A nonredundant phosphopantetheinyl transferase, PptA, is a novel antifungal target that directs secondary metabolite, siderophore, and lysine biosynthesis in *Aspergillus fumigatus* and is critical for pathogenicity.

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Details

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Abstract

Secondary metabolites are key mediators of virulence for many pathogens. *Aspergillus fumigatus* produces a vast array of these bioactive molecules, the biosynthesis of which is catalyzed by nonribosomal peptide synthetases (NRPSs) or polyketide synthases (PKSs). Both NRPSs and PKSs harbor carrier domains that are primed for acceptance of secondary metabolic building blocks by a phosphopantetheinyl transferase (P-pant). The *A. fumigatus* P-pant PptA has been

shown to prime the putative NRPS Pes1 in vitro and has an independent role in lysine biosynthesis; however, its role in global secondary metabolism and its impact on virulence has not been described. Here, we demonstrate that PptA has a nonredundant role in the generation of the vast majority of detectable secondary metabolites in *A. fumigatus*, including the immunomodulator gliotoxin, the siderophores triacetylfusarinine C (TAFC) and ferricrocin (FC), and dihydroxy naphthalene (DHN)-melanin. We show that both the lysine and iron requirements of a pptA null strain exceed those freely available in mammalian tissues and that loss of PptA renders *A. fumigatus* avirulent in both insect and murine infection models. Since PptA lacks similarity to its mammalian orthologue, we assert that the combined role of this enzyme in both primary and secondary metabolism, encompassing multiple virulence determinants makes it a very promising antifungal drug target candidate. We further exemplify this point with a high-throughput fluorescence polarization assay that we developed to identify chemical inhibitors of PptA function that have antifungal activity. IMPORTANCE Fungal diseases are estimated to kill between 1.5 and 2 million people each year, which exceeds the global mortality estimates for either tuberculosis or malaria. Only four classes of antifungal agents are available to treat invasive fungal infections, and all suffer pharmacological shortcomings, including toxicity, drug-drug interactions, and poor bioavailability. There is an urgent need to develop a new class of drugs that operate via a novel mechanism of action. We have identified a potential drug target, PptA, in the fungal pathogen *Aspergillus fumigatus* PptA is required to synthesize the immunotoxic compound gliotoxin, DHN-melanin, which *A. fumigatus* employs to evade detection by host cells, the amino acid lysine, and the siderophores TAFC and FC, which *A. fumigatus* uses to scavenge iron. We show that strains lacking the PptA enzyme are unable to establish an infection, and we present a method which we use to identify novel antifungal drugs that inactivate PptA.

Involved units

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