Mobile colistin resistance: From its origins to functional unification

With the support by the National Natural Science Foundation of China and National Key R&D Program of China, a research group led by Dr. Feng YouJun (冯友军) at the Department of Pathogen Biology & Microbiology and Department of General Intensive Care Unit of the Second Affiliated Hospital, Zhejiang University School of Medicine, provided mechanistic insights into mobile colistin resistance imparted by a growing body of MCR family, which appeared as back-to-back co-submissions in *Advanced Science* (doi/10.1002/advs.201900034 & doi/10.1002/advs.201900038).

Antimicrobial resistance is a prevalent health concern. Colistin is a last-resort defense against carbapenem-resistant bacterial pathogens. A rainbow coalition of mobile colistin resistance (MCR) genes raises significant global health concerns. Dr. Feng's research group is the first to describe the action and mechanism of colistin resistance imparted by MCR-4, a recently-identified member from the broader MCR family (*Commun Biol*, 2019, 2: 36). MCR-4 is proposed to originate from a silenced variant of the aquatic bacterium *Shewanella frigidimarina* by progressive evolution and forms a phylogenetically-distinct group from the well-studied MCR-1/2 family. To address this hypothesis, Dr. Feng elucidated a new family of non-mobile colistin resistance (from *nmcr-1* to *nmcr-1*. *8*) from *Shewanella*. Phylogenetic, genetic and biochemical data suggested that NMCR-1 acts as a progenitor of MCR-4 variants (*Adv Sci*, 2019, doi/10.1002/advs.201900038). Together, it constitutes a proposal for aquaculture involving an aquatic bacterium *Shewanella* as a source/natural reservoir of mobile MCR-4 colistin resistance.

As for MCR-5, a newly-identified member of the MCR family, Dr. Feng discovered that it is in a phylogenetically-distinct place from the well-studied MCR-1/2 members. In collaboration with Prof. Zong at the West China Hospital, Sichuan University, Dr. Feng reported the full genome sequence of a novel *mcr-5*-containing plasmid from the zoonotic pathogen *Aenomonas hydrophila* (*Adv Sci*, 2019, doi/10.1002/advs.201900034). Genomic context analysis suggestd that *mcr-5* disseminates via Tn3 transposon-based genetic events. Although domain-swapping indicated that MCR-4 (or MCR-5) and MCR-1/2 are not functionally-exchangeable, MCR-4 (or MCR-5) possesses a similar substrate-recognizable cavity and exploits an almost-identical 'ping-pong' catalysis mechanism. Evidently, these results illustrated, for the first time, a composite picture that MCR-4/5 proceeds in a unique evolutionary path to gain a common mechanistic capability, giving the phenotypic resistance to colistin. Very recently, Dr. Feng was invited to formulate a commentary on dissemination of MCR-1-producing *Salmonella* in *EBioMedicine* (2019, doi: 10.1016/j.ebiom.2019.03.073).

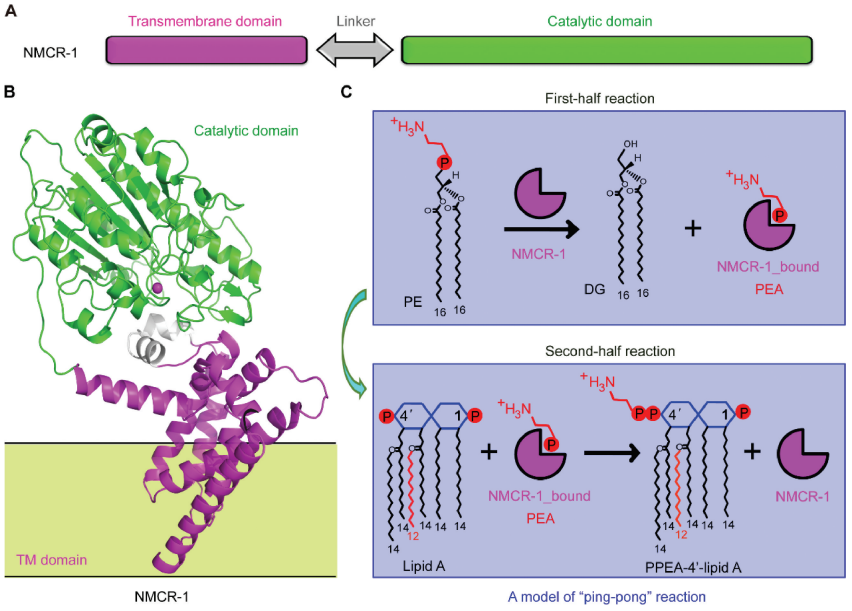

Figure A working model for NMCR-1 action.

Apart from tracking the origin of *mcr-4* variants, these data also underlined that a growing body of MCR family resistance enzymes are functionally unified. It paves a way for future efforts to develop small molecules that might reverse colistin resistance.