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AccD1 And AccA1 from M. tuberculosis form A dodecameric MCC-type holo complex

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Mycobacteria have an unusual redundancy of six putative carboxyltransferase genes that form high-molecular weight holo acyl coenzyme A carboxylase complexes with a complementary set of three biotin carboxylase genes. Most of these enzyme complexes use small fatty acid coenzyme A esters as substrate, to allow their extension by one methylene group via a carboxybiotin-mediated α-carboxylation reaction. Redundant occurrence of these complexes was assumed to be related to highly complex enzymatic requirements in lipid biosynthesis, as the mycobacterial thick cell wall comprises unusual very long chain fatty acids, including mycolic acid. We have solved two high-resolution crystal structures of the 350 kDa hexameric assemblies of two different acyl coenzyme A carboxylase hexameric assemblies, AccD5 and AccD6 [1; Anandhakrishnan et al., unpublished], and characterized these enzyme complexes functionally. In a second step we investigated the acyl coenzyme A carboxylase complex AccD1-AccA1 from Mycobacteria tuberculosis with hitherto unknown function. By using a metabolomics approach we found that AccD1-AccA1 is involved in branched amino acid catabolism, which was not investigated in mycobacteria before [Ehebauer et al, unpublished. Using an in vitro assay, we show that the enzyme complex uses methylcrotonyl coenzyme A as substrate]. We determined the overall architecture of the 700 kDa AccD1-AccA1 complex to be formed from three layers of a central AccD1 hexameric ring, flanked by two distal tiers composed of three AccA1 subunits each. Our electron microscopy data match the overall dimensions of a methylcrotonyl coenzyme A holo complex with known structure and thus support our functional findings. Our data suggest a unique functional role of the AccD1-AccA1 complex within the Mycobacterium tuberculosis acyl coenzyme A carboxylase interactome. Ultimately, it is our goal to solve this and related structures of ACCase holo complexes by high-resolution crystallography as well. The abstract is dedicated to Louis Delbaere with whom I shared time during my PhD at the University of Basel, Switzerland.

[1] *Holton et al. FEBS Lett. 2006 Dec 22;580(30):6898-902.*

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