Mark Ellerhorst

The biochemistry and physiology of the redox cofactor mycofactocin

Mycofactocin is a recently discovered ribosomally synthesized and post-translationally modified (RiPP) redox cofactor, encoded and synthesized by the gene cluster *mftABCDEF* [1]. It is present in the genomes of a variety of different bacteria and even archaea [2] but appears to be particularly conserved in mycobacteria [1], hence the name. It was proposed that mycofactocin acts as an electron acceptor for specific alcohol dehydrogenases *in vivo* [2]. The biosynthesis of mycofactocin was shown to be induced by the presence of ethanol and is necessary for alcohol metabolism in *Mycolicibacterium smegmatis* [3]. In addition, it was found that the redox-active core molecule can be glycosylated by MftF with up to nine hexoses in β-1,4-glycosidic bonds [4]. Until today, the role of mycofactocin *in vivo* remains widely unknown. Therefore, this project is aimed at further investigation of the physiology, biochemistry, and biosynthesis of mycofactocin and its derivatives. These investigations will be realized by state-of-the-art "-omics" methods, such as targeted and untargeted metabolomics using high-resolution liquid chromatography coupled to mass spectrometry as well as classical methods in genetics and biochemistry.

References

1 Ayikpoe, R., Govindarajan, V., & Latham, J. A. (2019). Occurrence, function, and biosynthesis of mycofactocin. Applied microbiology and biotechnology, 103(7), 2903–2912. https://doi.org/10.1007/s00253-019-09684-4.

2 Haft, D.H. (2011). Bioinformatic evidence for a widely distributed, ribosomally produced electron carrier precursor, its maturation proteins, and its nicotinoprotein redox partners. BMC Genomics, 12: 21. https://doi.org/10.1186/1471-2164-12-21.

3 Krishnamoorthy, G., Kaiser, P., Lozza, L., Hahnke, K., Mollenkopf, H. J., and Kaufmann, S. (2019). Mycofactocin Is Associated with Ethanol Metabolism in Mycobacteria. mBio. 10(3): e00190–19. https://doi.org/10.1128/mBio.00190-19.

4 Peña-Ortiz, L., Graça, A.P., Guo, H., Braga, D., Köllner, T.G., Regestein, L., Beemelmanns, C., and Lackner, G. (2020). Structure elucidation of the redox cofactor mycofactocin reveals oligo-glycosylation by MftF. Chem Sci, 11(20): 5182–5190. https://doi.org/10.1039/d0sc01172j.

Publications

Ellerhorst M, Barth SA, Graça AP, Al-Jammal WK, Peña-Ortiz L, Vilotijevic I, Lackner G (2022) S-Adenosylmethionine (SAM)-Dependent Methyltransferase MftM is Responsible for Methylation of the Redox Cofactor Mycofactocin. *ACS Chem Biol* 17(11), 3207-3217. Details PubMed

Supervisor

Gerald Lackner

Co-Supervisors

Dirk Hoffmeister

Start of PhD

November 1, 2020