Bacteria from the gut influence the host micronutrient status

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‘’Bacteria from the gut influence the host micronutrient status’’

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Abstract

Micronutrient malnutrition remains a serious public health problem in most low- and middle income countries, with severe consequences for child physical and psychomotor development. Traditional methods of treatment and prevention, such as supplementation and fortification, have not always proven to be effective and may have undesirable side-effects, including increased growth and virulence of pathogenic gut bacteria, resulting in diarrhea and gut inflammation. Commensal bacteria in the gut have demonstrated the ability to increase the bioavailability of certain micronutrients, notably by removing anti-nutritional compounds, such as phytates and polyphenols, or by the synthesis of vitamins or their derivatives. The intestinal microbiota is also, in symbiosis with the gastrointestinal mucosa, the first line of protection of the internal environment against the external environment. It thus contributes to the reinforcement of the integrity of the intestinal epithelium and to a better absorption of micronutrients. They represent a save alternative to prevent micronutrients deficiencies. However, the metabolic characterization of the intestinal microbiota is not yet complete and its role in micronutrient malnutrition is still poorly understood. The bacterial metabolism is also dependent of micronutrients acquired from the gut environment and resident bacteria may compete or collaborate to maintain micronutrient homeostasis. Gut microbiota composition can therefore be modulated by micronutrient availability. This review brings together current knowledge on this two-

way relationship between micronutrients and gut microbiota bacteria, with a focus on iron, zinc, vitamin A and folate (vitamin B9), which are respectively minerals and vitamins of interest in a global context.

key words

bacteria – gut microbiota – human – micronutrients – deficiency - prevention

1. Introduction

Micronutrients, including minerals and vitamins, are nutrients needed only in small quantities on a daily basis, but who are vital to human metabolic processes (1,2). Vitamin and mineral deficiencies, also called 'Hidden Hunger' to highlight the lack of visibility, is a serious public health problem, encountered in all social strata of the world, but especially affecting vulnerable groups in low- and middle income countries (3). Micronutrient deficiencies are widespread around the world, estimated to affect over 2 billion people, and are implicated in a wide range of adverse health outcomes such as increased prevalence of morbidity and mortality, anaemia, stunting and delayed cognitive development. In a global context, the diets of two-thirds of women and children, mainly from resource-poor households, are deficient in at least one micronutrient (4). The most prevalent micronutrient deficiencies worldwide include iron, zinc, vitamin A and folate (vitamin B9) (4,5).

Several strategies to improve micronutrient status of individuals or populations exist, with fortification of staple foods being regarded as the most cost-effective intervention to improve micronutrient status of populations (6). Nevertheless, strategies to fight micronutrients deficiencies are not always efficient. Absorption of micronutrients occurs mainly in the small intestine, through

different mechanisms depending on the micronutrient. For example, zinc and iron are mainly absorbed in the duodenum and jejunum through specific transport carriers (7,8), whereas folate is not only absorbed in the small intestine, but also in the colon (9).

In the digestive tract, there is a complex community of microorganisms with a concentration and diversity that increases from mouth to colon (10). Although other microorganisms (viruses, fungi) share this niche, most studies have dealt with bacteria, the phyla Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verrucomicrobia being the most represented (10). The role of the intestinal microbiota in human health is undeniable today (11). Indeed, the composition of the gut microbiota have been associated with diseases such as inflammatory bowel disease (Gonzalez and al. 2011), or obesity (Turnbaugh and al. 2007). And the intestinal microbiome plays an important role in the aetiology of severe acute malnutrition (14,15). Faecal bacterial composition strongly vary among individuals, which was found to be dictated by the host's genetics, but also by many environmental factors including diet (16,17).

For long, most research on the effect of food on the intestinal microbiota has focused on macronutrients (fats, carbohydrates, proteins) (18,19). However, bacteria need micronutrients for their survival. For example, bacteria require iron from external sources, and some of them even have developed specific mechanisms such as transferrin transporters to compete for iron sources (20). In contrast, many bacteria can directly synthesise vitamins such as folate (vitamin B9), thus, not necessarily requiring an external source.

Even though the absorption of most micronutrients by the host is now well described, the role of the intestinal microbiota on micronutrient absorption and/or availability is less clear. Considering the amount and the diversity of the bacteria along the digestive tract, there is a need to sum up the actual knowledge and to underline the gaps and research needed in this field. Absorption of micronutrients

generally occurs in the upper part of the digestive tract, usually in the duodenum or jejunum through specific transport mechanisms (21). However, typically only 5%-50% of micronutrients are absorbed, meaning that the most part of the ingested micronutrients reach the colon (22).

