Supporting Information

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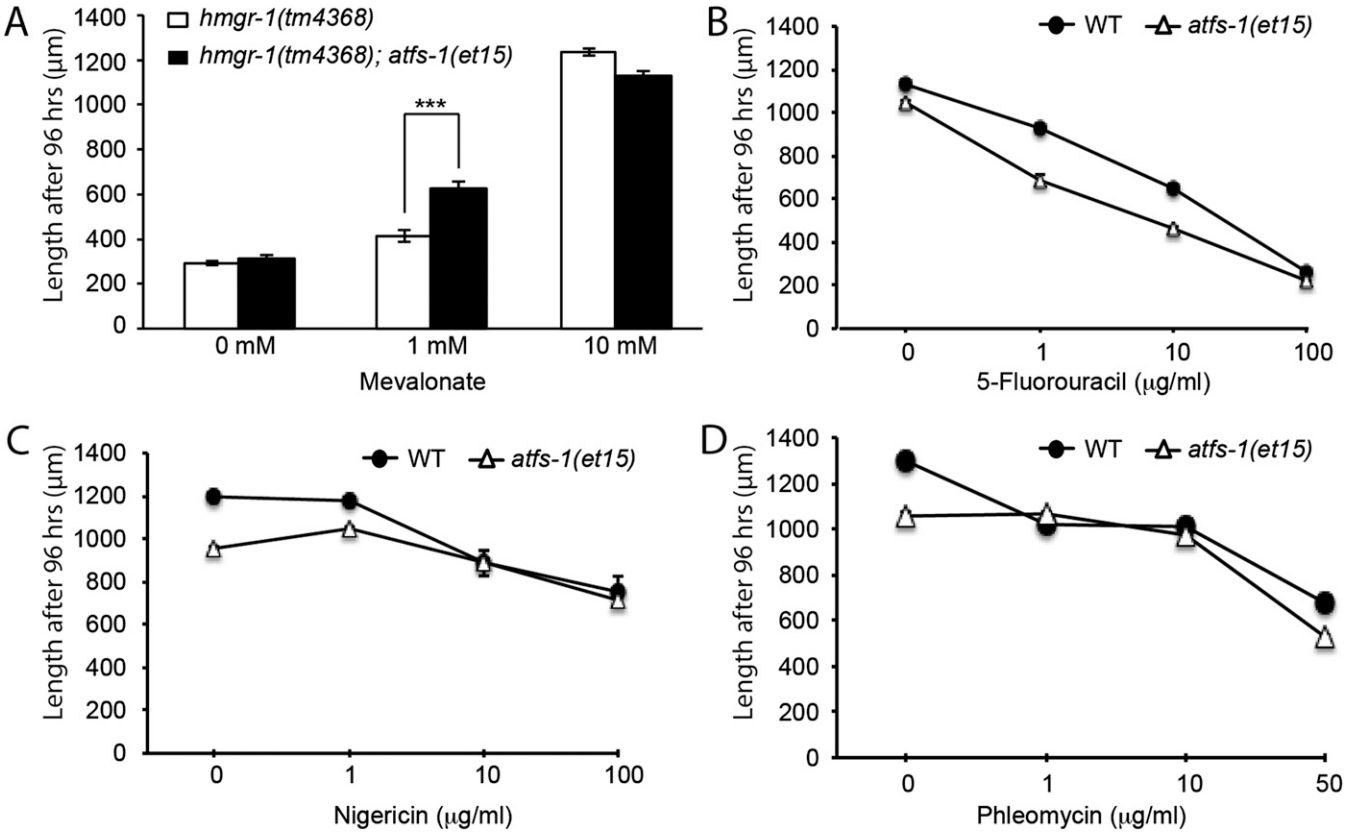

Fig. S1. The *atfs-1(et15)* allele partially rescues a *hmgr-1* null mutant and does not confer general xenobiotic resistance. (*A*) Presence of the *atfs-1(et15)* gain-of-function (*gof*) allele allows the *hmgr-1(tm4368)* mutant to grow significantly better when small, limiting amounts of mevalonate (1 mM) are provided. No such improvements are seen in the complete absence of mevalonate (0 mM) or when plentiful mevalonate (10 mM) is provided. (*B–D*) The *atfs-1(et15) gof* mutant does not confer resistance to three tested growth inhibitors.

