Supplemental Inventory

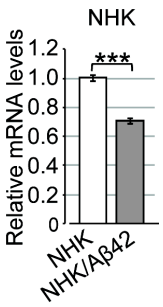

Figure S1. Co-expression of Aβ42 does not increase mRNA levels of null Hong Kong α-1 antitrypsin (NHK) transgene, Related to Figure 1

mRNA levels of NHK in heads of flies expressing NHK alone (NHK) or co-expressing NHK and Aβ42 (NHK/Aβ42) in neurons were analyzed by qRT-PCR. Data are presented as means ± SEM, n = 4, $^{***}p <$ 0.001 by Student's *t*-test. The flies used in these experiments were 7 days old. The genotypes of the flies were: (NHK): elav-GAL4/Y; UAS-NHK/CyO and (NHK/Aβ42): elav-GAL4/Y; UAS-NHK/UAS-Aβ42.

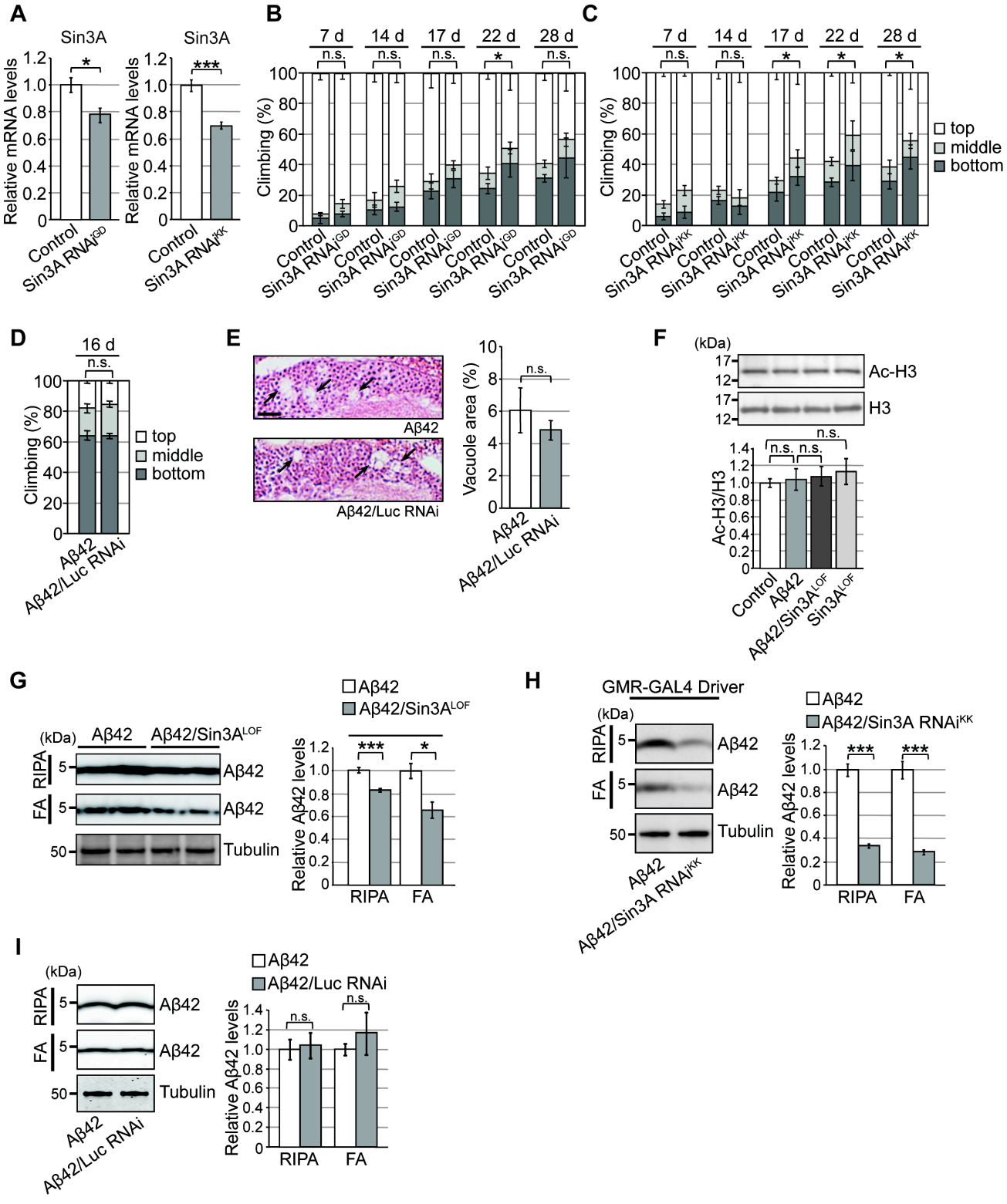

Figure S2. Neuronal knockdown of Sin3A protects against chronic ER proteinopathy in Aβ42 fly brains, Related to Figure 2

(**A**) mRNA levels of Sin3A in heads of flies carrying the elav-GAL4 driver (Control) or carrying both the elav-GAL4 driver and UAS-Sin3A RNAi (Sin3A RNAi^{GD} and Sin3A RNAi^{KK}) were analyzed by qRT-PCR. Data are presented as means ± SEM, n = 4, $^{*}p < 0.05$, $^{***}p < 0.001$ by Student's *t*-test. Sin3A RNAi did not

