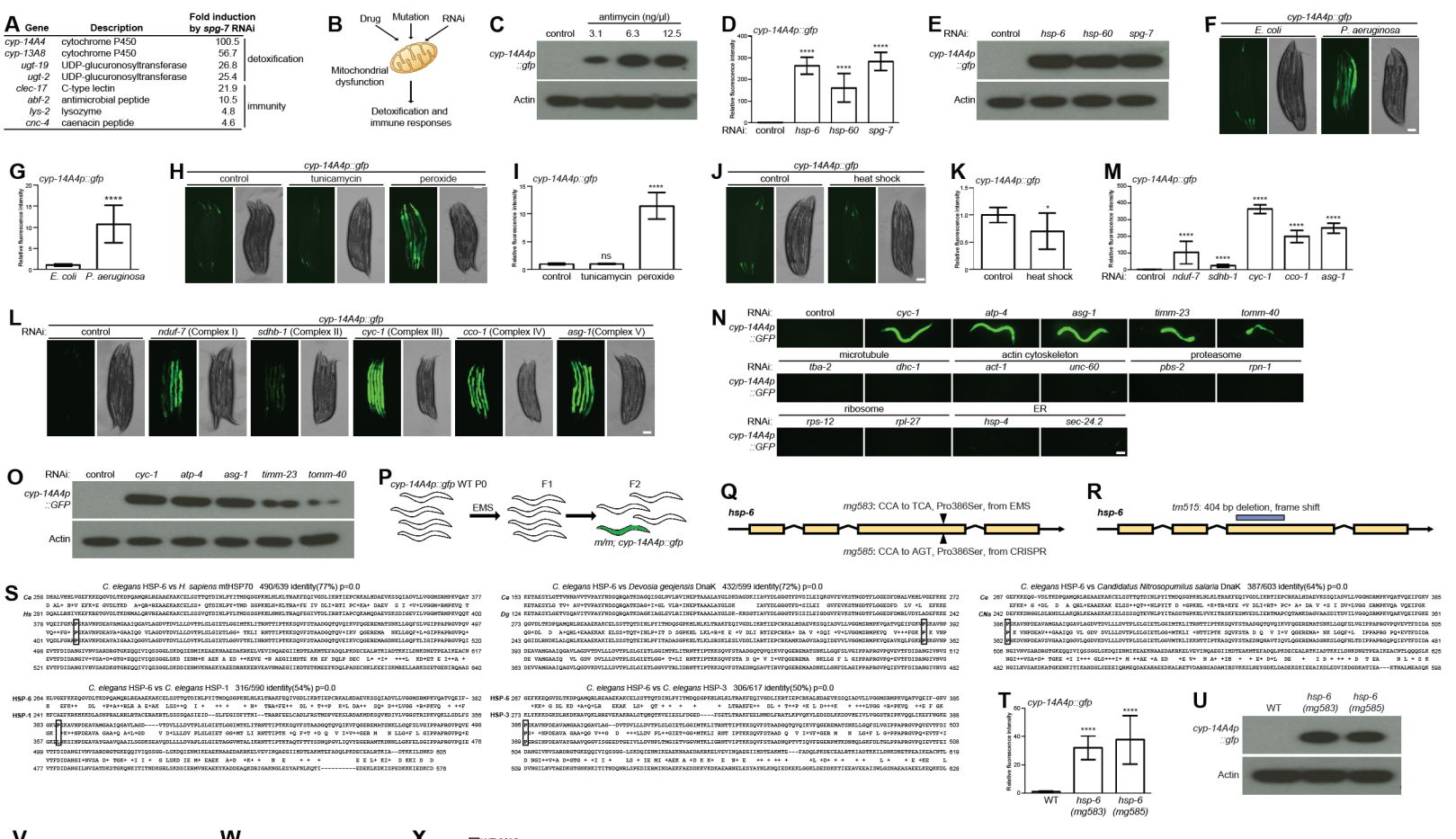


Figure S1. Mitochondrial dysfunction promotes xenobiotic response. Related to Figure 1.

(A) Genes involved in detoxification and immunity are induced by *spg-7* RNAi (Nargund et al., 2012).

(B) Model of mitochondrial surveillance and xenobiotic response.

(C) Animals were collected similar to those photographed in (Figure 1A) for western blot.

(D) Quantification of fluorescent intensities of animals shown in (Figure 1B); **** p<0.0001.

(E) Animals were collected similar to those photographed in (Figure 1B) for western blot.

(F-K) Animals carrying *cyp-14A4p::gfp* animals were challenged by *P. aeruginosa* (F and G), tunicamycin, hydrogen peroxide (H and I), and heat shock (J and K). Animals were photographed in (F, H and J), and the fluorescent intensities were quantified in (G, I and K). Scale bars, 100 µm. * p<0.05; **** p<0.0001; ns, not significant.

(L and M) *cyp-14A4p::gfp* animals feeding on control RNAi or RNAi of the subunits of mitochondrial electron transport chain at 20°C. Animals were photographed in (L), and the fluorescent intensities were quantified in (M). Scale bar, 100 µm. **** p<0.0001.

(N and O) *cyp-14A4p::gfp* animals feeding on control RNAi or RNAi of designated mitochondrial or other essential genes at 20°C. Animals were photographed in (N), and collected for western blot in (O). Scale bar, 100 µm.

(P) Strategy of genetic screen seeking mutants that activate *cyp-14A4p::gfp*.

(Q and R) Location and identities of *hsp-6* mutations used in the study.

