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Intestinal Microbiome and Metal Toxicity

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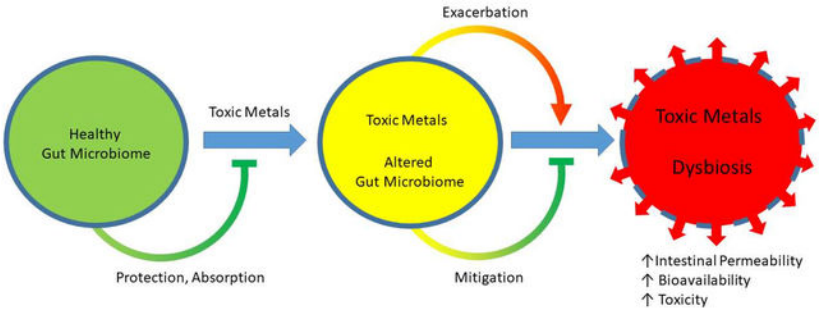
Abstract

The human gut microbiome is considered critical for establishing and maintaining intestinal function and homeostasis throughout life. Evidence for bidirectional communication with the immune and nervous systems has spawned interest in the microbiome as a key factor for human and animal health. Consequently, appreciation of the microbiome as a target of xenobiotics, including environmental pollutants such as heavy metals, has risen steadily because disruption of a healthy microbiome (dysbiosis) has been linked to unfavorable health outcomes. Thus, toxicology must consider toxicant effects on the host's microbiome as an integral part of the holobiont. We discuss current findings on the impact of toxic metals on the composition, diversity, and function of the gut microbiome as well as the modulation of metal toxicity by the microbiome. Present limitations and future needs in elucidating microbiome-metal interactions and the potential of harnessing beneficial traits of the microbiota to counteract metal toxicity are also considered.

Graphical Abstract



Keywords

Gut microbiome; microbiota; dysbiosis; heavy metal; toxicity; 16S rRNA; metagenomics; arsenic; cadmium; chromium; mercury; lead

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Conflicts of Interest

Nothing declared.

1. Introduction

A well-known quote from Paracelsus (1493 – 1541) states the founding principle of modern toxicology: “Solely the dose determines that a thing is not a poison” [1]. “Die wichtigsten Dinge des Lebens spielen sich zwischen Anfang und Ende des Verdauungskanals ab” [The most important things in life take place between the beginning and end of the digestive tract] is another quote ascribed to this ground-breaking physician and alchemist. These quotes combined are the basis of this brief review on the interactions of metals with the gut microbiome – the importance of dose in the toxicology of metals and our emerging comprehension how crucial the trillions of microorganisms in the gut are for human health and disease. As the most densely colonized site in the human body, the gastrointestinal tract (GIT) is inhabited by microbes in numbers ranging from 10^1–10^3 CFU/ml in the stomach to 10^{11}–10^{12} CFU/ml in the colon, while overall more than 1,100 known bacterial species were identified in a recent culturomics and metagenomics study [2]. Bacteria represent the vast majority of the intestinal microorganisms, while archaea, fungi, and protozoa are considered minor components of a healthy gut microbiota. Recent studies on the intestinal virome have estimated that the number of bacteriophage particles in the gut reaches, if not surpasses, the number of bacteria – appreciation of the potential impact of the virome on the microbiome-host interaction is just emerging [3–6].

The crucial role of the microbiome in development, function and homeostasis of the GIT, as well as its integration with the host immune and nervous systems [7–11], raises many questions on how this “organ” within an organ interacts with ingested xenobiotics and how the outcome of these interactions might affect the individual host [12–15]. While the human gut microbiotas exhibit commonalities in structure and metabolic activity, the uniqueness of individual microbiomes, especially at the species and strain levels, should be an important factor in the assessment of toxicity of any xenobiotic.

As gut microbiomes potentially are exposed to myriads of xenobiotics such as oral therapeutic drugs, drugs of misuse, and environmental chemicals and pollutants, we will focus this critical review on recent insights on the effects of a selection of heavy metals on the gut microbiome and conversely, potential actions of gut microbes affecting the toxicity of metals. Most of these deliberations stem from findings in experimental animal research, because the literature on the interrelationships of toxic metals and the intestinal microbiome in humans is still relatively scarce.

