The HMX/NKX homeodomain transcription factor MLS-2 mediates a cell non-autonomous UPR^{mt} that promotes host resistance during infection.

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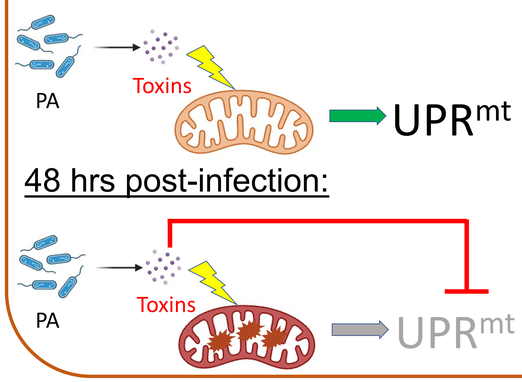
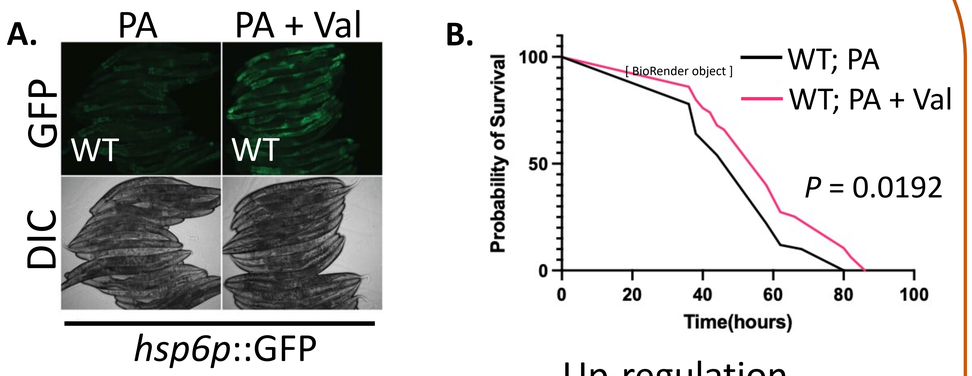
BACKGROUND



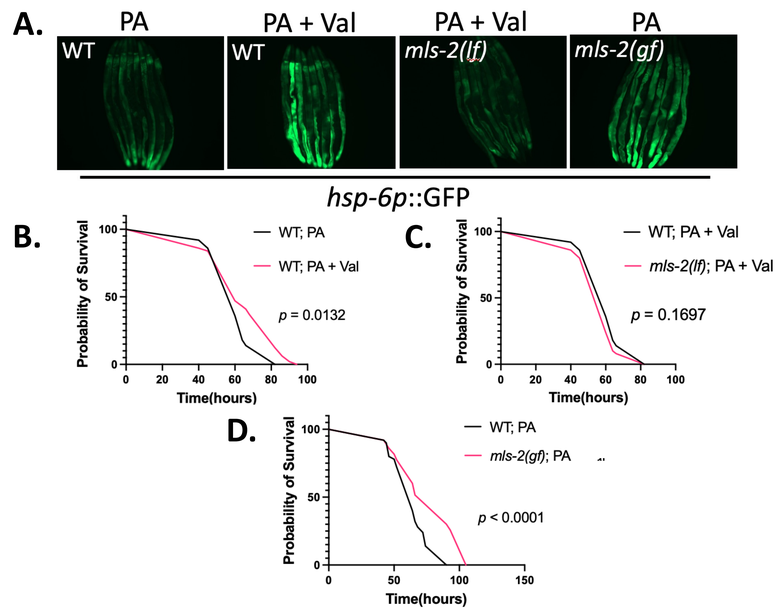
The UPR^{mt} is a stress response pathway that transcriptionally reprograms the cell to promote mitochondrial recovery during stress (Qureshi, Haynes, and Pellegrino 2017). The bacterial pathogen *P. aeruginosa* activates the UPR^{mt} but only transiently, suggesting a repressive force that is acting on this stress response during infection (Mahmud et al. 2020) .

