Supplemental Materials and Methods

Strains

C. elegans animals were grown on *E. coli* OP50 at 20 °C as described (Brenner, 1974), unless otherwise indicated. N2 (Bristol) was the reference wild type strain. Strains and mutations used in this study include:

CB4856 (Hawaiian) (WICKS *et al.* 2001)

CB767 *bli-3(e767lf) I* (BRENNER 1974)

CSM637 *skn-1(lax120gf) IV* (Paek et al., 2012; Xu et al., 2018)

CSM627 *bli-3(mac40lf) I* (XU *et al.* 2015)

CSM681 *tsp-15(mac33lf) I* (XU *et al.* 2015)

CSM684 *skn-1(mac53gf) IV* (XU *et al.* 2018)

CSM752 *doxa-1(mac55lf) III* (XU *et al.* 2018)

CSM753 *doxa-1(mac67lf) III* (XU *et al.* 2018)

CSM670 *csnk-1(mac397)* (XU *et al.* 2018)

CSM638 *skn-1(zu135lf) IV/nT1[qIs51] (IV; V)* (Bishop and Guarente, 2007; Bowerman et al., 1992)

CSM1124 *csnk-1(mac494lf)/hT2[qIs48] I; +/hT2[qIs48] III*

CSM1125 *csnk-1(mac495lf)/hT2[qIs48] I; +/hT2[qIs48] III*

CSM1199 *tsp-15(mac499lf) I*

CSM1200 *tsp-15(mac500KI) I*

CSM1201 *tsp-15(mac501KI) I*

CSM1212 *bli-3(mac40lf) csnk-1(mac494lf)/hT2[qIs48] I; +/hT2[qIs48] III*

CSM1213 *bli-3(mac40lf) csnk-1(mac495lf)/hT2[qIs48] I; +/hT2[qIs48] III*

CSM1218 *csnk-1(mac494lf)/hT2[qIs48] I; +/hT2[qIs48] III; skn-1(mac53gf) IV*

CSM1219 *csnk-1(mac495lf)/hT2[qIs48] I; +/hT2[qIs48] III; skn-1(mac53gf) IV*

CSM1220 *csnk-1(mac494lf)/hT2[qIs48] I; +/hT2[qIs48] III; skn-1(lax120gf) IV*

CSM1221 *csnk-1(mac495lf)/hT2[qIs48] I; +/hT2[qIs48] III; skn-1(lax120gf) IV*

CSM1257 *bli-3(e767lf) csnk-1(mac494lf)/hT2[qIs48] I; +/hT2[qIs48] III*

CSM1258 *bli-3(e767lf) csnk-1(mac495lf)/hT2[qIs48] I; +/hT2[qIs48] III*

CSM1259 *csnk-1(mac494lf)/hT2[qIs48] I; doxa-1(mac55lf)/hT2[qIs48] III*

CSM1260 *csnk-1(mac495lf)/hT2[qIs48] I; doxa-1(mac55lf)/hT2[qIs48] III*

C. elegans survival assay in excess iodide

The survival assay was performed as described (Xu et al., 2015) with modification. In short, bleached eggs were grown on OP50-seeded NGM plates with different concentrations of NaI (5 mM, 10 mM or 50 mM). The animals were observed for growth and survival from day 4 to day 8.

Mapping and cloning of *mac397*

mac397 was previously isolated as an F_1 progeny of EMS-mutagenized wiltype P0 animals that survived in 5 mM NaI (Xu et al., 2018). To map the chromosomal location of *mac397*, males of the Hawaiian strain CB4856 were crossed to *mac397* hermaphrodites. F_1 male progeny were crossed with CB4856 hermaphrodites in plates with 5 mM NaI to generate surviving F_2 male progeny. Similar crosses were performed for two more rounds to generate survived F_5 hermaphrodites, which were picked to individual plates with 5 mM NaI and allowed to propagate. Animals on these plates were used to determine the genetic location of *mac397* using single nucleotide polymorphisms (SNPs) (Davis et al., 2005; Wicks et al., 2001). We mapped *mac397* to a 19 mapping-unit region on Chr. I to the right of SNP *WBVar00240395* (SNP W03D8: 34384 D1 = T, genetic location: -5.68; GenBank accession no. FO081764) and to the left of SNP *WBVar00245221* (SNP F58D5: 17029-17032 D4 = ACTA, genetic location: 13.02; GenBank accession no. AL137227).

