MINIREVIEW

Response to sulfur in Schizosaccharomyces pombe

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One sentence summary: This mini review summarizes the latest sulfur metabolism mechanism and starvation response along with sulfate transporters identification in the fission yeast Schizosaccharomyces pombe.

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ABSTRACT

Sulfur is an essential component of various biologically important molecules, including methionine, cysteine and glutathione, and it is also involved in coping with oxidative and heavy metal stress. Studies using model organisms, including budding yeast (Saccharomyces cerevisiae) and fission yeast (Schizosaccharomyces pombe), have contributed not only to understanding various cellular processes but also to understanding the utilization and response mechanisms of each nutrient, including sulfur. Although fission yeast can use sulfate as a sulfur source, its sulfur metabolism pathway is slightly different from that of budding yeast because it does not have a trans-sulfuration pathway. In recent years, it has been found that sulfur starvation causes various cellular responses in S. pombe, including sporulation, cell cycle arrest at G2, chronological lifespan extension, autophagy induction and reduced translation. This MiniReview identifies two sulfate transporters in S. pombe, Sul1 (encoded by SPBC3H7.02) and Sul2 (encoded by SPAC869.05c), and summarizes the metabolic pathways of sulfur assimilation and cellular response to sulfur starvation. Understanding these responses, including metabolism and adaptation, will contribute to a better understanding of the various stress and nutrient starvation responses and chronological lifespan regulation caused by sulfur starvation.

Keywords: fission yeast; Schizosaccharomyces pombe; sulfate; sulfur; sul1+; sul2+

INTRODUCTION

Sulfur is an essential element for proteins, lipids and various metabolites, and it functions in the binding of metal ions and proteins (Zhang et al. 2004; Koprivova and Kopriva 2016). Various sulfur compounds, including cysteine (Cys), methionine (Met) and glutathione (GSH), are essential for cell growth, and the sulfur metabolism network regulates their synthesis (Marzluf 1997; Lee et al. 2010; Huang et al. 2017). In addition to its importance as a nutrient in cells, sulfur metabolism and responses are also studied from an applied point of view because sulfur-containing products are generally unfavorable for foods and beverages and considerably affect the flavor (Holt et al. 2011; Huang et al. 2017).

Although sulfur is present in biomolecules as reduced forms, such as thiols or sulfides, many available forms in nature are oxidized sulfates (SO42−), which plants, fungi and many bacteria can take up, reduce and incorporate into biomolecules (Olson 2012; Koprivova and Kopriva 2016). In contrast, animals, including humans, cannot take up sulfate to synthesize Cys and Met. Therefore, they must consume foodstuffs that contain sulfur-containing amino acids and proteins (Maruyama-Nakashita et al. 2006; Koprivova and Kopriva 2016; Ward and
Although there is no apparent homolog of Sla1 in S. pombe, a budding yeast, the viability of a cell population during the stationary phase but also nutrient responses (Hayles and Nurse 2018; MacKenzie and Lancefield 2020; Otsubo, Kamada and Yamashita 2020; Ohtsuka, Shimasaki and Aiba 2021a). Schizosaccharomyces pombe can sufficiently assimilate and utilize sulfate, thiosulfate, Cys and GSH as sulfur sources; its ability to use sulfite and Met is weak but observable (Bánszky, Simonics and Maráz 2003). Met is not a sufficient source of sulfur because S. pombe, unlike S. cerevisiae, which can synthesize Cys from Met, does not have a transulfuration pathway that converts Met or homocysteine to Cys (Brywczy et al. 2002; Hébert, Casaregola and Beckerich 2011; Takagi and Ohtsu 2017; Fig. 1). Furthermore, S. pombe has little ability to assimilate the sulfur compounds methane sulfonate, taurine, isethionate, heptane sulfonate, 3-morpholinosopropane-1-sulfonic acid, benzenesulfonate, dimethyl sulfoxide, diethyl sulfoxide, dibutyl sulfoxide, sulfamate, dimethyl sulfoxide, methyl phenyl sulfoxide, sulfamate, methyl sulfate, sodium dodecyl sulfate and 4-nitrobenzenesulfonate (Linder 2012).

Although S. pombe is a useful model organism for understanding various cellular processes, details regarding its sulfur response have not been reviewed for more than a decade. This MiniReview summarizes the latest findings on the sulfur metabolic pathways and sulfur starvation response.

