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Review

Unraveling the role of thiosulfate sulfurtransferase in metabolic diseases

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ABSTRACT

Thiosulfate sulfurtransferase (TST, EC 2.8.1.1), also known as Rhodanese, is a mitochondrial enzyme which catalyzes the transfer of sulfur in several molecular pathways. After its initial identification as a cyanide detoxification enzyme, it was found that its functions also include sulfur metabolism, modification of iron-sulfur clusters and the reduction of antioxidants glutathione and thioredoxin. TST deficiency was shown to be strongly related to the pathophysiology of metabolic diseases including diabetes and obesity. This review summarizes research related to the enzymatic properties and functions of TST, to then explore the association between the effects of TST on mitochondria and development of diseases such as diabetes and obesity.

1. Introduction

Thiosulfate sulfurtransferase (TST), is an abundant mitochondrial enzyme known to catalyze the in vitro transfer of a sulfur atom from a sulfane-containing donor to a nucleophilic acceptor [1,2]. TST was first characterized in 1933, with the assumption that its enzymatic function was solely required for the cyanide detoxification. At the time, sodium thiosulfate was known to be a sulfur donor for TST-catalyzed cyanide-sulfonation [1]. For several decades, the enzyme was used in toxicology against cyanide-intoxication and for detection and quantification of cyanide levels in blood [3]. As more of its characteristics are uncovered/revealed, the critical function of TST in regulating cellular homeostasis becomes apparent, in particular in situations of vulnerability such as cellular stress that ultimately result in human diseases [4,5].

The first part of this review describes the structural and biochemical characteristics of sulfurtransferases, followed by a detailed analysis of TST's intracellular physiological functions. The second part of the review provides an overview of the molecular pathways involved in diseases associated with alteration of TST expression and function.

2. Structural characteristics of TST

The family of eukaryotic sulfurtransferases is divided into three classes. TST belongs to the well-characterized tandem-domain sulfurtransferases, the other two classes are single-domain and multidomain sulfurtransferases [6]. In addition to TST, there is one other known tandem-domain sulfurtransferase: mercaptopyruvate sulfurtransferase (MST). MST and TST were found to share a high sequence homology, which led to the notion that these enzymes might be evolutionarily related [7]. Studies in 3-MST knock out mice shows that TST can serve as a back-up system for 3-MST [8].TST is solely localized at the mitochondrial sites [9], whereas MST is localized in both cytoplasm and mitochondria [10].

Human TST (hTST) consists of 297 amino acids with a molecular weight of 33.4 kDa. BLAST analysis shows that hTST (Fig. 1a) is 90% identical to extensively studied bovine TST (Fig. 1b). The crystal structure of both TST isoforms consists of two similar globular domains [11]. These domains are connected by a tether region and are associated by strong hydrophobic interactions. The sequence homology between the two domains however is rather poor [12,13]. The slightly smaller C-terminal domain hosts the active site, which is located near the interdomain surface [14] and the Cys-248 (247 in bovine TST [15]) is located in the active site cavity being directly involved in the enzymatic reaction. The expected large conformational change during catalysis has not yet been characterized structurally, likely due to the structural flexibility involved [2,16].

There are different structural conformations of TST, transitions

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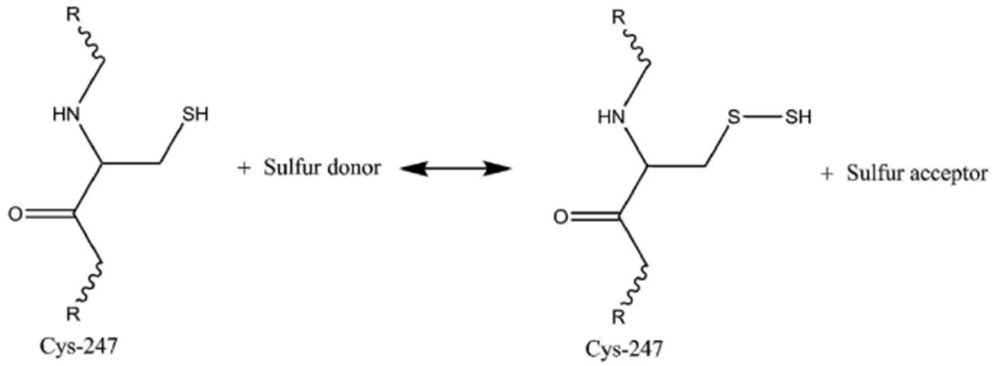


Fig. 1. The generalized reaction catalyzed by TST based on Nandi et al. [23].

