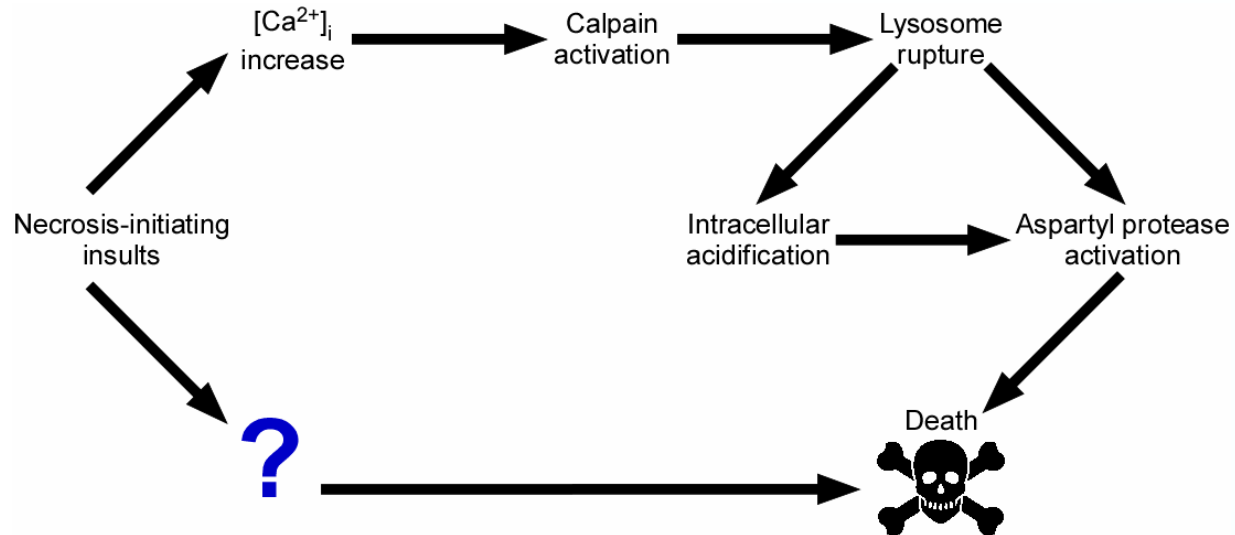
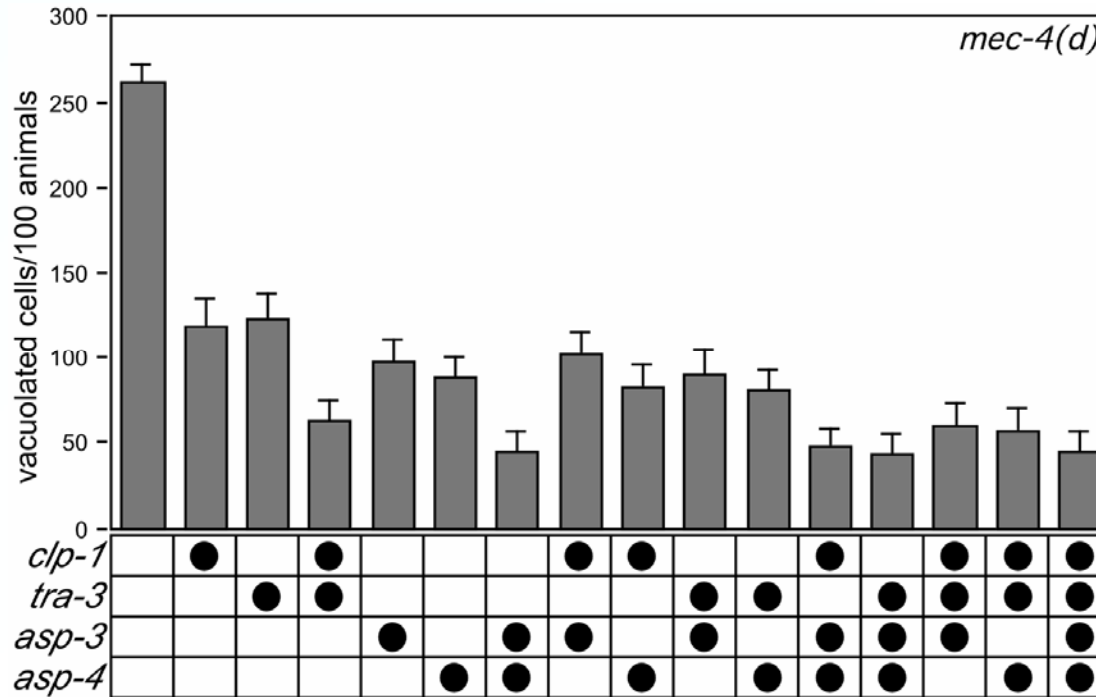
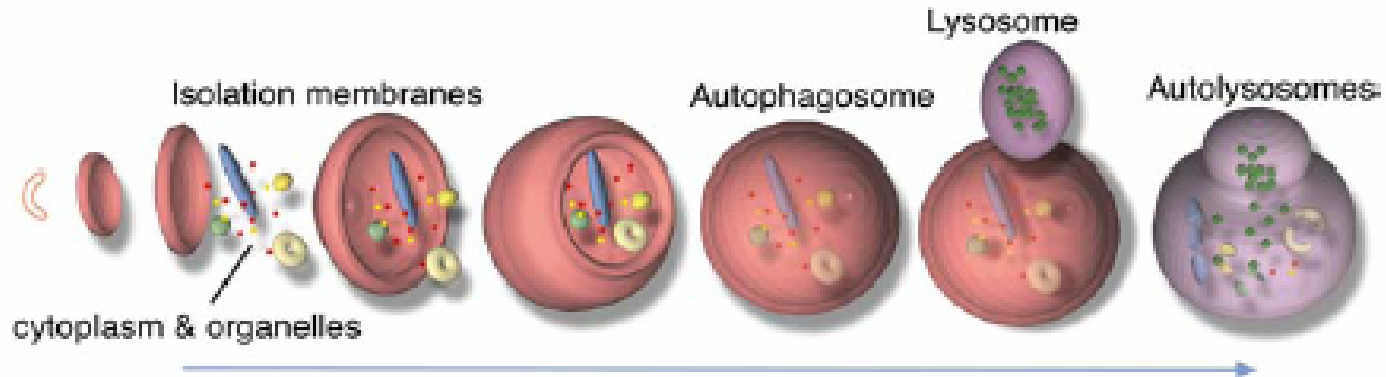