Valine enhances UPR^{mt} during infection



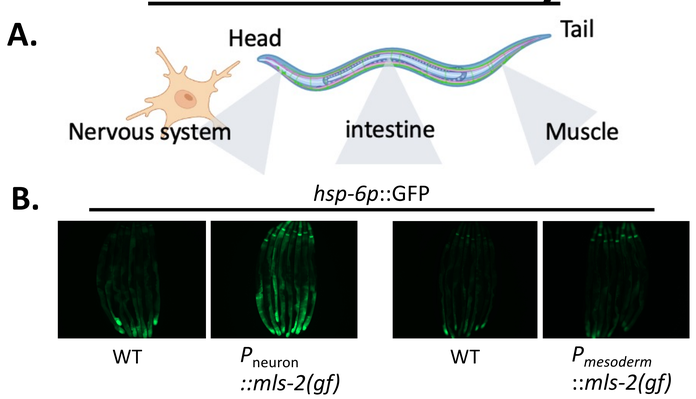
Chronic *P. aeruginosa* infection represses UPR^{mt} due to deficiencies in branched-chain amino acids such as valine. A) Supplementation with valine restores UPR^{mt} during chronic *P. aeruginosa* infection (visualized by the UPR^{mt} reporter transgene *hsp-6p*::GFP), and B) promotes the survival of the *C. elegans* host. C) Valine supplementation transcriptionally reprograms *C. elegans*.

MLS-2 HMX/NKX transcription factor mediates valine-induced UPR^{mt}



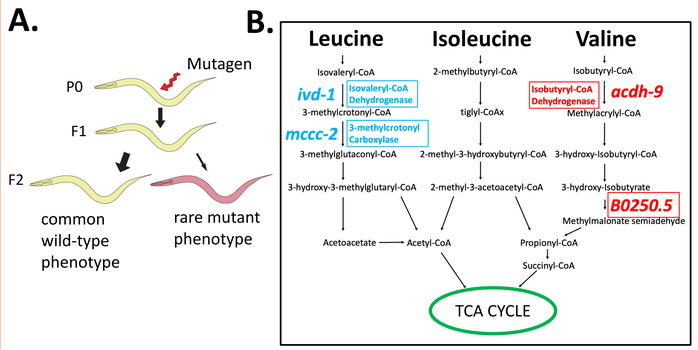
MLS-2 is required for valine-mediated UPR^{mt} phenotypes. A) *mls-2* loss of function mutant suppresses UPR^{mt} activation by valine during *P. aeruginosa* infection, B, C) as well as the survival benefit of this amino acid. D) *mls-2* gain of function is sufficient to promote host survival during infection.

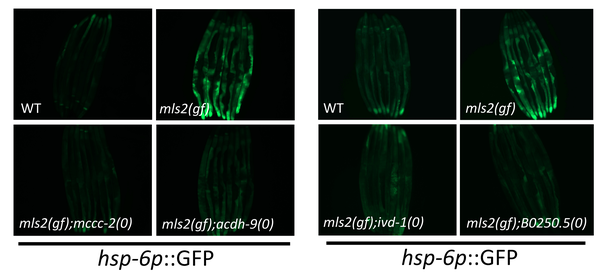
MLS-2 regulates UPR^{mt} cell non-autonomously



MLS-2 activates UPR^{mt} cell non-autonomously. A) Simplified scheme of *C. elegans.* B) Expression of *mls-2(gf)* cDNA in neurons activates UPR^{mt} in the intestine.

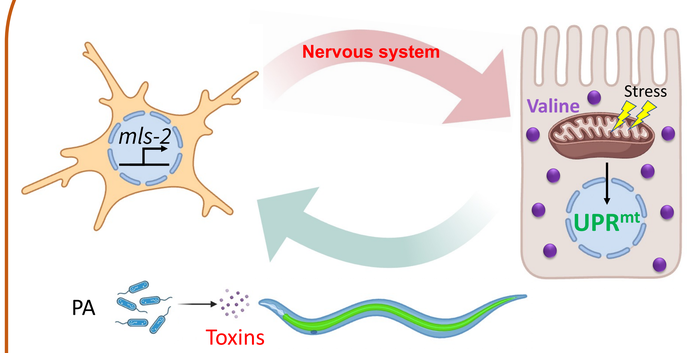
MLS-2 regulates UPR^{mt} via metabolic rewiring





BCAA catabolism is required for MLS-2-mediated UPR^{mt}. A) Forward genetics mutagenesis scheme. B,C) Loss of function mutations in leucine and valine catabolic genes suppress *mls-2(gf)*-UPR^{mt}.

Model



We find that MLS-2 acts cell non-autonomously in the nervous system to regulate the UPR^{mt} in the intestine, promoting the survival of the *C. elegans* host. Curiously, our genetic approaches suggest that MLS-2 stimulates the UPR^{mt} by modulating energy metabolism.