MS03-P09 | Crystal Structure Of Human AMACR Provides Insight Into Substrate Recognition And Catalytic Mechanism

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Human αmethylacyl CoA racemase (AMACR; P504S) plays a pivotal role in catalysing a key chiral inversion step in the metabolism of branchedchain fatty acid, ibuprofen, and related drugs. Recently, AMACR was found to be overproduced in prostate cancer and has been used as a cancer biomarker and an attractive drug target. Moreover, human AMACR is associated with human diseases because of function deficiency caused by single base mutation such as the SNP mutants S52P and L107P. Here, we report the crystal structures of human AMACR in apo form and in complex with a substrate analog, isobutytrylCoA (IBCoA). The structure of human MACR presents an interlocked dimeric architecture. In addition, the structural information delineates the residues involved in catalysis and identifies a hydrophobic plateau for acyl or aromatic groups binding. For the binding effect of large sidechain substrates, the evidence implies that the hydrophilic sidechain would not contribute to binding. Finally, based on the results of MD simulation and in vivo thermal shift assay, we find that L107P and S52P mutants located very close to the binding pocket, and S52P are less stable than wildtype AMACR. These studies will shed new light on the drug development and understanding of AMACR function, and thus will be of great research and therapeutic value.