**SULFATE TRANSPORT IN S. POMBE**

Each sulfate ion (SO\(_4^{2-}\)) is transported along with three H\(^+\) into cells in an energy-dependent manner (Mendoza-Cózatl et al. 2005). In S. cerevisiae, Sul1, Sul2 and SOA1 are genes encoding sulfate transporters (Cherest et al. 1997; Huang et al. 2017). Although there is no apparent homolog of Soa1 in S. pombe, the products of SPBC3H7.02 and SPAC869.05c in S. pombe, are considered to be homologs of Sul1p (Sc_Sul1) and Sul2p (Sc_Sul2) in S. cerevisiae due to the similarity of their amino acid sequences (Figure S1a, Supporting Information). However, these have not yet been identified. To contribute to the understanding of these genes, we conducted several experiments using SPBC3H7.02- and SPAC869.05c-deficient strains.

First, when grown in Edinburgh minimum medium with sulfate as the only sulfur source, growth inhibition was not obvious in either single-deletion mutant, indicating that both have the ability to take up sufficient sulfate in Edinburgh minimum medium (Figure S1b, Supporting Information). However, the double-deletion mutant did not grow in Edinburgh minimum medium, suggesting that the products of SPAC869.05c and SPBC3H7.02 are the only transporters involved in the uptake of sulfate in S. pombe.

Compared to SPAC869.05c, SPBC3H7.02 has a higher abundance of mRNA and is induced by sulfur starvation (Ohtsuka et al. 2017; Figure S1c, Supporting Information). Therefore, SPBC3H7.02 is called sul1\(^+\), and SPAC869.05c is called sul2\(^-\). However, the deletion of sul1\(^+\) or sul2\(^-\) did not cause growth defects. Thus, the amount of sulfate that decreased in the cultures of these mutants was quantified. Sulfate was slightly reduced in the cells with a single deletion of sul1\(^+\) or sul2\(^-\) compared to the wild-type cells (Figure S1d, Supporting Information). On the other hand, the amount of the double-deletion strain was found to be significantly reduced, suggesting that these gene products were essential for sulfur uptake although only one of them has the capacity sufficiently. Finally, we investigated whether the growth of these mutant strains could be restored by Cys or Met supplementation (Figure S1e, Supporting Information). Cys supplementation restored the growth of the double mutant in our study. On the other hand, Met supplementation restored the growth only slightly, suggesting that Met may not prove to be an effective sulfur source in S. pombe. Future analysis will reveal additional features of sul1\(^+\) and sul2\(^-\) in S. pombe.

**SULFUR METABOLISM IN S. POMBE**

Studies of the sulfur assimilation pathway in S. pombe, such as those using the growth inhibitor selenate (SeO\(_4^{2-}\)), which has the same metabolic pathway as sulfate (SO\(_4^{2-}\)), have revealed several metabolic mechanisms for synthesizing Cys, Met and GSH from sulfate (Simonics, Bánszky and Maráz 2002; Fig. 2).

Sulfate, an inorganic sulfur source, is taken up into S. pombe cells by the sulfate permeases Sul1 and Sul2 (Simonics, Bánszky and Maráz 2002; Fig. 2). Sulfate adenyllyltransferase (ATP sulfurylase) is encoded by sul1\(^+\) in S. pombe; it activates and adenylates sulfate to produce adenosine-5′-phosphosulfate (APS; Simonics and Maráz 2008). APS is phosphorylated to produce 3′-phosphoadenosine-5′-phosphosulfate (PAPS) by adenylyl-sulfate kinase (APS kinase; Koprivova and Kopriva 2016), which is encoded by met14\(^+\) in S. pombe (Fujita et al. 2006). PAPS reductase, which is encoded by met16\(^+\) (Fujita et al. 2006), acts on reduced thioredoxin and PAPS to produce free sulfite (SO\(_2^{2-}\); Mendoza-Cózatl et al. 2005). It has been suggested that thioredoxin (Trx1) acts as a primary electron donor for PAPS reductase at this point (Song and Roe 2008).

Because sulfite has antimicrobial and antioxidative activities, it is used as a regulated food additive (Park and Bakalinsky 2000), while S. pombe can use sulfate as the sulfur source (Bánszky, Simonics and Maráz 2003). In terms of homologous genes of the sulfate efflux transporter encoded by SSU1 in S. cerevisiae (Park and Bakalinsky 2000; Huang et al. 2017), S. pombe has four tandem duplication genes, SPBPB10D8.04c, SPBPB10D8.05c, SPBPB10D8.06c and SPBPB10D8.07c. These gene products may be involved in sulfate transport.