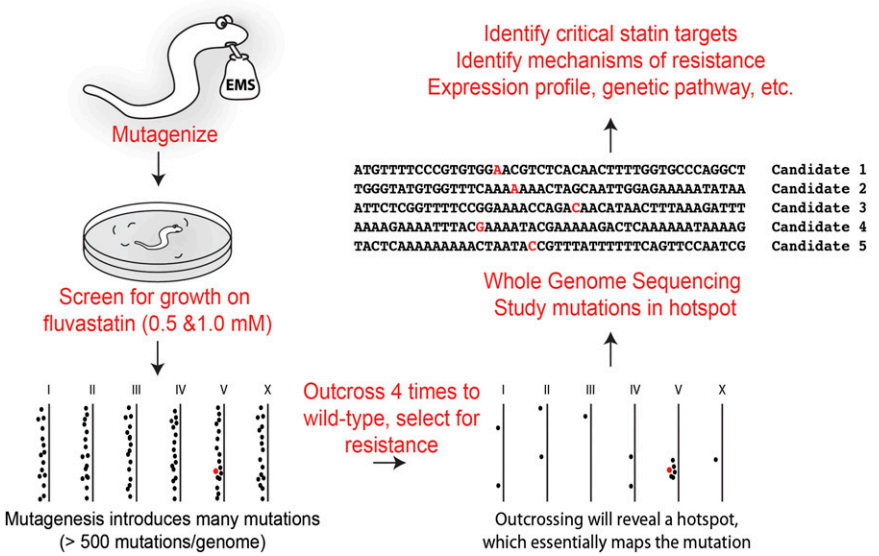

Fig. S2. Overview of the strategy to isolate and identify mutations that confer fluvastatin resistance in *Caenorhabditis elegans*.

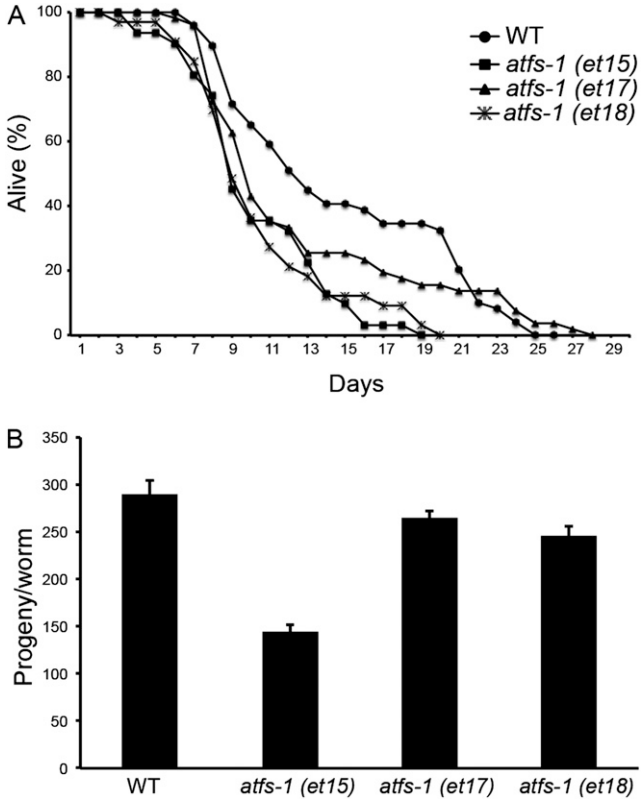

Fig. S3. The statin-resistant mutants are less healthy than wild-type worms. (*A*) The *atfs-1(gof)* mutants have reduced life span compared with wild-type worms. Mean life spans in days were: wild type (15.68 ± 0.85), *et15* (11.35 ± 0.64), *et17* (13.44 ± 0.82), and *et18* (12.62 ± 0.67). (*B*) The brood size of the *atfs-1 (gof)* mutants is smaller than for wild-type worms.