result in complete ablation of mRNA levels in either line because endogenous Sin3A is ubiquitously expressed and the RNAi transgenes were only expressed in neurons. The flies used in these experiments were 2 days old. The genotypes of the flies were: (Control): elav-GAL4/Y; +/+, (Sin3A RNAi^{GD}): elav-GAL4/Y; UAS-Sin3A RNAi^{GD}/+ and (Sin3A RNAi^{KK}): elav-GAL4/Y; UAS-Sin3A RNAi^{KK}/+. (**B-C**) RNAi-mediated knockdown of Sin3A (Sin3A RNAi^{GD} and Sin3A RNAi^{KK}) in neurons did not improve, but rather slightly worsened locomotor functions in flies. Data are presented as means ± SD, n = 5. $^{*}p < 0.05$ by Mann-Whitney U test. n.s.: not significant. The age of the flies (d, days after eclosion) used in these experiments are indicated on the top of the graph. The genotypes of the flies were: (Control): elav-GAL4/Y; +/+, (Sin3A RNAi^{GD}): elav-GAL4/Y; UAS-Sin3A RNAi^{GD}/+ and (Sin3A RNAi^{KK}): elav-GAL4/Y; UAS-Sin3A RNAi^{KK}/+. (**D-E**) Neuronal expression of luciferase RNAi (Luc RNAi) did not suppress Aβ42-induced locomotor defects and neurodegeneration. For (**D**), data are presented as means ± SD, n = 5, n.s.: not significant (Student's *t*-test). The age of the flies (d, days after eclosion) used in this experiment is indicated on the top of the graph. For (**E**), the percentages of vacuole areas (indicated by arrows in the images) in fly brain cortices are shown. Data are presented as means ± SEM, n = 9–12 hemispheres. Scale bar: 10 μm. n.s.: not significant (Student's *t*-test). The flies used in this experiment were 24 days old. The genotypes of the flies were: (Aβ42): elav-GAL4/Y; UAS-Aβ42/+ and (Aβ42/Luc RNAi): elav-GAL4/Y; UAS-Aβ42/UAS-luciferase RNAi. (**F**) Neither Aβ42 expression nor Sin3A mutation altered histone acetylation levels. Heads of flies carrying the elav-GAL4 driver (Control), expressing Aβ42 (Aβ42), expressing Aβ42 with the Sin3A^{LOF} (Aβ42/Sin3A^{LOF}) or carrying the Sin3A^{LOF} (Sin3A^{LOF}) were analyzed by western blotting with anti-acetyl histone H3 (Ac-H3) and anti-histone H3 (H3) antibodies. Data are presented as means ± SEM, n = 4, n.s.: not significant (Student's *t*-test). The flies used in this experiment were 24 days old. The genotypes of the flies were: (Control): elav-GAL4/Y; +/+, (Aβ42): elav-GAL4/Y; UAS-Aβ42/+, (Aβ42/Sin3A^{LOF}): elav-GAL4/Y; UAS-Aβ42/Sin3A^{08269}, (Sin3A^{LOF}): elav-GAL4/Y; Sin3A^{08269}/+. (**G**) Heterozygous loss-of-function mutation of the Sin3A reduced Aβ42 levels in fly brains. Detergent-soluble (RIPA) and -insoluble (FA) fractions made from heads of flies expressing Aβ42 alone (Aβ42) or Aβ42 with heterozygous loss-of-function mutation of Sin3A (Aβ42/Sin3A^{LOF}), were analyzed by western blotting with an anti-Aβ antibody. Tubulin was used as the loading control. Data are presented as means ± SEM, n = 3-4, $^{*}p < 0.05$, $^{***}p < 0.001$ by Student's *t*-test. The flies used in these experiments were 26 days old. The genotypes of the flies were: (Aβ42): elav-GAL4/+; UAS-Aβ42/+, (Aβ42/Sin3A^{LOF}): elav-GAL4/+; UAS-Aβ42/Sin3A^{08269}. (**H**) RNAi-mediated knockdown of the Sin3A reduced Aβ42 levels in fly eyes. RIPA and FA fractions made from heads of flies expressing Aβ42 (Aβ42) or co-expressing Aβ42 and Sin3A RNAi (Aβ42/Sin3A RNAi^{KK}) driven by the eye-specific driver GMR-GAL4 were analyzed by western blotting with an anti-Aβ antibody. Tubulin was used as the loading control. Representative blots and quantifications of Aβ42 levels are shown. Data are presented as means ± SEM, n = 4, $^{***}p < 0.001$ by Student's *t*-test. The flies used in these experiments were 7 days old. The genotypes of the flies were: (Aβ42): GMR-GAL4/+; UAS-Aβ42/+ and (Aβ42/Sin3A RNAi^{KK}): GMR-GAL4/UAS-Sin3A RNAi^{KK}; UAS-Aβ42/+. (**I**) Expression of luciferase RNAi in neurons did not reduce Aβ42 levels in fly brains. RIPA and FA fractions from fly heads expressing Aβ42 (Aβ42) or co-expressing Aβ42 and luciferase RNAi (Aβ42/Luc RNAi) were analyzed by western blotting with an anti-Aβ antibody. Tubulin was used as the loading control. Representative blots and quantifications of Aβ42 levels are shown. Data are presented as means ± SEM, n = 3, n.s.: not significant (Student's *t*-test). The flies used in these experiments were 12 days old. The genotypes of the flies were: (Aβ42): elav-GAL4/Y; UAS-Aβ42/+ and (Aβ42/Luc RNAi): elav-GAL4/Y; UAS-Aβ42/UAS-luciferase RNAi.

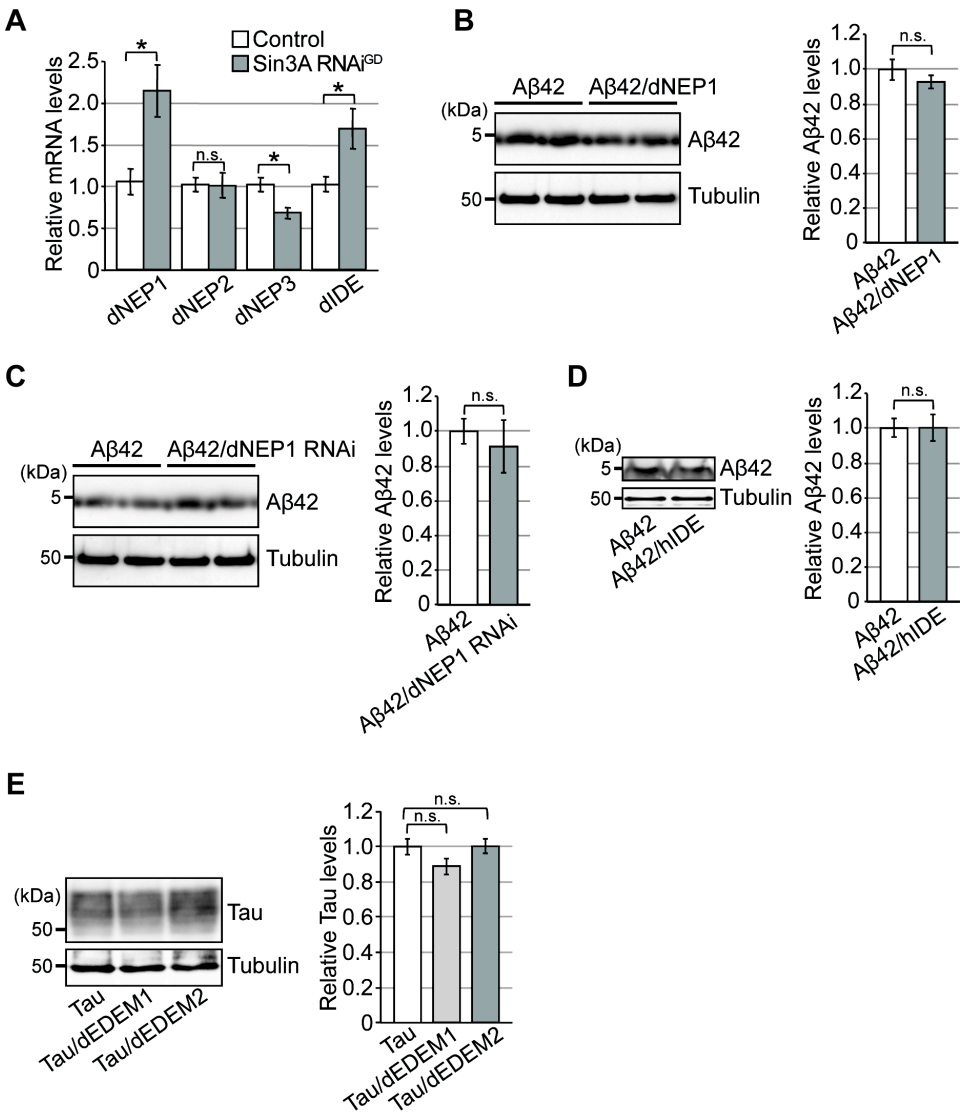

Figure S3. Reductions in Aβ42 levels are not mediated by fly homologs of mammalian Aβ-degrading enzymes, Related to Figure 3

