CellPress

Molecular Cell

Minireview

Competitors versus Collaborators: Micronutrient Processing by Pathogenic and Commensal Human-Associated Gut Bacteria

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https://doi.org/10.1016/j.molcel.2020.03.032

Co-evolution of gut commensal bacteria and humans has ensured that the micronutrient needs of both parties are met. This minireview summarizes the known molecular mechanisms of iron, zinc, and B vitamin processing by human-associated bacteria, comparing gut pathogens and commensals, and highlights the tension between their roles as competitors versus collaborators with the human host.

Micronutrients are essential elements or small molecules that are required in small amounts for the normal growth and development of an organism. For humans, they include minerals that are integrated into metalloproteins (Zn, Mn, Cu, Se, Fe, S, Co, Cu), elements important for cell signaling, hormone production, and organ function (Ca, P, K, Na, Cl, Mg, I), and organic molecules that serve as protein cofactors (vitamins A, D, E, K, C, and the B group vitamins: thiamine [B1], riboflavin [B2], niacin [B3], pantothenic acid [B5], pyridoxine [B6], biotin [B7], folate/folic acid [B9], and cyanocobalamin [B12]). Maintaining proper micronutrient balance is of extreme importance. Deficiency has devastating health consequences, especially during early stages of human development (Mach and Clark, 2017), whereas overabundance can increase susceptibility to bacterial infections and lead to toxicity (Lopez and Skaar, 2018; Kortman et al., 2014; Paganini and Zimmermann, 2017).

The human gut is a set of unique and complex microbial habitats, where fitness for a microbe is determined by its ability to compete or collaborate. These habitats are micronutrient scarce during systemic infection as a result of host defense mechanisms which starve opportunistic pathogens (Lopez and Skaar, 2018; Kortman et al., 2014), yet these are habitats to which commensal bacteria have adapted, so much so that many commensals are rarely found elsewhere (Dethlefsen et al., 2007; Ley et al., 2008). In the human gut, pathogenic bacteria are ''competitors'' with resident commensal bacteria and with the host, harboring molecular mechanisms that allow them to sequester metal ions voraciously in order to survive (Kortman et al., 2014; Lopez and Skaar, 2018), whereas commensal bacteria are generally ''collaborators,'' synthesizing molecules, such as B vitamins, for themselves, their auxotrophic bacterial community members, and the human host (Rodionov et al., 2019; Rowland et al., 2018; Sharma et al., 2019).

Given the plethora of microbe-microbe and microbe-host interactions, a holistic and mechanistic understanding of the human gut microbial ecosystem is a particularly difficult goal. Efforts to understand the interactions associated with micronutrients have largely focused on pathogenic species in the context of disease and have focused less on the interactions of commensals. Here, we summarize what is known about micronutrient processing by human gut-associated bacteria, comparing pathogens with commensals, and describe the themes that emerge. We restrict our scope to micronutrients for which there are mechanistic data, to the trace elements for which deficiencies are most prevalent in humans (zinc and iron), and to the vitamins that are essential to both humans and bacteria (B vitamins).

Micronutrient Homeostasis in Humans

Absorption of Zinc and Iron

The stability of zinc in its 2+ oxidation state and the ability of iron to modulate its oxidation state under biologically relevant conditions makes them useful for metalloproteins. Zinc and iron are involved in vital processes, such as DNA replication, response to oxidative stress, and ATP production. Demand for zinc and iron in humans is met from exogenous sources, namely diet and/or dietary supplements. Most absorption of dietary zinc and iron occurs in the jejunum and duodenum, respectively. Influx of Zn^{2+} into enterocytes occurs via the transmembrane zinc transporter protein Zip4, which is located on the apical surface of enterocytes (Figure 1A). Zn^{2+} is then shuttled to metalloprotein synthesis sites by the zinc-regulated proteins ZnT2-10 or exported into the extracellular space and then to the circulation by zinc transporter ZnT1 (Zhu et al., 2019). In the case of systemic zinc excess, Zn^{2+} is removed from the circulation via transport into enterocytes by Zip5 at the basolateral aspect of these cells, followed by its efflux from enterocytes into the gut lumen via ZnT5 and its eventual excretion as waste (Figure 1A).

