The gut microbiota affects host metabolism through a number of physiological processes. Emerging evidence suggests that gut microbes interact with the host through several pathways involving enteroendocrine cells (e.g. L cells). The activation of specific G protein coupled receptors expressed on L cells (e.g. GPR41, GPR43, GPR119 and TGR5) triggers the secretion of glucagon-like peptides (GLP-1 and GLP-2) and PYY. These gut peptides are known to control energy homeostasis, glucose metabolism, gut barrier function and metabolic inflammation. Here, we explore how crosstalk between the ligands produced by the gut microbiota (short chain fatty acids, or SCFAs), or produced by the host but influenced by gut microbes (endocannabinoids and bile acids), impact host physiology.

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Introduction
Obesity is associated with numerous metabolic comorbidities, such as insulin resistance, diabetes, cardiovascular disease and non-alcoholic fatty liver disease. The reduction of excessive body weight is effective for alleviating many of these metabolic abnormalities; however, the prevention of positive energy balance remains a widely practised cornerstone of obesity-prevention strategies [1]. Therefore, more effective weight loss induction strategies are needed to decrease the incidence and severity of metabolic abnormalities. Alternatively, approaches that can treat obesity-related metabolic abnormalities independent of weight loss are extremely attractive. Recent data indicate that certain microbes may provide templates for the development of such strategies (reviewed in [2,3]). Over the years, the understanding of the role of these cells (i.e. gut bacteria) has changed, leading to novel and interesting findings. The gut microbiota has profound impacts on host physiology, including in the control of energy homeostasis, the immune system, vitamin synthesis and digestion [4,5,6*].

Owing to its huge surface area and multiple functions, the intestine represents one of the most important organs, and it permits vital interactions with the external world, including the gut microbiota. The intestinal epithelium allows the absorption of nutrients and fluids while acting as an efficient barrier against toxins and microorganisms. The gut epithelium is comprised of different cell types, including epithelial absorptive cells, Goblet cells, Paneth cells and enteroendocrine cells. Enteroendocrine cells represent approximately 1% of all epithelial cells in the intestine and are subdivided into more than 10 different cell types based on their major secretory products and their localisation along the gastrointestinal tract. Given that multiple biological functions are physiologically regulated by the gut hormones produced by enteroendocrine cells (e.g. food intake, gastric emptying, gut motility, gut barrier formation, glucose metabolism) (Figure 1), these cells have been positioned at the forefront of research to find novel therapies. The enteroendocrine cells play key roles in the maintenance of gut homeostasis both by enabling nutrient absorption and by preserving the essential function of the gut as a barrier between the external environment (gut lumen) and the host tissues. Because enteroendocrine cells are distributed all along the gastrointestinal tract and are in close proximity to gut bacteria and/or metabolites produced by the metabolic activity of the gut microbiota, it is of utmost interest to unravel the crosstalk between the gut microbiota and these cells and the impact of this crosstalk on host physiology (Figure 1). However, the study of the gut microbiota and its relationship with the host represents a real challenge. Among the enteroendocrine cells, L cells have attracted particular interest because of the pleiotropic effects of their secreted peptides [7–9]. Although these cells are known to respond to nutrients present in the intestinal lumen, they are also able to detect many other luminal compounds. This is especially true in the colon, where the gut microbiota and most of its metabolites are largely present.

In this review, we discuss the body of evidence linking gut microbes (and specific metabolites produced by these bacteria) with enteroendocrine function and thereby host physiology.

Gut microbiota and enteroendocrine functions: effects on glucose and energy homeostasis
We have previously shown that the modulation of the gut microbiota using prebiotics in mice and humans
Figure 1

Schematic overview of the interactions between the gut microbiota, specific metabolites, enteroendocrine L cell functions and targeted organs. Enteroendocrine L cells express several G protein coupled receptors (GPCRs) (e.g. GPR43, GPR41, GPR119 and TGR5). The endogenous and physiological ligands of the different receptors are indicated above each receptor and connected with an arrow. The gut microbiota produces several metabolites, including short-chain fatty acids (SCFAs) that are able to trigger gut peptide secretion by acting directly on specific receptors such as GPR41 and 43. Specific changes in the gut microbiota have also been associated with changes in N-oleylethanolamide (OEA) and 2-oleylglycerol (2-OG). These bioactive lipids belong to the endocannabinoid family and serve as ligands of the GPR119 receptor. TGR5 (also known as M-BAR, GPBAR1 or GPR131) is targeted by bile acids. The stimulation of these receptors by their putative ligands promotes the secretion of gut peptides (GLP-1, GLP-2 and PYY) by the L cells. These peptides target several organs, including the gastrointestinal tract, brain, adipose tissue and liver, thereby contributing to improvements in gut barrier function and glucose and energy homeostasis.