(**A**-**D**) Fly homologs of mammalian Aβ-degrading enzymes did not mediate reductions in Aβ42 levels induced by Sin3A knockdown. (**A**) There are five neprilysin family genes (dNEP1-5) in *Drosophila*. Based on amino acid sequence homology comparisons, dNEP1 (CG5905) and dNEP2 (CG9761) are the closest fly homologs of human neprilysin and dNEP3 (CG9565) is the closest homolog of endothelin converting enzyme 1 and 2. In addition, *Drosophila* has a single homolog of insulin degrading enzymes (dIDE, CG5517). Neuronal knockdown of Sin3A increased the mRNA levels of dNEP1 and dIDE. The mRNA levels in heads of flies carrying the elav-GAL4 driver (Control) or expressing Sin3A RNAi (Sin3A RNAi^{GD}) were analyzed by qRT-PCR. Data are presented as means ± SEM, n = 5, $^{*}p < 0.05$ by Student's *t*-test. The flies used in these experiments were 2 days old. (**B**-**C**) Neither overexpression of dNEP1 (**B**) nor RNAi-mediated knockdown of dNEP1 (**C**) in neurons altered Aβ42 levels in fly brains. Heads of flies expressing Aβ42 (Aβ42), co-expressing Aβ42 and dNEP1 (Aβ42/dNEP1), or co-expressing Aβ42 and dNEP1 RNAi (Aβ42/dNEP1 RNAi) were analyzed by western blotting with an anti-Aβ antibody. Tubulin was used as the loading control. Representative blots and quantifications of Aβ42 levels are shown. Data are presented as means ± SEM, n = 4, n.s.: not significant (Student's *t*-test). The flies used in these

experiments were 3 days old. (**D**) Overexpression of IDE in neurons did not alter Aβ42 levels in fly brains. Fly heads expressing Aβ42 (Aβ42) or co-expressing Aβ42 and human IDE (Aβ42/hIDE1) were analyzed by western blotting with an anti-Aβ antibody. Tubulin was used as the loading control. Representative blots and quantifications of Aβ42 levels are shown. Data are presented as means ± SEM, n = 5, n.s.: not significant (Student's *t*-test). The flies used in these experiments were 7 days old. The genotypes of the flies were: (Control): elav-GAL4/Y; +/+, (Sin3A RNAi^{GD}): elav-GAL4/Y; UAS-Sin3A RNAi^{GD}/+, (Aβ42): elav-GAL4/Y; UAS-Aβ42/+, (Aβ42/dNEP1): elav-GAL4/Y; UAS-Aβ42/+; UAS-dNEP1/+, (Aβ42/dNEP1 RNAi): elav-GAL4/Y; UAS-Aβ42/+; UAS-dNEP1 RNAi/+, (Aβ42/hIDE): elav-GAL4/Y; UAS-Aβ42/+; UAS-hIDE$^{18\text{-}10}$/+. (**E**) Overexpression of neither dEDEM1 nor dEDEM2 reduced the levels of human tau protein in fly eyes. Heads of flies expressing human tau (Tau), co-expressing tau and dEDEM1 (Tau/dEDEM1), or co-expressing tau and dEDEM2 (Tau/dEDEM2) driven by the pan-retinal GMR-GAL4 driver were analyzed by western blotting with an anti-tau antibody. Tubulin was used as the loading control. Representative blots and quantifications of tau levels are shown. Data are presented as means ± SEM, n = 3, n.s.: not significant (Student's *t*-test). The flies used in this experiment were 1 day old. The genotypes of the flies were: (Tau): +/Y; GMR-GAL4, UAS-tau/+, (Tau/dEDEM1): +/Y; GMR-GAL4, UAS-tau/+; UAS-dEDEM1/+ and (Tau/dEDEM2): +/Y; GMR-GAL4, UAS-tau/+; UAS-dEDEM2/+.

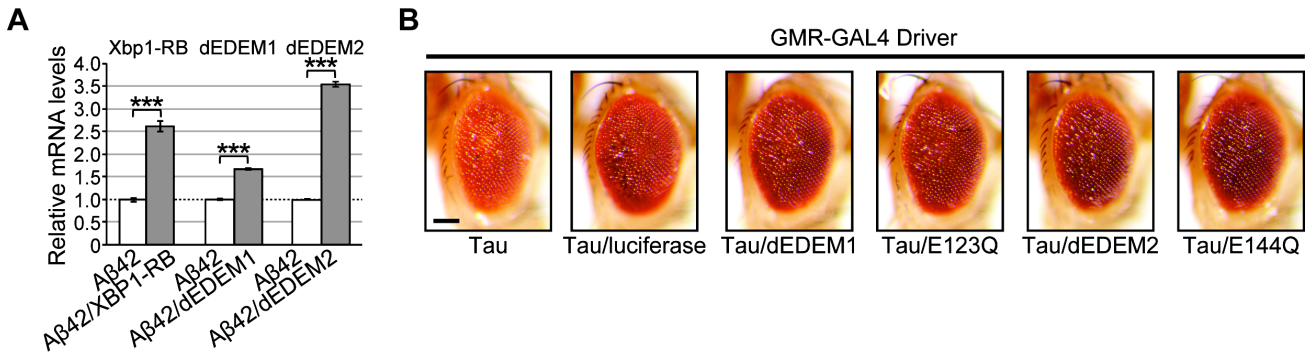

Figure S4. Overexpression of dEDEMs does not protect against retinal degeneration induced by human microtubule-associated protein tau, Related to Figure 4

(**A**) Fold increases in the corresponding mRNA levels of Xbp1-RB and dEDEMs transgenes were analyzed by qRT-PCR in heads from flies expressing Aβ42 (Aβ42), co-expressing Aβ42 and Xbp1-RB (Aβ42/Xbp1-RB), co-expressing Aβ42 and dEDEM1 (Aβ42/dEDEM1), or co-expressing Aβ42 and dEDEM2 (Aβ42/dEDEM2), respectively. Compared with the non-transgenic control, Xbp1-RB overexpression caused a 2.5-fold increase in brain mRNA levels, EDEM1 overexpression caused a 1.6-fold increase, and EDEM2 overexpression caused a 3.5-fold increase. Thus, the levels of overexpression of the mRNAs of these transgenes were comparable. Data are presented as means ± SEM, n = 4, $^{***}p < 0.001$ by Student's *t*-test. The flies used in these experiments were 9 days old (Xbp1-RB) and 14 days old (dEDEM1 and dEDEM2). The genotypes of the flies were: (Aβ42): elav-GAL4/Y; UAS-Aβ42/+, (Aβ42/Xbp1-RB): elav-GAL4/Y; UAS-Aβ42/+; UAS-Xbp1-RB/+, (Aβ42/dEDEM1): elav-GAL4/Y; UAS-Aβ42/+; UAS-dEDEM1/+ and (Aβ42/dEDEM2): elav-GAL4/Y; UAS-Aβ42/+; UAS-dEDEM2/+. (**B**) Overexpression of dEDEMs did not show any protective effect against the rough eye phenotypes induced by microtubule-associated protein tau. Fly eyes expressing human tau alone (Tau) or co-expressing human tau and luciferase, a control protein, (Tau/luciferase) or co-expressing human tau and dEDEMs (Tau/dEDEM1, Tau/E123Q, Tau/dEDEM2, Tau/E144Q) driven by the eye-specific driver GMR-GAL4 were shown. Scale bar: 100 μm. The flies used in these experiments were 7 days old. The genotypes of the flies were: (Tau): +/+; GMR-GAL4, UAS-tau/+, (Tau/luciferase): +/+; GMR-GAL4, UAS-tau/+; UAS-luciferase/+, (Tau/dEDEM1): +/+; GMR-GAL4, UAS-tau/+; UAS-dEDEM1/+, (Tau/E123Q): +/+; GMR-GAL4, UAS-tau/+; UAS-dEDEM1-E123Q/+, (Tau/dEDEM2): +/+; GMR-GAL4, UAS-tau/+; UAS-dEDEM2/+ and (Tau/E144Q): +/+; GMR-GAL4, UAS-tau/+; UAS-dEDEM2-E144Q/+.

