Cyclopropanol warhead in malleicyprol confers virulence of human- and animal-pathogenic *Burkholderia* species.

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Details



Abstract

Burkholderia species such as B. mallei and B. pseudomallei are bacterial pathogens causing fatal infections in humans and animals (glanders and melioidosis), yet knowledge on their virulence factors is limited. While pathogenic effects have been linked to a highly conserved gene locus (bur/mal) in the B. mallei group, the metabolite associated to the encoded polyketide synthase, burkholderic acid (syn. malleilactone), could not explain the observed phenotypes. By metabolic profiling and molecular network analyses of the model organism B. thailandensis we found that the primary products of the cryptic pathway are unusual cyclopropanol-substituted polyketides. First, we identified sulfomalleicyprols as still inactive precursors of burkholderic acid. Furthermore, we discovered a highly reactive upstream metabolite, malleicyprol, and obtained it in two stabilised forms, chemically trapped as a sulfonate, and as an adduct. By means of cell-based assays and a

nematode infection model we show that the rare cyclopropanol-containing natural product confers cytotoxicity and virulence.

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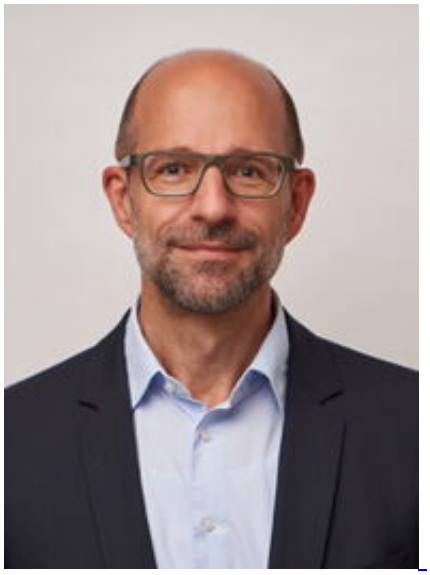
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