Actin cytoskeleton modulators reveal novel roles for autophagy in health and disease

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Summary

Autophagy is a well-conserved process that whereby lysosomes degrade cytoplasmic components which have been captured in double-membrane vesicles (autophagosomes). The physiological relevance of autophagy comes from its role in maintaining the normal turnover of cellular components and clearing pathogens, toxic damaged organelles, long-lived proteins and aggregates. Inhibition of autophagy at any step (initiation, maturation or fusion) will have a common outcome: accumulation of toxic materials and damaged mitochondria, which, in turn, makes cells susceptible to disease initiation and progression. The actin cytoskeleton, apart from managing the cell structure and intracellular vesicle trafficking, plays an important role in modulating the autophagy pathway. Here I have shown how actin biology serves to link key physiological and pathologically relevant processes to autophagy.

First, loss of function of CCT, the obligatory chaperonin for actin folding, blocks autophagy primarily through reducing the actin polymerization. CCT depletion and actin depolymerisation enhanced the accumulation of non-functional autolysosomes (unable to degrade the autophagic material), as a consequence of increased lysosomal pH and reduced delivery of cathepsin enzymes and V-ATPase to autolysosomes. The autophagy inhibition caused by CCT depletion led to the accumulation of classical autophagic substrates and effectors of neurodegeneration: mutant polyQ-huntingtin, p62, and tau in HeLa cells, primary mouse neurons and *Drosophila*. CCT loss of function in autophagy-incompetent cells or *Drosophila* was unable to further enhance the accumulation of these autophagic substrates, suggesting that these consequences of CCT compromise were autophagy-dependent.

Secondly, I identified the downstream effectors of the Hippo signalling (YAP and TAZ) as novel transcriptional regulators of the actomyosin system in response to cell density. At high cell density, which induces the contact inhibition of proliferation by inactivating YAP/TAZ, the intracellular actin tension is dramatically reduced due to the loss of F-actin stress fibres. This results in autophagy inhibition. Reactivation of YAP/TAZ at low cell density leads to cell proliferation, overgrowth, rescues the actomyosin defects and results in the reestablishment of basal autophagy. As actin dynamics governs cell migration and invasion, these observations might be relevant for many physiological and pathological conditions, like wound healing and cancer.