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MINI-REVIEW

Regulatory effects of transition metals supplementation/deficiency on the gut microbiota

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Abstract

Transition metal ions are essential micronutrients for all living organisms and exert a wide range of effects on human health. The uptake of transition metal ions occurs primarily in the gastrointestinal tract, which is colonized by trillions of bacterial cells. In recent years, increasing studies have indicated that transition metals have regulatory effects on the gut microbiota. In view of the significant effect of the gut microbiota on human health and involvement in the pathogenesis of a wide range of diseases, in this paper, we provide a comprehensive discussion on the regulatory effects of four kinds of transition metal ions on the gut microbiota. A total of 20 animal model and human studies concerning the regulatory effects of four types of transition metal ions (i.e., iron, copper, zinc, and manganese) on gut microbiota were summarized. Both the deficiency and supplementation of these transition metal ions on the gut microbiota were considered. Furthermore, the potential mechanisms governing the regulatory effects of transition metal ions on the gut microbiota were also discussed.

Key points

- *Regulatory effects of iron, copper, zinc, and manganese on gut microbiota were reviewed.*
- *Both deficiency and supplementation of metal ions on gut microbiota were considered.*
- *Mechanisms governing* effects of metal ions on gut microbiota were discussed.

Keywords Transition metal ions · Iron · Copper · Zinc · Manganese · Gut microbiota

Introduction

Transition metals are a series of elements in the d and ds regions of the periodic table, which have unfilled valence layer d tracks and have significant differences in properties from other elements. Transition metal ions exhibit a variety of biological activities, such as redox reactions, oxidative stress, and involvement in the production of energy in respiratory chains, as well as such functions as electronic transfer, oxygen transport, and enzyme activity centers (Lieu et al. 2001; Andreini et al. 2008; Waldron et al. 2009; Andrews 2000).

The gastrointestinal tract of mammals harbors trillions of bacteria, and it has been estimated that in humans, the numbers of gut microbiota may be equal to human body cells (Sender et al. 2016). In the past years, increasing studies indicated that gut microbiota has a wide range of functions, and it was not only a key contributor to the host metabolism but also dysbiosis was associated with a variety of diseases of the gastrointestinal tract and others like diabetes, liver diseases, and neurodegenerative diseases (Illiano et al. 2020; Lavelle and Sokol 2020; Bäckhed et al. 2012; Sekirov et al. 2010; Buret et al. 2019; Shen et al. 2017; Shen et al. 2019; Shen 2020; Sartor and Wu 2017). The availability of transition metals is highly important for many living organisms, particularly microbes. Both exogenous and endogenous environmental factors can alter the gut microbiota, and these changes can affect host health. Both in vitro and animal models have

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been employed to investigate the effects of transition metal ions, including iron, copper, zinc, and manganese, on gut microbiota and host health. Both deficiency and supplementation of these transition metal ions can affect the species abundance and diversity of the gut microbiota. The gut microbiota also affects the roles played by transition metal ions in humans.

Therefore, it is necessary to discuss the effects of transition metal ions on the gut microbiota, which may deepen the current knowledge about mechanisms underlying the effects of transition metal ions on host health. Herein, we discussed the 20 studies published from 2011 to 2019 regarding the effects of transition metal ions deficiency and supplementation on the gut microbiota.

Iron

Iron is a necessary biological metal and mammalian cells require sufficient iron to meet their metabolic needs. However, iron is also potentially toxic and can catalyze the generation of reactive oxygen species and other highly reactive radicals under aerobic conditions (Wang and Pantopoulos 2011). Iron can also affect on the composition and metabolic activity of the gut microbiota. Several studies have investigated the modulatory effect of iron on the gut microbiota of mice and humans. Information concerning the research subjects, designs, and results were extracted from these studies and summarized in Table 1. Five of these studies reported the effects of iron deficiency on the gut microbiota. As early as 2012, Dostal et al. found an increased relative abundance of *Lactobacillus* and *Enterobacteriaceae* and a decreased relative abundance of *Roseburia* after 26 d of an iron-deficient diet (2.6 mg iron·kg diet^{-1}) in Sprague-Dawley rats (Dostal et al. 2012). Another study by Dostal et al. on human gut microbiota-associated rats demonstrated that an iron-deficient diet (2.9 mg iron·kg diet^{-1}) had little significant effect on the host's dominant bacterial and gut microbiota metabolic activity (the diet decreased the relative abundance of *Bilophila spp.*, *E. hallii*, and *Coprococcus spp.*) (Dostal et al. 2014).