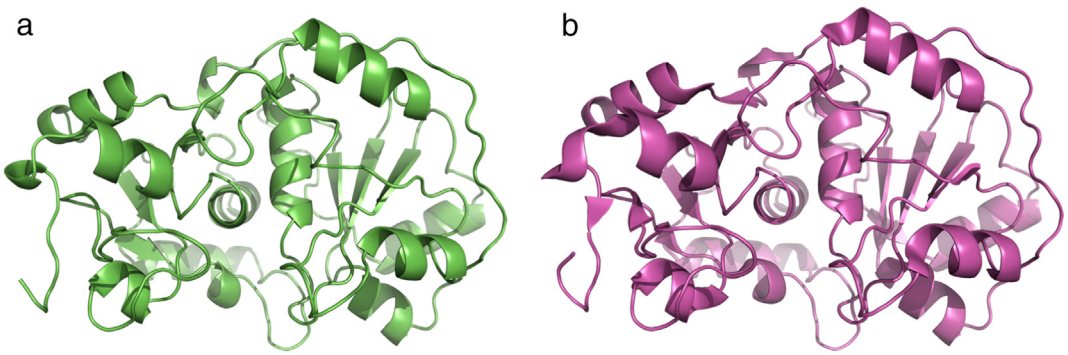


Fig. 2. a: Predicted three-dimensional structure for hTST. b: Crystal structure of bovine TST as an enzyme-substrate intermediate]. The three dimensional structure of bovine TST was obtained from the Protein Data Bank (www.rcsb.org). Homology modelling of human TST was performed using the SWISS-MODEL facility (http://swissmodel.expasy.org/SWISS-MODEL.html).

between which being affected by substrate interaction [17]. Although the enzyme is a homogeneous single-polypeptide chain, it is separable by electrophoresis into four forms which differ in net surface charge. The most positively charged form is the most abundant in vivo form [18]. The reason for this variability in net surface charge of TST is not well known, although it is suggested to be a consequence of various structural relaxation events that occur outside the catalytic cycle, as discussed in Section 4.1 [19]. The occurrence of a conformational change after oxidation results in both an increased exposure and also flexibility of the interdomain tether [20]. Oxidized TST adopts a new conformation containing extensively exposed apolar surfaces and this new form can result in both noncovalent and disulfide-bonded aggregates [21].

The other two classes: single-domain and multi-domain sulfurtransferases, have received less attention. In humans, three single-domain sulfurtransferases have been characterized, named TST-like domains (TSTD1, TSTD2 and TSTD3). In TSTD1, an enzyme known to contribute to cyanide detoxification, contains an active site characterized by catalytic cysteine Cys-32. Similar to the enzymes TST and MST, TSTD1 also catalyzes sulfur transfer to cyanide [22]. Recombinant human TSTD1 utilizes thiosulfate as a sulfur donor. TSTD3 lacks a reactive cysteine, and is therefore highly unlikely to catalyze sulfur transfer on its own, and TSTD2 has not yet been fully characterized. Multi-domain sulfurtransferases are probably not involved in sulfide signaling [6].

3. Enzymatic activity of TST

In sulfurtransferases, residues on an active-site loop containing the catalytic cysteine, are predicted to confer substrate specificity [24]. In TST specifically, the positive charges at the proximal arginine and lysine residues in the CRKGVT motif are predicted to interact with the negative charges on the substrate, such as the oxygen atoms in thiosulfate. Although the catalytic cysteine is the only cysteine strictly required for enzymatic activity, mutations of noncatalytic cysteines result in destabilization of the native structure of the enzyme [25]. The electrophilic site of TST is dependent on metal ions. Various metal ions can serve as the electrophilic site of TST; for instance, when oxalate is used to bind calcium ions, TST is completely inhibited provided that magnesium levels are low [26]. TST is inhibited reversibly and competitively with respect to thiosulfate by most anions at rather high concentrations. The most active inhibitors are aromatic anions [15]. Human MST has several important active site residues also seen in TST. The catalytic cysteine (Cys246), and the arginine which defines the substrate binding site (Arg185) are conserved. Two other active site residues (Arg247 and Lys248) are not conserved in MST [7]. Comparison of the active-site loop residues in TSTD1 versus TST and MST reveals significant stereo-electronic differences. The active site of TSTD1 is relatively surface-exposed, whereas it resides in a deep cleft in TST and MST, between the interdomain interfaces. For TSTD1, the shallow active-site pocket might promote interactions with larger substrates, namely proteins [22].

