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We use isogenic *C. elegans* to study non-genetic influences on phenotypic heterogeneity. Heat shock proteins (*hsps*) are collectively controlled by the transcription factor HSF-1 and are essential to maintain protein-folding homeostasis. Despite their essentiality, previous works has shown that upon exposure to stress, *hsp* induction is variable across worms dictating an individual's ability to both cope with stress and to reproduce. The dose-sensitive and critical nature of these phenotypes for survival, prompted us to study inter-individual transcriptional variability under normal, unstressed conditions. We developed a sensitive high-throughput quantitative PCR method and incorporated a Bayesian statistical approach to accurately quantify inter-individual steady-state transcript variability in single worms.
We find that *hsp* transcripts are highly variable across worms even in the absence of exogenous stress. Surprisingly we observed that *in vivo*, inter-individual variability stems primarily from head neurons (*n-hsp*). It has been previously shown that ectopic *hsf-1* expression in head neurons (*n-hsf-1*) protects better against exogenous stress. We find a similar phenotype happens to individual worms with greater number of *n-hsps* under physiological conditions. In addition, we observe that the number of *n-hsps* is temperature sensitive, suggesting that neuronal stress could modulate adaptation to ambient temperatures. We find that *n-hsps* anti-correlate with *fat* desaturases, known to contribute unsaturated fatty acids (UFAs) to both fat storages and membranes. Negative regulation of UFAs is also caused by n-HSF-1, demonstrating causality. We have identified the neurons and the signals critical to relay information across tissues and propose a model where neurons act as a sensitive thermostat that orchestrates homeo-viscous adaptation. The variable activation of the thermostat at normal ambient temperatures creates phenotypic heterogeneity with potential adaptive value.

94 A memory circuit for coping with impending adversity. *Y. Eliezer*, N. Deshe, L. Hoch, S. Iwanir, C.O. Pritz, A. Zaslaver Genetics Department, Hebrew University, Jerusalem, IL.

Organisms' capacity to anticipate future conditions is key for survival. Associative memories are instrumental for learning from past experiences, yet, little is known about the processes that follow memory retrieval and their potential advantage in preparing towards impending developments. Here, using *C. elegans* nematodes, we demonstrate that odor-evoked retrieval of aversive memories induces rapid and protective stress responses, which increase animal survival prospects when facing imminent adversities. The underlying mechanism relies on two sensory neurons: one is necessary during the learning period, and the other is necessary and sufficient for memory retrieval. Downstream to memory reactivation, serotonin secreted from two head neurons mediates the systemic stress response. Thus, evoking stressful memories, stored within individual sensory neurons, allows animals to anticipate upcoming dire conditions, and provides a head-start to initiate rapid and protective responses that ultimately increase animal fitness.

95 Axonal transport of an insulin-like peptide mRNA promotes stress recovery. *R Chandra*, L Li, Z Husain, S Mishra, J Alcedo Department of Biological Sciences, Wayne State University, Detroit, MI.

Stress-induced aberrations in insulin or insulin-like peptide (ILP) signaling in the brain causes many neurological diseases. Here we report that mRNAs of specific ILPs are surprisingly mobilized to the axons of *C. elegans*. Axonal transport of the ILP *ins-6* mRNA facilitates recovery from stress, whereas loss of axonal mRNA delays recovery. In addition, the axonal traffic of *ins-6* mRNA is regulated by at least two opposing signals: one that depends on the insulin receptor DAF-2 and a kinesin-2 motor; and a second signal that is independent of DAF-2, but involves a kinesin-3 motor. While Golgi bodies that package nascent peptides have not been previously observed in *C. elegans* axons, we show that axons of stressed *C. elegans* have increased Golgi ready to package the peptides for secretion. Thus, our findings present a mechanism that facilitates an animal's rapid recovery from stress through ILP mRNA mobilization in neurons.

96 Insulin-Dependent Quiescence and Arrest at Hatching. *Bruce Wightman*, Zhengying He Biology Department, Muhlenberg College, Allentown, PA.

