

A neuron's ambrosia: non-autonomous unfolded protein response of the endoplasmic reticulum promotes lifespan

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The ability to protect cellular components in the face of deleterious conditions, such as exposure to chemical poisons, damaging radiation, or excessive heat, is crucial to organismal viability. Several compartmentalized stress response pathways have evolved to mitigate damage and increase cellular fitness in such environments, including the unfolded protein response of the endoplasmic reticulum (UPR^{ER}). The UPR^{ER} serves a critical protective role by promoting proteome integrity and lipid homeostasis while preventing the accumulation of damaged proteins and protein aggregates. The ability to mount an effective UPR^{ER} is a key determinant of organismal lifespan and stress resistance, however, as with other stress responses, it has been shown to decline markedly during the aging process. This leaves the proteomes of aged animals susceptible to dysregulation and dysfunction, which in turn further contributes to an accelerated aging process, development of age-associated pathology, and proteotoxicity (Higuchi-Sanabria et al., 2018).

Multicellular organisms are faced with the additional challenge of coordinating effective stress responses across multiple tissues and cell types. Cell-nonautonomous communication of UPR^{ER} has been well documented in the nematode *Caenorhabditis elegans*, in which activation of the UPR^{ER} specifically in neurons has been shown to increase ER stress tolerance and lifespan by inducing UPR^{ER} activation in the periphery. More specifically, pan-neuronal overexpression of a gene encoding one of the UPR^{ER} transcription factors, spliced *xbp-1* (*xbp-1s*), triggers the release of small clear vesicles from the signaling neurons. Presumably, the released neurotransmitters and/or biogenic amines trigger intestinal *xbp-1* splicing by the endoribonuclease IRE-1 and subsequent activation of UPR^{ER} through a cell-nonautonomous mechanism. In these animals (referred to as neuronal *xbp-1s* animals), the age-related decline in UPR^{ER} activation is abrogated and robust neuronal and intestinal transcription of UPR^{ER} targets continues even in aged animals (Taylor and Dillin, 2013).

Two distinct and independent arms of UPR^{ER} have been identified to contribute to the lifespan extension and stress resistance that are experienced by neuronal *xbp-1s* animals: a protein homeostasis and lipid homeostasis arm (Daniele et al., 2020). The activation of genes encoding UPR-specific chaperones supplement ER-resident chaperones to provide additional protein folding machinery in times of mild to moderate unfolded protein stress. Neuronal *xbp-1s* directly induces the expression of these chaperones in peripheral tissues and maintains their expression throughout age, resulting in increased stress resistance and

lifespan (Taylor and Dillin, 2013). Traditionally, UPR^{ER} targets also include components important for ER-associated degradation and ER-specific autophagy, but whether these processes are also activated downstream of cues from neuronal *xbp-1s* overexpression is yet to be determined. However, a recent study has found that there is in fact an increase in the transcription of lysosomal genes, which results in increased lysosomal abundance and lysosomal acidity (Imanikia et al., 2019b). Surprisingly, the beneficial effects of the lysosomal expansion are independent of autophagy, and rather promote protein homeostasis through increased clearance of damaged and aggregation-prone proteins from the cell. Furthermore, knockdown of the lysosomal lysine and arginine transporter, *laat-1*, results in decreased lifespan and a significant increase in sensitivity to ER stress, also independent of general autophagy (Higuchi-Sanabria et al., 2020a). These studies shape lysosome-ER communication and interactions as pivotal in organismal homeostasis and uncover an intriguing regulatory link between two seemingly opposing metabolic hubs of the cell.

Beyond protein homeostasis, neuronal *xbp-1s* promotes the activation of a metabolic arm of UPR^{ER}, which results in upregulation of lysosomal lipases, desaturases, and lipophagy, which together contribute to the significant reduction in total body fat seen in these animals. This lipid depletion involves conversion of stearic acid into oleic acid by the upregulated intestinal $\Delta 9$ desaturase FAT-6, which has been demonstrated to increase longevity in *C. elegans* (Imanikia et al., 2019a). These processes are coincident with ER expansion and remodeling, and hyperactivation of a lipophagy machinery, which are also necessary and sufficient to promote the beneficial effects of UPR^{ER} activation (Daniele et al., 2020). Interestingly, the former study showed that changes in lipid homeostasis are sufficient to improve protein quality control. Specifically, oleic acid supplementation was sufficient to decrease toxicity associated with ectopic polyQ expression (Imanikia et al., 2019a). However, lipophagy-mediated effects had little to no change in sensitivity to protein misfolding stress, suggesting the coordination of the protein and lipid homeostatic arms of UPR^{ER} are complex and likely highly specific to which processes are activated (Daniele et al., 2020).

