https://doi.org/10.1038/s44324-025-00066-1

# Mechanisms and implications of the gut microbial modulation of intestinal metabolic processes



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Intestine-exclusive metabolic processes involve the degradation of dietary components and xenobiotics through intricate and dynamic interactions between the host epithelial cells and gut microbiota. Disruptions in this fragile equilibrium lead to metabolic and gastrointestinal diseases, highlighting the profound impact of the gut microbiota on the host intestinal metabolic processes. Gut microbes play a crucial role in influencing intestinal metabolic homeostasis by affecting nutrient sensing, gut hormones, neurotransmitters, and redox balance, collectively modulating mucosal gene expression and metabolic signaling pathways. These intestinal-level host-microbe metabolic interactions profoundly impact extra-intestinal tissues and organs. This comprehensive review provides mechanistic insights on the crucial role of gut microbiota in sustaining metabolic health by narrowing down to the gut-level metabolic interactions.

Intestinal metabolism implies the metabolic processes exclusively occurring within the intestines that facilitate the breakdown and absorption of dietary nutrients and xenobiotics, entailing a multifaceted interaction between the host and the gut bacteria. These processes include nutrient sensing, digestion, absorption, energy harvesting, detoxification, and immunomodulation, which dictate the overall human health and disease. Intestinal epithelial cells (IEC) are essential for nutrient absorption and converting macronutrients to usable energy sources. The unique enzymatic functions of the mammalian intestine, such as bile acid conversion and xenobiotic metabolism, facilitate the detoxification, and bioactivation of diverse chemicals[1]. Intestine-specific metabolic processes are also essential for hormone regulation, particularly incretin hormones, which enhance glucose homeostasis. This metabolic complexity enhances barrier function, modulates immunological responses, and affects systemic metabolic pathways. Interference with these processes may lead to metabolic diseases, mucosal inflammation and colorectal cancer, underscoring the pivotal role of the intestine in sustaining human health and the necessity of comprehending the influence of the gut microbes[1].

The intestinal mucosa remain in a dynamic and intricate interaction with the luminal microbes, commonly known as the gut microbiota, that play a crucial role in the regulation and maintenance of mammalian intestinal metabolic homeostasis[2,3]. Certain bacteria in the gastrointestinal (GI) tract can produce enzymes that facilitate the digestion of complex carbohydrates that the body cannot digest alone, enabling enhanced absorption of nutrients. The microbial fermentation of dietary fibers produces short-chain fatty acids (SCFA), which serve as a vital energy source and signaling molecules for intestinal cells, affecting epithelial integrity and immunological regulation. SCFAs positively influence health by regulating glucose metabolism, reducing inflammation, and preventing colon cancer[4]. The gut microbiome may also influence the expression of genes associated with metabolism[2,5]. Gut bacteria produce metabolites that can bind to DNA and influence the expression of genes regulating nutrient intake and metabolism. The cumulative metabolites produced by several intestine-specific metabolic processes, both host and microbe-derived, constitute the gut metabolome. These metabolites and small metabolic intermediates regulate intestinal immunometabolic homeostasis that includes energy metabolism, immune metabolism, and endocrine functions, and regulate the extent of mutualistic, commensal, and pathogenic relationships between the host and microbes[6,7]. Chronic metabolic conditions such as obesity, diabetes, cardiometabolic, and fatty liver disease are frequently associated with alterations in the gut metabolome[8].

Collectively, the microbiota significantly influences intestinal metabolism and the metabolome through diverse mechanisms, hence affecting overall human health (Table 1). Consequently, this review aims to provide a comprehensive overview of the fundamental concepts related to gut microbial influence on the intestinal metabolic processes. Comprehending the gut microbial modulation of intestine-specific metabolic processes is essential, since it directly affects nutrient absorption, gut barrier integrity, and localized immune responses. These processes are essential for preserving gut health and averting GI diseases. Dysregulation may result in localized inflammation, impairing nutrition absorption and potentially triggering systemic metabolic disorders. By concentrating on intestinal-

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https://doi.org/10.1038/s44324-025-00066-1



**Table 1 | Summarize the major intestine-specific metabolic processes that are modulated by gut microbiome, emphasizing their contributions to overall health**

| Intestinal metabolic process | Role in human health | Associated pathways | Impacting bacteria | Mode of bacterial modulation | Health impact |
|---|---|---|---|---|---|
| Fermentation of dietary fibers[198,199] | Produces SCFAs for colonocyte energy and systemic health | GPR41, GPR43 signaling | *Faecalibacterium*, *Roseburia* | Enhance SCFA production | Supports gut health, reduces inflammation |
| Conversion of primary to secondary bile acids[200,201] | Aids in lipid digestion and vitamin absorption | FXR, TGR5 signaling | *Clostridium*, *Bacteroides* | Transform bile acids | Modulates lipid metabolism, gut microbiota composition |
| Synthesis of vitamins[202,203] | Produces essential vitamins like K and B | Various metabolic pathways | *Bacteroides*, *Bifidobacterium* | Vitamin biosynthesis | Supports coagulation, energy, and neural health |
| Amino acid metabolism[204,205] | Produces bioactive amines and neurotransmitter precursors | Decarboxylation and deamination pathways | *Enterococcus*, *Clostridium* | Metabolize amino acids | Influences gut-brain axis, mood regulation |
| Choline metabolism[206,207] | Influences cardiovascular health through metabolite production | Conversion to TMA and TMAO | *Desulfovibrio*, *Bacteroides* | Convert choline to TMA | Affects cardiovascular risk |
| Polyphenol metabolism[1,208] | Produces antioxidant and anti-inflammatory compounds | Antioxidant response elements | *Lactobacillus*, *Bifidobacterium* | Metabolize polyphenols | Reduces oxidative stress, inflammation |
| Indole production[209,210] | Impacts immune function and gut barrier integrity | Aryl hydrocarbon receptor | *Escherichia*, *Bacteroides* | Convert tryptophan to indole | Modulates immunity and gut barrier function |
| Methanogenesis[211,212] | Affects gut motility and digestion efficiency | Methanogenesis pathways | *Methanobrevibacter* | Convert $CO_2$ and hydrogen to methane | Modulates gut motility and gas production |
| Hydrogen sulfide production[213,214] | Impacts mucosal integrity and inflammatory responses | Inflammatory signaling pathways | *Desulfovibrio*, *Bilophila* | Produce hydrogen sulfide | Can increase inflammation, adversely affect gut health |
| Lactate utilization[215,216] | Converts lactate to SCFAs, contributing to energy supply | Metabolic fermentation pathways | *Bacteroides*, *Veillonella* | Convert lactate to SCFAs | Supports energy metabolism, gut health |
| Ethanolamine utilization[217,218] | Influences cell signaling and lipid metabolism | Ethanolamine utilization pathways | *Parabacteroides, Escherichia* | Utilize ethanolamine | Modulates lipid metabolism, membrane integrity |
| Nitrate reduction[219,220] | Impacts nitrogen balance and nitric oxide pathways | Nitrate/nitrite reduction pathways | *Lactobacillus*, *Veillonella* | Reduce nitrates to nitrogen compounds | Modulates vascular function and microbial interactions |
| Xenobiotic metabolism[221,222] | Modifies metabolism of dietary and pharmaceutical compounds | Cytochrome P450 pathways | *Bacteroides*, *Escherichia* | Transform xenobiotics | Influences drug metabolism and detoxification |
| Modulation of mucus layer[223,224] | Influences gut barrier and microbial niche | Mucus degradation and re-synthesis pathways | *Akkermansia*, *Bacteroides* | Degrade mucins, produce mucin-derived metabolites | Enhances gut barrier function, microbial balance |
| Energy extraction from non-digestible carbohydrates[225,226] | Provides additional caloric intake through fermentation | Fermentation pathways | *Bacteroides*, *Ruminococcus* | Ferment complex carbohydrates | Contributes to caloric intake, impacts weight management |

*SCFA* short-chain fatty acid, *GPR* G-protein coupled receptor, *FXR* farnesoid X receptor, *TGR5* Takeda G protein-coupled receptor 5, *TMAO* trimethylamine N-oxide, *TMO* trimethylamine oxide.

specific mechanisms, personalized therapeutics can be formulated to improve gut health, offering precise interventions. This comprehension can reveal initial indicators of pathogenic alterations prior to the emergence of systemic manifestations, providing an opportunity for early intervention and the prevention of extensive metabolic problems.

## Intestinal dynamics and adaptability

Intestinal adaptability is crucial for responding to substantial nutritional stress and associated metabolic processes due to diminished absorptive surface, while also being vital to appropriate physiological responses to continuous environmental and dietary stresses. The small intestine demonstrates considerable compartmentalization in structure and function, shaped by nutritional gradients and bacterial abundance. Glutamate functions as a crucial energy substrate for enterocytes, where amino acid absorption and glucose metabolism occur predominantly[9]. The terminals of the villi have elevated expression of proteins involved in fatty acid metabolism and transporters, with analogous zonation observed in mesenchymal cells. Augmentation in food consumption, irrespective of the cause, be it temperature or diet, results in intestinal hypertrophy, which can be mitigated through dietary restriction in humans and mice[10,11]. Germ-free (GF) and antibiotic-treated mice have substantially altered intestinal development due to the significant role of their microbiota in digestion. These changes in intestinal-level metabolic processes due to lack of gut microbes are reflected in the altered extra-intestinal metabolism and neurological phenotype[12,13]. In fact, in mice treated with a broad-spectrum antibiotic cocktail for depleting gut microbes demonstrated a range of alterations including luminal secondary metabolite profile, mucosal metabolic signaling, and colonocyte transcriptome and metabolism[14]. Intestinal adaptations to high-fat diet (HFD) and high-fiber diets, as well as caloric restriction, demonstrate an intricate connection between stem cell proliferation and gut architecture. A high-fiber diet extends the GI tract, whereas a low-fiber diet diminishes it[9]. The specific nutritional composition, comprising medium-chain triglycerides and carbohydrates such as sucrose, affects villus height and intestinal stem cells (ISC) activity[15]. Diets high in sucrose expedite ISC differentiation and turnover, facilitating intestine growth, whereas fructose promotes villus elongation by enhancing cell viability via metabolic pathways[10]. Using intestinal organoid treated with filtered fecal supernatants from term or pre-term infants, Dougherty and team demonstrated that microbial metabolites can promote enterocyte proliferation and maturation[16]. This enhanced cell proliferation, accelerated and more frequent crypt domain formation, and heightened expression of stem cell and Wnt signaling markers, indicating that the varied microbiota in preterm infants generates metabolites that facilitate intestinal epithelial development.