Iron deficiency anemia (IDA) occurs when the body does not have enough iron. Muleviciene et al. revealed microbiota imbalance in infant IDA patients and observed a decrease in the *Bifidobacteriaceae*/*Enterobacteriaceae* ratio (Muleviciene et al. 2018). Parmanand et al. investigated the effect of iron on the growth of individual gut microbiota. They confirmed that the low iron availability inhibited the growth of *Bifidobacteria* in continuous colonic fermentation in vitro (Parmanand et al. 2019). However, Dostal et al. obtained a different result that an increase in *Bifidobacteria* was observed in continuous colonic fermentation in vitro (Dostal et al. 2013). The two in vitro studies used fecal samples from children and common fresh fecal samples, respectively. Dostal et al. concluded that *Bifidobacteria* could bind iron to the cell membranes and walls for growth advantage in the iron-deficient environment. In the study of Parmanand et al., the viable counts of *Bifidobacteria* varied in each sample. They speculated that it may be caused by individual differences of donors, and effects of metabolites and neighboring taxa. In addition, these two studies showed that iron deficiency significantly reduced the growth of *E. coli*, *S. Typhimurium*, *B. thetaiotaomicron*, *Eubacterium rectale*, *Clostridium Cluster IV* members, and *Bacteroides spp.*, while this deficiency increased the growth of *Lactobacillus spp.* (Parmanand et al. 2019; Dostal et al. 2013). A study in Crohn's disease-like ileitis model mice showed that low concentrations of iron in a sulfate-free diet (<10 mg iron·kg diet^{-1}, 11 weeks) affected the composition of the gut microbiota, and resulted in reduced abundances of *Bacteroides* and *Desulfovibrio spp.* and increased abundances of *Bifidobacterium*, *Succinivibrio*, *Turicibacter*, and *Clostridium* (Werner et al. 2011).

We also searched for five studies of iron supplementation altering the gut microbiota. Dostal et al. found that iron supplementation (35 mg iron·kg diet^{-1}) could significantly improve the metabolic activity of the gut microbiota, especially increased the abundance of *Bacteroides spp.*, which could be attributable to iron-dependent enzymes (Dostal et al. 2014). Although oral iron supplementation can effectively treat IDA, the safety of oral iron supplementation remains controversial in a subset of inflammatory bowel disease (IBD) patients (Ellermann et al. 2020). The imbalance between harmful and protective bacteria, or microbiota imbalance, is the main characteristic of IBD (Kaur et al. 2011). Importantly, dietary iron supplementation may worsen the disease or increase the risk of infection; the reason for this effect may be the alterations of the commensal microbiota (Buret et al. 2019; Paganini and Zimmermann 2017; Mahalhal et al. 2018; Lee et al. 2017), most significantly, the increased abundance of *Enterobacteriaceae* (Yilmaz and Li 2018). A study by Mahalhal et al. explored the effects of oral iron on C57BL/6 mice model of colitis (Mahalhal et al. 2018). The doubling of iron standards (400 ppm iron) led to major changes in the composition of the microbiome, including an increase in *Proteobacteria* and a decrease in *Firmicutes* and *Bacteroidetes*. Conversely, *Bacteroidetes* increased moderately in mice receiving a low-iron diet (100 ppm iron). This suggested that the growth of *Bacteroidetes* was influenced by iron. Iron reduced the growth of many pathogenic bacteria and may change the ratio of pathogenic to protective bacteria (Ng 2016). Jaeggi et al. reported that iron fortification affects the gut microbiome in African infants with diarrhea (Jaeggi et al. 2015). These results showed that the abundance of *Enterobacteria*, *Escherichia*/*Shigella*, and *Clostridium spp.* and the ratio of *Enterobacteria*/*Bifidobacteria* were increased in the iron-fortification groups. The sum of the pathogenic *E. coli* at the endpoint was higher in the iron groups than in

