A potential silver lining for antimicrobial treatments against certain bacteria

A study demonstrates the use of silver to enhance antimicrobial activity against Gram-negative pathogens.

A significant amount of research has been conducted regarding the development of effective antimicrobial treatments. This appears especially true in terms of combating difficult-to-treat Gram-negative bacteria. Silver is a known antimicrobial; however, its mechanism of action remains to be elucidated. Investigating this, Jose Ruben Morones-Ramirez (Boston University, MA, USA), James Collins (Boston University) and colleagues recently demonstrated that silver interrupts various bacterial cellular processes such as metabolism and iron homeostasis. This results in a higher level of reactive oxygen species production and increased membrane permeability of Gram-negative bacteria. This "can potentiate the activity of a broad range of antibiotics against Gram-negative bacteria in different metabolic states, as well as restore antibiotic susceptibility to a resistant bacterial strain."

The research, published in *Science Translational Medicine*, demonstrated *in vitro* and in a mouse model of urinary tract infection that the ability of silver to trigger oxidative stress could be utilized to potentiate antimicrobial activity. Furthermore, the group showed *in vitro* and in two mouse models of peritonitis, "Silver sensitizes Gram-negative bacteria to the Gram-positive-specific antibiotic vancomycin, thereby expanding the antibacterial spectrum of this drug." The researchers also used combinations of silver and antibiotics *in vitro* to eliminate bacterial persister cells. In addition, they demonstrated that silver is capable of enhancing antimicrobial action against biofilm-producing pathogens both *in vitro* and in a mouse biofilm infection model.

When conducting this research, the group had to overcome a number of challenges. As Morones-Ramirez told *Future Microbiology*, "The first was the experimental design and systems approach to understand the mechanism of antimicrobial action of silver. In addition, a very big challenge was the design and translation of the *in vitro* work *in vivo*. We had to think about the best and most relevant infection model in mice to test our *in vitro* activity of silver." The group chose to thoroughly test the effects using three different animal infection models: systemic; urinary tract infection; and a biofilm treatment in an implanted catheter. It was also necessary for the group to develop an appropriate toxicity study of silver. Therefore, they chose LD_{50} combined with blood chemistry studies of the treated mice, in addition to an *in vitro* toxicity test of silver in mammalian cells.

Taken together, the authors state, "This work shows that silver can be used to enhance the action of existing antibiotics against Gram-negative bacteria, thus strengthening the antibiotic arsenal for fighting bacterial infections." Furthermore, Morones-Ramirez explained, "In the future, with some more research regarding the toxicity and pharmacokinetics of silver in humans, I would recommend the development of therapies where the antibiotics will be accompanied by the respective concentrations of silver, to enhance their effect in fighting infections."

Source: Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. Silver enhances antibiotic activity against Gram-negative bacteria. *Sci. Transl. Med.* 5(190), 190ra81 (2013).

Study reveals potential new approach for tackling TB

Investigators demonstrate the use of thiophene compounds against *Mycobacterium tuberculosis* by Pks13 inhibition.

Mycobacterium tuberculosis (Mtb) causes TB in humans and there is an increasing number of drug-resistant Mtb strains across the globe. As a result, it is important that effective anti-TB agents are available. David Alland (University of Medicine and Dentistry of New Jersey, NJ, USA) and coworkers recently reported a new class of thiophene (TP) compounds that are able to destroy Mtb via Pks13 inhibition, a mechanism that was previously uncharacterized.

The authors of the paper, published in *Nature Chemical Biology*, stated that "An F79S mutation near the catalytic Ser-55 site in Pks13 conferred TP resistance, and overexpression of the $Pks13^{F79S}$ mutant conferred high resistance." *In vitro*, it was observed that TP inhibited fatty acyl-AMP loading onto Pks13. Furthermore, in wild-type Mtb, TP inhibited mycolic acid biosynthesis; however, in TP-resistant Mtb, this was observed to a significantly lesser extent.

Treatment with TP appeared to be bactericidal and the group claim it was "equivalent to treatment with the first-line drug isoniazid, but it was less likely to permit emergent resistance." In addition, the combination of isoniazid and TP treatment led to sterilizing activity. The group also employed computation docking to identify "a possible TP-binding groove within the Pks13 acyl carrier protein domain."

Taken together, the results of this study help demonstrate that Mtb Pks13 is necessary for mycolic acid biosynthesis. In addition, the group state that the research "validates it as a druggable target and demonstrates the therapeutic potential of simultaneously inhibiting multiple targets in the same biosynthetic pathway."

Source: Wilson R, Kumar P, Parashar V *et al.* Antituberculosis thiophenes define a requirement for Pks13 in mycolic acid biosynthesis. *Nat. Chem. Biol.* doi:10.1038/nchembio.1277 (2013) (Epub ahead of print).