Intestinal cell metabolism is essential for regulating cell division and apoptosis, with the proliferation and differentiation of ISCs and progenitors modulated by several critical signaling pathways. The Wnt-β-catenin pathway is pivotal for intestinal cell specification, enabling Wnt proteins, mostly secreted by mesenchymal and Paneth cells, to trigger signaling in neighboring cells[17]. Through this mechanism, the buildup of β-catenin triggers target genes that modulate the cell cycle, hence influencing ISC activity. Alongside Wnt, Notch signaling influences the commitment of progenitors to either a secretory or absorptive lineage. Dietary cholesterol influences Notch signaling, impacting the differentiation of enteroendocrine cells (EECs) from ISCs[18]. Ketogenic diets enhance ISC proliferation through β-hydroxybutyrate, which activates Notch signaling pathways[19]. Moreover, both HFD and caloric restriction stimulate peroxisome proliferator-activated receptors (PPAR)-α and associated pathways, which produce acetyl-CoAs essential for ketogenesis and supply substrates for energy metabolism, hence supporting intestinal development. PPARα is crucial for lipid metabolism and intestinal development; its deletion leads to compromised intestinal elongation under HFD feeding conditions[10], highlighting the significance of lipid processing in preserving gut architecture. PPARα facilitates fatty acid uptake and engages with perilipin 2, essential for lipid absorption; its expression is vital for the response to dietary lipids. The energy demands for augmenting gut size and sustaining the absorptive surface are considerable. Mice subjected to cold or displaying obesity demonstrate increased activation of metabolic pathways, such as glycolysis and lipid oxidation. Hexokinase-2, a glycolytic enzyme, contributes to intestinal homeostasis, and its deletion has been associated with diminished cell death and inflammatory bowel disorders[20]. The deletion of hexokinase-2, which is upregulated in inflammatory bowel illness, reduces mitochondrial respiration and intestinal cell mortality; however, the genetic deletion of essential metabolic enzymes such as hexokinase-2, phosphoenolpyruvate kinase, and glutamate dehydrogenase does not markedly affect the architecture of the small intestine[21]. Various PPAR isoforms affect distinct intestinal areas, with PPARα correlated with jejunal enlargement and PPARβ/δ associated with duodenal modifications. The transcription factor PRDM16 collaborates with PPARs to modulate fatty acid oxidation and progenitor differentiation in the upper gut[22]. The heterodimerization of PPARs with retinoid X receptors is essential for enterocyte differentiation, significantly influencing villus development and the repair of crypt integrity following injury. PPARs additionally regulate the canonical Wnt pathway by suppressing β-catenin[23], hence influencing intestinal differentiation and surface development. Collectively, these complex signaling networks guarantee the precise translation of metabolic conditions into cellular consequences related to the growth and regeneration of the intestinal lining. Additional examination of these networks may improve our comprehension of intestinal health and the effects of dietary factors on gut structure and function.

The intestinal dynamics and plasticity are also strongly influenced by the luminal microbiota. These microbial influences are likely mediated by the alterations in intestinal metabolomic homeostasis which is observed in animals with depleted gut microbiota[24]. For instance, GF mice have modified gut shape, characterized by diminished total intestinal mass, expanded cecum, shorter and thinner villi, and depleted mucus layers, decreased epithelial cell renewal, and impaired intestinal motility[12]. These animals exhibit digestive abnormalities linked to altered GI enzyme levels and compromised nutrition absorption. Consequently, GF mice exhibit reduced body mass and adiposity compared to normal mice, necessitate a greater caloric intake to sustain equivalent body weight as conventional animals, and require dietary supplementation with vitamins K and B due to their susceptibility to vitamin deficiencies[2,25]. Alterations in microbiota composition by cold exposure are adequate to enhance intestinal surface area and dietary calorie absorption[11]. The transplantation of cold-adapted microbiota results in modified intestinal gene expression that facilitates tissue remodeling and inhibits apoptosis, an effect that is attenuated by the co-transplantation *Akkermansia muciniphila*, during the transfer of cold microbiota[26]. Indeed, others have shown that depletion of gut microbiota in mice results in elongated intestines, reduced transit speed, elevated permeability, and loss of enteric neurons[27]. The microbiota restoration in GM mice reversed these alterations.

These evidences collectively indicate that intestinal plasticity is essential for adjusting to nutritional stress and preserving homeostasis, shaped by compartmentalization controlled by nutrient gradients and bacteria. Diverse signaling pathways, such as Wnt/β-catenin, Notch, and PPAR, govern intestinal stem cell proliferation and differentiation, with metabolic processes like fatty acid oxidation substantially influencing gut size and villus development, while microbiota significantly modulates intestinal structure and function, impacting morphology, motility, and nutrient absorption.

## Sensing of luminal metabolites

All biological activities are driven by metabolism, which derives energy from food. Metabolites generated in the gut from various microbial metabolic processes alter host-specific responses. Dispersed across the GI tract, EECs serve as the primary cell type that detects nutrients and triggers subsequent signaling, functions of which are closely modulated by the gut microbes. EECs have significant variations in hormone expression and secretion, which include the secretion of 20 different types of gut hormones[28]. The host

G-protein coupled receptors (GPCRs), essential for connecting the diet-microbiota-metabolites axis, have predominantly been attributed to the intestinal-metabolite sensing mechanism[29]. For example, SCFA receptors such as GPCR41 and GPCR43, medium and long-chain fatty acid receptors GPCR40 and GPCR120, and the chenodeoxycholic acid receptor farnesoid X receptor (FXR) expressed in intestinal cells and other tissues have been associated with the modulation of various host-specific metabolic processes, including the inhibition of insulin secretion, reduction of non-esterified fatty acid release, suppression of bile acid synthesis, and regulation of fatty acid metabolism[5]. A distinct category of metabolite sensors, known as aryl hydrocarbon receptors (AhR), assimilates environmental, dietary, and microbial signals to regulate immunometabolic homeostasis. Butyrate may function as an AhR ligand; nonetheless, tryptophan metabolites are the primary AhR ligands[30]. Intestinal AhR impairment[31] or the absence of AhR ligand[32] leads to enhanced mucosal inflammation and barrier failure, whereas the reciprocal interaction between microbiota and AhR may regulate FA and glucose metabolism in host tissue[33]. Recent findings suggest that modifying AhR-dependent signaling in the intestine may diminish cholesterol absorption facilitated by the GI cholesterol transporter Niemann-Pick C1-like 1 by inhibiting the transcriptional function of sterol regulatory element-binding protein-2[34].

Nutrient sensing, the method via which the body detects and responds to nutrients, is significantly influenced by the gut bacteria. Certain bacteria in the gut microbiota may directly detect chemicals such as glucose, amino acids, and fatty acids[28]. The bacteria produce signaling molecules in the presence of these nutrients, potentially altering the host's metabolic processes. Other bacteria in the gut microbiota indirectly sense nutrients by producing metabolites derived from those nutrients. The functions of a plethora of gut microbes are dependent on the quality and quantity of the nutrients present in the intestinal lumen. Several studies underscore the crucial function of gut microbiota in modulating nutrient-sensing processes, highlighting its impact via microbial metabolites, EEC physiology, and bile acid regulation. Microbial metabolites, especially SCFAs, promote the release of GI peptides from EECs[28]. SCFAs are predominantly generated in the distal intestine, but they are also present in the ileum and are recognized for their ability to diminish glucose synthesis through a gut-brain axis. Other metabolites, such as indole, abundant in the small intestine, furthermore modulate the release of glucagon-like peptide-1 (GLP-1), a crucial hormone in glucose metabolism[35]. Pingitore and colleagues conducted a study in which non-diabetic human participants were administered fermentable fibers[36]. Their findings indicated that SCFAs can stimulate intestinal L-cells to release the GLP-1. This illustrates that human gut microbiota can detect and react to changes in luminal metabolites resulting from fiber fermentation, connecting microbial metabolism with host hormone control.

The microbiome also holds the potential to directly modify EEC physiology. For instance, GLP-1-expressing cells from GF and normal mice exhibit distinct transcriptomes, which alter significantly within one day of microbiome colonization[37]. Furthermore, GF animals exhibit modified intestinal expression and altered circulating levels of gut peptides. HFD can elicit a nutrient-insensitive condition in the EECs of zebrafish, contingent upon the presence of gut microbiota; GF zebrafish do not display this modification[38]. Some bacterial species (e.g., *Acinetobacter*), can provoke nutrient-insensitive states, whereas others, particularly those affecting the GPCR120 receptor, influence lipid-induced GLP-1 production[39]. Furthermore, the gut flora alters the bile acid pool, influencing glucose and energy homeostasis. Conjugated bile acids, synthesized in the liver, serve as important signaling molecules that engage with several receptors, including FXR and Takeda G protein-coupled receptor 5 (TGR5)[40]. While the suppression of FXR typically enhances glucose metabolism, its signaling may suppress GLP-1 transcription, hence confounding bile acid signaling dynamics[28]. TGR5 signaling, conversely, promotes GLP-1 secretion, thereby illustrating a complicated interaction between gut microbiota and metabolic control. HFD diminishes the prevalence of *Lactobacillus* spp., which are essential for lipid-sensing functions[41]. The transfer of gut microbiota from HFD-fed mice to chow diet-fed counterparts diminishes their capacity to effectively detect lipids, hence impacting glucose tolerance. Conversely, the administration of *Lactobacillus gasseri* in rats subjected to an HFD can improve lipid sensing and reestablish appropriate bile acid signaling, indicating its potential therapeutic benefits[42]. Collectively, the complex interplay among gut microbiota, nutrient-sensing pathways, and metabolic health highlights the promise of microbiota-targeted strategies in addressing various metabolic diseases.

The gut microbiota generates a variety of metabolites that function as essential signaling molecules, influencing bacterial activity and host-microbe interactions. Acetate, propionate, and butyrate are essential microbial metabolites that in addition to host-centric functions in energy metabolism and immunological control, affect bacterial communities by modifying luminal pH, suppressing pathogenic overgrowth, and regulating quorum-sensing pathways[43]. Butyrate inhibits virulence genes in Clostridium difficile and facilitates commensal colonization by inducing mucosal hypoxia[44,45]. Secondary bile acids, modified by microbial bile salt hydrolases (BSH), function as signaling molecules through receptors such as FXR and TGR5, influencing microbial composition by selectively suppressing pathogens and promoting symbionts like Bacteroides[40,46]. Tryptophan-derived metabolites, such as indole and its derivatives, influence bacterial biofilm formation and pathogenicity through AhR-mediated pathways, concurrently influencing host immunological responses[47]. Furthermore, quorum-sensing molecules, including autoinducer-2 (AI-2), enable interspecies communication, orchestrating bacterial colonization and metabolic functions[48]. Polyamines, such as spermidine, synthesized by Bifidobacterium and Lactobacillus, augment bacterial stress resilience and biofilm development, hence indirectly affecting microbial community stability[49]. Hydrogen sulfide, generated from the metabolism of sulfur-containing amino acids, serves dual functions; facilitating mucosal healing at low concentrations while provoking dysbiosis and inflammation at elevated levels[50]. These metabolites illustrate the reciprocal signaling between the host and microbiota, highlighting their therapeutic potential in modulating microbial ecology to restore equilibrium. Finally, it is to be noted that the understanding of the bacterial inter-species and host-microbiota signaling is still in its infancy. With advancements in omics technology, newer techniques such as metaproteomics[51] can augment protein annotation, refine taxonomic resolutions, and boost the accuracy of bacterial species identification, providing novel insights into host-microbiota interactions.