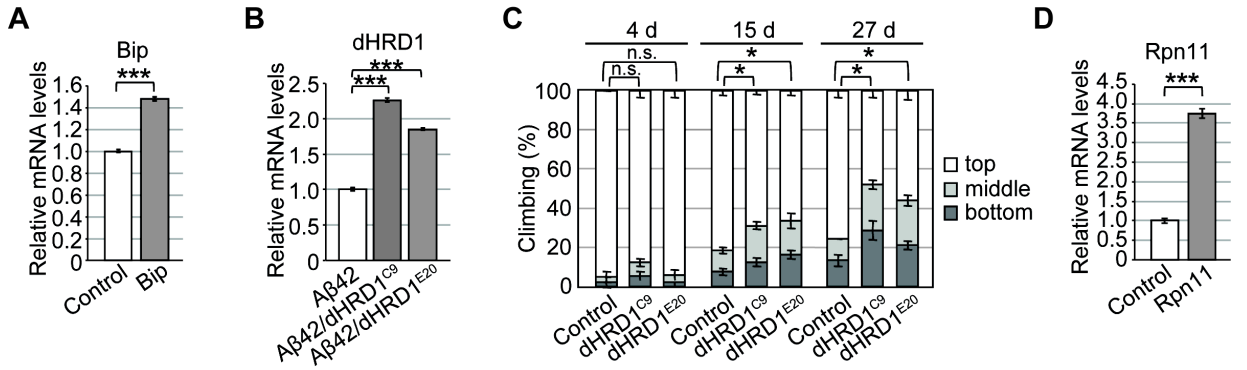

Figure S5. Expression of Bip, dHRD1 or Rpn11 transgene in fly brains, and the effects of neuronal overexpression of dHRD1 on locomotor functions, Related to Figure 5

(**A, B** and **D**) mRNA expression levels of Bip, *Drosophila* HRD1 (dHRD1^{C9} and dHRD1^{E20}), or Rpn11 transgenes in fly brains. Fold increases in the corresponding mRNA levels in heads of flies expressing Bip, dHRD1 or Rpn11 in neurons were analyzed by qRT-PCR. Data are presented as means ± SEM, n = 4, $^{***}p < 0.001$ by Student's *t*-test. The flies used in these experiments were 7 days old (Bip and Rpn11) and 27 days old (dHRD1). The genotypes of the flies were: (Control): elav-GAL4/Y; +/+, (Bip): elav-GAL4/Y; UAS-Bip/+, (Aβ42): elav-GAL4/Y;;UAS-Aβ42/+, (Aβ42/dHRD1^{C9}): elav-GAL4/Y; UAS-dHRD1^{C9}/+; UAS-Aβ42/+, (Aβ42/dHRD1^{E20}): elav-GAL4/Y; ; UAS-dHRD1^{E20}/UAS-Aβ42 and (Rpn11): elav-GAL4/Y; UAS-Rpn11/+. (**C**) The effects of neuronal overexpression of dHRD1 on locomotor functions. Neuronal overexpression of dHRD1 worsened locomotor functions in flies. Data are presented as means ± SD, n = 5, $^{*}p < 0.05$ by Mann-Whitney U test. The age of the flies (d, days after eclosion) used in these experiments are indicated on the top of the graph. The genotypes of the flies were: (Control): elav-GAL4/Y; +/+, (dHRD1^{C9}): elav-GAL4/Y; UAS-dHRD1^{C9}/+, (dHRD1^{E20}): elav-GAL4/Y;; UAS-dHRD1^{E20}/+.

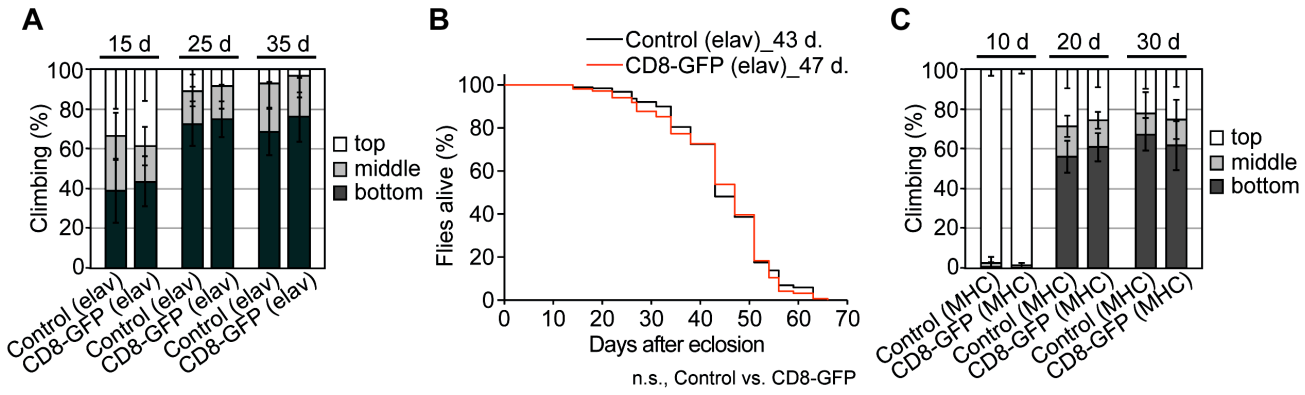

Figure S6. The effects of CD8-GFP expression in neurons or in muscle on locomotor functions and lifespan in flies, Related to Figure 7

(**A**) Neuronal overexpression of control CD8-GFP proteins did not improve locomotor functions in aged flies. (**B**) Neuronal overexpression of control CD8-GFP protein did not alter medium lifespan of flies (Control: 43d vs CD8-GFP: 47 day). n.s.: no significant difference by Kaplan-Meier survival analyses with log-rank tests (n = 189-318 per group). The genotypes of the flies were: (Control): elav-GAL4/Y; +/+ and (CD8-GFP): elav-GAL4/Y; UAS-CD8-GFP/+. (**C**) Overexpression of control CD8-GFP proteins in muscle did not improve locomotor functions in flies. The genotypes of the flies were: (Control): +/Y; MHC-GAL4/+ and (CD8-GFP): +/Y; MHC-GAL4/UAS-CD8-GFP. For (**A**) and (**C**), data are presented as means ± SD, n = 5. The age of the flies (d, days after eclosion) used in these experiments are indicated on the top of the graph.

