Gut microbiota, specifically, their composition, metabolites, and signaling, are associated with both systemic and local metabolic reprogramming. Systemic metabolic reprogramming is linked to the development and progression of diabetes, liver diseases, inflammation, obesity, and cancer.\(^1\)\(^-\)\(^7\) Local metabolic reprogramming, particularly within intestinal tissues, has emerged as a hallmark of intestinal pathobiology seen with Inflammatory Bowel Disease (IBD) and colon cancer.\(^2\)\(^-\)\(^7\)\(^-\)\(^10\) This special issue of *Gut Microbes* features review manuscripts and original research findings related to microbiota-driven systemic and local metabolic reprogramming with several major diseases, as depicted above.

Type 2 diabetes is characterized by dysbiosis in gut microbiota, which is recognized as a potential cause of insulin resistance.\(^1\)\(^,\)\(^11\)\(^,\)\(^12\) Studies using germ-free mice demonstrate that a lack of gut microbiota is protective against diet-induced diabetes.\(^13\) Bacterial lipopolysaccharides may leak from the gut lumen into portal circulation resulting in the activation of inflammatory response and consequent insulin resistance.\(^14\) Further, deficient signaling from the receptor of a bacterial product known as TLR5 contributes to aberrant microbiota and insulin resistance in mice.\(^15\)\(^,\)\(^16\) The transfer of these aberrant microbiota from TLR5-deficient mice to the gut of wild-type, germ-free mice also initiates insulin resistance.\(^15\)\(^,\)\(^16\) Similarly, findings in human cohorts demonstrate that patients with Type 2 diabetes have altered microbiota composition.\(^17\)\(^,\)\(^18\) Studies transplanting fecal microbiota or by administering probiotics positively impacted patients with Type 2 diabetes.\(^19\)\(^-\)\(^21\) Collectively, these animal models and clinical studies demonstrate that the modulation of gut microbiota could offer an effective approach for diabetes management, as reviewed in this issue by Adeshirlarijaney and Gewirtz.\(^1\)

Liver metabolic disease associated with alcohol abuse has recently been characterized by changes in gut microbiota.\(^3\)\(^,\)\(^4\) Individuals who abuse alcohol have an overgrowth of gut bacteria and alterations in their composition.\(^22\)\(^,\)\(^23\) Schnabl’s lab original study demonstrates that alcohol consumption increases bacterial presence in the intestinal mucosa and, with the progression of liver metabolic disease, increases bacterial translocation to mesenteric lymph nodes and the liver.\(^24\) This novel concept led Dr. Schnabl to perform a comprehensive microbiome analysis of intestine and liver in ethanol-fed mice.\(^25\) They showed that chronic ethanol consumption changes the alpha diversity of microbiota in the ileum and the liver. This effect is largely driven by an increase in the production of gram-negative bacteria, phyla-mediated endotoxins, and Prevotella in ileum and liver. These findings demonstrated that bacterial translocation to the liver, e.g. liver microbiota, due to alcohol-mediated changes of microbiota in the distal intestinal tract may drive liver metabolic disease.

Gut microbiota metabolize dietary fatty acids before they are absorbed and changes in microbiota composition lead to an imbalance in these metabolites that could facilitate metabolic disorders, inflammation, and tumor growth.\(^26\) Specifically, Hosomi et al. show that imbalances in the composition and production of fatty acid metabolites are critical in driving two major intestinal diseases, IBD and colon cancer.\(^2\) Further, with respect to IBD, patients have significantly elevated systemic lipid levels, mesenteric fat accumulation, and intracellular lipid accumulation.\(^27\)\(^,\)\(^28\) These elevated lipids can drive inflammation, and their blockade in mouse models ameliorates intestinal inflammation.\(^29\) Moreover, human colon cancer tissue highly expresses a substantial number of regulators of lipid metabolism, several of which can predict survival in colon cancer patients.\(^30\)\(^,\)\(^31\) Also, sphingolipids regulators and their pathways contribute to colonic tumorigenesis and, as such, are both potential targets for chemoprevention.\(^32\) Further, increased intracellular
lipids, in the form of lipid droplets, facilitate inflammatory and growth responses in human and mouse colon.33–37 These fatty acid-derived lipid mediators may drive intestinal inflammatory and tumorigenic demands by providing structural, energetic, and bio-synthetic precursors for tissue repair and growth.

Gut microbiota elicit intracellular metabolic alterations in local intestinal cells. The process is prominent in mitochondria, which are organelles essential to metabolic energy production and cell signaling.38–40 Certain microbiota has a positive effect on mitochondrial metabolic function by controlling PGC1α, a master regulator of mitochondrial biogenesis, leading to increased energy production.41 As reviewed by Jackson and Theiss, metabolic reprogramming of mitochondria is critical in the progression of IBD and colon cancer.9 In IBD-affected tissues, mitochondrial genes expression is decreased, leading to energy depletion.42–45 There is also an association between active bacterial signaling and reduced mitochondrial energy function, as demonstrated by comprehensive bioinformatics analysis of IBD transcriptomes conducted by Ruiz et al.46 By generating a transcriptional signature unique to intestinal cells with reduced mitochondrial energy production (Mito-0), Ruiz et al. demonstrated that bacterial TLR4 and NOD2 transcriptional signatures are strongly associated with the Mito-0 signature in inflamed IBD transcriptomes. Further, dysfunction in mitochondrial metabolism and signaling are also associated with cancer progression.38,39,47 Altered gut microbiota composition creates mutations in mitochondrial DNA; it also influences nuclear gene expression and methylation in the intestinal cells, thereby affecting oncogenes, tumor suppressors, and signaling pathways associated with tumor growth.48–51 Future studies are needed to better understand how bacterial-to-mitochondrial signaling enhances intestinal homeostasis and pathobiology within IBD and tumorigenesis.

In conclusion, aberrant gut microbiota composition, which also includes their products, metabolites, and signaling, is associated with metabolic reprogramming in diverse systemic and local pathobiology. The role of microbiota is highlighted by studies related to diabetes, metabolic changes in liver mediated by excess alcohol consumption, IBD, and colonic tumorigenesis.1,2,8,25,46 Forthcoming accumulation of scientific evidence of microbiota-mediated metabolic reprogramming will lead to a comprehensive understanding of different human pathobiology and targeting the gut microbiota-metabolism axis could offer an effective approach in the management of many diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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