## Microbiota, gut hormones, and metabolic processes

EECs are distributed along the length of the intestinal epithelium and serve as the major cell type for nutrient sensing and trigger subsequent signaling through the release of gut hormones (Fig. 1). Nutrients and metabolites sensed by EECs activate feedback mechanisms that inhibit postprandial energy surplus by reducing food consumption and endogenous nutrient synthesis. Gut hormones substantially influence metabolic processes, extending beyond the digestive system. The family of peptide hormones termed cholecystokinin (CCK), synthesized by duodenal L-cells, can increase pancreatic enzyme secretion, GI and gallbladder contraction, as well as pancreatic insulin secretion[52]. The incretin group of hormones influences several metabolic processes, including glucose uptake in adipose tissue and muscle, enhanced insulin biosynthesis and secretion via efficient GI glucose sensing, suppression of glucagon secretion, increased lipolysis and fatty acid synthesis in adipose tissue, and reduced hepatic gluconeogenesis[53]. Consequently, GLP-1, secreted by the EEC-L cells, plays a crucial role in gut barrier protection by diminishing mucosal inflammation and enhancing mucin synthesis[54]. A growing body of research suggests that dietary management of the gut microbiota, which affects GLP-1-dependent metabolic pathways, may boost the host's metabolic health[55]. Following fasting and calorie restriction, hormone insulin-like peptide 5 (INSL5) secreted by colonic L-cells is increased[56]. By influencing insulin production and pancreatic β-cell homeostasis, INSL5 may control glucose homeostasis[57]. Intriguingly, new research indicates that colonic INSL5 expression is lowered in GF mice, whereas microbial colonization or supplementing with an HFD increases INSL5 levels, and that INSL5-KO

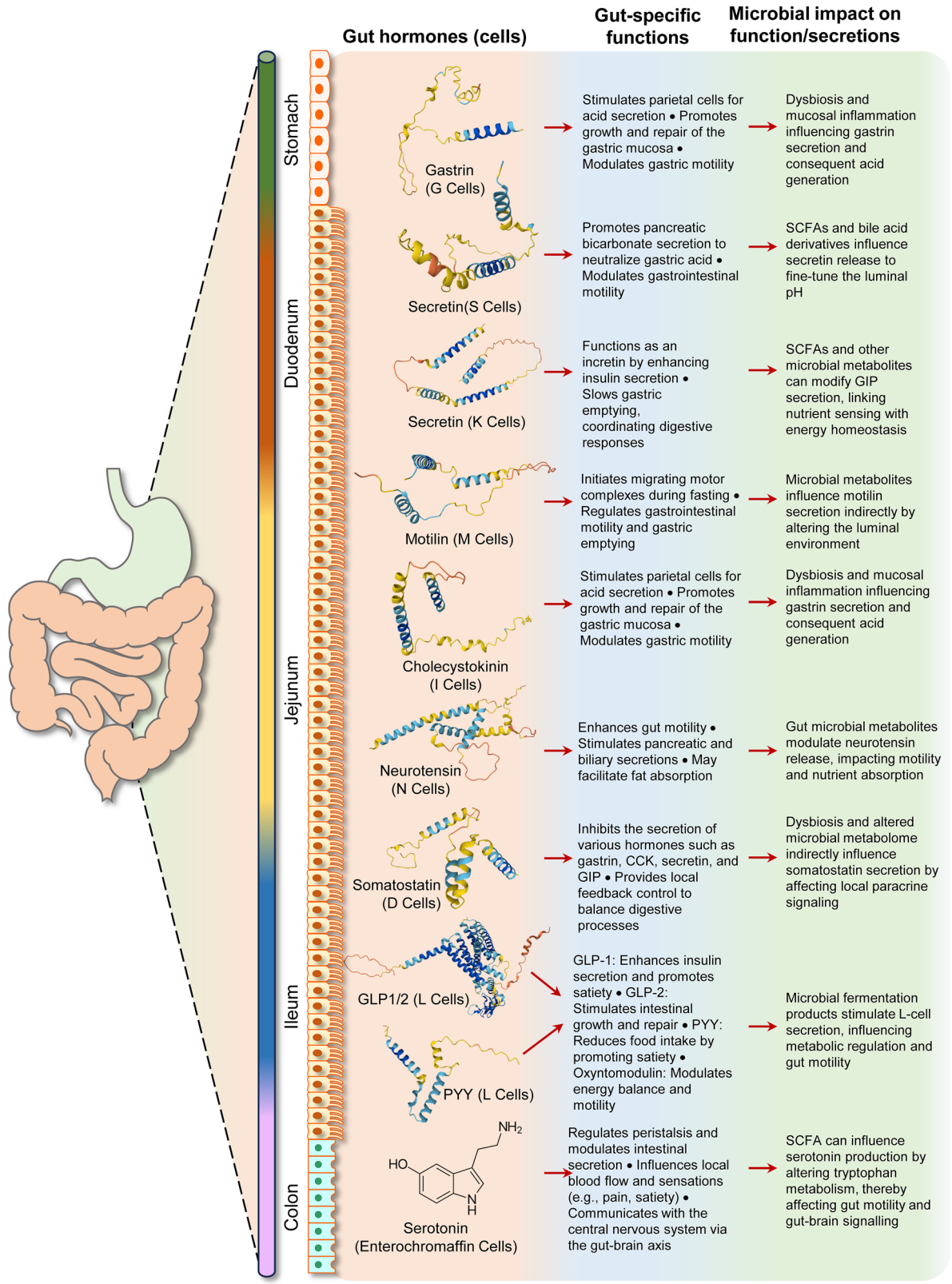


**Fig. 1 | Gut hormones are essential for controlling digestion, nutrition absorption, and energy homeostasis via communicating with numerous organs and systems, including the brain.** They regulate appetite, insulin secretion, and glucose metabolism, playing a crucial role in sustaining metabolic health and preventing disorders such as obesity and diabetes. This figure summarizes the interplay between various gut hormones and microbiota, demonstrating how microbial activity can affect hormone levels and thus influence human health. These interactions are crucial for sustaining gastrointestinal and systemic health. Abbreviation: CCK cholecystokinin, GIP gastric inhibitory peptide, GLP-1 glucagon-like peptide-1, PYY peptide YY, SCFA short-chain fatty acid.

animals have increased insulin tolerance and reduced hepatic glucose production[58]. These findings imply that INSL5 is likely regulated by microbes in order to maintain glucose homeostasis.

Microbiota-derived SCFA can induce the release of incretins, including peptide tyrosine-tyrosine (PYY) and GLP-1, which modulate hunger and glucose metabolism[59]. Gut microbes can generate and regulate the release of hormone-like substances that imitate the actions of host hormones. CCK, a GI hormone that modulates satiety and digestion, exemplifies a molecule that may be generated by specific bacteria[60]. These microbially produced chemicals may interact with gut epithelial cell receptors to modulate gut hormone signaling. Intestinal bacteria may interact with the intestinal cells and modulate the expression of certain genes. This interaction may affect the expression of genes associated with the synthesis, release, or control of GI hormones. Intestinal microorganisms may indirectly affect the synthesis and secretion of gut hormones by altering gene expression[61]. The gut-brain axis is a reciprocal signaling route that enables communication between intestinal microbes and the brain. Gut microorganisms may affect the central nervous system through this interaction, whereas the neurological system governs the generation and secretion of gut hormones. The precise processes of communication along the gut-brain axis are still being studied; nevertheless, it is thought that microbial metabolites and direct neuronal connections between the stomach and brain are crucial factors in these processes.

Finally, certain metabolites exclusive to the gut microbes can also function as endogenous hormones and signal through host-specific receptors to influence the metabolic processes. For instance, melanocortin-like peptide of *E. coli* (MECO-1), synthesized by *E. coli*, is a structural analog of adrenocorticotropin and melanocyte-stimulating hormone (MSH) in mammals. Mice exposed to a lethal endotoxin or those with sepsis exhibit reduced mortality due to inhibition of pro-inflammatory cytokine production in macrophages by MECO-1[62]. Caseinolytic peptidase B (ClpB), a peptide derived from *E. coli*, functionally mimics α-MSH and promotes satiety by enhancing the firing rate of pro-opiomelanocortin-expressing neurons in the hypothalamus[63]. Individuals with eating disorders, such as anorexia nervosa, exhibit elevated levels of ClpB in their bloodstream[64].

Over the years, there have been limited clinical studies providing mechanistic insights on the impact of gut microbiota on gut hormone levels. In one study, correlations between the gut microbiome and blood GLP-1 level were identified in Chinese patients with gestational diabetes mellitus (GDM), with Sutterella, Oscillibacter, and Bifidobacterium significantly positively correlated with blood GLP-1 level[65]. Zouhal et. al. reported that supplementation of glycine and branched-chain amino acid (BCAA)) impacts gut barrier and the microbiome composition in chronic hemodialysis patients in association with alterations in the gut hormone levels[66]. Specifically, mixed linear regression models demonstrated significant impact on GLP-1, CCK, and PYY levels, and BCAA supplementation reduced the abundance of Lacticaseibacillus paracasei and Bifidobacterium dentium. Cani & group assessed the effects of 2-week prebiotic treatment on satiety and gut hormones in a randomized, double-blind experiment including 10 healthy individuals[67]. Prebiotics elevated GLP-1 and PYY levels, decreased hunger and postprandial glucose responses, indicating a correlation between augmented microbial fermentation and markedly improved appetite control. Another study investigated whether microbial metabolite propionate stimulates the secretion of PYY and GLP-1, while assessing its immediate effects on energy intake and hormone levels in a randomized controlled cross-over study, alongside its long-term implications on weight gain in a 24-week randomized controlled trial involving overweight adults[68]. Data showed that propionate triggered the release of PYY and GLP-1, with both acute (10 g) and chronic (10 g/day) administration. Supplementation with inulin-propionate ester elevated hormone levels, decreased energy consumption, and markedly curtailed weight gain, abdominal adiposity, hepatic lipids, and the reduction in insulin sensitivity in overweight individuals. These data collectively indicated that dietary propionate can prevent weight gain by impacting the release of gut hormones. On the other hand, Byrne and colleagues examined the impact of increased colonic propionate production on brain anticipatory reward responses during the examination of food images, hypothesizing that increased propionate would reduce both reward responses and *ad libitum* calorie intake by promoting the release of anorexigenic gut hormones[69]. Collectively, the data from 20 healthy nonobese subjects indicated that elevated colonic propionate production diminished striatal blood oxygen level-dependent signals, especially in reaction to high-energy foods, indicating that propionate mitigates reward-driven eating behavior through striatal pathways, irrespective of alterations in plasma PYY, GLP-1, glucose, or insulin levels. Collectively, these data indicated that gut microbiota directly, or through the production of SCFAs, can impact the gut hormone levels, thereby influencing health and disease outcomes.

## Luminal oxygen tension and metabolic processes

Oxygen tension markedly affects intestinal metabolic, physiological, molecular, and cellular activities, with hypoxia (decreased oxygen availability) being a critical factor (Fig. 2). Under hypoxic settings, the gut modifies its metabolism, frequently transitioning from oxidative phosphorylation to glycolysis[70]. This adaptation facilitates cellular activities and survival, influencing processes such as nutrition intake, barrier integrity, and immune response, underscoring the significance of oxygen management. The gut microbiota is reportedly involved in intestinal hypoxia, although the precise mechanisms and relationships remain inadequately elucidated. The maintenance of the mucus layer that protects the intestinal epithelium is a vital function of gut bacteria. The mucus layer functions as a barrier between the intestinal cells and the gut microbes[1]. Disruption of the mucus layer may enhance microbial translocation and interaction with intestinal tissue, thereby affecting oxygen levels. Research indicates that alterations in the composition of gut microbiota may compromise the mucus layer and diminish its ability to protect against hypoxia[71]. Additionally, gut microbes may metabolize and utilize oxygen as part of their metabolic processes. An imbalanced composition of the gut microbiota, characterized by an excess of oxygen-utilizing bacteria, may elevate the oxygen consumption inside the intestinal lumen. The heightened microbial oxygen consumption may contribute to localized gut tissue hypoxia. Intestinal tissue may become inflamed due to dysbiosis. Localized hypoxia may arise from compromised blood flow and oxygen transport to the affected area due to inflammation[70]. Moreover, the inflammatory response may undermine the integrity of the intestinal barrier, exacerbating tissue hypoxia. It has been demonstrated that SCFAs exert positive effects on GI health[72]. Butyrate enhances blood circulation to the intestinal mucosa and promotes the maintenance of oxygen levels. Alterations in the composition of gut microbiota that result in diminished SCFA synthesis may influence the oxygen equilibrium within the intestines.