2. Metals change the microbiota

Physiologically essential metals (e.g., Mg, Mn, Fe, Co, Ni, Cu) at high concentrations and some non-essential metals such as mercury, silver, and lead at much lower concentrations are toxic to many microorganisms. While these antimicrobial effects may be advantageous for growth suppression or killing of pathogens (for review [16]), especially when these are multi-drug resistant, the indiscriminate nature of metal toxicity likely will also harm commensal and beneficial microbes in complex communities such as the gut microbiota. Metal toxicity results from oxidative stress via generation of reactive oxygen species (ROS) and depletion of antioxidants, protein dysfunction via oxidation, structural damage and

interference with catalysis, and from metal-induced damage to biological membranes. Furthermore, antimicrobial activity may also be based on disturbances of gene expression and DNA damage (genotoxicity) [16].

Exposure of the gut microbiota to toxic metals is likely to exert disparate effects on the resident species, depending on intestinal location (e.g., stomach, jejunum, ileum, cecum, or colon; lumen vs. mucus layer), microenvironmental conditions such as pH, oxygen availability and redox potential as well as the abundance of susceptible/resistant strains and overall diversity and metabolic activity of the local microbial community. In addition, a wide range of host factors including nutrition, sex, age, and immune status may influence the microbiome-metal interaction. In the following, we discuss a selection of the most toxic metals with emphasis on arsenic, whose compounds are arguably the most studied in context with the gut microbiome.

2.1. Arsenic

Arsenic is a highly relevant environmental toxicant found in food (e.g., rice, fish, seafood) and drinking water supplies. Arsenic exposure can lead to carcinogenesis and other adverse health outcomes affecting various organ systems [17]. Speciation of arsenic is crucial for health risk assessment and the potential for alteration of bioavailability through interactions with gut microbes. For example, water sources are almost exclusively contaminated with inorganic arsenic (arsenate, arsenite), while food may contain inorganic and organic species of arsenic. The trivalent arsenite and especially its methylated species (e.g., monomethylarsonous acid) are more toxic than the respective pentavalent states.

Richardson et al. [18] assessed the acute effects of toxic metal exposures on rat gut microbiotas by administering five different metals, each administered at a specific range of three different doses, for five consecutive days. Rats received daily oral gavages of sodium arsenite, cadmium chloride, cobalt chloride, sodium dichromate, or nickel chloride. Fecal samples for microbiota analyses were collected prior to the first administration and 24 hours after the fifth dosing [18]. Sequencing of 16S rRNA genes and computational prediction of microbial gene content (Phylogenetic investigation of communities by reconstruction of unobserved states; PICRUSt [19]) were used to characterize the early and metal-specific perturbations in the rat gut microbiota instigated by these toxicants with significant environmental and human health impacts (e.g., all are considered carcinogens [20,21]). Arsenic, cadmium, and nickel altered bacterial composition and diversity significantly and in a dose-dependent manner, while chromium and cobalt had weaker impacts on the microbiota, albeit still appeared to affect host physiology (e.g., causing weight loss) [18]. Importantly, the response to the metals were not uniform, showing specific changes in the microbiota depending on the administered compound. For example, the Bacteroidetes family S24–7 [22] was dramatically reduced by nickel, while other Bacteroidetes and Proteobacteria increased. The PICRUSt analyses showed increases of iron-importing gene functions in the nickel and arsenic-treated samples, which could be related to selection of bacteria capable of utilizing these genes to moderate the toxic metal effects.

Comparison of these results with other studies that employed different metal exposure regimens and dosages in other animal models illustrates how deeply experimental factors influence study outcomes.

Lu et al. [23] reported that arsenic exposure in drinking water (10 ppm arsenic for 4 weeks) alters the composition (e.g., decreases in some Firmicutes families) and metabolic profiles (e.g., alterations in indole metabolites, bile acid profiles) of the gut microbiota of female C57BL/6 mice. In another study with lower, environmentally relevant dosage of arsenic (100 ppb, 13 weeks), dysbiosis with alterations in composition and diversity of microbiota was accompanied by metagenomic changes in carbohydrate metabolism, short chain fatty acid synthesis and starch utilization systems [24]. Furthermore, arsenic increased oxidative stress indicators and DNA repair genes. Of particular concern is the observed enrichment of multidrug resistance and conjugative transposon genes in the arsenic-exposed animals, which could indicate that heavy metals promote the spread of multidrug resistance via horizontal gene transfer in the gut.

