Engineered “tailocins” to specifically control pathogenic bacteria

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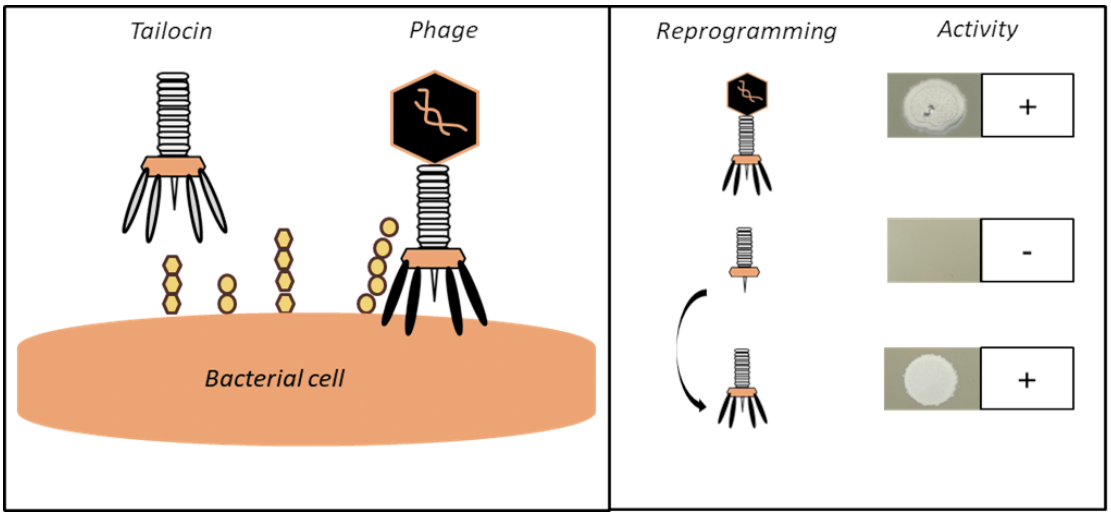
Pathogenic bacteria are on the rise. They cause infections in agriculture, productive livestock, other animals, and humans. Many of the pathogens are transferred to humans via contaminated food or drinking water. Due to the emergence of multi-drug resistant bacteria, the use of antibiotics is banned in food production. In the clinic, many standard antibiotics cannot be used for treatment anymore. Hence, novel antimicrobials are urgently needed to combat pathogenic bacteria in a “one health” approach.

Phage tail-like bacteriocins (PTLB) are encoded by many different bacterial genera and species. For simplicity, PTLBs are also termed “tailocins”. It seems that they have evolved from prophages. However, a tailocin only consists of a phage tail. Any other gene that would be needed to replicate and assemble an infective phage is absent from the bacterial chromosome. The tailocin genes are induced during starvation or after any other type of stress in bacteria. After induction, the tailocin is burst-released from the producing cell. Native tailocins usually target bacterial strains of the same species. They specifically adsorb to the cell surface. Adsorption is mediated by receptor-binding proteins, e.g., tail fibre or tail spike proteins, which specifically bind to the bacterial cell wall. After adsorption the target cell’s membrane, potential is rapidly disrupted and the cell finally dies. The producing cells are generally resistant to the encoded tailocin. In nature, tailocin production represents a form of altruism because a part of the producing cell population is lyzed to release the tailocin and to combat the closely related strain, thereby making room for the survivors of the tailocin producing population (non-induced cells), which then further occupy the ecological niche.

Because tailocins are encoded on the bacterial chromosome, they can easily be genetically modified. Genes encoding the tail fibre proteins can be deleted and then complemented in trans from an expression vector (Williams et al. 2008). The most challenging question is which alternative tail fibre gene can be used for the replacement. To select for a promising alternative AlphaFold, an artificial neural network that predicts the 3D structure of proteins is applied (Jumper et al. 2021). Using this approach, we recently reprogrammed several tailocins for the specific control of different pathogens (see figure).

Tailocin reprogramming could become an easily adaptable platform for the rapid and specific design of novel antimicrobials, the more tail fibre gene sequences are available from public databases. We intent to further develop this platform to supply users with tailored tailocins for any kind of bacterial target in agriculture, food, and even medical applications. ■

References:
Williams et al. 2008. Retargeting R-type pyocins to generate novel bactericidal protein complexes. Appl Environ Microbiol. 74(12):3868-76. doi: 10.1128/AEM.00141-08.
Jumper et al. 2021. Highly accurate protein structure prediction with AlphaFold. Nature. Aug;596(7873):583-589. doi: 10.1038/s41586-021-03819-2.



Schematic of a tailocin and a phage infecting a bacterial cell (left). A tailocin can be reprogrammed by replacing the native tail fibres with alternative tail fibres from a phage. The lytic activity can easily be monitored in vitro. Both phages and tailocins cause lysis of bacterial lawns (right).