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**Gut microbiota-derived metabolites as key mucosal barrier modulators in obesity**

Wei Y *et al*. Microbial metabolites in obesity

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**Abstract**

A significant breakthrough in the field of obesity research was the demonstration that an obese phenotype could be manipulated by modulating the gut microbiota. An important next step is to elucidate a human-relevant ‘‘map’’ of microbiota–host interactions that regulate the metabolic health of the host. An improved understanding of this crosstalk is a prerequisite for optimizing therapeutic strategies to combat obesity. Intestinal mucosal barrier dysfunction is an important contributor to metabolic diseases and has also been found to be involved in a variety of other chronic inflammatory conditions, including cancer, neurodegeneration, and aging. The mechanistic basis for intestinal barrier dysfunction accompanying metabolic disorders remains poorly understood. Understanding the molecular and cellular modulators of intestinal barrier function will help devise improved strategies to counteract the detrimental systemic consequences of gut barrier breakage. Changes in the composition and function of the gut microbiota, *i.e.*, dysbiosis, are thought to drive obesity-related pathogenesis and may be one of the most important drivers of mucosal barrier dysfunction. Many effects of the microbiota on the host are mediated by microbiota-derived metabolites. In this review, we focus on several relatively well-studied microbial metabolites that can influence intestinal mucosal homeostasis and discuss how they might affect metabolic diseases. The design and use of microbes and their metabolites that are locally active in the gut without systemic side effects are promising novel and safe therapeutic modalities for metabolic diseases.

**Key Words:** Obesity; Metabolic diseases; Microbiota; Mucosal homeostasis; Gut; Microbial metabolites

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**Core Tip:** The manner in which the gut microbiota influences obesity development remains incompletely understood. Recent studies have indicated that the changes in the gut barrier functions act as an important driver of metabolic disorders. There is currently an urgent need to define molecular and cellular modulators of intestinal mucosal barrier homeostasis. Here, we discuss the current understanding of microbiota-derived metabolites in regulating mucosal homeostasis and how they contribute to the metabolic health of the host.

**INTRODUCTION**

The gut microbiota is thought to function as an organ that can markedly influence human health and disease[1]. It plays an essential role in the progression of obesity and related metabolic syndromes[2-4]. Many effects of the microbiota on the host are mediated by microbiota-derived metabolites[5-8]. A complex interplay between the host immune system and the gut microbiota under normal physiological conditions maintains the mucosal barrier in a homeostatic state. This symbiotic relationship is often broken during the progression of obesity. Increased levels of circulating bacterial flagellin, lipopolysaccharides (LPS), and peptidoglycans are frequently observed in obesity and its complications due to mucosal barrier dysfunction[9-12]. The objective of this review is to provide an overview of the emerging field related to the role of gut microbiota-derived metabolites in regulating gut barrier function and metabolic health.

**MUCOSAL HOMEOSTASIS IN OBESITY**

Intestinal barrier dysfunction leads to the translocation of microbial molecules into the systemic circulation, resulting in a state of so-called “metabolic endotoxemia” that is considered to be one of the most important initiators of metabolic disease in obesity[13-16]. However, the mechanisms underlying barrier dysfunction accompanying metabolic syndrome remain poorly understood. Thus, there is an urgent need to elucidate the molecular and cellular modulators of intestinal mucosal barrier homeostasis to devise improved strategies to counteract metabolic disease progression. Hyperglycemia has been suggested as a contributor to obesity-associated dysfunctions of the intestinal barrier[17]; however, this condition may not be the initial trigger for barrier dysfunction, as hyperglycemia often occurs after metabolic syndrome manifestation. The gut microbiota is involved in the regulation of multiple host metabolic pathways *via* interactive host–microbiota interactions. Early phase alteration of the composition and function of the gut microbiota may induce intestinal barrier dysfunction and lead to the development of metabolic disorders. Here, we briefly review several microbial metabolites that regulate mucosal homeostasis.

***Microbiota-derived*** ***short-chain fatty acids as regulators of mucosal homeostasis***

Short-chain fatty acids (SCFAs) are derived predominantly from gut microbial fermentation of otherwise indigestible dietary fiber[18]. According to a clinical study, the major SCFA-producing bacteria promoted by dietary fibers in humans were found to be *Faecalibacterium prausnitzii* and *Eubacterium*, *Lactobacillus*, and *Bifidobacterium* species[19]. The roles of SCFAs in mucosal homeostasis and metabolic health are summarized in Figure 1.

