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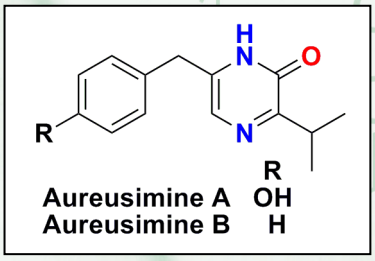
Aureusimines

Virulence Factors

A "master" switch

Infection is mediated by a range of virulence factors, mostly high molecular weight toxins, enzymes or other proteins acting alone or in concert by poorly understood mechanisms. In 2010, a collaboration led by Magarvey at McMaster University in Canada published a provocative article in Science suggesting two metabolites of non-ribosomal origin produced by *Staphylococcus aureus* were the master virulence regulators. Their simple but elegant hypothesis that the metabolites, **aureusimine A** and **aureusimine B**, exert control over the virulence cascade responsible for Golden Staph infection opens a unique strategy for antibiotic discovery.



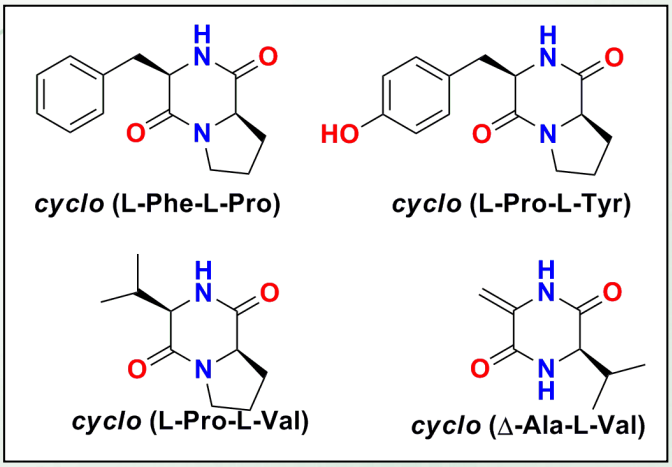
In the same year doubt was cast on the hypothesis by Bae and colleagues in Indiana and Chicago, who maintained the results were due to an artifact causing an unintended mutation.

Simple but unique structures

Interestingly, neither group of researchers looked to the chemistry of aureusimines for answers. **Aureusimine A** and **B** are monoketopiperazines, formed by the fusion of two amino acids. Interest in the biological function of these non-ribosomal fusions is not without precedence. Kjelleberg and colleagues at the University of NSW, Australia, reported in 1999 that the diketopiperazines, **cyclo(L-Phe-L-Pro)**, **cyclo(L-Pro-L-Val)**, **cyclo(L-Pro-L-Val)** and **cyclo(Δ-Ala-L-Val)** were dominant signaling metabolites controlling quorum sensing in *Pseudomonas aeruginosa*. Perhaps more convincing is the recent report by Bina & Bina from University of Tennessee that **cyclo(L-Phe-L-Pro)** was an inhibitor of virulence factors in *Vibrio cholerae.*

Virulence as a drug target?

Are **aureusimine A** and **B** virulence factors? Perhaps there is need to more fully explore the metabolites rather than pursue complex genetic arguments. Dipeptide coupled chemistry is frequently encountered in microbes and its role poorly understood. Is it too speculative to suggest that virulence is an extension of quorum sensing in pathogens?



Over 90% of the 25,000 microbial metabolites thus far described have no known biological role, perhaps trafficking, signaling and regulation may provide some answers.

1. *Staphylococcus aureus* nonribosomal peptide secondary metabolites regulate virulence. Wyatt M. A. et al *Science* **2010**, 329, 294.
2. Aureusimines in *Staphylococcus aureus* are not involved in virulence. Sun F. et al. *PLoS* **2010**. 5, e15103.
3. Quorum-sensing cross talk: isolation and chemical characterization of cyclic dipeptides from *Pseudomonas aeruginosa* and other gram-negative bacteria. Holden M. T et al. *Mol. Microbiol*. **1999**, 33, 1254.
4. The cyclic dipeptide cyclo(Phe-Pro) inhibits cholera toxin and toxin-coregulated pilus production in O1 El Tor *Vibrio cholerae*. Bina X. R & Bina J. E. *J. Bacteriol*. **2010**, 192, 3829.

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