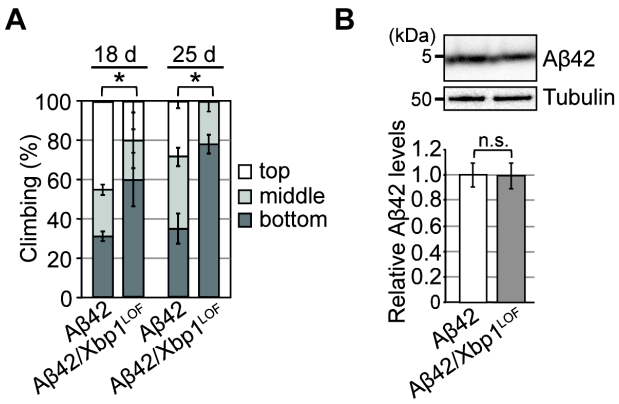

Figure S7. A loss of one copy of endogenous *Drosophila* Xbp1 significantly worsens behavioral deficits in Aβ42 flies without altering Aβ42 levels, Related to Figure 1 and Discussion

(**A**) A heterozygous loss-of-function mutation of Xbp1 ($Xbp1^{LOF}$) worsened locomotor defects in Aβ42 flies. The percentages of flies that stayed at the bottom were subjected to statistical analyses. Data are presented as means ± SD, n = 5, $^{*}p < 0.05$ by Mann-Whitney U test. The age of the flies (d, days after eclosion) used in these experiments are indicated on the top of the graph. (**B**) A heterozygous loss-of-function mutation of Xbp1 did not significantly alter Aβ42 levels in fly brains. Fly heads expressing Aβ42 (Aβ42) or expressing Aβ42 with $Xbp1^{LOF}$ (Aβ42/ $Xbp1^{LOF}$) were analyzed by western blotting with an anti-Aβ antibody. Tubulin was used as the loading control. Data are presented as means ± SEM, n = 3, n.s.: not significant (Student's *t*-test). The flies used in these experiments were 7 days old. The genotypes of the flies used in these studies were: (Aβ42): elav-GAL4/Y; UAS-Aβ42/+ and (Aβ42/$Xbp1^{LOF}$): elav-GAL4/Y; UAS-Aβ42/ $Xbp1^{K13803}$.

Table S1. Summary of a small-scale genetic screen searching for modifiers of neurotoxicity caused by overexpression Aβ42 peptides in the ER in *Drosophila*, Related to Figure 2

See attached an Exel file.

Table S2. Selected candidate genes for 2nd screen, Related to Figure 3

Function	Gene	FC in Sin3 KD background
ER quality control		
Recognition and Targeting	Hsc70-3/ Bip	0.97
	dEDEM1	1.18**
	dEDEM2	1.22**
Protein disulfide isomerase	CG9911/ dErp44	1.11
	dERP60	1.16***
	Ero1L	1.04
	CaBp1	1.19**
Retrotranslocation	Sec61β	1.02
	TER94	0.97
	dDer-1	1.43***
	dDer-2	1.22***
Other possible component	Spp	1.28**
Ubiquitylation	dHRD1	0.99
Proteasomal degradation	Prosβ1	1.20***
Autophagy	Atg8a	0.75***
	Atg12	1.00
Aβ degrading enzyme		
	dNEP1	2.14*
	dNEP2	1.00
	dNEP3	0.68*
	dNEP4	1.36**
	dNEP5	1.24*
	dIDE	1.69*

mRNA levels in heads of flies carrying elav-GAL4 driver or expressing Sin3A RNAi were analyzed by qRT-PCR and fold change (FC) was calculated for each gene. n = 4-6, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ by Student's *t*-test. The age of flies were 2 days old.

Table S3. GO terms that are used to select UPR-related genes, Related to Figure 6

GO term
response to heat
protein folding
chaperone mediated protein folding requiring cofactor
protein disulfide isomerase activity
protein disulfide oxidoreductase activity
unfolded protein binding
endoplasmic reticulum unfolded protein response
response to endoplasmic reticulum stress
esponse to unfolded protein
ER overload response
ER-associated protein catabolic process
misfolded or incompletely synthesized protein catabolic process
mannosyl-oligosaccharide 1,2-alpha-mannosidase activity
SRP-dependent cotranslational protein targeting to membrane, translocation
cellular response to unfolded protein
heat shock protein binding

Table S4. UPR-related genes that are upregulated in the aged fly brains, Related to Figure 6

Probe.Set.ID	Gene.Symbol	logFC	adj.P.Val	Xbp1binding
1623635_at	TotM	2.441361439	0.00052451	no
1629061_s_at	Hsp22.Hsp67Bb	2.312429167	0.00056134	no
1639323_at	TotC	1.250656957	0.0012573	no
1624748_a_at	Mnn1	1.174369144	0.004870307	yes
1624419_a_at	Cct5	0.852993451	0.00056134	no
1623829_at	CG31414	0.813978743	0.017736332	no
1630842_s_at	CG32640.CG32641	0.702512938	0.001004711	no
1635549_at	TotA	0.702182483	0.001424517	no
1627638_s_at	T-cp1	0.664774043	0.001336964	no
1630993_at	CG31414	0.614005521	0.008252494	no
1626845_at	Tcp-1eta	0.605580053	0.001687286	no
1636173_s_at	Mpk2	0.593744322	0.003115818	no
1634276_a_at	Adar	0.576841466	0.033628409	yes
1625478_at	Mnn1	0.576053541	0.02874686	yes
1628660_at	CG7130	0.569537415	0.004437182	no
1627382_at	Sec61beta	0.555439358	0.001687286	yes
1640155_at	Ire1	0.55257576	0.02961785	no
1635293_s_at	CG8336	0.523173135	0.00793867	no
1634866_at	CG4880	0.497885309	0.039874646	no
1639118_a_at	Hrb87F	0.483684953	0.005019221	no
1626823_a_at	CG7945	0.479383787	0.002087492	yes
1639441_at	Crc	0.477650083	0.002797556	no
1630132_at	Tcp-1zeta	0.467426041	0.002087492	no
1625164_at	TotX	0.460798913	0.006835104	no
1638663_at	Sec61alpha	0.456952561	0.00301887	yes
1629752_at	CG5525	0.449567777	0.004870307	no
1630076_at	Hop	0.443850565	0.004870307	no
1623862_at	ninaA	0.433800794	0.005620089	no
1640009_at	unc-45	0.433109291	0.020994172	no
1635355_a_at	Xbp1	0.432478725	0.005019221	yes
1630408_s_at	CG7033	0.417198533	0.004204303	no
1631876_at	l(2)35Cc	0.416981726	0.017736332	no
1641293_at	Ire1	0.404315929	0.017736332	no
1637650_at	CG4164.CR43080	0.39661067	0.004856144	no
1627497_at	Txl	0.392833944	0.004204303	no
1634700_at	CG8258	0.391704813	0.005316561	no
1630688_at	Hsp83	0.374431086	0.011655979	yes
1629598_at	FK506-bp1	0.369666997	0.004206514	no