Gut microbiota have different modes of action on the micronutrients, which can result in a better or a worse bioavailability for the host. These actions can be direct, targeting directly the micronutrients of interest. For example, bacteria can take up iron and zinc, but in case of excess efflux of these metals is possible. These mechanisms allow pathogenic bacteria to scavenge minerals efficiently and escaped nutritional immunity and develop in presence of commensal bacteria from the gut (Celis 2020). Similar mechanisms in commensal bacteria are not completely understood, even if it some authors underline that they should be less aggressive than the ones used by pathogens (Celis 2020). Actions can also be indirect, for example through production of short chain fatty acids (SCFA), which will result in a better health of the gut epithelium, resulting in a better absorption of the micronutrient by the host.

This review aims to summarise the current knowledge on the bilateral relationship that exists between the intestinal microbiota and micronutrients and discuss emerging themes. A recurrent theme will be the bi-directional character of the relationship, with micronutrient status of the host modifying the microbial composition of the gastrointestinal tract (Tian and al. 2018; Zimmermann and al. 2010), but with also the intestinal microbiota modulating the bioavailability of micronutrients and thereby the micronutrient status of the host (25). We have restricted the scope of this review to four micronutrients important for global public health: iron, zinc, vitamin A and vitamin B9.

2. Micronutrients and host health

Micronutrients play a central role in metabolism and the maintenance of tissue functions that govern human health (21). However, despite efforts to diversify diets to better meet micronutrients needs (26), the prevalence of micronutrient deficiencies remains very high in all parts of the world, including in industrialised countries (27). Children and women are the most affected, due to higher requirements to sustain growth and higher loses (e.g. menses). The clinical signs of single micronutrient deficiencies are varied and often micronutrient-specific (28).

Iron deficiency is considered the most common form of micronutrient malnutrition, with more than 2 billion people estimated to be iron-deficient (29). Iron deficiency anemia is a common disease associated to insufficient iron intake and iron stores (30). Factors contributing to iron deficiency include (i) a low intake of haem iron, which has a higher bioavailability than non-haem iron, (ii) diets with a high content of phytates or phenolic compounds responsible for a lower bioavailability (31) and (iii) chronic inflammation, leading to higher levels of hepcidin, downregulating iron absorption (32).

Zinc deficiency is not only associated with growth retardation in children, leading to stunting, but also diminished immunocompetence, thereby increase the susceptibility of children to diarrhoeal disease, pneumonia and perhaps malaria (33). Moreover, it seems that zinc deficiency can predispose to other micronutrient deficiencies (Biesalski 2016). Zinc deficiency is estimated to affect more than1 billion people worldwide (34).

Similarly, vitamin A deficiency leads to decreased immunocompetence, as well as reduced integrity of intestinal epithelial mucosa (35). Half-yearly high dose vitamin A supplements are given to children less than 5 years of age in many low- and middle income countries in a drive to decrease child mortality (36), but impact on vitamin A status is questionable.

Insufficient folate intake during pregnancy is associated with neural tube defects during the first weeks of embryonic life (37). In the general population, folate deficiency also leads to megaloblastic anaemia, and neurological symptoms that partly overlap with those found in vitamin B12 deficiency (28). It is estimated that more than 20% of women of reproductive age in low- and middle income countries are folate deficient (38).

3. The complexity of host-bacteria interaction: the case of iron.

For a complete overview on iron, bacteria and host interplay we would like to refer to a recent review (39). Here we have summarized the elements which describe the complexity of this relationship (39).

As human are not able to actively excrete iron, its absorption is tightly regulated in the duodenum (Figure 1) (29). Heme iron and non-heme iron are absorbed through two distinct pathways (40), with heme iron absorbed by a heme carrier protein 1 (HCP1) at the border of the duodenal brush membrane. Non-heme iron, usually in its ferric form, is not bioavailable and must be reduced to the ferrous form by duodenal cytochrome b (DCYTB), before being transported over the duodenal brush membrane by the divalent metal transporter (DMT1) (41). Iron is also absorbed in the ileum and colon since the presence of DMT1 has been described (42). But the role of these absorption sites on the host iron status remains to be estimated (43). Iron homeostasis is regulated by hepcidin, a hormone that circulates in the plasma and inhibits the release of iron into the plasma through different mechanisms (44). Hepcidin is upregulated during systemic inflammation, thereby reducing iron bioavailability. But pathogenic bacteria could induce systemic inflammation, thereby reducing the intestinal bioavailability of iron (Nicolas and al. 2002).

Iron is also essential for many bacteria, requiring it for their growth (46). Bacteria can acquire iron through different mechanisms such as using ferric-specific chelators called siderophores, absorbing ferrous iron after reducing ferric iron or using host iron compounds such as heme or transferrin. Despite its bacteriostatic function, lactoferrin, which is found in milk, can also be used by bacteria with specific receptors (47).

