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Challenges in the development of next-generation antibiotics: opportunities of small molecules mimicking mode of action of host-defense peptides

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1. Introduction

The rapid emergence of drug-resistance bacteria is a growing threat to human life which requires the development of alternative therapeutic approaches. As potential novel antibiotics, host defense peptides (HDPs) have less opportunities of inducing drug resistance due to their relatively non-specific and complex bactericidal mechanisms. In this editorial, we outline the mode of action of HDPs and highlight the recent development of a few examples of small molecules that mimic the mechanism of action of HDPs to combat antibiotic resistance.

Host defense peptides (HDPs) are short cationic amphipathic peptides which mediate a broad range of activities expressed among all complex life forms, including plants, mammalians and insect. After the identification of the first antimicrobial insect HDP, cecropin from silk moths, numerous HDPs with potential antibiotic activities were reported, such as magainin II, α-helical peptides SMAP 29 and BMAPs. Their higher activities against bacteria have made them a promising alternative strategy to combat emerging drug resistance.

Generally, most HDPs can directly act on the bacteria cell envelope depending on their positive charge and amphipathicity. As well known, the surface of a bacteria cell envelope is negatively charged, due to the presence of outer membrane components including lipopolysaccharides (Gram-negative bacteria) and lipoteichoic acids (Gram-

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Declaration of interests

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A peer review on this manuscript has disclosed that they have more than 60 patents on antimicrobial peptides and have started 3 companies in this space although the companies highlighted in this review are not direct competitors. All other peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

positive bacteria). Positive charged HDPs initially approach negatively charged bacterial membranes through electrostatic attraction, and then their hydrophobic groups insert into the membranes through hydrophobic interaction, leading to the destabilization and permeabilization of cytoplasmic membrane(1). Some models to explain membrane interruption mechanism have been proposed, such as barrel-stave model, carpet model and toroidal model(2). It is worth to note that the membranes of mammalian cells are compose of amphiphilic phospholipids, which are generally neutral. This difference is one of the most important reasons why HDPs usually have selectivity toward bacterial membranes over mammalian cell membranes. Virtually, except for membrane interruption, HDPs apply complex mechanisms to eradicate bacteria, such as inhibiting cell wall synthesis or directly binding to intracellular targets(3). The complex antibacterial mechanism and broad-spectrum activity of HDPs may enable them to be less prone to eliciting resistance than conventional antibiotics(4).

Many eukaryotic HDPs have been identified as broad-spectrum antibiotics with potent bactericidal activity, however, few of them have advanced to clinical use. The main drawbacks of HDPs are their possible systemic toxicity, susceptibility to protease degradation and high production cost(2),(5). Therefore, there have been extensive efforts in the development of antibiotic agents that mimic the mode of action of HDPs, but have smaller molecular weight, better selectivity, stronger activity, and important protease-resistance. For instance, antibacterial peptidomimetics include peptoids, β-peptides, γ-AApeptides, azapeptide, oligocarbamates. These are unnatural oligomers with comparable size to HDPs which possess enhanced stability and antibacterial activity. Nonetheless, to develop antibiotic agents with more practice applications, small molecules are more preferred due to their lower production cost, better druggability, large diversity and high market share. It is encouraging that some small molecules have been developed in recent years by mimicking bactericidal mechanism of HDPs and currently are investigated in clinical trials.

Two polymyxins, colistin (polymyxin E) and polymyxin B were discovered in 1940s. They were not subjected to clinical use due to their narrow antibacterial spectrum until rapid increase in resistance to other antibiotics. Encouragingly, more potential analogies of polymyxins are being explored recently(6). Brilacidin (PMX-30063), developing by Innovation Pharmaceuticals Inc. is among the most promising HDP mimic compounds to undergo the clinical evaluation (Figure 1a). Bearing both cationic and hydrophobic group, as well as an amphipathic structure, it exhibited similar to greater antibacterial efficacy when comparing with vancomycin. The most recent phase II clinical study result has been released on January 2019, which shows that Brilacidin has high potential for preventative treatment, as evidenced by a clear reduction of Severe Oral Mucositis among patients on Brilacidin when compared to those on placebo(7). Lytixar (LTX-109) is another HDP mimic as an antibiotic drug had been studied on phase II clinical trial for skin infection caused by Gram-positive bacteria (Figure 1b), impetigo and nasally colonized with MRSA and MSSA. Although Lytix Biopharma decided not to proceed with the planned clinical LTX-109 program in diabetic foot ulcers in 2015, it is another example of HDP-mimicking small molecule advanced into clinical trials(8).

