Structural insights into the transposition of antibiotic resistance

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Mobile genetic elements (MGEs) drive evolution and adaptation throughout the tree of life. In bacteria, MGEs frequently transfer antibiotic resistance gene (ARGs) and are major drivers of resistance spreading. Their movements have been linked to the emergence of multidrug-resistant pathogens, including VRE, MRSA and ESBL, which present major public health challenges world-wide. Transposase enzymes that catalyze MGE movement, are the most abundant and most ubiquitous proteins in nature. Yet, their structure and biochemical mechanisms are poorly understood [1].

In this talk, I will present our recent discoveries on a group of transposases, which can effectively transfer ARG-carrying MGEs between diverse bacterial species in microbial communities. We have mapped the most wide-spread transposases in bacterial genomes [2] and reconstituted their molecular mechanisms [3, unpublished data]. We further characterized the biochemical steps of these MGEs and determined high-resolution crystal and cryo-EM structures of the protein-DNA assemblies involved in their transposition [4, unpublished data]. The results shed new light on the molecular strategies of transposase enzymes and elucidate how specific DNA structures enable these proteins to insert into diverse genomic sites, thus expanding ARG transfer. These insights open new possibilities for future strategies to block or prevent transposition and thus help control the spread of antibiotic resistance.

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