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The Conundrums of 3'-Phoaphoadenosine 5'-Phosphosulfate (PAPS) synthase (PAPSS)

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Introduction

3′-Phoaphoadenosine 5′-Phosphosulfate (PAPS) synthase (PAPSS) of human is comprised of two domains [ATP sulfurylase (ATPS)] and [APS kinase (APSK)] [1-3]. ATP sulfurylase binds ATP and allows the sulfate anion to attack the alpha-phosphoryl by nucleophilic attack. This allows the elimination of pyrophosphate (PPi) and the formation of phospho-sulfate anhydride bond of APS which is energetically higher (~19 kcal/mol) compared to phospho-phosphate (~7.6 kcal/mol) nucleotide. However, nature chose to have sulfur as well as phosphorous nucleotide, one serving as a universal cellular energy currency, as well as a donor for phosphorylation. In contrast, PAPS was chosen as a universal donor of sulfuryl group for molecule/macromolecule modifications and not chosen as an energy source. PPi the eliminated product of ATPS is cleaved into two inorganic phosphates by the ubiquitous pyrophosphatase, a process that can drive the whole reaction of APS formation, to certain degree in the forward direction? with the help of substrate concentration gradient. (**Figure 1**)The energy of ~4 kcal must be invested in balance, to at least reach the equilibrium on the ATPS reaction.

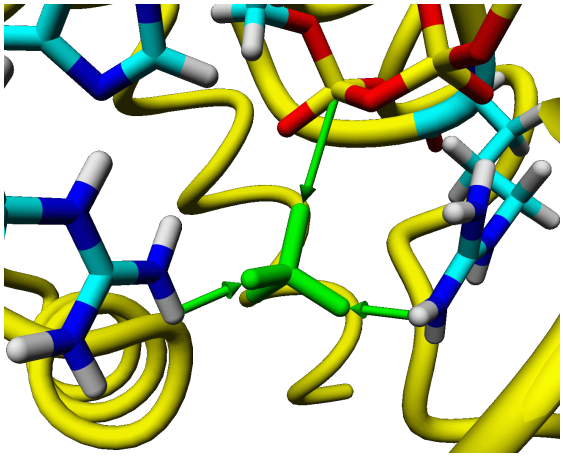

Figure 1: Sulfate and ATP binding PAPS is partly described.

Could it be driven by the APSK? Half reaction? After all, the APSK reaction involves splitting of second ATP at the beta-gamma position which not only releases energy but also provides the phosphoryl donor to modify APS at 3' position to form PAPS. Thus, it must be in fused protein PAPSS, that the APSK domain must be contributing molecular motion to offset the energy barrier/deficiency required to move away from the equilibrium to proceed overall in the forward direction to form PAPS. The energetics of ATP, APS binding and the aspects of PAPS formation is under investigation by fused ATPS+APSK (PAPSS).

The next conundrum about PAPSS is: the isozyme PAPSS1 is located in the nucleus as well as in the cytosol, whereas PAPSS2(a or b isoforms) is located mostly in the cytosol. What is the role of nuclear PAPSS? Could I remotely postulate that the nuclear PAPSS might be producing PAPS for nucleic acid/nuclear protein modification? If there is such a mechanism, it is fundamentally shaking in that we have one more epigenetic modifications amongst already known modification such as methylation, phosphorylation, acetylation, ubiquitylation, SUMoylation etc. I postulate similar to acetylation and phosphorylation, sulfurylation can impart change in charge (at least one negative charge)/mol of PAPS [4], which in turn can change the overall physico-chemical properties of the nucleic acid/bound protein (histones) and could consequently influence the gene expression. This is fundamentally striking question that needs to be answered and our lab is perusing on that to find a possible solution. Albeit, known diseases such as achondroplasia, spondylo epimetaphyseal dysplasia (SEMD) and osteoarthritis related to PAPS metabolism deficiency there are no other diseases/syndromes that we know of that is affected clearly/solely by PAPS/PAPSS defects. The developmental derangement due to PAPSS isozyme and or isoform defects must be studied which could answer some of the questions that are being posed. Does cancer cells have altered PAPS metabolism compared to normal cells? must be addressed as well. If there is a defect in the sulfate content from the diet can it influence the growth and development to cause metabolic syndrome related to PAPS, must also be addressed.

The tissue specific expression of PAPSS is an another, aspect that needs to be addressed [5]. In some tissues both PAPSS1 and PAPSS2 are expressed. Within PAPSS2a and PAPSS2b the tissue specific expression needs to be studied. We are looking ahead for multiple answers for PAPSS questions/conundrum in the near future.

References

1. Venkatachalam KV, Akita H, Strott CA (1998) Molecular cloning, expression and characterization of human bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthase and its functional domains. J Biol Chem 273: 19311-19320.
2. Venkatachalam K, Fuda H, et al. (1999) Site-selected Mutagenesis of a Conserved Nucleotide Binding HXGH Motif Located in the ATP Sulfurylase Domain of Human Bifunctional 3'Phosphoadenosine 5'-Phosphosulfate Synthase. J Biol Chem 274: 2601-2604.
3. Venkatachalam K (2003) Human 3′-phosphoadenosine 5′phosphosulfate (PAPS) Synthase: Biochemistry, Molecular Biology and Genetic Deficiency. IUBMB Life (International Union of Biochemistry and Molecular Biology: Life) 55: 1-11.

4. Venkatachalam K V (2016) Biochemical Sulfuryl Group Transfer From 3'Phosphoadenosine 5'-Phosphosulfate (PAPS) Versus Phosphoryl Transfer From ATP: What Can Be Learnt? Biochem Physiol 5:1

5. Sekulic N, Dietrich K, et al. (2007) Elucidation of the Active Conformation of the APS-Kinase Domain of Human PAPS Synthetase 1. J Mol Biol 367: 488-500.