Structure and function of terminal oxidases from *M. smegmatis*

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Causative agents of severe diseases like tuberculosis and leprosis are gram-positive bacteria from genus *Mycobacterium.* To address the growing need for new drugs against these increasingly drug-resistant pathogens, novel drug targets must be identified and studied. Some of the most promising potential targets are found in the respiratory chain, as many of its components possess unique features, not found in the human respiratory chain. To completely inhibit respiration in *mycobacteria*, branching of the respiratory chain must be taken into account. There are multiple mycobacterial terminal oxidases, each expressed and functional at different life conditions of the bacteria. In this study, we focused on analyzing the obligate respiratory chain supercomplex ($CIII_2CIV_2$), expressed at aerobic conditions, as well as the *bd*-oxidase, which is upregulated under limited oxygen conditions. The studied protein complexes were purified from *M. smegmatis* because of their high homology to their counterparts in *M. tuberculosis*. Using biochemical, structural and computational approaches we obtained insights into mechanisms of their function (1) and inhibition. We also analyzed new additional substrate binding sites and their functional role.

1) Riepl, D.; Gamiz-Hernandez, A. P.; Kovalova, T.; Krol, S. M.; Mader, S. L.; Sjöstrand, D.; Högbom, M.; Brzezinski, P.; Kaila, V. R. I., Long-Range Proton-Coupled Electron Transfer Dynamics in the Obligate Mycobacterial Supercomplex III_2IV_2. Nat. Commun. 2024, (accepted).