(S) BLAST of *C. elegans* HSP-6 to other HSP70 family proteins.

(T) Quantification of fluorescent intensities of animals shown in (Figure 1C); **** p<0.0001.

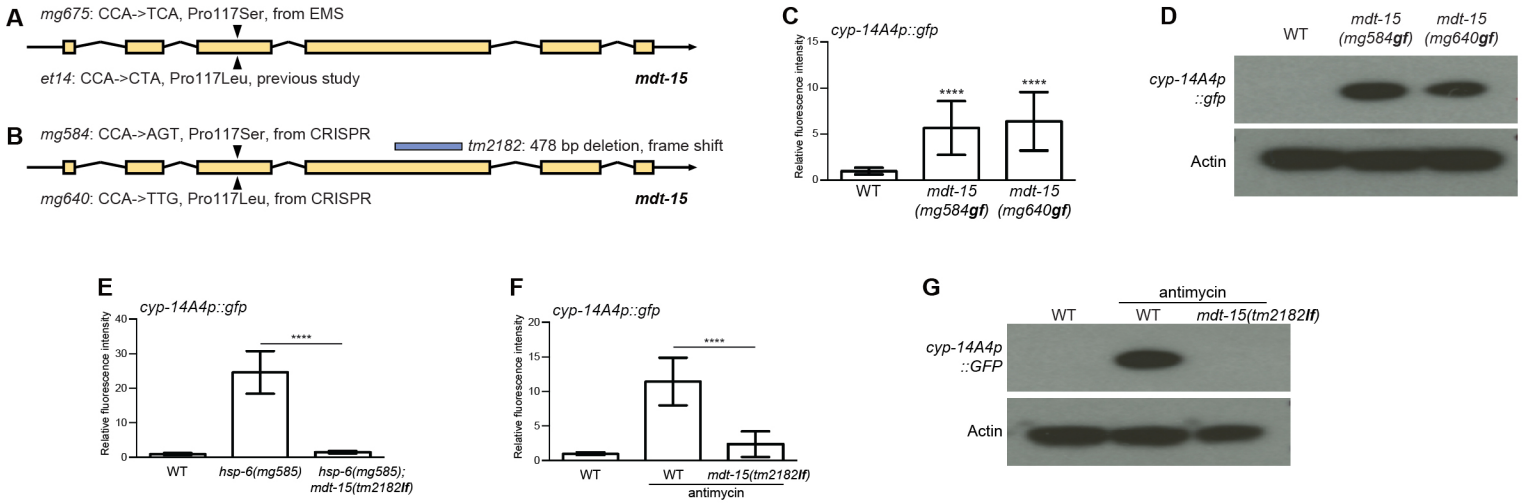
(U) Animals were collected from samples similar to those shown in (Figure 1C) for western blot.

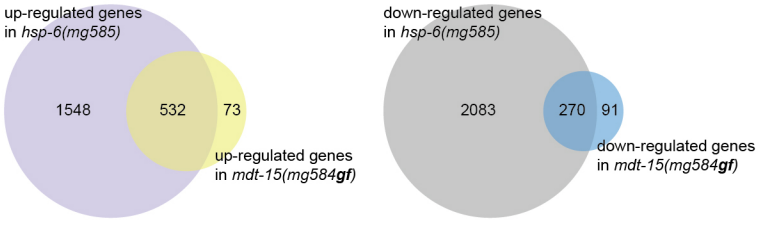
(V and W) Synchronized L1 larvae of wild-type and *hsp-6(mg585)* animals were grown at 20°C or 25°C. 2 days post L1 animals are shown in (V). Scale bar, 200 µm. Animals at each stage were counted in (W).

(X) The brood size of wild-type and hsp-6(mg585) animals.

(Y and Z) Comparison of the upregulated genes from *hsp-6(mg585)* mRNA-seq with previous *spg-7* RNAi microarray by Venn diagram and volcano analysis in (Y); and with previous *hsp-6* RNAi microarray by Venn diagram and volcano analysis in (Z).

nduf-7: mitochondrial complex I NADH dehydrogenase; *sdhb-1*: mitochondrial complex II succinate dehydrogenase; *cyc-1*: mitochondrial complex III cytochrome reductase; *cco-1*: mitochondrial complex IV cytochrome oxidase; *asg-1*: mitochondrial complex V ATP synthase; *atp-4*: mitochondrial complex V ATP synthase; *timm-23*: mitochondrial inner membrane translocase; *tomm-40*: mitochondrial outer membrane translocase; *tba-2*: alpha-tubulin; *dhc-1*: dynein heavy chain; *act-1*: actin; *unc-60*: actin depolymerizing factor/cofilin; *pbs-2*: proteasome beta subunit; *rpn-1*: 26S proteasome regulatory subunit; *rps-12*: ribosomal small subunit; *rpl-27*: ribosomal large subunit; *hsp-4*: Hsp70/grp78/BiP; *sec-24.2*: COPII SEC24B.