The catalytic activity of TST proceeds via double displacement mechanism: first the reactive cysteine in the active site (Cys247) accepts a sulfane sulfur from a suitable donor (e.g. thiosulfate) thereby forming a persulfide intermediate state (as shown in Fig. 2). The persulfide sulfur is subsequently transferred from the enzyme to a nucleophilic acceptor (e.g. cyanide), recovering the native enzyme form. The estimated Km of TST for thiosulfate is 39.5 mM, and its Km for cyanide is 29 mM [27]. The reaction is non-specific, as various sulfur donors and acceptors can interact with TST. Although many of these interactions are to some degree reversible, the sulfonation of cyanide is not. TST is able to mediate both reactions, of catalyzing sulfane transfer, and interconverting various forms of sulfanes [3]. These include inorganic thiosulfate, organic thiosulfonates ($RS(O_2)S^-$) and persulfides (RSS^-).

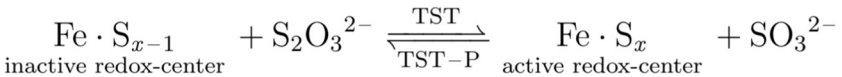


Fig. 3. Construction of iron-sulfur complexes as active redox-centers is (co-)dependent on TST activity, phosphorylated TST (represented as TST-P) is proposed to catalyze the reverse reaction [39]. TST phosphorylation is likely governed by cytoplasmic signaling, the details of which are yet unknown [33].

Table 1
Kinetic parameters reported for sulfurtransferase activity by TST, MST, TSTD1, glutathione (GSH), and sulfide:quinone oxidoreductase (SQR). C.I = Complex I, NADH dehydrogenase. C.II = Complex II, succinate dehydrogenase. XO = xanthine oxidase. NIR = nitrate reductase (NADH dependent). 2-ME = 2-mercaptoethanol. DTT = dithiothreitol. DHLA = dihydrolipoic acid. TRX = thioredoxin. Interactions marked with * have been reported, but not yet characterized.

Donor	Acceptor	Km donor	Km acceptor	Vmax	Kcat	Hill coeff.	Ref.
		μM	μM	μmol∗min^{-1}∗mg^{-1}	s^{-1}		
hTST							
$S_2O_3^{2-}$	CN	(39.5 ± 2.5) ∗ 10^3	29 ± 4	?	910	?	[27]
$S_2O_3^{2-}$	GSH	340 ± 50	21 ± 0.4	1.2 ± 0.02	0.67	2.3 ± 0.2	[27]
$S_2O_3^{2-}$	Cys	350 ± 60	20 ± 0.5	13 ± 0.3	7.4	?	[27]
$S_2O_3^{2-}$	Hcy	300 ± 100	20.5 ± 1.9	15.5 ± 0.9	8.7	?	[27]
$CH_3S(O_2)S^-$	TRX	(20 ± 4) ∗ 10^3	0.0185 ± 0.002	88 ± 5	*	*	[48]
$CH_3S(O_2)S^-$	DTT	*	16	*	*	*	[48]
$CH_3S(O_2)S^-$	Lipoate	*	10	*	*	*	[48]
$CH_3S(O_2)S^-$	SO_3^{2-}	450 ± 4	0.06 ± 0.01	609 ± 25	389	*	[27]
$S_2O_3^{2-}$	C.I	*	*	*	*	*	[40]
$S_2O_3^{2-}$	C.II	*	*	*	*	*	[34]
$S_2O_3^{2-}$	XO	*	*	*	*	*	[41]
$S_2O_3^{2-}$	NIR	*	*	*	*	*	[42]
hMST							
3-MP	2-ME	130 ± 30	108 ± 16	417 ± 38	229	*	[47]
3-MP	DTT	26 ± 5	4.6 ± 0.5	11 ± 2	6.1	*	[47]
3-MP	CN	350 ± 62	6 ± 1	4.3 ± 0.3	2.4	*	[47]
3-MP	DHLA	25 ± 6	4.4 ± 0.3	3.1 ± 0.3	1.7	*	[47]
3-MP	Cys	22 ± 2	4.1 ± 0.6	2 ± 0.2	1.1	*	[47]
3-MP	Hcy	30 ± 0.2	12.5 ± 1.6	1.6 ± 0.2	0.8	*	[47]
3-MP	GSH	20 ± 0.4	28 ± 2	0.61 ± 0.04	0.3	*	[47]
3-MP	TRX	350 ± 62	2.5 ± 0.4 ∗ 10^{-3}	2.3 ± 0.2	1.3	*	[47]
TSTD1							
$S_2O_3^{2-}$	CN	(22 ± 3) ∗ 10^3	0.270 ± 0.02	*	0.52	*	[22]
$S_2O_3^{2-}$	GSH	(17 ± 1) ∗ 10^3	11 ± 1	*	0.432	1.8 ± 0.2	[22]
$S_2O_3^{2-}$	Cys	(14 ± 2) ∗ 10^3	13.7 ± 1.9	*	0.7	1.9 ± 0.1	[22]
$S_2O_3^{2-}$	Hcy	(18 ± 1) ∗ 10^3	10.7 ± 0.4	*	0.61	2 ± 0.1	[22]
$S_2O_3^{2-}$	TRX	22 ∗ 10^3	(1.7 ± 2) ∗ 10^{-3}	*	0.116	*	[22]
SQR							
–	H_2S	–	0.32 ± 0.04	95 ± 5	74	–	[49]
H_2S	CoQ	*	0.019	*	*	*	[49]
H_2S	GSH	10	22 ± 3	144 ± 12	113	1.10 ∗ 10^7	[27]
H_2S	Cys	5	23 ± 4	120 ± 5	94	1.90 ∗ 10^7	[27]
H_2S	Hcy	7	22 ± 3.5	117 ± 6	92	1.30 ∗ 10^7	[27]
H_2S	SO_3^{2-}	13	0.22 ± 0.02	476 ± 16	373	2.90 ∗ 10^7	[27]

