

## RESEARCH COMMUNICATION

# SEMO-1, a novel methanethiol oxidase in *Caenorhabditis elegans*, is a pro-aging factor conferring selective stress resistance

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## Abstract

Methanethiol is a toxic gas produced through bacterial degradation of sulfur-containing amino acids. Applying a novel enzymatic assay, we here identified a methanethiol oxidase (MTO) that catalyzes the degradation of methanethiol in the nematode *Caenorhabditis elegans* (*C. elegans*). The corresponding protein, Y37A1B.5, previously characterized as a *C. elegans* ortholog of human selenium-binding protein 1 (SELENBP1), was renamed SEMO-1 (SELENBP1 ortholog with methanethiol oxidase activity). Worms rendered deficient in SEMO-1 not only showed decreased hydrogen sulfide production from methanethiol catabolism but they were also more resistant to oxidative stress and had an elevated life span. In contrast, resistance to selenite was significantly lowered in SEMO-1-deficient worms. Naturally occurring mutations of human SELENBP1 were introduced to recombinant SEMO-1 through site-directed mutagenesis and resulted in loss of its MTO activity, indicating a similar enzymatic mechanism for SELENBP1 and SEMO-1. In summary, SEMO-1 confers resistance to toxic selenite and the ability to metabolize toxic methanethiol. These beneficial effects might be a trade-off for its negative impact on *C. elegans* life span.

## KEYWORDS

aging, *Caenorhabditis elegans*, methanethiol, methanethiol oxidase, H<sub>2</sub>S, selenium

**Abbreviations:** *C. elegans*, *Caenorhabditis elegans*; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; H<sub>2</sub>S, hydrogen sulfide; MGL, methionine gamma-lyase; MT, methanethiol; MTO, methanethiol oxidase; PbS, lead sulfide; Se, selenium; SELENBP1, selenium-binding protein 1; SEMO-1, SELENBP1 ortholog with methanethiol oxidase activity.

## 1 | INTRODUCTION

Selenium (Se) is an essential trace element for mammals including humans. Both Se deficiency and oversupply are associated with impaired health.<sup>1</sup> Se acts mainly through its incorporation, as selenocysteine, into selenoproteins, many of which are enzymes involved in the maintenance of redox homeostasis.<sup>2</sup> Owing to its contribution to

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antioxidant defense, Se has been frequently investigated in relation to aging.<sup>3</sup> Nevertheless, a recent study unexpectedly found that the life span of mice fed a Se-deficient diet was not shortened, as pro-longevity mechanisms characterized by altered nutrient sensing became activated in response to Se and selenoprotein deficiency.<sup>4</sup> In comparison to humans and mice, with 25 (humans) or 26 (mice) genes encoding selenoproteins, the selenoproteome of *Caenorhabditis elegans* (*C. elegans*) is tiny, rendering it an interesting model organism for research into Se and aging. Remarkably, deletion of the gene encoding the only *C. elegans* selenoprotein, cytosolic thioredoxin reductase, TRXR-1,<sup>5</sup> does not shorten nematode life span, in contrast to deletion of its mitochondrial counterpart, TRXR-2, which is not a selenoprotein in *C. elegans*.<sup>6</sup>

In addition to selenocysteine, however, Se can also be present in proteins as selenite, binding cysteine residues in selenium-binding proteins.<sup>7</sup> Selenium-binding protein 1 (SELENBP1), discovered in 1989 in mice,<sup>8</sup> is phylogenetically well conserved and has orthologs in many species, ranging from bacteria and plants to humans. In mammals, SELENBP1 has mainly been implicated in cellular proliferation and differentiation,<sup>9,10</sup> and in the regulation of redox homeostasis.<sup>11</sup> Moreover, it attracted the attention of clinicians because of its pronounced downregulation in many types of cancers that correlates with tumor cell dedifferentiation and poor prognosis for the patients (for review, see<sup>7</sup>). Recently, human SELENBP1 was identified as a methanethiol oxidase (MTO) that catalyzes the conversion of methanethiol to hydrogen sulfide (H<sub>2</sub>S), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and formaldehyde.<sup>12</sup> Defective degradation of methanethiol due to inactivating mutations in the human *SELENBP1* gene manifests as extraoral halitosis.<sup>12</sup> Methanethiol, a toxic gas with a putrid smell, originates from bacterial decomposition of sulfur-containing amino acids and is found in near-surface water, soil, and in the mammalian gut.<sup>13,14</sup>

