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SEMO-1 (Y37A1B.5), a novel selenium-binding protein ortholog and hydrogen sulfide source, mediates selective stress resistance in the model organism *C. elegans*

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Question: The *Caenorhabditis elegans* ortholog of human selenium-binding protein 1 (SELENBP1), Y37A1B.5 (Y37), is a pro-aging factor. Knock-down of Y37 resulted in elevated lifespan and better resistance against oxidative stress [1]. SELENBP1 catalyzes the conversion of methanethiol to hydrogen sulfide (H_2S), hydrogen peroxide (H_2O_2) and formaldehyde, thus acting as methanethiol oxidase (MTO). Here, we tested whether Y37 has MTO activity, whether it is involved in selenium homeostasis, and whether energy metabolism is involved in the observed modulation of lifespan by Y37.

Methods: MTO activity was measured using a coupled assay based on *in situ*-generation of methanethiol as catalyzed by a bacterial recombinant L-methionine gamma-lyase, followed by detection of MTO-generated H_2S and H_2O_2 [2]. Lifespan analyses were performed using standard *C. elegans* culture. For stress resistance analyses, nematodes were exposed to toxic concentrations of selenite or paraquat. Worms employed included N2 wildtype and mutant strains deficient in Y37 or in the AMPK ortholog, AAK-1/-2.

Results: Like SELENBP1, isolated recombinant Y37 has MTO activity. While MTO activity was detected in lysates from wild-type nematodes, the Y37-deficient strain was devoid of it. A Y37-deficient mutant strain generated through CRISPR/Cas technology exhibited an extended lifespan, similar to the previously reported worms exposed to Y37-specific RNAi. Moreover, resistance against the redox-cycler paraquat was also improved in the Y37-deficient strain. In contrast to paraquat, selenite was more toxic in the Y37-deficient strain, as compared to wild-type worms. Lifespan extension following Y37 depletion was abrogated in a mutant strain deficient in both isoforms of the catalytic AAK subunit, while Y37 depletion through RNAi appeared to enhance AAK phosphorylation in wild-type worms.

Conclusions: (1) Y37 acts as MTO in *C. elegans*; thus, we named it SEMO-1 (SELENBP1 ortholog with MTO activity). (2) SEMO-1 mediates selective stress resistance. It renders worms susceptible to oxidative stress but also serves as selenium buffer, protecting against high doses of selenite. (3) SEMO-1 is involved in the AAK-mediated regulation of energy metabolism, thereby affecting organismal lifespan and stress resistance.

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[1] Köhnlein *et al.*, Redox Biol. 28:101323 (2020), [2] Philipp *et al.*, Redox Biol. 43:101972 (2021).