**Inhibiting fatty acid synthesis overcomes colistin resistance**

Carfrae, L.A., Rachwalski, K., French, S. et al. *Nat Microbiol* 8, 1026–1038 (2023).

**Presenter** : Wan-Jing Chen **Date/Time** : 2024/5/2 16:10-7:00

**Commentator** : Masayuki Hashimoto Ph.D. **Location** : Room 601, Med College Building

**Background** :

The global dissemination of colistin resistance is diminishing the therapeutic utility of polymyxins. Colistin can interact with LPS in the out leaflet of cytoplasmic membrane then disrupt the physical integrity. The plasmid-mediated resistance gene *mcr-1* confers resistance through modification of lipid A, which reduces the affinity of polymyxin for LPS. Combination therapy could prolong the clinical utility of polymyxin. It has been reported that biotin would respond to colistin-mediated membrane damage. In author’s previous study, they evaluated the potential of biotin synthesis inhibitor MAC13772 in combination with diverse antibiotics against *A. baumannii*. However, the potential of biotin synthesis inhibitor to against colistin resistance has not been discussed.

**Objective** :

To elucidate the potential of biotin or fatty acid synthesis (FAS) inhibitors in combination with colistin to overcome plasmid-mediated and chromosomal colistin resistance.

**Results** :

Firstly, the author measured the combinatory potential of MAC13772 with colistin against colistin-resistant and colistin-sensitive *E. coli* via chequerboard assay. The data shows that MAC13772 and colistin were synergistic against *mcr-1*expressing *E. coli.* Since the acetyl-CoA carboxylase, which catalyzes the first committed step of FAS, is biotin-dependent enzyme. They posited that inhibiting FAS would elicit interactions with colistin. They found that cerulenin (a FabB inhibitor) and triclosan (a FabI inhibitor) synergized with colistin against *mcr-1* expressing *E. coli* and colistin-resistant pathogens. Moreover, FAS inhibitors reduced the emergence of colistin resistance. Furthermore, the combination of colistin and Debio1452-NH3 is effective against a systemic *mcr-1* expressing *K. pneumoniae* and colistin-resistant *E. coli* infection in mice. They found that biotin biosynthesis and FAS inhibitors decreased membrane fluidity and altered lipid profile in *mcr-1* expressing *E. coli*. These data indicates that inhibiting biotin or FAS can overcome polymyxin resistance and prevent the development of resistance.

**Conclusion** :

The combination of FAS inhibitors and colistin can overcome colistin resistance and prevent the development of spontaneous resistance.

**Reference :**

Carfrae, Lindsey A., et al. "Inhibiting fatty acid synthesis overcomes colistin resistance." *Nature Microbiology* 8.6 (2023): 1026-1038.