**SCFAs regulate gut epithelial cell metabolic programming:** Gut epithelial cells express peroxisome proliferator-activated receptor gamma (PPAR-γ)[20], which can sense microbial-derived SCFAs (*e.g.*, butyrate). The activation of PPAR-γ by butyrate drives the energy metabolism of colonic epithelial cells toward beta-oxidation and limits the luminal bioavailability of oxygen[21-24]. This is important for maintaining the colonic surface in a physiological hypoxic state, thereby limiting the aerobic outgrowth of facultative anaerobic bacteria[25]. Short-term high-fat diet (HFD) consumption can perturb epithelial PPAR-γ signals and disrupt the microbial and physiological ecosystems within the gut[26].

PPAR-γ activation by SCFAs can also increase angiopoietin-like protein 4 (ANGPTL4/FIAF) secretion from the gut epithelium[27]. ANGPTL4 is a circulating lipoprotein lipase inhibitor, and its expression levels can affect the process of dietary energy harvesting and storage in the host[28]. Additionally, PPAR-γ activation inhibits the transcription of proinflammatory genes induced by interferon (IFN) gamma and/or LPS[29].

**Effects of SCFAs on gut hormones:** The gut is the largest endocrine organ within the body and can release more than 20 different peptide hormones that are sensitive to gut nutrient content stimulation and function to regulate a variety of physiological processes[30]. As a gut nutrient, free fatty acids (FFAs) can serve as not only cellular energy sources but also natural ligands for a group of orphan G protein-coupled receptors (GPCRs), which are known as FFA receptors (FFARs) and are expressed in the gut epithelial cells to regulate gut peptide hormone production[31-34]. In particular, FFAR3 (GPR41) and FFAR2 (GPR43) are activated by SCFAs, primarily acetate, butyrate, and propionate[32]. SCFAs can stimulate the release of the anorexigenic hormone peptide tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) from colonic L cells[30] *via* their cognate FFARs. The release of PYY into circulation after food intake can reduce energy intake[35]. GLP-1 can act directly on pancreatic beta cells to activate insulin secretion in a glucose-dependent manner[36]. Thus, SCFA-induced release of PYY and GLP-1 from colonic L-cells may play a role in preventing the development of obesity and its related complications[37].

**Role of SCFAs in maintaining mucosal immune homeostasis:** The gut microbiota has co-evolved with the intestinal immune system to facilitate the maintenance of mucosal homeostasis[38]. Regulatory T cells (Tregs) are critical for limiting intestinal inflammation[39]. SCFAs play an important role in the generation of peripheral Tregs and control Treg homeostasis and function within the gut[40,41]. Butyrate, acetate, and propionate are the major bacteria-derived SCFAs that control mucosal Treg differentiation and function[40]. Several mechanisms are involved in the promotion of mucosal Treg differentiation and function by SCFAs. First, SCFAs can regulate the size and function of the colonic Treg pool through the activation of GPCRs (GPR43 and/or GPR109)[40,42]. Second, SCFAs can regulate Treg differentiation by inhibiting histone deacetylase (HDAC)[43]. HDAC activity in T cells can be suppressed by acetate, propionate, and butyrate[43]. Butyrate enhances the acetylation of histone H3 Lysine 27 at the promoter and conserved non-coding sequence regions of the Foxp3 locus, which is critical for peripheral Treg generation to promote Foxp3 gene expression[41,44]. Furthermore, the HDAC inhibitory activity of butyrate and propionate promotes the ability of dendritic cells to support Treg differentiation by repressing the expression of LPS-responsive genes and by rendering lamina propria macrophages hyporesponsive[41,45]. Additionally, the binding of SCFAs with GPR43 expressed on neutrophils and eosinophils has been reported to dampen gut inflammatory responses[46]. Collectively, these data indicate that SCFAs can maintain mucosal immune homeostasis, particularly by inducing Treg generation and function, which may be beneficial for alleviating obesity and its related metabolic syndrome[37]. Consistent with this idea, fat-resident Tregs have been reported to be significantly reduced in obese hosts and Tregs protect against obesity-associated inflammation, insulin resistance, and other related metabolic disorders[47-49].