The *fax-1* nuclear hormone receptor and *unc-42* homeobox gene control interneuron identities in *C. elegans*. Both transcription factors function in specifying the identities of an overlapping subset of nematode interneurons including AVA, AVE, and AVK. Both *fax-1* and *unc-42* mutations cause a novel peri-hatching arrest in combination with *daf-2* insulin receptor mutations. Mutations in both *fax-1* and *unc-42* also enhance other aspects of insulin pathway function, including dauer formation and adult arrest, but not longevity, suggesting that disrupting the differentiation of specific interneurons leads to a reduction in insulin signaling. Peri-hatching arrest can be reversed by a mutation in the *daf-16* forkhead transcription factor, which functions downstream of *daf-2*, but not by mutations in the parallel TGFβ pathway. Arrest can also be suppressed by mutations in the *daf-12* nuclear receptor, indicating that the canonical insulin and steroid pathways that regulate dauer formation also promote arousal and developmental progression at hatching. Arrested *fax-1;daf-2* and *unc-42;daf-2* embryos typically display normal L1 morphology, but often remain coiled in a broken eggshell in a state of quiescence with weak or absent pharyngeal pumping. Arrested embryos can be prompted to vigorous movement by stimulation with blue light. Temperature-shift experiments suggest that embryogenesis, not L1 feeding after hatching, is the critical stage for quiescence and arrest. This phenotype is similar to that observed when embryos are subjected to osmotic stress. The *ssu-1* sulfotransferase gene is expressed in the ASJ sensory neurons and is required for peri-hatching arrest in response to NaCl, which is also dependent on insulin signaling (Burton et al., 2018). The peri-hatching arrest of both *fax-1;daf-2* and *unc-42;daf-2* double mutants is suppressed by a mutation in *ssu-1*. This result places the interneuron peri-hatching arousal function downstream of the osmotic stress signal and a putative steroid signal produced by the ASJ interneurons. Several models are consistent with the combined action of a steroid signaling pathway and neuroendocrine functions of insulin signaling in promoting arousal and developmental progression at hatching.

97 The flight response impairs cytoprotective mechanisms through neural inhibition of the insulin pathway. *D. Rayes*[1], María José De Rosa[1], Tania Veuthey[1], Jeremy Florman[2], Jeff Grant[2], Gabriela Blanco[1], Natalia Andersen[1], Mark Alkema[2] 1) Instituto de Investigaciones Bioquímicas de Bahía Blanca (CONICET), Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur,- Bahía Blanca, Argentina; 2) Department of Neurobiology, University of Massachusetts Medical School, Worcester, MA, USA.

An animal uses different survival strategies to cope with life-threatening situations. For instance, it can engage in a rapid and energy-demanding "fight-or-flight" response when encountering a predator, or it can induce the gradual and long-lasting activation of highly conserved cytoprotective processes in response to environmental stressors such as hypoxia, heat, oxidative stress, or food shortage. In animals across the evolutionary spectrum the continued activation of the fight-or-flight response weakens the animal's resistance to environmental challenges. In humans, for instance, the recurrent experience of stress in patients that suffer from post-traumatic stress disorder (PTSD) has been associated with decreased antioxidant capacity, accelerated aging and increased susceptibility to metabolic, cardiovascular and infectious diseases. However, the molecular and cellular mechanisms that regulate the trade-off between flight response and long-term stressors are poorly understood. Here we show that repeated induction of the C. elegans flight response shortens lifespan and inhibits conserved cytoprotective mechanisms. The flight response activates neurons that release tyramine, the invertebrate analog of adrenaline/noradrenaline. Tyramine stimulates the DAF-2/Insulin/IGF-1 pathway and precludes the induction of stress response genes by activating an adrenergic-like receptor in the intestine. In contrast, long-term environmental stressors, such as heat or oxidative stress, reduce tyramine release allowing the induction of cytoprotective genes. These findings demonstrate that a neural stress-hormone supplies a state-dependent neural switch between acute

flight and long-term environmental stress responses and provides mechanistic insights into how the flight response impairs cellular defense systems and accelerates aging.