Sex-specific responses to arsenic exposure were explored by Chi and coworkers [25] who found not only differences in the resultant fecal microbiota compositions of male and female mice, but also clear distinctions in functional profiles as determined by metagenomics sequencing. Interestingly, sex-specific effects of arsenic exposure also were found in 6-week-old human infants who were part of the New Hampshire Birth Cohort Study [26]. Despite the relatively low arsenic exposure levels in this cohort, significant associations of elevated urinary arsenic levels with stool microbiome composition (e.g., reduced abundance of *Bifidobacterium*, *Bacteroides*, and *Lactobacillus*) were found in formula-fed male infants, but not in female formula-fed infants or breast-fed infants of both sexes.

The fecal microbiotas from a cohort of Bangladeshi children, who were exposed to low and high arsenic levels during prenatal development and early life, revealed higher abundance of Proteobacteria, in particular Gammaproteobacteria, in children with high exposure [27]. Concomitantly, virulence and multidrug resistance genes were enriched after high exposure; especially *E. coli* strains with arsenic resistance genes (ArsB, ArsC) were increased.

Gokulan et al. [28] investigated the impact of single and short-term repeated (8 days) arsenite exposure on gut microbiome composition as well as intestinal immune status in adult and juvenile CD-1 mice. Dose, duration of exposure, and developmental status of the animals effected distinct changes in bacterial recovery and microbiota composition. Repeated exposure increased the abundance of bacteria harboring arsenic resistance genes and induced arsenite methylation for detoxification by the host. Furthermore, reduction of bacteria involved in protein to butyrate conversion as well as indications of host immune modulation by arsenic exposure were revealed. Single doses of arsenite in juvenile mice elicited distinct bacterial populations, which illustrates how early-life arsenic exposure may have long-term consequences for development of a healthy gut microbiota.

Mitigation of acute arsenic toxicity (25 or 100 ppm inorganic sodium arsenate) by the microbiota was demonstrated by Coryell at al. [29] using antibiotic-treated, transgenic (arsenite methyltransferase As3mt detoxification enzyme knock-out), germ-free, and

gnotobiotic mice. While microbiome disruption by antibiotic treatment increased arsenic bioaccumulation, germ-free status in concert with As3mt-deficiency was associated with high mortality after acute exposure. Interestingly, transplantation of human stool microbiota to the hypersensitive germ-free transgenic mice protected the recipients from arsenic-induced mortality. Moreover, gnotobiotic mouse experiments showed that *Faecalibacterium prausnitzii*, a bacterium commonly associated with healthy human microbiomes [30], provided at least partial protection against arsenic toxicity [29] – thus, specific microbiome manipulation may aid in prevention and treatment of arsenic poisoning.

2.2. Cadmium

Cadmium is another toxic metal with significant environmental impact [31]. For the general population, cadmium accumulated in food poses the main risk of exposure [31]. The GIT is a main target for cadmium toxicity [32]. Impairment of the gut barrier function in concert with Cd-induced changes in viability of components of the gut microbiota lead to increases in proinflammatory molecules (e.g., lipopolysaccharide, LPS) and may result in systemic inflammation. In addition to the aforementioned study by Richardson et al. [18], the impact of Cd toxicity on the intestinal microbiome of mice was investigated by several other research groups [33–35] who all reported significant alterations in bacterial communities; however, in detail, changes were disparate, even opposite, most likely due to differences in dosing, animal model, and sequencing methodology.

2.3. Lead

A similar situation is encountered with lead. Exposure to lead remains a public health issue, globally and in the U.S., as the water crisis in Flint, MI, has demonstrated [36–38]. A recent multi-omics study by Gao and coworkers [39] assessed the effects of lead on the gut microbiota composition, diversity, and metabolic activity (via whole-genome metagenomics sequencing and gas chromatography-mass spectrometry metabolomics) revealing that lead exposure altered the development of the gut microbiota and concomitantly affected multiple metabolic pathways, including some related to oxidative stress and detoxification. Such a multipronged approach certainly provides a more comprehensive insight into the impact of toxic metals on the gut microbiome.

