Resensitising bacteria to antibiotics

STRUCTURAL RESEMBLANCE TO THE BACTERIAL CELL WALL – AND REPEATED UNITS OF THE AMINO ACID LYSINE. The scientists believe that chitosan's structural similarity to the bacterial cell wall helps the peptide interact with and embed itself in it, causing defects in the wall and membrane that eventually kill the bacterium.

HOW IT WORKS

Antimicrobial peptides, which carry a positive electric charge, typically work by binding to the negatively-charged bacterial membranes, disrupting the membrane and causing the bacteria to eventually die.

The more positively charged a peptide is, the more efficient it is in binding to bacteria, and thus killing them. However, the peptide's toxicity to the host also increases in line with the peptide's positive charge – it damages the host organism's cells just as it kills bacteria.

As a result, engineered antimicrobial peptides to date have met with limited success, explains Assoc Prof Kline, who is also from the NTU School of Biological Sciences.

CSM5-KS is able to cluster together to form nanoparticles when it is applied to bacteria biofilms, which are slimy coats of bacteria that can cling onto surfaces such as living tissues or medical devices in hospitals, and are difficult for traditional antibiotics to penetrate.

This clustering results in a more concentrated disruptive effect on the bacterial cell wall, compared to the activity of single chains of peptides, meaning that it has high antibacterial activity, but does not cause undue damage to healthy cells.

To examine CSM5-KS's efficacy on its own, the scientists developed separate biofilms comprising methicillin-resistant Staphylococcus aureus (MRSA), a highly virulent multidrug-resistant strain of Escherichia coli (MDR E. Coli) and vancomycin-resistant Enterococcus faecalis (VRE).

In lab experiments, CSM5-KS killed over 99% of the biofilm bacteria after four hours of treatment.

In infected wounds on mice, the peptide killed more than 90% of the bacteria.

When CSM5-KS was used with conventional antibiotics, the researchers found that the combination led to a further reduction in the bacteria in both lab-formed biofilms and infected wounds in mice, compared to when only CSM5-KS was used. This suggests that the peptide made the bacteria sensitive to drugs they would otherwise be resistant to.

More importantly, the team found that the three strains of bacteria studied developed little to no resistance against CSM5-KS. While MRSA did develop low-level resistance against CSM5-KS, this actually made the bacteria more sensitive to the antibiotic it was otherwise resistant to.

The amount of antibiotics used in this combination therapy was also at a concentration lower than what is commonly prescribed. Says Assoc Prof Kline: "Our findings show that our antimicrobial peptide is effective, whether used alone or in combination with conventional antibiotics, to fight multidrug resistant bacteria. Its potency improves when used with antibiotics, restoring the bacteria's sensitivity to drugs again.

"More importantly, we found that the bacteria we tested developed little to no resistance against our peptide, making it an effective and feasible addition to antibiotics as a viable combination treatment strategy as the world grapples with rising antibiotic resistance."

Prof Chan adds: "While efforts are focused on designing drugs to combat the Covid-19 pandemic, we should also remember that antibiotic resistance continues to be a growing problem, where secondary bacterial infections that develop in patients could complicate matters, posing a threat in the healthcare setting."

"For instance, viral respiratory infections could allow bacteria to enter the lungs more easily, leading to bacterial pneumonia, which is commonly associated with Covid-19."

She also says: "Developing new drugs alone is no longer sufficient to fight difficult-to-treat bacterial diseases, as bacteria continue to evolve and outsmart antibiotics."

"It is important to look at innovative ways to tackle difficult-to-treat bacterial infections associated with antibiotic resistance and develop new antibiotics that can address the bacterial defence mechanisms."

"A more effective and economic method to fight bacteria is through the use of a combination therapy approach like ours."

The next step forward for the team is to explore how such a combination therapy approach can be used for rare diseases or wound dressing.

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