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Expanding Role of Gut Microbiota in Lipid Metabolism

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Abstract

Purpose of review—This review highlights recent advances in the emerging role that gut microbiota play in modulating metabolic phenotypes, with a particular focus on lipid metabolism.

Recent findings—Accumulating data from both human and animal studies demonstrate that intestinal microbes can affect host lipid metabolism through multiple direct and indirect biological mechanisms. These include a variety of signaling molecules produced by gut bacteria that have potent effects on hepatic lipid and bile metabolism and on reverse cholesterol transport, energy expenditure, and insulin sensitivity in peripheral tissues. Additionally, host genetic factors can modulate the abundance of bacterial taxa, which can subsequently affect various metabolic phenotypes. Proof of causality for identified microbial associations with host lipid-related phenotypes has been demonstrated in several animal studies but remains a challenge in humans. Ultimately, selective manipulation of the gut microbial ecosystem for intervention will first require a better understanding of which specific bacteria, or alternatively, which bacterial metabolites, are appropriate targets.

Summary—Recent discoveries have broad implications for elucidating bacterially-mediated pathophysiological mechanisms that alter lipid metabolism and other related metabolic traits. From a clinical perspective, this newly recognized endocrine organ system can be targeted for therapeutic benefit of dyslipidemia and cardiometabolic diseases.

Keywords

gut microbiota; lipid metabolism; metabolic homeostasis

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Conflicts of Interest

None.

Introduction

It has become widely appreciated that our gut symbionts play integral roles in human health since perturbations of this bacterial community or the products they can produce have been associated with increased susceptibility to a variety of diseases (see Figure). The first indications of these associations were for colitis and inflammatory bowel disease, but altered gut microbial composition or function has now been established in the development of cardiometabolic phenotypes, including obesity and related abnormalities [1–6], and atherosclerosis [7]. There is also evidence that the microbiota can even be a potential contributor to risk of neurobehavioral conditions, such as autism [8]. In this review, we focus on recent studies that indicate an emerging role for gut microbiota in modulating lipid metabolism.

Characterization of Gut Microbial Diversity

The human intestinal tract is home to at least 1000 distinct species of bacteria, which collectively number over 100 trillion organisms. This diverse ecosystem is shaped by early life events but can evolve over time through interactions between its constituents as well as with exogenous factors or those that are endogenous to the host. Until recently, characterization of the gut microbiome relied mostly on conventional culture-based microbiological techniques, which was a major hindrance since the vast majority of bacteria in the gut are not readily amenable to cell culture. However, advances in next generation genomic technologies now allow us to identify and classify gut bacterial composition in an unprecedented manner. One widely used approach has typically involved in-depth sequencing of the variable regions of bacterial 16S rRNA genes to determine the diversity and proportion of bacterial taxa within the microbial community [9]. Based on the sequence data obtained, microbial richness and diversity are then organized into operational taxonomic units (OTUs). Although more challenging, recent studies have also begun to characterize microbial communities through unbiased metagenomics analyses, which involves untargeted shotgun sequencing of all genetic material recovered from the intestine or feces [10].

Both 16S and metagenomic analyses have revealed that the human gut is mostly comprised of a common core of bacteria from two major phyla, *Firmicutes* and *Bacteriodetes*, with the remainder of the gut microbiota being remarkably diverse. This diversity often includes less abundant representation from the phyla *Proteobacteria*, *Verrumicrobia*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria*, as well as the domain *Archaea* [11]. It is also important to note that the human gut microbiome can also be dynamic and altered dramatically, for example, by antibiotic use, but less so by age, host genetics, chronic dietary patterns, and other environmental exposures [12–17].

Association of Gut Microbiota with Lipid Metabolism

Early studies comparing germ free versus conventionally raised mice first supported a role for gut microbes in both affecting host energy metabolism and modulating lipid levels [18]; however, the design of these early studies did not permit identification of candidate microbes

involved in promoting the observed phenotypic changes in conventionalized (microbe colonized) mice. Given the known clinical correlation between obesity, related metabolic disorders, and dyslipidemia, it is possible that the observed associations between gut bacterial taxa and lipid levels are mediated through effects on BMI or other metabolic disturbances. This notion is supported by a recent analysis in a population-based cohort that not only confirmed previously known associations between obesity and certain bacterial taxa, such as *Akkermansia*, *Christensenellaceae*, and *Tenericutes* [19, 20], but also demonstrated that some of the associations with microbial composition were shared between BMI and levels of triglycerides and high-density lipoproteins [••21]. Importantly, however, these analyses revealed microbial taxa whose proportions were associated with lipids independent of BMI as well, including novel associations with *Eggerthella*, *Pasteurellaceae*, and *Butyricimonas*. Surprisingly, only weak relationships were noted between microbial variation and total cholesterol or low-density lipoprotein cholesterol levels, suggesting that gut bacteria affect specific aspects of lipid metabolism and/or distinct classes of lipoproteins. Taken together, these observations provide new avenues for validation and follow up studies.