It should be noted that although SCFAs are generally thought to play positive roles in maintaining mucosal homeostasis, they exert negative impacts on host metabolism. In experimental studies involving mice, treatment with acetate promoted metabolic syndrome through the action of the gut–nervous system axis[50]. In a clinical trial, consumption of a propionate-containing meal resulted in the activation of catecholamine-related insulin counter-regulatory signals, thus leading to insulin resistance[51]. Approaches to avoid such negative impacts of SCFAs on host metabolism are warranted.

***Role of microbiota-derived amino acid metabolites in mucosal homeostasis***

**Microbiota-derived** **tryptophan metabolites protect the gut barrier:** Recent discoveries indicate that the gut microbiota modulates immune homeostasis and mucosal barrier physiology by modulating amino acid metabolism. Among the amino acids, the effects of aromatic amino acid tryptophan (Trp) derivatives produced by bacterial fermentation are relatively well studied. Gut microbiota can directly utilize Trp as a biosynthetic precursor for a large number of microbial metabolites, and approximately 4%–6% of Trp can also be further metabolized to indole, indican, tryptamine, skatole, and indole acid derivatives[52,53]. Trp can be converted into indole by tryptophanase, which is expressed in *Escherichia coli* and *Lactobacilli*[54], or into tryptamine by a Trp decarboxylase found in *Clostridium sporogenes*[55]. It can also be transformed into indoleacetic acid *via* an uncharacterized oxidative pathway or into indolepropionic acid (IPA) *via* a reductive pathway that requires a phenyllactate dehydratase that is found in *C. sporogenes*, *Peptostreptococcus anaerobius* CC14N, and three strains of *Clostridium cadaveris*[56].

Many indole derivatives, including IPA and indoleacrylic acid (IA) are ligands for the aryl hydrocarbon receptor (AhR)[54,57,58]. AhR signaling is crucial for intestinal homeostasis because it influences epithelial renewal, barrier integrity, and immune cell activity[59]. AhR mediates the activation of type 3 innate lymphoid cells to produce IL-22[60]. IL-22 plays an important role in maintaining the mucosal barrier and regulating host metabolic functions[61,62]. IPA induces IL-10R1 by activating AhR, thus exerting anti-inflammatory effects in the intestinal mucosa[58]. IA-AhR signaling promotes barrier function and mitigates LPS-stimulated inflammatory responses[63]. Indole-3-aldehyde (IAld) promotes AhR-dependent-IL22 production to provide mucosal protection against inflammation induced by the fungus *Candida albicans*[57]. Trp-derived AhR ligands are reduced in both HFD-induced metabolic impairments in animals and in individuals with metabolic syndrome, and supplementation with an AhR agonist or an AhR ligand-producing *Lactobacillus* strain leads to the improvement of metabolic disorders[64,65].

Additionally, IPA has been reported to act as a ligand for the pregnane X receptor (PXR), and *in vivo*, PXR signals regulate mucosal integrity through toll-like receptor 4[66]. Indole and IAld can also activate enteroendocrine cells through transient receptor potential ankyrin A1 to increase gut motility[67]. Gut microbiota-produced tryptamine activates intestinal epithelial GPCR serotonin receptor-4 (5-HT4R) to increase cAMP levels and drive colonic fluid secretion[68]. Collectively, Trp metabolites produced by the microbiota can protect gut barrier functions.

**Microbiota-derived** **tyrosine metabolites regulate mucosal homeostasis:** The aromatic amino acids phenylalanine, tyrosine (Tyr), and Trp share a decarboxylation pathway to generate trace amines, including phenylethylamine, tyramine, and tryptamine, respectively. Tyramine and tryptamine are high-affinity ligands for trace amine-associated receptor 1, which is expressed in the stomach, intestinal neuroendocrine cells, and pancreatic β cells, and regulates energy metabolism and modulates immune homeostasis[69,70].

Another common pathway involves aminotransaminase-mediated transamination, which subsequently undergoes oxidation and reduction, ultimately leading to the production of the corresponding acetic acid or propionic acid derivatives[56]. Desaminotyrosine (DAT, also known as 4-hydroxyphenylpropionic acid or p-hydroxyhydrocinnamic acid) is a degradation product derived from microbial Tyr metabolism. DAT can also be produced from microbial degradation of dietary flavonoids[71,72]. A recent study revealed that DAT protects the host from influenza virus infection by enhancing type I IFN signals[73]. Our recent data demonstrated that DAT supplementation alleviated HFD-induced fat mass accumulation and body weight increment, both of which are correlated with the anti-inflammatory effect of DAT with regard to maintaining mucosal immune homeostasis[7] (Summarized in Figure 2).

