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SPOTLIGHT

Getting under the skin: Cuticle damage elicits systemic autophagy response in *C. elegans*

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In this issue, Zhang et al. (2019. *J. Cell. Biol.* https://doi.org/10.1083/jcb.201907196) describe a molecular mechanism by which cuticular damage in the nematode *C. elegans* leads to systemic induction of autophagy by signals propagated from sensory neurons via the TGF-β signaling pathway.

The cellular recycling process of macroautophagy (hereafter referred to as autophagy) promotes cell survival by the lysosomal degradation of cytoplasmic components, including macromolecules and organelles. Autophagy is induced by different environmental stressors including starvation and infection and is regulated extensively by posttranslational mechanisms, which ensure an immediate response to such stressors and intracellular signals. Upstream regulators of autophagy include the conserved nutrient sensors mTOR and AMP-activated kinase (AMPK), which directly phosphorylate the autophagy-initiating kinase ULK1/Atg1 (1). Interestingly, up-regulation of AMPK or ULK1/Atg1 in the nervous system of the fruit fly *Drosophila melanogaster* does not only induce autophagy cell autonomously, but also cell nonautonomously in the intestine (2). Similarly, in *Caenorhabditis elegans*, the glutamate receptor homologues MGL-1 and MGL-2, which are expressed in specific interneurons, are required for autophagy induction in distal pharyngeal muscles in a starvation model (3). Since autophagy can influence organismal health it is important to identify the mechanisms by which environmental changes or intracellular signals (such as neuronal AMPK and ULK1/Atg1 overexpression, or reduced nutrition) elicit autophagy either systemically or in distal tissues. In this issue, Zhang et al. describe a novel circuit in which a damaged cuticle in *C. elegans* leads to the systemic induction of autophagy during larval development (Fig. 1).

In a genetic screen for novel autophagy regulators in *C. elegans*, Zhang et al. identified several loss-of function alleles in collagen genes, including *dpy-10*, that enhance degradation of the autophagy receptor SQST-1 (mammalian p62/SQSTM1) by boosting autophagy (4). Mutation of *dpy-10* disrupts collagen organization, which causes the cuticle to lack specific structural components called furrows. Zhang et al. discovered that such a damaged cuticle leads to a decrease in the accumulation of SQST-1/p62 in distal tissues, i.e., the hypodermis, muscle, and intestine, consistent with increased autophagy (4).

How can signals from a damaged cuticle lead to the activation of systemic autophagy? Taking advantage of the tractable genetics in *C. elegans*, Zhang et al. found that functional cilia of sensory neurons are required for the activation of autophagy in *dpy-10* mutants (4). Cilia are present in the dendritic ends of sensory neurons in *C. elegans* and some cilia extend through the cuticle to the environment, whereas others project into the cuticle or other cells (5). While cilia seemed intact in *dpy-10* mutants, loss of function of two neuronal genes involved in ciliogenesis, *che-3* and *osm-3*, was found to be required for the activation of autophagy in distal tissues of *dpy-10* animals, implying that autophagy could be controlled cell nonautonomously by neuronal signals. Interestingly, the nervous system of *C. elegans* can nonautonomously control protein homeostasis by the activation of systemic stress responses (6), and a few neuronal signals have been found to mediate such responses, including the neurotransmitters serotonin (5-HT) and octopamine, as well as the neuropeptide FLP-2 (6). While neuronal overexpression of the active form of the UPR^{ER} transcription factor XBP-1 in *C. elegans* has been reported to drive expression of lysosomal genes in the intestine (7), the specific neurons and secreted molecules that induce systemic autophagy have yet to be identified. To this point, Zhang et al. found that a secreted peptide, the growth factor DAF-7/TGF-β, acts downstream of cilia in the autophagy response induced by cuticle damage in *dpy-10* animals (4). DAF-7/TGF-β is exclusively released by *C. elegans* ASI amphid neurons, which are activated by environmental signals including food availability and pheromones (8). It will be interesting to determine by which mechanism DAF-7/TGF-β is released from the ASI neurons for autophagy induction, since *unc-31/CAPS*, which is essential for dense-core vesicle release, was not required for autophagy induction in *dpy-10* mutants.

DAF-7/TGF-β acts via the TGF-β receptors DAF-1/DAF-4, which in turn activate the receptor-regulated Smad transcription factor complex DAF-8/DAF-14 to translocate into the nucleus. In the nucleus, the DAF-8/DAF-14 complex inhibits the common-partner Smad transcription factor complex DAF-3/DAF-5, which promotes development and mediates a TGF-β response. To test the role of this signaling pathway, Zhang et al. tested *dpy-10* mutants that lack the growth hormone *daf-7*/TGF-β in addition to the pro-dauer Smad *daf-3* and found autophagy to be systemically induced. In