Biological Mechanisms through which Gut Microbes May Affect Lipid Metabolism

As with any gut microbiota study that is associative in nature, such as those in humans, a major challenge is elucidating the underlying biological mechanisms and proving whether the associations are due to a causal relationship. In this regard, evidence from animal studies supports the notion that the gut microbiome can mechanistically impact host lipid levels. For example, certain facultative and anaerobic bacteria in the large bowel produce secondary bile acids from the pool of bile salts secreted into the intestine (Figure). A small fraction of these bacterially derived bile acids is absorbed into the bloodstream and can modulate hepatic and/or systemic lipid and glucose metabolism through nuclear or G protein-coupled receptors (GPCRs), such as FXR or TGR5, respectively [22–24].

Another potential mechanism through which gut microbes could affect lipid metabolism may involve fermentation of nondigestable carbohydrates. Humans are not capable of breaking down many common forms of complex carbohydrates, whereas a subset of anaerobic bacteria found in the cecum and proximal colon can ferment several compounds, such as pectins, gums, hemicelluloses, and galactose-oligosaccharides [25]. One class of metabolites produced by these bacteria are short chain fatty acids (SCFAs), which can subsequently be metabolized by the host or alternatively act as hormones (Figure). SCFAs, such as acetate, propionate, and butyrate, are known to regulate intestinal immune homeostasis and serve as an energy source for colonic epithelial cells. However, SCFAs have been shown to have metabolic benefits as well, which are mediated, in part, through induction of intestinal gluconeogenesis [26]. SCFAs are also absorbed from the gut and can have potent effects on energy expenditure and insulin sensitivity in peripheral metabolic tissues through different GPCRs, such as GPR41 and GPR43 [27, 28].

It is also possible that gut bacteria generate intermediate precursors that are further metabolized by the host to products that exert direct effects on lipid levels. For example,

recent studies have linked high levels of trimethylamine *N*-oxide (TMAO) to atherosclerosis in both mice and humans [7]. TMAO is derived secondarily through hepatic oxidation of trimethylamine (TMA), which is first produced through gut microbe-mediated metabolism of dietary choline and L-carnitine [29, 30] (Figure). Possible mechanisms for the pro-atherogenic effect of TMAO have been suggested to involve perturbations of reverse cholesterol transport, cholesterol and sterol metabolism, and/or the quantity and composition of bile acids [7, 29, •31, •32]. Interestingly, host DNA variation appears to only play a marginal role in the regulation of TMAO levels, particularly in humans, suggesting that dietary factors and/or gut bacterial composition are more important determinants [33].

The Role of Host Genetic Factors

Another potentially important aspect to how gut microbiota can impact lipid metabolism may be related to genetic factors of the host. This concept is supported by evidence in humans demonstrating that gut bacterial composition has a significant heritable component and can vary across taxa or members of different phyla [34, ••35]. In the TwinsUK cohort, the abundance of the obesity-associated taxa *Christensenellaceae* was more highly correlated within monozygotic twins than dizygotic twins, and its heritability was shown to be independent of BMI [••35]. It is reasonable to assume that bacterial taxa that influence lipid metabolism could similarly have heritable components as well.

Given the observed heritability of intestinal microbiota, attempts have been made to identify the genetic variants that are associated with gut bacterial composition. A targeted candidate approach with ~250 previously validated variants for lipid levels and BMI did not find any evidence for association of microbiome composition with these SNPs, either alone or as a risk score [••21]. This may be explained, in part, by the fact that the selection of variants to test was only based on their main effects on lipids and BMI. One might speculate that host genetic variants that are involved in regulating bacterial abundance within the host would be more likely to be associated with proportions of gut microbial taxa. However, given the enormous genetic diversity of intestinal bacteria and variability in dietary intake, it is likely that sample sizes in most human microbiome studies are still insufficient to permit identification of robust genetic associations. Moreover, linking these taxa proportions to changes in host lipid levels will pose additional challenges as well.