Intracellular sulfate is reduced to H\(_2\)S and sulfide (S\(^-\)) by sulfite reductase using three NADPH molecules (Vande Weghe and Ow 1999; Mendoza-Cózatl et al. 2005). Sulfite reductase has two types of structures; α, β and γ heteromeric structure and α2β2 heterotetrameric structure (Bránzanic, Ryde and Silaghi-Dumitrescu 2020). The sulfite reductase complex of S. pombe is expected to be the α2β2 type. Sir1 is the β subunit in S. pombe (Miki et al. 2008). Additionally, the sulfite reductase from S. cerevisiae is also considered to be the α2β2 type, which has an α subunit Met10 protein (Hansen, Cherest and Kielland-Brandt 1994). Owing to sequence similarity, it is expected that S. pombe also has Met10 as the α subunit ortholog.

H\(_2\)S is a toxic and biologically active gas that is reportedly involved in lifespan extension in S. cerevisiae and nematodes, and it has been shown to be involved in aging in mammals (Huang et al. 2017; Sokolov et al. 2021). At physiological solutions, approximately 80% of H\(_2\)S exists in dissociated form, so hydrosulfide anion (HS\(^-\)), 20% of H\(_2\)S and vanishingly little S\(^2-\) (Olson 2012; Sokolov et al. 2021). In S. pombe, H\(_2\)S and sulfide are thought to have three possible fates. The first is that sulfide-quinone oxidoreductase Hmt2 and FAD in mitochondria oxidize sulfide through ubiquinone reduction (Vande Weghe and...
Figure 1. Sulfur metabolism in budding yeast Saccharomyces cerevisiae and in fission yeast Schizosaccharomyces pombe. Sulfate is used to synthesize cysteine (Cys), methionine (Met) and glutathione (GSH). In the reduction process, sulfate is converted to adenosine 5′-phosphosulfate (adenylyl sulfate; APS), 3′-phosphoadenosine-5′-phosphosulfate (3′-phosphoadenylyl sulfate; PAPS), sulfite (SO₃²⁻) and hydrogen sulfide (H₂S) or sulfide (S₂⁻). Cys is used for the synthesis of GSH and Met via γ-Glutamyl-cysteine (γ-Glu-Cys).

Ow 1999, 2001). In not only the gutless clam, lugworms, ribbed mussels and chicken mitochondria but also mammalian cells, it has been reported that this mitochondrial electron transport also contributes to ATP production when the sulfide is proper level (Olson 2012; Módis et al. 2013; Quinzii et al. 2017), suggesting that Hmt2 may also contribute the energy production in S. pombe. Meanwhile, because sulfide is toxic to cells when it is excess, it is thought that this reaction by Hmt2 controls cellular sulfide levels (Zhang et al. 2008; Kawamukai 2009). Consistent with this idea, ubiquinone-deficient mutants and respiration-deficient mutants have been reported to accumulate sulfide (Miki et al. 2008; Kawamukai 2009). Although sulfide can be oxidized to sulfate in mammals via thiosulfate reductase, sulfur dioxygenase and sulfite oxidase in mitochondria (Quinzii et al. 2017), the details of the mechanism after oxidation by Hmt2 are unknown in S. pombe.

Because S. pombe does not have a trans-sulfuration pathway, it cannot directly synthesize Cys from Met (Brzywczy et al. 2002; Hébert, Casaregola and Beckerich 2011), but it can still convert Cys to Met. met3 is a gene involved in Met auxotrophy (Kohli et al. 1977), which is thought to encode the cystathionine γ-synthase, which catalyzes the first step in the pathway to produce Met from Cys by converting Cys to cystathionine. Similarly, it has been suggested that SPAC23A1.14c also encodes cystathionine γ-synthase (Harrison et al. 2005). Cystathionine β-lyase encoded by SPCC11E10.01 converts cystathionine to homocysteine (Ejim et al. 2004; Holt et al. 2011). Although SPCC11E10.01 was reported as str3 in 2004, SPAC1F8.03c encoding a heme transporter was already identified using the same name in 2003 (Pelletier et al. 2003; Plante and Labbé 2019). Therefore, to avoid confusion, we refer to SPCC11E10.01 as cbl1 because it encodes cystathionine β-lyase (Fig. 2). The homocysteine produced here can be converted to Met by Met26 as described above.