# Additional pathways mediating death?



# Autophagy

- The primary intracellular catabolic mechanism for degrading and recycling proteins and organelles



Yoshimori, 2003

## Autophagy physiological roles:

- Response to stress  
(hypoxia, overcrowding, high temperature, accumulation of damaged cytoplasmic components)
- Growth regulation & development
- Innate immunity
- Ageing

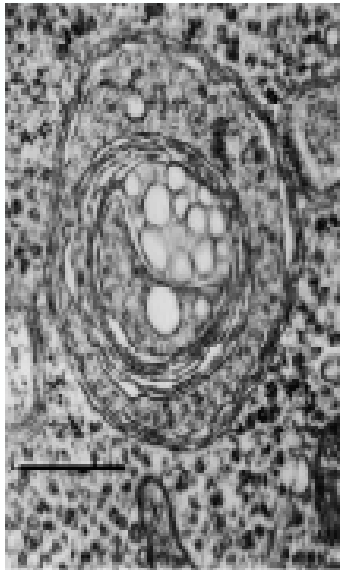
# Is autophagy involved in necrosis?

---

→ Upregulation of autophagy in neurodegenerative diseases

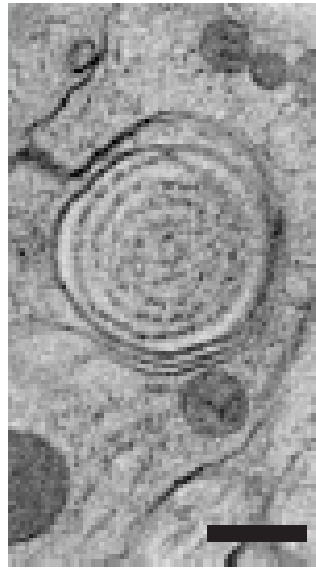
(also in cancer, cardiomyopathy, muscular disorders)

**Autophagosomes  
in mouse neurons**



(Yue et al. 2002)

**Autophagosomes  
in *C. elegans***



(Melendéz et al., 2003)

**Rats: Glu excitotoxicity**



(Rothstein et al., 1996)

→ Multivesicular structures in both autophagy and necrosis

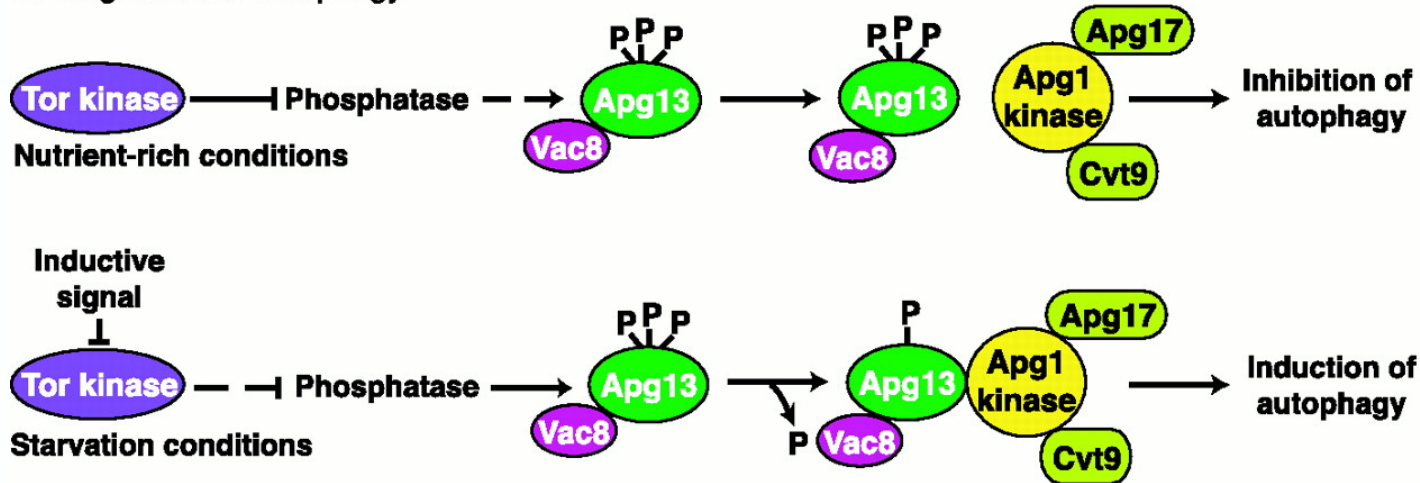
# Upregulation of autophagy in neurodegenerative diseases:

