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Science Vision 2020 on Sulfur Metabolism: What is Needed and What can be Achieved?

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PAPs synthesis

Many intracellular compounds are sulfonated. The universal sulfonate donor is 3'-phosphoadenosine 5'-phosphosulfate (PAPS). In humans PAPS is synthesized from inorganic sulfate by PAPS synthase (PAPSS) in two steps. First inorganic sulfate combines with adenylate moiety of ATP to form 3'-AdenosinePhosphosulate (APS) by ATP sulfurylase activity of the PAPSS. This enzyme domain activity is one of unique ATP α-βphospho-anhydride bond splitting enzyme that is much similar to type I tRNA synthetases. Pyrophosphate which is one of the byproduct is cleaved into two inorganic phosphates by ubiquitous pyrophosphates. APS in the next step is phosphorylated at the 3'-OH by another molecule of ATP by APS kinase domain of the PAPSS. APS kinase is a β-γ phospho anhydride bond splitter of ATP that possess Walker motif such as GxxGxxK to form the phosphoryl for transfer reaction. Years ago I was the first to molecularly clone, express, dissect the domain activities of human PAPSS from fetal brain. Currently we are interested in the developmental roles of PAPSS during mice brain development and its clinical correlations. Deficiency of PAPSS2 isoform leads to Spondylo Epimetaphyseal Dysplasia (SEMD) in humans. Thus we are interested in the biochemistry, molecular biology and the clinical relevance of the oxidized form of the sulfur, PAPS the sulfuryl donor in human biology and development.

Methionine Metabolism

Methionine is a sulfur amino acid that has (C-S-C) thioether bond. The sulfur in methionine and cysteine (thiol) forms are in the reduced state. The reductive process of the conversion of sulfate into sulfide and its incorporation into cysteine and eventually methionine are absent in mammals. Mammals obtain methionine mainly through diet which then can be used for s-adenosylmethionine (SAM) and de novo cysteine synthesis. SAM is the universal methyl group donor. The role of SAM in histone, DNA and mRNA methylation is extremely crucial in epigenetic regulations of the genome/genetic expressions. Once the methyl group is transferred to a recipient compounds such as nucleic acids, lipids, proteins and sugars the side product s-adenosyl homocysteine is cleaved into homocysteine and adenosine. Free homocysteine can condense with serine to form cystathionine with the elimination of H_2O, catalyzed by pyridoxal phosphate [PLP, (coenzyme derivative of vitamin B6)] dependent cystathionine beta-synthase (CBS) (EC 4.2.1.22). Cystathionine, then can be cleaved by a cystathionine gamma-lyase (CGL) (E.C. 4.4.1.1), at trans-gamma position to release cysteine and the rest of the moiety is released as alpha-ketobutyrate and ammonia. The free homocysteine is converted into methionine by methionine synthase [5-methyltetrahydropteroyl-L-glutamate: L-homocysteine S-methyltransferase, (E.C. 2.1.1.13)] using homocysteine, methyl group from 5-methyl-tetrahydrofolate and the coenzyme methylcobalamin (vitamin B12). In bacteria methionine pools are channeled into anabolism by simple formylation of methionine to form formyl-methionine (fmet). In the catabolic pathway methionine, can undergo degradation to form methylthiol, a-ketobutyrate and ammonia catalyzed by methionine gammalyase-deaminae (*mgld*). We have molecularly cloned the methionine degrading enzyme mgld and are looking in to the structure/function aspects of the enzyme. We have also transfected the mgld gene into mammalian cancer cells and we are investigating the cytosolic and various cellular effects. Currently we have localized the mgld in the nucleus of various cancer cell types and asking the question what? global methylation effects would there be on the chromatin morphology.

Investigation of methylation/demethylation pathways in normal brain and cancer cells

Methylation/demethylation pathways are critical in controlling the epigenetic mode of gene suppression/expression. For the methylation cycle MetS, CBS, SAM synthase and methyltransferase must be tightly regulated. For the demethylation cycle the cytosine methyl hydroxylase, oxidase and the decarboxylase must be tightly regulated. The vitamin B6 dependent cytosine 5-decarboxylase is a poorly understood enzyme that needs to be characterized thoroughly (Venkatachalam unpublished). Cytosine 5-decarboxylase would be controlled developmentally, temporally and chronologically. De/dysregulated activity of cytosine 5-decarboxylase would result in uncontrolled cell division and metabolism. We plan to investigate the expression and the activities of all the relevant enzymes of methylation/demethylation during normal mice development and in cancer cells during cell division in the presence and absence of transfected *mgld* gene. The study will help understand the epigenetic control mechanisms that play in neurodegenerative and various debilitating diseases that are regulated by methylation/demethylation patterns.