***Bile acid modification by gut microbiota impacts mucosal homeostasis***

Primary bile acids (BAs) are cholesterol metabolites that are produced in the liver and converted to secondary BAs by the gut microbiota[74]. The two key microbiota-dependent processes are BA deconjugation and 7α-hydroxylation. The enzyme bile salt hydrolase, which is produced by many commensal genera such as *Bacteroides*, *Clostridium*, and *Enterococcus*, deconjugates primary BAs. However, only a small number of known bacteria from the *Lachnospiraceae* and *Ruminococcaceae* families perform subsequent 7α-dehydroxylation to generate secondary BAs[75]. BAs are lipid solubilizers that are crucial for dietary lipid absorption and function as signaling molecules that coordinately regulate host metabolism and inflammation by interacting with their cognate cellular receptors, including the nuclear receptors farnesoid X receptor (FXR), PXR, vitamin D receptor, membrane G protein-coupled BA receptor 1 (also known as GPCR19 or TGR5), and sphingosine-1-phosphate receptor[76,77]. Different BA profiles can produce both agonists and antagonists of their cognate receptors, thus creating a great deal of complexity regarding the beneficial or deleterious inﬂuence of BAs and their derivatives on health and disease. In the gut, BA-TGR5 signaling leads to GLP-1 expression and secretion, whereas BA-FXR signaling inhibits GLP-1 production[78]. BAs influence gut-associated inflammation by regulating gut mucosal immune cells, including T helper cells expressing IL-17a and Tregs[79-81]. The BA-TGR5–cAMP–PKA axis inhibits NLRP3 inflammasome activation in macrophages[82]. Certain BAs can exert protective effects on the gut epithelium[83] or inhibit intestinal pathogens such as *Clostridium difficile*[84]. In an experimental model, tauroursodeoxycholic acid inhibited intestinal inflammation and barrier disruption in mice with nonalcoholic fatty liver disease[85]. *Parabacteroides distasonis*, one of the core members of the gut microbiota of humans, alleviates obesity and obesity-related dysfunction in mice, at least partially, based on its ability to produce secondary BAs[86] (Summarized in Figure 3).

***Other dietary-derived microbial metabolites in regulating mucosal homeostasis***

Polyphenols are a class of plant-derived macromolecules[87]. Approximately 90%–95% of dietary polyphenols are poorly absorbed and are partially processed by the gut microbiota[88]. Fermentation of polyphenols by the gut microbiota results in the production of bioactive metabolites that can affect host physiology. Urolithins are gut microbial metabolites derived from the polyphenol compounds, ellagitannins that are present in some fruits, nuts, and seeds (*e.g.*, pomegranates, black raspberries, raspberries, strawberries, walnuts, and almonds)[89]. Ellagitannins are hydrolyzed to ellagic acid under physiological conditions *in vivo*, and ellagic acid is then gradually metabolized by the gut microbiota to produce different types of urolithins. Urolithins have been demonstrated to protect against obesity and related metabolic diseases in animal studies[90]. These effects are related to their protective role in mucosal epithelial integrity and anti-inflammatory functions[91,92].

Omega-6 polyunsaturated fatty acids (PUFAs) are abundant in the Western diet and can contribute to obesity and metabolic syndrome[93,94]. The increased ratio of omega-6/omega-3 fatty acids correlates with the incidence and prevalence of overweight individuals and obesity[94,95]. The gut microbiota confers host resistance to HFD-induced obesity by modulating dietary PUFA metabolism[96]. One of the metabolites is 10-hydroxy-cis-12-octadecenoic acid (HYA). HYA promotes GLP-1 secretion in colonic L cells and improves glucose homeostasis *via* the activation of GPR40 and GPR120. Additionally, HYA promotes intestinal peristalsis by acting as a low-affinity prostaglandin EP3 receptor agonist[96].

**CONCLUSION**

The gut microbiota plays a key role in obesity. Our current understanding of host–microbiota interactions remains in its early phase. Several challenges must be resolved before the field can be advanced. The design and use of microbes and their metabolites that are locally active in the gut without systemic side effects are promising novel and safe therapeutic modalities for metabolic diseases.