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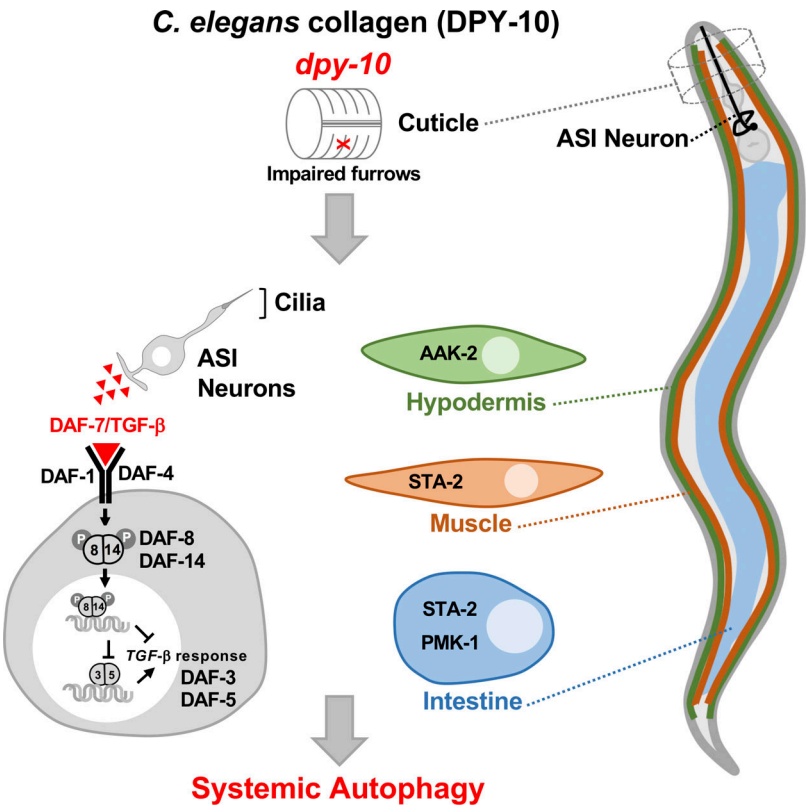

Figure 1. **Cuticle damage in *C. elegans dpy-10* mutants induces autophagy.** Cuticle damage caused by the impairment of furrows in *dpy-10* mutants is sensed by cilia of sensory neurons. The ASI sensory neurons secrete the TGF-β ligand DAF-7, which then acts on distal tissues to induce systemic autophagy. In distal cells, DAF-7/TGF-β is bound by the TGF-β receptors DAF-1/DAF-4, which activate the receptor-regulated SMADs DAF-8/DAF-14 that translocate into the nucleus. There, the common partner SMADs DAF-3/DAF-5 are inhibited and a TGF-β response is activated. Tissue-specific induction of autophagy is ensured in *dpy-10* mutants via the cell-autonomous regulation mediated by AAK-2/AMPK in the hypodermis, by STA-2/Stat in the muscle, and by both STA-2/Stat and PMK-1/MAPK in the intestine.

powerful genetic experiments, Zhang et al. subsequently demonstrated that the tissue-specific restoration of DAF-3/Smad, which suppresses the signals from TGF-β signaling, is sufficient to prevent autophagy induction in the hypodermis, muscle, and intestine, but not in ASI neurons (4). These results indicate that DAF-7/TGF-β released from ASI neurons mediates the autophagy induction in distal tissues via cross-organ communication. This raises the question of how autophagy is induced in the target tissues of *dpy-10* mutants. Zhang et al. evaluated the cell-autonomous role of the upstream autophagy regulator AMPK in *dpy-10*-mediated autophagy by monitoring the accumulation of SQST-1/p62 aggregates (and therefore block in autophagy) in different tissues (4). They found that *aak-2/AMPK*, the *C. elegans* orthologue of the catalytic α subunit of AMPK, is required for *dpy-10*-induced autophagy exclusively in the hypodermis and not in the muscle or intestine. This indicates that there are distinct tissue-specific mechanisms for the induction of autophagy in response to *dpy-10* loss-of-function.

Since mutants with cuticle damage, such as in *dpy-10* mutants, have been found to increase osmotic resistance (9, 10) by the activation of specific stress responses (11), Zhang et al. (4) next investigated whether the autophagy response and other stress responses were similarly regulated in *dpy-10* animals. The *dpy-10*–induced osmotic stress and antimicrobial defense responses were not altered by loss of *che-3*/ciliogenesis or *daf-7*/TGF-β; therefore, the circuit by which a damaged cuticle triggers the systemic induction of autophagy is likely parallel to the *dpy-10*–induced stress responses. While *daf-7*/TGF-β was not required for the *dpy-10*–induced stress responses, mediators of the antimicrobial defense, such as the transcription factor STA-2/STAT (11) and the p38 MAPK signaling cascade (12), were notably found to be required for the autophagy induction in select tissues. Specifically, Zhang et al. (4) discovered a role for the transcription factor *sta-2/STAT* and the p38 MAPK *pmk-1* in the intestine, but not in the hypodermis of *dpy-10* animals. In muscle cells, only *sta-2/STAT* but not *pmk-1/MAPK* was required for *dpy-10*–induced autophagy. It will be interesting to further investigate the coordinated regulation of stress responses and autophagy in a tissue-specific manner, since it remains unclear in which tissues *sta-2/STAT* and *pmk-1/MAPK* are required for the induction of the antimicrobial defense. Similarly, it will be useful to determine whether and where autophagy is required for the antimicrobial response and the osmotic resistance phenotypes of *dpy-10* animals.

Taken together, Zhang et al. (4) describe an elegant yet complex circuit in which signals elicited from a damaged cuticle activate systemic autophagy via tissue-specific signal transduction by upstream neuronal signals involving DAF-7/TGF-β during *C. elegans* development. Since autophagy plays important roles in development as well as in many age-related diseases (13), new information on the regulatory circuits that control autophagy in and between tissues could have important implications for future efforts to modulate the process to improve human health.

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