Table 1 Summary of studies concerning effects of iron on gut microbiota

	References	Research subjects	Research designs	Methods	Gut microbiota alteration	
Iron deficiency	Dostal et al. 2012	Male Sprague-Dawley rats	Fe-deficient diet for 24 days, repleted for 14 days with $FeSO_4$ or electrolytic Fe at 10 and 20 mg Fe kg $diet^{-1}$	TGGE and qPCR	↑ *Lactobacillus* ↑ *Enterobacteriaceae* ↓ *Roseburia*	
	Dostal et al. 2014	Germ-free female Fischer 344 rats	Fe-deficient diet for 12 weeks	pyrosequencing and qPCR	↓ *Bilophila spp.* ↓ *E. hallii* ↓ *Coprococcus spp.*	
	Parmanand et al. 2019	In vitro colonic fermentations	Cultured independently in iron-deficient media	16S rRNA gene sequence	↓ *Escherichia coli* ↓ *Salmonella typhimurium* ↓ *Thetaiotaomicron* ↓ *Bifidobacterium*	
	Dostal et al. 2013	In vitro colonic fermentations	Very low iron conditions	16S rRNA gene sequence and qPCR	↑ *Lactobacillus spp.* ↑ *Enterobacteriaceae.* ↓ *Roseburia spp.* ↓ *Eubacterium rectale* ↓ *Clostridium Cluster IV*	
	Werner et al. 2011	Wild type and heterozygous $TNF^{\Delta ARE/WT}$ mice	Iron sulfate free diet (<10 mg Fe/kg) for 11 weeks	16S rRNA gene sequence	↑ *Turicibacter* ↑ *Bifidobacterium* ↑ *Succinivibrio* ↑ *Clostridium* ↓ *Desulfovibrio* ↓ *Bacteroides* ↑ *Peptostreptococcaceae* ↓ *Proteobacteria* ↓ *Helicobacter*	WT mice heterozygous $TNF^{\Delta ARE/WT}$ mice
Iron supplementation	Dostal et al. 2014	Germfree female Fischer 344 rats	Fe-deficient diet for 12 weeks and 35 or 70 mg Fe·kg $diet^{-1}$ for 4 weeks	pyrosequencing and qPCR	enhances the concentration of beneficial gut microbiota metabolites	
	Ellermann et al. 2020	Germ-free mice	Dietary iron restriction	16S rRNA gene sequence	↑ *Enterobacteria* ↑ *Enterotoxigenic Escherichia coli* ↑ *Salmonella*	
	Mahalhal et al. 2018	Female C57BL/6 mice	100/200/400 ppm iron	16S rRNA gene sequence	↓ species richness (400 ppm iron fed) ↑ *Proteobacteria* ↓ *Firmicutes* ↓ *Bacteroidetes*	
	Lee et al. 2017	Population with Crohn's disease UC and control subjects with iron deficiency	Participants received iron sulfate or iron sucrose over 3 months	16S rRNA gene sequence	↓ *Faecalibacterium prausnitzii* ↓ *Ruminococcus bromii* ↓ *Dorea sp.* ↓ *Collinsella aerofaciens*	
	Jaeggi et al. 2015	6-month-old Kenyan infants	2.5 mg iron as NaFeEDTA, 12.5 mg iron as ferrous fumarate	16S rRNA gene sequence and qPCR	Provision of iron-containing MNPs to weaning infants adversely affects the gut microbiome, increasing pathogen abundance and causing intestinal inflammation	

the no-iron groups. Ellermann et al. studied the dietary iron modulating assembly of the gut microbiota in colitis-resistant and colitis-susceptible mice (Ellermann et al. 2020). The results showed that increased oral iron intake increased pathogenic *Enterobacteria*, including enterotoxigenic *Escherichia coli* and *Salmonella*. These findings indicated that the means of supplying iron was also important. Lee et al. evaluated the effect of different methods of iron supplementation on patients with IBD. Compared with intravenous treatment, peroral treatment reduced the abundance of *Faecalibacterium prausnitzii*, *Ruminococcus bromii*, *Dorea sp.*, and *Collinsella aerofaciens* (Lee et al. 2017). *Bifidobacteria* and *Lactobacillus* have beneficial effects in maintaining remission in IBD patients. In addition, *Bifidobacteriaceae* can bind iron to the cell membranes and walls, which subsequently reduce radical formation in the surrounding environment, thereby reducing the risk of colorectal cancer (Saha et al. 2016; Skrypnik and Suliburska 2018).

