S-Adenosylmethionine (SAM)-Dependent Methyltransferase MftM is Responsible for Methylation of the Redox Cofactor Mycofactocin.

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Projects

The biochemistry and physiology of the redox cofactor mycofactocin
Details

Abstract

Mycobacteria produce several unusual cofactors that contribute to their metabolic versatility and capability to survive in different environments. Mycofactocin (MFT) is a redox cofactor involved in ethanol metabolism. The redox-active core moiety of mycofactocin is derived from the short precursor peptide MftA, which is modified by several maturases. Recently, it has been shown that the core moiety is decorated by a β-1,4-glucan chain. Remarkably, the second glucose moiety of the oligosaccharide chain was found to be 2-O-methylated in Mycolicibacterium smegmatis. The biosynthetic gene responsible for this methylation, however, remained elusive, and no methyltransferase gene was part of the MFT biosynthetic gene cluster. Here, we applied reverse genetics to identify the gene product of MSMEG_6237 (mftM) as the SAM-dependent methyltransferase was responsible for methylation of the cofactor in M. smegmatis. According to metabolic analysis and comparative genomics, the occurrence of methylated MFT species was correlated with the presence of mftM homologues in the genomes of mycofactocin producers. This study revealed that the pathogen Mycobacterium tuberculosis does not methylate mycofactocins. Interestingly, mftM homologues co-occur with both mycofactocin biosynthesis genes as well as the putative mycofactocin-dependent alcohol dehydrogenase Mdo. We further showed that mftM knock-out mutants of M. smegmatis suffer from a prolonged lag phase when grown on ethanol as a carbon source. In addition, in vitro digestion of the glucose chain by cellulase suggested a protective function of glucan methylation. These results close an important knowledge gap and provide a basis for future studies into the physiological functions of this unusual cofactor modification.

Identifier

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