Siderophores are a wide family comprising hundreds of forms produced and secreted by many-microorganisms (48). The resulting ferric-siderophores complex are internalised via specific outer membrane proteins. Bacteria can also use siderophores produced by other bacteria, through the production of outer membrane receptors with different ligand-binding sites. Siderophores are expressed in case of bacterial iron deficiency, thus not in iron-sufficient environments (49).

In anaerobic conditions and at low pH, iron is mainly in the form of ferrous iron, which can be transported directly by bacteria, mainly through the dedicated transport system feo (50). Transportation of heme-iron, transferrin, lactoferrin is through specific receptors or direct absorption (39). Regulation of iron uptake is highly important in bacteria since iron is toxic at high doses. The Fur regulation system represses transcription of genes involved in iron uptake when iron concentration is too high (51).

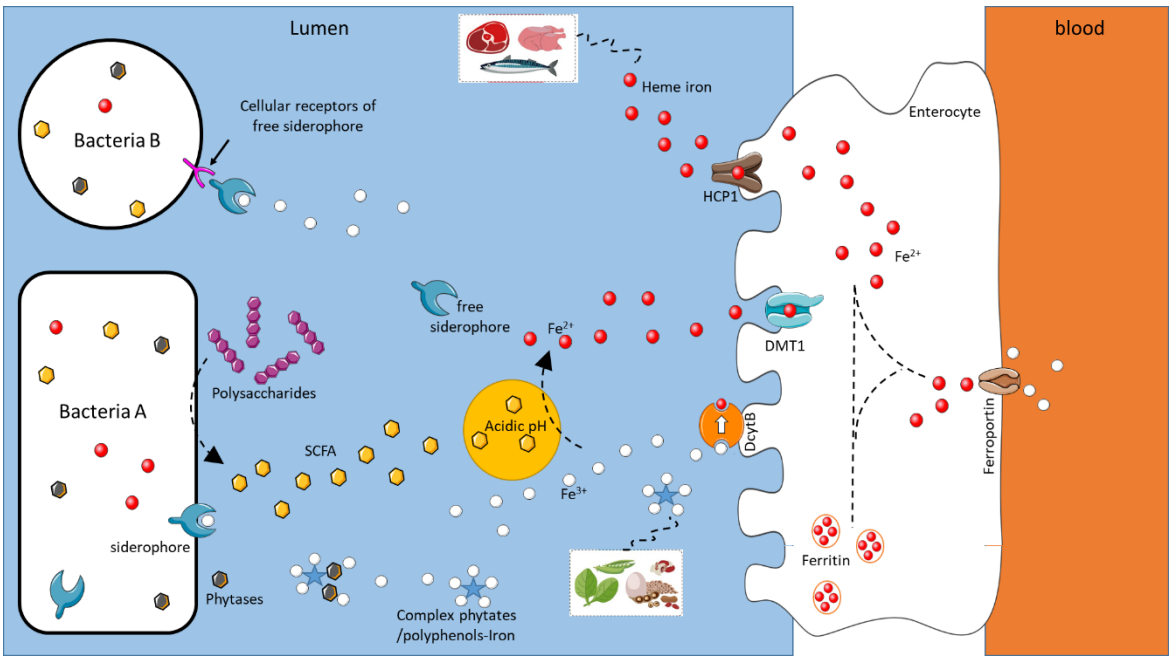

Figure 1. Schematic representation of the gut microbiota role in the intestinal absorption of iron. SCFA : short-chain fatty acids ; HCP1 : haem carrier protein 1 ; DMT1 : Divalent metal-ion transporter-1 ; DctyB : duodenal cytochrome b

It is important to note that most of our knowledge of bacterial iron absorption comes from research done on pathogenic bacteria. It has been considered for a long time that a few beneficial bacteria, such as members of *Lactobacillus* genus, do not require iron for their growth (52). Nevertheless, specific systems have been identified in *L. plantarum* and *L. sakei* (53,54). Most probably, other systems may exist, and studying these bacteria may reveal new iron absorption pathways. At the main site of iron absorption, in the duodenum, there are roughly 10^3 bacteria/g, which is less than in the jejunum (10^4 bacteria/g) and far less that in the colon where up to 10^{12} bacteria/g of content can found (55). Also, members of *Lactobacillus* genus are numerous in the small intestine where iron absorption is maximum, thus the role of these bacteria on iron absorption by the host should receive more attention, to determine whether they play or not a role in bioavailability of iron for the host.