1630283_at	Cdc37	0.366216178	0.004437182	no
1634782_s_at	Cctgamma	0.362699235	0.005316561	no
1636741_s_at	Hsc70Cb	0.354266808	0.008988232	no
1636639_at	Spp	0.352876121	0.004870307	yes
1628008_a_at	TER94	0.351800746	0.005234996	yes
1631379_a_at	ERp60	0.344570249	0.006783745	yes
1629373_at	CG5199	0.337475479	0.037933675	no
1626196_at	CaBP1	0.329934675	0.006667684	yes
1623458_at	Der-2	0.328420467	0.011655979	yes
1623256_at	GstE1	0.326752101	0.017736332	no
1631827_at	CG15863	0.321289979	0.013194816	no
1637602_at	CG32801.Edem1	0.309513306	0.01371786	no
1628875_at	pain	0.296304928	0.027900852	no
1640897_at	sip3	0.294708585	0.026181471	no
1637059_s_at	DnaJ-1	0.292425688	0.030605237	no
1630637_s_at	Hsc70-4	0.291185439	0.013054203	no
1624372_at	Der-1	0.290466085	0.011655979	yes
1636451_a_at	Atf-2	0.285961819	0.056033726	no
1627525_a_at	Ero1L	0.278919193	0.011728062	yes
1625141_at	CG14715	0.277763319	0.031187422	no
1623009_at	cyp33	0.277018231	0.039897493	no
1638036_at	Cyp1	0.271893653	0.018985071	yes
1639895_at	mgr	0.262657985	0.030605237	no
1632200_s_at	CG32801.Edem1	0.259797642	0.030605237	no
1634890_at	UK114	0.2589988	0.056033726	no
1627399_at	CG17266	0.258424492	0.017359287	no
1639357_at	Cypl	0.25087234	0.056033726	no
1636427_a_at	Mt2	0.249076418	0.03609821	no
1624611_a_at	CG2852	0.247369659	0.027341409	no
1624499_s_at	CG9911	0.24435137	0.017736332	yes
1635423_s_at	Hsc70-3	0.242285241	0.037651233	yes
1628429_at	Sec61gamma	0.241628258	0.020994172	yes
1640995_at	CG7048	0.240704989	0.037651233	yes
1631565_a_at	crc	0.225513863	0.020994172	no
1635861_a_at	Tpr2	0.225060075	0.034400004	no
1636528_at	Gp93	0.219248903	0.056854476	yes
1628831_at	Torsin	0.208617704	0.031142506	no
1638229_at	l(3)01239	0.197623472	0.056854476	no
1639419_at	CG8860	0.172910407	0.053244191	no

Table S5. Genotype and age of flies used in this study, Related to Figures 1-7 and STAR Methods

Figure #	Label	Genotype	Age
Figure 1	Control	elav-GAL4/Y;+/+	Fig. 1 **A** (7d), **C** (25d), **G** (described in figures).
	Aβ42	elav-GAL4/Y;UAS-Aβ42/+	Fig. 1 **A** (7d), **B** (20d), **C** (25d), **F** (9d), **G** (described in figures).
	Control	elav-GAL4/Y;UAS-Mito-GFP/+	Fig. 1 **D** (10d).
	Aβ42	elav-GAL4/Y;UAS-Aβ42/UAS-Mito-GFP	Fig. 1 **D** (10d).
	NHK	elav-GAL4/Y;UAS-NHK/CyO	Fig. 1 **E** (7d).
	NHK/Aβ42	elav-GAL4/Y;UAS-Aβ42/UAS-NHK	Fig. 1 **E** (7d).
	Aβ42/Xbp1-RB	elav-GAL4/Y;UAS-Aβ42/+;UAS-Xbp1-RB/+	Fig. 1 **F** (9d), **G** (described in figures).
	Xbp1-RB	elav-GAL4/Y;+/+;UAS-Xbp1-RB/+	Fig. 1 **G** (described in figures).
Figure 2	Aβ42	elav-GAL4/Y;UAS-Aβ42/+	Fig. 2 **A**-**B** (described in figures), **C** (25d), **D** (20 or 26d), **E** (2d).
	Aβ42/Sin3A^{LOF}	elav-GAL4/Y;UAS-Aβ42/Sin3A^{08269}	Fig. 2 **A** (described in the figure), **C** (25d).
	Control	elav-GAL4/Y;+/+	Fig. 2 **A** (described in figures), **C** (25d).
	Sin3A^{LOF}	elav-GAL4/Y;Sin3A^{08269}/+	Fig. 2 **A** (described in figures).
	Aβ42/Sin3A RNAi^{GD}	elav-GAL4/Y;UAS-Aβ42/UAS-Sin3A RNAi^{GD}	Fig. 2 **B** (described in figures), **D** (20d)
	Aβ42/Sin3A RNAi^{KK}	elav-GAL4/Y;UAS-Aβ42/UAS-Sin3A RNAi^{KK}	Fig. 2 **B** (described in figures), **C** (25d), **D** (26d), **E** (2d).
	CD8-GFP	elav-GAL4/Y;UAS-CD8-GFP/+	Fig. 2 **F** (7d).
	CD8-GFP/Sin3A RNAi^{GD}	elav-GAL4/Y;UAS-CD8-GFP/UAS-Sin3A RNAi^{GD}	Fig. 2 **F** (7d).
Figure 3	Control	elav-GAL4/Y;+/+	Fig. 3 **A** (2d), **C** (7d), **J** (2d).
	Sin3A RNAi^{GD}	elav-GAL4/Y;UAS-Sin3A RNAi^{GD}/+	Fig. 3 **A** (2d), **J** (2d).
	Aβ42	elav-GAL4/Y;UAS-Aβ42/+	Fig. 3 **B** (2d), **E**-**F** (24d), **K** (2d).
	Aβ42/Sin3A RNAi^{GD}	elav-GAL4/Y;UAS-Aβ42/UAS-Sin3A RNAi^{GD}	Fig. 3 **B** (2d), **K** (2d).
	dEDEM1	elav-GAL4/Y;;UAS-dEDEM1/+	Fig. 3 **C** (7d).
	E123Q	elav-GAL4/Y;;UAS-dEDEM1-E123Q/+	Fig. 3 **C** (7d).
	dEDEM2	elav-GAL4/Y;;UAS-dEDEM2/+	Fig. 3 **C** (7d).
	E144Q	elav-GAL4/Y;;UAS-dEDEM2-E144Q/+	Fig. 3 **C** (7d).
	NHK	elav-GAL4/Y;UAS-NHK/+	Fig. 3 **D** (7d).
	NHK/dEDEM1	elav-GAL4/Y;UAS-NHK/+;UAS-dEDEM1/+	Fig. 3 **D** (7d).
	NHK/E123Q	elav-GAL4/Y;UAS-NHK/+;UAS-dEDEM1-E123Q/+	Fig. 3 **D** (7d).
	NHK/dEDEM2	elav-GAL4/Y;UAS-NHK/+;UAS-dEDEM2/+	Fig. 3 **D** (7d).
	NHK/E144Q	elav-GAL4/Y;UAS-NHK/+;UAS-dEDEM2-E144Q/+	Fig. 3 **D** (7d).
	Aβ42/dEDEM1	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM1/+	Fig. 3 **E**-**F** (24d).
	Aβ42/E123Q	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM1-E123Q/+	Fig. 3 **E**-**F** (24d).
	Aβ42/dEDEM2	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM2/+	Fig. 3 **E**-**F** (24d).
	Aβ42/E144Q	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM2-E144Q/+	Fig. 3 **E**-**F** (24d).
	Aβ42	+/Y;GMR-GAL4,UAS-Aβ42/+	Fig. 3 **G**-**H** (7d).
	Aβ42/dEDEM1	+/Y;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM1/+	Fig. 3 **G**-**H** (7d).
	Aβ42/E123Q	+/Y;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM1-E123Q/+	Fig. 3 **G**-**H** (7d).
	Aβ42/dEDEM2	+/Y;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM2/+	Fig. 3 **G**-**H** (7d).