GSH (γ-Glu-Cys-Gly) is present at high concentrations in the cells of many organisms. It is not only involved in the detoxification of xenobiotics and oxidative stress response but is also
Figure 2. Sulfur metabolism in fission yeast, Schizosaccharomyces pombe. Sulfate taken up by sulfate transporters is used to synthesize cysteine (Cys), methionine (Met) and glutathione (GSH). In the reduction process, sulfate is converted to adenosine 5′-phosphosulfate (adenylyl sulfate; APS), 3′-phosphoadenosine-5′-phosphosulfate (3′-phosphoadenylyl sulfate; PAPS), sulfite (SO₃²⁻) and hydrogen sulfide (H₂S) or sulfide (S²⁻). Cys is used for the synthesis of GSH via γ-Glutamyl-cysteine (γ-Glu-Cys) and for the synthesis of Met via cystathionine and homocysteine. The SPBC3H7.02 protein is denoted as Sul1, and the SPAC869.05c protein is denoted as Sul2. The cystathionine β-lyase encoded by SPCC11E10.01 is referred to here as Cbl1. The at least doubled expression after 3 or 6 h of sulfur starvation is marked with a green circle on the left or right side of each factor, respectively (Ohtsuka et al. 2017). The expression that was suppressed to less than half after 3 or 6 h of sulfur starvation is marked with a red circle on the left or right side of each factor, respectively (Ohtsuka et al. 2017). It has been confirmed that Cys11 and Hmt2 is localized in the mitochondria (Vande Weghe and Ow 1999; Matsuyama et al. 2006). The broken line indicates expectations. The details of each process are described in the text.

a major reservoir of non-protein reduced sulfur (Mutoh, Nakagawa and Hayashi 1995; Mendoza-Cózatl et al. 2005; Lushchak 2010). GSH is synthesized from Cys in a two-step reaction (Coblenz and Wolf 1995; Huang et al. 2017). Conversely, it is considered that GSH can be converted to Cys in two two-step reactions. Cys is converted to the dipeptide γ-glutamylcysteine (γ-Glu-Cys) in an ATP-dependent manner by the glutamate-cysteine ligase encoded by gcsc1 (γ-glutamylcysteine synthetase) (Coblenz and Wolf 1995; Mutoh, Nakagawa and Hayashi 1995; Chaudhuri, Ingavale and Bachhawat 1997). This reaction is the rate-limiting step in GSH biosynthesis (Chaudhuri, Ingavale and Bachhawat 1997). Gcs2 is a homolog of GCLM, human glutamate-cysteine ligase modifier subunit (Gipp, Bailey and Mulcahy 1995; Vilella et al. 2009). Gcs2 is expected to be a regulatory subunit of glutamate-cysteine ligase and may also be involved in regulating the catalytic reaction. Subsequently, glutathione synthetase encoded by gsa1+ synthesizes GSH from γ-Glu-Cys and glycine (Gly) (Mutoh et al. 1991; Wang and Oliver 1996).

In S. cerevisiae, there are two pathways for the degradation of GSH to Cys. The first is that GSH is decomposed into γ-Glu-Cys via the amidotransferase Dug2-Dug3 complex and then Cys is produced by the dipeptidase Dug1; the second is that GSH is decomposed to L-cysteinyl-glycine by γ-glutamyltranspeptidase
S. pombe

detailed mechanism of uptake and utilization of thiosulfate in
analysis of the membrane protein YeeE, which engages in thio-
hashi
et al.
formed when using sulfate and thiosulfate as sulfur sources
sulfate, a comparative analysis of metabolism has been per-
fur, namely met14+, met16+, sir1+, cys11+, gcs1+ and gsa1+, also
prevent normal growth on glycerol medium (Zuin et al. 2008;
Malecki et al. 2016).

Schizosaccharomyces pombe sufficiently assimilates thiou-
fate, which possesses more reduced sulfur atom than sulfate
and so it is energetically-favored over sulfate, in addition to sul-
fate, Cys and GSH (B´anszky, Simonics and Mar´az 2003;F u n a-
masaki and Aiba2021a;Fi g .3).

