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INVITED EDITORIAL

Microbiota as a reservoir of antibiotic resistance genes: relevance and urgency

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Antimicrobial resistance (AMR) is one of the top threats to global public health and development. Antimicrobial resistance is expected to cause US$ 1 trillion additional health care costs by 2050, and US$ 1-3.4 trillion gross domestic product (GDP) loss every year by 2030.(1) Antimicrobial resistance is a natural process, occurs over time through genetic modification in the pathogens, so called evolution of antibiotic resistance genes (ARGs).(2) The acquisition of ARGs makes the pathogenic microorganisms fully or nearly unresponsive to the antibiotics. There are several reservoirs of ARGs in the environment;(3) however, waste water treatment plants (WWTPs) are becoming principal hotspots of ARGs as they concentrate the ARGs by collecting the sewage (e.g., human, healthcare, and industrial sources).(4) Now, to the list of environmental hotspots of ARGs have been added human gut microbiota, which are becoming a fundamental reservoir of ARGs. Due to ARGs, gut microbiota are resistant to antibiotics, therefore these microbiota can be referred to as 'resistomes'.(5) Thus, as a source of ARGs, the gut microbiome has evolved as a significant component of the resistome. Antibiotics, in fact, can alter the microbiota composition by favoring antibiotic-resistant bacteria, which leads to opportunistic infections. The major concern now is the horizontal transfer of ARGs from gut microbiota to pathogens, thus, the resistome greatly threatens human health by transferring ARGs to pathogens.

In the recent past, several investigations have focused on ARGs in microbiota and revealed interesting insights; these include but are not limited to correlation between increased resistomes in gut microbiota and autism spectrum disorder (ASD) in children, linking of ARGs to a limited set of gut microbiome taxa worldwide, influence of ARGs on gut microbiota to intervene in the treatment of specific disorders, etc. Therefore, knowing the distribution of ARGs in microbiota is crucial in improving human health by predicting the diseases, treatments against specific disorders, etc. A strong correlation between increased resistome and ASD in 3- to 5-year-old children has been found in Moscow, Russia.(6) Antibiotic resistance genes against aminoglycosides, β-lactams, macrolides, and tetracyclines in the bacteria of gut microbiota were found to be higher in the children with ASD than in healthy children. Early life exposure to antibiotics can influence the composition and functions of gut microbiota, which can be associated with disorders such as ASD.(6) With respect to the linkage between ARGs and gut microbiota, it has been found that clinically relevant ARGs have not been distributed in diverse gut commensal microbiota. For instance, upon the examination of 14,850 human metagenomes and 1666 environmental metagenomes from 33 countries, as well as 600,000 isolate genomes, it has been found that the *cfiA* gene (ARG encoding carbapenemase on a mobilizable plasmid) was tightly restricted to

Bacteroides (human gut microbiome).[7] However, the tight relationship between certain ARGs and microbiota is unclear; future studies should focus on the factors that allow or restrict these ARGs from establishing within the microbiota. Nonetheless, the increase in ARGs in the gut microbiota is strongly influenced by antibiotic use on an individual level.[8]

Gut microbiota with ARGs may influence the therapeutic effects against major depressive disorder (MDD). A metagenomic sequencing study has determined the composition of ARGs of gut microbiota in MDD patients and found that ARGs in *Eggerthella*, *Weissella*, and *Lactobacillus* significantly affected the drug efficacy against MDD.[9] These insights explore our knowledge on the complex interplay among "gut microbiota—ARGs—antidepressants" in finding better therapeutics for MDD. In a very recent investigation,[10] a strong correlation has been found between enrichment of ARGs in gut microbiota and an increased risk of in-hospital mortality of acute gastrointestinal injury (AGI) patients. Shotgun metagenomic sequencing with co-occurrence patterns confirmed the enrichment of more ARG subtypes in gut microbiota (e.g., *Clostridium* and *Methanobrevibacter*) in the death group over the survival group of AGI patients.[10] Such insights are helpful not only in reflecting gastrointestinal injury and identifying disease biomarkers, but also in preventing and treating AGI-related diseases. Longer stays in intensive care units with antibiotic treatment could be a possible reason for the hike in ARGs in the gut microbiota of the death group over the survival group. However, other factors cannot be ignored in the establishment of ARGs in the microbiota. For instance, using a mice model, it has been confirmed that there was an increment in ARGs in western diet-fed mice over standard diet-(low-fat, high-fiber)-fed mice.[11] Western diet-fed mice have showed increased ARGs in both cecal microbiota (e.g., *CfxA2*, *ErmG*, *TetQ*, and *LnuC*) and stool samples (e.g., *ErmG* and *CfxA2*). Exposure to polystyrene microplastics (PS-MPs) has been found to induce ARG emergence (e.g. glycopeptide and aminoglycoside ARGs) and mobility (e.g. glycopeptide and macrolide-lincosamide-streptogramin ARGs) in rat gut microbiota at an environmentally relevant concentration.[12] Key ARG hosts found in PS-MPs-exposed rats belonged the phylum *Firmicutes* and the order *Clostridiales*. Interestingly, the spread or mobility of ARGs from gut microbiota can be minimized by using certain natural products. Acetylshikonin (ASK) is a naphthoquinone derivative from the medicinal plant *Lithospermum erythrorhizon* and has been found to reshape the microbiota by boosting probiotics and inhibiting the transfer of *mcr-1* IncX4 plasmid in the gut microbiota.[13] Therefore, natural products not only modulate the gut microbiota, but also block the spread of ARGs by horizontal gene transfer (HGT) in the gut community. In conclusion, the human gut is a major hotspot for ARG-harboring resistomes which threaten human health by increasing the risk of diseases (e.g. ASD, AGI etc.), and decreasing drug efficacy (as in case of MDD). The establishment and HGT of ARGs in the gut microbiota are influenced by various host, environmental, and microbial factors. Strategies to minimize health risks involve using specific agents and broader public health measures.

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