We recently identified a SELENBP1 ortholog, Y37A1B.5, in *C. elegans*, whose amino acid sequence shows 52% identity with that of human SELENBP1.<sup>15</sup> Y37A1B.5 appears to be involved in the regulation of aging processes in the nematode: levels of Y37A1B.5 mRNA decreased with age; moreover, knockdown through RNA interference resulted in a ~10% increase in life span and enhanced resistance of the worms to oxidative stress, whereas their survival in the presence of high selenite concentrations was attenuated.<sup>15</sup> Selenite, in turn, stimulated the expression of this SELENBP1 ortholog.<sup>16</sup> Using a newly generated *C. elegans* strain deficient in Y37A1B.5, we here demonstrate that Y37A1B.5 is an MTO; Y37A1B.5 is therefore renamed SEMO-1 (SELENBP1 ortholog with methanethiol oxidase activity). Moreover, SEMO-1-deficient worms showed an extended

life span and elevated tolerance to oxidative stress but lower selenite resistance.

## 2 | EXPERIMENTAL PROCEDURES

### 2.1 | Reagents

Chemicals were purchased from Sigma-Aldrich (Munich, Germany) or Carl Roth (Karlsruhe, Germany), unless stated otherwise. Primers were obtained from Life Technologies (Darmstadt, Germany).

### 2.2 | Cloning, mutagenesis, bacterial overexpression, and isolation of recombinant proteins

Total RNA was isolated from *C. elegans* (wild type, N2 strain) using Trizol reagent, and 1 µg was used for cDNA synthesis. From cDNA, the *semo-1* coding sequence was amplified by PCR using Phusion DNA polymerase (Thermo Fisher Scientific, Waltham, MA, USA) and the following primers: 5'-atgtcccaactgtggtttaaagt-3' and 5'-ttaaattccaaatccgatgtacaatctcc-3'. Thereafter, a second PCR (primers: 5'-agctcgtctccaatgtcccaactgtggt-3', 5'-agctcgtctcctccatcaatccaaatccgatgtacaat-3') was used to generate recognition sites for the restriction enzyme Esp3I that was used for cloning into the Twin-Strep-tag pASG-IBA102 vector (IBA Lifesciences, Göttingen, Germany; #5-4102-001) according to the manufacturer's instruction. Subsequently, a DNA fragment containing the open reading frame for *semo-1* and the Twin-Strep-tag was cut out and ligated into the DHFR control template vector (New England Biolabs, Ipswich, MA; #E6800S), using NdeI and XhoI restriction sites. For generation of SEMO-1 mutants (Gly223Trp, His331Tyr), site-directed in vitro-mutagenesis was performed by PCR using Q5 DNA-Polymerase (New England Biolabs). Ensuing methylated templates were digested with DpnI. All applied restriction enzymes were purchased from Thermo Fisher Scientific.

Expression plasmids for human SELENBP1 and methionine gamma-lyase (MGL) from *Brevibacterium aurantiacum* were generated as previously described.<sup>17</sup> Bacterial overexpression and isolation of the recombinant proteins also occurred as previously described.<sup>17</sup>