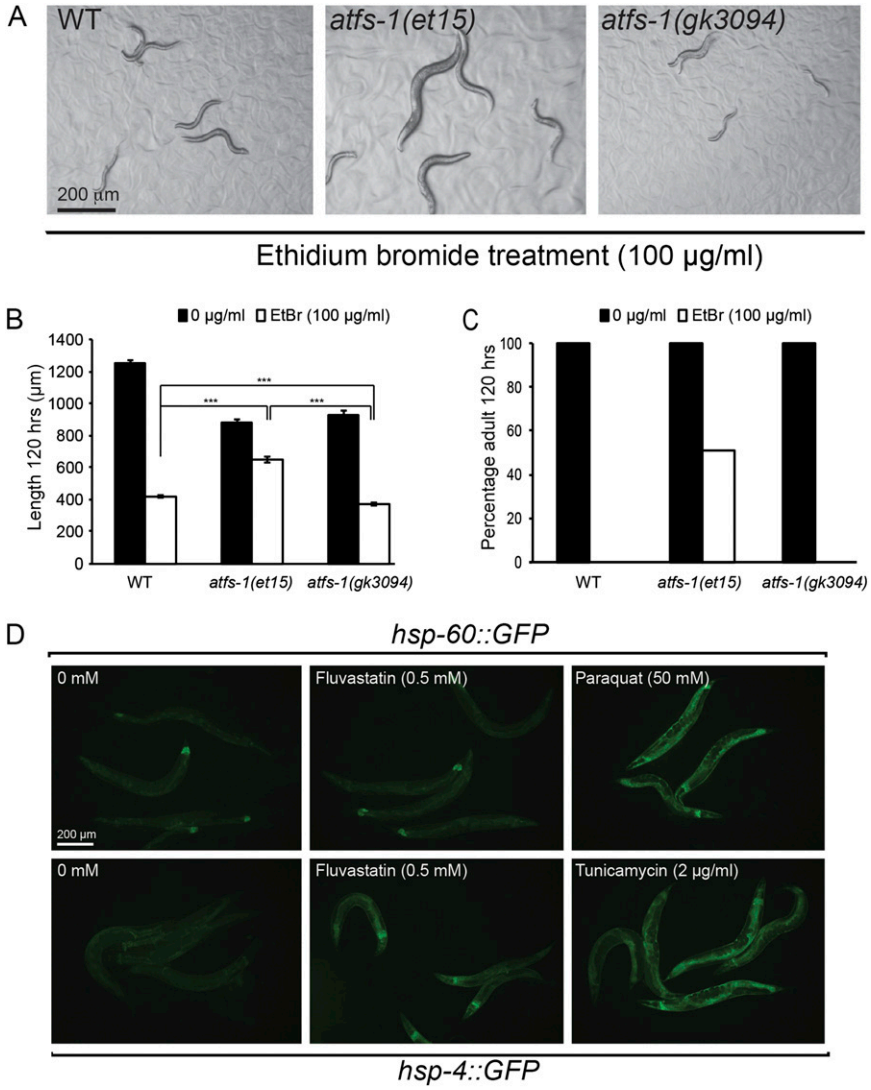

Fig. S4. The *atfs-1(et15) gof* allele confers resistance to ethidium bromide and fluvastatin does not induce the mitochondrial unfolded protein response (UPR^{mt}). (*A*) Images of worms with the indicated genotypes grown on 100 μg/mL ethidium bromide for 120 h after hatching. Note that the *atfs-1(et15)* grows best, whereas the *atfs-1(gk3094)* grows most poorly. (*B*) Average length of worms treated as in *A*. (*C*) Percentage of worms that reach adulthood when treated as in *A*. Adulthood was determined by scoring for the presence of an everted vulva. (*D*, *Upper*) Fluvastatin does not induce expression of the UPR^{mt} reporter *hsp-60::gfp*; paraquat was used as a positive control and efficiently induced this reporter. (*Lower*) fluvastatin induces the endoplasmic reticulum unfolded protein response (UPR^{er}) reporter *hsp-4::gfp*, as does the potent inducer tunicamycin. Error bars show SEM; $***P < 0.001$.