By comparison, investigating the genetic determinants of bacterial composition has been more successful among inbred mouse strains, where environment (i.e. diet) and other confounding variables (i.e. age and sex) are tightly controlled. Notably, a recent genetic analysis with ~110 strains in the Hybrid Mouse Diversity Panel, all of which were maintained on equivalent dietary and housing conditions, identified seven host loci that were associated with common bacterial genera [••36]. Among the candidate genes at these loci were those implicated in processes related to innate immunity, glucose/insulin regulation, and the rapid acute-phase response to lipopolysaccharide. Additional noteworthy observations from this study were that one of the two host genetic loci that were associated with the proportion of *Akkermansia muciniphila* was also associated with gonadal fat mass and triglyceride levels [••36]. It is likely that similar genetic associations exist in humans as

well, but their identification will require larger sample sizes, broader interrogation of genes, and/or new discovery approaches.

The Challenges of Gut Microbiota Studies and Proving Causality

For the most part, metagenomic analyses on the human gut microbiota have used fecal samples but it is clear from animal studies that certain anaerobic organisms, such as *Akkermansia muciniphila*, reside primarily in the mucosal layers of the gut and are not readily detected in analyses of only feces. Indeed, the microbial composition throughout the gut varies considerably, both with respect to the anatomic location along the intestinal tract and within a given site, according to the micro-environment. For example, at a given site of intestinal mucosa/lumen, distinct microbes can uniquely reside deep within the crypts, versus on the surface of the mucosal villi, versus within the fecal material. Thus, without invasive procedures to get samples from distinct anatomical regions through the intestines, obtaining a more complete picture of the full spectrum of gut microbiota, at least in humans, poses significant challenges.

Next generation sequencing technology has been a major step forward by permitting more robust, time-efficient, and cost-effective characterization of intestinal microbiota. However, the evolutionary resolution provided by 16S sequencing is still limited with current platforms since bacterial composition with this approach is typically identified only down to the genus level. Untargeted metagenomics studies are beginning to overcome these challenges but these types analyses require much more sophisticated types of algorithms and are more expensive to carry out. Nonetheless, these efforts will improve our ability to identify and quantitate distinct species of bacteria and may have implications for understanding the pathological mechanisms through which specific bacteria affect both human health and disease processes.

Fecal microbial composition studies are associative, and thus hypothesis generating. Ultimately, proof of causality for identified microbial associations with host phenotypes requires additional experimentation, such as manipulating gut bacterial composition and observing changes in physiological parameters that were identified in the initial associations. In this regard, intestinal microbial transplantation studies in both animal models and humans have provided evidence for a causal role of gut bacteria in treating various intestinal diseases, most notably *Clostridium difficile* infection. Bacterial transplantation experiments have also been shown to modulate metabolic and cardiovascular phenotypes. For example, studies in mice have elegantly demonstrated that transfer of gut microbes from either obese mice or humans can transmit obesity phenotypes to the recipients [34, •37]. By contrast, administration of *Akkermansia muciniphila* to an obesity-prone mouse strain significantly improved several metabolic parameters, including substantial decreases in total cholesterol, triglycerides, and, most strikingly, insulin resistance [••36]. A similar strategy has provided evidence that atherosclerosis susceptibility in mice could also be transmitted to a host by gut microbial transplantation [•38]. Although such approaches have yet to be implemented in humans for treating dyslipidemia or other cardiometabolic traits, fecal transplantation studies have shown that transfer of gut microbes from lean donors through a duodenal infusion into patients with metabolic syndrome can improve insulin sensitivity [39]. These

observations underscore the therapeutic potential of interventions that alter gut microbial composition or function.

Targeting the Gut Microbiota for Therapeutic Applications

An important clinical implication from studies on gut microbiota is how to leverage findings for therapeutic purposes. Selective manipulation of the gut microbial ecosystem might provide new avenues to treat and/or prevent dyslipidemia and cardiometabolic diseases, but this will first require a better understanding of which specific bacteria, or alternatively, which bacterial metabolites, are the appropriate targets for intervention and manipulation. The simplest point of intervention may be to limit consumption of dietary constituents that either foster the growth of undesirable bacteria or serve as substrates for microbe-dependent generation of products that disrupt lipid homeostasis or other metabolic processes.