Dietary iron exists in two ionic states (Fe^{2+} or Fe^{3+}) and as inorganic iron and heme-associated iron. In the human gut, iron occurs predominantly as inorganic Fe^{3+}, where it is reduced to Fe^{2+} by duodenal cytochrome b (Dcytb) using cytosolic or dietary ascorbate (Ganasen et al., 2018) and then imported into enterocytes by divalent metal transporter DMT1 (Wu et al., 2015) (Figure 1A). Once inside the cell, Fe^{2+} is oxidized to Fe^{3+} by, and stored in, ferritin, or exported by ferroportin (FPN1) for

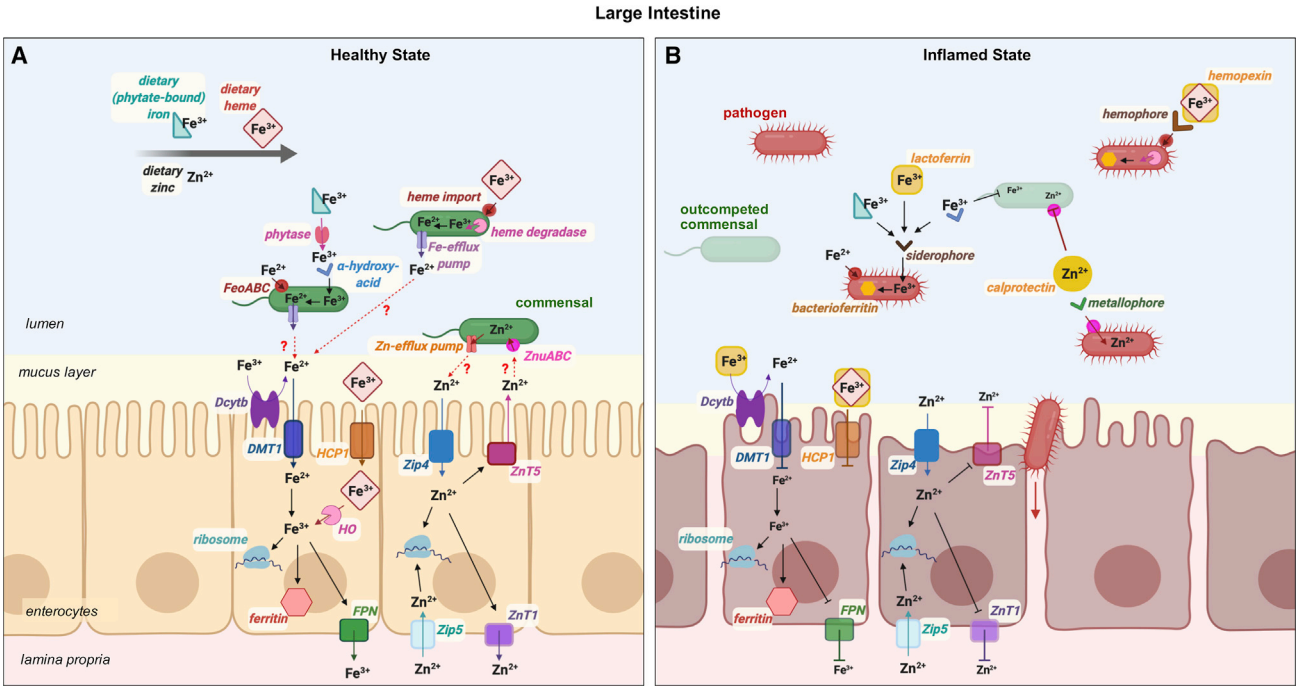

Figure 1. Iron- and Zinc-Dependent Host-Bacterial Interactions Are Different in Healthy versus Inflamed Conditions

Enterocytes express duodenal cytochrome b (Dcytb) and dimetal transporter 1 (DMT1) and heme carrier protein 1 (HCP1) on their apical side, which allows for absorption of iron and heme, respectively. Fe^{3+} in heme is released by heme oxygenase (HO). Fe^{3+} is then transported to the ribosome for incorporation into metalloenzymes, stored in ferritin, or exported by ferroportin (FPN1). Dietary zinc is absorbed on the apical side of enterocytes via the Zrt- and Irt-like protein 4 (Zip4) transporters and then transported to the ribosome for incorporation into metalloenzymes or exported into circulation via ZnT1. Enterocytes also express Zip 5 and ZnT5 on the basolateral side, which allows for zinc removal from circulation and its efflux from enterocytes into the colon.