To determine the genomic sequences of *mac397* mutants, mixed progeny of unbackcrossed original isolate were washed and starved for ~4 hrs in H_2O. Genomic DNAs were extracted by proteinase K digestion, followed by RNase A treatment and two rounds of phenol–chloroform extraction. Three genomic DNA libraries (350 bp inserts) were constructed by Annoroad Gene Technology Corporation (Beijing) using Illumina's paired-end protocol. Paired-end sequencing (100-bp reads) was performed on the Illumina HiSeq X Ten. 4G clean bases were mapped to the N2 genome (Wormbase release 220) after removal of duplicated reads.

Genomic sequencing identified 7 homozygous and 4 heterozygous mutations (nonsense or missense) between the mapped SNPs on Chr. I of *mac397* mutants, among which were a homozygous mutation in *tsp-15* and a heterozygous mutation in *csnk-1* (Table S1). It is worth noting that homozygosity of the *tsp-15* mutation might be caused by propagation of the original isoloate in 5 mM NaI before the strain was sequenced (see below).

Since *tsp-15(lf)* mutants can survive in 5 mM NaI as homozygotes (Xu et al., 2015), we initially suspected that the identified *tsp-15* mutation (exon3:c.G331A:p.G111R, named *mac499*) in *mac397* mutants could be dominant negative, which might have caused the survival of the original isolate as heterozygotes. To test this, we generated two knock-in mutations genocopying *mac499* (Table S3, *mac500* and *mac501*). The heterozygous knock-in mutants failed to survive in excess iodide, while the homozygotes mutants could (Table S3). We futher verified the recessiveness of *mac499* and found that a *tsp-15* gDNA transgene can rescue the survival phenotype of *mac499* mutants in 5 mM NaI (Table S3). These results suggest that the *tsp-15(mac499)* mutation is recessive and another mutation, either alone as heterozygote or together with *tsp-15(mac499)*/+*,* might have caused the survival of the original isolate in 5 mM NaI.

To identify this gene, we treated wildtype animals with RNAi clones that targeted most genes with identified variations in *mac397* mutants (Table S1). Interestingly, *csnk-1(RNAi)* caused the animals to survive in 5 mM NaI (Table S1 and S2). We named the corresponding mutation in *csnk-1* as *mac397.*

While identifying the causal gene of *mac397*, an unexpected event happened in maintaining the strain. After we found that *csnk-1(mac397)* might be a new mutation in promoting the survival in excess iodide by RNAi, we re-examined our frozen *mac397* stock but were only able to recover the *tsp-15(mac499)* mutation. We further examined

multiple individual animals from the frozen stock but failed to detect the presence of *csnk-1(mac397)* as heterozygotes or homozygotes.

We postulate that a prolonged propagation of the original isolate before we froze this strain probably caused this phenomenon. In the original isolate, *csnk-1(mac397)* was likely heterozygous (Table S1, based on genomic sequencing of animals in the early propagation phase). Like *csnk-1(lf), csnk-1(mac397)* homozygous mutation probably caused lethality and/or sterility. An extended propagation of the strain in 5 mM NaI, with either *tsp-15(mac499) csnk-1(mac397)/+* + or *tsp-15(mac499) +/+ csnk-1(mac397)* as the starting genotype, would cause *tsp-15(mac499)* to outcompete *csnk-1(mac397)* in the population. At the time of being frozen, most, if not all, animals might have carried *tsp-15(mac499)* homozygous mutations and lost *csnk-1(mac397)* mutation.

We previously found that *bli-3(lf)/+; doxa(lf)/+* double heterozygous mutants can survive in 5 mM NaI, while *bli-3(lf)/+* or *doxa-1(lf)/+* single mutants could not (Xu et al., 2015, 2018), suggesting a nonallelic noncomplementation interaction between the two genes. We postulate that *csnk-1(mac397)* and *tsp-15(mac499)* probably interacted in a nonallelic noncomplementation manner to cause the survival of the original *mac397* isolate in our screen (Xu et al., 2018).