98 ALA / RIS-dependent, neuropeptide-mediated quiescence follows mild sensory arousal during a *Caenorhabditis elegans* stress state. *P. McClanahan*[1], J. Dubuque[1], D. Kontogiogos-Heintz[1], B. Habermeyer[1], J. Xu[1], A. Ma[1], D. Raizen[2], C. Fang-Yen[1] 1) Department of Bioengineering, University of Pennsylvania, Philadelphia, PA; 2) Department of Neurology, University of Pennsylvania, Philadelphia, PA.

In vertebrates, threat responses often include quiescent behaviors such as freezing and tonic immobility. These quiescent behaviors can be modulated by internal states in ways that are not fully understood. Here we describe a quiescent behavior, post-response quiescence (PRQ), that occurs following the *C. elegans* locomotor response to aversive stimuli. PRQ occurs at low frequency in unstressed wild-type animals and is upregulated following exposure to stressors such as UV irradiation. We use a variety of stressors, as well as EGF overexpression, to induce a quiescent state called stress-induced sleep (SIS). Following either vibration or blue light stimuli, worms respond by forward or reverse movement, and then enter a brief (~45 second) period of increased movement and feeding quiescence. Using analysis of *aptf-1* and *ceh-17* mutants, we show that PRQ requires the function of the peptidergic sleep active neurons RIS and ALA, respectively. We further show that carboxypeptidase EGL-21 and calcium-dependent activator protein for secretion UNC-31 are required for PRQ, indicating the involvement of neuropeptide signaling. While these observations might suggest that PRQ is a form of rebound sleep following movement, we show that PRQ is not accompanied by a decrease in arousability, is not itself under homeostatic control, and does not increase when the stimulus duration or amount of quiescence interruption is increased, suggesting a function other than sleep homeostasis. We propose that PRQ represents a defensive freezing behavior commonly observed in other taxa, but not yet described in *C. elegans*. Besides its potential ethological significance, PRQ represents a simple, tractable model for studying how internal states like stress alter behavioral responses to external threat.

99 Suppression of distinct mitochondrial mutants by hypoxia. *J.D. Meisel*[1,2,3,4], T. Ast[1,2,3,4], V.K. Mootha[1,2,3,4], G. Ruvkun[1,2] 1) Department of Molecular Biology, Mass General Hospital, Boston, MA; 2) Harvard Medical School, Boston, MA; 3) Howard Hughes Medical Institute, Mass General Hospital, Boston, MA; 4) Broad Institute, Cambridge, MA.

Molecular oxygen (O_2) is central to mitochondrial physiology and disease – it is the driving force for oxidative phosphorylation and required for many biochemical reactions within the mitochondria, but can also combine with electrons leaked from the respiratory chain to form damaging species, or directly inhibit oxygen-sensitive processes. Recent work has shown that hypoxia (11% oxygen) is an effective treatment for a mouse model of Leigh Syndrome that carries a deletion in *Ndufs4* encoding a subunit of Complex I. However the precise molecular mechanism underlying the rescue by hypoxia remains elusive, and it is unknown whether hypoxia rescue will extend to other mitochondrial mutants and disease models. Here, we establish that hypoxia can rescue a Complex I mutant in *C. elegans*, as *nduf-7(et19)* animals benefit from 1% oxygen, displaying increased growth rate and reduced expression the mitochondrial stress reporter *hsp-6::gfp*. We also extend this finding to frataxin/FRH-1, a mitochondrial protein thought to be required for iron sulfur (Fe-S) cluster biosynthesis and classified as an essential gene. Loss of frataxin in humans underlies Friedreich's ataxia, for which there are no proven therapies. We show that *C. elegans* carrying a deletion in *frh-1* are viable when propagated at 1% oxygen. Remarkably, when grown in hypoxia, *frh-1(tm5913)* mutants are competent for Fe-S cluster biosynthesis, while animals lacking other Fe-S cluster biosynthesis components, namely NFS-1 and ISCU-1, are not viable in any oxygen tension. These results extend to human cell culture and yeast, and we show that hypoxia is able to increase bioavailable iron in cells as well as directly promote frataxin-independent Fe-S synthesis *in vitro*. Both *frh-1* and *nduf-7* mutants are exquisitely sensitive to hyperoxia (50% oxygen), and in ongoing work we have identified genetic suppressors which may shed light on the mechanisms underlying hypoxia's beneficial effects, as well as provide new candidates for therapeutic pathways.