It has been calculated that iron concentration in the colon should be high, which is by far more than the minimum requirement for bacterial grow (56). But the bioavailability of iron for bacteria depends also on a range of factors (form of iron, iron speciation, pH, oxygen levels). For bacteria and human, non-heme iron is the most affected by the composition of the food matrix and the physico-chemical composition of the lumen. Indeed, non-heme iron is linked in many food matrixes to inhibitors, such as polyphenols, fibres or phytates, which can be degraded by dedicated bacterial enzymes, thus resulting in a better iron absorption (57). This property is usually utilised in fermentation, where bacteria to reduce the concentration of inhibitors in the food, resulting in higher iron bioavailability. But the presence of phytases has been demonstrated also for a number of bacteria found in the gut (including the ones in the small intestine). It was suggested that whatever the phytates content of the food, all iron in the food matrix should be liberated since bacteria from the gut exhibit phytase activity (58). However, this appears to be in conflict with real-life observations, where phytate-high diets are linked to iron deficiency.

Also, some promoters of iron bioavailability, such as lactic acid, are produced by a number of bacteria, present all along the digestive tract. The acidified intestinal environment could also degrade complexes chelating micronutrients and facilitate absorption of iron (59). Bacteria can also produce short chain fatty acids (SCFA) by fermentation of non-digestible carbohydrates from the diet, which will lower the luminal pH, and thus reduce ferric to ferrous iron, thereby improving its absorption by bacteria and host (60).

It is obvious from above that gut bacteria play an important role in modulating the bioavailability of iron for the host. However, host factors can modulate iron uptake by bacteria, for example, in the case of inflammation, through the synthesis of lipocalin, which will bind to the siderophores and thus counter the trapping of iron by the intestinal bacteria (61). Recently, is has been suggested that rather than a battle for minerals, commensal bacteria use different mechanisms not only to liberate and capture iron, but also to share iron among themselves and with their host (62,63).

Overall, it appears that depending on the model used (*in vitro*, animals or humans) results are dramatically different, making any generalization difficult. One of the few consistent results is the decrease in the proportion of bacteria of the phylum Actinobacteria in case of iron-deficiency anemia (64). In the case of iron supplementation or fortification, the chemical form of iron used (ferrous sulfate, ferrous furamate, NaFeEDTA, ferric sodium ethylenediaminetetraacetate) seems to affect bacterial composition differently (65–67). Surprisingly, no general trends could be identified, even in the same model and using the same method with iron supplementation (39). For example, in human models, iron supplementation was associated with an increase (68), a decrease (69) and had no effect (70) on the population of bacteria of the phylum Firmicutes. The only consistent results were for Lactobacillaceae family and the phylum Actinobacteria. Indeed, Lactobacillaceae always decreased during iron supplementation, whatever the model used (68,71,72). Also, against all expectations, the effect of iron supplementation was not directly opposite to that of iron deficiency (39).

4. Role of bacteria in zinc bioavailability

Zinc is involved in vital processes such as DNA synthesis, transcription, and translation (73). Zinc absorption occurs in the duodenum and involve the transmembrane zinc transporter protein Zip4 (figure 2). Zinc is then shuttled to the metalloprotein synthesis sites by the zinc-regulated proteins ZnT2-10 or exported to the circulation by Zinc transporters ZnT1 (74). Contrarily to iron, zinc can also be actively excreted in case of excess. It will go from the circulation to the enterocytes by the protein Zip5 at the basolateral side of these cells and an efflux from the enterocyte to the lumen via ZnT5 (75).

In food, zinc can be complexed with antinutrient factors such as phytates or polyphenols, thus reducing its absorption (76). Zinc that is not absorbed in the small intestine will reach the colon and

its possible absorption by colonocytes where the zinc transporters are also expressed (77). As for iron, the phytase activity found in many members of the commensal bacteria as well as their ability to metabolise polyphenols could increase the bioavailability of zinc for the host.

In bacteria, zinc is rapidly bound to small molecules such as metallothionein or is transported to metalloprotein synthesis sites by zinc chaperones (78). Zinc uptake by bacteria is regulated by the zinc uptake repressor Zur and the zinc efflux repressor CzrA (78). As in the case for iron, most studies were done on pathogens, rather than on commensal bacteria. Some pathogenic bacteria can overcome zinc limited conditions (nutritional immunity produced by host through sequestration of essential micronutrients such as zinc by secreting calprotectin) by expressing a high affinity transporter (ZnuABC) (79). Zinc can also be actively exported in case of excess (80).

