THE PROMISE OF ANTIMICROBIAL PEPTIDES

Brian P. Lazzaro, Liberty Hyde Bailey Professor at Cornell University, highlights the promise of antimicrobial peptides (AMPs) as powerful agents in the ongoing battle against antibiotic resistance

Antimicrobial peptides (AMPs) are natural antibiotics that provide frontline defence against bacterial infection. They are continuously present in wet mucosal surfaces, such as those of the lungs and gut, and the presence of pathogens significantly upregulates their production. AMPs are generally effective at micromolar concentrations and exhibit pharmacodynamic properties that reduce the evolution of resistance in target microbes, making them attractive for development as therapeutics and surface antiseptics. Furthermore, they can synergize with conventional antibiotics, raising the prospect that antibiotics which have been lost to resistance could be resurrected.

However, if we are to deploy AMPs and sustain their value effectively, we must understand how AMPs naturally function and evolve to lessen the risk of collateral harm and avoid the crisis of resistance now facing conventional antibiotics.

Thousands of different AMPs have been described from varied plant and animal sources, with dozens discovered on the skin of frogs alone! Most plant and animal genomes encode 5-10 distinct AMP gene families, each composed of 1-15 gene copies. AMPs are short peptides with simple biochemical structures. Their structural simplicity allows AMPs to be repeatedly invented de novo by evolution, resulting in distinct and often unrelated suites of AMPs in different species.

Nevertheless, common modes of action evolve recurrently. One stereotypical mechanism of AMP action is to destabilize bacterial membranes, but many AMPs have intracellular activity, such as blocking bacterial metabolism or protein synthesis.

How do AMPs work, and how can they be harnessed?

AMPs have historically been considered broad-spectrum antimicrobials with generic modes of action. However, recent evidence demonstrates unexpected degrees of antibacterial specificity by some peptides.

Much of the evidence for specificity comes from the study of insect model systems, but the general principles of AMP function are likely to be universal. Disruption of individual AMP genes in mealworms and fruit flies results in acute sensitivity to specific infections, indicating that many AMPs may be able to target pathogens at the molecular level.

Our research team is currently working to understand the basis for that specificity and to harness it for translational application.

Naturally co-occurring AMPs with distinct functions can synergize. AMPs that permeabilize membranes can allow the passage of other AMPs with intracellular targets. For example, bumblebee hymenoptaecin opens pores in bacterial membranes, allowing abaecin to enter and block bacterial stress responses. Similarly, vertebrate perforins create pores that allow lethal molecules to enter the bacterial cell. Distinct AMPs that individually destabilize bacterial membranes can also synergize to disrupt bacterial cell integrity more effectively.

AMPs may also potentiate the activity of conventional antibiotics while reducing the risk of bacterial resistance evolution. Thus, deployment of synergistic AMP-AMP and AMP-antibiotic combinations could be very powerful in applied contexts. Identifying the best combinations and most effective methods of joint delivery remains a significant research challenge.

Bacterial resistance to AMPs

A commonly proposed explanation for the observation that plants and animals naturally deploy AMPs in cocktails is that diverse AMPs simultaneously target distinct elements of bacterial biology, thereby ensuring microbial death and preventing bacterial evolution of resistance, as no microbial mutation could offer protection against every killing mechanism. Any mutant with resistance to one AMP would still be sensitive to the rest.

However, this logic rests on the implicit assumption that resistance mechanisms are specific to each AMP and so would need to be evolved independently. In practice, bacteria employ a range of nonspecific mechanisms to evade or resist AMP-mediated killing. These include the

secretion of proteases that digest AMPs and exopolymers, which create a physical barrier around the bacterial cell, as well as alterations to the bacterial cell membrane that reduce AMP adherence and efficacy. These defenses provide general protection against AMPs.

The fact that some AMPs are disproportionately effective against particular bacteria suggests a specific targeting, which implies that evasion could evolve to generate resistance. Indeed, bacterial resistance to AMPs can be experimentally evolved in the laboratory.

Nevertheless, bacterial resistance to AMPs evolves much more slowly than resistance to antibiotics. This may be due in part to the favorable pharmacodynamics of AMPs. Whereas antibiotics require hours to kill bacteria, AMPs kill within minutes, reducing the number of bacterial generations in which resistance could evolve.

Furthermore, the difference between the concentrations at which there is complete bacterial killing versus no effect at all is generally much smaller for AMPs than for antibiotics. This means there is only a narrow dose window where the bacteria are under selection for resistance to AMPs and still alive to evolve it. These benefits are amplified when AMPs are deployed in combinations.

We should not be naively sanguine about the risks associated with resistance evolution if AMPs are deployed in therapeutic or agricultural settings. Especially because many bacterial anti-AMP defenses are inducible, their physiological costs may be low, and resistance might emerge under regularly imposed AMP pressure. Because the defenses can be generic, there is a risk of cross-resistance to host-produced AMPs that could undermine natural host immunity or to antibiotics with related modes of action.

Potential resistance evolution is particularly concerning when the therapeutic AMP is derived from the host being treated, as is the case for several human AMPs that are currently in clinical trials. Given the enormous number of plant and animal AMPs available, it is wise to exploit exogenous AMPs in agricultural, veterinary, and human clinical applications.

To this end, we should actively engage in biological prospecting for novel AMPs with desirable activities. As large as the catalog of known AMPs is, it is still just a tiny glimpse into the universe of unknown AMPs. This is acutely illustrated by the fact that only ~15% of described AMPs have been isolated from insects and other arthropods.

However, arthropods comprise more than 75% of the animal species on Earth. Insects alone provide a vast reservoir of AMPs that could be potentially transformative in applied settings, and the experimental tractability of insects means accessing these AMPs is within our reach.

The path forward

AMPs have enormous untapped potential in the prevention and treatment of bacterial infections, especially as conventional antibiotics continue to be compromised by resistance. As we begin to leverage AMPs, we can apply lessons learned from the antibiotic resistance crisis to the specific biology of AMPs.

Instead of the massive application of individual AMPs, we should forestall resistance by judiciously applying synergistic and efficacious AMP cocktails that clear the infection before resistant bacterial cells can emerge. These cocktails could be intentionally designed through prior understanding of the modes of action of and bacterial sensitivity to each component.

Alternatively, and in addition, random and diverse AMP mixtures could be screened for efficacy against target pathogens. The approaches are complementary, and both necessitate new research and experimentation.

AMPs provide a promising path forward out of the antibiotic resistance crisis, so discovering novel AMPs, characterizing them, and developing them for application is an urgent priority.

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