4. Sulfurtransferase cellular functions of TST

Understanding of the sulfurtransferase function has broadened considerably in the 85 years after initial characterization of TST and MST. Their widespread occurrence suggests a vital role [7,15,26,27,28,30,29,31]. In addition to the cyanide detoxification, several additional functions of TST have been suggested [31,32]. TST could modulate respiratory activity in the mitochondria through the iron-sulfur centers in redox-capable proteins [33–35]; it interacts with mitochondrial antioxidant systems [22,23,36], and it may regulate inorganic sulfide metabolism [37]. A summary of the most important interactions of TST and peripheral enzymes is shown in Fig. 3 and Table 1.

4.1. Phosphorylation model and respiratory function of TST

TST can be phosphorylated, likely as the result of cytoplasmic cellular signaling [33]. The predicted phosphorylation site (serine 124 in bovine TST) is accessible in unsulfurylated TST, yet rendered inaccessible in the persulfide intermediate form. The consequence of phosphorylation is a conformational change in the enzyme, which brings the side chain containing cysteine 247 into proximity with either Cys-254 or Cys-263 [38]. In presence of an electrophile acceptor these cysteines can form a disulfide bridge, rendering the phosphorylated TST incapable of metabolizing sulfane sulfur donors. Instead, oxidized phosphorylated TST can extract labile sulfide from an iron-sulfur center of the respiratory chain. The labile sulfide reduces the newly-formed disulfide bridge, creating an enzymatic persulfide. This persulfide sulfur is transferred to a sulfur acceptor, after which the phosphorylated TST either undergoes oxidation to accept more labile sulfide or is dephosphorylated by a yet unknown protein phosphatase. The sulfur in the iron-sulfur centers of complexes III and IV serves to stabilize the iron-sulfur centers by which the electron transport chain (ETC) proteins execute their function. Therefore, the removal of a sulfur by phosphorylated TST would result in a decrease in the rate of electron transport and ATP production. Conversely, dephosphorylated TST could increase the rate of electron transport and ATP production, by catalyzing the reverse reaction and mobilizing sulfur for the formation or repair of iron-sulfur clusters [39]. As such, TST was shown to interact with enzymes of oxidative metabolism, like succinate dehydrogenase [34], NADH dehydrogenase [40], xanthine oxidase [41], and NADH nitrate reductase [42]. Besides the rate of electron transport, reduced

availability of iron-sulfur centers also results in an increase of protein reduction, which increases the formation of superoxide anions [43]. The iron-sulfur clusters of ferrodoxins, succinate dehydrogenase, and mitochondrial NADH dehydrogenase can be reconstituted by incubation with TST, a sulfur donor and acceptor, and an iron source [6,34,40,44]. In the course of its interaction with enzymes of the ETC, TST would directly control mitochondrial respiratory activity.

The phosphorylation state of the TST enzyme could be a highly dynamic process with a steady-state level of modification of iron-sulfur centers in the ETC. Teleologically, TST phosphorylation represents a mechanism by which mitochondria adjust the rate of oxidative metabolism in response to energetic demand.

