Modular Strategies for Structure and Function Employed by Marine Cyanobacteria: Characterization and Synthesis of Pitinoic Acids

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Introduction

The Gram-negative bacterium *Pseudomonas aeruginosa* causes serious opportunistic infections in different host tissues and organs, such as cystic fibrosis infections in the lungs and microbial keratitis in the eyes. Bacterial quorum sensing (QS) has been shown to play a major role in bacterial pathogenesis, where several QS-regulated virulence factors facilitate the infection and tissue destruction. Tissue damage is also aggravated by the host's defense response, where the release of pro-inflammatory mediators and the prolonged inflammatory response are other contributors to tissue pathology. Accordingly, inhibiting QS pathways in *P. aeruginosa* and simultaneously controlling the associated inflammatory response is a promising strategy for the treatment of infections caused by this organism. In our continuous quest for drug discovery, we explored a population of a marine cyanobacterium morphologically similar to *Lyngbya* sp. collected from a channel at the north end of Piti Bay at Guam, through NMR-guided fractionation, targeting novel bioactive peptides and lipids.

Experimental

^{1}H and 2D NMR spectra were recorded on a Bruker Avance II spectrometer (600 MHz, 5 mm TXI cryogenic probe).

Results and Discussion

The cyanobacterial sample was extracted with organic solvents. This organic extract was subjected to solvent partitioning followed by NMR-guided fractionation to yield the novel lipids pitinoic acid A (5-methylene decanoic acid) and its chlorinated ester, pitinoic acid B. The planar structure was elucidated using 1D/2D NMR and MS experiments. Additionally, the structure of pitinoic acid B was confirmed by synthesis, which also allowed for biological evaluation. Pitinoic Acid A inhibits QS in *P. aeruginosa*, while the chlorinated ester prevents the induction of pro-inflammatory cytokine expression in LPS-induced THP-1 macrophages. In addition, we were able to identify the presence of pitinoic acid C, the alcohol moiety in pitinoic acid A, in one HPLC fraction, which also maintained the anti-inflammatory effect detected for pitinoic acid B. Based on this, pitinoic acid B appears to be a nature-designed prodrug which could deliver two essential moieties with different bioactivities upon hydrolysis, the QS-inhibitory module pitinoic acid A and the anti-inflammatory module pitinoic acid C.

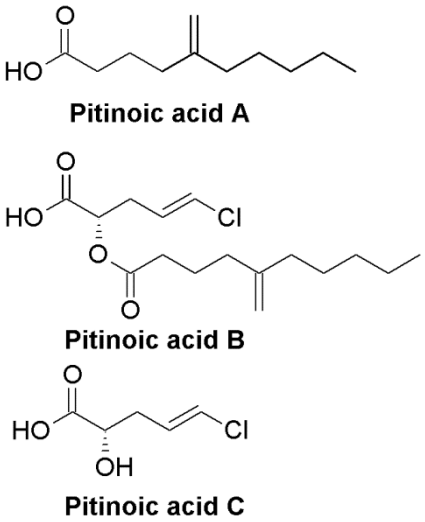

Figure. Structures of pitinoic acids.

Conclusions

Marine cyanobacteria utilize a clever modular strategy to produce interesting bioactive secondary metabolites, such as pitinoic acid B which represents a prodrug strategy to liberate dual biological activity for the management of *P. aeruginosa* infections and their associated inflammation. Accordingly, continuous investigation of these organisms could lead to the discovery of novel compounds with promising biomedical potential.

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