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Microbial interactions as the key to understanding and controlling environmental spread of antibiotic resistance genes

Haining Huang, Litao Wei, Ling Li, Zishan He, Kehan Zhang, Minglu Bao, Wen Sun, Xinyi Li, Junya Zhang, Pingfeng Yu, Jinfeng Wang & Yinguang Chen

Beyond abiotic factors, microbial interactions are critical yet understudied regulators of environmental antibiotic resistance gene (ARG) spread, whose neglect hinders control efforts. We synthesize their dual roles in ARG dissemination and advocate for integrated advanced methodologies combining tracking, modeling, and validation to decode interaction networks. Moreover, we propose novel interventions strategies that range from molecular disruption to network re-engineering, leveraging ecological insights to mitigate resistance spread across environmental compartments.

The relentless dissemination of antibiotic resistance genes (ARGs) across ecosystems, driven by horizontal gene transfer (HGT) through mechanisms such as conjugation, transformation, and transduction, poses a significant threat to global health. Although the "One Health" framework has rightly shifted focus from ARG occurrence to transmission dynamics[1], prevailing research remains disproportionately focused on abiotic stressors (e.g., antibiotics, heavy metals, nanoparticles, microplastics)[2]. This narrow perspective obscures a fundamental truth: microbial interactions, which are shaped by niche partitioning, trophic dependencies, and coevolution, may sculpt ARG dissemination trajectories within community networks. Relationships ranging from symbiosis to predation can modulate ARG transfer efficiency, host range, and persistence across environmental matrices. This comment contends that neglecting this biological dimension critically undermines efforts to predict or control environmental ARG spread. We synthesize evidence positioning microbial interactions as dualistic ARG regulators, advocate for methodological innovation to decode their complexity, and propose targeted interventions leveraging ecological network engineering.

Microbial interactions: a double-edged sword in resistance spread

Microorganisms engage in intricate, context-dependent relationships that can paradoxically either accelerate or impede ARG spread through multiple interconnected mechanisms. Predatory interactions exemplify this duality. Although protozoan grazing in soil reduces the absolute abundance of ARG-carrying plasmids, it simultaneously enhances conjugative transfer among surviving microbes by inducing stress responses and increasing membrane permeability[3]. Similarly, phage predation eliminates resistant strains in wastewater, but can also spread ARGs through phage-bacterium symbiosis in plastisphere or by reshaping spatial structures to favor donor-recipient contact[4–6]. Metabolic interactions among bacteria, between fungi and bacteria, and with plants further complicate this landscape[7–12]. Some natural antibiotics (e.g., pyocyanin)[10], bacteriocins[12], and common metabolites (e.g., carbon dioxide[13], nitric oxide[8], and sulfide[14]) can boost HGT by inducing bacterial stresses. In contrast, compounds such as carotenoids can diminish HGT efficiency by alleviating oxidative stress[9]. Moreover, competing microbes can release extracellular nucleases that degrade free DNA, thereby limiting transformation potential[15]. Even community spatial architecture has conflicting effects: biofilms, often regarded as hotspots for HGT due to high cell density, may hinder plasmid diffusion when mature three-dimensional structures act as physical barriers[16].

Bridging the knowledge gap through integrated methodologies

Despite these compelling insights, the prevailing limitation in current research lies in its reliance on reductionist pure-culture models at the strain-level or static metagenomic correlations at the community-level. These fail to capture the dynamic, multitrophic nature of interactions within authentic communities. Predictive capacity remains elusive without methodologies accounting for environmental conditionality, such as nutrient shifts or pollutant pulses that reconfigure networks. Bridging this gap necessitates an integrated approach that advances from mere correlation to mechanistic causation through three synergistic strategies.

First, in situ tracking of ARG-host dynamics requires cutting-edge tools capable of resolving these interactions within intact microbiomes. Promising methodologies include: (1) Single-cell sequencing techniques (e.g., Microbe-seq, emulsion, paired isolation, and concatenation PCR (epicPCR)) that link ARG carriage to transcriptional heterogeneity and host taxonomy at strain-level resolution[17,18]; (2) Hi-C metagenomics, which reveals physical interactions between plasmid and chromosome across diverse hosts in settings like wastewater and gut microbiomes[19], supplemented by deep targeted metagenomics using gene-capture platforms for higher sensitivity and specificity[20]; and (3) Fluorescence-based systems, including dual-reporter constructs (GFP/mCherry) combined with

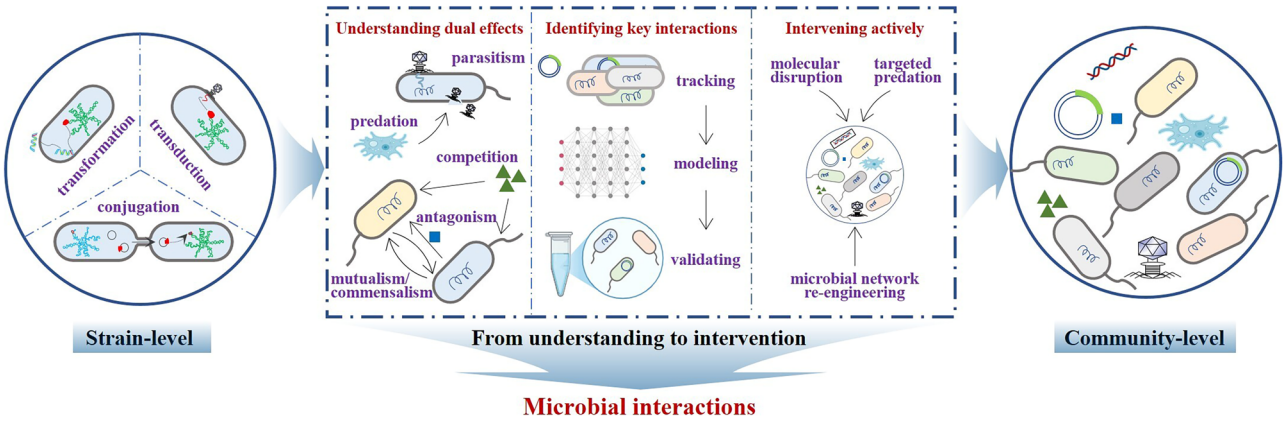

Fig. 1 | Microbial interaction pathways shape ARG dissemination and provide targets for intervention. A comprehensive understanding of how microbial interactions sculpt the dissemination patterns of ARGs from the strain-level to the community-level is crucial for developing effective interventions.