(A) In a healthy state, dietary iron, heme, and zinc not absorbed in the small intestine reach the colon (brown arrow) and are available to colonocytes and/or commensal bacteria (in green). Commensal bacteria might acquire iron by release and uptake of α-hydroxy acids or by digesting food-borne molecules, such as phytate or heme. We speculate that commensal bacteria provide iron and zinc (that would otherwise not be bioavailable) to the human host via these mechanisms and the use of Fe- and Zn-efflux pumps (red question marks). Similarly, through enterocyte efflux of zinc into the lumen via ZnT5, the host might provide zinc to commensal bacteria (red question mark).

(B) Under conditions of inflammation, host systemic iron and zinc levels are reduced as DMT1, FPN1, and ZnT1 are downregulated (Wu et al., 2015; Zhu et al., 2019). Zinc and iron levels are also reduced in the colon as these metals become sequestered by host calprotectin and lactoferrin. A decrease in expression of ZnT5 and thus zinc efflux from enterocytes into the lumen additionally contributes to the reduction in zinc levels at this location. Pathogens (in red) overcome this so-called "nutritional immunity" and outcompete commensal bacteria (light green) for these metals by releasing siderophores, hemophores, and other metallophores, which give them access to these metals (Kortman et al., 2014). (Created with BioRender.com.)

eventual systemic dissemination in the circulation (Ward and Kaplan, 2012). Heme-associated iron is taken up by enterocytes via heme carrier protein 1 (HCP1). Fe^{3+} is then enzymatically released from the tetrapyrrole by heme oxygenase 1 (HO1) (Staroń et al., 2017) and stored or released from enterocytes into the circulation as above. Unlike zinc, there are no mechanisms to actively rid the human body of excess iron. Iron homeostasis is therefore regulated at the point of absorption by enterocytes and released into the circulation.

Complexation of zinc and iron to food-derived molecules reduces absorption (~20% of total ingested) in the small intestine (Kortman et al., 2014). The remaining zinc and iron make their way to the colon with its dense microbiota. Whether significant amounts of zinc and/or iron are absorbed in the colon and, if so, whether gut bacteria play a role is an area of active investigation. In support of colonic iron absorption and a role for the microbiome, Dcytb, DMT1, and HCP1 transporters are expressed in the colon, and their levels are modulated by gut microbes (Staroń et al., 2017; Deschemin et al., 2016).

Absorption of B Vitamins

B vitamins play an important role in a variety of essential processes in humans, including DNA synthesis, electron transport, gluconeogenesis, amino and fatty acid metabolism, and gene expression (Said, 2013; Engevik et al., 2019; Rowley and Kendall, 2019). Humans cannot synthesize B vitamins (except for niacin) and must obtain these from exogenous sources. Unlike the case for iron and zinc, the idea that both diet and gut bacteria are sources of B vitamins for humans is widely accepted (Said, 2013; Rowland et al., 2018). Absorption of dietary B vitamins occurs in the ileum via vitamin-specific transporters (THTR-1,2 for thiamine; RFC, PCFT, and FOLR1,2 for folate; RFVT-1 for riboflavin), non-specific vitamin transporters (SMVT for pantothenic acid and biotin), pH-dependent transporters and facilitated diffusion (for pyridoxine), or via endocytosis (for cyanocobalamin). Regulation of transporter expression and of endocytosis is dependent on intra- and extracellular B vitamin levels and in some cases on intestinal cell differentiation (Said, 2013). Absorption of bacteria-derived