The distal portion of the tubular intestine becomes increasingly hypoxic. The preservation of the anaerobic bacterial population, the regulation and segregation of mucosal immunometabolic activities, and the energy metabolism are all contingent upon intestinal oxygen tension. These actions require the sustained generation of ATP by oxidative phosphorylation. The counter-current blood flow results in a reduction of partial $O_2$ pressure from the tip of the villus to the crypt, decreasing from 10 $pO_2$ to 85 $pO_2$[73]. The basolateral $Na^+/K^+$-ATPase and mucosal sodium absorption, which regulate fluid absorption, may influence the metabolic regulation of intestinal epithelial blood flow[74]. $Na^+/K^+$-ATPase derives the majority (79%) of its energy from oxidative phosphorylation[75]. Experimental inhibition of the $Na^+/K^+$ pump markedly reduces oxygen consumption in the human colon[76]. The intestinal synthesis of SCFAs, which influences energy equilibrium at the epithelium level, indicates a modification in energy metabolism affecting mucosal tissue dynamics. IECs may utilize glucose generated from acetyl CoA by the oxidative phosphorylation of pyruvate under typical conditions. The oxidative metabolism of pyruvate is suppressed by heightened expression of pyruvate dehydrogenase kinase; nevertheless, colonocytes may preferentially utilize butyrate as the principal energy source that inhibits histone deacetylation in response to elevated luminal SCFA production[77]. Consequently, in the presence of increased

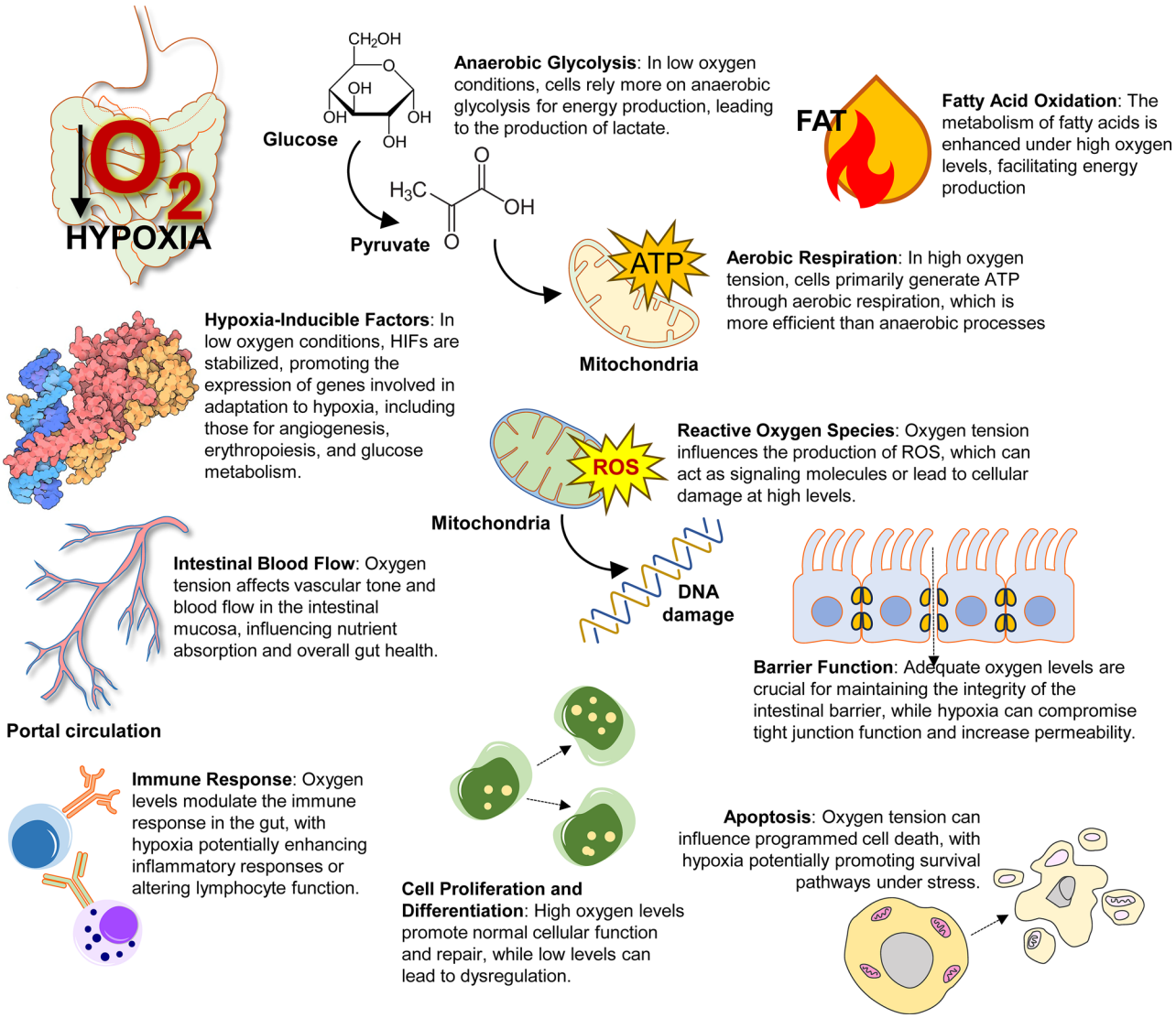


**Fig. 2 | Oxygen tension and hypoxia in the intestine are essential for regulating the equilibrium between oxidative metabolism and glycolysis, affecting nutritional absorption, barrier integrity, and immunological function.** Optimal oxygen levels facilitate an anaerobic environment conducive to beneficial gut bacteria, while hypoxia-induced signaling pathways regulate crucial protective genes necessary for gut homeostasis. This figure summarizes the major metabolic, molecular, cellular, and physiological activities at the gut that are impacted by luminal oxygen level.

luminal butyrate, butyrate is transformed into acetyl CoA, essential for oxidative metabolism. Elevated mucosal expression of hypoxia-inducible factor (HIF), which transcriptionally regulates genes associated with gut barrier protection, results in greater levels of butyrate that are essential for sustaining intestinal immunometabolic balance[78]. By diminishing the DNA binding capacity of hypoxia response elements in Caco-2 and IEC-6 cells, contradictory findings suggest that butyrate suppresses the transcriptional activity of HIF-dependent hypoxia-sensitive genes[79]. Nonetheless, hypoxia-induced stabilization of HIF is essential for intestinal homeostasis owing to its regulatory role in the transcription of barrier-protective genes, mucin secretion, antimicrobial peptide synthesis, nucleotide signaling, iron metabolism, and metabolic genes including hexokinase, lactate dehydrogenase, pyruvate kinase, aldolase, phosphofructokinase, and phosphoglycerate kinase, among others[73,80]. In luminal hypoxia, oxygen-deprived cells require sustenance to fulfill their elevated metabolic energy demands. The intestine's highly proliferative stem cells, transit-amplifying progenitor cells, and post-mitotic differentiated cells continually perform high energy-consuming regenerative, digestive, secretory, and absorptive tasks[70]. Intestinal fatty acid oxidation is now recognized to be substantially regulated by the PR-domain-containing 16 (PRDM16) proteins, which are essential for the survival and proliferation of transit-amplifying progenitor cells[22]. PRDM16 expression exhibited a strong correlation with gut microbiota in subcutaneous adipose tissue obtained from morbidly obese patients post-gastric bypass surgery, indicating that gut bacteria may influence PRDM16-mediated regulation of human energy metabolism and insulin sensitivity[81].

Clinical studies related to the impact of gut microbiota on the hypoxia have been limited and are mostly associated with individuals residing in high altitude geolocations. For instance, in one study, the gut commensal Blautia has been concluded to play pivotal role in the hypoxic-adaptation in individuals residing in high altitude regions[82]. Šket and colleagues reported that physical inactivity, rather than hypoxia alone, is the principal driver of gut inflammation and disrupted bowel function[83]. In this study, hypoxia with minimal exercise did not adversely affect gut health; however, the combination of hypoxia and bedrest exacerbated inflammatory indicators and constipation. Consistently engaging in even little physical exercise in hypoxic environments aids in sustaining gut function and microbial equilibrium. In another study, based on the fact that individuals residing at high altitudes have a reduced prevalence of type 2 diabetes mellitus, Shepherd and colleagues investigated the impact of repeated nocturnal normobaric hypoxic exposure on glycemic regulation, appetite, gut microbiota, and

inflammation in persons with type 2 diabetes mellitus[84]. Data showed that despite severe nocturnal hypoxia over 10 nights not inducing substantial alterations in gut microbiota or inflammation, there were lower microbial diversity and enhanced insulin sensitivity. In similar lines, others showed that mild intermittent hypoxia exposure could modify gut microbiota composition in overweight and obese individuals[85]. Specifically, mild intermittent hypoxia exposure modified the gut microbiota composition in overweight/obese males, enhancing certain butyrate-producing anaerobic taxa. Diversity remained constant, however declines in *Christensenellaceae* and *Clostridiaceae* were noted. The alterations in microbial composition correlated with variations in insulin sensitivity and metabolic indicators, indicating a connection among hypoxia, microbiota, and host metabolism. Finally, Karl and colleagues investigated the interactions among diet, the gut microbiota, and host responses to weight loss in individuals in high altitude[86]. At high altitude with prevalent hypoxia, the composition of gut microbiota was mostly unaltered by macronutrient consumption but exhibited correlations with host responses. A higher abundance of Prevotella and increased microbial diversity were associated with more severe gastrointestinal distress. These data indicate that gut microbiota may affect individual variability in high altitude hypoxia responses, irrespective of diet.

## Redox-associated metabolic responses

By the age of 12-mo, commensals anaerobes (e.g., *Bifidobacterium, Bacteroides*, *Clostridium*) are colonized 100–1000 times more frequently than aerobic bacteria due to a substantial increase in the populations of facultative bacteria throughout infancy (e.g., *Enterobacteriaceae*, *Enteroccocus*, *Streptococcus*)[87]. Although the intestinal lumen is deprived of oxygen, maintaining redox balance is essential for preserving mucosal cellular integrity and supporting metabolic and immunological functions. In contrast, oxidative damage induced by inflammatory infiltrates has been associated with the initiation and progression of various chronic illnesses, such as inflammatory bowel disease (IBD), diabetes, and intestinal malignancies. Generally, GI overproduction of reactive species with oxidative potential can be attributed to both exogenous factors (e.g., smoking, diet, alcohol, and drugs) and endogenous factors (e.g., cellular respiration, respiratory burst, xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase (COX), transition metals, nitric oxide synthase (NOS), and myeloperoxidase (MPO), which can collectively lead to pathological conditions[88]. Severe oxidative stress at the intestinal mucosa may lead to the loss of tight junction proteins through processes including the thiol oxidation, nitration, phosphorylation, and carbonylation of cytoskeletal proteins, tight junction proteins, and intracellular regulatory proteins[89]. Under normal circumstances, a dense mucus layer and antimicrobial peptides inhibit direct interaction between gut epithelia and luminal microorganisms; yet, both in vitro and in vivo studies demonstrate that enteric commensals can rapidly stimulate the generation of free radicals upon contacting epithelial cells[90]. Antioxidant treatment (e.g., n-acetylcysteine) can mitigate mucosal oxidative stress while enhancing the population of gut commensals (e.g., *Akkermansia*), hence alleviating mucosal inflammation and '*leaky gut*' in mice with modified gut microbiota[91].