I

gene	hsp-6(mg585)	mdt-15(mg584gf)	gene description	
cyp-14A4	36.8	5.3	cytochrome P450 CYP2	
cyp-13B1	10.2	118.8	cytochrome P450 CYP3	detoxification
cyp-13A12	8.1	7.7	cytochrome P450 CYP3	
clec-180	18.5	3.2	C-type Lectin	
clec-265	8.6	3.1	C-type Lectin	immunity
clec-1	5.1	3.0	C-type Lectin	
hsp-6	2.2	1.1	mitochondrial DnaK/Hsp70	
dnj-10	2.7	1.1	mitochondrial DnaJ	mitochondrial quality contorl
dct-1	2.4	1.5	mitophagy receptor BNIP3	
fat-5	0.3	4.4	delta-9 fatty acid desaturase	
fat-7	0.2	9.8	delta-9 fatty acid desaturase	fat metabolism

fold induction

J

C. elegans MDT-15 vs *Ancylostoma ceylanicum* MED15 351/843 identity(42%) p=6e-135

```
Ce   1 MSEEDWPSPKFREHVIQRLEPELARNRQNAPNLPVPGDARQVEEYVFAKCMSKDEYMRTIAKVINAINCNSKSAAVPSVLQPSQFHSPPCTTPAALLGNTPAGGTPCYRAPVPPDPQPTSA 120
           M+++DWPS +FR+HVI RLEPELARNRQNAPNLPVPGDARQVEEYVF KC+SKDEYMRTIAKVINAINCNSKSAAVPSVLQPS FHSPPC+   +       T YR  VPPDPQPT
Ac   1 MADDDWPSQRFRDHVINRLEPELARNRQNAPNLPVPGDARQVEEYVFQKCLSKDEYMRTIAKVINAINCNSKSAAVPSVLQPS-FHSPPCSAPNVNNTNNTNSTTSYRTSVPPDPQPTQT 119

Ce 121 QARNPPVTVATTQASTTPSAPNPPGGLPAPSASATAAVAAAVASFPSPDTSIRPGCQITPGSQAPGGGPTPAPNVPFPNGSSQMNGGPAMGQPPPQM---GAP---NMGGPFNGYGGYGM 234
           + ++ P   +TTQ                    A     FPSPD S                GP P                G P +GQPPPQM   G P       P  G   Y M
Ac 120 RNQSQPTPSSTTQQ-----------------VPIQQQPPAPNQPGFPSPDQS---------------RGPPPT-------------YGAPPLGQPPPQMQPTGQPVPQQQMMPQGGCPPYQM 196

Ce 235 MNGPPGSGAPMGGNPYNQQIKKDMDQ---ARPWDPSAHMY---QQQ-----PQWGAMPPQQPHGYPGRPMNGQGATP--TGPSSVLESLINQPQQYP------GHHNQM---GPPGDRNVA 333
           M+             PY+ +++K   Q   +R WD     Y   QQQ    P +G  P  QQ          + QG  P  +G S+VLE+LINQP QYP      G H QM   GP
Ac 197 MSPQQSQQQQQLLPPYDARMQKQPKQEPLSRSWDAQGMHYPPPQQQWAPHPGYGQPPQQQQMPPHHSQQSQQGQQPPVSGQSTVLEALINQP-QYPSTPHQMGRHPQMMMSGPNAPMGAG 315

Ce 334 AQRAAAQQQQQQQQQQQQRPGMVPNQGMMSSEDQTVYSAKLRNMRGSCDSLRTRARQCRHEGNHEAAHKLEVMLSVLEGKRVVSLEYLNHLEMWIARKQDFL------NIAPMSQNQNHM 448
                Q  QQQ                        +Y+ KLR +R  C++L+ RA+QCR EGN EAA KLE ML VLEG+RVVSLEYL +LE WI +K DFL     N    +    HM
Ac 316 GHMGGPMDSQHDQQQ----------------------IYNQKLRMLRPYCENLKLRAQQCRMEGNMEAAQKLETMLGVLEGRRVVSLEYLLNLENWIHKKADFLAATTHNPHAAAMQNGHM 414

Ce 449 GM-NDPMMNGEHAMLGNGQVPNP---YGGHPGYGHQQYMGPPPPHMQMHQPPMWHQQ------QHQQQQRMMPQDHMMMQGGGGPVHGMYRGDMGHDPMTSPVNNHRHAPYPNPAAMRNNM 559
           GM    M++G +A+L      +P   YG   GY        PPP  Q   PPM  QQ     QH QQQ MM    M    GGGP+   YR         SPV +HR  PYP   +MR  M
Ac 415 GMAGQGMVDGINAVLNASSDHHPNSMYGAQTGYV--------PPPMHQGSYPPMHPQQMWPPPQHLQQQSMMMGPPMSQSQGGGPMQS-YR---------ESPVEHHR--PYP---SMRPQM 513

Ce 560 RMP-----NGPGPIGRDRNSMSGSSMSGPSSGAPSMNPMGTPNQKMGTP----------------GSMGGMSGLLDDL-NYDDFLPNPTPIDALQPTLHVGQNSMNAGPPVQRSNLNETARK 658
           R P       P P+   R   SG+SM    + AP+      P     TP                        G+DDL N DDFL  PTP++A      VG    N   P    +L + AR+
Ac 514 RPPPVVQSVPQPVDPLRMG-SGASMEPILNAAPAPVIPPRPTTSATTPVMTGSGNGGNGSAGSAGSAEQPGVDDLYNMDDFL--PTPMEA------VGNVQGNGNKP----SLPDAARR 620

Ce 659 ELQILDARFEIDPN-HQRHDANHIIVVCKIRNQQFPPLRLVVPTTYPAGNVTVDRAVIDLDAYLYDDLQNSVYERLSRPCLSSITDYLNAWEEQVNQYQNQTSGGLDVAFNVGNDFF--Y 775
           E   L  RFE D N    HD +  +V CKI+ QQ P LRLV+P +YPA +VTVDRA IDLDA+ YDDLQN V+ERL+RPCL SIT++LN WE  V QY +  +   +   + ++ F  Y
Ac 621 EFSQLSDRFEFDNNPESHHDPHCALVKCKIKGQQVPALRLVIPLSYPASSVTVDRAAIDLDAFFYDDLQNVVHERLARPCLHSITEFLNTWETTVRQYTSNQNNA-NTTISPFDELFQNY 739

Ce 776 DNL 778
           DN+
Ac 740 DNI 742
```