Zinc deficiency has been repetitively associated with chronic diarrhoea (59). The effect of zinc supplementation on the intestinal microbiota has been mainly studied in animal models. It has been used in poultry and pig industry at pharmaceutical dose to reduce gastrointestinal infections and diarrhoea (81). Zinc has antimicrobial activity and different studies underlined the changes of bacterial composition of the different parts of the gut (from stomach to colon) induced by such high doses of zinc (82–85). Depending on the studies, there was a reduction or an increase of Enterobacteriaceae and lactic acid bacteria (82–85). One study showed that *Ruminococcus* genus was predicting host zinc adequacy (86). Bacterial compositional changes were accompanied by changes in the metabolism of the bacteria as shown the increase colonic concentration of short chain fatty acids (SCFA) (83).

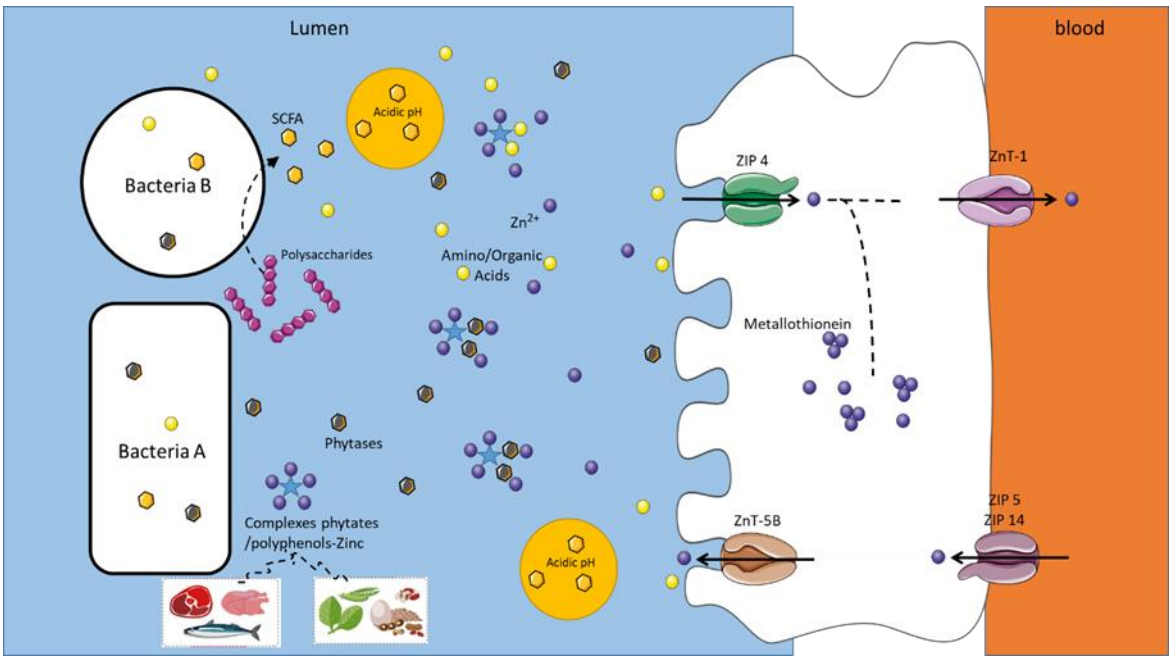

Figure 2. Schematic representation of the gut microbiota role in the intestinal absorption of zinc. SCFA: short-chain fatty acids ; ZIP : Zrt-/Irt-like proteins ; ZnT : Zinc transporters.

An original study using initially germ-free mice inoculated with different bacterial species from the human gut microbiota shown almost no effect on zinc depletion or repletion on the bacterial composition of faecal samples in non pathogenic conditions (87).

As for iron, studies on zinc status and host microbiota mainly focused on pathogenic conditions, and little is known about the role of bacteria in a normal situation.

5. Acquisition of folates by host and bacteria

Several commensal bacteria have been shown to synthesize certain vitamins. The role of intestinal bacteria in the production of vitamin K has been known for several decades, but bacteria can also be a source of folates for the host, even if the extent of the overall contribution is still unknown (88). Folate or vitamin B9 is necessary for DNA methylation and replication, as well as for cell division,

which is characteristic of better growth (89). Folates from the diet exist in mono and poly-glutamate forms, which are deconjugated to the monoglutamate form and then absorbed in the ileum via specific transporter FFLR1,2 (proton-coupled folate transporter (PCFT). In the epithelium, folate monoglutamate is converted into an active form, tetrahydrofolate (THF). Then, it is transported to the blood (90,91). In the colon, a version of the same receptors has been identified (92).