Plasmids

To construct the *csnk-1p::GFP* plasmid, a *csnk-1* promoter (3.1 kb upstream of the *csnk-1* start codon) was amplified by PCR and subcloned to the pPD95_79 vector using *BamH*I and *Kpn*I sites.

To construct the *csnk-1p::csnk-1_cDNA* plasmid, the *csnk-1* cDNA fragment was amplified from first strand cDNAs and used to replace *GFP* of *csnk-1p::GFP* using *Kpn*I and *EcoR*I sites.

To construct the *dpy-7p::csnk-1_cDNA* plasmid, a *dpy-7* promoter (430 bp upstream of the *dpy-7* start codon) (Gilleard et al., 1997) was subcloned to the pPD95_79 vector using *Hind*III and *BamH*I sites. The *csnk-1* cDNA fragment was subcloned to the pPD95_79-*dpy-7p* backbone using *Kpn*I and *EcoR*I sites.

To construct the *nhx-2p:: csnk-1_cDNA* plasmid, a *nhx-2* promoter (4.1 kb upstream of the *nhx-2* start codon) (Nehrke, 2003) was subcloned to pPD95_79 using *Pst*I and *Xma*I sites. The *csnk-1* cDNA fragment was subcloned to the pPD95_79-*nhx-2p* backbone using *Kpn*I sites.

To construct the *dpy-7p:: HsCSNK1G1/2/3_cDNA* plasmids, the *HsCSNK1G* cDNA fragments were amplified from a human cDNA preparation and subcloned to the aforementioned pPD95_79-*dpy-7p* backbone using *BamH*I and *EcoR*I sites.

To construct the *csnk-1p::csnk-1_cDNA(p.C388-390S)*, *csnk-1p::csnk-1_cDNA(p.C388_K407del)* and *csnk-1p::csnk-1_cDNA(mac397)* plasmids, the aforementioned *csnk-1p::csnk-1_cDNA* plasmid was mutated by the Q5 Site-Directed Mutagenesis Kit (New England Biolabs) to introduce the mutations.

To construct the *dpy-7p:: csnk-1_cDNA::mCherry* plasmid, the *mCherry* coding fragment was amplified from pCFJ90 (*myo-2p::mCherry*) (Frokjaer-Jensen et al., 2008) and subcloned to the aforementioned *dpy-7p::csnk-1_cDNA* plasmid using NEBuilder HiFi DNA Assembly kit (New England Biolabs).

To construct the *dpy-7p::doxa-1cDNA::GFP* plasmid, a *doxa-1* cDNA fragment was subcloned to the pPD95_79-*dpy-7p* backbone using *BamH*I and *Age*I sites.

To generate the *doxa-1p::doxa-1_cDNA(p.T343A), (p.S346A)* or *(p.S364A)* construct, the *p. T343A, p.S346A* or *p.S364A* mutation was introduced to a previously described *doxa-1* rescue construct (Xu *et al.* 2018) using the Q5 Site-Directed Mutagenesis Kit (New England Biolabs).

To construct the *pcDNA3.1::doxa-1_cDNA::HA* plasmid, a *doxa-1* cDNA fragment was subcloned to the *pcDNA3.1* backbone using *Kpn*I and *EcoR*I sites. *HA* tag was introduced using the Q5 Site-Directed Mutagenesis Kit (New England Biolabs).

To construct the *pCMV-Tag2B(FLAG)::csnk-1_cDNA* plasmid, a *csnk-1* cDNA fragment was subcloned to the *pCMV-Tag2B* backbone using *BamH*I and *EcoR*I sites.

To construct the *pcDNA3.1::HsDUOXA2_cDNA::HA* plasmid, a human *DUOXA2* cDNA fragment was subcloned into the *pcDNA3.1* backbone using *Kpn*I and *EcoR*I sites. *HA* tag was introduced using the Q5 Site-Directed Mutagenesis Kit (New England Biolabs).

