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Autophagy functions in programmed cell death

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Abstract

Autophagic cell death is a prominent morphological form of cell death that occurs in diverse animals. Autophagosomes are abundant during autophagic cell death, yet the functional role of autophagy in cell death has been enigmatic. We find that autophagy and the *Atg* genes are required for autophagic cell death of *Drosophila* salivary glands. Although caspases are present in dying salivary glands, autophagy is required for complete cell degradation. Further, induction of high levels of autophagy results in caspase-independent autophagic cell death. Our results provide the first in vivo evidence that autophagy and the *Atg* genes are required for autophagic cell death and confirm that autophagic cell death is a physiological death program that occurs during development.

Keywords

autophagy; cell death; *Atg*; caspase; *Drosophila*

Autophagy is a catabolic process that promotes cell survival during starvation. The presence of autophagosomes in dying cells suggested that autophagy may function in cell death,[1] but this was a controversial hypothesis given the association of autophagy with survival.[2,3] The presence of caspases in dying autophagic cells[4, 5] increased the controversy with speculation that these cells die via apoptosis, and thus autophagosomes were not involved in the death process. We show that under physiological conditions during development, autophagy and the *Atg* genes are required for programmed cell death.[6] Apoptotic factors are active, yet complete cell degradation does not occur in the absence of autophagy. Our findings indicate that the function of autophagy needs to be carefully evaluated in the context of the cell and system physiology as autophagy functions in both cell survival and cell death.

To evaluate the function of autophagy in cell death, we analyzed *Drosophila* larval salivary glands as an in vivo model system of autophagic cell death. Expression of either of the growth regulators Dp110, Akt or activated Ras, or decreased function of any one of 8 different *Atg* genes, including *Atg1*, *Atg2*, *Atg3*, *Atg6*, *Atg7*, *Atg8*, *Atg12*, and *Atg18*, blocked autophagy[7-11] and prevented complete degradation of salivary glands during development.[7] Significantly, loss of *Atg* gene function did not lead to premature cell death, indicating that autophagy does not promote survival of these dying cells. The incomplete degradation of cells when autophagy is inhibited provides the first definitive evidence that autophagy and the *Atg* genes are required for cell degradation in the physiological context of development.

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As autophagy can either protect or kill a cell, the mechanistic differences that distinguish these two cell fates are critical to determine. We find that autophagic cell death utilizes much of the same molecular machinery as starvation-induced autophagy, suggesting that other factors may differentiate the role of autophagy in survival and death. Autophagy can be either selective or non-selective in its recruitment of cargo for lysosomal degradation.[12] Autophagic degradation of the antioxidant catalase leads to accumulation of reactive oxygen species and cell death,[13] illustrating that selective degradation of survival factors can promote cell death. Similarly, the recruitment of mitochondria by mitophagy[14] in a metabolically active cell could result in cell death. Alternatively, the quantity of autophagy might decide between cell survival and death as excessive levels of autophagy could deplete cellular resources to a point incompatible with cell survival.[15] In salivary glands, growth arrest leads to the induction of low levels of autophagy that do not result in cell death.[7] A subsequent rise of the steroid ecdysone triggers transcription of *Atg* genes followed by an increase in autophagosomes and rapid degradation of salivary glands.[6,16] Similarly, high levels of autophagy induced by Atg1 expression cause cell death,[7,9] supporting the notion that excess autophagy contributes to cell death. Finally, the presence of cell death factors may shift autophagy toward cell killing. Caspases are present during autophagic cell death of salivary glands and in vitro models of lumen formation,[4,5,17,18] and the addition of these cell death molecules might lead to autophagic death. Indeed, the combined inhibition of caspases and autophagy leads to an increased block in salivary gland degradation, suggesting that both autophagy and caspases function in autophagic cell death. However, inhibition of caspases alone does not completely prevent gland degradation. Further, multiple in vitro studies indicate that autophagic death occurs following the inhibition of apoptotic factors[19, 20] allowing the possibility that autophagic cell death is an alternate and non-physiological form of cell death that occurs only when apoptotic factors are inhibited. Our in vivo results show that even in the presence of apoptotic factors, autophagy is required for physiological autophagic cell death during development.

How do we now assimilate the opposing roles for autophagy in cell survival and death, and the necessity for multiple forms of cell death? Autophagy may be required to generate energy for phagocytosis of cell corpses[18]. We do not observe an association of phagocytes with dying salivary gland cells[5], however, suggesting that the mechanistic role of autophagy in cell death may be context-dependent. One possibility is that phagocytes may be temporally and/or spatially restricted from dying cells, and autophagy may be required to complete self-degradation. Further, the size and mass of dying cells and tissues, such as the giant salivary gland cells may exceed the capacity of available phagocytes and require autophagy for bulk removal of abundant cytoplasm. Finally, perhaps we should consider survival of a cell compared to survival of a multi-cellular organism. In a single cell organism such as yeast, breakdown of cellular content provides resources to the cell, protecting the cell against starvation conditions. In multi-cellular organisms, the breakdown of cellular components, or of entire cells or tissues, could be utilized as a nutrient resource for the organism. Fly salivary glands undergo autophagic cell death during metamorphosis, a life stage in which the fly does not eat and must complete the development of adult structures in the absence of an external nutrient source. The degradation of larval salivary glands by autophagy could provide an internal nutrient source for development of adult structures and survival of the organism. Autophagic cell death is also observed in amphibians during metamorphosis of the tadpole tail[21], and it has been speculated that the tail provides nutrients for the rapidly growing froglet. Although autophagy kills the individual cells in a tissue, the resources generated promote survival of the organism. In this way, we can consider autophagic cell death as another way autophagy promotes survival. Understanding that autophagy can either protect or kill cells requires us to consider autophagy more fully and in the context of the physiology of the cell, the system and the organism in order to better grasp an understanding of its function.

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