

Opposed effects of enzymatic gliotoxin N- and S-methylations.

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Abstract

Gliotoxin (1), a virulence factor of the human pathogenic fungus *Aspergillus fumigatus*, is the prototype of epipoly(thiodioxopiperazine) (ETP) toxins. Here we report the discovery and functional analysis of two methyl transferases (MTs) that play crucial roles for ETP toxicity. Genome comparisons, knockouts, and in vitro enzyme studies identified a new S-adenosyl-L-methionine-dependent S-MT (TmtA) that is, surprisingly, encoded outside the gli gene cluster. We found that TmtA irreversibly inactivates ETP by S-alkylation and that this detoxification strategy appears to be not only limited to ETP producers. Furthermore, we unveiled that GliN functions as a freestanding amide N-MT. GliN-mediated amide methylation confers stability to ETP, damping the spontaneous formation of tri- and tetrasulfides. In addition, enzymatic N-alkylation constitutes the last step in gliotoxin biosynthesis and is a prerequisite for the cytotoxicity of the molecule. Thus, these specialized alkylating enzymes have dramatic and fully opposed effects: complete activation or inactivation of the toxin.

Involved units

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