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Opinion

Antimicrobial Peptides versus Microbial Resistance Mechanisms

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Development of resistance by pathogenic microbes to conventional antibiotics forced the search of novel molecules that may not develop resistance. AMPs were one such drug candidate for which resistance development was thought to be unlikely because the primary target of AMPs being anionic biological membrane. Any modifications in the membrane would hamper its functional and structural integrity and challenge the bacterial survival. Secondly, their multiple low affinity target sites makes it difficult for the microbe to modify every target, and the presence of large number of AMPs in the host is challenging as they have to develop resistance against the vast array of AMPs [1]. Even though it is highly challenging on the part of the microbes to become resistant, nature always favors the survival of all organisms and hence many microbial resistance mechanisms against AMPs have been investigated in recent years [2].

Co-evolution with AMPs has forced microbes to evolve various mechanisms to resist their action. The resistance mechanism developed against AMPs are broadly classified into intrinsic and acquired. Intrinsic resistance refers to the mechanisms present in the microorganisms, which are activated by factors others than AMPs but also help to evade AMPs. The resistance developed as result of continues exposure to AMPs is called acquired resistance [3]. Intrinsic resistance is further classified into passive and adaptive/inducible, passive resistance to AMPs is exhibited by certain bacteria, which have positively charged lipids on their membrane (eg. *Proteus, Morganella*), which resist AMP action [4]. Incorporation of positively charged molecules is one of the common adaptive mechanisms evolved to reduce AMP activity. Temporary and reversible nature of these modifications reduces the energy burden imposed on attaining resistance [5]. As noted earlier intrinsic adaptive mechanisms are triggered by factors like nutrient starvation, low divalent cations, low pH, high iron etc. In all these situations, LPS modifications are triggered in gram negative bacteria. They are (1) Addition of 4-aminoarabinose (Ar4N) to lipid A, makes LPS less negative, this is found in *P. aeruginosa* and *S. Typhimurium* (2) Palmitoylation of lipid A in *S. Typhimurium*, which also prevents interaction with AMPs (3) Glycylation of LPS in *V. cholerae* confers resistance to AMPs (4) Development of anionic capsule by *Klebsiella pneumoniae, P. aeruginosa,* and *S. pneumoniae* bestows resistance by acting as a binding site for AMPs and preventing their influx [3]. In gram negative bacteria, two signaling cascades, PhoPQ system and Rcs phosphorelay system, regulate the above mentioned modifications involved in resistance development. In gram positive bacteria, modifications are incorporated in cell wall teichoic acid (TA), primary site of AMP binding. A sensor/regulator system is responsible for inducing AMP resistance in gram positive bacteria (*S. aureus* and *Bacillus* sps) by (1) D-alanylation of TA (2) incorporation of lysophosphatidyl glycerol in the membrane (3) Addition of L-lysine to membrane lipids. All these reversible modifications prevent AMP interaction with bacterial membrane. Other than membrane modifications bacteria recruit proteases (PgtE and OpmT) and activate efflux pumps (ABC transporters and Sap) [3].

The existence of acquired resistance to AMP was mainly proved *in vitro* by serial passaging and direct plating of microorganisms with different concentrations of AMPs. Serial passage of *E. coli* and *P. aeruginosa* in pexiganan showed resistance after 600 - 700 generations [6]. *Staphylococcus aureus* and *S. typhimurium* apart from exhibiting resistance to the tested AMPs (pexiganan and LL-37), they developed cross resistance to an array of other AMPs [7]. Direct plating identified spontaneous mutants of *S. typhimurium* showing resistance to polymyxin E, pig cathelicidin and protamine (salmon sperm cell) in different experiments [3].

Acquiring a particular resistance mechanism and fixing it in their population is highly challenging task on the part of the microbe. As most mutations are deleterious in nature, the mutations acquired by the resistant pathogen should be fit enough for its own survival and for transmitting to its population. This fitness is thought to be achieved by compensatory mutations, which are additional mutations that reduce the cost of the former mutation [4]. Convincing evidence on compensatory mutations is sparse.

Despite of such large body of evidence for microbial resistance to AMPs *in vitro*, it cannot be simply extended to *in vivo* conditions [8]. In all studies, the mechanism of resistance was illustrated with a single target, which could be true for conventional antibiotics with single target even *in vivo*, but can't be taken as conclusive evidence for AMPs with multiple targets. Apart from having antimicrobial effect (membrane /intracellular), AMPs also function as immune-modulators that enhances/diversifies its activity, which also should be considered while drawing conclusions on microbial resistance [9]. Selection pressure for AMP resistance might not occur in natural systems as AMPs are generated as an array from the host, and it is hard to speculate that microbes develop resistance to all AMPs at the same time. The probability of developing cross resistance may not be possible as the array of AMPs produced are not of the same kind they are diverse in their composition, structure and function, so resistance if at all development against one AMP will not be suitable for another. Collateral sensitivity, the resistance mechanism to a particular AMP causing increased susceptibility to other AMPs, could occur in natural conditions, where one peptide, which makes the microbe permissible for the other to act [4]. This could also justify the production of an array of AMP rather than a single one. Collateral sensitivity and synergistic effect of AMPs are the areas that are to be carefully studied to arrive at conclusions regarding AMP resistance and their clinical use.

Bibliography

1. Mahlapuu M., *et al*. "Antimicrobial peptides: an emerging category of therapeutic agents". *Frontiers in Cellular and Infection Microbiology* 6 (2016): 194.

2. Lofton H., *et al*. "Mechanisms and fitness costs of resistance to antimicrobial peptides LL-37, CNY100HL and wheat germ histones". *PloS One* 8.7 (2013): e68875.

3. Andersson DI., *et al*. "Mechanisms and consequences of bacterial resistance to antimicrobial peptides". *Drug Resistance Updates* 26 (2016): 43-57.

4. Viljanen P and Vaara M. "Susceptibility of gram-negative bacteria to polymyxin B nonapeptide". *Antimicrobial Agents and Chemotherapy* 25.6 (1984): 701-705.

5. Anaya-López JL., *et al*. "Bacterial resistance to cationic antimicrobial peptides". *Critical Reviews in Microbiology* 39.2 (2013): 180-195.

6. Perron GG., *et al*. "Experimental evolution of resistance to an antimicrobial peptide". *Proceedings of the Royal Society of London B: Biological Sciences* 273.1583 (2006): 251-256.

7. Habets MG and Brockhurst MA. "Therapeutic antimicrobial peptides may compromise natural immunity". *Biology Letters* 8.3 (2012): 416-418.

8. Yount NY and Yeaman MR. "Immunocontinuum: perspectives in antimicrobial peptide mechanisms of action and resistance". *Protein and Peptide Letters* 12.1 (2005): 49-67.

9. Peschel A. "How do bacteria resist human antimicrobial peptides?" *Trends in Microbiology* 10.4 (2002): 179-186.

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