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Support cells in the brain promote longevity:

Glial cells in the brain use neuropeptides to communicate stress responses and longevity

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Aging is a multifaceted process that results in organismal decay. At the cellular level, protein homeostasis is a key system that becomes dysregulated with age, causing the accumulation of aberrant or unfolded proteins. In a youthful individual, unfolded proteins normally trigger the unfolded protein response (UPR), which up-regulates the protein clearance machinery and returns cells to a homeostatic state. The UPR is typically induced in a cell-autonomous manner. But some cells communicate protein folding stress to distal cells. For example, neurons communicate activation of the UPR to peripheral tissues to promote longevity in the worm *Caenorhabditis elegans* (1). On page 436 of this issue, Frakes *et al.* (2) show that support cells in the brain called glial cells (3) can also initiate long-range activation of the endoplasmic reticulum UPR (UPR^{ER}) in distal cells to coordinate stress resistance and longevity in *C. elegans* and that this occurs through neuropeptide secretion.

A key component of the UPR^{ER} is the conserved transcription factor X-box-binding protein 1 (XBP-1), which coordinates a stress response program. Frakes *et al.* show that overexpressing a constitutively active form of XBP-1, *xbp-1s*, in glia is sufficient to extend life span in *C. elegans*. The authors identify four astrocyte-like cephalic sheath (CEPsh) glial cells as the specific subpopulation of glia that controls UPR^{ER} activation in distal intestinal cells, promoting life-span extension. XBP-1 expression in glia selectively triggers the UPR^{ER} but not other stress responses (such as mitochondrial UPR) in intestinal cells.

How do glial cells communicate with distal intestinal cells? In a previous study, neurons expressing *xbp-1s* induce the UPR^{ER} in a non-cell-autonomous manner by releasing small clear synaptic vesicles containing neurotransmitters that could in turn, directly or indirectly, affect intestinal cells (1). Frakes *et al.* show that unlike neurons, glia do not use the machinery involved in the release of small clear synaptic vesicles to regulate signaling with distal intestinal cells. The authors reasoned that the distance a signal from CEPsh glial cells would need to travel to intestinal cells (~300 mm in *C. elegans*) might require long-range-acting neuropeptides, which are secreted from neurons, neuroendocrine cells, and glia. There are 119 neuropeptide precursor genes in *C. elegans*, and their peptide products regulate key physiological processes, including cell-to-cell communication (4). Neuropeptides go through a series of processing steps before they are packaged in dense-core vesicles and transported out of the cell. Frakes *et al.* show that disruption of dense-core vesicle export and neuropep-

tide processing in glial cells suppresses UPR^{ER} activation in intestinal cells. Thus, neuropeptide secretion mediates the effect of glial cells on the periphery (see the figure).

Many interesting questions remain. The specific neuropeptide(s) being secreted are not known, nor are their downstream targets and mode of action. In mammals, several neuropeptides and neurohormones (such as growth hormone–releasing hormone) are secreted by neurons or neuroendocrine cells in the hypothalamo-pituitary axis and exert effects on energy metabolism in peripheral tissues (5). Conversely, other peptide hormones are produced by peripheral tissues—such as leptin (adi-POSE), ghrelin (stomach), and insulin (pancreas)—and act in various regions of the brain and other organs (6). Some neuropeptides are conserved between *C. elegans* and humans (7). In *C. elegans*, the 119 neuropeptide precursor genes can be divided into three categories: 31 FMRFamide (Phe-Met-Arg-Phe-amide)–like peptides and 40 insulin-like peptides, both of which share some homology with neuropeptide precursor genes in mammals, and 48 neuropeptide-like protein genes (4). Leveraging single-cell RNA-sequencing data and targeted screens could identify the key neuropeptides expressed by CEPsh glia. Because *C. elegans* CEPsh glia share similarities with mammalian glia (8)—notably, astrocytes—it will be interesting to determine whether similar neuropeptides are produced by astrocytes in the human brain and whether they could mediate long-range signaling.

Once a specific neuropeptide or group of neuropeptides are identified, a key step will be to understand the mechanisms by which they influence life span. Neuropeptides could act directly on distal target cells or indirectly by affecting neuronal function. Identifying receptors for glial neuropeptides will be essential to decipher their mechanisms of action in distal cells. In previous studies, *xbp-1* expression in neurons resulted in lipid metabolism remodeling and lysosomal activity increase in the intestine, mediating life-span extension (9, 10). It would be interesting to explore whether the mode of action of neuropeptides secreted by glia reveals unknown longevity pathways in target cells.

Glia have unexpected roles in guiding nervous system development (3), in facilitating neurotransmission at synapses (3), and in whole-organism functions such as susceptibility to obesity (11). Glial cells (astrocytes, oligodendrocytes, Schwann cells, and microglia) can be equal or even greater in number than neurons in mammalian brains (12). A key question is whether glia in mammals also express specific neuropeptides that can signal at a distance and whether this is triggered by environmental stimuli. Glia can secrete some peptides, such as neuropeptide Y (13), which is involved in feeding behavior, circadian rhythm (body clock), learning, and memory (14). Discovering how different types of glial cells interpret their environment and what other cells they modulate will be essential for understanding the response to loss of protein homeostasis and how it evolved.

As Frakes *et al.* and others have shown, changes in protein homeostasis can be communicated in a non-cell-autonomous manner. This may be advantageous to generate a rapid physiological response to remove unwanted proteins and return homeostasis to the organism. Using *C. elegans* as a model to investigate these communication networks at a molecular level will reveal how biological systems communicate with one another and ideally uncover mechanisms of action that are conserved in humans. Understanding how

glial cells respond to stress and what neuropeptides they secrete may help identify specific therapeutic interventions to maintain or rebalance these pathways during aging and age-related diseases.

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Distant longevity signaling

Glial cells can communicate stress resistance to distal cells through neuropeptide secretion. Activating the endoplasmic reticulum unfolded protein response (UPR^{ER}), a key component of which is XBP-1 (X-box-binding protein 1), in glial cells results in a non-cell-autonomous UPR^{ER} activation in distal intestinal cells, which leads to increased stress resistance and longevity in *Caenorhabditis elegans*. Neuropeptide secretion by glial cells is critical for this communication.