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H_2S producing enzyme, 3-mercaptopyruvate sulfurtransferase

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3-Mercaptopyruvate sulfurtransferase (MST, EC 2.8.1.2) is a cystine-catabolizing enzyme involved in the mercaptopyruvate pathway and evolutionarily related to mitochondrial rhodanese (TST, EC 2.8.1.1). MST is a 33 kDa simple protein enzyme, which catalyzes transsulfuration reaction. An active site Cys^{247} is the site of persulfide formation during catalysis (Nagahara *et al*., J Biol Chem, 2005, Nagahara & Sawada, 2006, Nagahara *et al*., J Biol Chem, 2007). MST is found in all the tissues in rat and mouse; however, its activity differs in each tissue. Subcellular fractionation analysis revealed that eukaryotic MST activity was observed in both the cytoplasm and mitochondria (Nagahara *et al*., Histochem. Cell Biol, 1998, Tomita *et al*., Molecules, 2016). Interestingly, it is distributed in both prokaryotes and eukaryotes. MST has been demonstrated to serve multiple roles (Nagahara et al., Methods Enzymol, 2015, Nagahara, Bri J Pharmacol, 2018) as H_2S and polysulfide production (Ida *et al*., Proc Natl Acad Sci USA, 2014, Kimura *et al*., Sci Rep, 2015, Mikami *et al*., Biochem J, 2011, Shibuya *et al*., Antioxid Redox Signal, 2008, Yadav *et al*., J Biol Chem, 2013, Nagahara *et al*., Biochem Biophys Res Commun, 2018), antioxidant action (Nagahara and Katayama, J Biol Chem, 2005, Nagahara *et al*., J Biol Chem, 2007), possible SOx production (Nagahara *et al*., Antioxid Redox Signal, 2012), and possible anxiolytic-like effect (Nagahara *et al*. Sci Rep, 2013).

It has been reported that hydrogen sulfide and polysulfides were produced by cystathionine β-synthase (EC 4.2.1.22) (Abe and Kimura, J Neurosci, 1996), cystathionine γ-lyase (EC 4.4.1.1) (Hosoki *et al*., Biochem Biophys Res Commun, 1997), TST (Kimura *et al*., Sci Rep, 2015; Mikami *et al*., J Biol Chem, 2011) and MST. As to antioxidative function, MST activity is regulated by thioredoxin-dependent redox-sensing molecular switches; one switch is a catalytic site cysteine forming a low redox potential sulfenate under oxidized conditions which is reversibly converted to an inactive form MST. The other one is exposed cysteines outside enzyme forming a disulfide between MSTs under oxidized conditions to be inactive dimeric form. We are now investigating physiological role of MST using MST-knockout (KO) and double TST and MST-KO mice. Recently, we further reported H_2S and polysulfide production by MST *in vitro* (Nagahara *et al*., Biochem Biophys Res Commun, 2018).

Speaker Biography

Noriyuki Nagahara, MD., PhD., Biochemistry and Pathological Chemistry, is associate professor of Nippon Medical School. He makes a special study of medical biochemistry, molecular biology and organic chemistry, especially reaction mechanism and enzyme kinetic study on a transsulfuration enzyme, mercaptopyruvate sulfurtransferase (MST). He first purified rat MST to homogeneity and succeeded cloning. He found MST was evolutionarily related to mitochondrial rhodanese via substitution of amino acids in the active site by genetic engineering techniques. He certified that MST was an antioxidant enzyme. Recently, he produced MST-knockout mouse to clarify physiological roles of MST and a pathogenesis of congenital metabolic disease caused by deficiency of MST, mercaptolactate-cysteine disulfiduria.

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