These findings suggested that dietary iron imbalance may disrupt the assembly of the gut microbiota and promote changes in bacterial composition, including an increase in the family *Enterobacteriaceae*, which is associated with various microbial-driven diseases. Iron availability is a critical signal for the expression of virulence genes by pathogens and hosts. In general, the availability of intestinal iron has a large influence on the virulence of pathogenic microorganisms. Overall, these findings indicate that the gut microbiota can be influenced by oral iron intake in the short term. However, the potential effect of long-term oral iron supplementation on gut microbiota needs to be explored.

Copper

The effect of unbalanced copper intake on the gut microbiota remains unclear (Wei et al. 2015). Five studies revealed the effect of dietary copper supplementation on the gut microbiota, and the main information extracted from these studies was listed in Table 2. Song et al. evaluated the effect of dietary copper on male weanling Sprague-Dawley rats. The results showed that while increased *Firmicutes* in low-copper-fed (1.5 ppm copper carbonate) rats were predominantly due to the increases in *Lachnospiraceae* and *Peptostreptococcaceae*, the increases in *Firmicutes* in high-copper-fed (60 ppm copper carbonate) rats might be due to the increases in *Lactobacillaceae* (*Lactobacillus*), *Lachnospiraceae*, and *Erysipelotrichaceae*. The common features of the alterations of the gut microbiota were the depletion of *Akkermansia* (Song et al. 2018). Meng et al. investigated the effect of waterborne copper exposure on the gut microbiota of juvenile common carp (*Cyprinus carpio* L.), which showed a decrease in *Akkermansia* abundance. Moreover, the abundances of small putative short-chain fatty acid-producing bacteria, including *Allobaculum*, *Blautia*, *Coprococcus*, *Faecalibacterium*, *Roseburia*, *Lactobacillus*, *Bacillus*, and *Ruminococcus*, decreased significantly, and those of *Pseudomonas* and *Acinetobacter* were found to be increased. Copper exposure disturbs the composition of the gut microbiota related to immunity in juvenile common carp, thereby increases the risk of invasion by pathogens (Meng et al. 2018). Ruan et al. investigated the effect of high doses of copper on caecal microbiota in mice. The results showed that compared with the control group, the abundances of bacteria genera *Rikenella*, *Jeotgailcoccus*, and *Staphylococcus* were significantly decreased, whereas the bacteria genus *Corynebacterium* was significantly increased, in the copper supplementation group (5 mg/kg-bw Copper) (Ruan et al. 2019). Di Giancamillo et al. studied the effects of dietary supplementation with copper sulfate on weaning piglets, which showed that the total bacterial and *Enterobacteriaceae* bacterial counts were lower in the caecum than was observed in the other groups, and in the colon, *Streptococci spp.* was lower in both copper sulfate-supplemented groups than in the controls. Copper dietary supplementation may act by restoring gut morphology, improving duodenal structure, and positively modulating the large gut microbiota (Di Giancamillo et al. 2018). Yang et al. studied how exposure to copper affected the gut microbiota in Chinese brown frog (*Rana chensinensis*). The results showed that the relative abundance of *Fusobacteria* was significantly decreased, and at the genus level, *Flavobacterium* had a significantly higher abundance (Yang et al. 2020). Dai et al. investigated the effects of early-life exposure to copper on the gut microbiota in Sprague-Dawley rats. The results showed that copper exposure decreased the ratio of *Firmicutes* to *Bacteroidetes* (Dai et al.,2020).

