



**Supplementary Figure 4** *atfs-1* in neurons is required for the peripheral induction of UPR<sup>mt</sup>. (A) qRT-PCR measures RNAi efficiency of UPR<sup>mt</sup> pathway genes in *rab-3p::Cas9+u6p::spg-7-sg; hsp-6p::GFP* worms. (B-C) RNAi against *atfs-1* or *dve-1* significantly suppresses non-autonomous UPR<sup>mt</sup> in worms with neuronal *spg-7* knockout.  $n \geq 60$ , error bars indicate mean  $\pm$ SE. A Student's t-test was used to assess significance: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . (D) RNAi against *atfs-1* or neuronal *atfs-1* knockout robustly block the peripheral induction of *hsp-6p::GFP* in *unc-119p::Tom20::KillerRed* strain. *mec-7p::RFP* is used as co-injection marker. (E) Knockout of *atfs-1* in each indicated neuron block the peripheral induction of *hsp-6p::GFP* in animals with *spg-7* knockout in the same neuron. *odr-1p::dsRed* is used as co-injection marker.