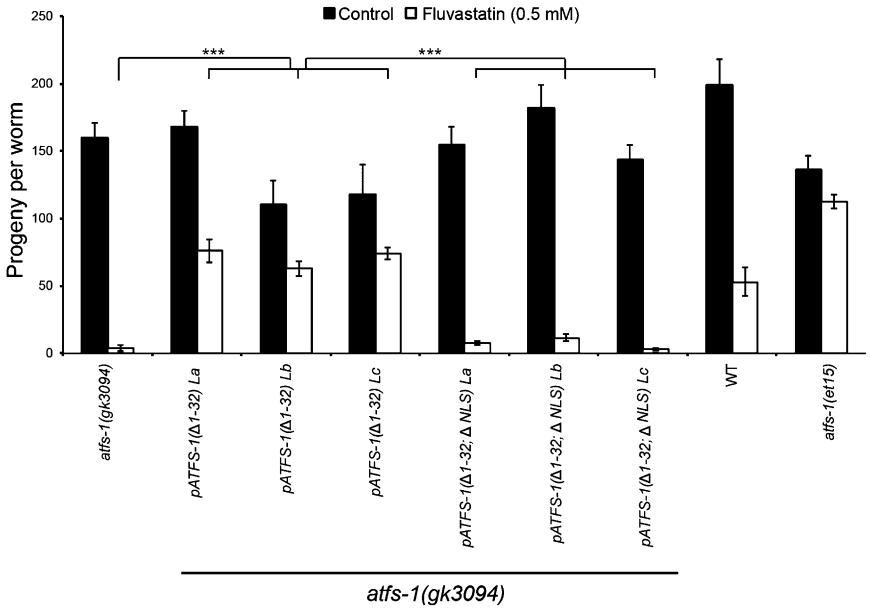

Fig. S5. The nuclear localization signal (NLS) of ATFS-1 is required to confer statin resistance. The *atfs-1(gk3094)* null mutant lays almost no progeny when L4s are transferred to 0.5-mM fluvastatin plates but have total brood sizes of well over 50 eggs per worm in three separate lines that carry an *atfs-1* transgene lacking the mitochondrial targeting signal (MTS), *pATFS-1(Δ1–32)*. A transgene that lacks both the MTS and the NLS of ATFS-1, *pATFS-1(Δ1–32 ΔNLS)* shows little or no statin resistance. Wild-type and *atfs-1(et15)* brood sizes are provided as reference. Error bars show the SEM; ***$P < 0.001$.

