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Systemic regulation of autophagy in *Caenorhabditis elegans*

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Abstract

When no supply of environmental nutrients is available, cells induce autophagy, thereby generating a source of emergency metabolic substrates and energy to maintain the basal cellular activity needed for survival. This autophagy response to starvation has been well characterized in various multicellular organisms, including worms, flies and mice. Although prosurvival effects of autophagy in response to starvation are well known in animals, the mechanisms by which animals regulate and coordinate autophagy systemically remain elusive. Using *C. elegans* as a model system, we found that specific amino acids could regulate starvation-induced autophagy, and that MGL-1 and MGL-2, *Caenorhabditis elegans* homologs of metabotropic glutamate receptors, were involved. MGL-1 and MGL-2 specifically acted in AIY and AIB neurons, respectively, to modulate the autophagy response in other tissues such as pharyngeal muscle. Our recent study suggests that the autophagy response to starvation, previously thought to be cell-autonomous, can be systemically regulated, and that there is a specific sensor for monitoring systemic amino acids levels in *Caenorhabditis elegans*.

Keywords

autophagy; starvation; metabotropic glutamate receptor; amino acid response; *Caenorhabditis elegans*; hormesis

When faced with nutritional deprivation or starvation, individual cells can make physiological changes by modulating intracellular signaling so as to cope with nutrient starvation. One of the key responses against starvation is autophagy, which generates a source of metabolic substrates and energy to maintain basal cellular activities needed for cells to stay alive. This prosurvival function of autophagy in response to starvation has been well studied in various organisms including yeast, worms, flies and mice, suggesting the possibility that autophagy evolved as a key survival mechanism to cope with nutrient starvation.

Since too much self-destruction can be deleterious for cells, even during starvation, autophagy must be regulated within a tolerable range for survival. This necessity of tight regulation of autophagy is even more stringent in multicellular organisms because of the danger that uncoordinated autophagy responses in essential tissues could impair their function and eventually be harmful for survival of the organism. In *Caenorhabditis elegans*, for example, we reported previously that excessive autophagy in pharyngeal muscle, a critical organ for recovery from starvation, causes its malfunction and eventually leads to death after starvation. Thus, it is reasonable to suppose that autophagy responses must be coordinated in multicellular organisms both cell-autonomously and cell-nonautonomously. Although cell-autonomous regulation of autophagy is well known, little is known about the mechanism by which autophagy is regulated systemically, especially in response to environmental change.

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Using *C. elegans*, we found that treatment with a subset of amino acids rescues the starvation hypersensitivity of *gpb-2* mutants, and *mgl-1* and *mgl-2* metabotropic G-protein-coupled glutamate receptors are involved in the modulation of amino acid response and starvation response. We also found that treatment with specific amino acids including leucine, alanine and glutamine can decrease excessive autophagy in pharyngeal muscle, one cause of death in *gpb-2* mutants during starvation, and *mgl-1* and *mgl-2* are involved in the modulation of autophagy by amino acids. Interestingly, *mgl-1* and *mgl-2* are mainly expressed in a limited subset of neurons, not in pharyngeal muscle, leading to the intriguing possibility that *mgl-1* and *mgl-2* can modulate starvation responses including autophagy in a cell-nonautonomous manner. Using transgenic rescue lines with neuronal-specific expression of *mgl-1* and *mgl-2*, we found that *mgl-1* and *mgl-2* mainly act in AIY and AIB neurons, respectively, to modulate a starvation response, suggesting that autophagy regulation by *mgl-1* and *mgl-2* is likely cell-nonautonomous.

We also found that specific amino acids can suppress starvation-induced hormesis—also likely a systemic response—and *mgl-1* and *mgl-2* are involved in the process. Since autophagy plays a protective role in heat shock response, oxidative stress response, and aging, and starvation induces autophagy, it is possible that autophagy plays an important role in starvation-induced hormesis in multicellular organisms. It will be interesting to test if inhibition of autophagy affects starvation-induced hormesis.

For many years, it has been generally assumed that autophagy may be regulated cell nonautonomously by hormonal regulation, based on the fact that insulin-PI3K-AKT-mTOR signaling is one of the key regulators of autophagy. Although growth factor signals of the insulin and other families can modulate autophagy in mammalian cell culture systems, it had not been directly shown that autophagy can be regulated systemically in multicellular organisms, especially in response to environmental change. Our results provide in vivo evidence that animals can modulate autophagy systemically, specifically in response to amino acids.

Amino acids can suppress the autophagy response in different mammalian cell lines by activating mTOR signaling. Among the 20 amino acids, leucine is the most potent inhibitor of autophagy in cultured cells. Interestingly, we found that leucine, alanine and glutamine suppress starvation-induced autophagy, whereas glutamate instead enhances it, suggesting that multicellular organisms have an additional level of autophagy regulation in response to amino acids beyond the individual cell level. In fact, we found that the amino acid response is regulated by *mgl-1* and *mgl-2*, which mainly act in specific neurons. These data suggest that *C. elegans* senses specific amino acids through specific neurons, regulating starvation responses including autophagy systemically. It remains unknown how specific neurons modulate autophagy systemically, yet it is reasonable to think that specific hormones, perhaps neuropeptides, are involved in the process. Our model system might help to find such peptide signals.

In summary our data suggest that amino acids, which may be a component of the signals by which animals detect food, modulate specific neurons by modulating the activities of metabotropic glutamate receptors, which in turn cell-nonautomously modulate starvation responses including autophagy in a multicellular organism, *C. elegans*.

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