Musca domestica MED15 vs *Homo sapiens* MED15 117/281 identity(42%) p=6e-57

```
Md 465 PVNTPGQVTQNSPFNPQ------EDQLYREKYKQLTKYIEPLRRVVDKLRIGCNNNAENYKKMNKLLEILTNPSQRVPLETLLKCEKVLENT--DINSYSDHSFGKS--------SNPLMDV 570
           P+NTP  V  +S  +P       E+Q Y +K KQL+KYIEPLRR+++K+     +  ++  KM  LL+ILT+PS+R PL+TL KCE  LE    D+   +                PL+D
Hs 124 PLNTP---VNPSSVMSPAGSSQAEEQQYLDKLKQLSKYIEPLRRMINKID-KNEDRKKDLSKMKSLLDILTDPSKRCPLKTLQKCEIALEKLKNDMAVPTPPPPPVPPTKQQYLCQPLLDA 240

Md 571 INTTLQSPLANHTLYRTFRPSLELLFGTDIAAPPAKMPRPAEKPSKGDLEIPHVLQGEIARLDQKFKVSLDPAAQNNPKSIRLICCLDDKKLPCVPPVSINIPEDYPWSSPECSLIEHDY 690
           +   ++SP+ NH+LYRTF P++  + G  I AP     R           IP VLQGE+ARLD KF V+LDP+  +N  ++ LIC LDDK LP VPP+ +++P DYP  SP      +  Y
Hs 241 VLANIRSPVFNHSLYRTFVPAMTAIHGPPITAP-VVCTRKRRLEDDERQSIPSVLQGEVARLDPKFLVNLDPSHCSNNGTVHLICKLDDKDLPSVPPLELSVPADYPAQSPLWIDRQWQY 359

Md 691 SATPFLKAVQNALVARIAKLPKLHSLSHLLDTWEMSVRQAC 731
           A PFL++V   + +R+ +LP  HS++ LL+TW  SV QAC
Hs 360 DANPFLQSVHRCMTSRLLQLPDKHSVTALLNTWAQSVHQAC 400
```

Loa loa MED15 vs *Homo sapiens* MED15 28/107 identity(26%) p=1.2

```
Ll 582 LPEAVRQELLAFGDRFLVDPNVEQVADSHSVTIKFSLTSHN---VPPLLLIIPKTYPNGEVLVGRAALDLDSF-FFDDLQNVIHERLA-LPGLRTVTDFLETWESTV 683
           +P  ++ E+     +FLV+ +     +++ +V +   L   +   VPPL L +P  YP    L        D+  F   +   +  RL  LP   +VT  L TW  +V
Hs 653 IPSVLQGEVARLDPKFLVNLDPSHCSNNGTVHLICKLDDKDLPSVPPLELSVPADYPAQSPLWIDRQWQYDANPFLQSVHRCMTSRLLQLPDKHSVTALLNTWAQSV 759
```

C. elegans MDT-15 vs *Wuchereria bancrofti* MED15 73/87 identity(84%) p=2e-37

```
Ce 1 MSEEDWPSPKFREHVIQRLEPELARNRQNAPNLPVPGDARQVEEYVFAKCMSKDEYMRTIAKVINAINCNSKSAAVPSVLQPSQFHS 87
           M ++DWPS +FR+HVI  RLEPELARNRQNAPNLPVPGDARQVEEYVF KC+SKDEYMRTIAKVINAINCNSKS+AVPS LQPS+   S
Wb 1 MGDDDWPSQRFRDHVINRLEPELARNRQNAPNLPVPGDARQVEEYVFNKCVSKDEYMRTIAKVINAINCNSKSSAVPSFLQPSRIQS 87
```

C. elegans MDT-15 vs *Musca domestica* MED15 21/61 identity(36%) p=0.077

```
Ce 4 EDWPSPKFREHVIQRLEPELARNRQNAPNLPVPGDARQVEEYVFAKCMSKDEYMRTIAKVI 64
        EDW SPKFR++VI ++E      ++          +A  +E ++F+K  S+DEY+  +AK+
Md 3 EDWQSPKFRQNVINKIEMMQITTQEGK--------NASFMENHIFSKSKSQDEYLGLVAKLF 58
```

C. elegans MDT-15 vs *Drosophila melanogaster* MED15 22/61 identity(36%) p=0.011

```
Ce 4 EDWPSPKFREHVIQRLEPELARNRQNAPNLPVPGDARQVEEYVFAKCMSKDEYMRTIAKVI 64
        EDW S KFR++VI ++   L  + Q+       +A  +E ++F K  SKDEY+  +AK+
Dm 3 EDWQSSKFRQNVISKIHDLLPPHAQDQTK-----NASVMENHIFRKSRSKDEYLGLVAKLF 58
```

Figure S2. MDT-15 couples mitochondrial surveillance to detoxification and immunity responses. Related to Figure 2.

(A and B) Locations of *mdt-15* mutations used in this study.

(C) Quantification of fluorescent intensities of animals shown in (Figure 2A); **** p<0.0001.