Alternative viable therapeutic strategies may be the use of prebiotics or probiotics to produce a desired change in microbial composition and/or function that favorably impacts host lipid metabolism. Prebiotic therapy consists of ingestion of select nutrients or dietary constituents (nonmicrobial compositions) that provide a growth advantage of beneficial bacteria, whereas probiotic therapy involves the ingestion of one or more live bacterial strains, attempting to take advantage of the mutualism of microbes. Therapeutic intervention could also rely on the use of broad or class-specific antibiotics to eliminate bacterial species or their products associated with dyslipidemia and other metabolic disturbances. However, this approach is not a sustainable long-term option. Many gut microbial products are beneficial to the host and even infrequent antibiotic treatment, particularly in very young children whose gut microbiota has yet to be fully established, can adversely impact host global metabolism via changes in the gut microbial community [40] and facilitate the emergence of antibiotic-resistant bacterial strains.

Another promising therapeutic approach may involve pharmaceutical targeting of gut microbe-specific biological processes. This concept was recently demonstrated in a series of elegant experiments with respect to the association of TMAO with atherosclerosis [••41]. Several important insights were revealed by this study. For example, Wang et al. designed a small molecule choline analog, 3,3-dimethyl-1-butanol (DMB), that competitively inhibited diverse and phylogenetically distant classes of microbial TMA lyases, which were previously identified as enzymes that catalyze the conversion of choline to TMA [42, 43]. Notably, these effects were observed in physiological polymicrobial cultures derived from both cecal contents of mice and fecal samples of healthy humans. Most importantly, chronic feeding of DMB to mice in the context of a high-choline diet led to shifts in the proportions of some bacterial taxa and substantial reductions in plasma TMAO levels, macrophage cholesterol accumulation, foam cell formation, and atherosclerotic lesions, without any evidence of toxicity or adverse cardiometabolic effects in the animals [••41]. Taken together, these results suggest that targeting gut microbial production of TMA through specific and non-lethal means may serve as a potential therapeutic approach for the treatment of cardiometabolic diseases and that microbial inhibitors in general may represent a novel therapeutic strategy for other disorders that involve intestinal dysbiosis.

Conclusions

For many years, the community of bacteria living in our gut was largely ignored. However, emerging evidence clearly demonstrates that our microbial symbionts play multiple fundamentally important roles in maintaining normal metabolic homeostasis. These discoveries have broad implications for elucidating bacterially-mediated pathophysiological mechanisms that alter lipid metabolism and other related metabolic traits. From a clinical perspective, this newly recognized endocrine organ system can be targeted for therapeutic benefit or prevention of cardiometabolic diseases and risk factors. The ability to manipulate the gut microbiome for improved health and prevention of diseases is still in the early phases of development, but recent rapid advances in gut microbiome studies highlight both the potential and promise of targeting intestinal microbes for therapeutic gain.

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Key Points

- The gut bacterial community is increasingly being recognized as an endocrine system that can modulate a variety of cardiometabolic processes, including host lipid metabolism.
- A variety of signaling molecules produced by gut bacteria have potent effects on hepatic lipid and bile metabolism and on reverse cholesterol transport, energy expenditure, and insulin sensitivity in peripheral tissues.
- Host genetic factors can modulate the abundance of bacterial taxa, which can subsequently affect metabolic phenotypes.
- Proof of causality for identified microbial associations with host lipid-related phenotypes has been demonstrated in animal studies but remains a challenge in humans.
- Manipulation of gut microbiota may serve as a novel therapeutic strategy for treatment and/or prevention of dyslipidemia and cardiometabolic diseases, but this will first require a better understanding of which specific bacteria are the appropriate targets for intervention.