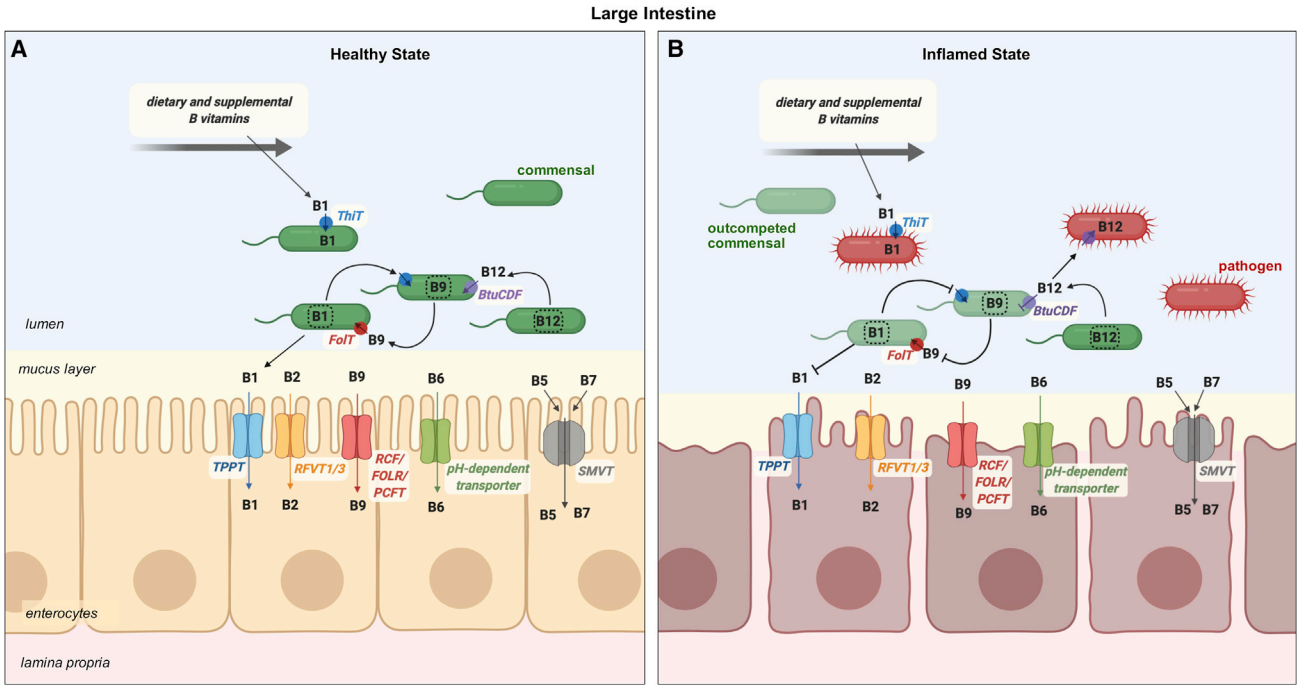

Figure 2. Sharing of B Vitamins among Bacterial Members of the Gut Microbiota Fosters Stability in Community Composition and Diversity but Is Disrupted during Microbial Pathogenesis

(A) Bacteria-derived B vitamins (represented by dotted squares) are circulated among members of the gut microbiome (in green) and are absorbed in the colon via B vitamin-specific transporters (thiamine pyrophosphatase transporter [TPPT], riboflavin transporter 1 and 3 [RFVT1/3], reduced folate carrier [RFC], proton-coupled folate transporter [PCFT], and folate receptors [FOLR]), non-specific transporters (sodium-dependent multivitamin transporter [SMVT], and pH-dependent transporters). B vitamin needs of auxotrophic species (including humans) are met as bacteria participate in a collaborative "give-and-take". Bacteria and enterocytes might also uptake or absorb dietary and supplemental B vitamins (except cyanocobalamin) that are not absorbed in the small intestine and reach the colon.

(B) During infection, bacterial pathogens (in red) selfishly make use of any available B vitamins. This one-sided interaction disrupts the established circulation of B vitamins, starving auxotrophic commensal bacteria (in light green) and the human host. (Created with BioRender.com.)