(D) Animals were collected from samples similar to those shown in (Figure 2A) for western blot.

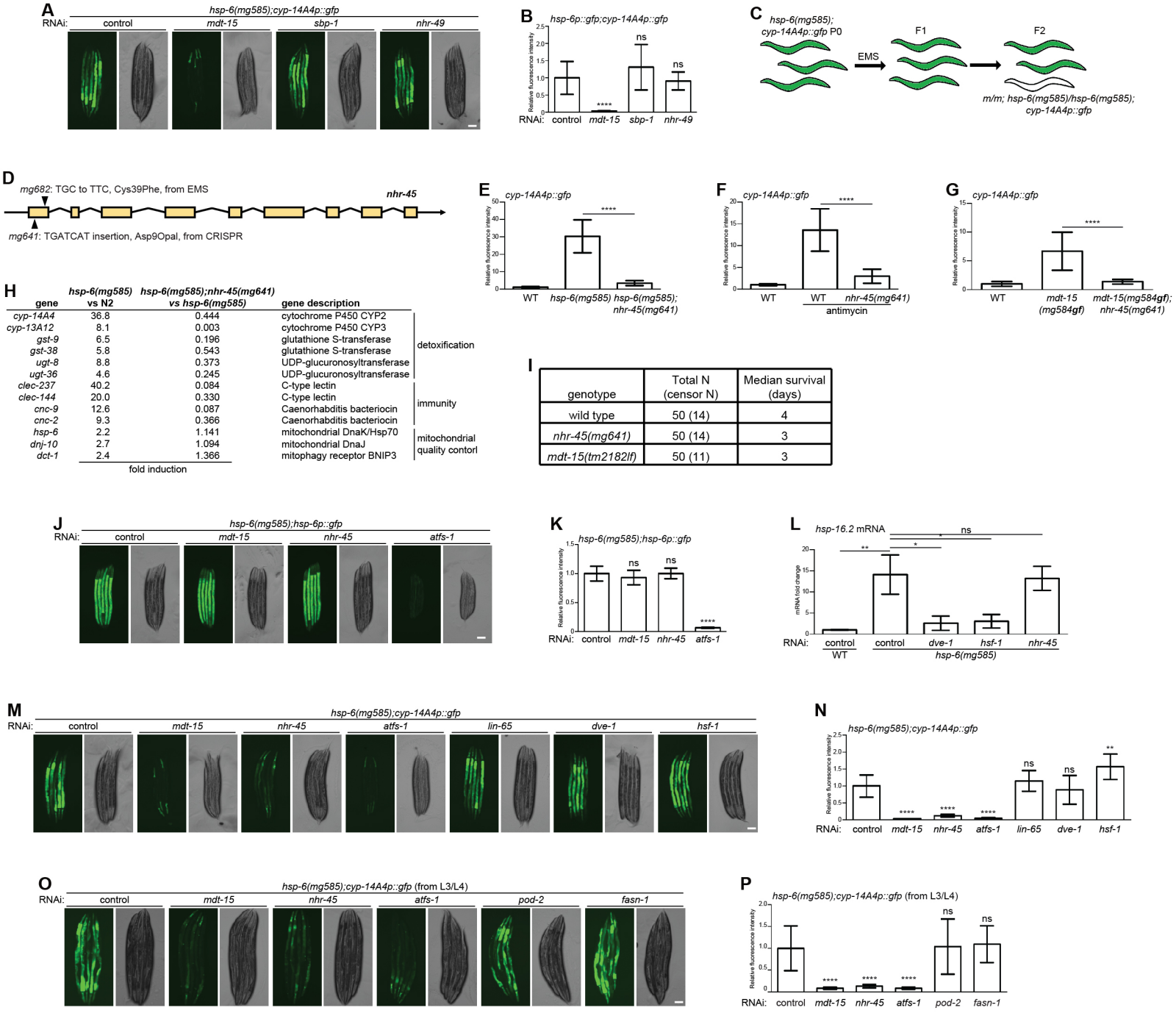
(E and F) Quantification of fluorescent intensities of animals shown in (Figure 2B and 2C); **** p<0.0001.

(G) Animals were collected from samples similar to those shown in (Figure 2C) for western blot.

(H) Diagram of overlapped upregulated (left) and downregulated (right) genes of *hsp-6(mg585)* and *mdt-15(mg584gf)*.

(I) Representative genes that are regulated by *hsp-6(mg585)* and *mdt-15(mg584gf)* mutants.

(J) BLAST of C. elegans MDT-15 to the orthologs in other organisms.



H

gene	hsp-6(mg585) vs N2	hsp-6(mg585);nhr-45(mg641) vs hsp-6(mg585)	gene description	
cyp-14A4	36.8	0.444	cytochrome P450 CYP2	
cyp-13A12	8.1	0.003	cytochrome P450 CYP3	
gst-9	6.5	0.196	glutathione S-transferase	detoxification
gst-38	5.8	0.543	glutathione S-transferase	
ugt-8	8.8	0.373	UDP-glucuronosyltransferase	
ugt-36	4.6	0.245	UDP-glucuronosyltransferase	
clec-237	40.2	0.084	C-type lectin	
clec-144	20.0	0.330	C-type lectin	immunity
cnc-9	12.6	0.087	Caenorhabditis bacteriocin	
cnc-2	9.3	0.366	Caenorhabditis bacteriocin	
hsp-6	2.2	1.141	mitochondrial DnaK/Hsp70	
dnj-10	2.7	1.094	mitochondrial DnaJ	mitochondrial quality contorl
dct-1	2.4	1.366	mitophagy receptor BNIP3	
	fold induction			

I

genotype	Total N (censor N)	Median survival (days)
wild type	50 (14)	4
nhr-45(mg641)	50 (14)	3
mdt-15(tm2182lf)	50 (11)	3

Figure S3. MDT-15 and NHR-45 regulate xenobiotic responses to mitochondrial dysfunction. Related to Figure 3.