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the gut microbiota itself [16,29,30]. Moreover, several studies have reported that SCFA receptors colocalise in the epithelium with the enteroendocrine cells that secrete key modulators of glucose homeostasis such as PYY, GLP-1 and GIP [31]. Among these receptors, GPR41 is expressed in the intestinal mucosa and is particularly abundant in an immortalised murine L cell line [32], which is consistent with a potential role in peptide secretion from L, K, and other enteroendocrine cells, but the role of GPR41 in the regulation of energy balance and glucose metabolism is poorly understood (Figure 1). To address this question, a GPR41-deficient mouse line was generated. These mice have body weights similar to those of control mice on both normal and high-fat diets and exhibit normal fasting GLP-1 levels but attenuated GLP-1 secretion in response to butyrate. The GIP and PYY levels of GPR41-deficient mice were similar to those of their littermates. These data suggest that only butyrate stimulation of GLP-1 secretion from L cells is partially mediated by GPR41 [26]. Tolhurst et al. generated knockout mice deficient in GPR43 [25], another SCFA receptor that is normally expressed in the rat and human colon wall, mucosa and PYY-expressing enteroendocrine cells [33]. They found that GPR43-deficient mice have reduced colonic GLP-1 protein content, reduced basal and glucose-stimulated levels of GLP-1 and impaired glucose tolerance (Figure 1). Other receptors can also stimulate GLP-1 secretion by L cells. For instance, bile acids can bind to both nuclear and cell surface receptors. Yet, the gut microbiota regulates both bile acid synthesis and the production of secondary bile acids [34]. Two bile acid receptors are involved in glucose homeostasis. TGR5 is a GPCR, and its activation improves liver function and glucose tolerance in obese mice by regulating intestinal GLP-1 production (Figure 1) [35]. FXR is a nuclear receptor that is essential for maintaining glucose tolerance and insulin sensitivity but acts via mechanisms other than enteroendocrine regulation [36].

Although convincing studies have supported a link between GPR43/41, enteroendocrine functions and gut microbiota metabolites (i.e. SCFAs), compelling evidence suggests that other bioactive compounds and receptors contribute to the secretion of GLP-1/2 and PYY by the L cells [7]. For instance, bioactive lipids belonging to the N-acylethanolamine and acylglycerol families are also able to activate the L cell-specific receptor GPR119 (Figure 1) [37,38,39**].

To date, few studies have characterised the roles of specific bacterial species that are able to produce metabolites with bioactive effects on these gut hormones. Interestingly, Akkermansia muciniphila, a mucin-degrading bacterium that resides in the mucus layer, is able to produce acetate and propionate [40], which can act on GPR43. We recently showed that this bacterium was present at lower levels in obese and type 2 diabetic mice than in healthy mice [41] and that the daily administration of A. muciniphila for 4 weeks reversed high-fat diet-induced obesity and type 2 diabetes [41**]. Strikingly, we also showed that the abundance of A. muciniphila was associated with L cell number and secretory capacity [12].

Therefore, it appears clear that the gut microbiota and specific associated metabolites are key partners in the control of glucose and energy homeostasis. Although the mechanisms underlying this regulation are still unclear, the gut microbiota constitutes an important potential target for treatment of metabolic disorders such as obesity and type 2 diabetes.

**Gut microbiota and enteroendocrine functions: effects on gut barrier function**

Gut barrier disruption has been observed in several pathological situations and is involved in the pathophysiologic process of multiple diseases. Obesity is associated with an increase in gut permeability that leads to the abnormal translocation of gut bacteria or gut bacteria components from the intestinal lumen through the host blood circulation and tissues [42–45]. We have shown that these changes in gut barrier activity are associated with increased plasma levels of gram-negative bacterial cell wall components, namely lipopolysaccharides (LPS). Importantly, the increase in plasma LPS levels, which is defined as metabolic endotoxemia, has been shown to trigger low grade inflammation and metabolic disorders associated with obesity and type 2 diabetes [42]. Given the implications of gut barrier alterations on the onset of metabolic endotoxemia, inflammation and metabolic disorders associated with obesity and type 2 diabetes, it is of the utmost importance to determine the underlying mechanisms and the potential opportunities to reverse the increase in gut permeability related to this pathology.