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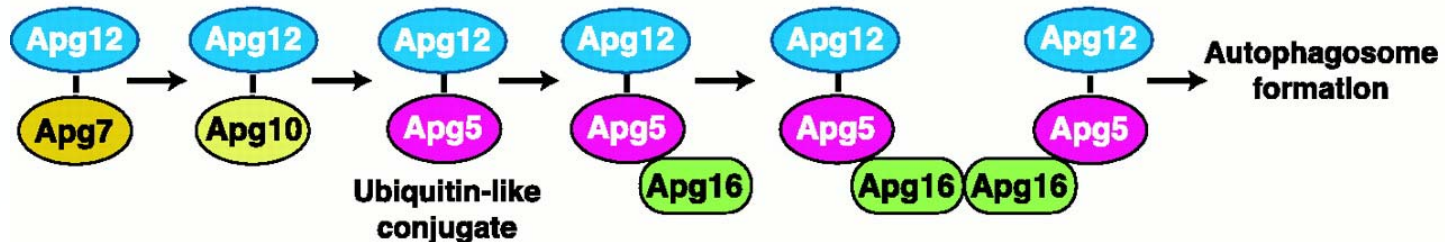
**A guardian angel or a mediator of cell death?**

# Molecular mechanisms of autophagy

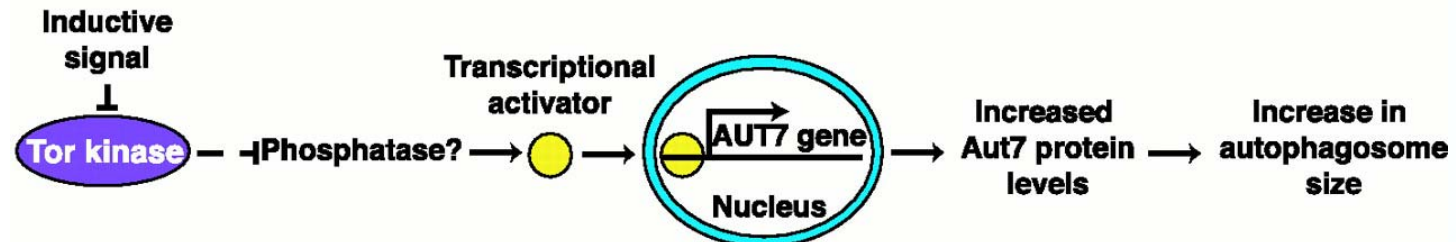
## A Regulation of autophagy



## B Autophagosome formation



## C Size regulation of the autophagosome



## Autophagy-Related Genes

## Protein