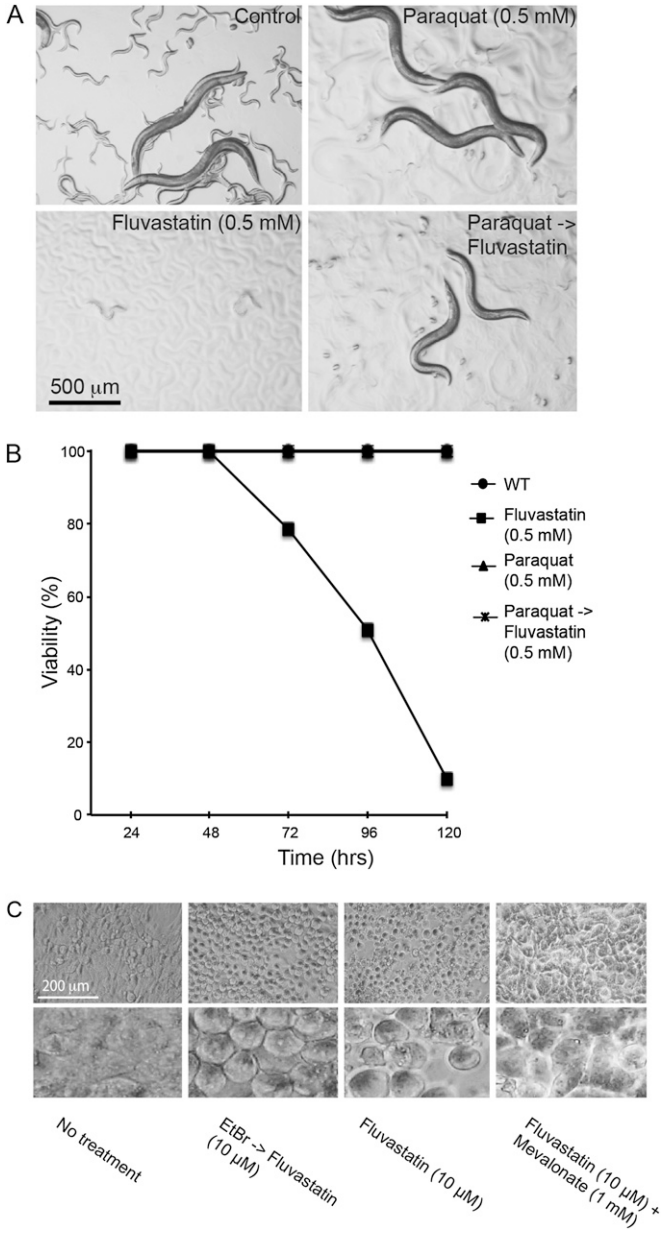

Fig. S6. Preinduction of the UPR^{mt} protects *C. elegans* and mammalian cells from the effects of statins. (*A*) Worms pretreated with paraquat are able to reach adulthood and reproduce, whereas worms placed directly on fluvastatin arrest as small larvae. (*B*) Paraquat pretreatment protects *C. elegans* from the lethal effects of statins. (*C*) NIH 3T3 cells pretreated with ethidium bromide show better cell morphology and adhesion when subsequently cultured in the presence of 10 μM fluvastatin. The deleterious effects of statins on NIH 3T3 are on-target effects because they can be abrogated by including 1 mM mevalonate in the culture medium.

