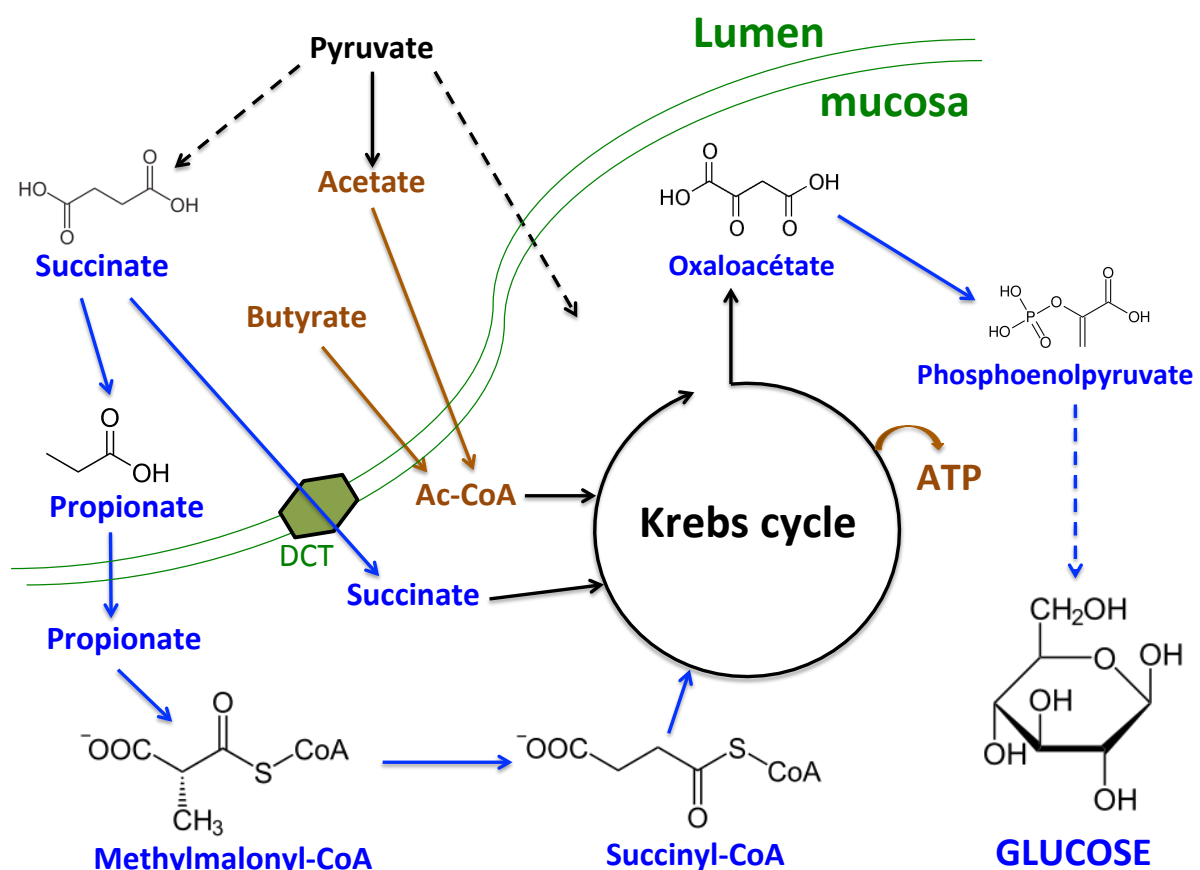
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**Figure 1: Fate of bacterial metabolites in the intestinal mucosa**



DCT: dicarboxylate transporter; in brown: pathways contributing to ATP production; in blue: pathways contributing to gluconeogenesis.