2.4. Mercury

Elemental, inorganic and organic forms of mercury are global pollutants with disparate toxicity (Hg^0 < inorganic Hg, mostly Hg^{2+} < organic Hg, mostly CH_3Hg). As a potent neurotoxicant, methylmercury is most concerning, especially because of its tendency to bioaccumulate in fish relevant for dietary consumption [40]. A recent study by Rothenberg et al. [41] investigating potential correlations of the gut microbiota structure and metabolic activities with fetal methylmercury exposure in pregnant women revealed a significant correlation of 17 bacterial genera with mercury biomarkers. Dietary methylmercury also led to changes in the gut microbiome and metabolome of mice and larval fish [42].

3. Microbiotas change metals

In addition to host metabolism, biotransformation by gut bacteria such as reduction, oxidation, methylations or demethylations may modulate metal toxicity (Fig. 1). For example, trivalent arsenite and especially its methylated species (e.g., monomethylarsonous acid) are more toxic than the respective pentavalent states. Both host cells and gut microbes can act on arsenic and transform it into less or more toxic forms (for review [43]. Other examples are the reduction of highly toxic chromate [Cr(VI)] to its less-toxic form [44–46] or the potential biotransformations of mercury [44,47]. The high neurotoxicity of organic mercury has drawn attention to microorganisms that can methylate mercury and concomitantly increase its bioavailability. The gene pair *hgcAB*, first described in two sulfate-reducing bacteria [48], has become a genetic marker used to screen for orthologous methylation genes in bacterial and archaeal genomes as well as many metagenomes [49–52]. While the evidence for effective mercury methylation in the vertebrate intestine remains scarce, potential detoxification reactions by the microbiota such demethylation of methylmercury or reduction of inorganic mercury to its least toxic elemental form (via activities encoded by bacterial *mer* operons) are actively investigated [47,51]. Another mechanism how the microbiota may interfere with metal toxicity is the binding of metals by intestinal microorganisms, which could aid in elimination of the toxicants from the GIT (Fig. 1). A recent study in pregnant women and children has provided evidence for such beneficial effects exerted by certain bacteria: a probiotic-supplemented yogurt reduced the bioaccumulation of arsenic and mercury [53]. In summary, the resident gut microbiota is likely to interfere with bioavailability and toxicity of metals. Consequently, the gut microbiome could have a substantial influence on an individual's susceptibility to toxic metal exposure.

4. Challenges, Limitations, and Opportunities

Undoubtedly, the gut microbiome does have a profound impact on the toxicity of metals and their health effects on humans and animals. Current challenges and limitations in understanding the microbiome-metal interrelationship are posed by differences in experimental design (animal model, metal dosing, mode of exposure, sequencing technologies, data analytics, etc.), quality control (QC) measures, and by the sheer overwhelming complexity of the microbiome-host interactions. Each individual's microbiome is unique and dynamic, constantly influenced by environmental, dietary, and biological factors.

At present, strong efforts are underway to make microbiome research more reliable and reproducible; for example, by using mock communities and spike-in controls for QC as well as standardized sampling procedures and data analysis pipelines [54,55]. As briefly summarized in this review, correlations of microbiome structure with metal toxicity are not enough - for elucidation of the mechanisms operating at the metal-microbiome-host interface, mechanistic confirmation using multiple omics such as metagenomics, transcriptomics, proteomics, and especially metabolomics will be necessary. Furthermore, the gut virome's involvement needs to be evaluated.

Similarly, careful and considerate use of experimental models is required, but must be cognizant of the many potential pitfalls in design and transferability of results [56]. Alternative preclinical models, such as microbiome research in the highly social prairie voles (*Microtus ochrogaster*), can provide novel insights into the microbiome-gut-brain behavior axis [57,58]. Additionally, most animal studies to date have addressed single exposure, however, exposure to multiple metals or pollutants is frequent. Therefore, research studies with exposures to two or more toxicants must be conducted that are more realistic scenarios of exposure [59].

Environmental pollution by toxic metals is a global threat to human health and well-being. Therefore, well-designed surveillance studies are necessary to uncover, combat, and prevent human exposure. Microbiome research will continue to be essential for our understanding of toxicology and precision medicine. An individual's microbiome must be considered in risk assessment and treatment of toxic metal exposure.

