3MST produces redox regulators Cys-SSH and GSSH as well as signaling molecules H2S and H2Sn

3-Mercaptopyruvate sulfurtransferase (3MST) together with cysteine aminotransferase (CAT) produces hydrogen sulfide (H_2S), a well-known toxic gas, from L-cysteine. 3MST also produces H_2S from D-cysteine in concert with D-amino acid oxidase (DAO). Cystathionine β–synthase (CBS) and cystathionine γ–lyase (CSE) are also known as H_2S producing enzymes. H_2S has physiological roles such as the formation of memory, regulation of blood pressure, protection of tissues/organs from various insults including oxidative stress and ischemia, anti-inflammation activity and energy formation.

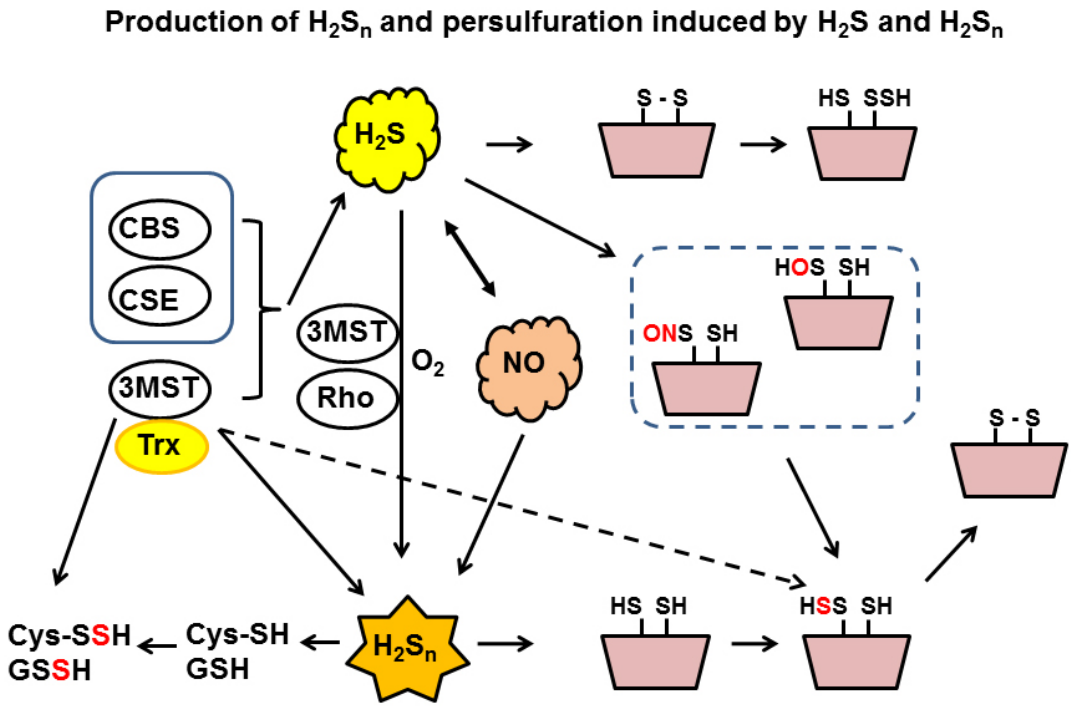

Fig. 1. Production of H2S, H2Sn, cysteine- and glutathione-persulfide by 3MST, and their mode of activation of target proteins.

3MST also produces hydrogen polyfulfides (H_2S_n) which have higher number of (sulfane) sulfur atoms than H_2S. H_2S_n regulate ion channels, a tumor suppressor, protein kinases involving in the regulation of blood pressure, and transcription factors to up-regulate antioxidant genes. H_2S_n can also be produced by the chemical interaction of H_2S with nitric oxide (NO) that provides a mechanism of a synergy between H_2S and NO.

Cysteine-persulfide (Cys-SSH) is a cysteine whose sulfhydryl group is covalently bound to sulfur (sulfane sulfur). Cys-SSH and its glutathione (GSH) counterpart (GSSH) have been recognized as

cellular redox regulators, some of which were previously ascribed to cysteine and GSH. However, the production of Cys-SSH and GSSH is not well understood. In the present study we demonstrated that 3MST produces Cys-SSH, GSSH, and persulfurated proteins (Pro-SSH). It is concluded by the following observations. 1) 3MST produced Cys-SSH and GSSH as well as H_2S_n in vitro. 2) Cells expressing 3MST produced persulfurated species greater than a control, while those expressing 3MST defective mutants did not. 3) The administration of L- or D-cysteine to mice increased the levels of persulfurated species in tissues. 4) The levels of persulfurated species in the brains of 3MST knockout mice were less than half of those in the wild-type mouse brains. Although 3MST can also produce polysulfide species such as Cys-SS_nH ($n \geq 2$) and GSS_nH in vitro, persulfurated species are predominantly produced under physiological conditions.

We proposed two potential mechanisms for the production of the persulfurated species: 3MST produces H_2S_n which react with cysteine, GSH and protein to produce Cys-SSH, GSSH and Pro-SSH. Alternatively, 3MST directly transfers sulfur to cysteine, GSH and protein without the mediation of H_2S_n.

The mode of action of H_2S_n is mediated by S-sulfuration (sulfhydration) of the cysteine residues of target proteins that causes the conformational changes, leading to the alternation of activity. Two cysteine residues are involved in the activation of some target proteins by H_2S_n: an S-sulfurated cysteine residue by H_2S_n may react with a thiol of another cysteine residue to form disulfide bond. Transient receptor potential ankyrin 1 (TRPA1) channels has two cysteine residues responsible for the activation by H_2S_n. The same is true for the regulation of a tumor suppressor, phosphatase and tensin homolog (PTEN). An inactive monomer of protein kinase G1a (PKG1a) turns to the active dimer formed through S-sulfuration. Some other proteins such as ATP-dependent K^+ (K_{ATP}) channels have one cysteine residue responsible for their activation through S-sulfuration.

H_2S can modify the activity of target proteins by reducing their cysteine disulfide bond as well as by S-sulfurating cysteine sulfinic acid (Cys-SOH) produced under oxidative stress or S-nitrosylated cysteine (Cys-SNO) generated by NO signaling. S-sulfuration may also play roles even under pathological conditions. For example, cysteine residues of parkin whose disruption is the most common cause of inherited Parkinson's disease (PD) are S-nitosylated in the brain of PD patients, while those of healthy individuals are S-sulfurated. H_2S may be involved in S-sulfuration of Cys-SNO to Cys-SSH.

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Publication

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