(A and B) Synchronized L1 larvae of *hsp-6(mg585);cyp-14A4p::gfp* animals were grown with control RNAi or RNAi of indicated genes at 20°C for three days. Animals were photographed in (A), and the fluorescent intensities were quantified in (B). Scale bar, 100 μm.

(C) Strategy of genetic screen seeking mutants that abolished the activation of *cyp-14A4p::gfp* in *hsp-6(mg585)* genetic background.

(D) Information of *nhr-45* mutants.

(E-G) Quantification of fluorescent intensities of animals shown in (Figure 3A-3C); **** p<0.0001.

(H) Representative genes that are regulated by *nhr-45*.

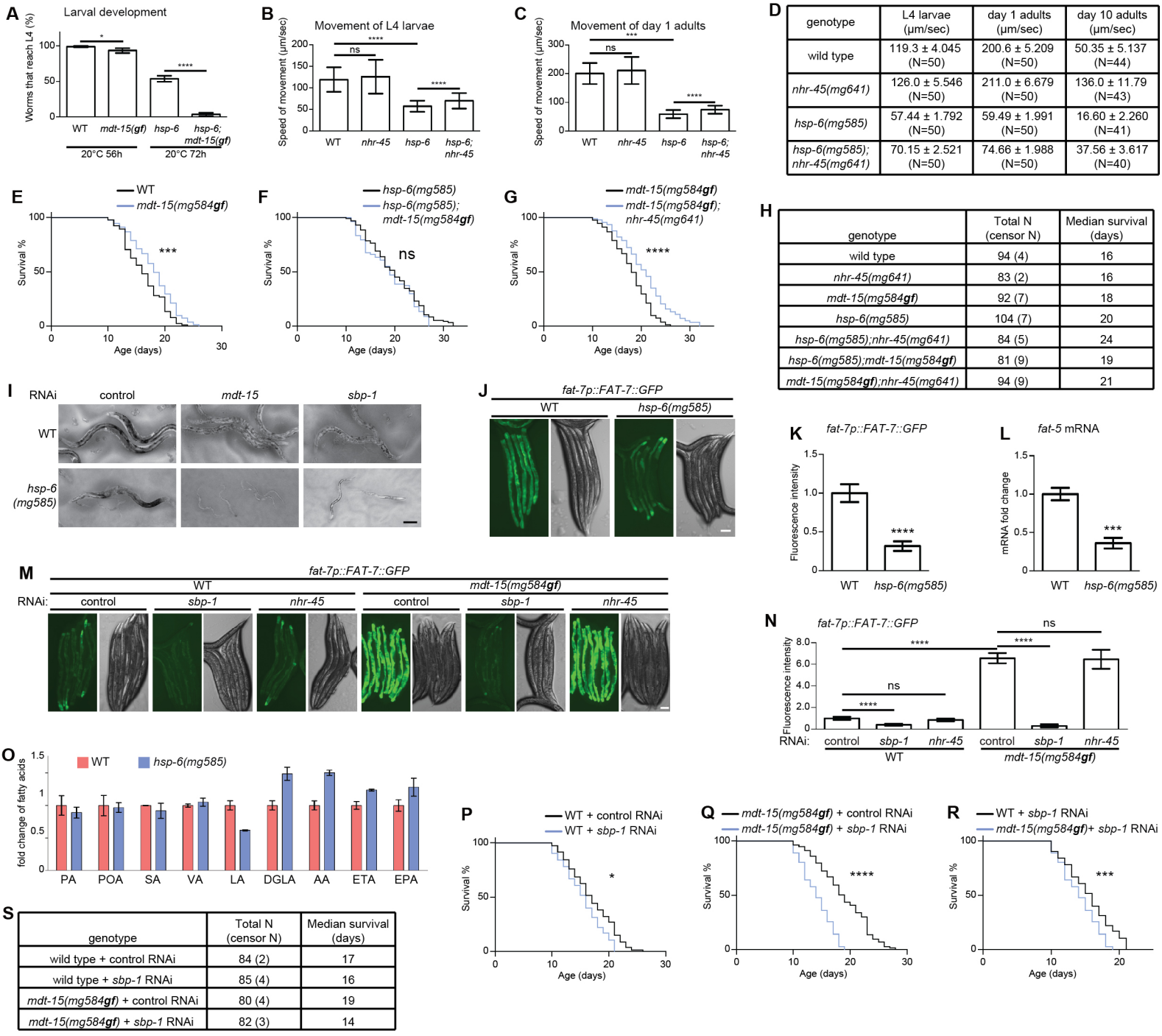
(I) Survival analysis of wild-type, *mdt-15(tm2182lf)*, and *nhr-45(mg641)* on *P. aeruginosa* PA14 strain.

(J and K) Synchronized L1 larvae of *hsp-6(mg585);hsp-6p::gfp* animals were grown with control RNAi or RNAi of indicated genes at 20°C for three days. Animals were photographed in (J), and the fluorescent intensities were quantified in (K). Scale bar, 100 μm. **** p<0.0001; ns, not significant.