B vitamins occurs in the colon via the colonic version of the above-mentioned receptors, except for thiamine, which is absorbed as thiamine pyrophosphate (TPP) by the TPP transporter, and cyanocobalamin, which is not absorbed in the colon at all (Figure 2).

Micronutrient Availability, Bacteria, and the Human Host

The human body, and especially the intestinal tract after a nutrient-rich meal, presents a micronutrient smorgasbord to microorganisms. However, upon sensing a bacterial infection, the human body sequesters zinc and iron. As part of a general strategy called nutritional immunity, host proteins, such as lactoferrin, calprotectin, and lipocalin-2, are released from neutrophils and macrophages to bind iron and zinc and reduce their concentrations at systemic sites and in the intestinal tract (Lopez and Skaar, 2018; Zhu et al., 2019; Fischbach et al., 2006). In parallel, pathogenic bacteria have developed sophisticated and aggressive mechanisms (outlined below) to overcome the scarcity of micronutrients, making the intestinal tract a battlefield.

The absence of a micronutrient-sequestering response in times of health suggests homeostasis with respect to micronutrient availability to humans and their commensal bacteria and perhaps a set of distinct features that distinguish micronutrient-associated interactions between humans and microbes in health and disease. Microbiota-host specificity, vertical transmission of gut microbiotas, and evidence that gut microbiotas provide a wide variety of beneficial services to the host, all support the concepts of mammalian-gut microbiota co-evolution and co-adaptation (Dethlefsen et al., 2007; Ley et al., 2008) and more specifically, mechanisms to ensure that the micronutrient needs of both parties are met.

Micronutrient Processing by Human-Associated Bacteria

Acquisition, Storage, and Efflux of Zinc and Iron by Pathogenic Bacteria

Iron and zinc are essential for almost all bacteria, yet also toxic when in excess. Intracellular levels of zinc and iron must therefore be tightly regulated. Bacteria have evolved uptake and storage mechanisms to meet their cellular needs, as well as efflux machinery for use when intracellular concentrations are too high.

Mechanisms for acquisition of iron have been extensively characterized for pathogenic bacteria. Pathogens can acquire iron in both its ionic states. Uptake of inorganic iron is transcriptionally regulated by the ferric uptake regulator (Fur) and mediated by the FeoABC protein transport system (for Fe^{2+}) or by bacterial species-specific siderophores (e.g., enterobactin, salmochelin, staphyloferrin) and their cognate binding and cell

membrane transporter proteins (for Fe^{3+}) (Lopez and Skaar, 2018; Zhu et al., 2019) (Figure 1B). Biosynthesized and released into the extracellular environment under iron-deficient conditions, bacterial siderophores have an affinity for Fe^{3+} that supersedes that of lactoferrin and calprotectin and/or can evade capture by lipocalin-2 (Fischbach et al., 2006; Zhu et al., 2019). If not immediately incorporated into metalloproteins, iron is transported to the roughly spherical and hollow ferritin and bacterioferritin proteins, which oxidize Fe^{2+} to Fe^{3+} via the O_2-dependent ferroxidase reaction and incorporate this metal into their core (Carrondo, 2003). Iron is kept inside these proteins in reserve for times of need and at the same time prevented from participating in the Fenton reaction, which results in generation of toxic hydroxy radicals (Khare et al., 2017; Chandrangsu et al., 2017).

Pathogenic bacteria can also obtain iron in the form of heme from hemoglobin and hemopexin via heme-binding proteins called hemophores (Cescau et al., 2007) or by binding free heme directly through bacterial heme import systems (Choby and Skaar, 2016; Zhu et al., 2019) (Figure 1B). Intracellular heme can be directly incorporated into heme-binding proteins or stored in bacterioferritin. Heme can also be enzymatically degraded, releasing Fe^{3+}, which can then be used or stored as above.

