

A widespread bacterial phenazine forms conjugates with biogenic thiols and crosslinks proteins.

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Abstract

Phenazines are redox-active compounds produced by a range of bacteria, including many pathogens. Endowed with various biological activities, these ubiquitous N-heterocycles are well known for their ability to generate reactive oxygen species by redox cycling. Phenazines may lead to an irreversible depletion of glutathione, but a detailed mechanism has remained elusive. Furthermore, it is not understood why phenazines have so many protein targets and cause protein misfolding as well as their aggregation. Here we report the discovery of unprecedented conjugates (panphenazines A, B) of panthetheine and phenazine-1-carboxylic (PCA) acid from a *Kitasatospora* sp., which prompted us to investigate their biogenesis. We found that PCA reacts with diverse biogenic thiols under radical-

forming

conditions, which provides a plausible model for irreversible glutathione depletion. To evaluate the scope of the reaction in cells we designed biotin and rhodamine conjugates for protein labelling and

examined their covalent fusion with model proteins (ketosynthase, carbonic anhydrase III, albumin). Our

results reveal important, yet overlooked biological roles of phenazines and show for the first time their

function in protein conjugation and crosslinking.

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