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• special interest

•• outstanding interest.

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- Heavy metal exposure can alter the composition of the intestinal microbiome
- Heavy metals may affect the diversity of the gut microbiota
- Metabolic activities of the gut microbiota may change during heavy metal exposure
- Components of the gut microbiome can mitigate or exacerbate the toxicity of heavy metals

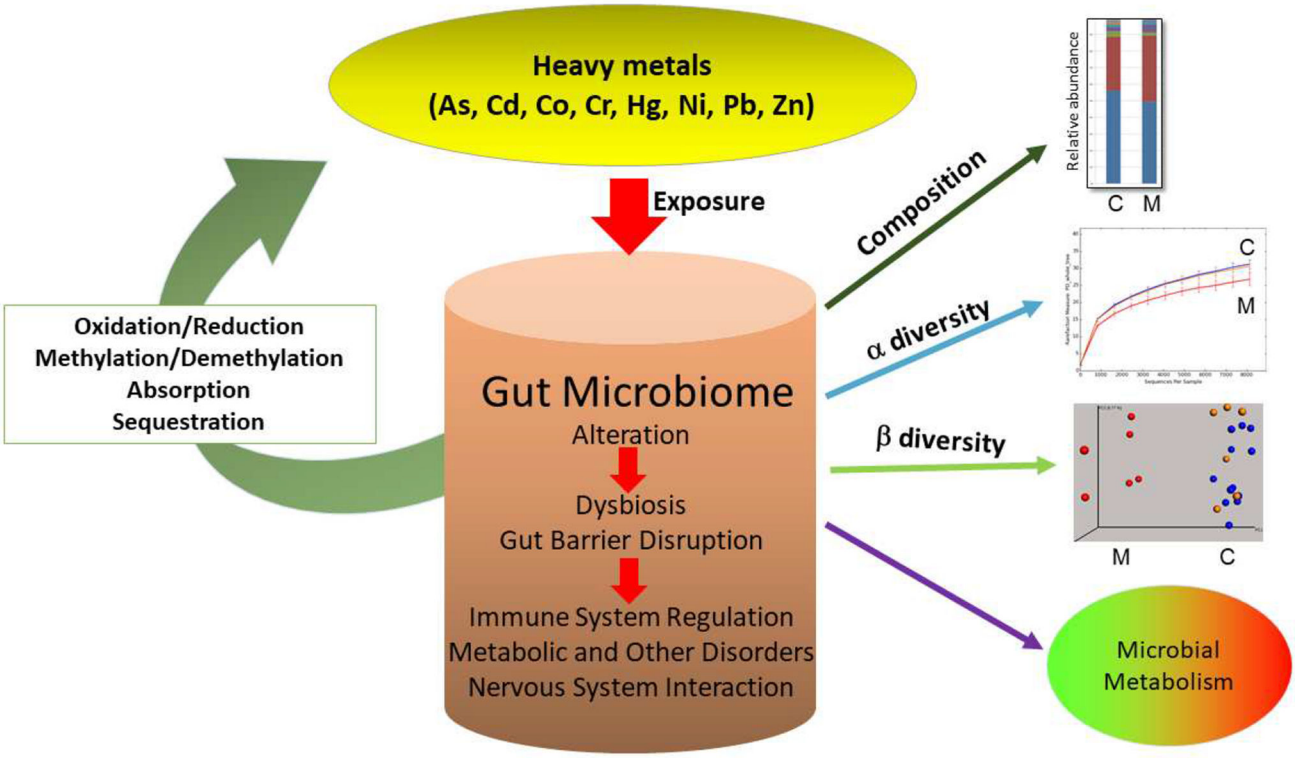

Fig. 1. Metal-Gut Microbiome Interactions.

Ingested toxic metals exposure can alter the composition (abundance of taxa), alpha and beta-diversity, and metabolic activities of resident microbiota in the gut. Dysbiosis and gut barrier disruption may activate the immune system, lead to metabolic and other disorders, and also could affect the bidirectional communication with the CNS (gut-brain axis). However, members of the gut microbiota could also modulate the toxicity of ingested metals via oxidation, reduction, methylation or demethylation reactions as well as binding and sequestration of metal species. M: Metal-exposed; C: control.