**[MS5-P42] Structure of malonyl CoA decarboxylase provides insight in catalysis and disease mutations**

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Malonyl-CoA decarboxylase (MLYCD, EC 4.1.1.9) regulates the cellular level of malonyl-CoA by catalysing its degradation to acetyl-CoA. The importance of MLYCD in maintaining flux balance between fatty acid and glucose metabolism is highlighted by (i) a rare but severe disorder *malonic aciduria* caused by inherited mutations on the *mlycd* gene, and (ii) the involvement of MLYCD in obesity, diabetes and cardiovascular disease, of which there is mounting pharmacological interest. To date, the understanding of this crucial enzyme has been hampered by a lack of biochemical and structural characterization. With this background, we have crystallized human MLYCD using the surface entropy reduction strategy, and determined its structure to 2.8 Å resolution. The structure unexpectedly reveals a protein core related to GCN5-related N-acetyltransferases, appended with an N-terminal helical domain that is involved in forming a dimer of dimers, an oligomeric state supported by electron microscopy. Kinetic studies on site-directed mutants further identify Ser329 and His423 as essential residues that purportedly stabilize a tautomerized enolate intermediate during the decarboxylation reaction. Mapping patient mutations on the structure reveals no localized hot-spot regions, but allows the categorization of each substitution into defects on protein localization (e.g. G3D and M40T), folding (e.g. A69V and L161P) or catalysis (e.g. S290F and Y456S). Together, our data provide the first template to understand the molecular basis of malonic aciduria, and allow structure-guided design of small molecule inhibitors for therapeutic applications.