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Homologues of F420H2-dependent reductases from the biosynthesis of Lincomycin, Hormaomycin, and Pyrrolobenzodiazepines have different reaction specificity

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In contrast to taxonomically ubiquitous flavin-dependent oxidoreductases, deazaflavin F420/F420H2 dependent oxidoreductases are limited to the phyla *Euryarchaeota* and *Actinobacteria*. Within *Euryarchaeota*, these enzymes play a key role in the central catabolic CO2 reducing and methylotrophic pathways. Within *Actinobacteria*, their function is less explored and possibly more diverse, including participation in the biosynthesis of secondary metabolites. However, the only functionally elucidated example is the reduction of a double bond of dehydrooxytetracycline during the final step of tetracycline antibiotic biosynthesis. Homologues of F420/F420H2 dependent oxidoreductases are encoded also within the biosynthetic gene clusters of three groups of structurally and functionally distinct natural products, which all incorporate an unusual 4-alkyl-L-proline into their structures: (1) lincomycin, a clinically used lincosamide antibiotic, (2) pyrrolobenzodiazepines with antitumor properties, and (3) hormaomycin, a signal molecule involved in the quorum-sensing system. In this work, we prepared five recombinant homologues of F420H2 dependent enzymes putatively involved in the biosynthesis of 4-alkyl-L-proline of the above-mentioned metabolites. Further, we isolated the substrates and a deazaflavin cofactor from the culture broths of *streptomycetes* and *mycobacteria* and we set up in vitro enzymatic assays, which we monitored by LC-MS. We revealed that the reductase from the biosynthesis of lincomycin catalyzed an unusual reduction of two conjugated double bonds, while the reductases from pyrrolobenzodiazepines and hormaomycin biosynthesis converted the same substrate into a product, in which one of the double bonds remained intact. These results comply and fit within the biosynthetic pathways of the relevant metabolites and they represent the first example of homologues of F420H2 dependent reductases exhibiting different reaction specificity.

Biography

Lucie Steiningerova has been a member of the Laboratory for Biology of Secondary Metabolism since her bachelor degree. Currently, she is a student of the third year of Doctoral studying program Microbiology at the Charles University in Prague. The aim of her PhD thesis concerns biosynthesis of secondary metabolites in *Streptomyces*-lincosamide antibiotics, anticancer pyrrolobenzodiazepines, and hormaomycin.

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