

Regioselective Dichlorination of a Non-Activated Aliphatic Carbon Atom and Phenolic Bismethylation by a Multifunctional Fungal Flavoenzyme.

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Abstract

The regioselective functionalization of non-activated carbon atoms such as aliphatic halogenation is a major synthetic challenge. A novel multifunctional enzyme catalyzing the geminal dichlorination of a methyl group was discovered in *Aspergillus oryzae* (Koji mold), an important fungus that is widely used for Asian food fermentation. A biosynthetic pathway encoded on two different chromosomes yields mono- and dichlorinated polyketides (diaporthin derivatives), including the cytotoxic dichlorodiaporthin as the main product. Bioinformatic analyses and functional genetics revealed an unprecedented hybrid enzyme (AoiQ) with two functional domains, one for halogenation and one for O-methylation. AoiQ was successfully reconstituted in vivo and in vitro, unequivocally showing that this FADH₂-dependent enzyme is uniquely capable of the stepwise gem-dichlorination of a non-activated carbon atom on a freestanding substrate. Genome mining indicated that related hybrid enzymes are encoded in cryptic gene clusters in numerous

ecologically relevant fungi.

Beteiligte Forschungseinheiten

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