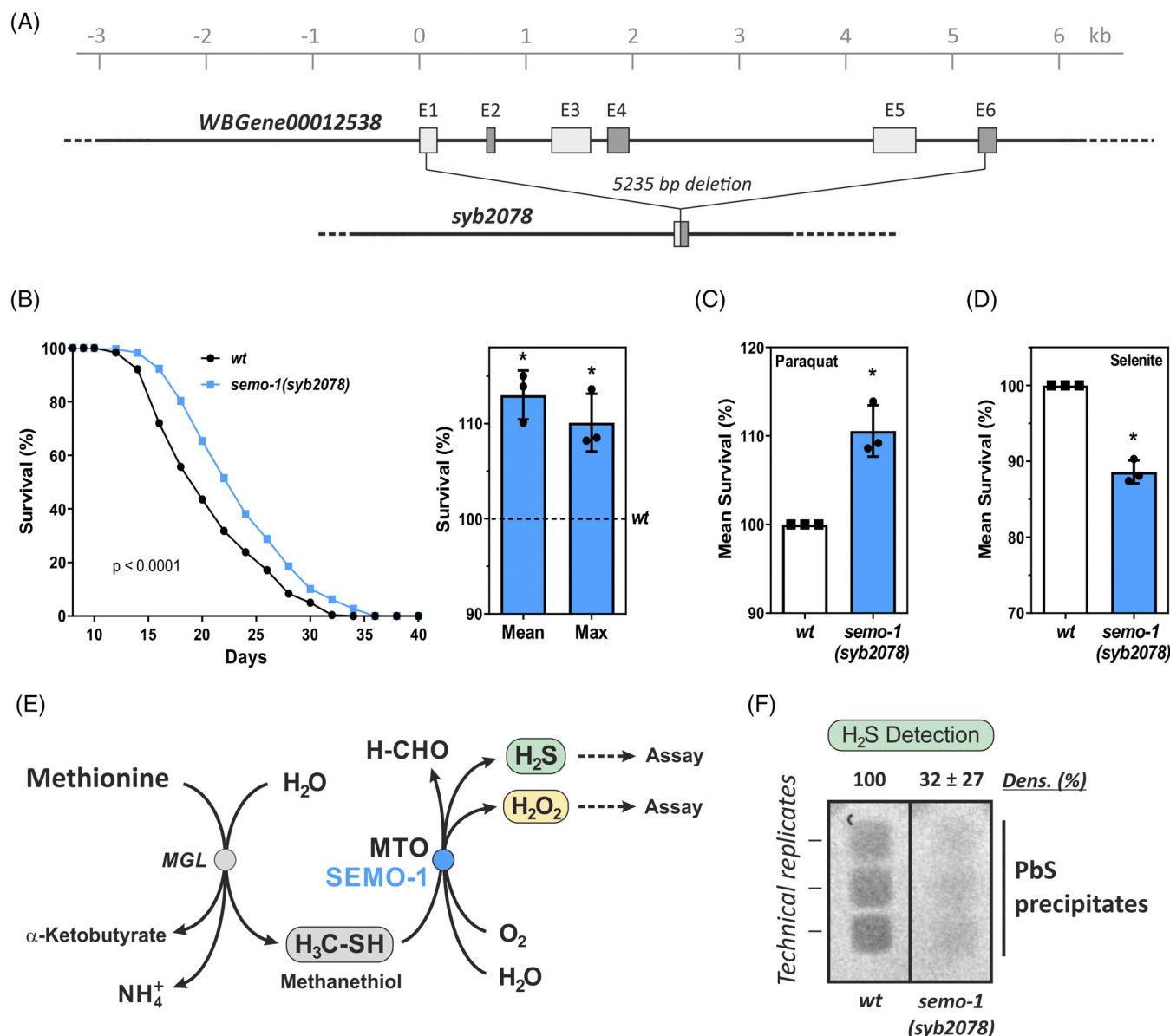
### 2.3 | Methanethiol oxidase assay

MTO activity was assessed through a coupled enzymatic assay, using recombinant MGL as source of methanethiol as previously described in detail.<sup>17</sup> The

following modifications were applied: the soluble protein fraction of *C. elegans* whole worm lysates was used at a final protein concentration of 1–2 mg/ml in HEPES-buffered saline (HBS; 50 mM HEPES, 150 mM NaCl, pH 7.4). The enzymatic reactions took place at 37°C and under shaking at 200 rpm for 4 h both for recombinant proteins and for *C. elegans* lysates.

## 2.4 | SDS-PAGE and immunoblot analysis

SDS-PAGE and immunoblotting were performed for the detection of purified recombinant proteins as previously described.<sup>17</sup> The following antibodies were used: mouse monoclonal antibody anti-Strep-Tag II/StrepMAB (IBA Lifesciences) and horseradish peroxidase (HRP)-coupled anti-mouse IgG (Thermo Fisher Scientific).