Function

## *C. elegans* Homologs

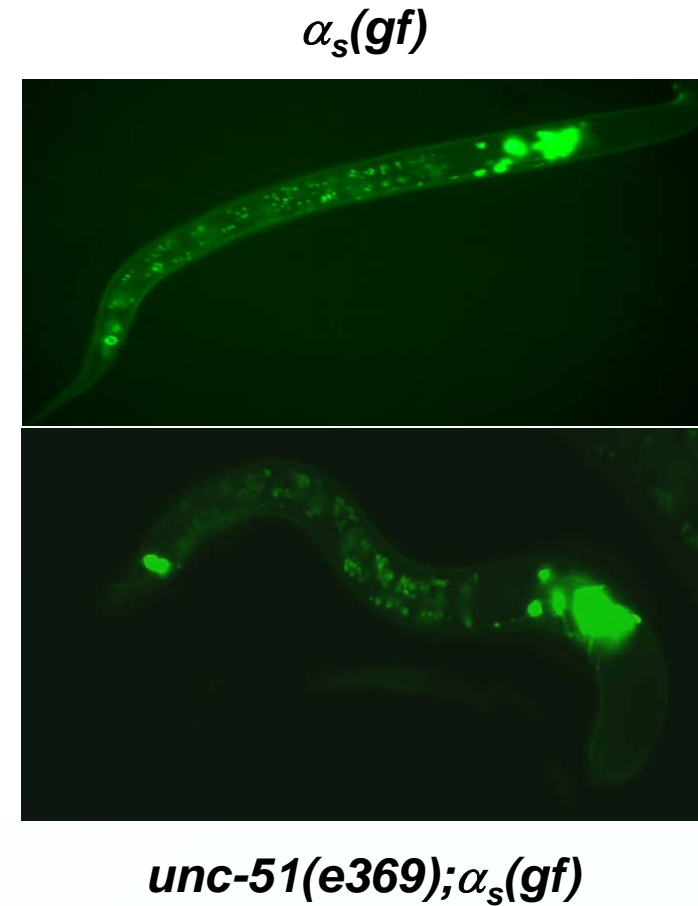
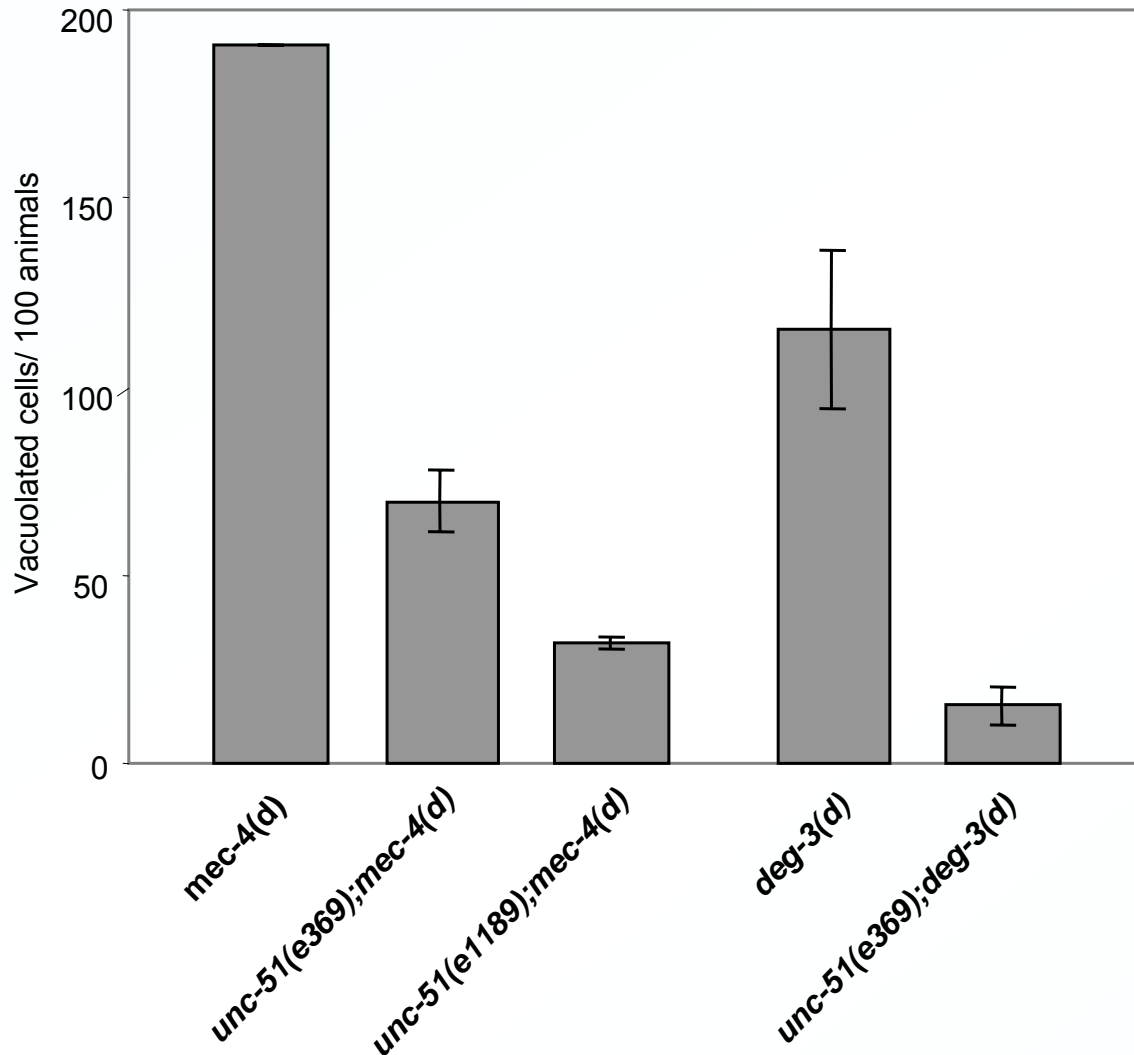
### Regulation of Autophagy

<i>Sc TOR2</i>	<i>Sc TOR2</i>	Rapamycin-sensitive protein kinase	<i>let-363</i>
<i>Sc ATG6</i>	<i>Mm beclin1</i>	Component of PI3-kinase complex	<i>bec-1</i>
<i>Sc ATG1</i>	<i>Hs ULK2</i>	Protein kinase	<i>unc-51</i>

