MetabERN AOA subnetwork

Analysis of hydrogen sulfide metabolism in selected ultra-rare IEMs

proposal by Viktor Kožich, January 16, 2019

Rationale: Hydrogen sulfide is an important endogenous signaling molecule implicated in vasculature, neuromodulation, immunomodulation and other (pato)physiological processes. Endogenous sources of H_2S include microbiota, and sulfur amino acids Cys and Hcy that are converted to H_2S by several enzymes (e.g. CBS, CTH-gamma-cystathionase, MPST, MTO and CARS2). Hydrogen sulfide is further catabolized in mitochondria by several enzymes including SQOR, thiosulfate transferase and sulfite oxidase. IEMs in sulfur metabolism represent a unique model to explore poorly described disorders in H_2S production and catabolism.

Preliminary results: So far we analyzed H_2S and related metabolites in small cohorts of treated patients with CBS deficiency and remethylation defects and we showed that deficiency of these enzymes is associated with only minor changes in H_2S homeostasis (paper in press https://www.ncbi.nlm.nih.gov/pubmed/30341787). An extension of this project focuses on other-ultra-rare- IEMs in sulfur metabolism. With help of several colleagues we have so far analyzed "sulfurome" in 3 patients with ethylmalonic encephalopathy due to *ETHE1* mutations, 2 patients with sulfite oxidase or molybdenum cofactor deficiencies and 2 patients with CTH deficiency. In contrast to CBS or RM defects, these patients exhibit severely disturbed metabolism of inorganic sulfur compounds and these analyses may contribute to better understanding of pathophysiology of these diseases.

Eligible patients: We are searching for samples from additional patients with **ethylmalonic aciduria** due to *ETHE1* mutations, **isolated or combined sulfite oxidase deficiency** due to mutations in *SUOX*, *MOCS1, MOCS2* or *GPHN* genes and **cystathioninuria** due to mutations in *CTH* gene.

Ethics: Project was approved by the IRB in the General University Hospital in Prague, information sheets for adults and minors, assent and informed consents forms in English have been approved for use.

Samples: Since sulfite and hydrogen sulfide are quite unstable, only prospectively and freshly collected samples can be used. From each patient and at least one control the following samples are needed: at least 300 microliters of lithium heparin plasma and 5 ml of freshly collected urine, and one empty Li Hep tube for blank. Samples have to kept on ice/water bath prior centrifugation or further processing, quickly frozen at -80 C and have to be shipped on dry ice to the lab in Prague. Detailed sampling/shipping protocol is available.

Patient sampling period: February to April/May, 2019

Output: Collaborative paper on H_2S metabolism in these patients.

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