	Aβ42/E144Q	+/Y;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM2-E144Q/+	Fig. 3 **G**-**H** (7d).
Figure 4	Aβ42	elav-GAL4/Y;UAS-Aβ42/+	Fig. 4 **A** (described in the figure), **B** (25d).
	Aβ42/dEDEM1	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM1/+	Fig. 4 **A** (described in the figure), **B** (25d).
	Aβ42/E123Q	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM1-E123Q/+	Fig. 4 **A** (described in the figure), **B** (25d).
	Aβ42/dEDEM2	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM2/+	Fig. 4 **A** (described in the figure), **B** (25d).
	Aβ42/E144Q	elav-GAL4/Y;UAS-Aβ42/+;UAS-dEDEM2-E144Q/+	Fig. 4 **A** (described in the figure), **B** (25d).
	Aβ42	+/+;GMR-GAL4,UAS-Aβ42/+	Fig. 4 **C** (7d).
	Aβ42/CD8-GFP	+/+;GMR-GAL4,UAS-Aβ42/+, UAS-CD8-GFP	Fig. 4 **C** (7d).
	Aβ42/dEDEM1	+/+;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM1/+	Fig. 4 **C** (7d).
	Aβ42/E123Q	+/+;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM1-E123Q/+	Fig. 4 **C** (7d).
	Aβ42/dEDEM2	+/+;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM2/+	Fig. 4 **C** (7d).
	Aβ42/E144Q	+/+;GMR-GAL4,UAS-Aβ42/+;UAS-dEDEM2-E144Q/+	Fig. 4 **C** (7d).
Figure 5	Aβ42	elav-GAL4/Y;UAS-Aβ42/+	Fig. 5 **A** (7d), **E** (24d), **B** and **F** (described in figures).
	Aβ42	elav-GAL4/Y;;UAS-Aβ42/+	Fig. 5 **C** (10d), **D** (described in the figure).
	Aβ42/Bip	elav-GAL4/Y;UAS-Aβ42/UAS-Hsc70-3/Bip	Fig. 5 **A** (7d), **B** (described in the figure).
	Aβ42/ dHRD1^{C9}	elav-GAL4/Y; UAS-dHRD1^{C9}/+;UAS-Aβ42/+.	Fig. 5 **D** (described in the figure).
	Aβ42/ dHRD1^{E20}	elav-GAL4/Y;;UAS-Aβ42/UAS-dHRD1 ^{E20}.	Fig. 5 **C** (10d), **D** (described in the figure).
	Aβ42/Rpn11	elav-GAL4/Y;UAS-Aβ42/UAS-Rpn11	Fig. 5 **E** (24d), **F** (described in the figure).
Figure 6	7 day-old and 30 day-old	elav-GAL4/Y;+/+	Fig. 6 **A**-**B** (described in figures).
	Young	+/Y;elav-GeneSwitch/UAS-NHK	Fig. 6 **C** (7d).
	Aged	+/Y;elav-GeneSwitch/UAS-NHK	Fig. 6 **C** (30d).
	1 week and 3 weeks	elav-GAL4/Y;UAS-CD3δ-YFP/+	Fig. 6 **D**-**E** (described in figures).
Figure 7	Control	elav-GAL4/Y;+/+	Fig. 7 **A**-**B** and **G** (described in figures), **H** (7d).
	dEDEM1	elav-GAL4/Y;+/+;UAS-dEDEM1/+	Fig. 7 **A**-**B** and **G** (described in figures), **H** (7d).
	E123Q	elav-GAL4/Y;+/+;UAS-dEDEM1-E123Q/+	Fig. 7 **A**-**B** (described in figures).
	dEDEM2	elav-GAL4/Y;+/+;UAS-dEDEM2/+	Fig. 7 **A**-**B** and **G** (described in figures), **H** (7d).
	E144Q	elav-GAL4/Y;+/+;UAS-dEDEM2-E144Q/+	Fig. 7 **A**-**B** (described in figures).
	Control	+/Y;MHC-GAL4/+	Fig. 7 **C**-**D** (described in figures).
	dEDEM1	+/Y;MHC-GAL4/+;UAS-dEDEM1/+	Fig. 7 **C**-**D** (described in figures).
	E123Q	+/Y;MHC-GAL4/+;UAS-dEDEM1-E123Q/+	Fig. 7 **C**-**D** (described in figures).
	dEDEM2	+/Y;MHC-GAL4/+;UAS-dEDEM2/+	Fig. 7 **C**-**D** (described in figures).
	E144Q	+/Y;MHC-GAL4/+;UAS-dEDEM2-E144Q/+	Fig. 7 **C**-**D** (described in figures).
	Control	+/Y;Myo1A-GAL4/+	Fig. 7 **E**-**F** (described in figures).
	dEDEM1	+/Y;Myo1A-GAL4/+;UAS-dEDEM1/+	Fig. 7 **E**-**F** (described in figures).
	E123Q	+/Y;Myo1A-GAL4/+;UAS-dEDEM1-E123Q/+	Fig. 7 **E**-**F** (described in figures).
	dEDEM2	+/Y;Myo1A-GAL4/+;UAS-dEDEM2/+	Fig. 7 **E**-**F** (described in figures).
	E144Q	+/Y;Myo1A-GAL4/+;UAS-dEDEM2-E144Q/+	Fig. 7 **E**-**F** (described in figures).