### Formation of Autophagosomes

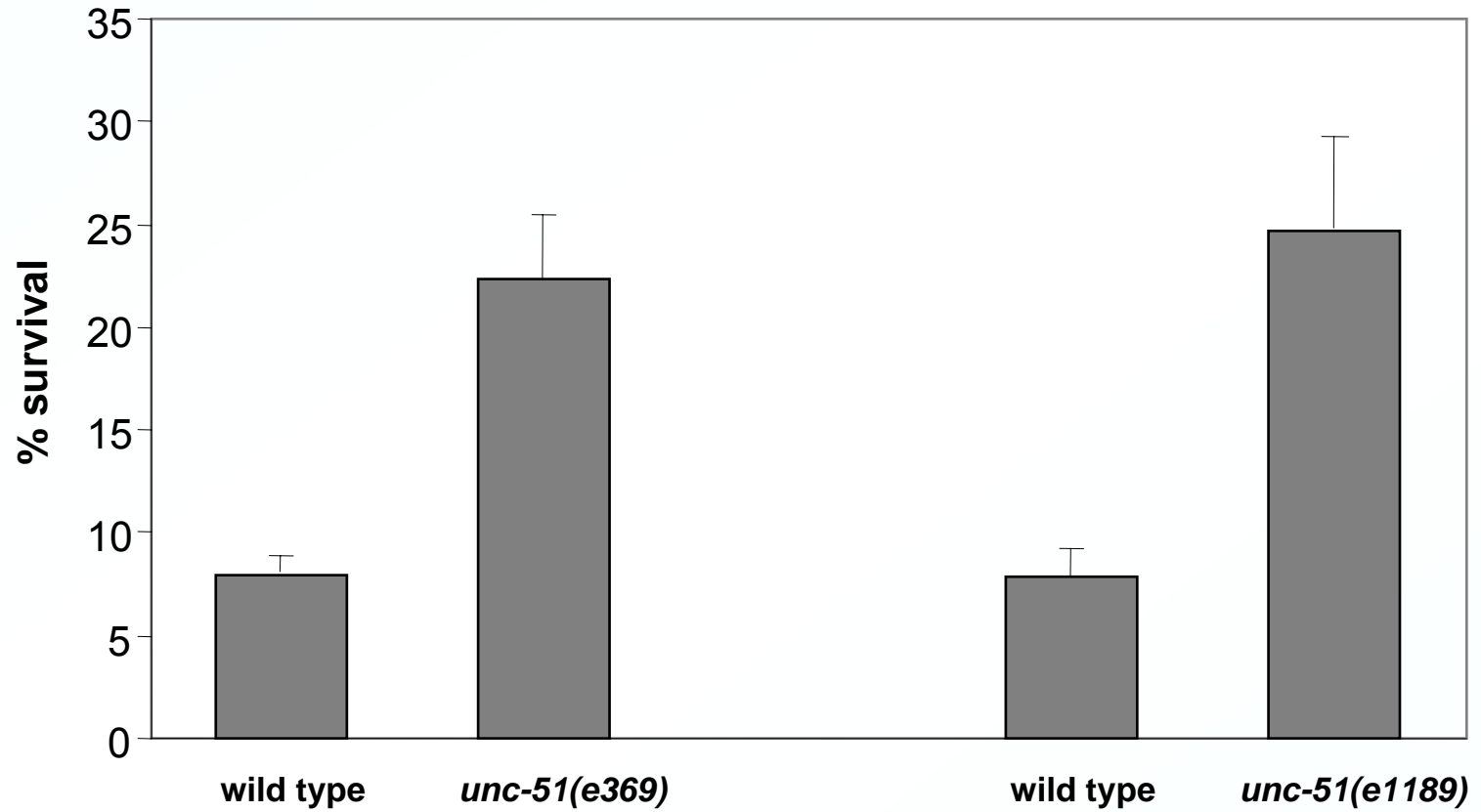
<i>Sc ATG3</i>	<i>Mm Apg3/Aut1-like</i>	E2-like enzyme; conjugates Atg8 to PE	Y55F3AM.4
<i>Sc ATG4</i>	<i>Mm autophagin 1</i>	Cleaves C-terminal extension or PE from Atg8	Y87G2A.3
<i>Sc ATG5</i>	<i>Mm Autophagy 5-like</i>	Conjugated to Atg12 through internal lysine	Y71G12B.12
<i>Sc ATG7</i>	<i>Mm APG7</i>	E1-like enzyme; activates Atg8 and Atg12	M7.5
<i>Sc ATG8</i>	<i>Mm GABARAP-like 1</i>	Ubiquitin-like protein conjugated to PE	<i>lgg-1</i>
<i>Sc ATG9</i>	<i>Hs APG9-like 1</i>	Integral membrane protein	T22H9.2
<i>Sc ATG10</i>	<i>Mm autophagin 10-like</i>	E2-like enzyme; conjugates Atg12 to Atg5	D2085.2
<i>Sc ATG12</i>	<i>Hs APG12</i>	Ubiquitin-like protein conjugated to Atg5	<i>lgg-3</i>
<i>Sc ATG16</i>	<i>Hs APG16-like isoform 2</i>	Component of Atg12-Atg5 complex	K06A1.5
<i>Sc ATG18</i>	<i>Sc ATG18</i> <i>Hs AAQ96867</i>	Localization of Atg2	F41E6.13