Zinc

As an indispensable metal element for growth and development, imbalance of zinc can also affect gut microbiota. The main information obtained from the studies of the modulation of the gut microbiota by zinc was summarized in Table 3. *Clostridium difficile* as a nosocomial pathogen exists widely. The gut microbiota is altered by zinc supplementation in the diet and decreases resistance to *C. difficile* infection (CDI) (Lessa et al. 2015; Zackular et al. 2016; Zackular and Skaar 2018). Zackular et al. investigated the effects of zinc on mice colonized with *C. difficile* and excess dietary zinc resulted in *C. difficile*-associated disease exacerbated. The study showed that high dietary zinc generated a dysbiosis that favored expansion of *Enterococcus*, *Porphorymonadaceae*, *Lachnospiraceae*, and *Clostridia XI* while reduced the population of *Turicibacter* (Zackular et al. 2016). An impacting effect of excess dietary zinc is the selection for *Enterococci*

Table 2 Summary of studies concerning effects of copper on gut microbiota

	References	Research subjects	Research designs	Methods	Gut microbiota alteration	
Copper supplementation	Song et al. 2018	Male weanling Sprague-Dawley rats	Fed diets with copper (1.5/6/20 ppm Cu) for 4 weeks	16S rRNA gene sequence	↑ *Firmicutes* ↑ *Lachnospiraceae* ↑ *Peptostreptococcaceae* ↑ *Lactobacillaceae* ↑ *Lachnospiraceae* ↑ *Erysipelotrichaceae* ↓ *Akkermansia*	
	Meng et al. 2018	Cyprinus Carpio L.	Cu (0, 0.07, 0.14, 0.28 mg/L) for 8 weeks	16S rRNA gene sequence	↑ *Pseudomonas* ↑ *Acinetobacter* ↓ *Allobaculum* ↓ *Blautia* ↓ *Coprococcus* ↓ *Faecalibacterium* ↓ *Roseburia* ↓ *Lactobacillus* ↓ *Bacillus* ↓ *Ruminococcus*	
	Ruan et al. 2019	Kunming mice	High doses of copper for 90 days	16S rRNA gene sequence	↑ *Corynebacterium* ↓ *Rikenella* ↓ *Jeotgailcoccus* ↓ *Staphylococcus*	
	Yang et al. 2020	Rana chensinensis	0, 0.1, 0.25, 0.75 μM $CuSO_4$	16S rRNA gene sequence	↑ *Rahnella* ↑ *REscherichiaShigella* ↑ *Ruminococcus* ↓ *Enterobacter* ↓ *Klebsiella* ↓ *Citrobacter*	0.1 μM $CuSO_4$
					↑ *Propionivibrio* ↑ *Tyzzerella_3* ↓ *Lachnospiraceae*	0.25 μM $CuSO_4$
					↑ *Flavobacterium* ↑*Anaerotruncus* ↓ *Citrobacter* ↓ *Ruminococcus*	0.75 μM $CuSO_4$
	Dai et al. 2020	Sprague-Dawley rats	0, 0.04, 0.20, 1.00 mg/kg $CuSO_4$ for 15 days	16S rRNA gene sequence	↑ *Erysipelatoclostridium* ↑ *Treponema* ↓ *TRomboutsia* ↓ *Chlamydia* ↓ *Bifidobacterium* ↓ *Lactobacillus*	
					↑ *Alloprevotella* ↑ *Lachnospiraceae* ↑ *Ruminiclostridium* ↑ *Ruminococcaceae*	0.04 mg/kg $CuSO_4$

in the microbiota (Zackular and Skaar 2018). Enrichment of members of the *Enterococci* genus has been reported in the gut microbiota in patients with CDI (Poduval et al. 2000). This genus is highly resistant to zinc toxicity (Abrantes et al. 2011).