Zinc uptake by pathogens is regulated by the zinc uptake repressor (Zur) and at least in *S. aureus*, the zinc efflux repressor (CzrA) (Capdevila et al., 2016). Uptake of zinc is mediated by the ZnuABC transport system and siderophore-like broad spectrum metallophores, such as staphylopine in *S. aureus* (Zhu et al., 2019; Capdevila et al., 2016) (Figure 1B). Once inside the cell, zinc participates in rapid chemical exchange among small molecules, such as metallothionein, or is transported by zinc chaperones to metalloprotein synthesis sites (Capdevila et al., 2016). Storage proteins for zinc have not been documented; however, synthesis and metalation of essential Zn-dependent proteins is prioritized under Zn-sufficient conditions (Capdevila et al., 2016).

Although iron and zinc limitation is perhaps a more prevalent challenge than is iron and zinc excess, efflux of these metals is also important to pathogen fitness (Knippel et al., 2018). As Fe- and Zn-dependent regulators, Fur and Zur are also responsible for regulating iron and zinc efflux, respectively. Zn^{2+} export is mediated by ZntA/B and CzcABCD efflux systems, as well as the Yiip transporter, which also exports iron (Lu and Fu, 2007; Zhu et al., 2019; Capdevila et al., 2016). Fe^{2+} efflux pumps have been identified in a variety of bacterial pathogens and include PfeT and Yiip (Pi and Helmann, 2017). Iron in the form of heme can also participate in redox chemistry and cause oxidative damage to membrane lipids, membrane proteins, and DNA. To avoid the effects of heme toxicity, bacteria employ heme efflux systems, such as HrtAB, which are regulated by the heme-binding transcriptional protein HssR and orthologs (Choby and Skaar, 2016; Knippel et al., 2018). These mechanisms allow pathogenic bacteria to scavenge iron and zinc fiercely, overcome nutritional immunity, and outcompete commensal bacteria in the gut.

Zinc and Iron Needs of Gut Commensals

Siderophore production and high-affinity Fe^{3+} uptake proteins like the ones used by pathogenic bacteria have been shown to be expressed by commensal bifidobacteria to enhance their growth in iron-limiting conditions *in vitro* (Lanigan et al., 2017). Mutations in the associated genes have not affected colonization by these commensals in a mouse or nematode model during states of health; however, other data suggest that *Bifidobacterium* iron uptake mutants might be less capable than wild-type strains in competing with *Salmonella* under iron-limiting conditions in the murine gut (Christiaen et al., 2014). How commensal bacteria meet their iron and zinc needs is not completely understood. Although transcriptional regulation by Fur and Zur appears to be similar, there is reason to believe that acquisition of iron and zinc might be achieved via different, less "aggressive" means than those used by pathogens. For example, Fe^{+3} bound to food molecules, such as polyphenols and phytate, which is not available to humans, might be available to gut commensals because they express proteases that degrade these molecules (Kortman et al., 2014) (Figure 1A). α-hydroxyacids and α-keto-acids, which are primary metabolites of commensal bacteria, are known to bind divalent metals and might function as low-affinity metal chelators and a source of zinc and iron to these species. Furthermore, equipped with iron-, heme-, and zinc-efflux pumps (Pi and Helmann, 2017; Lechardeur et al., 2012), as well as the ability to produce and release siderophores into their surroundings, it is possible that commensal bacteria share iron and zinc among themselves (Kramer et al., 2020), as well as with the human host. Perhaps there is no battle for micronutrients between gut commensal bacteria and the human host but rather a détente or mutual understanding. As with B vitamins (see below), there might be a pool of iron and zinc that is available to members of the gut microbiota from which the human host is also capable of deriving benefits.

Sharing of B Vitamins between Prototrophic and Auxotrophic Gut Bacteria

Bacteria require B vitamins to live and grow. Some species have complete biosynthetic pathways to make these molecules (prototrophs), whereas others must acquire them from exogenous sources (auxotrophs). Because acquisition of a complex molecule from the local environment is generally less costly than its *de novo* synthesis, both prototrophic and auxotrophic bacteria express transporters for B vitamins or B vitamin precursors (Jaehme and Slotboom, 2015; Putnam and Goodman, 2020). Prototrophs make use of import mechanisms when they find themselves in a B vitamin-abundant setting like the human intestinal tract (Figure 2B). Import of B vitamins into the cell occurs mainly via energy-coupling factor (ECF)-transporters (e.g., ThiT for thiamine) or other ATP-binding cassette (ABC)transporters (e.g., BtuCD for cyanocobalamin) and auxiliary transport proteins (e.g., BtuB, BtuF, BtuG2) (extensively reviewed in Jaehme and Slotboom, 2015 and Putnam and Goodman, 2020) (Figure 2A). Despite their importance and relevance to human health, molecular characterization of B vitamin bacterial transporters is incomplete and remains an area of ongoing research. Similarly, export of B vitamins, which is likely mediated by ABC-type exporters, lacks mechanistic explanation.

