27c - Discovery and Characterization of the Fully Decorated Nocardiosis-Associated Polyketide Natural Product

Sunday, October 27, 2024

4:28 PM - 4:46 PM

Room 30A (Upper Level, San Diego Convention Center)

Abstract

The genomes of 40 strains of *Nocardia*, most of which were associated with life-threatening human infections, encode a highly conserved assembly line polyketide synthase designated as the NOCAP (NOCardiosis-Associated Polyketide) synthase, whose product structure has been previously described. Here we report the structure and inferred biosynthetic pathway of the fully decorated glycolipid natural product. Its structure reveals a fully substituted benzaldehyde headgroup harboring an unusual polyfunctional tail and an O-linked disaccharide comprising a 3-α-epimycarose and 2-*O*-methyl-α-rhamnose whose installation requires flavin monooxygenase-dependent hydroxylation of the polyketide product. Production of the fully decorated glycolipid was verified in cultures of two patient-derived *Nocardia* species. In both *E. coli* and *Nocardia* spp., the glycolipid was only detected in culture supernatants, consistent with data from genetic knockout experiments implicating roles for two dedicated proteins in installing the second sugar substituent only after the monoglycosyl intermediate is exported across the bacterial cell membrane. With the NOCAP product in hand, the stage is set for investigating the evolutionary benefit of this polyketide biosynthetic pathway for *Nocardia* strains capable of infecting human hosts.

The genomes of 40 strains of *Nocardia*, most of which were associated with life-threatening human infections, encode a highly conserved assembly line polyketide synthase designated as the NOCAP (NOCardiosis-Associated Polyketide) synthase, whose product structure has been previously described. Here we report the structure and inferred biosynthetic pathway of the fully decorated glycolipid natural product. Its structure reveals a fully substituted benzaldehyde headgroup harboring an unusual polyfunctional tail and an O-linked disaccharide comprising a 3-α-epimycarose and 2-*O*-methyl-α-rhamnose whose installation requires flavin monooxygenase-dependent hydroxylation of the polyketide product. Production of the fully decorated glycolipid was verified in cultures of two patient-derived *Nocardia* species. In both *E. coli* and *Nocardia* spp., the glycolipid was only detected in culture supernatants, consistent with data from genetic knockout experiments implicating roles for two dedicated proteins in installing the second sugar substituent only after the monoglycosyl intermediate is exported across the bacterial cell membrane. With the NOCAP product in hand, the stage is set for investigating the evolutionary benefit of this polyketide biosynthetic pathway for *Nocardia* strains capable of infecting human hosts.

Presenting Author

D

Antonio Del Rio Flores
Stanford University

Author

K

Chaitan Khosla
Stanford University

View Related