

Plant-like biosynthesis of isoquinoline alkaloids in *Aspergillus fumigatus*.

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Abstract

Natural product discovery efforts have focused primarily on microbial biosynthetic gene clusters (BGCs) containing large multimodular polyketide synthases and nonribosomal peptide synthetases; however, sequencing of fungal genomes has revealed a vast number of BGCs containing smaller NRPS-like genes of unknown biosynthetic function. Using comparative metabolomics, we show that a BGC in the human pathogen *Aspergillus fumigatus* named fsq, which contains an NRPS-like gene lacking a condensation domain, produces several new isoquinoline alkaloids known as the fumisoquins. These compounds derive from carbon-carbon bond formation between two amino acid-derived moieties followed by a sequence that is directly analogous to isoquinoline alkaloid biosynthesis in plants. Fumisoquin biosynthesis requires the N-methyltransferase FsqC and the FAD-dependent oxidase FsqB, which represent functional analogs of coclaurine N-methyltransferase and berberine bridge enzyme in plants. Our results show that BGCs containing incomplete NRPS modules may reveal new biosynthetic paradigms and suggest that plant-like isoquinoline biosynthesis occurs in diverse fungi.

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