100 ATFS-1 extends cellular longevity by protecting mitochondrial DNA from double-strand breaks. Chuan-Yang Dai, Chai-Chee Ng, Arnaud Ahier, *Steven Zuryn* Queensland Brain Institute, The University of Queensland, St Lucia, AU.

Owing to its highly oxidative microenvironment, the mitochondrial genome (mtDNA) is a faced with constant molecular insult during life. Molecular damage to mtDNA threatens cellular viability and is associated with ageing and a wide range of heritable and acquired diseases. The polyploid nature of the mtDNA can act as a defence mechanism by buffering the effects of molecular lesions. However, it remains poorly understood whether other processes mitigate the accumulation of genomic damage. Here, we invoked spatiotemporally controllable mtDNA double-stranded breaks in *C. elegans* to screen for nuclear factors that modify the penetrance and expressivity of mitochondrial genome lesions. We found that the nuclear-encoded factor ATFS-1 mediated dichotomous roles during mtDNA damage, depending upon its subcellular localisation. While, mtDNA double-stranded breaks induced nuclear translocation of ATFS-1 and activated the conserved mitochondrial unfolded protein response, nuclear restricted ATFS-1 severely enhanced the penetrance of mtDNA lesions. Oppositely, ATFS-1 restricted to the mitochondria strongly suppressed cellular dysfunction caused by mtDNA damage. We found that mitochondria-localised ATFS-1 acted cell-autonomously and independent of TFAM to protect mtDNA from double-stranded breaks, in a manner dependent upon its DNA binding capacity. Moreover, mitochondrial-localised ATFS-1 protected mtDNA from a variety of insults, and extended the functional longevity of cells in which it was expressed. Together, our results suggest that ATFS-1 can physically protect the mtDNA from accumulation of damage caused by exogenous and endogenous genotoxic insults, thereby improving cellular longevity.

101 Wnt signaling mediates intercellular mitochondrial stress response and aging. Qian Zhang, Xueying Wu, Peng Chen, *Ye Tian* State Key Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, 100101, China.

The mitochondrial unfolded protein response (UPR^{mt}) can be triggered in a cell-non-autonomous fashion across multiple tissues in response to mitochondrial dysfunction. The ability to communicate information about the presence of mitochondrial stress enables a global response that can ultimately better protect an animal from locally sensed stresses. Studies in *C. elegans* have established that the expression of the HD (Huntington Disease)-causing polyQ40 protein in neurons initiates the UPR^{mt} in the intestine, a process that induces global alteration of transcription networks to maintain a functional mitochondrial proteome. These studies have led to the concept of a "mitokine"— a signal generated in cells experiencing mitochondrial stress that is secreted, propagated, and subsequently perceived by peripheral tissues to regulate mitochondrial proteostasis. We found that loss-of-function mutations of retromer complex components responsible for recycling the Wnt secretion-factor/MIG-14 prevent Wnt secretion and thereby suppress cell-non-autonomous UPR^{mt}. Neuronal expression of the Wnt ligand/EGL-20 is sufficient to induce cell-non-autonomous UPR^{mt} in the intestine in a retromer- and serotonin-dependent manner, clearly implicating Wnt signaling as a strong candidate for the 'mitokine' signal.

102 The anti-cancer drug cisplatin selectively perturbs membrane protein targeting to the ER via oxidation of ASNA-1. *D. Raj*[1], O. Billing[2], A. Podraza[1], O. Hemmingsson[2], P. Naredi[1], G. Kao[1] 1) Department of Surgery, Gothenburg University, Gothenburg, Sweden; 2) Department of Surgery, Umea University, Umea, Sweden.

The anti-cancer drug cisplatin kills both mitotic and post-mitotic cells, but most (90-99%) tumor cells are post-mitotic. However its killing effect is best understood in dividing cells by DNA damage. *C. elegans* uniquely is a model both for mitotic and post-mitotic cells to study the effects of cisplatin.