Auxotrophic bacterial species generally live in taxonomically diverse communities where other members of the community might provide the nutrients needed by the auxotrophs (Figure 2A) (Rodionov et al., 2019; Sharma et al., 2019). The

human gut microbiota is such a setting, with some members containing full biosynthetic pathways for all B vitamins, others containing none, and yet others containing partial pathways (Magnúsdóttir et al., 2015; Rowland et al., 2018). *In silico* genomic reconstruction and prediction of community-wide metabolic phenotypes show that, although almost all gut-associated members of the Bacteroidetes, Fusobacteria, and Proteobacteria phyla possess the necessary pathways for riboflavin and biotin, and members of the Firmicutes and Actinobacteria phyla can produce thiamine, an estimated 20% of bacterial species in the human gut are auxotrophic for B vitamins (Magnúsdóttir et al., 2015; Rowland et al., 2018). Notably, experiments with gnotobiotic mice and fecal bacterial isolates show that the relative abundance of auxotrophic species in a community containing B vitamin prototrophs is unaltered in the absence of an exogenous B vitamin source (Sharma et al., 2019), providing support for the idea that B vitamin exchange increases species fitness and promotes stability of community composition.

Influence of Micronutrient Processing by Commensal Gut Bacteria on Human Health

Micronutrient deficiency and excess are both associated with altered gut microbiome compositions. Both conditions create an opportunity for enhanced colonization by pathogenic bacteria (Mach and Clark, 2017; Rowley and Kendall, 2019; Lopez and Skaar, 2018; Kortman et al., 2014; Paganini and Zimmermann, 2017). Increased levels of iron are pro-inflammatory, which in turn might lead to conditions that select for routine and opportunistic pathogens (Kortman et al., 2014; Lopez and Skaar, 2018; Paganini and Zimmermann, 2017). Micronutrient availability from diet or dietary supplements, therefore, directly shapes the taxonomic composition and the metabolic functions of the gut microbial community. Of equal or greater interest, however, is the question as to whether, beyond the direct effect of micronutrients passing through the intestinal tract, the gut microbiota is affected indirectly by systemic levels of micronutrients in the host (i.e., deficient, adequate, or excess amounts). Similarly, is adsorption or secretion of micronutrients by humans influenced by the amounts made or stored by the gut microbiota?

Evidence that the gut microbiota senses the iron status of its host is provided by experiments on mice with iron-deficiency anemia. When these mice were treated with iron via intravenous administration or with blood transfusions, changes in gut microbial community composition were recorded as the mice regained iron sufficiency (La Carpia et al., 2019). Again, in mice, *Lactobacillus* species affect expression of host iron absorption pathways via inhibition of HIF-2α (which regulates Dcytb and DMT1), as well as enterocyte iron storage by upregulating expression of FPN1 (Das et al., 2020). In addition, *Lactobacillus reuteri* FolC (involved in folate biosynthesis) can influence host uptake of folate by altering the expression of colonic reduced folate transporter in human enteroid monolayers (Engevik et al., 2019).

Yatsunenko et al. found that the fecal microbiomes of babies six months of age or less are enriched for genes involved in the biosynthesis of folate and relatively impoverished for genes involved in cobalamin (vitamin B12), biotin (B2), and thiamine (B1) biosynthesis compared to those of adults and that with increasing age, the relative representations of these genes reversed (Yatsunenko et al., 2012). These age-dependent features were shared among subjects from Malawi, the Amazonas State of Venezuela, and the United States.