(L) Synchronized L1 larvae of wild-type and *hsp-6(mg585)* animals were grown with control RNAi or RNAi of indicated genes at 20°C for two days until L4 larval stage. Animals were collected and analyzed by RT-qPCR toward *hsp-16.2* with *act-1* as control. * p<0.05; ** p<0.01; ns, not significant.

(M and N) Synchronized L1 larvae of *hsp-6(mg585);cyp-14A4p::gfp* animals were grown with control RNAi or RNAi of indicated genes at 20°C for three days. Animals were photographed in (M), and the fluorescent intensities were quantified in (N). Scale bar, 100 μm. ** p<0.01; **** p<0.0001; ns, not significant.

(O and P) Synchronized L1 larvae of *hsp-6(mg585);cyp-14A4p::gfp* animals were grown 20°C for two days until L3/L4 larval stage and then transferred to control RNAi or RNAi of indicated genes at 20°C for another three days. Animals were photographed in (O), and the fluorescent intensities were quantified in (P). Scale bar, 100 μm. **** p<0.0001; ns, not significant.



genotype	L4 larvae (μm/sec)	day 1 adults (μm/sec)	day 10 adults (μm/sec)
wild type	119.3 ± 4.045 (N=50)	200.6 ± 5.209 (N=50)	50.35 ± 5.137 (N=44)
nhr-45(mg641)	126.0 ± 5.546 (N=50)	211.0 ± 6.679 (N=50)	136.0 ± 11.79 (N=43)
hsp-6(mg585)	57.44 ± 1.792 (N=50)	59.49 ± 1.991 (N=50)	16.60 ± 2.260 (N=41)
hsp-6(mg585); nhr-45(mg641)	70.15 ± 2.521 (N=50)	74.66 ± 1.988 (N=50)	37.56 ± 3.617 (N=40)

genotype	Total N (censor N)	Median survival (days)
wild type	94 (4)	16
nhr-45(mg641)	83 (2)	16
*mdt-15(mg584**gf**)*	92 (7)	18
hsp-6(mg585)	104 (7)	20
hsp-6(mg585);nhr-45(mg641)	84 (5)	24
*hsp-6(mg585);mdt-15(mg584**gf**)*	81 (9)	19
*mdt-15(mg584**gf**);nhr-45(mg641)*	94 (9)	21

genotype	Total N (censor N)	Median survival (days)
wild type + control RNAi	84 (2)	17
wild type + *sbp-1* RNAi	85 (4)	16
*mdt-15(mg584**gf**)* + control RNAi	80 (4)	19
*mdt-15(mg584**gf**)* + *sbp-1* RNAi	82 (3)	14

Figure S4. Dissection of detoxification response and fat metabolism in *mdt-15(mg584gf)* mutant. Related to Figure 4.

(A) Egg laying was performed to adult animals of indicated genetic background at 20°C for 1 h. After removal of the mothers, eggs were grown at 20°C for 56 h or 72 h. Worms that reach L4 larval stage were counted. * p<0.05; **** p<0.0001.

(B-D) The movements of L4 larvae (B) and day 1 adults (C) of indicated genetic background were estimated, and the detailed information was listed in (D). *** p<0.001; **** p<0.0001; ns, not significant.

(E-H) Life span analysis of animals of indicated genetic background. *** p<0.001; **** p<0.0001; ns, not significant.

(I) Synchronized L1 larvae of wild-type and *hsp-6(mg585)* animals were grown with control RNAi, *mdt-15* RNAi, or *sbp-1* RNAi at 25°C for 56 h or 80 h. Scale bar, 100 μm.

(J and K) Day 1 adult of wild-type and *hsp-6(mg585)* animals harboring nIs590[*fat-7p::fat-7::GFP*] transgene were photographed (J) and fluorescent intensities were quantified (K). Scale bar, 100 μm. **** p<0.0001.

(L) L4 larvae of wild-type and *hsp-6(mg585)* animals were analyzed by RT-qPCR toward *fat-5* with *act-1* as control. *** p<0.001.

(M and N) Synchronized L1 larvae of wild-type and *mdt-15(mg584gf)* animals harboring nIs590[*fat-7p::fat-7::GFP*] transgene were treated with control RNAi or RNAi of *sbp-1* or *nhr-45* at 20°C for 3 days. The worms were photographed (M) and fluorescent intensities were quantified (N). Scale bar, 100 μm. **** p<0.0001; ns, not significant.

(O) Fatty acids analysis of wild-type and *hsp-6(mg585)* L4 stage animals by gas chromatography. PA: palmitic acid; POA: palmitoleic acid; SA: stearic acid; VA: vaccenic acid; LA: linoleic acid; DGLA: dihomo-γ-linolenic acid; AA: arachidonic acid; ETA: eicosatetraenoic acid; EPA: eicosapentaenoic acid.

(P-S) Life span analysis of wild-type and *mdt-15(mg584gf)* animals with control RNAi or *sbp-1* RNAi. * p<0.05; **** p<0.0001.

