

A highly conserved basidiomycete peptide synthetase produces a trimeric hydroxamate siderophore.

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Abstract

The model white-rot basidiomycete *Ceriporiopsis* (*Gelatoporia*) *subvermispora* B encodes putative natural product biosynthesis genes. Among them is the gene for the seven-domain nonribosomal peptide synthetase CsNPS2. It is a member of the as-yet uncharacterized fungal type VI siderophore synthetase family which is highly conserved and widely distributed among the basidiomycetes. These enzymes include only one adenylation (A) domain, i.e., one complete peptide synthetase module and two thiolation/condensation (T-C) di-domain partial modules which, together, constitute an AT1C1T2C2T3C3 domain setup. The full-length CsNPS2 enzyme (274.5 kDa) was heterologously produced as polyhistidine fusion in *Aspergillus niger* as soluble and active protein. N(5)-acetyl-N(5)-hydroxy-L-ornithine (I-AHO) and N(5)-cis-anhydromevalonyl-N(5)-hydroxy-L-ornithine (I-AMHO) were accepted as substrates, as assessed in vitro using the substrate-dependent [(32)P]ATP-pyrophosphate radioisotope exchange assay. Full-length holo-CsNPS2 catalyzed amide bond formation between three I-AHO molecules to release the linear I-AHO trimer, called basidioferrin, as product in vitro, which was verified by LC-HRESIMS.

Phylogenetic analyses suggest that type VI family siderophore synthetases are widespread in mushrooms and have evolved in a common ancestor of basidiomycetes. Importance: The basidiomycete nonribosomal peptide synthetase CsNPS2 represents a member of a widely distributed but previously uninvestigated class (type VI) of fungal siderophore synthetases. Genes orthologous to CsNPS2 are highly conserved across various phylogenetic clades of the basidiomycetes. Hence, our work serves as a broadly applicable model for siderophore biosynthesis and iron metabolism in higher fungi. Also, our results on the amino acid substrate preference of CsNPS2 supports further understanding of the substrate selectivity of fungal adenylation domains. Methodologically, this report highlights the *Aspergillus niger*/SM-Xpress-based system as suitable platform to heterologously express multimodular basidiomycete biosynthesis enzymes in the > 250 kDa range in soluble and active form.

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