To construct the *pCMV-Tag2B(FLAG)::HsCSNK1G2_cDNA* plasmid, a human *CSNK1G2* cDNA fragment was subcloned to the *pCMV-Tag2B* backbone using *BamH*I and *EcoR*I sites.

PCR primers for constructs are listed in Table S6.

We generated RNAi constructs targeting *rpb-7, asic-2, ate-1*, *kin-1, kin-2, kin-19, kin-20, nsy-1, lin-45, pmk-1* or *sek-1* by subcloning a 400-1000 bp genomic fragment of each genes into the pPD129.36 vector using *Pst*I and *Hind*III sites respectively. PCR primers are listed in Table S7.

All plasmids were verified by restriction digestions and sequencing.

Generation of *csnk-1* or *tsp-15* mutations using CRISPR/Cas9

We followed the method (Farboud and Meyer, 2015) with modifications. The DNA mixture for injection contained 50 ng/µl pPD162 (*Peft-3::Cas9-SV40_NLS*), 25 ng/µl *PU6::sgRNA* (specific for *csnk-1* or *tsp-15*), and 25 ng/µl *PU6::sgRNA* (specific for *dpy-10*) plasmid as co-injection marker. To generate *tsp-15* knockin mutations, we included a 130 nt synthesized oligo (500 nM) containing the desired *tsp-15* mutation as the repair template and a repair template for *dpy-10* as described (Arribere et al., 2014). F_1 animals with the Dpy/Rol phenotype were picked to individual plates and their progeny were analyzed for the desired mutations by Sanger sequencing. Target sequences of sgRNAs and the sequences of *tsp-15* repair template are shown in Table S8.

We found that *mac494* and *mac495* homozygous mutants derived from heterozygous parents can grow into adults and able to lay multiple eggs with normal morphology. However, these eggs had very low hatching rates. Interestingly, *mac494* homozygous mutants, if starting with a large population, can propagate and consume all the food on a plate eventually. To analyze these mutants efficiently, we maintained *csnk-1(lf)* using *hT2 [bli-4(e937) let-?(q782) qIs48] (I;III)* balancer.

Transgene experiments

Germline transgene experiments were performed as described (Mello et al., 1991).

For *csnk-1* rescue experiments, the transgene mixtures contained 0.5 ng/µl or 5 ng/µl of the transgenes of interest, with 20 ng/µl pPD95_86 (*myo-3p::GFP*) as co-injection marker, and was injected to wildtype animals to generate at least two stable lines. The transgenes were then crossed into *csnk-1(mac494lf)/hT2[qIs48]* animals and *csnk-1(mac494lf)* homozygous progeny carrying the transgenes were examined. For survival test of transgenic lines, transgenic adults were bleached and eggs were placed on

regular or 5 mM NaI NGM plates for 12 hrs to hatch. ~100 homozygotes *csnk-1(mac494lf)* transgenic L1 larva were picked to a new 5 mM NaI NGM plates. The number of adults was counted after 4 days.

Hoechst 33258 staining

Hoechst 33258 staining was performed as described (Moribe et al., 2004; Xu et al., 2015) with modifications. Yound adult animals (24 hrs post mid-L4) were washed off plates and incubated for 15 min in M9 containing 1 μg/ml Hoechst 33258 (Sigma, 861405) at 20 °C with gentle shaking. After staining, animals were washed three times with M9 and observed under a Leica DM5000B fluorescence microscope.

RNA interference

L4 animals or bleach eggs were fed HT115 (DE3) bacteria expressing dsRNAs on NGM plates with 1 mM IPTG, 0.1 mg/ml Ampicillin with or without 5 mM NaI. The progeny were examined under dissecting microscope for survival. The RNAi feeding bacterial strains for *lrp-2, rbpl-1, uggt-2, K07A1.1, sys-1, gsk-3* and *mpk-1* were obtained from a whole-genome RNAi library (Kamath et al., 2003), and the inserts were confirmed by sequencing. RNAi plasmids for other genes were generated in this study (see Plasmids).

