Transannular disulfide formation in gliotoxin biosynthesis and its role in self-resistance of the human pathogen *Aspergillus fumigatus*.

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Abstract

Gliotoxin (1), the infamous representative of the group of epipolythiodioxopiperazines (ETPs), is a virulence factor of the human pathogenic fungus Aspergillus fumigatus. The unique redox-sensitive transannular disulfide bridge is critical for deleterious effects caused by redox cycling and protein conjugation in the host. Through a combination of genetic, biochemical, and chemical analyses, we found that 1 results from GliT-mediated oxidation of the corresponding dithiol. In vitro studies using purified GliT demonstrate that the FAD-dependent, homodimeric enzyme utilizes molecular oxygen as terminal electron acceptor with concomitant formation of H(2)O(2). In analogy to the thiol-disulfide oxidoreductase superfamily, a model for dithiol-disulfide exchange involving the conserved CxxC motif is proposed. Notably, while all studied disulfide oxidases invariably form intra- or interchenar disulfide bonds in peptides, GliT is the first studied enzyme producing an epidithio bond. Furthermore, through sensitivity assays using wild type, Delta gliT mutant, and complemented strain, we found that GliT confers resistance to the producing organism. A

phylogenetic study revealed that GliT falls into a clade of yet fully uncharacterized fungal gene products deduced from putative ETP biosynthesis gene loci. GliT thus not only represents the prototype of ETP-forming enzymes in eukaryotes but also delineates a novel mechanism for self-resistance.

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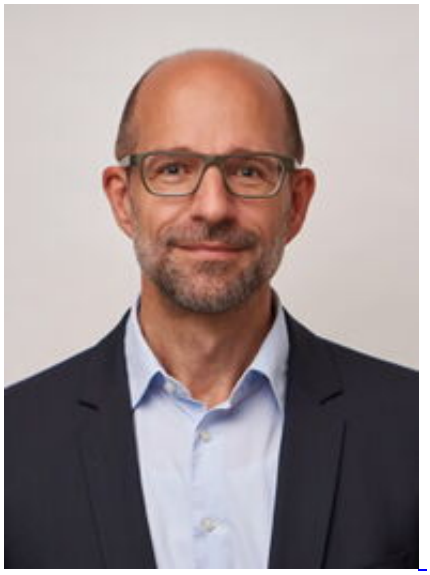

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