One of the principal players involved in the changes in gut barrier function in obesity and type 2 diabetes is the gut microbiota. Indeed, it is now well established that obesity is associated with changes in the diversity and composition of the gut microbiome [46–49]. Moreover, we have demonstrated that this link is causal because modulations of the gut microbiota using prebiotics can improve gut barrier function and ameliorate metabolic endotoxemia and inflammation in obesity and type 2 diabetes through mechanisms associated with enteroendocrine cell function [12,41**,50,51]. To date, the main enteroendocrine peptide known to be involved in gut barrier functions and produced by enteroendocrine cells is the glucagon-like peptide-2 (GLP-2) (Figure 1). This peptide is produced by L cells; its production is regulated by the nutritional status of the host, and it increases the nutrient absorption capacity of the host. Importantly, GLP-2 maintains gut barrier functions through different mechanisms. First, GLP-2 has been demonstrated to induce intestinal epithelial cell proliferation and thereby
Importantly, we have shown that the beneficial effects of gut microbiota modulation on gut barrier function are associated with an increase in GLP-2 production related to an increase in the number of L cells in the intestine [12,53]. It is worth noting that treatment with a GLP-2 antagonist completely abolished the improvements in gut barrier function following prebiotic-induced changes in the gut microbiota. These data suggest that specific interactions between the gut microbiota and enteroendocrine L cells control gut permeability and inflammation in obesity and type 2 diabetes.

As discussed above, we have recently identified A. muciniphila as one species that is involved in the crosstalk between the gut microbiota and intestinal epithelium in the context of obesity and type 2 diabetes. Compelling evidence suggests that A. muciniphila seems to play a special role in gut barrier function. Indeed, several pathologies associated with increased gut permeability are also associated with a decrease in the abundance of A. muciniphila in the gut [56,57]. Importantly, the abundance of this bacterium negatively correlates with the levels of gut permeability markers and inflammatory markers [41*]. In a recent study, we found that A. muciniphila treatment decreases metabolic endotoxemia and inflammation by improving intestinal mucosal barrier function in high-fat fed mice [41*]. Our data suggest that the effects of A. muciniphila on gut barrier function could be mediated through enteroendocrine L cells.

Indeed, we demonstrated that A. muciniphila administration significantly increases the intestinal levels of 2-oleoylglycerol (2-OG), a bioactive lipid belonging to the endocannabinoid system [41*]. Interestingly, 2-OG stimulates the secretion of glucagon-like peptides through the activation of GPR119 localised on intestinal L cells (Figure 1) [39**].

It is worth noting that L cells and their secretory products are not the only enteroendocrine peptides and cells involved in the relationship between the gut microbiota and gut barrier function. For instance, intestinal signalling by serotonin (another enteroendocrine product) is involved in gut barrier function during obesity. Levels of serotonin and the type 3 serotonin receptor (5-HT₃R) are increased in mice with genetic or high-fat diet-induced obesity, and 5-HT₃R antagonists increase the expression of intestinal tight junction proteins such as occludin and claudin-1, an effect that is associated with decreases in metabolic endotoxemia and fatty acid liver diseases associated with obesity [58,59]. A link between specific gut microbes and the modulation of serotonin production has been proposed [60,61]; however, the connections between serotonin, the gut microbiota and the secretory capacity of other enteroendocrine cells remain to be elucidated.

Conclusions
Several studies have shown that modification of the gut microbiota affects various physiological processes. However, it has so far proven difficult to determine the precise mechanisms linking gut microbiota composition and/or activity with specific metabolic pathways involved in energy and glucose homeostasis. The gut microbiota represents an extremely diverse group of microbes and is not a static ecosystem but is subject to rapid modifications that are directly associated with nutrient intake. Several studies have suggested that targeting the gut microbiota and thereby the production of specific metabolites may be one interesting approach toward improving metabolic features associated with obesity and type 2 diabetes. However, it remains to be determined whether these modifications are a cause or a consequence of the metabolic changes observed.

Emerging evidence suggests that the gut microbiota interacts with their hosts through several pathways involving the enteroendocrine cells. Thus, specific GPCRs expressed on enteroendocrine L cells may constitute a putative therapeutic target.

To date, it is not known whether the modifications of enteroendocrine cell activities by the microbiota are strain or metabolite dependent. The next challenge is to develop approaches to decipher the mechanisms involved in molecular signalling modulated by gut microbes to ultimately identify new therapeutic targets for the management of various metabolic conditions. Thus, additional research is needed to further isolate and identify the key mechanisms involved in gut microbe–host interactions.

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


This review outlines different mechanisms involving the gut microbiota interactions and host metabolisms. This review is elegantly discussed and illustrated.


A dense review discussing data supporting the link between gut microbe and immune system, in both pathological and physiological situations.


This is an excellent review of the relationship between different nutrients (fat, protein, carbohydrates) and the gut microbiota.


An outstanding review examining the role of G protein-coupled receptors as signaling molecules in the context of energy and glucose metabolism.