Confocal microscopy

Fluorescent images of transgenic animals expressing GFP and/or mCherry reporters were captured using a 63 X DIC/fluorescent Leica TCS SP5 II laser confocal microscope.

PA14 survival assay

Pseudomons aeruginosa PA14 survival assays were performed as described (Tan et al., 1999) with modifications. PA14 was cultured in Luria broth (LB) overnight, seeded on slow-killing plates covering the whole plate surface and incubated for 12 hrs at 37°C

and then 24 hrs at 25°C. ~30 L4 larva were transferred to each replicate plate and the number of live animals remaining on the plates after 24 hrs was counted as the starting number. Animals were scored as live or dead by gental touch for behavioral responses.

Cell culture and transfection

HeLa for immunofluorescence and HEK293T cells for immunoprecipitation were cultured in DMEM medium supplemented with 10% fetal bovine serum (Gibco, 12484028) and 1% penicillin/streptomycin (ThermoFisher Scientific,15140163). Cells were maintained at 37 °C with 5% CO_2. Transfection for transient expression was performed at 80% confluency using Lipofectamine 3000 Reagent (Invitrogen, L3000015) according to the manufacturer's instructions. Cells were analyzed after 48 hrs.

Immunostaining

For immunostaining, HeLa cells grown on coverslips were fixed with 4% PFA in PBS at room temperature for 15 min and permeabilized with 0.25% PBST (PBS containing 0.25% Triton X–100) at room temperature for 15 min. Cells were blocked in 5% normal goat serum for 1 hr at room temperature. The samples were incubated overnight at 4°C with primary antibodies: rabbit anti-HA-tag (1:500; Cell Signaling Technology, #3724) and mouse anti-FLAG-tag (1:500; Sigma, F9291). Cells were washed three times in PBS and blocked in 5% normal goat serum for 1 hr at room temperature. Alexa Fluor 488-anti-rabbit (1:200; Jackson Immuno Research, 115545174) and Cy3-anti-mouse (1:200; Jackson Immuno Research, 111165003) were used as the secondary antibodies. The samples were then stained with DAPI (1 µg/mL; Sigma, D9542) for 5 min at room temperature, washed, and mounted with Fluoromount aqueous mounting medium (Sigma, F4680).

Immunoprecipitation and western blotting

For immunoprecipitation, HEK293T cells were lysed in ice-cold IP buffer (Beyotime, P0013) with 1% protease inhibitor cocktail and phosphatase inhibitor cocktail (Bimake, B14001). Lysed cells were incubated at 4°C for 4 hrs and centrifuged at 12000 rpm for 20 min at 4°C. The clear supernatants were transferred to a new tube and incubated with HA antibody (Cell Signaling Technology, #3724)–conjugated beads (Bimake, B23201, 10 μl) at 4°C overnight. The beads were centrifuged and washed 5 times in TBST. Proteins associated with the beads were mixed with 32 μl 2x SDS lysis buffer and 8 μl 5x SDS loading buffer and boiled for 5 min at 95°C. Proteins were separated by SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membranes (Immobilon-P, IPVH00010). The membranes were incubated with primary antibodies (rabbit anti-HA-tag, 1:5000; Cell Signaling Technology, #3724 or mouse anti-FLAG-tag, 1:5000; Sigma, F9291) at 4°C overnight. On next day, the membranes were washed 3 times in TBST at room temperature, incubated with secondary antibodies (1:10000; Jackson Immuno Research, anti-mouse 115035146 or anti-rabbit 111035144) at room temperature for 1 hr. Protein bands were visualized using an ECL detection system (YEASEN, 36222ES60).

ROS measurement

Whole-animal ROS levels were measured using 2,7-dichlorofluorescein diacetate (DCFDA) (Sigma, D6883) following a previous method (Gruber et al., 2011) with modifications. Synchronized L4 larval animals were collected and washed with H_2O for three times. The population density was adjusted with H_2O to 50 to 200 animals per 100 µl. Two to three 100 µl aliquots were transferred to individual wells of a black-walled 96-well plate. DCFDA dissolved in DMSO was added to the wells at a final concentration of 50 µM. Animals were incubated at 20 °C for 30 min and measured for DCFDA fluorescence intensity using a fluorimeter (BioTek, Synergy 2) at the excitation wavelength of 485 nm and the emission wavelength of 528 nm at room temperature. After the measurement, animals in each well were emptied to an agar plate and counted.