4.2. Interaction of TST with antioxidant systems

Living organisms are equipped with a variety of antioxidant systems, which coordinate removal of reactive oxygen species (ROS) and reactive nitrogen species (RNS). In mammalian cells, there are two major thiol-dependent antioxidant systems, the thioredoxin system and the glutathione (GSH) system. GSH is the most abundant non-protein thiol in the mammalian cells [45]. GSH can accept its sulfurs from human sulfide:quinone oxidoreductase (SQR) or TST forming glutathione persulfide (GSSH), which in turn can reduce thioredoxin (TRX). TSTD1 and MST can also directly feed sulfurs into both antioxidant systems (as shown in Table 1). Therefore, increased activity of sulfurtransferases directly and indirectly increases the activity of ROS scavengers [14,22]. TST is also capable of using GSSH as a sulfur donor, possibly using GSSH as a source for the sulfonation of cyanide, or the interconversion of sulfane sulfurs [3,46]. The ability of TST to catalyze the sulfur transfer both forward and reverse is possibly governed by the phosphorylation state of the enzyme (Section 4.1). In this case, the kinetic behavior of these enzymes implies that there is flow of sulfide from SQR via GSH to TST (Fig. 4). The reverse reaction is not catalyzed by any other enzyme from the sulfurtransferase family [14]. The GSH system participates in the defense against oxidative stress via ROS-scavenging by glutathione peroxidase (Grx). It also has a regulatory function, through the reversible coupling of GSSH to proteins under conditions of oxidative stress.

4.3. TST and selenium metabolism

Besides transferring sulfur, TST plays a role in selenium metabolism. The oxidized form of TST can bind selenium at a 1:1 molar ratio in vitro, leading to the formation of the stable perselenide form of TST [66]. TST has been proposed to be critical in generation of the reactive form of selenium for synthesis of selenophosphate ($SePO_3$). $SePO_3$ is the active selenium-donor compound required for synthesis of SeCys-tRNA, precursor of selenocysteine in selenoenzymes. Selenoenzymes may facilitate the removal of hydrogen peroxide by GSH, as well as providing reducing equivalents to TRX, indicating its role in both antioxidant systems. Furthermore, they are required for both activation and inactivation of thyroid hormones, and they also facilitate ER-associated protein degradation [67]. By merit of these functions, selenoenzymes – and by extension TST – play an important role in immunoregulation. In a manner that is not yet fully understood, selenoenzymes may additionally have pro- and anticancer activities [67].

The role of TST in sulfur and selenium metabolism, the regulation of respiratory function and the interaction with antioxidant systems, make a case for TST to be a tightly regulated link between diverse mitochondrial processes. Consistent with the diversity of mechanisms, an imbalance in TST activity or availability may have implications for an equally diverse range of pathological processes.

4.4. The thioredoxin system

The thioredoxin system, a disulfide reductase system, is comprised of TRX, NADPH and thioredoxin reductase (TRXr). Like the glutathione system, it has many functions, including ROS-scavenging, DNA synthesis and H_2S-signaling. The antioxidant activity of the TRX system is mainly accomplished by the reduction of periredoxins (Prx), methionine sulfoxide reductases (MSR), and several redox-sensitive transcription factors. Reduced Prx isoforms can scavenge hydrogen peroxide (H_2O_2), peroxide (ROOH), and peroxynitrite ($ONOO^-$) radicals. Besides providing reducing equivalents to antioxidant enzymes, TRX is involved in redox-signaling by regulating the activity of redox-sensitive transcription factors. TRX is also found to be critical for DNA synthesis and repair through the reduction of ribonucleotide reductase [50], as well as dealing with oxidative stress [51]. Both the persulfidated and thiol forms of TRX can be respectively oxidized and reduced, by all members of the sulfurtransferase family [22,47]. TRX may also be activated through H_2S-signaling [52–54].

The activity of many redox-related transcription factors and signaling factors are mediated by both the glutathione and thioredoxin systems [45,55]. The activity of transcription factors such as nuclear factor-κβ (NF-κB) and thyroid-specific promotors is affected by the cellular redox environment. If there is a lack of reduced GSH or TRX, the transcription factors lose their ability to bind to DNA efficiently [55,56]. Conversely, transcription factors such as activator protein-1 (AP-1) and heme oxygenase are activated with GSH depletion [55]. The antioxidant systems also mediate signaling factors such as apoptosis signal-regulating kinase 1 (ASK1) and protein tyrosine phosphatase 1b (PTP1B). Unbound ASK1 increases the level of p38 MAPK pathway activity. Reduced TRX as well as glutaredoxins have the ability to inhibit ASK1 and its release [57,58]. By merit of its interaction with antioxidant systems, ASK1 functions as a sensor for mitochondrial ROS-production. Glutathione can also react with the active site cysteine in PTP1B, as a form of reversible inhibition. This process, called glutathionylation, is named as an important regulator in PTP1B activity in vivo [59]. TRX is able to reactivate oxidized PTP1B, allowing it to act as a modifier in growth-factor induced signaling [60].