fluorescence-activated cell sorting (FACS) to allow visualize real-time conjugation, and mobile genetic elements-Fluorescence in situ hybridization (MGEs-FISH) to visualize plasmid-host co-localization in biofilms[17]. Second, potential microbial interactions with ARG-hosts can be elucidated through co-occurrence and complementarity networks derived from metagenomic sequencing and computational modeling[21]. However, such predictions depend heavily on large, high-quality datasets. Third, predicted interactions must be tested in controlled systems. Synthetic communities allow precise manipulation of interactions to identify transmission pathways, whereas microcosm experiments reveal how networks respond to disturbance. This iterative cycle, including tracking, modeling, and validating, is essential to uncover the ecological and mechanistic principles behind ARG persistence and spread.

Toward environmentally informed interventions: concepts and challenges

A mechanistic understanding of microbial interaction networks holds promise for a shift from passive monitoring to proactive environmental management aimed at suppressing ARG dissemination. However, translating this potential into reliable interventions requires addressing critical knowledge gaps regarding the context-dependency, ecological side effects, and long-term stability of such strategies.

Primary intervention concepts, explored mainly in model systems, aim to disrupt specific interaction mechanisms that facilitate HGT (Fig. 1), aligning with previously proposed Eco-evo strategies[22]. For instance, quorum sensing inhibitors such as vanillin can suppress plasmid conjugation in wastewater microbiota[23]. Yet, the broader ecological consequences of such signal disruption, including impacts on non-target microbial functions and community stability, remain poorly understood. Similarly, although engineered nucleases secreted by *Shewanella oneidensis* can cleave extracellular DNA and reduce transformation risk[15], their efficacy and ecological safety across diverse environmental matrices require further validation. Introducing antioxidant-producing bacteria to reduce the SOS response[9], a known HGT trigger, also raises questions regarding their survival, niche adaptation, and potential to alter resident community composition. Secondary strategies propose leveraging biotic interactions such as predation. For example, deploying phage consortia or CRISPR-Cas-equipped phages to target keystone ARG hosts like *Streptomyces* in soil[24]. Although promising, these approaches entail non-trivial risks, including off-target effects, phage-host coevolution, and potential facilitation of transduction. A more fundamental understanding of phage-bacteria dynamics across environmental gradients is essential to minimize unintended ARG dissemination.

The most ambitious frontier involves rationally redesigning microbial networks to inherently reduce ARG transfer. Proposed concepts include tuning functional guild composition to create metabolic bottlenecks unfavorable to plasmid stability, manipulating cross-feeding to favor low-HGT lineages, or engineering biofilm spatial architectures to limit donor-recipient contacts. Success in this arena will require advancements beyond laboratory validation, including the development of engineered ecosystems, integrated One Health monitoring of ARG flux across reservoirs, machine learning-guided adaptive intervention strategies, and rigorous assessments of network stability to ensure ecological sustainability. Future efforts will depend on interdisciplinary collaboration across environmental engineering, ecology, microbiology, synthetic biology, and bioinformatics.

Conclusion: microbial interactions as leverage points for mitigating ARG spread

Microbial interactions represent candidate key ecological control points that govern the dissemination of ARGs in the environment. Integrating advanced methodologies to decipher these complex networks enables both predictive ecology and precision interventions, ranging from targeted signal disruption to proactive community reprogramming, to establish effective environmental barriers against the spread of resistance. This strategy provides a scientific foundation crucial for protecting the One Health continuum. The critical next step is to translate ecological insights into adaptive solutions tailored to environmental heterogeneity. By decoding microbial interactions, which function as nature's evolved governance system, we can transform knowledge into actionable strategies to counter the growing ARG crisis.

Data availability

No datasets were generated or analysed during the current study.

Haining Huang[1], Litao Wei[1], Ling Li[1], Zishan He[1], Kehan Zhang[1], Minglu Bao[1], Wen Sun[1], Xinyi Li[1], Junya Zhang[2], Pingfeng Yu[3], Jinfeng Wang[4] & Yinguang Chen[1] ✉

[1]State Key Laboratory of Water Pollution Control and Green Resource Recycling, School of Environmental Science and Engineering, Tongji University, Shanghai, China. [2]State Key Joint Laboratory of Environmental Simulation and Pollution Control, Research Center for Eco-Environmental

Sciences, Chinese Academy of Sciences, Beijing, China. [3]College of Environmental and Resource Sciences, Zhejiang University, Hangzhou, China. [4]State Key Laboratory of Water Pollution Control and Green Resource Recycling, School of the Environment, Nanjing University, Nanjing, Jiangsu, China.
✉e-mail: yinchentj@163.com; yinguangchen@tongji.edu.cn

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Author contributions

H.H., L.W., L.L. and X.L. created the first draft, Z.H., K.Z., M.B. and W.S. helped the revision, J.Z., P.Y. and J.W. provided feedback on the manuscript, Y.C. made extensive changes, and edits. All authors have read the final version.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Yinguang Chen.

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