Bacteria require folate for their growth, with some bacteria being prototrophic and can synthesize folate from precursors present in the environment (figure 3). The others, auxotrophic, must acquire folate from the environment. All of them have transporters for folates or folates precursors (93,94). The ability to synthesize folate is found in different taxonomy communities (95). Some bacteria also have uncomplete synthesis pathways in their genome (93). A body of data are in favour of a significant contribution of bacterial folates synthesis to host status. Early studies reported that human folate concentration in faecal samples where 300-500 µg/day, while dietary intakes were below 100 µg/day, suggesting a synthesis of folate by the gut bacteria (96,97). Modification of gut microbiota composition due to fibers consumption may result in increased folate concentration in colonic content or in circulation (98,99). Also, despite that folate absorption rate in the large intestine is 100 time slower than in the small intestine, labelled folates specifically encapsulated to reach and disintegrate in the colon, were incorporated in host tissue (100,101).

Direct ingestion of folate producing bacteria can also improve folate status of rodents on folic acid deficient diets (102–104). Another study showed that, in a model of *Caenorabditis Elegans*, bacteria can convert folic acid into tetrahydrofolates, which are better absorbed by the host (105).

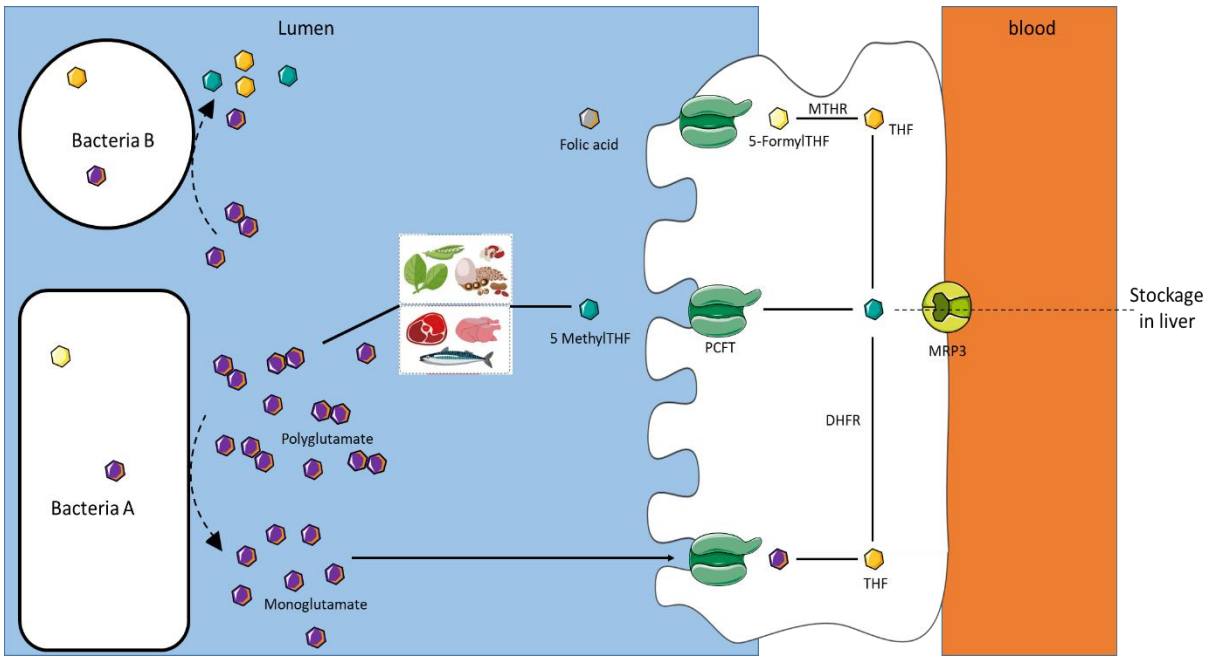

Figure 3. Schematic representation of the gut microbiota role in the intestinal absorption of vitamin B9. PFCT : proton coupled folate transporter ; THF : tetrahydrofolate ; MRP : multidrug resistance protein ; DHFR : dihydrofolate reductase ; MTHFR : methylenetetrahydrofolate reductase

The metabolic capacity of the gut microbiota depends on its composition but also on the physiological characteristics of the host. For example, genes coding enzymes involved in the folate biosynthesis, are found more frequently in gut microbiota of babies young children as compared to adults (106). Interestingly, the microbiome of children suffering from malnutrition showed a significant lower abundance of genes in multiple path-ways involved in B-vitamin metabolism (Gehrig and al. 2019).

Contrarily to irons and zinc, it has been shown that the dietary folate deficiency doesn't affect the gut bacterial composition (108). Perhaps because of the presence of phototrophic bacteria, producing folates in periods of deficiency, fluctuations in folate intake have less impact on gut flora. (95,109).