Table S6. Primer sequences for qRT-PCR, Related to STAR Methods

Name	Sequence	Product size
PERK (*Drosophila*), Forward	5'- CTGCGCAGTCTTCGGGACGG -3'	241 bp
PERK (*Drosophila*), Reverse	5'- AGCTGCTGAAGGTGCGGCTG -3'	
Xbp1-RB (*Drosophila*), Forward	5'- CAACCTTGGATCTGCCGCAGGG -3'	238 bp
Xbp1-RB (*Drosophila*), Reverse	5'- CGCTCCAGCGCCTGTTTCCAG -3'	
NHK (Human), Forward	5'- CCAAGGCTGACACTCACGAT -3'	181 bp
NHK (Human), Reverse	5'- TCCACTAGCTTCAGGCCCTC -3'	
dHRD1 (*Drosophila*), Forward	5'- AGCCAGCTCAGCGTCTCCGA -3'	109 bp
dHRD1 (*Drosophila*), Reverse	5'- GCTAACTGCCTCCGTGGCCG -3'	
Sin3A (*Drosophila*), Forward	5'- ATGTCCACCGAGGAATTGAG -3'	227 bp
Sin3A (*Drosophila*), Reverse	5'- CGCCATTGCTTATTGAAGGT -3'	
Aβ42 (Human), Forward	5'- GCGCAGTTCCTGAGACTTTGC -3'	211 bp
Aβ42 (Human), Reverse	5'- GACAACACCGCCCACCATGAG -3'	
dEDEM1 (*Drosophila*), Forward	5'- TCCTCGCCCCAGTTGGCTCA -3'	144 bp
dEDEM1 (*Drosophila*), Reverse	5'- AATGCGAACACCGGCCTCCG -3'	
dEDEM2 (*Drosophila*), Forward	5'- CAAAGCGCGACTGGCCCAGA -3'	175 bp
dEDEM2 (*Drosophila*), Reverse	5'- GACCGCCGACAGTTTGCCGA -3'	
Bip (*Drosophila*), Forward	5'- TCCCGATGCCGATCCCGAGG -3'	95 bp
Bip (*Drosophila*), Reverse	5'- CGCCAGCACCCTGGTACAGC -3'	
dNEP1 (*Drosophila*), Forward	5'- GATGACGCAGGGCGAGAA -3'	150 bp
dNEP1 (*Drosophila*), Reverse	5'- TGGGCGTAGTTGAGAAAGAACA -3'	
dNEP2 (*Drosophila*), Forward	5'- CCGCAGATGGGCTGAGAA -3'	150 bp
dNEP2 (*Drosophila*), Reverse	5'- TGCACGCCGGTAGTAATACG -3'	
dNEP3 (*Drosophila*), Forward	5'- GTCCAGCCGCACCAAAAA -3'	150 bp
dNEP3 (*Drosophila*), Reverse	5'- CCATTGATTGCAGGAATATCCA -3'	
dNEP4 (*Drosophila*), Forward	5'- ACGCTCTCGAACTCCGTTGA -3'	150 bp
dNEP4 (*Drosophila*), Reverse	5'- AGGAATGTGTGGCATATGTCATG -3'	
dNEP5 (*Drosophila*), Forward	5'- GCACCCACCTGGAGAACCT -3'	151 bp
dNEP5 (*Drosophila*), Reverse	5'- GGCACAGTGATTGCATTCGA -3'	
dIDE (*Drosophila*), Forward	5'- TGGCGCCGGACAAGTT -3'	150 bp
dIDE (*Drosophila*), Reverse	5'- GCTTGATGCGCCACAGATC -3'	
Atg8a (*Drosophila*), Forward	5'- CTGCTGCGCACGGTCACTCT -3'	259 bp
Atg8a (*Drosophila*), Reverse	5'- CCGGGGCAGGTGCAAATGTCTG -3'	
Atg12 (*Drosophila*), Forward	5'- TGAACGCCACTGGCAATGTGC -3'	162 bp
Atg12 (*Drosophila*), Reverse	5'- CCGGGGCAGGTGCAAATGTCTG -3'	
Rpn11 (*Drosophila*), Forward	5'- TTCCATCAACGAGGACACC -3'	150 bp
Rpn11 (*Drosophila*), Reverse	5'- ACCTTCTCCTCCAAATGCCG -3'	
Gp93 (*Drosophila*), Forward	5'- CTGACCCAGACGCACTTCAT -3'	150 bp
Gp93 (*Drosophila*), Reverse	5'- GTCGGTGATGAAAACACGGC -3'	

dDer-1 (*Drosophila*), Forward	5'- TGGCCGCCTTCGAGTTTATT -3'	143 bp
dDer-1 (*Drosophila*), Reverse	5'- CTTCAAGAACTGCGGCGTTT -3'	
dDer-2 (*Drosophila*), Forward	5'- ACACTGTCCAACGGCTACAG -3'	178 bp
dDer-2 (*Drosophila*), Reverse	5'- CCTCATCCTGTCCATCAGCC -3'	
CG9911 (*Drosophila*), Forward	5'- TCAGTGACATGTACTCGCCG -3'	176 bp
CG9911 (*Drosophila*), Reverse	5'- GGATGGGCCAAGTTCCTTGA -3'	
CaBP1 (*Drosophila*), Forward	5'- TCTCCAAGGACGGCATCAAC -3'	110 bp
CaBP1 (*Drosophila*), Reverse	5'- CCAAGGATCCACGGACACAA -3'	
CG7945 (*Drosophila*), Forward	5'- ACATGAGCGAAGCTGAACGA -3'	104 bp
CG7945 (*Drosophila*), Reverse	5'- AGAGTTGTCCCGAACAGTGC -3'	
Sec61β (*Drosophila*), Forward	5'- GTGGCATGTGGCGTTTCTAC -3'	103 bp
Sec61β (*Drosophila*), Reverse	5'- AGCATGAAGACGGAAGCGAT -3'	
Sec61γ (*Drosophila*), Forward	5'- CCGCAAGGAGTTCCAGAAGA -3'	130 bp
Sec61γ (*Drosophila*), Reverse	5'- TCAGCGCATTTAAGAGCCCA -3'	
TER94 (*Drosophila*), Forward	5'- AACTGTTGTTGAGGTGCCCA -3'	132 bp
TER94 (*Drosophila*), Reverse	5'- GGCTGCATGCCAAACTTCAA -3'	
Hsp83 (*Drosophila*), Forward	5'- AAGCAGCTGGAGATCAACCC -3'	143 bp
Hsp83 (*Drosophila*), Reverse	5'- TCCAGCGAGAATCCAGAGGA -3'	
dERp60 (*Drosophila*), Forward	5'- GGCTCGCGACGAAAAGAATC -3'	134 bp
dERp60 (*Drosophila*), Reverse	5'- TCGACTCGGGAATAGGCTCA -3'	
Spp (*Drosophila*), Forward	5'- CAAGCTAGTGTTCCCCCAGG -3'	187 bp
Spp (*Drosophila*), Reverse	5'- CAGGCCAAGGAAGTAGGCAA -3'	
Ero1L (*Drosophila*), Forward	5'- CACTGGCTGCGAAACCTCTA -3'	184 bp
Ero1L (*Drosophila*), Reverse	5'- CGTTCTCGTCGAAGTGGGAT -3'	
Prosβ1 (*Drosophila*), Forward	5'- CCACGATGGCAGCTCCGGTG -3'	102 bp
Prosβ1 (*Drosophila*), Reverse	5'- ACAGCCGATGCGCCCGATTC -3'	
Actin (*Drosophila*), Forward	5'- TGCACCGCAAGTGCTTCTAA -3'	150 bp
Actin (*Drosophila*), Reverse	5'- TGCTGCACTCCAAACTTCCA -3'	
RP49/RpL32 (*Drosophila*), Forward	5'- GCTAAGCTGTCGCACAAATG -3'	105 bp
RP49/RpL32 (*Drosophila*), Reverse	5'- GTTCGATCCGTAACCGATGT -3'	
GAPDH1 (*Drosophila*), Forward	5'- GACGAAATCAAGGCTAAGGTCG -3'	109 bp
GAPDH1 (*Drosophila*), Reverse	5'- AATGGGTGTCGCTGAAGAAGTC -3'	
CD3δ (*Drosophila*), Forward	5'- CATGGGTAGAGGGAACGGTG -3'	164 bp
CD3δ (*Drosophila*), Reverse	5'- ACAGCTCTGGCACATTCGAT -3'	