The role of nuclear envelope components in the regulation of autophagy

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ABSTRACT

The crosstalk between autophagy and the nucleus in the context of physiology and pathology remains largely elusive. We investigated this potential association by dissecting the involvement of nuclear membrane components in the autophagic process. To this end, we examined the role of the highly conserved, *Caenorhabditis elegans* nuclear envelope anchorage protein 1 (ANC-1) and its mammalian orthologues Nesprin 1 and 2 in autophagy. These are large, multi-domain, outer nuclear membrane proteins that maintain nuclear integrity. Nesprin 1 and 2 isoforms are highly abundant in multiple tissues, including the brain, heart, liver and kidney. In humans, polymorphisms in Nesprin 1 and 2 have been implicated in neurodevelopmental disorders, such as learning disability, autism and ataxia, as well as, in muscular dystrophies, in cancer and ageing. Using both *C. elegans* and mouse models we uncovered a novel link between these nuclear envelope components and autophagic processes. We find that autophagy regulates Nesprin 1 and 2 protein levels under both basal conditions and nutrient stress. Conversely, both *C. elegans* ANC-1 and mouse Nesprins interact with, and regulate the abundance and localization of general and selective autophagic machinery components such as LGG1/LC3B and SQST-1/p62. Notably, these nuclear envelope components act downstream of autophagy under nutrient stress to maintain nucleolar shape and integrity. Thus, cross-regulation between autophagy and ANC-1/Nesprin proteins promotes nuclear homeostasis and safeguards the nucleolus and nuclear proteins under stress and during ageing.