Zinc is usually added to animal feed as an alternative to antibiotics (Bednorz et al. 2013). Shao et al. studied the effects of zinc on the caecal microbial community in broilers. The results showed that zinc regulated the caecal microbial community by increasing the populations of total bacteria and beneficial *Lactobacillus* bacteria in broilers and decreasing the populations of *Salmonella* (Shao et al. 2014). It has been indicated that dietary zinc supplementation might help maintain the stability of the gut microbiota, increasing the populations of beneficial bacteria and reducing the chance of *S. typhimurium* colonization in the caecum (Sommer and Bäckhed 2013). Mayneris-Perxachs et al. investigated the effects of protein- and zinc-deficient diets on the murine microbiome and metabolic phenotype. The results showed

Table 3 Summary of studies concerning effects of zinc on gut microbiota

	References	Research subjects	Research designs	Methods	Gut microbiota alteration
Zinc supplementation	Zackular et al. 2016	C57BL/6 S100a9 -/- mice	0/29/1000 mg/kg zinc	16S rRNA gene sequence and qPCR	↑ *Enterococcus* ↑ *Clostridium XI* ↓ *Turicibacter* ↓ *Clostridium*
	Zackular and Skaar 2018	C57BL/6 Δs100A9 mice	0/29/1000 ppm zinc	16S rRNA gene sequence	↑ *Enterococcus* ↑ *Clostridium XI* ↓ *Turicibacter*
	Shao et al. 2014	Male Cobb 500 broiler chicks	120 mg/kg zinc	qPCR	↑ *Lactobacillus* ↓ *Salmonella.*
Zinc deficiency	Mayneris-Perxachs et al. 2016	C57BL/6 mice	<2 ppm zinc, 20% protein, 8 days	16S rRNA gene sequence	No notable differences
	Reed et al. 2015	broiler chicken model	Control group: 42 μg/g zinc Deficiency group: 2.5 μg/g zinc for 28 days	16S rRNA gene sequence	↑ *Enterococcus* ↑ *Enterobacteriaceae* ↑ *Ruminococcaceae* ↓ *Clostridiales* ↓ *Peptostreptococcaceae*

that after zinc malnutrition the fecal microbiota exhibited only marginal changes. The abundance of *Proteobacteria* increased significantly from the age of 36 d. Several species within this phylum may gain a growth advantage by ZnuABC (Mayneris-Perxachs et al. 2016). Reed et al. used the broiler chicken model to explore changes in the gut microbial ecology of the host under zinc deficiency. They observed that zinc deficiency significantly reduced the species richness and diversity of the gut microbiota. Zinc deficiency significantly increased the relative abundance of *Enterococcus*, *Enterobacteriaceae*, and *Ruminococcaceae* and significantly decreased the relative abundance of *Clostridiales* and *Peptostreptococcaceae* (Reed et al. 2015).

Manganese

Manganese is an important trace element that is very important for the normal development of the host (Bowman et al. 2011). It has been observed that the effect of manganese exposure on the gut microbiota may be sex-specific. The main information obtained from the studies of the modulation of the gut microbiota by manganese is summarized in Table 4. For example, the abundance of *Firmicutes* significantly increased in Mn^{2+}-exposed male mice but decreased in Mn^{2+}-exposed female mice (Chi et al. 2017). Chi et al. also observed that the genus *Lactobacillus* was specifically enriched in Mn^{2+}-exposed female mice (Chi et al. 2017). In fact, despite the prevalence of manganese and the potential risk that it poses to human health, the mechanisms by which manganese exerts its effects on the gut and the gut microbiota have not been elucidated to date (Ghaisas et al. 2016).

Conclusions and remarks

Transition metals are essential for animal and human health. Gut microbiota can affect the content of transition metals in the body, and the availability of transition metals determines the state of the gut microbiota (Skrypnik and Suliburska 2018). Unbalanced metal intake may lead to changes in the gut microbiota. These findings imply that the regulation of the gut microbiota may represent an important action pathway underlying its impact on health. In this article, we reviewed 20 studies on transition metal elements (i.e., iron, copper, zinc, and manganese) in the gut microbiota. On the basis of these studies, a variety of potential mechanisms underlying the effects of transition metals on the gut microbiota were proposed as summarized in Fig. 1.