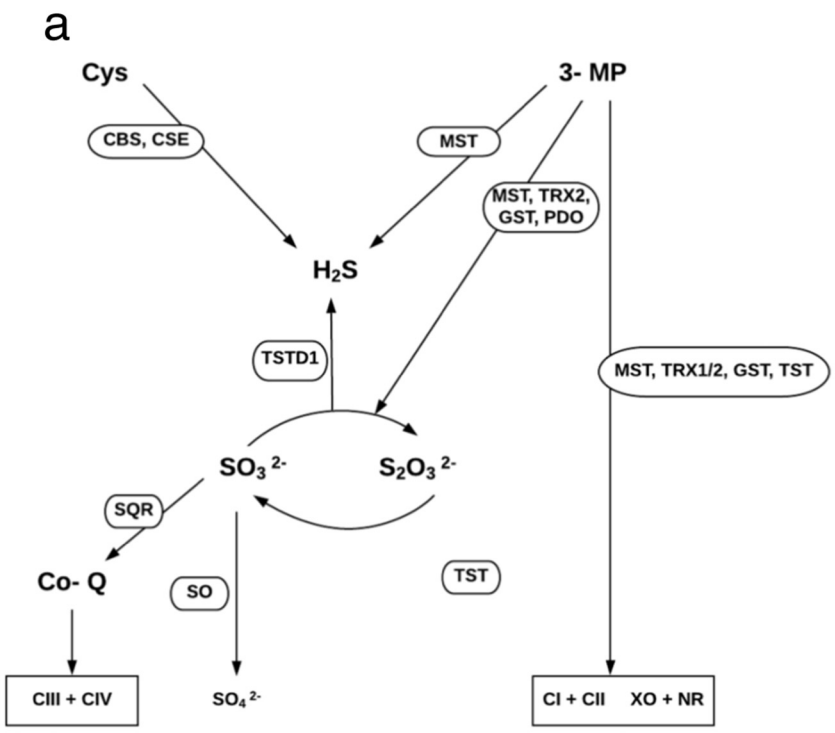
Thioredoxin system activity can be linked quite directly to disease susceptibility, through thioredoxin interacting protein (TXNIP), which downregulates TRX activity. Knocking out TXNIP causes the cell to change its glucose metabolism to increase anaerobic glycolysis and release TRX in order to increase ROS-scavenging [61–65]. High levels of TXNIP are suggested to induce high glucose-induced ROS generation and mitochondrial pathway apoptosis in β-cells, and it is therefore closely linked to glucose-intolerance and diabetes. Conversely, knocking out TXNIP causes the cell to change its glucose metabolism to increase anaerobic glycolysis and release TRX in order to increase ROS-scavenging. TXNIP deficiency and TRXr and TRX overexpression is linked to several forms of cancer, as cancer cells appear to rely on the TRX system for ROS-scavenging [45]. Therefore, through the thioredoxin system, antioxidant function may be linked to both diabetes and cancer. A direct link between thioredoxin and TST activity has not yet been shown.

5. Clinical associations with TST activity

The availability and activity of TST is closely linked to metabolic diseases where it has a beneficial role through effects on mitochondrial activity and increasing antioxidants. It may also play a positive role in colonic diseases and neuropathy where it functions primarily by decreasing H_2S and cyanide, respectively. Analysis of the function and interactions of TST will hopefully lead to new insights in a wide array of diseases. In the following paragraphs we will discuss some examples.

5.1. TST and diabetes mellitus

TST is currently the only gene that is validated as a positive predictor in metabolic health, displaying a distinct negative correlation with the development of adiposity and insulin resistance [68].



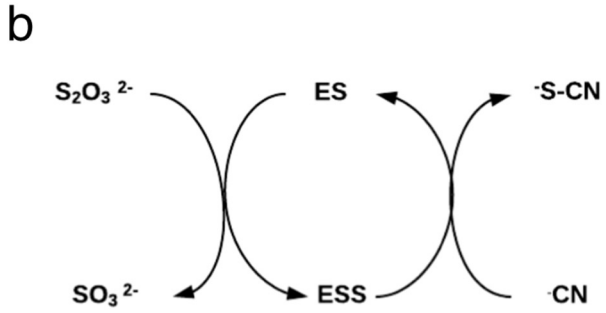


Fig. 4. a: Sulfur oxidation pathway in the human mitochondria [22,27,33,47]. The cyanide detoxification reaction was omitted from this subfigure. b: Cyanide sulfonation reaction schematically represented. ES represents the native enzyme, and ESS represents the persulfidated enzyme [23]. The kinetic parameters observed for the interactions displayed, are detailed in Table 1.
Abbreviations in alphabetical order: CI–CIV: mitochondrial electron transport complexes 1–4, CBS: cystathione beta synthase, CoQ: coenzyme Q, CSE: cystathionine gamma-lyase, Cys: cysteine, GST: glutathione, MST: mercaptopyruvate sulfurtransferase, 3-MP: 3-mercaptopyruvate, NIR: nitrite reductase, PDO: persulfide deoxygenase, SO: sulfite oxidase, SQR: sulfide:quinone oxidoreductase, TST: thiosulfate sulfurtransferase, TSTD1: thiosulfate sulfurtransferase-like domain 1, XO: xanthine oxidase.