**FIGURE 1** Increased life span, selective stress resistance, and depressed MTO activity of *semo-1* knockout worms. (A) *C. elegans semo-1* gene and the deleted region in *semo-1* knockout worms [*semo-1(syb2078)*]. (B) Survival of wild type (wt, black) and *semo-1* knockout (blue) worms. One representative experiment is shown and means  $\pm$  SD for mean and maximum life span of all three independent experiments are provided in the bar graph. (C, D) Survival of wt and *semo-1* knockout worms in the presence of paraquat (10 mM) or selenite (10 mM). (E) Sketch of MTO assay.<sup>17</sup> (F) H<sub>2</sub>S production of lysates from wt and *semo-1* knockout worms, measured by MTO assay. H<sub>2</sub>S was detected as PbS precipitate. Results of one representative experiment (three technical replicates) of three independent experiments are shown; means  $\pm$  SD of densitometry data of all biological replicates is given. Original data and membranes are provided in the Supporting Information

## 2.5 | *Caenorhabditis elegans* maintenance and treatments

*C. elegans* wild type strain Bristol N2 and *E. coli* OP50/OP50-1 were provided by the *Caenorhabditis* Genetics Center (CGC, University of Minnesota, USA), which is supported by the National Institutes of Health-Office of Research Infrastructure Programs. The SEMO-1-deficient strain (Figure 1A) PHX2078, *semo-1(syb2078)* was generated by SunyBiotech (Fuzhou, China) and outcrossed twice into N2 wild type worms in our laboratory before use.

Nematodes were grown, maintained, and treated as described previously.<sup>18,19</sup> For stress resistance assays, heat-inactivated bacteria (45 min at 65°C) were used. Synchronized worm populations were used in all experiments. Eggs were held in M9 buffer and kept in L1 arrest on a rocking platform for 24 h. L1 larvae were transferred to nematode growth medium (NGM) agar plates and grown for 48 h to young adulthood (L4 larvae) before being transferred to fresh plates for further experiments. For long-term incubations, nematodes were washed off the plates with S-basal buffer daily and were transferred to freshly prepared NGM agar plates to separate nematodes from progeny and to ensure food supply. On the evening before the experiment, agar plates were spotted with *E. coli* OP50 or *E. coli* OP50-1 and allowed to dry overnight.

## 2.6 | *Caenorhabditis elegans* life span assays

Life span analyses were performed with synchronized worm populations. For the first 10 days, worms were transferred to new NGM agar plates with *E. coli* OP50 daily. Thereafter, they were transferred to plates containing streptomycin with *E. coli* OP50-1 every other day. Worms showing no movement, no reaction to gentle stimulation and no pharyngeal pumping were scored as dead. Worms lost or disintegrated, for example due to internal hatchings, were censored. Each independent experiment was performed in at least three technical replicates.

## 2.7 | *Caenorhabditis elegans* paraquat and selenite resistance assays

L4 larvae were washed off culture plates with S-basal buffer daily for 5 (paraquat) or 3 (selenite) days and transferred to freshly prepared NGM agar plates spotted with *E. coli* OP50 to separate nematodes from progeny.

Thereafter, worms were transferred to plates spotted with heat-inactivated (45 min at 65°C) *E. coli* OP50 and containing 10 mM paraquat or 10 mM sodium selenite. Survival was scored daily by transferring worms to new plates. Each of the independent experiments was performed in three technical replicates.

