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Editorial

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Exogenous glutamate plus antibiotics kills multidrug-resistant bacteria through a novel pathway that controls the TCA cycle

Editorial

The emergence and ongoing spread of multidrug-resistant bacteria puts humans and other species at risk of potentially lethal infections. Thus, novel antibiotics or alternative approaches are needed to kill the drug-resistant bacteria. Here, the mechanism by which multidrug-resistant Edwardsiella tarda evades killing by the traditional antibiotic kanamycin is explored using a reprogramming metabolomics-based approach. The results demonstrate that exogenous glutamate restores the ability of kanamycin to kill E. tarda in vitro and in vivo. It stimulates the P cycle containing the TCA cycle, which stimulates production of NDAH, increases proton-motive force and stimulates antibiotic uptake. Elimination of non-TCA P cycle enzymes blocks TCA metabolism even when there are ample other carbon sources to support the TCA. These results reveal a metabolic mechanism of the glutamate-potentiated killing, and lead to a novel understanding for the TCA cycle and the energy-generated chemical reaction cycle, suggesting a general mechanism for central carbon metabolism. Furthermore, the P cycle is tested in a model of bacterium, Escherichia coli. As E. tarda, the enzymes that feed pyruvate into the TCA cycle are also essential for energy homeostasis. Compounds that inhibit or deplete the enzymes in this pathway shut down the TCA cycle even in the presence of excess carbon sources. In contrast to pyruvate recycling in mammalian cells, which is limited to specific cells/tissues, the P cycle operates routinely as a general mechanism for energy production and for regulating the TCA cycle in several bacterial species. These findings address fundamental questions about bacterial biochemistry and energy metabolism.