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Extended Abstract

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Investigating the role of NS2B dynamics in dengue virus NS3 protease function

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ε-trimethyllysine hydroxylase (TMLH) is a non-heme Fe(II) and 2-oxoglutarate (2OG) structured dioxygenase located in the submitochondrial matrix. This enzyme is vital for the stereospecific oxidation of ε-trimethyllysine (TML) to β-hydroxytrimethyllysine (HTML), the first step in the biosynthesis of L-carnitine. It is proposed that the law of enzymatic activity of TMLH might also have greater strong cardioprotective effect than meldonium (clinically used anti-ischemia drug) that is an inhibitor of γ-butyrobetaine hydroxylase (GBBH), the closing step of the L-carnitine production. Due to failure of the crystallographic strategies there is still lack of information about the shape of the TMLH and specially about its active site. In this work, we applied in silico and in vitro techniques to design the viable lively website of TMLH. The shape of the TMLH was once modeled the use of homology modeling strategy primarily based on the closest homolog, GBBH (used as template). However, the standard similarity between both enzymes used to be slightly under 30%. Thus, various modeling softwares were tested, and the resulting structures have been optimized during molecular dynamics simulations. This strategy gave the insights into viable enzyme fold. Next, the NMR protein-ligand binding experiments (T1ρ, waterLOGSY and ST1D) and the enzymatic assay (reaction monitored by 1D 1H-NMR) published some crucial structure-activity relationships (SAR) that in aggregate with molecular docking and previous in silico facts allowed to construct estimated active site of TMLH. The biologically important carnitine biosynthesis pathway in people proceeds with the aid of 4 enzymatic steps. The first step in carnitine biosynthesis is catalyzed by using trimethyllysine hydroxylase (TMLH), a non-heme Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase, which catalyzes the stereospecific hydroxylation of (2S)-Nε-trimethyllysine to (2S,3S)-3-hydroxy-Nε-trimethyllysine. Here, we record biocatalytic studies on human TMLH and its 19 variations delivered through site-directed mutagenesis. Amino acid substitutions at the web sites involved in binding of the Fe(II) cofactor, 2OG cosubstrate and (2S)-Nε-trimethyllysine substrate furnish a simple insight into the binding necessities that determine an efficient TMLH-catalyzed conversion of (2S)-Nε-trimethyllysine to (2S,3S)-3-hydroxy-Nε-trimethyllysine. This work demonstrates the significance of the cognizance sites that make contributions to the enzymatic pastime of TMLH: the Fe(II)-binding H242–D244–H389 residues, R391–R398 concerned in 2OG binding and numerous residues (D231, N334 and the aromatic cage comprised of W221, Y217 and Y234) associated with binding of (2S)-Nε-trimethyllysine. Carnitine (L-3-hydroxy-4-N,N,N-trimethylaminobutyrate) is an necessary metabolite that allows the transport of lengthy fatty acids from the cytosol into mitochondria in humans, different eukaryotes, many plant life and microorganisms. Humans achieve carnitine by food regimen (e.g. meat) or endogenous biosynthesis. The carnitine biosynthesis pathway proceeds with the aid of 4 enzymatic steps from (2S)-Nε-trimethyl lysine to L-carnitine. The first and the ultimate steps are catalyzed by using trimethyllysine hydroxylase (TMLH) and γ-butyrobetaine hydroxylase (BBOX), individuals of non-heme Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenases. The 2nd step of carnitine biosynthesis is catalyzed by way of 3-hydroxy-Nε-trimethyl lysine (HTML) aldolase, an enzyme that has not yet been recognized in humans, whereas the third step is mediated via NAD+ dependent 4-trimethylaminobutyraldehyde (TMABA) dehydrogenase (ALDH9 in humans). Targeting enzymes concerned in the carnitine biosynthesis pathway has a possibility in drug discovery as a method for therapeutic intervention in cardiovascular diseases. A biomedical relevance of carnitine biosynthesis has been exemplified by the improvement of 3-(2,2,2-trimethylhydrazine)propionate (also recognised as Mildronate or Meldonium), a substrate-competitive notably selective inhibitor of BBOX, which is used for the therapy of myocardial infarction. Recent work also proposed that a dysregulation of the carnitine biosynthesis pathway with the aid of TMLH deficiency or mutations is linked with an extended threat for autism

Bottom Note: *This work is partly presented at 10th Edition of International Conference on Structural Biology* March 15-16, 2018 Barcelona, Spain