Enzymatic thioamide tormation in a bacterial antimetabolite pathway.

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Details

Abstract

6-Thioguanine (6TG) is a DNA-targeting therapeutic used in the treatment of various cancers. While 6TG was rationally designed as a proof of concept for antimetabolite therapy, it is also a rare thioamide-bearing bacterial natural product and critical virulence factor of Erwinia amylovorans, plant pathogens that cause fire blight. Through gene expression, biochemical assays, and mutational analyses, we identified a specialized bipartite enzyme system, consisting of an ATP-dependent sulfur transferase (YcfA) and a sulfur-mobilizing enzyme (YcfC), that is responsible for the peculiar oxygen-by-sulfur substitution found in the biosynthesis of 6TG. Mechanistic and phylogenetic studies revealed that YcfA-mediated 6TG biosynthesis evolved from ancient tRNA modifications that support translational fidelity. The successful in vitro reconstitution of 6TG thioamidation showed that YcfA employs a specialized sulfur shuttle that markedly differs from universal RNA-related systems. This study sheds light on underexplored enzymatic C-S bond formation in natural product biosynthesis.

Beteiligte Forschungseinheiten

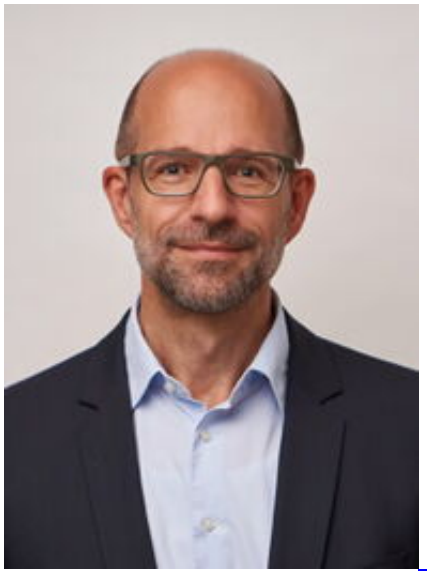
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