# *unc-51* mutations generally suppress neurodegeneration



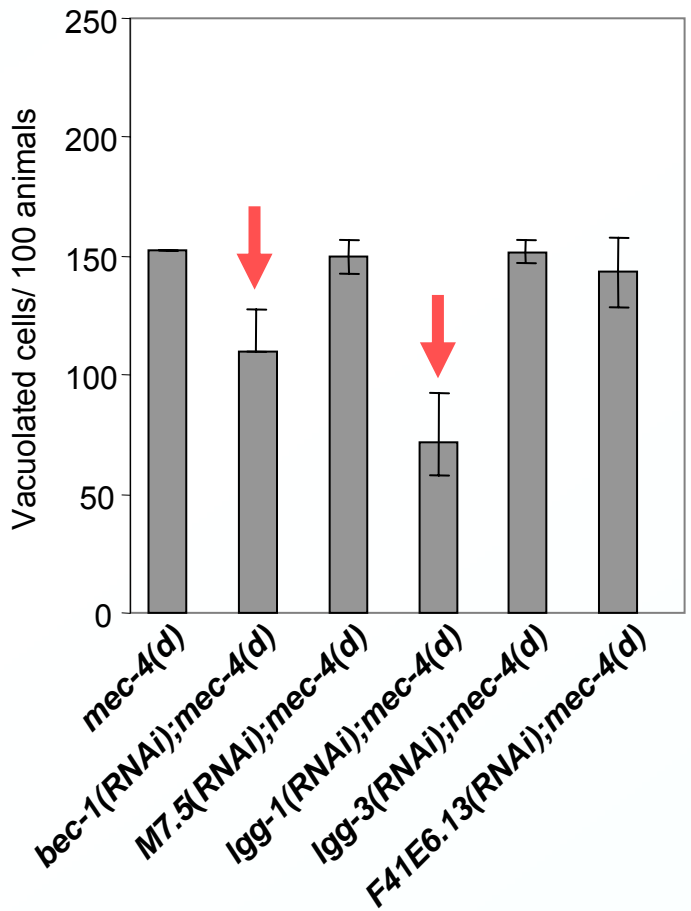
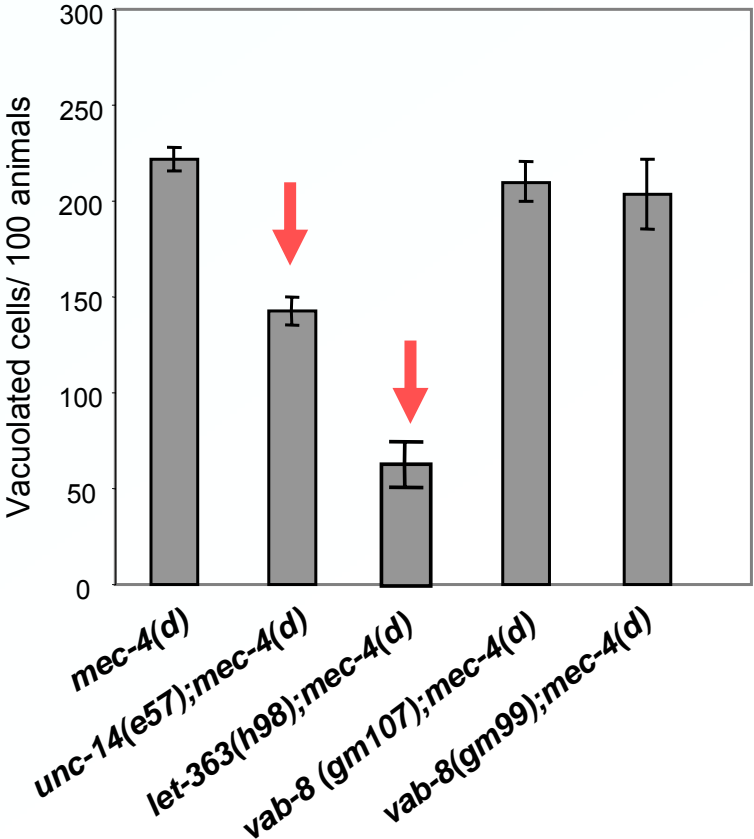
# *unc-51* mutations improve survival under hypoxia

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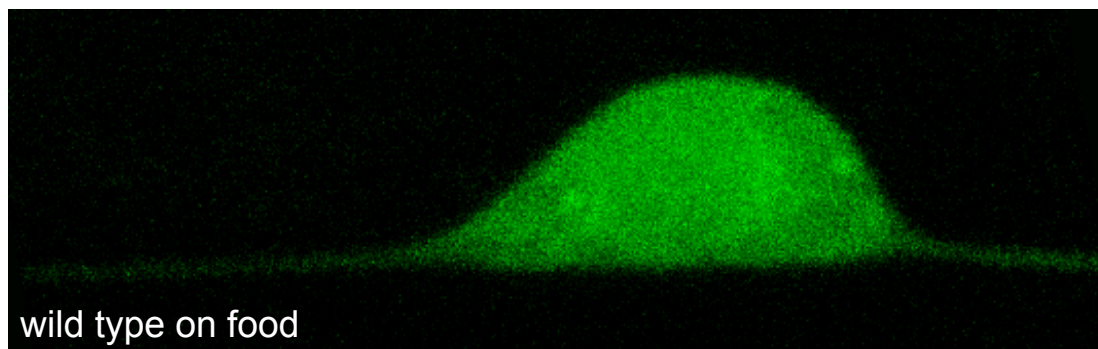
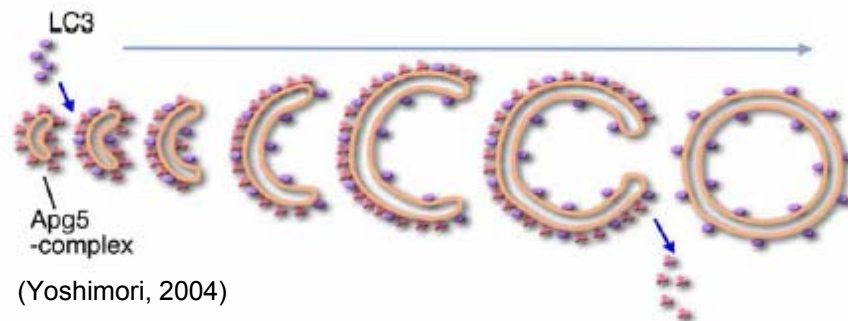
# Specific autophagy genes are required for necrotic cell death



