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Thioredoxin-dependent Redox-sensing Molecular Switches in Hydrogen Sulfide and/or Polysulfides Producing Enzyme, 3-Mercaptopyruvate Sulfurtransferase

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Abstract

The rat 3-mercaptopyruvate sulfurtransferase (MST), a multifunctional enzyme, has redox-sensing molecular switches, a catalytic Cys^{247} and two cysteines, Cys^{154} and Cys^{263}, on the outer surface of the enzyme. These switches are reduced or oxidized according to the redox state of their surrounding environment and require a redox active cysteine in thioredoxin (Trx) to interact with MST. Recently, MST has been demonstrated to be involved in the production of possible signaling molecules such as hydrogen sulfide, polysulfides, and/or sulfur oxides. However, the relationship between the production of signaling molecule(s) and action of these redox-sensing molecular switches has not been clarified, and a precise investigation of this relationship is underway.

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Background

3-Mercaptopyruvate sulfurtransferase (MST, EC 2.8.1.2) is an enzymes involved in cysteine catabolism [1]. MST is present in various tissues and exists in both the mitochondria and cytosol [2,3]. Its activity ratio differs depending on the tissue [2,3]. MST catalyzes transsulfuration of a sulfur-donor substrate to a sulfur-acceptor substrate, and prefers 3-mercaptopyruvate to thiosulfate as sulfur-donor substrate. In cyanide detoxification, MST uses cyanide as a sulfur-acceptor substrate to produce thiocyanate [2]. When the sulfur-acceptor substrate is a thiol, persulfide is created, and hydrogen sulfide is generated by the reaction between persulfide and thiol [4]. Recently, it was reported that MST is involved in the production of hydrogen sulfide[4-7], polysulfides [7], and/or sulfur oxides [8]. Polysulfides are more effective as signaling molecules compared to hydrogen sulfide [9]. In humans, a congenital lack of MST causes mercaptolactate-cysteine disulfiduria [10,11], and the patients with this condition often presented with mental retardation [10,12]. Recently, MST-knockout mice were produced as animal models of the human congenital disease and displayed an increase of anxiety-like behavior [13]. Oxidation suppresses cysteine degradation and reduction promotes it. MST activity is controlled by the redox state via redox-sensing molecular switches, which are exposed cysteines. Rat MST (*Rn*MST) has five cysteines, Cys^{64}, Cys^{154}, Cys^{247}, Cys^{254}, and Cys^{263}. Cys^{64} and Cys^{254} are buried cysteines, while the other cysteines are exposed [14]. Cys^{247} is a catalytic cysteine, and Cys^{154} and Cys^{263} are positioned at the surface of the enzyme; these cysteines function as redox-sensing molecular switches. Cys^{154} is a unique residue in *Rn*MST. Furthermore, thioredoxins (Trxs) have redox-active cysteines. *Escherichia coli* Trx (*Ec*Trx) has two redox active cysteines, one of which interacts with *Rn*MST [15].

Properties of intermolecular switches of *Rn*MST

Cys^{154} and Cys^{263}, which are positioned the surface of *Rn*MST, form dimers via disulfide bonds [15]. Activities of wild-type and C64S (Cys^{64} is replaced with Ser) and C254S mutant *Rn*MSTs were significantly increased after treatment with reduced *Ec*Trx or *Ec*Trx with a reducing system (*Escherichia coli* Trx reductase and NADPH) [15]. However, activities of C154S, C263S, and C154S/C263S (Cys^{64} and Cys^{64} are replaced with Ser) mutant *Rn*MSTs were not significantly increased by reduction [15]. These findings suggest that Cys^{154} and Cys^{263} are Trx-dependent redox-sensing molecular switches for regulation of MST activity, probably via the induction of conformational changes [15].

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Properties of intramolecular switch of *Rn*MST

The catalytic cysteine of *Rn*MST (Cys^{247}) is easily oxidized by hydrogen peroxide, which cause the inhibition or inactivation of *Rn*MST [16]. During oxidation, Cys^{247} was sulfenated, sulfinated, and finally sulfonated by hydrogen peroxide **(Figure 1).** The sulfenated Cys^{247} was reduced and MST activation was restored by dithiothreitol (DTT), reduced *Ec*Trx, or *Ec*Trx with the reducing system [16]. However, reduced glutathione or glutathione with its reducing system (glutathione reductase and NADPH) could not restore the *Rn*MST activity [16]. Moreover, sulfenate formation at Cys^{247} was confirmed by Trx peroxidase activity on addition of *Rn*MST to the mixture of hydrogen peroxide and Trx with the reducing system [16].