6. Role of gut microbiota in vitamin A absorption and metabolism

Dietary vitamin A is found in the form of carotenoids and retinyl esters, respectively present in vegetables and animal products (110). The uptake of carotenoids and retinol occurs in the upper half of small intestine (110,111).

Vitamin A directly contributes to the maintenance of the gut barrier by regulating proliferation and differentiation of immune cells in the intestinal epithelium and plays a crucial role in the resistance to pathogens invasion in the gut (35,112,113). The epithelial and mucosal cells, in symbiosis with commensal bacteria, constitute a first physical barrier against external bacteria and contribute to the regulation of the gut microbiota composition (114,115). Disruption of the integrity of the intestinal barrier can lead to poor absorption of nutrients, and various diseases in the host, including inflammatory bowel disorders (116,117)

Vitamin A and carotenoids are dietary fat-soluble components that require solubilization by micelles prior to absorption in enterocytes (118). An emulsification phase into droplets occurs in the stomach and duodenum, with vitamin A being incorporated into micelles formed with bile salts (119,120).

Carotenoids can be absorbed by passive diffusion, while retinoid are absorbed through carrier-dependent proteins (111). Only free forms of retinoids can be absorbed so that retinyl-esters must be hydrolyzed to retinol either by pancreatic enzymes or by a retinyl esters hydrolase (REH) present in the mucus (121,122). After absorption retinol is reesterified with long-chain fatty acids by the enzyme lecithin-retinol acyltransferase (LRAT) or by retinol dehydrogenases (RDHs) into retinal (figure 4).

In the enterocyte, carotenoids are directly converted into all-trans retinal by carotene-15,15'-dioxygenase [BCO(D)M] (123). Retinaldehyde can be irreversibly converted with retinal-deshydrogenases (RALDH) into bioactive retinoic acid molecules or converted into retinol ester by LRAT, to be stored in the liver (124). The secretion of secondary or tertiary bile salts produced by bacteria belonging to *Lactobacillus*, *Bifidobacterium*, *Bacteroides* or *Clostridium* genus could favour

the solubilisation of vitamin A and improve its absorption (125) since bile salts are essential for the micellarisation process (126).

One role of bacteria is a direct synthesize of carotenoids or an indirect effect on their bioavailability. Indeed, the genome of bacteria from the gut has analogues of different enzymes, found in animal and plant products, which allow the synthesis of carotenoids and retinoids from Acetyl-CoA through the mevalonate pathway (MVA) (127,128). In addition, bacteria from the genus *Bacteroides*, *Enterococcus* and *Streptococcus* possess the genes *brp/blh* that are similar to the host BCM(D)O genes, and hence could convert β-carotene into all-trans retinal (129).