## 2.8 | Statistical analysis

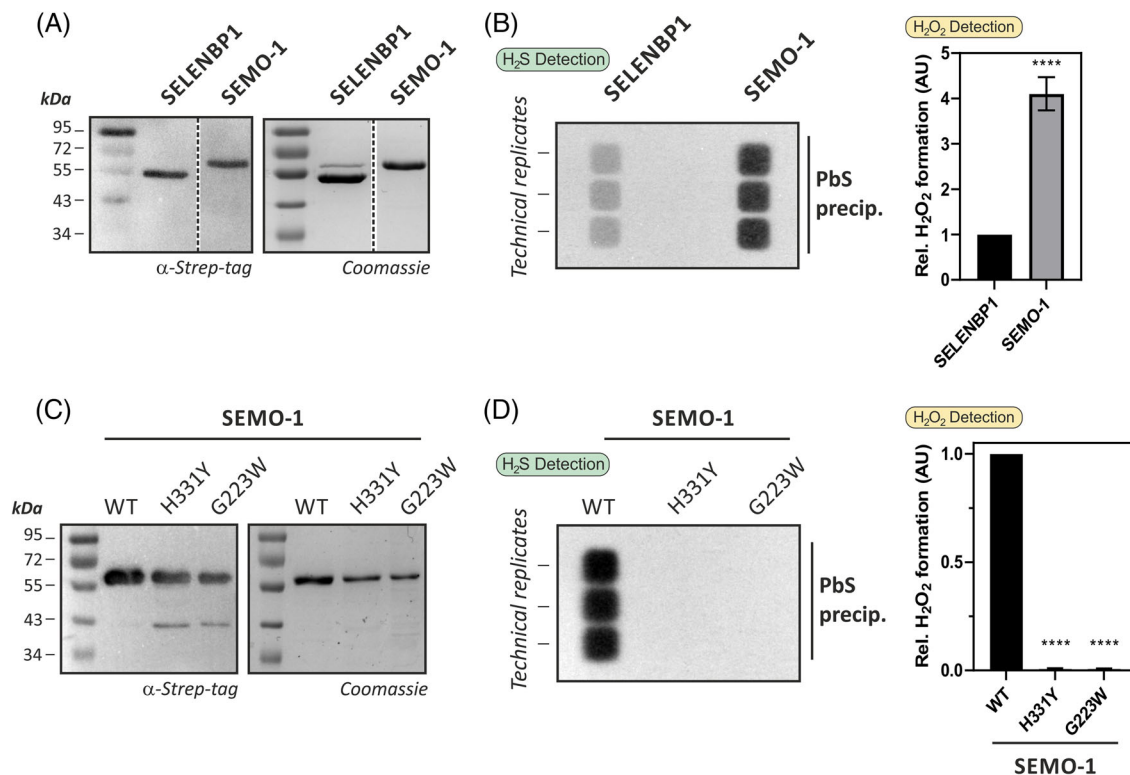
Data are expressed as means + SD unless stated otherwise. For life span analyses, statistical calculations were performed using JMP software (SAS Institute Inc., Cary, NC), applying the log-rank test. Median and mean survival were calculated for each of the technical replicates in one experiment (i.e., biological replicate). Maximum life span in each technical replicate was defined as the last day on which a worm was scored as alive. Mean, median, and maximum life span for each biological replicate was then determined as the mean of all technical replicates. All other calculations were performed using GraphPad Prism (GraphPad Software, San Diego, CA) and statistical significances were calculated using Welch's *t*-test due to heterogeneity of variances. The minimum level of significance was set to  $p < 0.05$ .

## 3 | RESULTS AND DISCUSSION

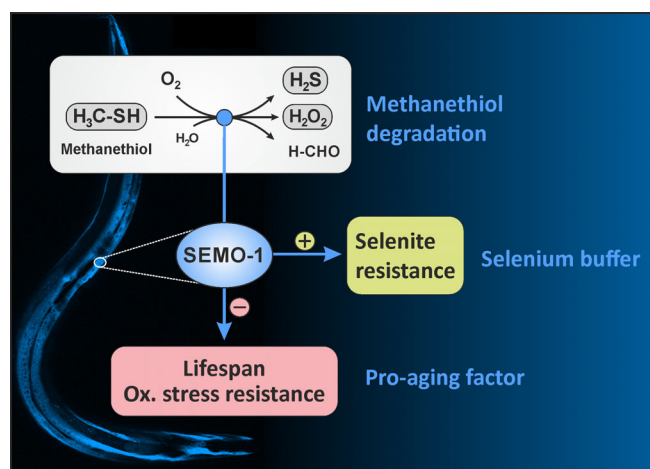
The *semo-1* gene contains 6 exons, and splicing of the primary *semo-1* transcript results in a mature mRNA of 1530 bp. Knockout worms with a genomic deletion of 5235 bp, spanning exons 1–6, were generated using CRISPR/Cas9 technology (SunyBiotech; Figure 1A), and successful deletion was confirmed by PCR and RT-PCR (data not shown).