For DCFDA signals of individual aniamls, synchronized L4 animals were resuspended in M9 after three washes in H_2O to a final volume of 95 µl. 5 µl 1 mM DCFDA solution was added to generate a final DCFDA concentration of 50 µM. Animals were incubated at 20 °C for 30 min, washed in M9 for three times, transferred to a glass slide and covered with a cover glass. GFP fluorescent pictures of multiple animals were taken immediately with the same exposure intervals. Whole animal fluorescence intensities of individual animals were measured with ImageJ (NIH).

Transcriptome analyses

~3,000 *csnk-1(lf)* mutants at the L4 larval stage (progeny of *csnk-1(lf)/hT2* hermaphrodite parents) were individually picked under a fluorescence microscope and washed three times with H_2O. In parallel, synchronized L4 wildtype animals were washed off plates and washed three times with H_2O. RNA was extracted using TRIzol (Invitrogen) and chloroform-isopropanol and treated with DNase I (NEB, M0303). RNA-Seq was performed by GENERGY Bio-TECHNOLOGY (Shanghai).

DESeq2 v1.6.3 was used for differential gene expression analysis between two samples with biological replicates under the theoretical basis obeying the hypothesis of negative binomial distribution for the value of count. DESeq2 estimates the expression level of each gene in each sample by the linear regression, then calculates the *p*-value with the Wald test. *p* value was corrected by the BH procedure. Genes with $p \leq 0.05$ and |log2_ratio| ≥ 0.58 (1.5 fold change) were identified as differentially expressed genes (DEGs).

According to the expression level of differentially expressed genes in each sample, the Euclidean distance was calculated with |log2_FPKM|, and the Hierarchical Cluster method was used to generate the heatmap.

The GO (Gene Ontology, http://geneontology.org/) enrichment of DEGs was implemented by the hypergeometric test, in which *p*-value is calculated and adjusted by FDR (False Discovery Rate), and data background is gene expression of the whole genome. GO terms with $p < 0.05$ were considered to be significantly enriched.

The KEGG (Kyoto Encyclopedia of Genes and Genomes, http://www.kegg.jp/) enrichment of DEGs was implemented by the hypergeometric test, in which *p*-value was adjusted by Benjamini and Hochberg multiple comparisons. KEGG terms with $p < 0.05$ were considered to be significantly enriched.

Phosphoproteomics analyses

Two biological replicates of synchronized wildtype controls and ~40,000 Individually picked *csnk-1(lf)* mutants at the L4 larval stage were grinded by liquid nitrogen into cell powder, sonicated (Scientz) in four volumes of lysis buffer (8 M urea, 1% Protease inhibitor cocktail) and centrifuged at 12,000 g at 4 °C for 10 min to remove debris. The supernatant protein concentration was determined with BCA kit according to the manufacturer's instructions.

Protein samples were digested with trypsin, desalted and labeled with TMT/iTRAQ kit (ThermoFisher Scientific, 90066), fractioned by HPLC, enriched with IMAC microspheres and subjected to tandem mass spectrometry (MS/MS) in Q ExactiveTM Plus (Thermo) coupled online to the UPLC. The resulting MS/MS data were processed using Maxquant search engine (v.1.5.2.8) against a *C. elegans* protein database (www.uniprot.org/taxonomy/6239). FDR was adjusted to < 1% and minimum score for modified peptides was set > 40.The cutoff change of phosphorylation level was set at 20%.

Proteins with altered phosphorylation in *csnk-1(lf)* mutants were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses using online tools (www.wormbase.org and biit.cs.ut.ee/gprofiler/).

Protein-protein association analyses were performed using an online tool as described (https://string-db.org/) (Szklarczyk et al., 2019).

Statistics

p values were determined by two-tailed unpaired Student's *t*-test for comparisons between two samples or log-rank test for survival curves. *p* values are explained in appropriate figures or tables.

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