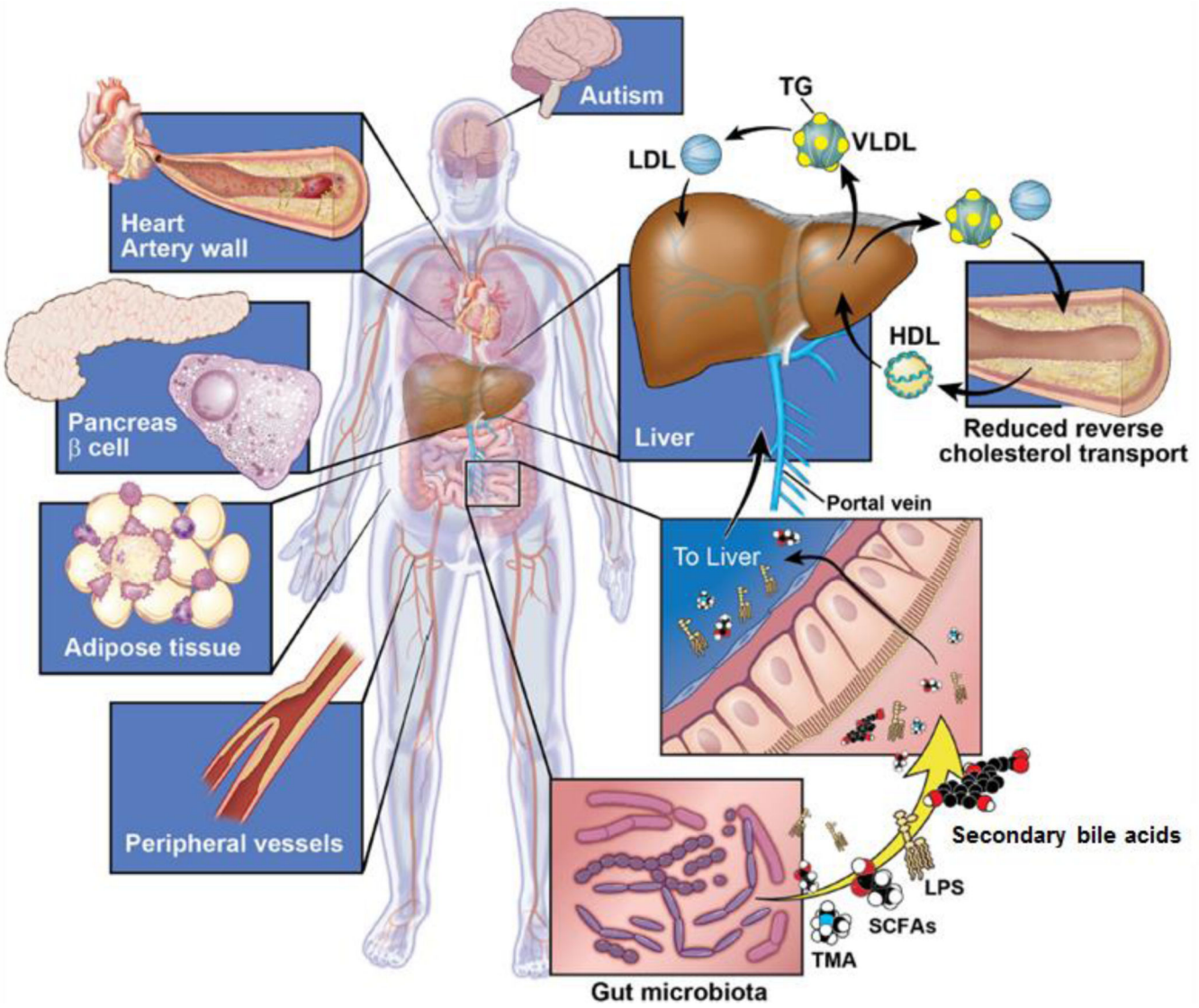

Figure. Schematic illustration of organ systems and tissues that can be affected by the gut microbiota

Multiple lines of evidence support a role for altered gut microbial composition or function as a contributor to the development of obesity and related metabolic abnormalities (i.e. type 2 diabetes), peripheral and coronary artery disease, and even neurobehavioral conditions such as autism. Recent observations of significant associations between proportions of specific intestinal bacteria taxa with lipid levels suggest a role for gut microbes in modifying host lipid metabolism. Gut microbe effects may be mediated through multiple mechanisms, including elaboration of lipopolysaccharide (LPS) or other bioactive metabolites that act fundamentally as hormones since they can circulate within the host and act at distant sites. Gut microbial production of short chain fatty acids (SCFAs) and secondary bile acids are two such examples that have been shown to affect lipid levels and other metabolic phenotypes. Evidence shows that gut bacteria can also generate intermediate precursors (e.g. trimethylamine) from certain dietary nutrients, that can then be further metabolized by the host to generate biologically active products (e.g. trimethylamine *N*-oxide), which then can

exert direct effects on lipid metabolism and contribute to disease development or progression. Biological mechanisms impacted by gut microbial metabolites can involve reverse cholesterol transport, hepatic cholesterol and sterol metabolism, intestinal lipid transport, bile acid composition and pool size, glucose and insulin metabolism, energy harvest/expenditure, as well as others.