Activated Acinus boosts basal autophagy

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Acinus (Acn) is a nuclear protein that participates in the regulation of autophagy. Loss of Acn function prevents autophagy in starving cells. Conversely, Acn activation induces basal autophagy. This enhances the quality control functions of autophagy such as the removal of misfolded proteins, thereby reducing neurodegeneration and prolonging lifespan. Acn activity is enhanced by Akt1-mediated phosphorylation, which counteracts the cleavage of Acn by a caspase-3 homolog.

Macro-autophagy (here simply referred to as “autophagy”) is a catabolic process that helps cells cope with starvation by non-specifically degrading cellular content to reclaim necessary nutrients. In a second role, autophagy operating at basal levels contributes to quality control in cells and aids in the removal of aberrant proteins or organelles that can accumulate in response to a variety of cellular stresses. It is important to understand how the basal level of autophagy is adjusted to varying degrees of stress in the absence of starvation as failures in quality control have been linked to neurodegenerative diseases, inflammation, and cancer.¹

Our recent work² indicates that Acinus (Acn) protein may play a role in that regulation. Acn is a conserved nuclear protein that interacts with the exon junction complex and spliceosomes and thereby modulates specific RNA splicing events.³,⁴ The first indication of a role in autophagy came from acn loss-of-function mutations, which interfere with autophagosome maturation.⁵ In well-fed Drosophila autophagy is inhibited by target of rapamycin (TOR) signaling,⁶ but this inhibition can be bypassed by Acn overexpression. Even more strikingly, high-level Acn expression is lethal, but viability is restored when autophagy is blocked.⁵ These observations emphasize the importance of the control of Acn activity for adjusting the levels of autophagy. In our recent study⁷ we explored how multiple intracellular signals can modulate Acn levels, which might serve as a focal point for adjusting the basal level of autophagy.

The dynamic regulation of Acn is exemplified in the developing eye where its expression in photoreceptor cells changes rapidly depending on cell type and developmental stage.⁵ To our surprise, a GFP reporter transgene detected little regulation at the transcriptional level; instead, Acn is primarily regulated at the level of protein stability.² Two conserved elements that contribute to its regulation are a caspase cleavage site ⁷ and a pair of Akt1 consensus target sites.⁸ To test their importance in vivo we generated transgenic flies in which endogenous Acn was replaced by mutant proteins designed to prevent cleavage by caspases (Acn⁵D527A) or mimic phosphorylation at the Akt1 target sites (Acn S641,731D). Both of these mutations stabilized Acn and yielded interesting physiological consequences.

In these mutant animals, all stages of autophagy were enhanced, whether evaluated by live imaging of GFP-Atg8a fluorescence in early autophagosomes, antibody staining for endogenous Autophagy-related 8a (Atg8a) protein, or lysotracker accumulation in autolysosomes. Electron microscopy revealed a remarkable increase in size and abundance of autolysosomes compared to control animals. The relative increase in autophagy was most pronounced in fed animals, indicating that elevated Acn levels enhanced basal, starvation-independent levels of autophagy. The resulting improved cellular quality control was...
evident from an enhanced ability to clear aggregation-prone poly-Q huntingtin protein from photoreceptors and, maybe most strikingly, a significantly prolonged longevity (Fig. 1).

To identify the protease responsible for Acn cleavage we used a targeted RNAi screen. Acn overexpression in the eye causes mild eye roughness that served as readout. Among the 9 Drosophila caspases tested in this screen only knockdown of death caspase-1 (Dcp-1), a homolog of mammalian caspase-3, enhanced Acn function. Elevated levels of Acn in dcp-1 mutant cells and the resulting upregulation of autophagy substantiated the physiological relevance of the genetic interactions in the eye.

Sahara and colleagues first detected cleavage of mammalian Acn proteins by caspase-3 activity that was upregulated in the context of apoptotic cells. Our observations extend their original finding to the context of apoptotic cells. Our observation that a nuclear pool of Akt1 may phosphorylate Acn, and possibly other nuclear targets yet to be identified, leading to increased basal autophagy.

How Acn induces basal autophagy remains unclear. As Acn is primarily nuclear and part of the apoptosis-and splicing-associated protein (ASAP) complex, one possible mechanism may relate to the regulated splicing of genes involved in autophagy. Alternatively, we detected cytosolic Acn in a subset of cells in developing eyes, raising the possibility that Acn functions outside the nucleus. Deciphering the mechanisms by which Acn regulates basal autophagy will be an important goal of our future research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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