In this way, it is considered that S. pombe metabolizes sul-
fate as a sulfur source and synthesizes sulfur-containing amino
acids and GSH, which can be used for sulfur storage and counter-
measures against oxidative and heavy metal stresses, while
maintaining a mechanism that limits excessive levels of the
toxic intermediate products, sulfite and sulfide.

RESPONSE TO SULFATE STARVATION IN S.
POMBE

Schizosaccharomyces pombe is considered to have various mecha-
nisms for adjusting intracellular sulfur concentrations through
the above-mentioned metabolism. Conversely, during sulfur
starvation, cells perform not only these metabolic responses
but also the intracellular responses necessary for environmen-
tal adaptation. Sulfur starvation leads to cell cycle arrest at G2,
translational repression, autophagy induction, sporulation and
CLS extension; all of these processes depend on the Ecl1 family
genes (Ohtsuka et al. 2017; Shimasaki et al. 2020; Ohtsuka, Shi-
masaki and Aiba 2021a;Fig. 3).

In S. pombe, there are three homologous Ecl1 family genes,
ecl1+, ecl2+ and ecl3+, which play a central role in the sulfur star-
vation response. Because overexpression of each extends CLS,
they were named Ecl genes (extendor of chronological lifespan;
Ohtsuka et al. 2008, 2009; Ohtsuka and Aiba 2017). These genes
are induced weakly by nitrogen starvation (ecl1+) and strongly by
nutrient starvation (amino acids, sulfur and magnesium) (ecl2+);
they are also induced by oxidative stress (ecl1+) and heat shock
(ecl2+) (Miwa et al. 2011; Ohtsuka et al. 2011, 2019, 2021; Shii-
masaki et al. 2014). Therefore, they are thought to act not only
in response to sulfur starvation but also as part of the cellular
responses to these various environmental changes. These fac-
tors are also required for the starvation response for trace met-
als such as iron and zinc, and they lead sexual development and
CLS extension (Ohtsuka et al. 2015; Shimasaki et al. 2017), sug-
gesting that Ecl1 family genes act in response to various types
of nutrient starvation. Ecl1 family genes are induced by multiple
transcription factors, including Atf1, Ffl1, Hsf1 and Zip1, which
correspond to various individual stimuli (Ohtsuka et al. 2019,
2021).

Under sulfur starvation, ecl1+ is induced by the transcription
factor Zip1 (Ohtsuka et al. 2017). During the vegetative growth
phase, Zip1 binds to the F-box protein PoF1 of the E3 ubiqui-
tin ligase complex, Skp, Cullin and F-box containing complex
(SCF complex) and is degraded through ubiquitination (Harrison
et al. 2005). Conversely, under sulfur depletion, Zip1 stabilizes,
undergoes nuclear translocation and regulates the transcription
of target genes (Ohtsuka et al. 2017). Schizosaccharomyces pombe
Zip1 is the ortholog of S. cerevisiae Met4, which negatively reg-
ulatesthegenecodingfor sulfatesynthase(formet16+,S. pombe met14+)
and PAPS reductase (MET16, S. pombe met16+;Wu et al. 2009).
In S. pombe, Zip1 regulates the expression of ecl1+ and also sulfur
metabolism-related genes, such as sual1+, sul2+ (SPAC869.05c),
sir1+, met10+ and SPBBP10D8.04c (Harrison et al. 2005; Guo et
al. 2012). This suggests that both Zip1 and its ortholog Met4 act in
the sulfur starvation response.

Sulfur starvation also induces Sty1 phosphorylation (Zuin et
al. 2010), which is a stress-activated protein kinase and

Figure 3. Schizosaccharomyces pombe responds to sulfur starvation, causing sporu-
lation induction, G2 arrest, autophagy induction, translational repression and
chronological lifespan (CLS) extension.
homolog of human p38 and S. cerevisiae Hog1 (Gaits et al. 1998). Although the mechanism how the starvation activates Sty1 is unclear, Styl activation phosphorylates and activates the transcription factor Atf1, which also regulates ecl1+ (Shimasaki et al. 2014). Therefore, in addition to Zip1, the Sty1 pathway might also contribute to the induction of ecl1+ expression under sulfur starvation. Thus, in S. pombe, sulfur starvation results in ecl1+ induction, while in S. cerevisiae, Ecl1 family genes might be involved as well. S. cerevisiae has one Ecl1 gene, ECL1 (Azuma et al. 2012), which is also induced by sulfur starvation (Saldanha, Brauer and Botstein 2004).