Table 4 Summary of studies concerning effects of manganese on gut microbiota

	References	Research subjects	Research designs	Methods	Gut microbiota alteration	
Manganese supplementation	Chi et al. 2017	C57BL/6 mice	100 ppm $MnCl_2$ for 10 weeks	16S rRNA gene sequence	↑ *Firmicutes* ↑ *Lactobacillus* ↓ *Firmicutes*	Male mice Female mice

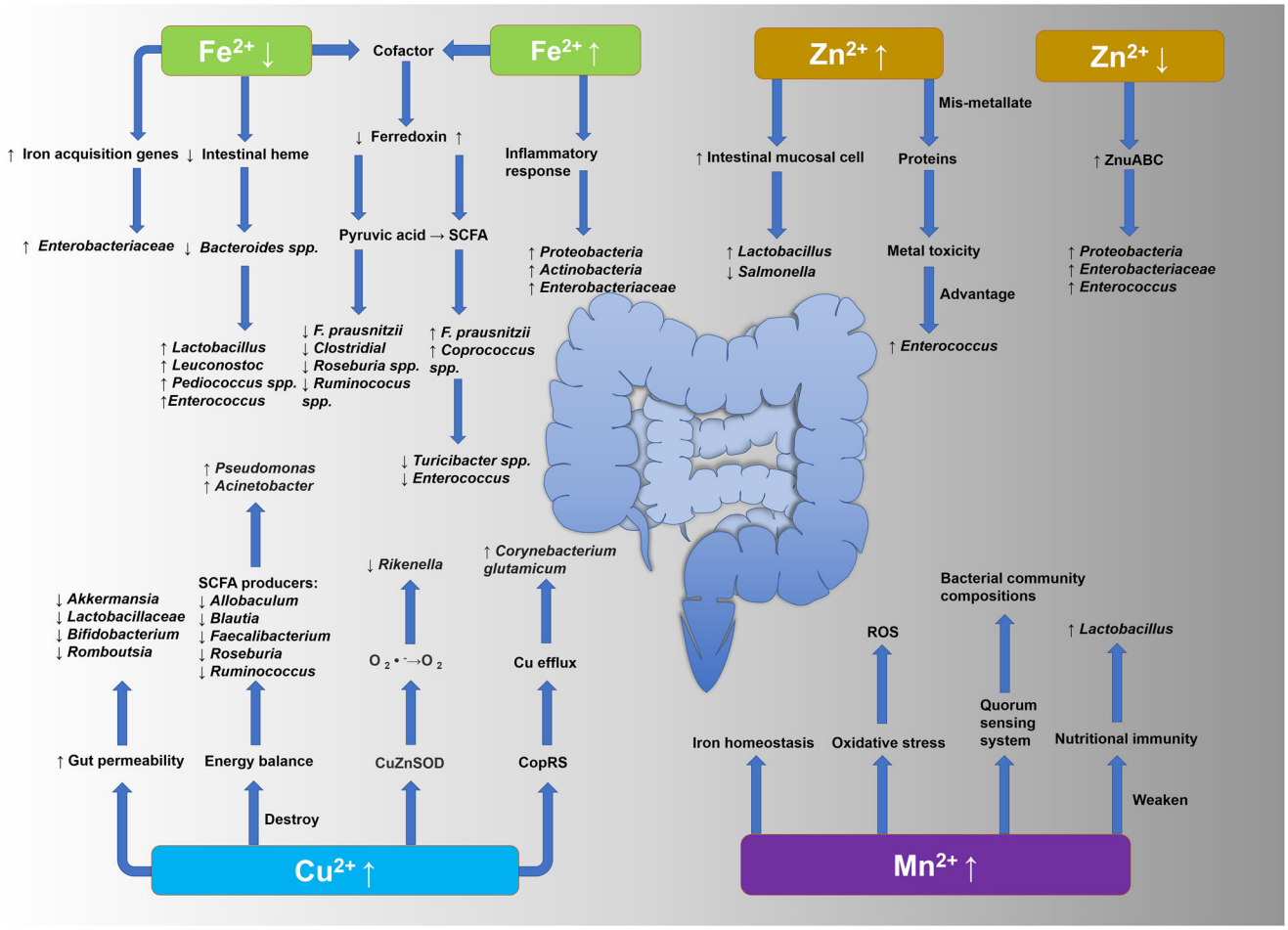

Fig. 1 Regulatory effects and possible mechanisms of transition metal ions on the gut microbiota