Compared to wild type nematodes, the *semo-1* knockout strain showed a 10%–15% increase in both mean and maximum life span (Figures 1B and S1, Table S1). Moreover, the *semo-1* knockout strain was more resistant to acute oxidative stress, induced by the redox cycler paraquat (Figures 1C and S2, Table S2). On the other hand, wild type worms better coped with a high dose (10 mM) of selenite (Figure 1D and S3, Table S3), which is known to exert toxic effects in *C. elegans* at millimolar concentrations.<sup>20</sup> These features of the *semo-1* knockout strain confirm that SEMO-1 acts as a pro-aging factor in *C. elegans*, as previously proposed by us<sup>15</sup>: A decrease in SEMO-1 levels triggers adaptive cytoprotective responses, at the cost of less protection against high Se concentrations in the environment.

Next, we assessed MTO activity in lysates prepared from wild type and *semo-1*-deficient worms. We



**FIGURE 2** SEMO-1 is a methanethiol oxidase. (A, C) SELENBP1 and SEMO-1 as well as two SEMO-1 mutants (His331Tyr, Gly223Trp) were produced in *E. coli* as recombinant proteins with a C-terminal StrepTag.<sup>17</sup> Following SDS-PAGE, proteins were detected by immunoblotting as well as Coomassie staining. (B, D) MTO assay using recombinant SELENBP1 and SEMO-1 (B: 9 μg each) or SEMO-1 and mutants thereof (D: 6.5 μg each): H<sub>2</sub>S was detected as in Figure 1F. H<sub>2</sub>O<sub>2</sub> was quantitated using a peroxidase-based assay using a fluorescent probe. Means ± SD of three independent experiments are given. All original blots and membranes are provided in the Supporting Information



**FIGURE 3** Biological activities of SEMO-1. SEMO-1 is a *Caenorhabditis elegans* methanethiol oxidase that confers selenite resistance and may therefore be regarded as a selenium buffer. In parallel, it decreases *C. elegans* life span and lowers oxidative stress resistance. The background image (modified from<sup>15</sup>) indicates the hypodermal expression of SEMO-1 in *C. elegans*

employed a coupled enzyme assay detecting MTO activity,<sup>17</sup> analyzing two of the three products of the MTO reaction: H<sub>2</sub>S is detected through precipitation as lead sulfide (PbS), while H<sub>2</sub>O<sub>2</sub> formation is assessed fluorimetrically using peroxidase (Figure 1E). Using this assay, we recently measured MTO activity of recombinant human SELENBP1 as well as in lysates from Caco-2 cells, a human colorectal adenocarcinoma cell line.<sup>17</sup> We here demonstrate that wild type (N2) *C. elegans* lysates harbor significant MTO activity, whereas production of the MTO product H<sub>2</sub>S is drastically diminished in the *semo-1* knockout strain (Figure 1F). Both H<sub>2</sub>S and H<sub>2</sub>O<sub>2</sub> are cytotoxic at high doses but may serve as signaling molecules at low levels<sup>21–23</sup>; they have been reported to modulate life span of *C. elegans*, through interaction with signaling pathways and cell respiration.<sup>24</sup>

Remarkably, exposure to slow-releasing H<sub>2</sub>S donors has been reported to extend the life span of *C. elegans* and to provide some health benefits, while genetic deficiency of another H<sub>2</sub>S-producing enzyme, the

3-mercaptopyruvate sulfurtransferase ortholog MPST-1, resulted in a shorter life span of the worms.<sup>25,26</sup> Thus, lowered H<sub>2</sub>S production due to SEMO-1 deficiency is unlikely to mediate the observed beneficial effects of the *semo-1* knockout. The pro-aging effect of SEMO-1 might be caused by toxic properties of the two additional MTO products, H<sub>2</sub>O<sub>2</sub> and formaldehyde, or by properties of the protein that are unrelated to its MTO activity. It should be noted as well that *E. coli*, used in the described experiments to feed the worms, have been found to produce very little of the MTO substrate methanethiol.<sup>27</sup> Therefore, MTO activity in worms grown in the laboratory might be considerably lower than in worms living in their environmental soil habitat. Nevertheless, the question of whether the diminished MTO activity in the *semo-1* knockout nematodes may directly contribute to their increased life span will require future experimental analyses.