Under sulfur starvation, S. pombe cells do not die immediately because of their adaptive response, and they can even survive for a considerable period of time. In haploid cells, sulfur starvation leads to CLS extension via Ecl1 family genes, which maintain viability (Ohtsuka et al. 2017). At this time, unlike in nitrogen starvation, sulfur starvation does not cause arrest at the G1 phase, but at G2; this does not lead to haploid conjugation (Ohtsuka et al. 2017). Conversely, in diploid cells, sporulation occurs in an Ecl1 family gene-dependent manner (Ohtsuka et al. 2017). Consistent with this, sulfur starvation induces genes related to sexual development, including ste11+ and meio2+, in an Ecl1 family gene-dependent manner (Ohtsuka et al. 2017). Through such a response, S. pombe is considered to survive even under sulfur starvation.

CLS is defined as the viability of a cell population in the stationary phase and is considered to be a model for non-dividing cellular lifespan in higher organisms (Takuma et al. 2013; Lin and Austriaco 2014; Hibi et al. 2018; Banerjee, Joshi and Nagotu 2020; Ohtsuka, Shimasaki and Aiba 2021b). There are several mechanisms of CLS extension by sulfur starvation. Under sulfur depletion, autophagy induction and translational repression occur in Ecl1 family gene-dependent manner (Ohtsuka et al. 2017; Shimasaki et al. 2020). In autophagy-deficient cells, CLS extension was significantly reduced under sulfur starvation, so autophagy induction is considered to be one cause of CLS extension (Shimasaki et al. 2020). In addition, under this condition, the levels of ribosomal factors also decrease in Ecl1 family gene-dependent manner (Ohtsuka et al. 2017, 2021). Similar to sulfur starvation, leucine starvation leads to ecl1+ induction, decreasing ribosome and CLS extension (Ohtsuka et al. 2019, 2021). Using riboziinindole-1, which inhibits ribosome biogenesis (Kawashima et al. 2016), artificial suppression of ribosomes in the Δecl1/2/3 triple mutant, which does not have suppressed ribosomes and has short CLS under starvation, restores cell viability and extends CLS. This suggests that the suppression of ribosome levels is necessary to maintain cell survival under leucine starvation (Ohtsuka et al. 2021). Similarly, it is considered that appropriately reducing the level of ribosomes, which can suppress metabolism and energy consumption under nutrient starvation, also contributes to the maintenance of cell survival under sulfur starvation.

**CONCLUSION**

There have been several reports of fission yeast responses to sulfur, but very few have reviewed them for more than a decade. In this MiniReview, the sulfur response reported so far has been summarized. In addition to the identification of the sulphate transporters, sulfur metabolism pathway and starvation response of fission yeast have mainly been described.

Schizosaccharomyces pombe can sufficiently use sulfate as a sulfur source, and its uptake depends on two transporters, Sul1 and Sul2, which are similar to Sul1 and Sul2 in S. cerevisiae. If these are both deleted, growth does not occur when sulfate is the only sulfur source, so it is considered that there are only these two sulfate transporters in S. pombe.

Unlike S. cerevisiae, S. pombe does not have a trans-sulfuration pathway, so there is no simple conversion from Met to Cys. For this reason, Met does not appear to be a useful sulfur source for this yeast. Because sulfur is also important for GSH synthesis, the sulfur source is not only a nutrient source but also affects oxidative stress and heavy metal stress responses.

In S. pombe, the sulfur starvation response has similarities and differences with other types of nutrient starvation response. The similarities include induction of sporulation, decreased translation, autophagy induction and CLS extension, whereas the differences include cell cycle arrest at G2 instead of G1, and no mating response. Understanding the molecular mechanism of each nutrient depletion response by comparing these similarities and differences is expected to contribute to further understanding of the diversity of cellular responses and the cellular mechanism itself.

**CONSENT TO PARTICIPATE**

Not applicable

**AVAILABILITY OF DATA AND MATERIAL**

All the data have been presented in the manuscript.

**ETHICS APPROVAL**

Not applicable

**CONSENT FOR PUBLICATION**

Not applicable

**AUTHOR CONTRIBUTIONS**

HO has made major contributions to this study and toward writing the manuscript. TS performed experiments for characterization of sulfur transporters. TS and HA have contributed to the factual and logical confirmation, and revision of this manuscript.

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