Interaction between *Rn*MST and *Ec*Trx

*Ec*Trx has two redox active cysteines, Cys^{32} and Cys^{35}. DTT-treated *Rn*MST was activated by the reduced C35S *Ec*Trx mutant and not by the reduced C32S *Ec*Trx mutant [15]. Further, HPLC analysis showed that *Rn*MST formed a complex with C35S *Ec*Trx and not with C32S *Ec*Trx [15]. These results indicate that the Cys^{32} of *Ec*Trx attacks and cleaves the intermolecular disulfide bond between dimeric *Rn*MST molecules and forms a complex with *Ec*Trx. Then, Cys^{35} attacks and cleaves the disulfide bond between *Rn*MST and *Ec*Trx **(Figure 2)** [15]. In the case of plants, a recent study on mouse-ear cress sulfurtransferases and mouse-ear cress Trxs confirmed that both redox-active cysteines of Trx were necessary for the interaction between MSTs and Trxs [16].

Do hydrogen sulfide and polysulfides interact with redox-sensing switches as reductants?

MST produces hydrogen sulfide and polysulfides in the catalytic process [5-7]. Oxidative stress inhibits MST activity, resulting in a decrease in the production of hydrogen sulfide and polysulfides. However, there is no report on the effect of hydrogen sulfide and polysulfides on MST activity via interaction with the thioredoxin-dependent redox-sensing switches. The low redox potential of sulfenate at a Cys^{247} catalytic site in an inactive MST is reduced by the addition of thioredoxin ($E^0 = -270$ mV), but not by the addition of glutathione ($E^0 = -240$ mV [17,18]. Therefore, hydrogen sulfide ($E^0 = -140$ mV [19]) may not reduce the cysteine-sulfenate group. Conversely, polysulfides ($E^0 > -260$ mV [19,20]) could reduce the sulfenate and convert the inactive MST to an active form. Thioredoxin effectively reduces inactive dimeric MST to an active monomeric form by reducing one of the intersubunit disulfide bridges that link the two subunits, *i.e.*, the reduction of the disulfide bridges between Cys^{154} and Cys^{154}, Cys^{263} and Cys^{263}, or Cys^{154} and Cys^{263} results in the formation of an active form of MST [15]. Therefore, polysulfides other than hydrogen sulfide may also cleave these intersubunit disulfide linkages.

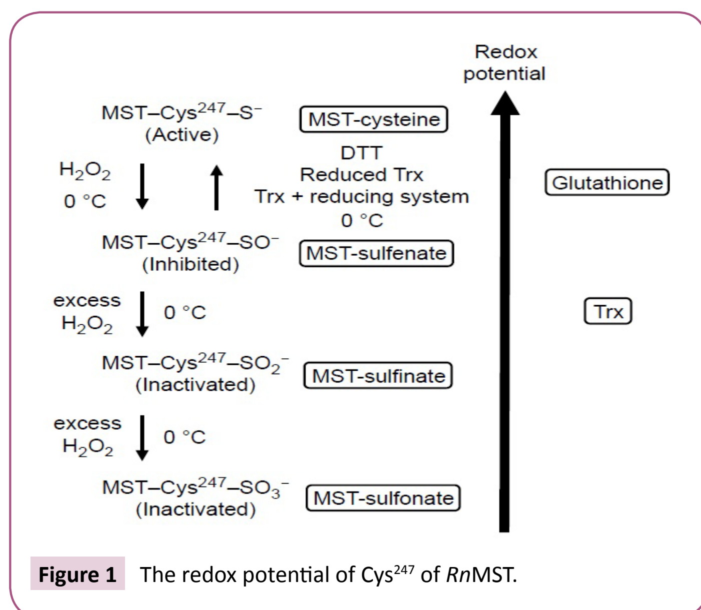

Figure 1 The redox potential of Cys^{247} of *Rn*MST.

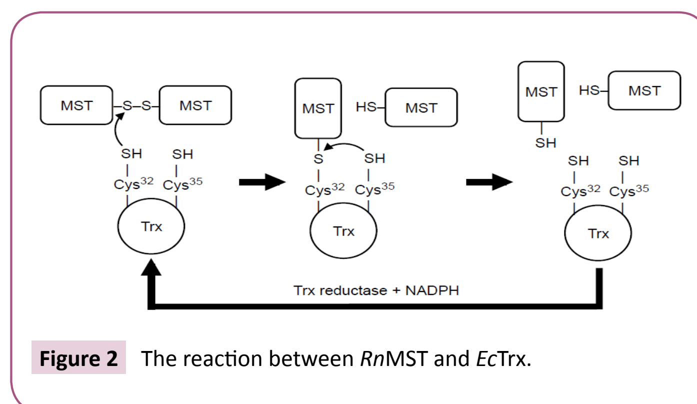

Figure 2 The reaction between *Rn*MST and *Ec*Trx.

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