Environmental Dissemination of Antibiotic Resistance Genes Driven by Microbial Metabolites

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The dissemination of plasmid-mediated antibiotic resistance genes (ARGs) in the environment has become a global threat to ecological security and human health. In contrast to previous studies focusing mainly on abiotic factors such as coexisting pollutants affecting plasmid conjugation, this study reveals for the first time that typical microbial metabolites of carbon (CO_2), nitrogen (NO), and sulfur (H_2S) are important yet overlooked biological drivers facilitating the spread of ARGs. These metabolites modulate the efficiency of plasmid conjugation by inducing various microbial stress responses, including oxidative, nitrosative, and reductive stress, which alter the cell surface properties of donor and recipient bacteria, intracellular key ion levels, and amino acid metabolism. Taking H_2S as an example, even at environmentally relevant concentrations, it significantly enhances the conjugation frequency of plasmid RP4 within sewage microbial communities and expands its transmission range. Mechanistic investigations demonstrate that H_2S exposure activates the plasmid RP4-encoded protein Upf32.8, thereby relieving the suppression of genes encoded by plasmid RP4 and intensifying its hijacking of glutamine metabolism in donor bacteria. Notably, evolutionary analysis shows that GlsS32.8 is conserved across globally prevalent IncP-1α plasmids, underscoring a universal risk of ARG spread in H_2S-rich environments. These findings provide novel theoretical perspectives and a scientific basis for understanding and controlling the environmental spread of antibiotic resistance genes.