Pseudomonas aeruginosa secondary metabolite activates lysis–lysogeny switch leads to prophage induction in *Staphylococcus aureus*

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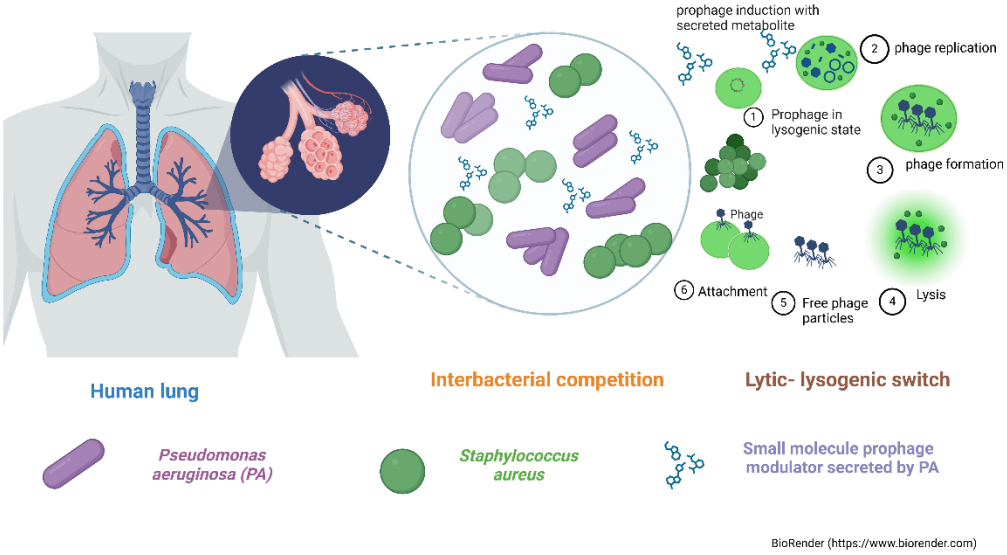

Abstract:

Bacteriophages (phages) are viruses that infect bacteria, which play an important role in shaping microbial communities by impacting their ecology, physiology, and evolution. Most of the phages found in nature and in the human body are lysogenic and they are integrated in the genomes of their microbial hosts as prophages. Prophages can get activated under specific environmental stressors enabling them to enter into lytic cycle, leading to the production of large number of phage particles that can kill their bacterial host. However, the ecologically relevant triggers for prophage induction remain largely underexplored. The identification of novel prophage-inducing molecules plays an important role in understanding the behavior of prophages and developing strategies for controlling deadly bacterial infections.

We hypothesized that during interbacterial competition in shared niches; secondary metabolites produced by closely associated species have potential to activate lysis–lysogeny switch through small molecule mediated prophage induction of their competitors. We have developed and adapted the induction assay that allow us to detect and quantify the presence of phage particles; which are then used to screen the bioactivity of our own library of secondary metabolite extracts. Using activity guided fractionation performed by semi-preparative HPLC followed by compound identification with 1&2D NMR and MS, we found the novel role of a phenolic compound from P. *aeruginosa*, triggering prophage induction in S. *aureus*. Due to their frequent coexistence in many polymicrobial infections, including in patients with cystic fibrosis and with burn or chronic wounds, P. *aeruginosa* rapidly outcompetes S. *aureus* by using several of its virulence factors. These virulence factors potentially generate reactive oxygen species and cause membrane damage into S. *aureus*.

Overall, our findings add a new role of a compound secreted by Gram-negative pathogen P. *aeruginosa* to compete with S. *aureus* for resources in shared niches. Our results demonstrate that human pathogens can produce prophage-inducing small molecules triggering the lytic-lysogenic switch and could affect overall microbial population dynamic. In future this strategy could led to the formulation of a novel therapeutic such as ‘prophage induction therapy’ an alternative to antibiotics for treating deadly bacterial infections.