Treatment with thiosulfate as the main substrate for TST, has been found to improve the impaired glucose-uptake symptoms of diabetic mice, and reverse the effects of insulin resistance on 3T3-L1 adipocytes. Morton et al. [68] found analogous data in human adipose tissue, where TST expression correlated negatively with body mass index (BMI) and positively with levels of GLUT4, insulin receptor substrate 1 (IRS1) and peroxisome proliferator activated receptor gamma (PPARG). TSTs quantitative trait locus was the only one found to have a strong negative correlation with fat mass and plasma glucose levels while having a positive correlation with adiponectin expression. Adiponectin is a well-recognized antidiabetic protein hormone [69]. This indicates that TST is a prime candidate as a drug target against obesity and diabetes.

As discussed in Section 4, TST may be the switch between two important mitochondrial systems. Both of these systems could positively influence diabetic symptoms. Firstly, TST is able to influence respiratory capacity through interaction with the iron-sulfur centers in the electron transport chain suggesting a direct link of TST to glucose intolerance. Secondly, TST is able to feed electrons into the antioxidant systems. Since diabetes appears strongly influenced by inflammation [70], increased activity of antioxidant systems could be vital to obesity resistance.

5.2. TST and colonic diseases

Impaired or deficient sulfur metabolism may play a major role in the progression of common colonic diseases. TST is likely to be the responsible enzyme for H_2S metabolism in rectal mucosa [71]. Expression of TST in colon mucosa is often markedly reduced in patients with ulcerative colitis and colon cancer when compared to normal mucosa, although the evidence is not completely consistent [72]. This decrease in TST activity corresponds with the development of colitis, and is followed by an elevation of TST activity in erythrocytes [71–73]. Conversely, mucosal healing was associated with an increased TST gene expression. It is not clear whether this abnormality is a primary defect or the result of inflammation. The activity and expression of TST in the colonic mucosa can be significantly increased by induction with either butyrate or sulfide, which protects the mucosa from sulfide-induced cytotoxicity. The capacity of the mucosa to oxidize butyrate is

decreased in patients with ulcerative colitis. Failure of colonocytes to differentiate appropriately may increase the exposure of colonocytes and other cells in the crypt to the toxic effects of luminal H_2S. This could result in cell death and the inflammation seen in ulcerative colitis. Persistent insult may result in the genetic changes seen in colorectal cancer. Elevations in H_2S-levels can be caused by a disturbed balance of sulfate-reducing bacteria, and inadequacies in sulfur detoxification. This may aggravate inflammatory bowel disease and it could ultimately progress to colorectal cancer [9,71,74]. Besides colonic diseases, there is also evidence that the reduction of TST activity in the intestinal mucosa is an age-related process. Deterioration of mitochondrial capacity and decline of antioxidant activity are likely to play a role the aging of colonic epithelium [75]. Polymorphic variations that are distant from the active site might influence sulfurtransferase reactive efficiency, which might prove important in understanding the varying susceptibility to inflammatory bowel diseases.

5.3. TST and other diseases

There is some evidence of TST activity playing a role in several other diseases, such as Lebers Hereditary Optic Disease (LHOD) [76–78], human gliomas [36] and hemodialysis patients [43]. Mitochondrial dysfunction has also been linked to neuro-inflammation in LHOD [79]. In LHOD, one study found a marked decrease in the TST expression and specific activity in liver biopsies [75], and it is suggested that the impairment of the cyanide detoxification pathway plays a role in the disease progression. Another study found a significant size increase in the mitochondria in anterior tibial muscle from LHOD patients [77]. The enlargement could be attributed to a compensation for a metabolic defect. The activity of TST in rectal mucosa was also found to be six fold lower in patients with LHOD, suggesting that TST deficiency either causes LHOD or is directly involved in its development. This hypothesis was later disputed by Whitehouse et al. [80], who found no evidence of quantitative or qualitative defects on the liver TST isozyme patterns of subjects with LHOD. To our knowledge, the studies into TSTs role in human gliomas and hemodialysis mortality have not received follow-up.