A similar paradigm of cell-nonautonomous communication is seen in mammalian systems, where UPR^{ER} induction in hypothalamic pro-opio-melanocortin (POMC) neurons of mice induces metabolic changes in the periphery (Figure 1A). Specifically, elevated levels of Xbp1

in mouse POMC neurons induce *Xbp1* splicing by IRE1 and UPR^{ER} activation in the liver, which ultimately results in improved glucose levels, increased metabolic rate, and protection against obesity and diabetes. These effects are dependent on increased cellular sensitivity to leptin and insulin, which results from UPR^{ER}-mediated protection of the POMC neuronal proteome (Williams et al., 2014). Furthermore, POMC neurons have been shown to promote *Xbp1* splicing in the liver during sensory food perception, which proactively maintains organismal homeostasis by priming the liver for digestion of incoming nutrients. This suggests that cell-nonautonomous UPR^{ER} activation has important implications for organismal homeostasis *in vivo*, and is not merely some artificial system activated by exogenous genetic manipulations (Brandt et al., 2018). Indeed, the direct conservation of these signaling mechanisms across phyla suggests that they are of critical importance to organismal fitness, and that an improved understanding of their mechanistic subtleties and cellular consequences may have significant implications on the study of ER-related pathologies and aging.

To this end, Higuchi-Sanabria et al. (2020a) performed a neurotransmitter screen in *C. elegans* in an effort to identify neuronal subtypes involved in cell-nonautonomous communication of UPR^{ER} to the periphery. This study identified two neuronal populations as being critical in the neuron-to-periphery communication of ER stress: serotonergic and dopaminergic neurons. Perhaps most intriguingly, this work showed that not only can the protein homeostatic and metabolic roles of UPR^{ER} be separated, but unique neuronal circuits exist to elicit these divergent responses. Specifically, overexpression of *xbp-1s* in serotonergic neurons was sufficient to drive chaperone induction in the periphery to promote increased resistance to protein misfolding stress. However, serotonergic *xbp-1s* failed to promote the lipid depletion found in previous studies of neuronal *xbp-1s* signaling. Instead, dopaminergic *xbp-1s* was found to be sufficient to drive lipophagy-mediated lipid depletion, yet failed to drive protein homeostasis. Thus serotonergic and dopaminergic neurons, although both driving cell-nonautonomous activation of UPR^{ER} through *xbp-1s* in the periphery, ultimately initiate two distinct transcriptional programs, the coordinated efforts of which provide the beneficial effects on organismal lifespan and stress resistance conferred by pan-neuronal *xbp-1s* overexpression (Figure 1B) (Higuchi-Sanabria et al., 2020a).

Yet to be determined is how serotonergic and dopaminergic signaling of stress fits into the broader context of *C. elegans* neurobiology. Although serotonin and dopamine are required for the cell-nonautonomous communication of UPR^{ER} seen in this model, it is unclear whether their endogenous communication is dependent on the release of other neurotransmitters. Indeed, other neuronal cell types have been implicated in peripheral communication of UPR^{ER} in *C. elegans*. Expression of *xbp-1s* in RIM and RIC neurons, which are involved in tyramine communication, has been shown to induce intestinal UPR^{ER} activation and altered feeding behavior (Özbey et al., 2020). Additionally, glial