Other small molecules being explored in preclinical phase are also quite meaningful(9). Teng *et al*. reported a series of small antibacterial compounds based on the acylated reduced amide scaffold, which has excellent broad-spectrum bactericidal activity(5). They built their HDPs mimics through systematically adjusting cationic parts such as amino or guanidino group, and hydrophobic portion including adamantyl group, phenyl group, biphenyl group and naphthyl group. The best compound (Figure 1c) showed good and rapid bactericidal activity against both Gram-positive and Gram-negative strains with high selectivity. Su *et al.* greatly improved the antibacterial activity of hydantoin derivates through combining the hydantoin core and the characteristics of HDPs (Figure 1d), which exhibited much better activity than nitrofurantoin. They applied a panel of alkyl lipid tail as hydrophobic domain and used versatile short alkyl chains or bulky groups to modify the hydantoin core(10).

It is well known that dimerization is widely applied during the drug development. Niu *et al*. synthesized dimeric lysine N- alkylamides as HDPs mimics(11). Antibacterial assays revealed their strong, rapid bacterial killing activity and high selectivity between mammalian cells and bacterial cells. The design and synthesis of these structures are straightforward. Cationic groups were provided by amino in lysine amino acid and hydrophobic groups were all alkyl chain with different carbon numbers. Among them, the structure with C8 alkyl chain showed the strongest and broad-spectrum antibiotic activity (Figure 1e) and did not elicited drug resistance readily. The dimerization strategy has also been adopted to develop bis-cyclic guanidines (Figure 1f) by Teng *et al*. to kill a panel of Gram-positive and Gram-negative strains such as MRSA and *E.coli*(12). This class of molecules also exhibited high potency against *Clostridium difficile* both *in vitro* and *in vivo*.

2. Conclusion

Overall, small molecular HDP mimics have already achieved substantial progress in the past decades. These mimics cannot only reach parallel or better antibacterial activity when comparing conventional antibiotics, but also have great potential to overcome drug resistance, hemolysis and cytotoxicity. Moreover, these small molecular HDP mimics have several advantages over HDPs and other antibiotics with large molecular weight, such as synthetic flexibility, enhanced stability and higher tolerability. A better understanding and further exploration of HDP mimics will potentially facilitate the widespread clinical use of this new antibacterial strategy.

3. Expert opinion

The emergent antibiotic resistance leads to the rapid development of small molecule based HDP mimics with excellent and broad-spectrum activity against both Gram-positive and Gram-negative bacteria, which provided significantly more promising candidates for clinical research. Unlike conventional antibiotics, these small molecules are not only drug-like, but also possess membrane-active activity analogues to that of HDPs, and therefore are expected to have less probability to induce resistance in bacteria. Current success exemplified their promising therapeutic potential. The main challenge preventing the development of small molecule HDP mimics are the indeterminate design principles and complex bacterial-killing mechanism. However, the past research findings already shed light on the future design.

For instance, Choi *et al.* delineated the importance of rigidity of molecular scaffold for HDP mimicking, as seen for their hydrogen-bonded (N−H···S, N−H···O) arylamide template to limit the flexibility of compounds(13) However, Thaker *et al.* developed a series of triaryl scaffolds which led to their conclusion that the overall hydrophobicity exhibited more significant impact than conformational stiffness(14). Similarly, Ivankin *et al.* also believed that conformational preorganization is not obligatory(15). Indeed, as shown in Figure 1, except bralacidin (**a**), none of the other molecules has a very rigid scaffold. These findings may provide rationale for the design of new antibiotic agents based on small molecules to mimic HDPs. For instance, as rigidity is not critical, more molecular scaffolds could be adopted to develop antibiotic agents. One may just have to explore the ratio and nature of hydrophobic and cationic groups in order to improve their activity and selectivity. The recent experience suggested that even a known antibiotic molecular scaffold (Figure 1d) could be used for the development of HDP mimetics, which could lead to antibiotics not only retaining their original antibacterial activity, e.g., an intracellular target, but also bearing membrane-disruptive activity akin to HDPs. The dual or multi- antibacterial mechanisms may be the advantage of new generation of antibiotics with therapeutic potential to combat drug resistance.