5.4. Thiosulfate treatment

Some information about TSTs effect in vivo can be inferred based on the effects of clinical treatment with its substrate: thiosulfate. In healthy patients, thiosulfate is excreted renally and hepatically in equal proportions [81]. Metabolism of thiosulfate in humans is mostly based on sulfurtransferase activity (primarily TST and TSTD1, see Section 4). Historically, thiosulfate has been used clinically as an antidote for cyanide poisoning. In recent years however, sodium thiosulfate has been successfully used as an off-label drug in calciphylaxis. Calciphylaxis is an uncommon complication in patients with end-stage kidney disease on dialysis which is associated with high mortality. Thiosulfate could combine with insoluble tissue calcium salts to form highly soluble calcium thiosulfate [82]. The fast rate of plasma clearance implies that the effect of thiosulfate on chelating vascular calcification is perhaps less important than initially thought or that the by-products of its metabolism are more therapeutically active than thiosulfate itself. This implies that sulfurtransferase activity is required for the therapeutic effect of thiosulfate. In addition to calciphylaxis treatment, thiosulfate is thought to restore endothelial homeostasis by increasing nitric oxide synthase activity and regenerating GSH through sulfurtransferase activity. It is also found to be protective in experimental cardiac ischemia and angiotensin-II induced cardiac and renal disease [83–85] Endogenous thiosulfate has been hypothesized to act as a precursor in H_2S-sigaling, as multiple enzymes may facilitate the reaction from thiosulfate to H_2S. Beneficial effects of H_2S have been extensively reviewed elsewhere [86–89] When thiosulfate is dissolved in tissue in very high concentrations, it inhibits the mitochondrial cytochrome complex IV in addition to directly causing profound sulfide-generated oxidative stress [81]. This effect contrasts its ability to reduce oxidative stress in lower concentrations, as it may feed sulfur and reducing equivalents to the antioxidant systems via TST. Interestingly, another sulfur compound derived from garlic, i.e. diallyl trisulfide, has recently shown to not only increase MPST but also TST in cultured cells [90].

6. Concluding remarks and outlook

This review demonstrates TSTs diverse functionality and clinical relevance. When summarizing the academic developments of the past 85 years, it becomes apparent that despite the wide range of studies, the description of TSTs characteristics is composed of as much hypothesis as proof. In the years following its initial characterization, TST-related research has been primarily focused on the detoxification of cyanide as well as biochemical and structural studies. The interaction with sulfur-dependent antioxidants became the second point of focus, linking sulfur metabolism directly to the detoxification of reactive oxygen species. When researching positive predictors for diabetes and obesity, Morton et al. [68] found TST to be singularly important to metabolic health. Their study implies a link between TST activity and mitochondrial health, thereby implicitly explaining the abundance of the enzyme.

From a clinical perspective, the implications for diabetes are paramount. The strength of the evidence linking enzymatic activity to positive clinical outcomes, makes TST a supremely interesting drug target. The upregulation or artificial increase of TST activity would make sense in familiar adiposity and diabetes. It is slightly surprising that the link between TST and diabetes has not led to further published research since 2016, given the strength of the evidence and implications to one of the most affecting diseases of our time. For colonic diseases, the form of association between disease progression and sulfurtransferase activity warrants serious academical effort.

The diversity of cellular functions however creates interesting pharmacological cross-roads. Finding an activating substance for TST appears to be the most direct path to success. This might prove challenging however, seeing as efforts to provide structural analyses of the enzyme have failed. In vivo there are also hampering physiological circumstances in which e.g. NO mediated S-nitrosylation can cause inactivation of TST [91]. The exceptional flexibility observed in human TST might be inherent to its functions but will also complicate pharmacological research. Elucidating the tertiary structure of hTST and perhaps connecting the conformation to enzymatic function, might significantly alleviate said efforts. Moreover, it is still unknown which of the cellular functions (respiratory, anti-oxidant or other) provides the protective effect against metabolic diseases. There is even a possibility that the beneficial effect is not achieved through one function, but rather through the phosphorylative regulation of these functions. The sulfur reactivity of TST may function as a gauge of mitochondrial activity and the concomitant requirement of antioxidant and detoxification activity. The nuance that this creates could be the key to its contribution to mitochondrial health. As such, TST provides not one but multiple pharmacological challenges. Finding the kinase/phosphatase that governs TSTs phosphorylation state should be the primary focus from an intercellular signaling perspective. It would also be supremely interesting and helpful to examine the direct link between sulfurtransferase activity and mitochondrial function.

Altogether, thiosulfate sulfurtransferase plays an important role in mitochondrial health, linking sulfur metabolism to antioxidant and respiratory function. The enzyme provides challenges to several fields, and taking them on could not only improve the understanding of metabolic diseases, it can also provide a way to treat them.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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