Siderophores promote cooperative interspecies and intraspecies cross-protection against antibiotics in vitro

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Presenter : Wan-Jing Chen **Date/Time** : 2024/10/3 15:10-16:00
Commentator : Jenn-Wei Chen Ph.D. **Location** : Room 601, Med College Building

Background :

Pseudomonas aeruginosa is a typical opportunistic pathogen and a leading cause of multidrug-resistant infections in hospital. *P. aeruginosa* causes acute urinary tract infections (UTI) , and its drug resistance worsens outcomes in UTI patients with chronic renal failure, advanced liver disease and diabetes mellitus. *P. aeruginosa* also remains the leading cause of morbidity and mortality in patients with cystic fibrosis. Due to the intrinsic drug resistance and the ability to evolve resistance to antibiotics, the treatment options for *P. aeruginosa* infections are limited. Cefiderocol (CFDC) was approved for UTI caused by Gram negative bacterial infections in 2019. The catechol group of CFDC confers siderophore activity, which allows CFDC to chelate ferric iron and across the outer membrane via iron transport system. Compare to other cephalosporins, CFDC has more stability to against β–lactamase degradation and leads to less spontaneous drug resistance. However, clinical isolates non-susceptible to CFDC have been reported and the resistance mutations remain incompletely characterized.

Objective :

To investigate how different bacterial lifestyles affected CFDC resistance and the mechanisms of CFDC resistance in *P. aeruginosa.*

Results :

Firstly, the authors used two host mimicking media to evolve *P. aeruginosa* in planktonic and biofilm aggregates condition to mimic modes of growth. The nutritional environment affected rates of CFDC resistance emergence and resistance mutation in *P. aeruginosa*. Mutations were recurrently detected in *cpxS* and iron homeostasis genes. Besides, CFDC resistance mutations acquired fitness costs in the absence of antibiotic. They found that evolved population drove the cross protection of CFDC susceptible cells via upregulation of CPX two component system and *muxABC-opmB* efflux pump. Since MuxABC-OpmB is associated with pyoverdine secretion, the authors further found that pyoverdine attenuated CFDC activity by displacing Fe(III) from CFDC. Pyoverdine also reduced CFDC killing of *Klebsiella pneumoniae* and *Escherichia coli.* These data indicates that CFDC cross protection is conferred by increased pyoverdine secretion which competes for iron, limiting CFDC uptake by bacterial cells.

Conclusion :

P. aeruginosa increases siderophore secretion to limit CFDC uptake and promote intraspecies and interspecies protection.

Reference :

Galdino, Anna Clara M., et al. "Siderophores promote cooperative interspecies and intraspecies cross-protection against antibiotics in vitro." *Nature Microbiology* 9.3 (2024): 631-646.