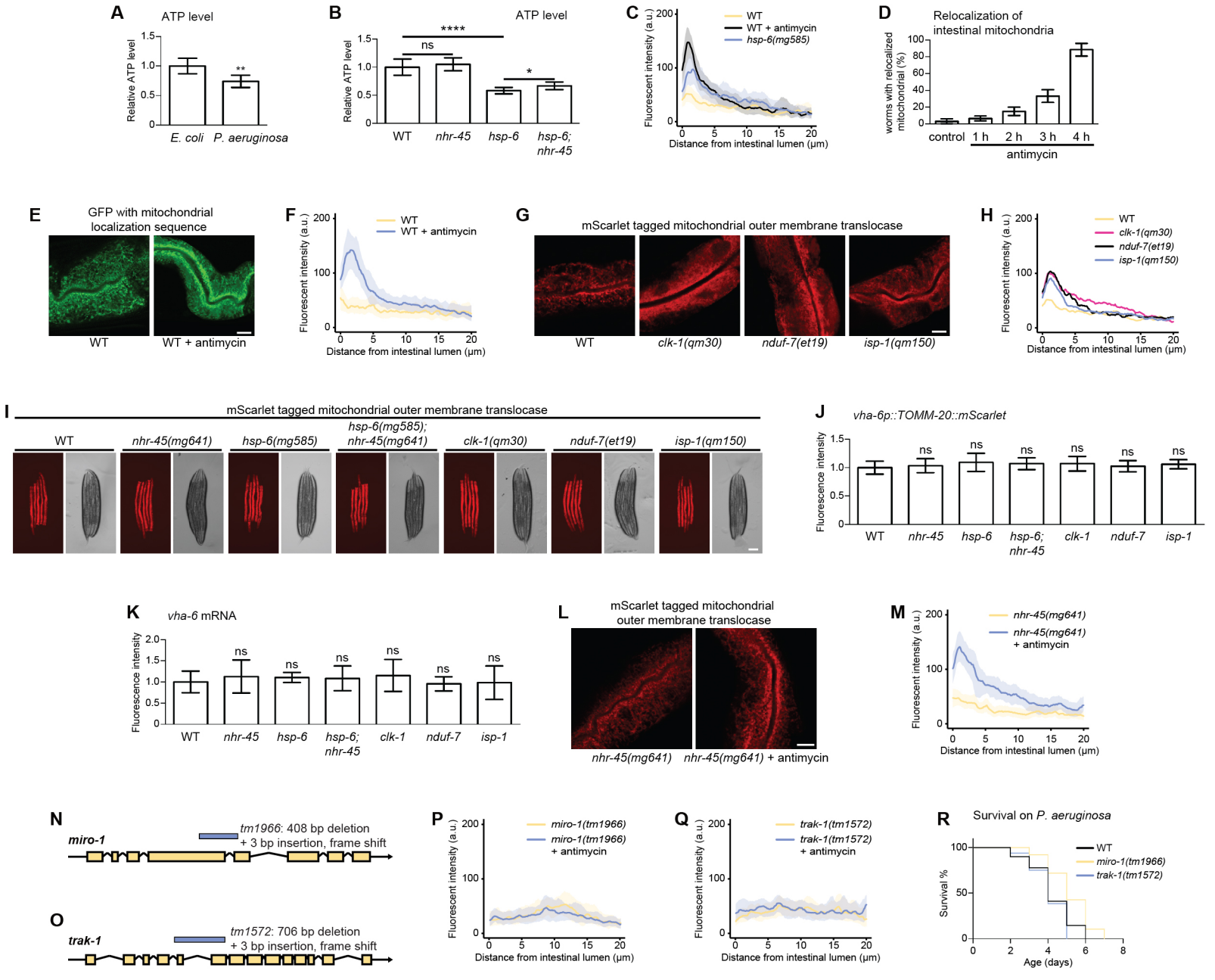


Figure S5. Mitochondrial dysfunction causes the redistribution of mitochondria in intestinal cells. Related to Figure 5.

(A) Synchronized wild-type L1 larvae were grown on *E. coli* OP50 or *P. aeruginosa* PA14 at 25°C until L4 larval stage. Worms were collected for determination of ATP level. ** p<0.01.

(B) L4 larvae of indicated genetic background were collected for determination of ATP level. * p<0.05; **** p<0.0001; ns, not significant.

(C) The fluorescent intensities of animals shown in (Figure 5B) was analyzed. The shading area indicates standard error.

(D) Wild-type L4 larvae were treated with antimycin, and the percentage of worms with relocalized intestinal mitochondria was calculated.

(E-H) Animals of indicated genetic background with zcIs17[*ges-1p::GFP(mit)*] in (E and F), and mgTi33[*vha-6p::tomm-20(1-54)::mScarlet*] transgene in (G and H) were grown with or without antimycin. Day one adults were photographed in (E and G). Scale bars, 10 μm. The fluorescent intensity was analyzed by Fiji-ImageJ, and five different lines were drawn in each animal from three individuals in (F and H). The shaded area indicates standard error in (F), and was hidden in (H) for display of the data clearly.

(I and J) L4 larvae with indicated genetic background were pictured in (I), and the fluorescent intensities were quantified in (J). ns, not significant.

(K) L4 larvae of indicated genetic background were collected and analyzed by RT-qPCR toward *vha-6* with *act-1* as control. ns, not significant.

(L and M) Day one adults of *nhr-45(mg641)* animals with mgTi33[*vha-6p::tomm-20(1-54)::mScarlet*] transgene were photographed. Antimycin treatment was performed at L4 larvae. Scale bars, 10 μm.

(N and O) Information of *miro-1* and *trak-1* mutants.

(P and Q) The fluorescent intensities of (Figure 5C) were analyzed. The shading area indicates standard error.

(R) Survival analysis of wild-type, *miro-1(tm1966)*, and *trak-1(tm1572)* animals on *P. aeruginosa* PA14 strain.