According to studies reviewed in this paper, intestinal iron concentration directly affects the number of short-chain fatty acid producers (such as *F. protococcus XIVa*, *Roseburia* spp., *Ruminococcus spp.*, and *Coprococcus spp.*), the reason is that the synthesis of short-chain fatty acids is influenced by iron as a key cofactor (Dostal et al. 2012; Dostal et al. 2013; Dostal et al. 2014; Lee et al. 2017). Siderophilic bacteria can steal iron from the host by using aggressive iron removal methods, which further limits the local iron availability of their non-siderophilic counterparts (Ellermann and Arthur 2017). Low iron-demand bacteria gain or lose competitive advantages with iron concentration changes (Parmanand et al. 2019; Dostal et al. 2013; Werner et al. 2011). As an important signal for pathogens and hosts to express virulence genes, iron can promote the replication and virulence of gut enteric pathogens; it is one of the main factors affecting gut microbiota (Yilmaz and Li 2018). In addition, for most intestinal gram-negative bacteria, such as *Salmonella*, *Shigella*, and pathogenic *E. coli*, iron acquisition plays a critical role in virulence and colonization (Dostal et al. 2014; Parmanand et al. 2019; Ellermann et al. 2020).

Copper in the diet plays an important role in the destruction of intestinal barrier function. High concentrations of copper ions improve intestinal permeability, and this effect is supported by a significant downregulation of intestinal connexin and a reduction in the number of goblet cells (Song et al. 2018; Dai et al. 2020), leading to the reduction of intestinal barrier-related microorganisms (e.g., *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, and *Romboutsia*) and the number of core genera producing short-chain fatty acids (such as *Allobaculum*, *Blautia*, *Faecalibacterium*, *Roseburia*, and *Ruminococcus*) (Meng et al. 2018; Yang et al. 2020). Excessive zinc shows metallic toxicity, mismatches proteins, and releases metals that have oxidative activity. In mice colonized with *C. difficile*, excessive dietary zinc not only increases toxin activity but also affects the host immune response, which exacerbates *C. difficile*-associated disease (Zackular and Skaar 2018). Some bacteria (e.g., *Proteobacteria*, *Enterobacteriaceae*, and *Enterococcus*) can gain a growth advantage by increasing ZnuABC (Zackular et al. 2016; Zackular and Skaar 2018; Mayneris-Perxachs et al. 2016; Reed et al. 2015). Furthermore, due to lower zinc levels, some families of bacteria may gain an advantage by either having less demand for zinc, more sufficient intake mechanisms, or lack of

competition through more zinc-sensitive bacteria (Paganini et al. 2016). Overexposure to manganese may affect the gut microbiota by inducing oxidative stress, which may impair nutritional immunity. In addition, high concentrations of manganese interfere with the equilibrium of ions, especially regarding iron homeostasis. The gender differences in the effects of manganese on the gut microbiota may arise from two aspects: manganese transport genes and changes in the quorum-sensing system (Chi et al. 2017).

In summary, as discussed above, four types of transition metal ions, i.e., iron, copper, zinc, and manganese, possess regulatory effects on gut microbiota through multiple pathways, which may be involved in the effects of these metals on host health and disease conditions. Both supplementation and deficiency of these transition metals can affect the gut microbiota. Thus, manipulating the transition metal ion-mediated interactions between the gut microbiota and the host is expected to be an attractive intervention strategy developed in the future. Despite several possible acting mechanisms have been proposed by previous studies, more mechanistic elucidation still need to be conducted as the interactions of these metal with gut microbiota are rather complex. In addition, the availability of transition metals in the gut tract also deserves special attention, and estimating the availability of metals and their effects on gut microbiota can help provide clues to understand how transition metals affect host health and better supplementation use of these transition metals to maintain health.

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Compliance with ethical standards

Conflict of interest CYL declares that he has no conflict of interest. XYL declares that he has no conflict of interest. HFJ declares that she has no conflict of interest. LS declares that he has no conflict of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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