Enzymes related to glutathione, such as glutathione reductase, glutathione peroxidase, glutaredoxin, and glutathione-S-transferases are pivotal in the antioxidant defense of the mucosa[87]. The epithelium possesses millimolar levels of glutathione, essential for absorption, detoxification, and maintenance of the mucus layer[92]. Mucus-associated glutathione may mitigate mucosal damage by promoting the conjugation and detoxification of reactive electrophiles, carcinogens, and pharmaceuticals[93]. The oxidative process may be employed by neutrophils and macrophages at the mucosa to inhibit invading bacteria from the lumen. The concentration of reactive oxygen species (ROS) in the ileum is modulated by bacterial load and can inhibit bacterial reflux from the distal intestine through inducible NOS and NADPH oxidase 1, resulting in the production of nitric oxide and superoxide radicals[94]. The gut microbiota may affect intestinal glutathione levels regardless of food intake. Although possessing diminished quantities of its precursor methionine, it was demonstrated that inoculating GF mice with fecal samples from human neonates resulted in jejunal glutathione levels comparable to those of conventional mice[95]. Oxidative responses are associated with inflammation. In severe combined immunodeficient mice having colitis, it was demonstrated that gut inflammation is preceded by a glutathione/glutathione disulfide redox imbalance, challenging the notion that oxidative stress is a subsequent reaction to inflammation[96]. Lipopolysaccharide (LPS) binding to Toll-like receptor 4 (TLR4) on immune cells not only activates nuclear factor NF-κB (NF-κB) but also generates ROS that activate NADPH oxidase. Additionally, mice deficient in cytoprotective ROS signaling or devoid of antioxidant proteins such as sulfiredoxin, peroxiredoxin 2, and 3, or macrophages, exhibit exacerbated inflammation when exposed to LPS[97]. Furthermore, administering certain microbial metabolites to mice, such as urolithin A, can enhance barrier function by upregulating AhR and nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent signaling[98].

Previous studies have demonstrated that enteric commensal bacteria stimulate the production of ROS in the intestine, which may facilitate epithelial regeneration, improve gut barrier integrity, and support recovery from dextran sulfate-induced colitis in mice, in contrast to the detrimental effects of oxidative stress on the mucosa[99]. Oral supplementation of catalase-producing *Lactococcus lactis* can reduce colon cancer generated by 1,2-dimethylhydrazine in mice[100], *L. rhamnosus* GG can mitigate acetaminophen and ethanol-induced hepatic oxidative stress in murine and *Drosophila* liver via activating Nrf2-dependent cytoprotective and redox homeostatic mechanisms[101]. Other *Lactobacillus* strains have demonstrated the presence of specific oxidative stress resistance genes, including thioredoxin reductase, catalase, and NADH dehydrogenase[102]. Nonetheless, an elevation in commensal small intestinal bacteria may intensify oxidative injury to the mucosa. *Lactobacillus*, due to its capacity to generate substantial amounts of ROS and induce NFκB-dependent inflammation, can lead to mucosal injury through overgrowth and mucosal invasion. Dextran sodium sulfate-induced colitis may be treated more rapidly with genetically engineered *L. johnsonii* that generates $H_2O_2$ within physiological limits, while excessive $H_2O_2$ production can lead to bacteremia[103]. Since ROS is likely an advanced form of cellular communication[104], the preservation of redox homeostasis is essential for efficient host-microbiota interaction. Changes in redox homeostasis may potentially lead to mucosal injury.

Similar results are also obtained from clinical studies, especially from patients with IBD, that show impact of gut microbes on the mucosal oxidative stress. For instance, Cao et al. demonstrated that the commensal microbiota of IBD patients generate genotoxic chemicals that cause mucosal oxidative damage[105]. A novel class of microbiome-derived genotoxins, termed indolimines, generated by Morganella morganii, which was predominant in patients with colorectal cancer. These chemicals induced oxidative DNA damage, and only strains that produced indolimines facilitated tumor development in experimental mice. Interestingly, the emergence of Crohn's Disease (CD) in children with Chronic Granulomatous Disease (CGD) during the initial phase of life indicates that alerted phagocyte ROS production may be a crucial mechanism in the pathogenesis of mucosal inflammation[106,107]. Genome-wide Association Studies (GWAS) of Crohn's Disease (CD) have associated processes such as autophagy and ROS generation with disease development and severity[108,109]. In children with very early onset (VEO, <age 6) IBD, rare missense mutations in the CYBB, NCF1, NCF2, and NCF4 genes, which govern neutrophil NADPH oxidase activity and ROS generation, have been documented[110,111]. Longitudinal multi-omics investigations of stool samples from individuals with IBD have shown reduced amounts of SCFA levels and purine deprivation, necessary for glutathione formation and maintenance of a redox microenvironment[112]. In line, a plethora of studies have demonstrated that prophylactic interventions that favorably modulate the gut microbiome can reduce systemic oxidative stress by improving the cytoprotective enzymes[113–115]. However, detailed discussion on extra-intestinal effects is beyond the scope of current review.

## Intestinal lipid metabolism by microbes

The gut microbiota is frequently termed a *'metabolic organ'* because of its involvement and impact on energy metabolism, the metabolism of dietary components, and its modulation of the host's nutritional, physiological, metabolic, and immune systems, as well as the host's behavior, motor functions, and endocrine activities[116]. The abundance of Bacteroidetes in obese patients is generally lower, whereas Firmicutes higher compared to lean controls[117]. In lean individuals, a decrease in Firmicutes relative to Bacteroidetes was linked to fecal calorie loss. An increase in Bacteroidetes abundance correlated with weight loss but not with alterations in dietary calorie intake over time[118]. Alternatively, some studies have attributed obesity risk to reduced abundances of Actinomycetes (*Bifidobacterium* spp.) or Verrucomicrobia (*A. muciniphila*) instead of the Firmicutes or Bacteroidetes phylum[119]. A reciprocal association between intestinal lipid metabolism and gut microbiota has been established, corroborated by studies indicating that an HFD augments the gut microbiota's capacity to harvest energy from the diet[120] and that GF mice are remain lead despite feeding HFD[121]. Mice deficient in perilipin 2 (Plin2), a protein associated with fat storage, exhibited modified microbiota, namely an elevated Firmicutes to Bacteroidetes ratio, even when subjected to a chow diet[122]. Rats administered antibiotics and subjected to microbiota alteration have diminished mucosal apolipoproteins, compromised intestinal lipid absorption, and decreased chylomicron formation[123]. Gut bacteria are essential for adapting to variations in dietary lipids due to their role in intestinal lipid breakdown and absorption[124]. Regardless of dietary fat intake, GF mice receiving microbiota from HFD-fed counterparts demonstrate enhanced lipid absorption in the intestine. Prior study indicates that about 50% of fecal lipids originate from microbial sources[125] and that the majority of them are cis/trans saturated and unsaturated fatty acids. Phospholipase C-active intestinal bacteria generate diacylglycerols (DAG) from phospholipids which may affect intestinal signal transduction and other cellular processes since it can act as a cellular messenger to activate protein kinase C[126]. The metabolic activities of gut bacteria, such as lactate consumption, propionate metabolism, succinate production and decarboxylation, sulfate reduction, acetate utilization, and butyrate synthesis, may be associated with fatty acid metabolism[127].

Particularly, certain Firmicutes possess the enzyme IsmA, which catalyzes the conversion of cholesterol into cholestenone and coprostanol[128], while Bacteroides can sulfonate cholesterol, influencing serum cholesterol levels in mice via a sulfotransferase enzyme gene cluster[129]. This cluster also sulfates steroid hormones and sterols, including analogs of vitamin D3. Bacteroidetes generate and biotransform dietary sphingolipids through glycan-degradation enzymes, decomposing compounds such as gangliosides and supporting immunity[130]. *Bifidobacterium*, despite the absence of sphingolipid synthesis enzymes, use sphingolipids for dihydroceramide formation and contain enzymes for sphingolipid degradation[131]. Enzymatic activities of the microbiome affect sphingolipid species and enhance gut barrier integrity. Certain bacterial enzymes can biotransform polyunsaturated fatty acids prior to their entry into host metabolic pathways, hence impacting the host lipid metabolism. Bifidobacterium and Lactobacillus species possess CLA-HY, an enzyme that catalyzes the conversion of linoleic acid to conjugated linoleic acid, subsequently yielding a molecule that interacts with GPR40 and GPR120 to provide an anti-inflammatory signal and restrict the conversion of linoleic acid to downstream metabolites[132]. CLA enzymes are prevalent in human microbiomes and may influence the heterogeneity in susceptibility to metabolic syndrome and obesity. Dietary polyunsaturated fatty acids can be saturated by prevalent gut microbial enzymes, hence reducing the number of double bonds and their oxidative potential[133].

The mechanism through which gut microbes modulate intestinal lipid metabolism has been predominantly attributed to the gut microbiota-derived metabolites that impact the absorption and metabolism of dietary lipids. Among those metabolites, the effects of SCFA on host lipid metabolism have been studied extensively. These results collectively suggest that SCFA enhances β-oxidation and lowers lipid accumulation, which contributes to insulin sensitivity and lower fat accumulation in the adipocytes. This signaling primarily occurs through GPR43 and GPR109A[134]. Microbes-derived secondary bile acids are essential for lipid metabolism as they emulsify dietary lipids, thereby facilitating their digestion and absorption. Gut microbes contain BSH, enzymes that transform conjugated bile acids into free bile acids, that impacts intestinal cholesterol uptake and turnover, leading to decreased serum cholesterol levels[135]. The reduced solubility and absorption efficacy of free bile acids, in contrast to their conjugated counterparts, may lead to lipid malabsorption[136]. This could result in decreased hepatic and blood triglyceride levels. Cholesterol may co-precipitate with free bile acids, facilitating its elimination through feces and further reducing serum cholesterol levels[137]. This BSH activity can assist in sustaining reduced cholesterol levels, hence promoting cardiovascular health.