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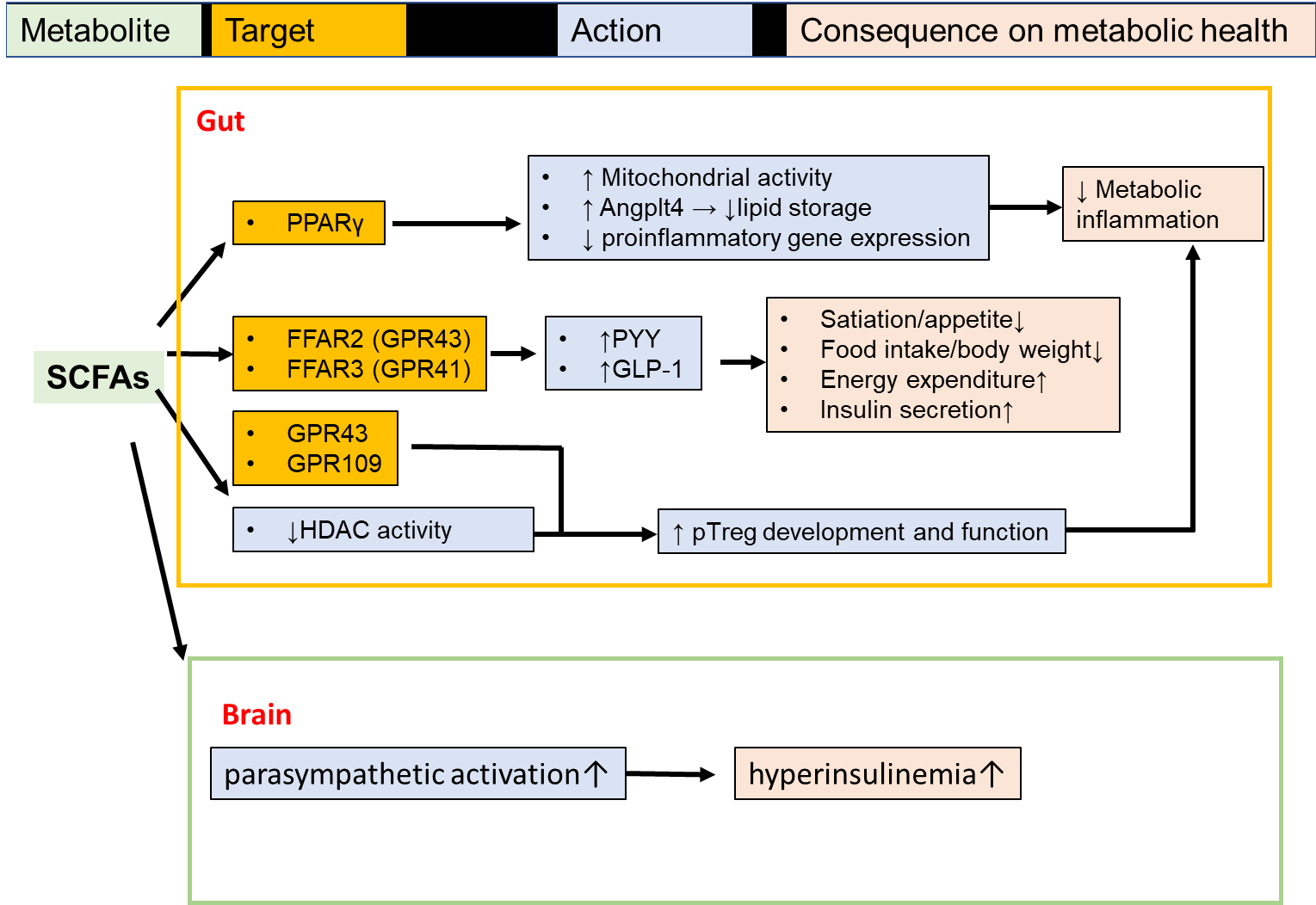
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