Antimicrobial peptides: the future of tuberculosis therapeutics?

Tuberculosis (TB) is a life-threatening disease that caused 1.2 million deaths, of a total 9.6 million new diagnosed cases, in 2014 alone, according to data from the World Health Organization (WHO). These data rank TB on top of the world's deadliest infectious diseases, alongside HIV/AIDS.

The disease is caused by *Mycobacterium tuberculosis*, considered one the most successful human pathogens due to its ability to infect and mask itself within the host's immune cells. This prevents its recognition by the immune system, thus allowing it to proliferate within the organism.

From a socio-economic standpoint, TB represents a major challenge. The only vaccine available - Bacille Calmette-Guérin (BCG), prevents TB in children but the disease still can re-emerge during adulthood. Additionally, standard anti-TB therapies rely on the daily and long-term (from 6 to 24 months) administration of multiple (between 4 and 8) antibiotics, often resulting in low patient compliance to the treatments. Such abuse and/or misuse of antibiotics ultimately lead to the emergence of multidrug-resistant TB strains, which are even more difficult to treat. In terms of health care-associated costs, treatments may range from US$19-22 per patient (for a 6-month therapy of non-resistant TB) to US$4000-6000 per patient (for up to 24-month treatment of multidrug-resistant strains).

Although new drugs are constantly being developed, they usually fail to go through the advanced stages of clinical trials. Additionally, such drugs are far from addressing issues like therapy length and prevention of drug resistance.

In this context, Antimicrobial Peptides (AMPs) arise as promising candidates to treat tuberculosis. AMPs comprise a diverse group of small, positively-charged, amphipathic molecules that are usually associated to mammalian innate immunity. These peptides may kill bacteria through many mechanisms, either directly - through the disruption of bacterial cell membranes or the direct modification of bacterial cell components – or indirectly, by activation of the host's innate immune system. Although a few bacteria exhibit resistance against some AMPs, self-modifications required to avoid a mixture of such non-specific and diverse killing mechanisms (often combined in the same molecule), would demand high metabolic costs and compromise bacteria functionality. For these reasons, acquisition of resistance against AMPs is still very rare.

Currently, there are many *in vitro* and *in vivo* assays demonstrating the efficacy of AMPs against *M. tuberculosis*, including multidrug-resistant strains. Interestingly, despite the great ascension in new AMP development, to date no AMP has reached clinical trials for the treatment of TB (despite some being already in the market and others in clinical trials, for cancer therapy and infection treatment). However, it is only reasonable to expect that, considering their advantages over antibiotics, a rising

peptide market, and the recent changes in the regulations for new drug approval, that AMPs will hold a great therapeutic potential against tuberculosis, provided some drawbacks related with their pharmacological properties, like production costs, toxicity and delivery are properly addressed.

João Pedro Silva
CEB - Centre of Biological Engineering, University of Minho,
Campus de Gualtar, Braga, Portugal

Publication

Antimicrobial peptides as novel anti-tuberculosis therapeutics.
Silva JP, Appelberg R, Gama FM
Biotechnol Adv. 2016 Sep-Oct