Data from human studies related to intestinal-level lipid metabolism and gut microbiota are mostly confined within the domain of SCFA. Haghikia and group investigated the impact of propionate on the intestinal metabolism of cholesterol in relation with atherosclerosis[138]. The results indicated that the total and LDL cholesterol levels were reduced by propionate supplementation. Participants with elevated baseline LDL cholesterol levels displayed substantial reductions in their cholesterol levels during this 8-week trial. Others conducted a double-blind, randomized controlled study to investigate the chronic effects of milk polar lipid consumption on lipid metabolism and intestinal microbiota[139]. Milk phospholipids (PL) significantly reduced fasting and postprandial plasma cholesterol levels and enhanced lipid cardiovascular disease markers, such as the ApoB/ApoA1 ratio, over a 4-week period. The maximum dose of milk PL resulted in a decrease in intestinal chylomicron particles and an increase in the loss of coprostanol (cholesterol metabolites) in the feces, independent of changes in the microbiota and SCFA. The acute ingestion of milk PL in ileostomy patients resulted in a decrease in cholesterol absorption and an increase in ileal cholesterol efflux. These results suggest that milk PL has a beneficial impact on lipid metabolism without affecting the composition of the gastrointestinal microbiota. Based on the fact that antibiotics disrupt the gut microbial community, the impact of amoxicillin and vancomycin on cholesterol metabolism was investigated in obese, pre-diabetic men[140]. Cholestanol, marker of cholesterol absorption, exhibited a negative correlation with plasma secondary bile acids, while lathosterol, a marker of cholesterol synthesis, exhibited a positive correlation. Compared to placebo, the fasting plasma secondary bile acid levels decreased significantly after vancomycin treatment. Nevertheless, neither amoxicillin nor vancomycin had an effect on plasma lipid levels, cholesterol, or non-cholesterol sterol levels.

## Intestinal carbohydrate metabolism by microbes

Humans largely depend on gut microbes for the degradation and energy harvesting of complex polysaccharides. Unlike humans, gut microbes are equipped with an array of carbohydrate-catabolizing enzymes that facilitate the carbohydrate metabolic process. For instance, the genome of gut commensal *Bacteroides thetaiotaomicron* codes for more than 250 glycoside hydrolases, highlighting the evolutionary necessity for adaptation to optimize the consumption of resistant starch and other fibers in the carbohydrate-rich human diet[141]. Once completion of the primary degradation, microbiota-generated monosaccharides can give rise to pyruvate and energy[142]. Acetate (C2), propionate (C3), and butyrate (C4) are the predominant SCFAs in the human body that have been studied extensively (Fig. 3). SCFAs are generated through the microbial fermentation of complex carbohydrates like resistant starch and dietary fiber. They influence various metabolic pathways and contribute to IR and obesity[4]. Consequently, nutrition may influence the composition and function of the gut microbiota, the production of SCFAs, and metabolic outcomes. Ten percent of the host's daily energy requirements may derive from diverse metabolites generated by microbial metabolic processes[143]. The anaerobic fermentation of dietary fibers, refractory starches, and undigested proteins by specific gut bacteria, including *Faecalibacterium prausnitzii*, *Roseburia* spp., and *Butyricicoccus pullicaecorum*, generates SCFAs such as butyrate, acetate, and propionate[144]. The host may encounter numerous beneficial effects from this

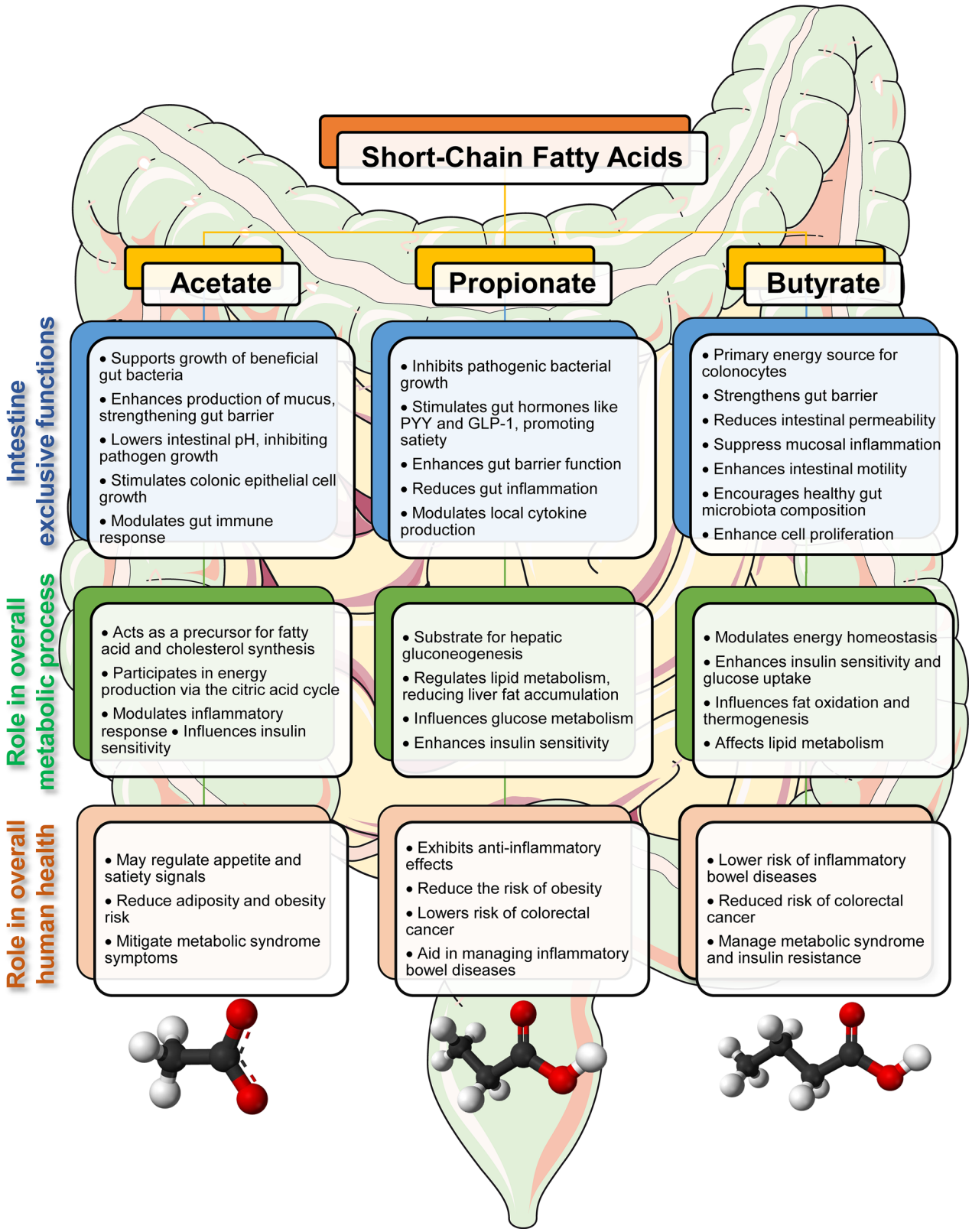


**Fig. 3 | Short-chain fatty acids, generated through the fermentation of dietary fibers by gut microbiota, are essential metabolites that promote intestinal health by strengthening gut barrier integrity and regulating immune responses.** They contribute to systemic metabolic processes, affecting glucose metabolism and mitigating inflammation, thus aiding in the prevention of diseases such as obesity and colon cancer. This figure summarizes the specific functions of acetate, propionate, and butyrate in the intestine, their contributions to overall metabolism, and their effects on human disorders, providing an overview of their importance in health.

SCFA. Phytochemicals may confer health benefits by promoting butyrogenic bacteria in the colon or augmenting their capacity for SCFA metabolism; SCFA, especially butyrate, has been associated with the reduction of weight gain[145]. SCFA signaling through GPCR may influence a wide array of actions, including the secretion of ghrelin, insulin, GLP-1, PYY, neutrophil migration, inflammasome formation, and the establishment of a pro-inflammatory milieu[146]. SCFAs, particularly at the intestinal epithelium, can regulate immune homeostasis by influencing signal transduction pathways, activating dendritic cells and macrophages, differentiating T-cells, and modulating the chemotaxis and proliferation of other immunocompetent cells, thereby maintaining the equilibrium of pro- and anti-inflammatory cytokines. SCFA can enhance the epithelial HIF-dependent response, leading to the transcriptional upregulation of barrier protective genes such as claudin, occludin, zonula occludens, mucin, and defensins, thereby diminishing the gut-to-systemic translocation of bacterial pyrogenic metabolites, including LPS.

Unutilized excess SCFAs are translocated through the hepatic vein to the liver, where they may serve as precursors for gluconeogenesis, lipogenesis, and cholesterologenesis[147]. Propionate is gluconeogenic, while acetate and butyrate are lipogenic. The propionate to acetate ratio is considered significant, as propionate may impede the conversion of acetate into cholesterol and fat[148]. Low amounts of alcohols, including as ethanol, propanol, and 2,3-butanediol, may be produced as byproducts of carbohydrate fermentation. Proteobacteria are recognized for their proficiency in alcohol production and are notably correlated with dysbiosis in IBD, a condition that predisposes individuals to NAFLD[149]. Collectively, The microbial break-down of carbohydrates in the human gut entails a sophisticated assortment of enzymes generated by microbiota, which metabolize dietary polysaccharides that human cells cannot effectively degrade, thereby facilitating the release and utilization of monosaccharides essential for metabolic pathways such as the Embden-Meyerhof-Parnas, Entner-Doudoroff, or Pentose phosphate pathways for energy and ATP production. This microbial fermentation produces SCFAs including acetate, propionate, and butyrate, which are crucial for host metabolic health, providing energy, exerting immunomodulatory effects, and potentially affecting processes such as gluconeogenesis, lipogenesis, and overall glucose homeostasis.

## Intestinal protein metabolism by microbes

Microbial protein metabolism exhibits greater variability than other macronutrients, affected by food processing methods, macronutrient ratios, transit durations, and the origin of the protein (plant or animal)[150]. This difference influences the amino acid contents accessible to gut microbes, leading to a range of fermentation by-products. While protein catabolism in the GI tract can yield deleterious molecules such as amines, phenols, indoles, and sulfurous substances, not all fermentation byproducts are poisonous; SCFAs are prevalent and advantageous end products[50]. The adverse impacts on hosts may arise from particular metabolic mechanisms rather than from protein catabolism itself. Microbial amino acid catabolism commences with either deamination, yielding carboxylic acid and ammonia, or decarboxylation, resulting in an amine and $CO_2$[151]. Ammonia, capable of inhibiting specific biological processes, is frequently rapidly ingested by microorganisms or transformed by host cells into less deleterious chemicals[152]. Deamination is common, resulting in the formation of SCFAs and the utilization of intermediates such as pyruvate in energy pathways. Certain *Clostridia* spp. are capable of conducting Stickland reactions, yielding ATP directly from amino acids and creating branched-chain fatty acids (BCFAs), which are indicators of protein catabolism[153]. Despite the association of BCFAs, such as isovalerate and isobutyrate, with health hazards, they can also positively affect glucose and lipid metabolism and act as energy sources for intestinal cells. Certain members of the genera *Bacilli*, contain a specific branched-chain keto acid dehydrogenase complex that generates energy from the oxidized forms of branched-chain amino acids, resulting in the formation of BCFAs[152].