To provide direct evidence for MTO activity of SEMO-1, we cloned the *semo-1* coding sequence from wild type *C. elegans* (N2) and overexpressed it in *E. coli* as a recombinant protein. As positive control, human SELENBP1 was produced accordingly and as previously described<sup>17</sup> (Figure 2A). SEMO-1 showed MTO activity, which was even higher than with its human ortholog (Figure 2B).

Two naturally occurring mutations of key amino acids in human SELENBP1 (Gly225Trp; His329Tyr) have been reported to cause loss of its MTO activity.<sup>12,17</sup> We here generated the corresponding SEMO-1 mutants (Gly223Trp; His331Tyr) through in vitro-mutagenesis of the *semo-1* coding sequence and produced them as recombinant proteins (Figure 2C). MTO activity was abolished in both SEMO-1 mutants (Figure 2D), suggesting that the enzymatic reaction mechanism is evolutionarily conserved. The amino acid residue Gly223/225 is found in all currently known methanethiol oxidases, while His329/331 is conserved only in eukaryotic SELENBP1 orthologs.<sup>12</sup> These two crucial amino acids are located within identical motifs in both SEMO-1 and SELENBP1 (Gly-Leu-Tyr-Gly; Trp-Leu-His-Gly). If Gly225 is mutated to Trp, the indole ring of the tryptophan residue might sterically interfere with adjacent side chains, as compared to the small glycine residue in the wild type protein.<sup>12</sup> Mutation of His329/331 might diminish substrate- or cofactor-binding, as histidine is the most common amino acid at active and binding sites of enzymes.<sup>28</sup>

MTO enzymes are phylogenetically conserved among all domains of life, a feature that also indicates the environmental abundance of methanethiol as a key intermediate in the biogeochemical cycle of sulfur.<sup>29,30</sup> Clearance of methanethiol is of key physiological relevance, as elevated concentrations are considered toxic. For

nematodes, the capability to degrade this toxic gas is advantageous, as their soil habitats may exhibit high levels of methanethiol.<sup>14</sup> Consistently, highest SEMO-1 levels in *C. elegans* were observed in the hypodermis<sup>15</sup> (Figure 3), a tissue that is close to the environment. A SEMO-1-mediated ability to cope with high methanethiol and Se concentrations in the environment might be a trade-off for a decreased life span.

## 4 | CONCLUSION

Taken together, we characterized SEMO-1 (formerly Y37A1B.5) as a structural and functional *C. elegans* ortholog of human SELENBP1, capable of acting as an MTO and thus serving as a novel endogenous source of H<sub>2</sub>S and H<sub>2</sub>O<sub>2</sub> in the nematodes. Knocking out *semo-1* resulted in an extension of life span and selective modulation of stress resistance. The issue of whether SELENBP1 may affect the life span of mammals has not yet been explored. Neither *Selenbp1* knockout mice<sup>31</sup> nor patients with defective MTO activity due to mutations in their *SELENBP1* gene<sup>12</sup> showed any apparent phenotypic changes that indicated alterations of life span. From the pro-senescence and tumor-suppressing activity of SELENBP1,<sup>7</sup> however, a parallel between the life span-attenuating effect of SEMO-1 in *C. elegans* and the tumor proliferation-attenuating activity of SELENBP1 in mammals can be drawn. It remains to be evaluated to what extent MTO activity and Se are involved in these processes; due to the similarities between SELENBP1 and SEMO-1, *C. elegans* is an excellent model organism to study these aspects.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## AUTHOR CONTRIBUTIONS

Study conception and design: Thilo Magnus Philipp, Holger Steinbrenner, and Lars-Oliver Klotz; acquisition of data: Thilo Magnus Philipp, Weiye Gong, Karl Köhnlein, Verena Alexia Ohse, and Frederike Iris Müller; analysis and interpretation of data: Thilo Magnus Philipp, Verena Alexia Ohse, Josephine Priebs, Holger Steinbrenner, and Lars-Oliver Klotz; manuscript

preparation: Thilo Magnus Philipp, Holger Steinbrenner, and Lars-Oliver Klotz.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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