Development of membrane targeting antimicrobials against resistant bacteria

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Abstract: Steady increases in bacterial resistance resulting from overuse of antibiotics have become a critical global healthcare problem. Membrane-targeting antimicrobials offer a potential solution to circumvent this problem because they act on the bacterial membrane rather than any specific biosynthetic or enzymatic activity. However, the development of such molecules is hindered due to the lack of molecular principles and poor understanding of the action mechanism of the membrane targeting antimicrobial. Here we show the development of a pharmacophore model for rational design of membrane targeting antimicrobials using a combination of in silico simulations and experimental validations. The pharmacophore model consists of three fragments: one large hydrophobic scaffold, two cationic groups and two linker groups. By fine-tuning the chemistry of the fragments, we have obtained a series of compounds that act on the bacterial membrane. These compounds showed excellent activity against Gram positive bacteria, including MRSA. These compounds also displayed synergy with outer membrane permeabilizers against Gram negative bacteria. For example, the combination of one of the compounds LC100 with colistin can effectively kill colistin resistant bacteria mcr-1. Biophysical experiments showed that the combination of LC100 and colistin can break up the outer and inner membranes of mcr-1, while either LC100 or colistin along does not work. The pharmacophore model provides a useful tool for practical design of membrane targeting molecules and to tackle the issue of antimicrobial resistance.

Keywords: Membrane-targeting antimicrobials; antibiotic combination; in silico drug design; colistin-resistant bacteria