Gut microbes, including Bifidobacteria, Clostridia, Lactobacilli, Enterococci, Streptococci, and Enterobacteriaceae, play a predominant role in the decarboxylation of basic amino acids into amine by-products[154]. The catabolism of arginine results in the production of chemicals such as agmatine, putrescine, spermidine, and spermine, which are essential to numerous physiological functions. Agmatine diminishes fatty acid metabolism, potentially facilitating weight management and hormonal equilibrium associated with obesity[155]. It also demonstrates anti-inflammatory and neuroprotective characteristics, functioning via several receptor pathways. Excessive agmatine may reduce polyamine levels, requiring a balance to prevent adverse effects under normal settings. Putrescine, spermidine, and spermine promote the proliferation of IEC, mitigate oxidative stress, extend cellular lifetime, and preserve gut integrity by augmenting tight junction proteins and mucus secretion[156]. Furthermore, the conversion of arginine to glutamate and subsequently to γ-aminobutyric acid (GABA), an essential inhibitory neurotransmitter, influences neurological health by alleviating depression, anxiety, and stress responses[157]. Specific gut bacteria that produce GABA demonstrate potential in alleviating visceral pain and improving immunological function. Histidine catabolism generates histamine, which, despite its recognized inflammatory activity, can suppress pro-inflammatory cytokines and avert bacterial translocation, while also participating in neurotransmitter activities that affect cognition and motor control[158]. Microbial catabolism of lysine yields cadaverine, which, although not extensively understood, may enhance histamine toxicity and is associated with ulcerative colitis at elevated doses[150]. The catabolism of sulfur-containing amino acids, cysteine and methionine, yields hydrogen sulfide and methanethiol. Numerous bacterial species possess enzymes capable of degrading these amino acids, including those from Proteobacteria, Bacilli, Clostridium, and Bifidobacterium[152,159]. Hydrogen sulfide can undergo methylation to form the less toxic methanethiol and subsequently dimethyl sulfide as a detoxifying process[160]. Methanethiol can revert to hydrogen sulfide, be oxidized to sulfate, and be consumed by sulfate-reducing bacteria, so contributing to the intestinal sulfur cycle.

The breakdown of aromatic amino acids in the GI tract produces several metabolites that have differing physiological effects. For instance, tryptophan metabolism produces tryptamine and indoles. Tryptamine, a neurotransmitter, modulates intestinal motility and immunological function through interactions with receptors such as indoleamine 2,3-dioxygenase and the AhR[161]. Specific Firmicutes, including *Ruminococcus gnavus*, synthesize tryptamine, establishing a connection to IBD[162]. Indole, a metabolite of tryptophan, fortifies the intestinal barrier and mitigates inflammation via receptor interactions, enhancing satiety and affecting bacterial communication[47]. Although advantageous in low quantities, excessive indole may adversely affect the liver and exacerbate chronic renal disease. Tyrosine metabolism of certain Firmicutes (e.g., *Enterococcus faecalis*) yields tyramine, phenols, and p-coumarate[163]. Tyramine influences blood pressure and the neurotransmitter serotonin, but may induce hypertension and migraines. Phenolic metabolites, such as phenol and p-cresol, can harm the intestinal lining, with p-cresol associated with genotoxicity and immune response impairment[150]. The breakdown of phenylalanine yields phenylethylamine and trans-cinnamic acid. Phenylethylamine, functioning as an endogenous amphetamine, can elevate mood and energy levels, although excessive consumption presents hazards[164]. It is associated with Crohn's disease. Several of the aromatic amino acid metabolic pathways could be seen in Clostridium and Peptostreptococcus species, indicating that aromatic amino acid metabolites are crucial in health and illness. Collectively, although many amino acid fermentation products are advantageous, the detrimental effects of sulfurous, basic, and aromatic amino acids persist as a danger due to their pro-inflammatory and cytotoxic properties. Each of these compounds has substantial consequences for GI health, inflammation, brain function, and disease management.

## Microbiota impacting micronutrient metabolism

Micronutrients are essential for cellular processes, including immunology and energy synthesis, while commensal gut bacteria significantly contribute to the biosynthesis, metabolism, and absorption of these micronutrients. The gut microbiota functions as a bioreactor within the intestines, affecting

nutrient bioavailability by converting substances into either beneficial or detrimental metabolites. Microbiota generates substantial quantities of vitamins, including vitamin K and B vitamins, and facilitates the absorption of minerals such as iron and calcium[144]. Engevik and colleagues conducted a study assessing 512 gut microbial strains from 6 phyla for their ability to biosynthesize folate[165]. It was shown that merely 13% of these strains, all belonging to the *Proteobacteria* phylum, contained the entire genetic apparatus for folate production. A further 39% of organisms, predominantly from Firmicutes, Actinobacteria, and Verrucomicrobia, exhibited an incomplete capacity for folate synthesis[165]. This provides a glimpse of the complex involvement of gut bacteria in the production and availability of micronutrients. Others investigated the biosynthetic potential of gut microbiota and determined that the majority of the B-vitamins were synthesized by these microorganisms[166]. For these vitamins to be advantageous to the body, synthesis must transpire prior to the absorption regions of the intestines. B12-producing bacteria in the colon may not enhance B12 bioavailability, as absorption takes place in the ileum. Escherichia coli facilitates the metabolism of vitamin B9 by improving its bioavailability and generating tetrahydrofolate, while simultaneously serving as a conduit for vitamin B12[167]. Certain Firmicutes, found using 16S sequencing, are associated with serum vitamin D levels, modulated by butyrate-producing bacteria that augment vitamin D receptor expression[168]. Furthermore, gut microbiota can negatively influence vitamin bioavailability, seen by enhanced vitamin E bioavailability following antibiotic therapy and diminished vitamin C absorption attributable to lipopolysaccharides produced by bacteria[169].

The gut microbiota is essential for mineral metabolism, influencing their absorption and facilitating their release from dietary components. Colonic microorganisms synthesize phytases that facilitate the liberation of calcium, magnesium, and phosphate from phytic acid in plants[170]. The prevalence of *Lactobacilli* is decreased in iron-deficient females, indicating a potential correlation between this genus and iron absorption[171]. Lactobacillus plantarum improves iron absorption by elevating hydrated ferric iron levels via lactic acid fermentation[172]. The interplay between gut bacteria and mineral availability is apparent in bone health. Vitamin D consumption facilitates calcium absorption via calbindin D9k, while microbiota improves calcium bioavailability under conditions of low intake[173]. Prebiotics enhance gut microbiota to augment calcium absorption, hence enhancing bone density in animal models. SCFA generated by bacteria lower cecal pH, enhancing calcium solubilization and absorption[174]. The intake of probiotics sustained serum calcium levels in pregnant women, whereas treatment with Enterococcus faecium elevated phosphate levels in bones and enhanced butyrogenic bacteria[175]. These findings highlight the substantial influence of the gut microbiota on mineral absorption and bone health via many routes.

It is noteworthy that micronutrient deficiency can also lead to physiological defects in association with distinct alterations of the gut microbiota. For instance, in mice with 4-wk dietary supplementation deficient in zinc, folate, iron, vitamin A, and vitamin B12 resulted in impaired glucose and insulin tolerance[176]. In addition, these mice showed altered gut microbial profile in association with greater metabolic preference for simple sugars compared to complex sugars. Vitamin A deficit significantly alters microbial communities by influencing gene expression; it promotes the proliferation of particular species, such as *Bacteroides vulgatus*, which may adapt by upregulating specific transcription factors to mitigate retinol scarcity[177]. Zinc deficiency can hinder the growth of helpful commensals due to its function as a vital cofactor in several enzymatic processes needed for bacterial metabolism, whereas folic acid deficiency may hinder DNA synthesis and repair in bacteria, hence further disrupting microbial activity[178]. Others suggested that dietary iron deficiency can lead to serious metabolic dysfunction with altered gut microbiota composition in contradictory manner[179]. With certain bacterial taxa (e.g., *Dialister, Helicobacter*) depleting in response to supplementation, whereas others (e.g., *Lachnospiraceae*) decrease under both deficiency and supplementation, underscoring inconsistent trends across research. These inconsistencies likely stem from diversity in experimental models (human versus rat), host genetics, age, and methodological techniques, rendering general conclusions difficult despite occasional logical patterns. Collectively, the micronutrient deficiencies, especially during the early phase of life, could result in reduced microbial diversity and richness, compromise the intestinal barrier, and diminished metabolic capacity of the microbiota.

## Intestinal drug metabolism

The metabolism of oral medications and xenobiotics is affected by gut microbial enzymes. The cytochrome P450 enzyme class is primarily accountable for the initial-phase metabolism of numerous therapeutically important medicines and dietary phytochemicals that can modify the mucosal immune equilibrium. The bioavailability of the unmetabolized parent medication is enhanced when the cytochrome P450 reductase (CPR) gene, responsible for encoding NADPH-cytochrome P450 reductase, is selectively downregulated in the intestinal epithelium[180,181]. The metabolism of nifedipine and lovastatin is markedly diminished. Furthermore, the first-pass clearance of pravastatin, a cholesterol-lowering statin not processed by Cytochrome P450, remains unaltered by the inhibition of CPR, demonstrating that CPR is only linked to metabolism rather than intestinal drug disposition[181]. The predominant cytochrome in the intestinal epithelium is cytochrome P450 family 3 subfamily A (CYP3A), and the application of ketoconazole to selectively inhibit CYP3A has resulted in enhanced oral bioavailability of many immunosuppressive drugs[182]. Intestinal CYP1A1 expression in mice, whether at baseline or upon activation, is contingent upon the recognition of pathogens by TLR-2[183]. Chronic inflammation in the colon may inhibit the expression of CYP3A. The expression of CYP3A and P-glycoprotein, crucial for intestinal drug transport and metabolism, is reduced in mice with inflammatory colitis[184]. The interaction between the host and the microorganism may influence certain host-dependent cytochrome P450-mediated drug metabolism. The expression of CYP1A1, CYP2E1, and CYP3A9 in the intestinal epithelium was consequently diminished in mice administered probiotic microorganisms such as *Lactobacillus casei* or *Escherichia coli* Nissle 1917[185,186]. This impaired the host's ability to metabolize drugs. Treatment with the broad-spectrum antibiotic clarithromycin in humans inhibits intestinal CYP3A4 and CYP3A5 activity, independent of alterations in protein expression[187]. Reports indicate that *Lactobacillus acidophilus* supplementation in human volunteers diminishes fecal α-glucuronidase, nitroreductase, and azoreductase activity[188]. Oral supplementation of prebiotics (e.g., *Lactobacillus casei*, *Bifidobacterium adolescentis*) can diminish fecal activities of α-glucuronidase, α-glucosidase, tryptophanase, and urease, leading to advantageous outcomes such as cancer regression and enhanced immunological functions[189,190]. In addition to the GI tract, GF mice exhibit notable changes in cytochrome P450-related gene expression in the liver, characterized by a 200% rise in Cyp4a and a 57% drop in Cyp2b[191]. These alterations demonstrate the influence of gut microbiota on the host's xenobiotic metabolism system. Finally, the metabolism of orally consumed cardiac glycosides could also be differentially altered by the gut microbiota, resulting in diverse health outcomes[192,193]. A well-studied classic case of toxic digoxin to non-toxic dihydrodegoxin conversion is dictated by the glycoside metabolizing Cgr operon in the gut microbe *Eggerthella lenta*[194]. Figure 4 provides a comprehensive summary of the role of gut bacteria on the intestinal drug metabolism processes.