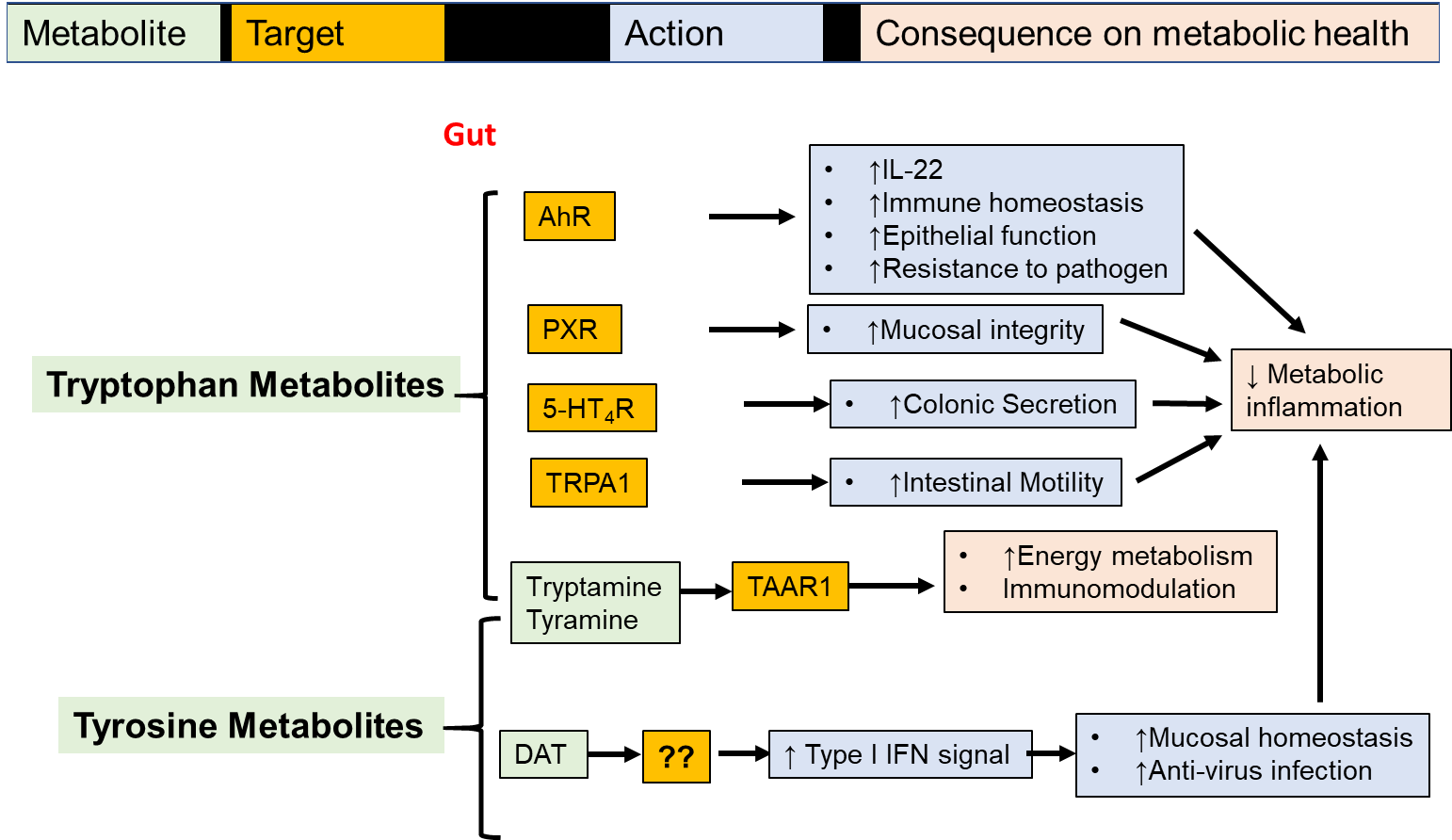
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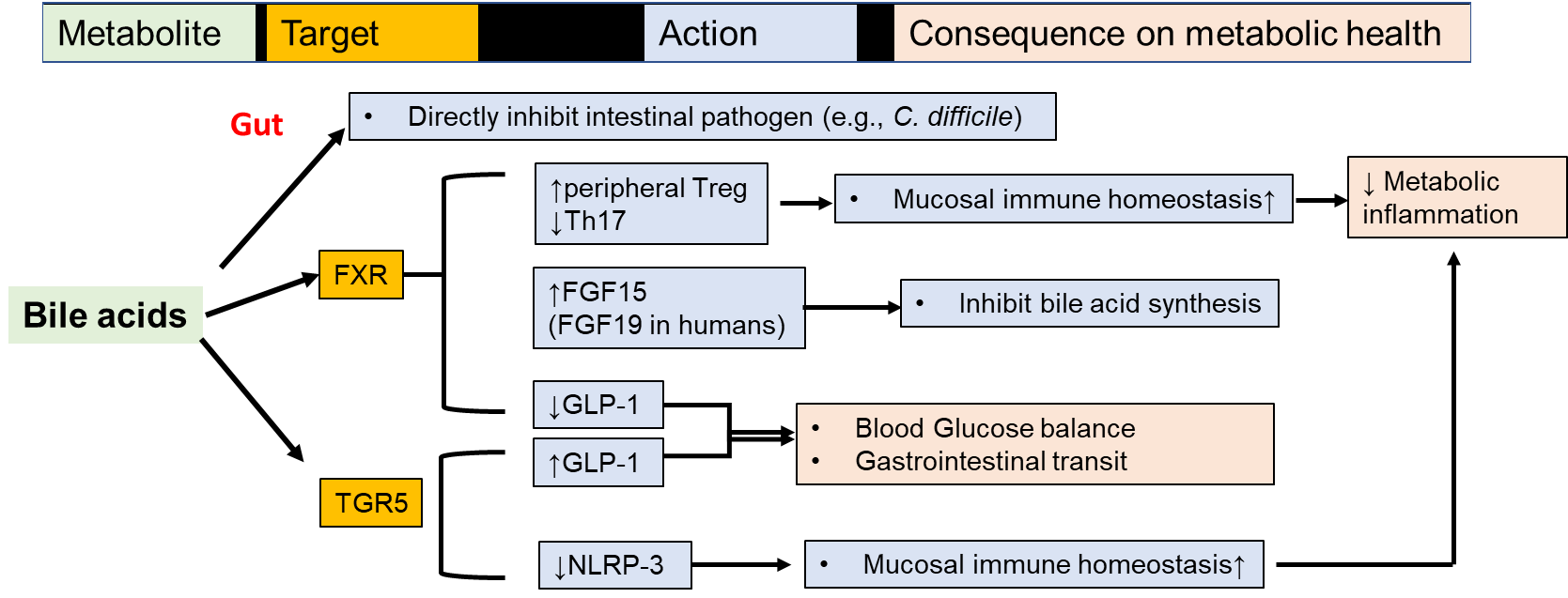
**Figure Legends**