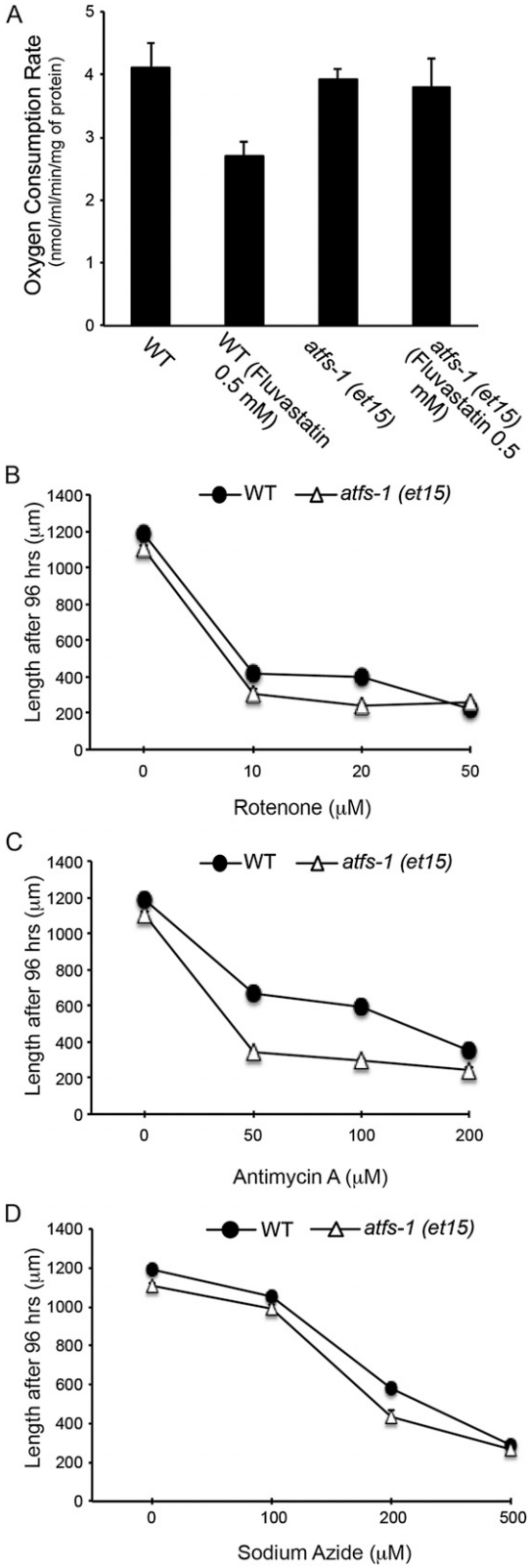

Fig. S7. The *atfs-1(et15)* allele confers resistance to the respiration inhibitory effects of fluvastatin (*A*), but not to the growth inhibitory effects of three respiratory chain inhibitors (*B–D*).

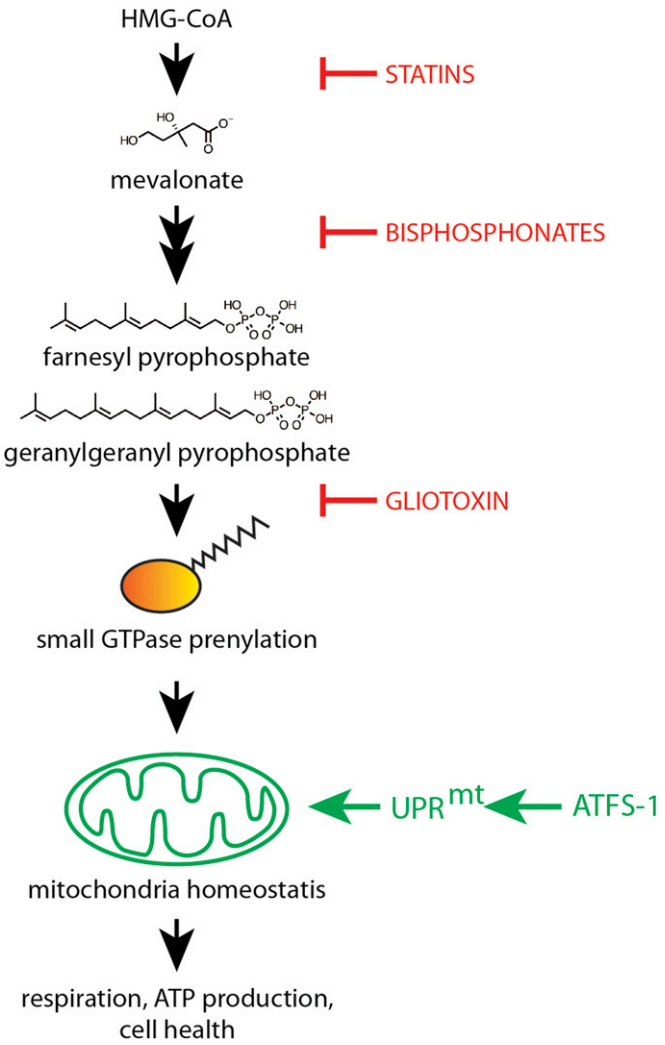

Fig. S8. Model illustrating the effects of statins on mitochondria and the protective induction of UPR^{mt} by ATFS-1. Inhibition of the mevalonate pathway with statins or bisphosphonates, or of the prenylation subbranch with gliotoxin, interferes with small GTPase(s) important for mitochondria homeostasis but without causing the type of defects that would lead to strong UPR^{mt} activation. Activation of ATFS-1, for example through gain-of-function mutations, causes UPR^{mt} activation that maintains mitochondria function despite diminished output from the mevalonate pathway, leading to improved cell health and better utilization of the residual mevalonate pathway output.