BRC Science Highlight
October 2018

Rapid Screening of Lanthipeptide Analogs via In-Colony Removal of Leader Peptides in *Escherichia coli*

Background/objective

Ribosomally synthesized and post-translationally modified peptides (RiPPs) exhibit important biological activities. A challenge in engineering microbial hosts to produce foreign antibiotic RiPPs is the tendency for the antibiotics to kill the microbial host due to difficulty in reconstructing self-immunity. Researchers tested a method for producing mature, active RiPPs in *E. coli* colonies to rapidly study structure-activity relationships and isolate new antibiotic analogs with improved potency.

Approach

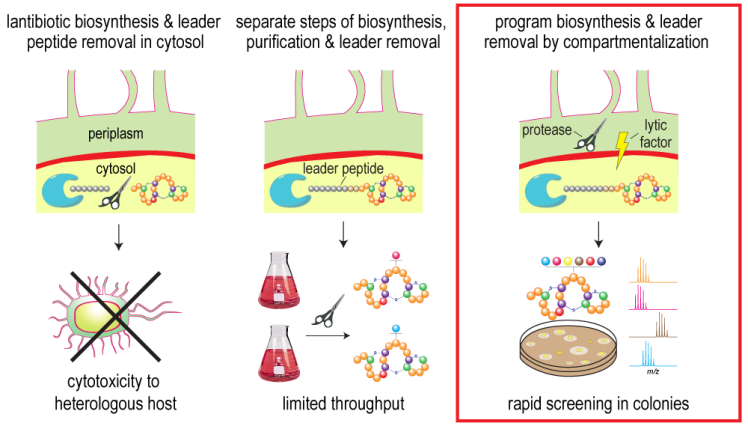
- Cellular compartments were dynamically programmed to control biosynthetic and self-immunity machinery, such that the final, toxic product was only produced following cell harvest and lysis.
- RiPP variants were rapidly profiled using coupled MALDI-ToF MS and bioactivity analysis of whole *E. coli* colonies.

Results

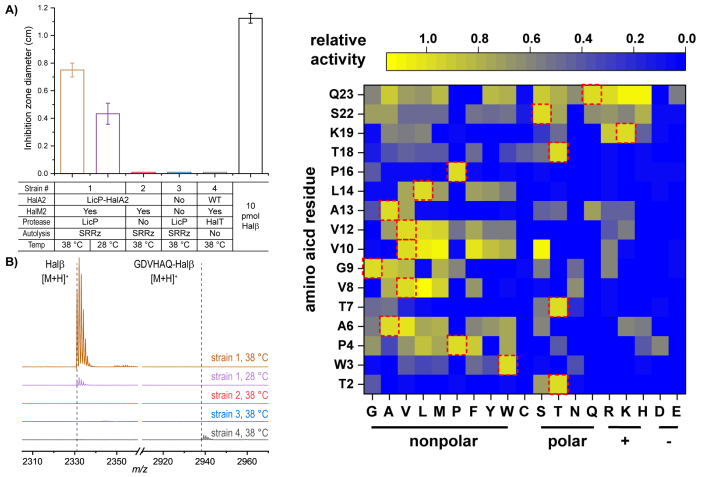
- The method was demonstrated for rapid screening of >100 analogs of haloduracin and lacticin 481, two model RiPPs.

Significance

- The method addresses one of the main limiting factors to achieving high titers of toxic foreign products in microbial hosts, expanding the potential for production of such bioproducts via microbial fermentation.
- This method enables the release of intracellular products by cell autolysis for rapid colony-level MALDI-MS screening.



Synthetic biology enables production of mature lantibiotics in *E. coli* colonies and greatly accelerates analog screening.



Si et al. 2018. "Rapid Screening of Lanthipeptide Analogs via In-Colony Removal of Leader Peptides in Escherichia coli*." **Journal of the American Chemical Society**, 140, 11884-11888,* DOI: 10.1021/jacs.8b05544.

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