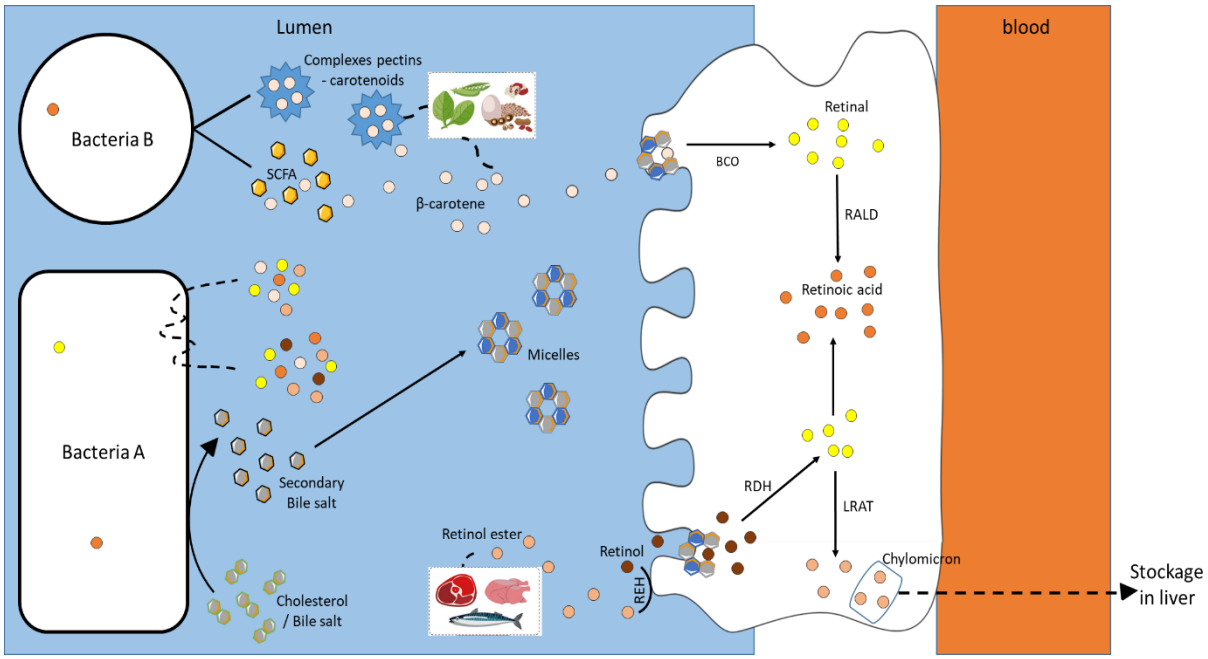

Figure 4. Schematic representation of the the gut microbiota in the intestinal absorption of vitamin A. REH : retinyl ester hydrolase ; RDH : retinol dehydrogenase ; BCO : Beta-carotene 15,15′-mono ou dioxygenase ; RALDH : Retinal dehydrogenase; LRAT : Lecithin retinol acyltransferase.

The bioavailability of carotenoids can be affected by various food components among which the cell wall structure and composition of vegetables in the food matrix which form a physical barrier, thus limiting the action of digestives enzymes (130). Pectins and some polyphenols such as naringenin have been shown to decrease the carotenoid bioavailability *in vitro* by binding cholesterol and bile salts in the lumen, and thus inhibiting the micelles formation (131). In contrast, pectins can be degraded by numerous commensals bacteria (132) and this degradation in the gut may increase the bioavailability of carotenoids. Also, the gut microbiota synthesizes enzymes or complement proteins, such as bacterial lipocalins, which could contribute to the transport of retinoid in enterocyte (133,134). Similarly, the intestinal microbiota can digest dietary fibers and thus release β-carotene or others entangled micronutrients (59).

Additionally, gut bacterial population can also regulate the host metabolism of retinol modulating the production of retinoic acid (RA) which drives the immune responses. Grizotte-Lake showed that bacteria of *Clostridium* class can regulates RA concentration in the gut epithelium by suppressing the gene Rdh7 expression, which pilot the transformation of retinol into retinoic acid (135). Moreover, this study showed that commensal bacteria communities lower RA production which is balanced by an increase in the liver storage form and favour the RE pathways; whereas potentially pathogenic bacteria promoted RA production.

The availability of retinoids in the gut environment can modulate the microbial composition. For example, the gut microbial composition of vitamin A-deficient mice had lower abundance of bacteria of genus *Enterococcus, Lactobacillus* and of the species *Clostridium difficile* from the phylum Firmicutes, as well as species from the genus *Escherichia* from the Proteobacteria phylum compared to non-deficient mice (136). The effect of vitamin A deficiency on a model of initially germ-free mice inoculated with a community of bacterial species found in human gut, resulted in a strong increase of *Bacteroides vulgatus* proportion (87). In this last study, it was suggested that the modulation of gut

microbiota composition can be can induced by the altered bile acid metabolism associated with acute vitamin A deficiency.

In mice, the proportion of Bacteroides members was lower in vitamin A deficient mice, and several class family and genus proportion were different between vitamin A deficient and vitamin A sufficient groups (23). In children with autism, vitamin A supplementation increased the proportion of bacteria from the order Bacteroidales and reduced the one of the genus *Bifidobacterium* (137). The modulation of gut microbiota composition by vitamin A can also serve as indirect pathway to modulate immune responses at the intestinal level. For example, according to experiments conducted in a mouse model, vitamin A can modulate the abundance of Segmented Filamenteous Bacteria (SFB), a group of bacteria able to induce the differentiation of Th17 Cells (136,138).

Conclusion

In summary, there is a lack of data on the effect of micronutrients (vitamin A, vitamin B9, iron and zinc) on gut microbial composition, but it seems likely that the interplay between micronutrients and the microbiome is an important factor in determining risk for vitamin and mineral deficiencies, and thus for global public health. Hence, policies designated to fight micronutrient deficiencies should start to take this compartment into consideration.

Given the huge differences among protocols, the outcomes measured and the interpretation of results, harmonization is urgently needed (106). Also, studies on micronutrient metabolism should be expanded to include the general gut microbial composition, not just pathogenic bacteria, as has long been done in the case of iron. Better cooperation between microbial scientists, food scientists, nutritional scientists, would create the opportunities to fight micronutrient deficiencies in an innovative way.

The effects of iron on the intestinal microbiota has been the most studied, as iron deficiency is likely the most widespread nutritional deficiency (29). But more studies into the effects of other micronutrients (vitamin A, zinc, B-vitamins) are needed, alone or in combination, to elucidate the interaction between micronutrients, the microbiome and the host.

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