Perspective

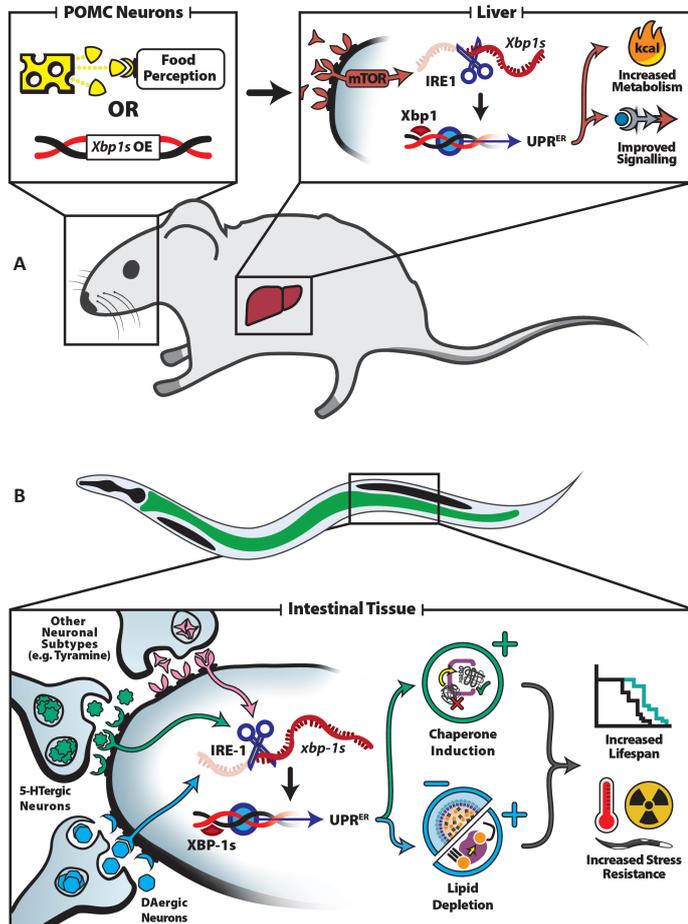


Figure 1 | Cell-nonautonomous UPR^{ER} signaling mechanisms in mice and *C. elegans*.

(A) Exogenous overexpression of Xbp1s in mouse POMC neurons or sensory food perception activate mTOR and initiate Xbp1 splicing by IRE1 in the liver, which results in an increased metabolic rate and a decreased incidence of obesity, which is mediated through improved sensitivity to leptin and insulin signaling. (B) Serotonergic and dopaminergic signaling in *C. elegans* drive intestinal *xbp-1* splicing by IRE-1 and upregulation of UPR^{ER} transcriptional targets, yet induce distinct mechanisms which increase organismal lifespan and stress resistance independently of one another. Serotonergic neurons trigger chaperone induction, which increases protein refolding within the ER; dopaminergic neurons induce lipid depletion, which globally decreases lipid levels within the cell and drives conversion of triglycerides to monounsaturated fatty acids. Tyramine has also been implicated in peripheral communication of stress, although its specific effects on intestinal tissue remain unclear. 5-HT: Serotonin; DA: dopamine; mTOR: mammalian target of rapamycin; OE: overexpression; POMC: pro-opio-melanocortin; UPR^{ER}: unfolded protein response of the endoplasmic reticulum.

cells have also been implicated in intestinal induction of UPR^{ER}: *xbp-1s* overexpression in a subset of four astrocyte-like glial cells increases lifespan and organismal resistance to ER stress (Frakes et al., 2020), showing evidence that neuronal cells are not the only cells important for driving non-autonomous UPR^{ER}. Therefore, it is critical to further characterize and map the complex neuronal circuits and cellular mechanisms involved in cell-nonautonomous UPR^{ER} transmission. Do neurons or glia directly and independently relay a signal to the periphery, or is there a concerted and coordinated effort? Which neural subtypes are actually important for sensing ER stress? In addition, the neuronal subtypes involved in mediating lysosomal changes in the periphery have yet to be identified. Are serotonergic, dopaminergic, or tyraminerbic neurons involved or are there still unidentified neuronal subpopulations critical for initiating a lysosomal response?

Beyond mapping the neuronal circuitry involved in initiating the transmission of stress, further work is necessary to identify how exactly peripheral cells receive and respond to these cues. While tyraminerbic receptors have been

identified directly in the intestine (Özbeý et al., 2020), whether serotonin or dopamine cues are received directly by peripheral tissue or relayed through an additional cell-type is unclear. In addition, it is intriguing how the same tissue – the intestine – responds to signals from serotonergic neurons and dopaminergic neurons in different ways, despite the transcription factor, XBP-1s, being shared in both responses. This begs the question of how one cell can coordinate two different responses solely based on the source of the signal received. Finally, it should be noted that there exist some circumstances in which hyperactivation of UPR^{ER} can be detrimental, and how a cell is able to identify such situations and differentiate between beneficial and detrimental stress responses is not well understood. An ongoing challenge will be to integrate these distinct and diverse signaling modalities – and those still yet to be identified – into a single, cohesive paradigm of organismal stress response coordination.

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