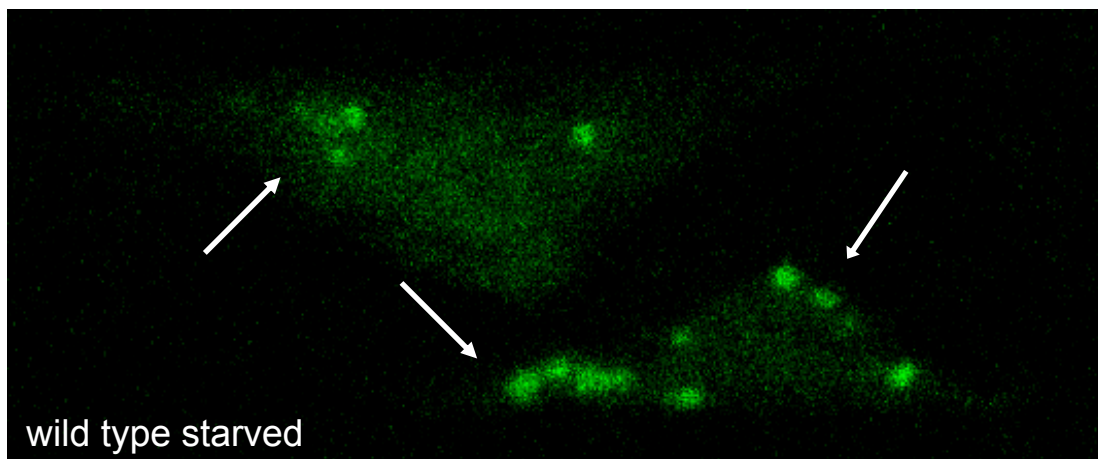
- *let-363*
- *unc-51*
- *unc-14*
- *bec-1*
- *lgg-1*