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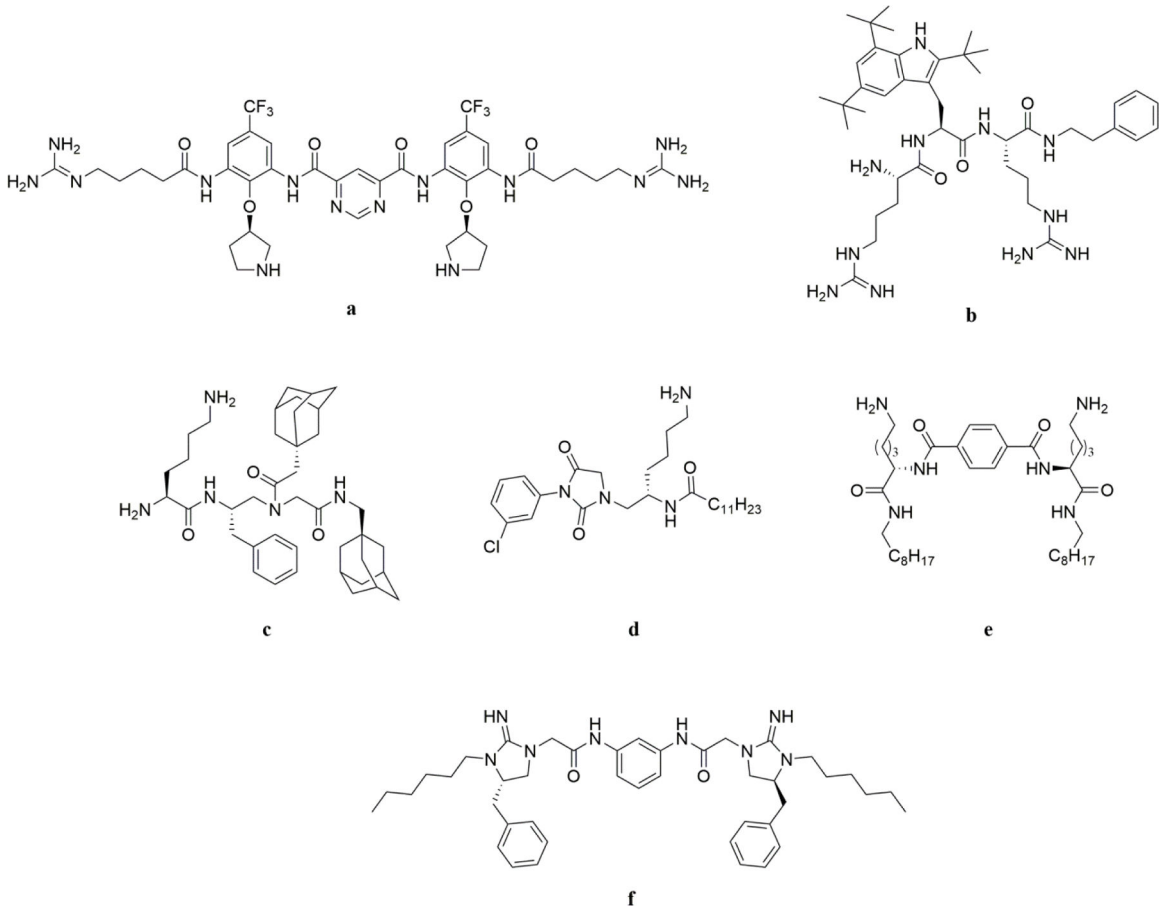

Figure 1.
Structures of small-molecule antibiotics.