The fact that absorption of diet- and bacteria-derived vitamins takes place in different intestinal locations (and in the case of thiamine, by different receptors) suggests that micronutrients might be utilized differently by the host depending on their source. Crosstalk between gut microbiota and humans provides a basis for the bidirectional coupling of micronutrient-associated metabolism between the two parties. Micronutrient homeostasis in humans and gut commensal bacteria is likely the product of a well-evolved collaboration and not an antagonistic relationship.

Concluding Remarks

Multiple associations have been identified between gut microbiota composition and micronutrient status of the human host. In many cases, these associations fail to be replicated or are contradictory upon closer scrutiny. In order to characterize the nature of these host-microbiota interactions associated with micronutrient availability and exchange, several approaches will be useful: multiple time point longitudinal studies that examine micronutrient supplement interventions, large cross-sectional studies of hosts with and without micronutrient deficiencies but controlled for many of the known confounding factors that affect the microbiota (e.g., other nutrients, infectious diseases), microbiota characterization at the level of strains, complete genomes, and community-wide transcript, protein, and small-molecule inventories.

Concentrations of micronutrients are not homogeneous throughout the gut, suggesting the possibility that obligate microbe-microbe interactions due to auxotrophy help to shape the spatial structure of these communities. Regardless of whether this possibility is true, characterization of the spatial structure of the gut microbiota is likely to prove an essential component to our understanding of this complex ecosystem (Tropini et al., 2017). Optimization of current MALDI-MS imaging techniques (Dunham et al., 2017; Dunham et al., 2018) to visualize spatial arrangement of commensal bacterial species and the distribution of their metabolites inside the host (Perry et al., 2019), as well as metagenomic plot sampling techniques (MaPS-seq) (Sheth et al., 2019), are exciting and promising approaches toward addressing this goal.

Lastly, most micronutrient absorption does not occur in the colon but instead in the small intestine. Albeit much less dense and diverse, the role of the small intestinal microbiome in human micronutrient-associated health likely looms large and yet, to date, has been neglected due to difficulty in access under normal conditions. New devices that could retrieve samples from the small intestines of subjects during routine daily regimes would be immensely valuable in elucidating micronutrient-microbiota-host interrelationships in this important habitat and should be pursued.

Bioinformatic tools, although limited by imperfect gene annotation, have revealed the magnitude of auxotrophy present in gut commensal bacteria and have highlighted the probable dependence of gut commensals on micronutrient sharing with other

microbes, as well as the human host. The detailed roles of specific species and strains in a community remain to be determined experimentally and, importantly, might be obscured if studied outside of this context (i.e., as isolates). Iron and zinc requirements by gut commensals, local ambient metal concentrations and metal tolerance, mechanisms employed by commensals to meet their metal needs, and the nature of metal sharing by gut commensal bacteria among themselves and with their host are key topics that remain inadequately understood.

In various ecological settings, competitive microbe-microbe interactions might be favored over cooperative interactions as the latter create inter-species dependencies and compromise community stability in the event that a key provider species is lost (Coyte et al., 2015). However, cooperative interactions have greater metabolic efficiency and in the context of micronutrient homeostasis, where exogenous resources are made available by multiple sources (i.e., diet, multiple prototrophic species, the human host), cooperative interactions might be favored, as is suggested by the results presented by Sharma et al. (2019). Quite distinct from the selfish, competitive, and one-sided micronutrient processing strategies that human-associated pathogens employ, the processing of B vitamins by commensal bacteria highlights the collaborative nature of the gut microbiota. Assumptions that commensals and pathogens deploy similar strategies and mechanisms for managing micronutrient needs might be ill-advised. For pathogenic bacteria, the general approach is to subvert, steal, and coopt; for commensals, to share. It is reasonable to think that in order to achieve these different lifestyles these two classes of human-associated bacteria must have evolved different mechanisms to meet their nutritional needs.

ACKNOWLEDGMENTS

This work was supported by the Thomas C. and Joan M. Merigan Endowment at Stanford University (D.A.R.), the Chan Zuckerberg Biohub Microbiome Initiative (D.A.R.), and the Stanford Microbiome Therapies Initiative (D.A.R. and A.I.C.).

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