## Limitations of current techniques and future prospects

Although the gut microbiome-centric fundamental and applied research has been booming in the last two decades, several limitations in current studies and neglected areas necessitate further investigation to progress the line of research. For instance, the matter of causality vs correlation in host-microbe interactions is critically lacking scientific advancement. Although several research indicate correlations between microbial metabolites (e.g., SCFAs, bile acids) and metabolic outcomes, causal links are not sufficiently proven. For example, while SCFAs such as butyrate improve gut barrier integrity, the majority of evidence is from GF murine models or in vitro systems. Human studies are constrained, and interventions frequently lack controls for confounding variables, like nutrition, genetics, or baseline

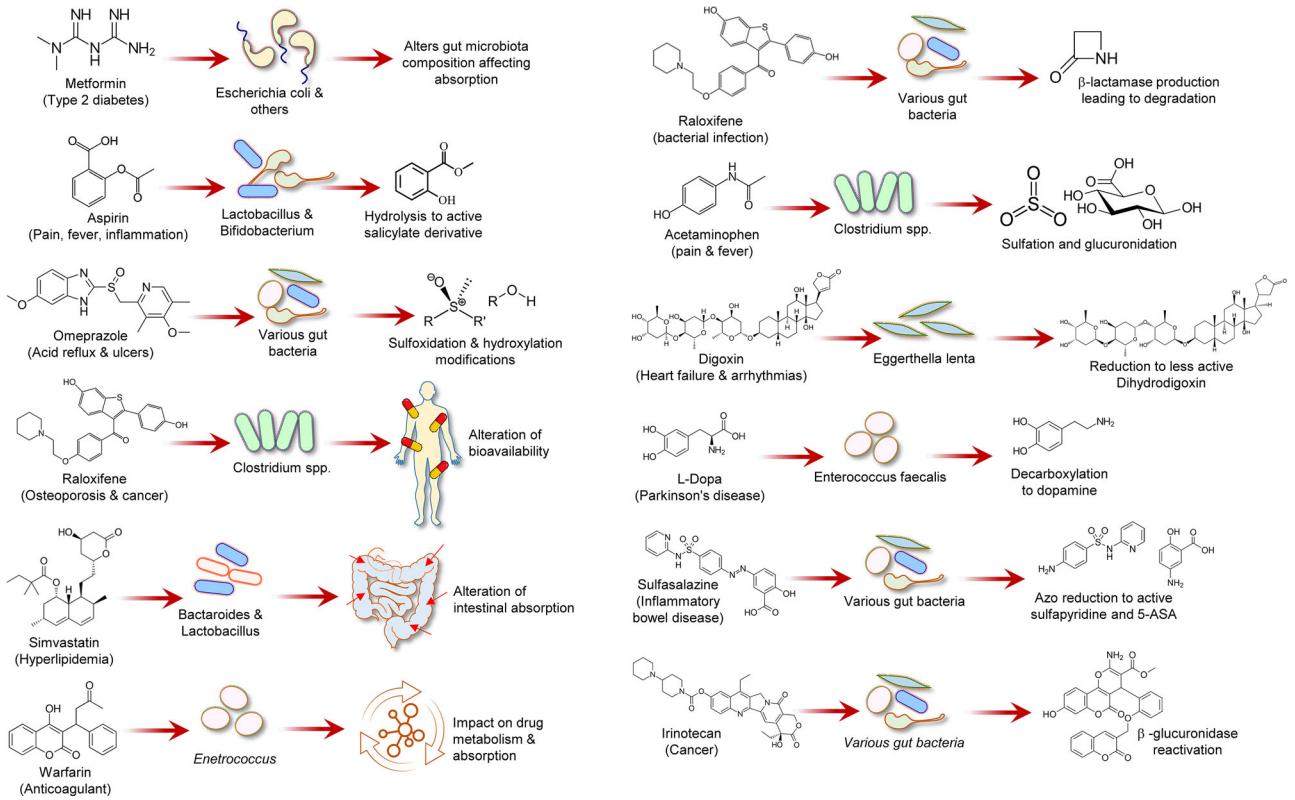


**Fig. 4 | The gut microbiota significantly influences the metabolism of pharmaceuticals and xenobiotics by modulating enzyme activity, including cytochrome P450, hence impacting medication bioavailability and efficacy.** Changes in gut microbial composition might influence drug metabolism, potentially affecting therapeutic outcomes and resulting in diverse health repercussions. This figure summarizes the gut microbiota-dependent metabolism of various drugs, the mode of mechanism, and gut microbes associated with the process.

microbiome composition. Future research should emphasize human trials utilizing longitudinal designs and gnotobiotic models to elucidate cause-effect linkages. Moreover, the inter-personal gut microbial variability and contextual influences on overall health and long-term disease risk remain underappreciated. The metabolic impact of gut microbiota is extremely individualized and strongly influenced by host genetics, lifestyle, and environmental factors. Nevertheless, research often neglects this heterogeneity. Despite Bacteroides and Firmicutes being associated with obesity, their functions differ among groups, indicating strain-specific or context-dependent influences. Customized microbiome profiling, in conjunction with metabolomics, may clarify how individual variations influence responses to nutritional or pharmacological interventions. Essential pathways, including AhR activation by tryptophan metabolites and PPAR-mediated lipid metabolism, are identified as pivotal regulators of intestinal homeostasis. The specificity of microbial ligand-receptor interactions remains ambiguous. Do structurally analogous metabolites (e.g., indole derivatives) engage overlapping or different pathways, and what happens under nutrient/metabolite-depleted conditions? Advanced methodologies like as single-cell transcriptomics and receptor knockout models are essential for delineating these precise pathways and to provide mechanical insights.

The translational obstacles in drug-microbiome interactions is another domain that requires extensive mechanistic studies. This review emphasizes microbial enzymes, such as cytochrome P450, that modify drug bioavailability; nonetheless, the majority of evidence is derived from preclinical models. The relevance to humans is constrained by microbial diversity and confounding variables such as polypharmacy. The bidirectional influence of pharmaceuticals on microbiota composition remains inadequately investigated. Longitudinal studies examining microbiome-drug interactions in patient groups could enhance precision medicine approaches. Form the gut microbial point of view, majority of current research provide end-point data while the temporal and spatial dynamics of microbial communities remain underexplored. Contemporary research frequently regards the gut microbiota as a fixed entity, overlooking its dynamic characteristics. Diurnal variations in microbial activity or geographical disparities, such as oxygen gradients in the crypt-villus axis, may significantly affect metabolic outputs. Spatial transcriptomics and real-time metabolomic profiling may elucidate these spatiotemporal intricacies. The inadequately researched metabolite families and associated pathways present an additional difficulty to address. For instance, although SCFA and bile acids predominate in the literature, lesser-known metabolites (e.g., branched-chain fatty acids, polyamines) and microbial activities (e.g., vitamin K2 production, sphingolipid metabolism) are inadequately addressed. Their functions in immunological regulation and neuroendocrine signaling give significant opportunities for exploration. Since gut microbial studies are highly dependent on technical and methodological advancements, overcoming the methodological constraints could facilitate a better understanding of gut-level host-microbe interaction and its impact on overall health. While culturing the whole gut microbial community is a challenge due to its anaerobic nature, advancement in culturomics techniques could bring better understanding of the gut microbial dynamics. Dependence on 16S rRNA sequencing constrains functional understanding, whereas metabolomic analyses frequently do not differentiate between host- and microbe-derived metabolites. Integrated multi-omics methodologies, synthetic microbial consortia, and organoid-based systems may address these deficiencies. Undertaking mechanistic studies utilizing gene-editing technologies (e.g., CRISPR) to confirm the roles of microbial genes in metabolic processes, development of targeted probiotics or phage therapy that influence the gut-level metabolic activities, and integrating host-microbe interactions utilizing organ-on-chip devices to replicate intestinal complexity could be some of the exciting avenues in deciphering the gut-level host-microbiota interaction and to harness the power of gut microbes to achieve optimum health.

A greater reliance on animal studies poses considerable limitations in comprehending intestine-specific metabolic mechanisms, primarily owing to interspecies variations in gut physiology, microbiota composition, and metabolic pathways. Although animal models offer controlled settings for examining metabolic relationships, they frequently do not accurately reflect the intricacies of human intestinal metabolism[195]. Differences in gut microbiome diversity among species can profoundly affect metabolic results, resulting in inconsistencies when applying findings to human health. Moreover, germ-free and antibiotic-treated animal models frequently discussed in this review demonstrate modified intestinal growth and metabolic processes, hence confounding the extrapolation to human systems[196]. The absence of human studies constrains our comprehension of intestine-specific metabolic pathways, especially in pathological circumstances where host-microbe interactions are crucial. Progress in human-relevant models, including organoids and in vivo human research[197], is essential to close this gap and yield more precise insights into metabolic control and therapeutic interventions. Collectively, by resolving these deficiencies, future research can evolve from mere descriptive correlations to pragmatic insights, facilitating the development of microbiome-targeted treatments for metabolic disorders.

## Conclusion

The complex and dynamic interaction between the human gut and its microbiota significantly affects host metabolism, immunity, and overall health. The gut functions not just as a conduit for nutrient absorption but also as a dynamic ecosystem where various bacterial populations enable and influence metabolic processes. This encompasses the transformation of complex carbohydrates into absorbable forms, the production of essential metabolites such as SCFAs, and the control of immunological and hormonal responses. The disturbance of this delicate balance can result in a wide range of diseases, including metabolic syndromes, inflammatory disorders, and cancers. The gut microbiota functions as a crucial regulator of intestinal metabolic equilibrium. It achieves this in many ways, including modulating the expression of host genes related to metabolism and promoting microbial fermentation activities. SCFAs, essential metabolic byproducts, serve many functions, including aiding energy equilibrium, regulating immunological responses, maintaining gut barrier integrity, and affecting systemic metabolic pathways. These roles demonstrate the ability of gut microbes to influence not only GI health but also systemic health, linking it to the etiology of illnesses such as obesity, diabetes, and colorectal cancer. Considering the crucial significance of the microbiome in health and disease, future opportunities in this field involve utilizing the gut microbiota for translational applications such as in the field of improved drug development and personalized medicine, better understanding of intestinal host-microbe interaction related to metabolic diseases, and development of medications targeting intestine-specific metabolic pathways. This comprehension could also facilitate the creation of targeted and personalized interventions such as prebiotics, probiotics, and dietary strategies that specifically influence the gut microbiome to improve health and prevent or manage chronic diseases. Advanced analytical tools and computational models are crucial for delineating the intricate interactions within the gut microbiota. These technologies may facilitate the identification of biomarkers for the early diagnosis of diseases associated with dysbiosis and provide insights into personalized medicine strategies customized to individual microbiome profiles. Further, translational research is essential for converting discoveries from gut microbiome investigations into therapeutic applications. This entails the formulation of microbiome-centric nutritional strategies and the identification of certain bacterial strains that may be utilized as innovative therapies. Comprehending the impact of dietary constituents and pharmacological drugs on gut microbial communities would enhance the management of chronic disorders. Finally, intestine-specific metabolomics may identify distinctive metabolic fingerprints linked to certain illnesses, assisting in the development of biomarkers and early disease diagnosis. These biomarkers may be used to track illness development and discover diseases early, resulting in earlier treatments and better results.

## Data availability

No datasets were generated or analysed during the current study.

Received: 26 January 2025; Accepted: 6 May 2025;
Published online: 10 June 2025

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## Acknowledgements

Funding received from the Indian Council of Medical Research (IIRPIG-2024-01-00034) is thankfully acknowledged.

## Author contributions

P.D. conceived the idea, J. performed the initial literature search and wrote the first draft, and P.D. finalized the manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

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