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**Figure 1 The roles of short-chain fatty acids in mucosal homeostasis and metabolic health.** Short-chain fatty acids (SCFAs) can engage various molecular targets in the gut, and play positive roles in maintaining mucosal barrier integrity and systemic metabolic health *via* regulating gut epithelial cell metabolic programming by activating peroxisome proliferator-activated receptor gamma signals, maintaining immune homeostasis by promoting peripheral regulatory T helper cell development and functions, and stimulating energy expenditure and insulin secretion by releasing the gut hormones peptide tyrosine and glucagon-like peptide-1. SCFAs also exert some negative influences on host metabolic health *via* the gut–brain axis. Angplt4: Angiopoietin-like protein 4; FFAR: Free fatty acid receptor; GLP-1: Glucagon-like peptide-1; GPR: G-coupled receptor; HDAC: Histone deacetylase; PPAR: Peroxisome proliferator-activated receptor; pTreg: Peripheral regulatory T helper cell; PYY: Peptide tyrosine.



**Figure 2 The roles of the indicated amino acid metabolites in mucosal homeostasis and metabolic health.** Tryptophan and tyrosine metabolites can engage various molecular targets in the gut, and play positive roles in maintaining mucosal barrier integrity and regulating systemic metabolic health at least in part by modulating mucosal immune and epithelial cell functions *via* cytokine IL-22 or type I interferon, *etc.*, or by promoting host energy metabolism *via* trace amine-associated receptor 1. The question mark indicates that the molecular target of desaminotyrosine is currently unknown. 5-HT4R: Serotonin receptor-4; AhR: Aryl hydrocarbon receptor; DAT: Desaminotyrosine; PXR: Pregnane X receptor; TAAR1: Trace amine-associated receptor 1; TRPA1: Transient receptor potential ankyrin A1.



**Figure 3 The roles of bile acids in mucosal homeostasis and metabolic health.** Bile acids (BAs) have complicated roles in regulating mucosal immune cell activation and gut epithelial cell functions. Different BA profiles can produce both agonists and antagonists of their cognate receptors. Only the well-characterized intestinal targets of BAs and their actions are indicated here. FGF15: Fibroblast growth factor 15; FXR: Farnesoid X receptor; NLRP3: NLR family pyrin domain containing 3; TGR5: Membrane G protein-coupled bile acid receptor 1; Th17: T helper cells expressing IL-17a; Treg: Regulatory T helper cells.



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