Induction of autophagy  
Formation of autophagosomes

# Detection of autophagosomes in degenerating neurons

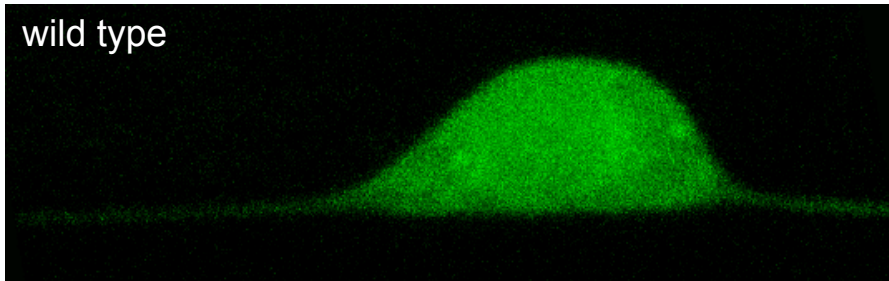


$P_{mec-7}$  GFP::LGG-1

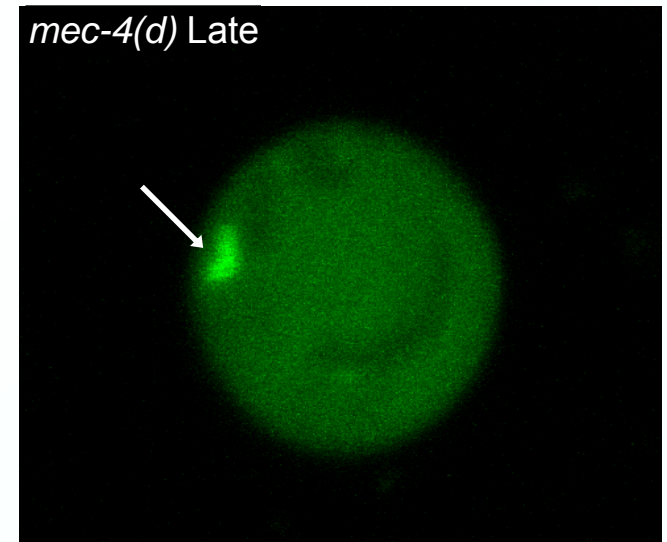
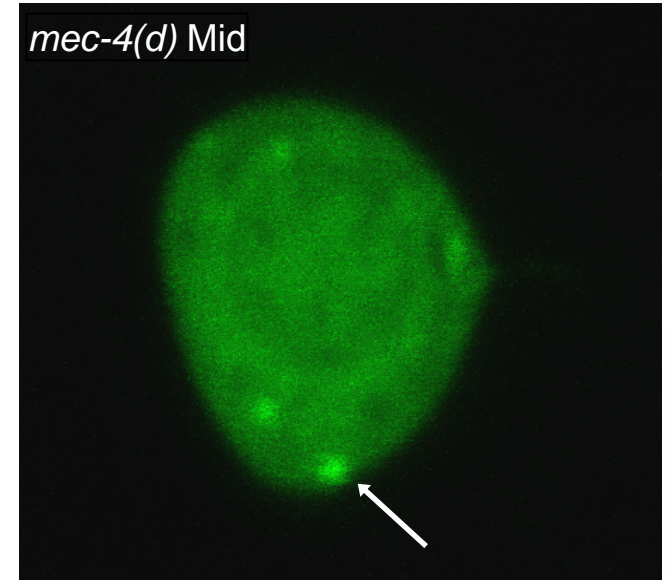
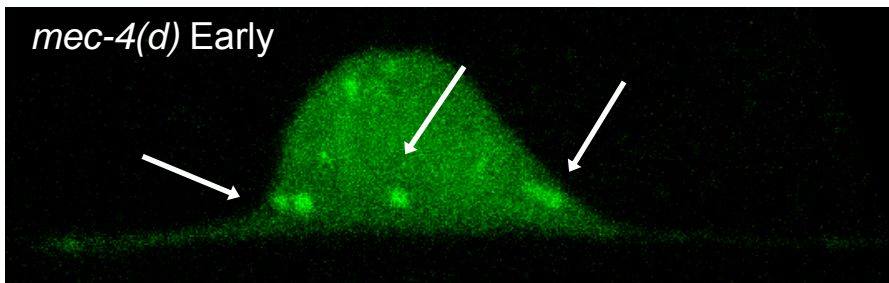


# Upregulation of the autophagosomal system precedes degeneration of *mec-4(d)* neurons

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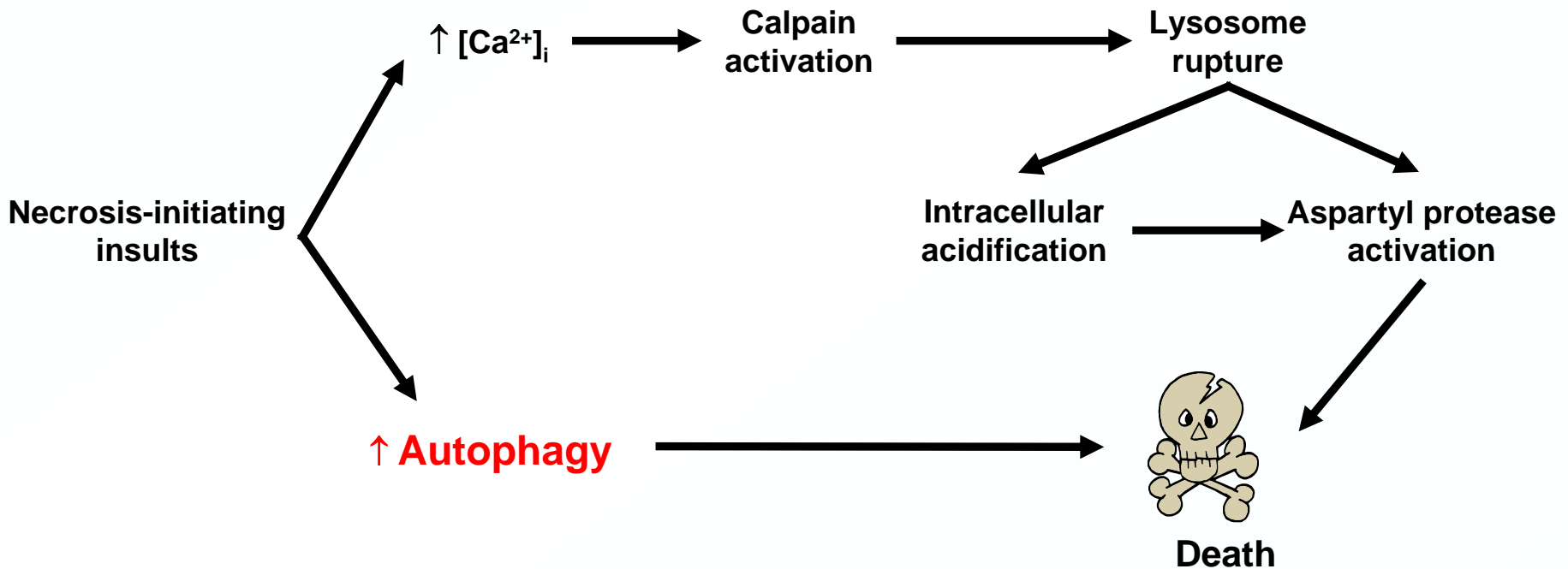


$P_{mec-7}$  GFP::LGG-1



# Autophagy is required for, and is induced during, neurodegeneration in *C. elegans*

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# Many Thanks...

- Marta Artal
- Dafni Bazopoulou
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- James Rothman (NY)
  
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- *Caenorhabditis* Genetics Center



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