

Mitochondrial Permeability Uncouples Elevated Autophagy and Lifespan Extension

Zhou B. et al

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Aging

Hallmarks:

Molecular damage

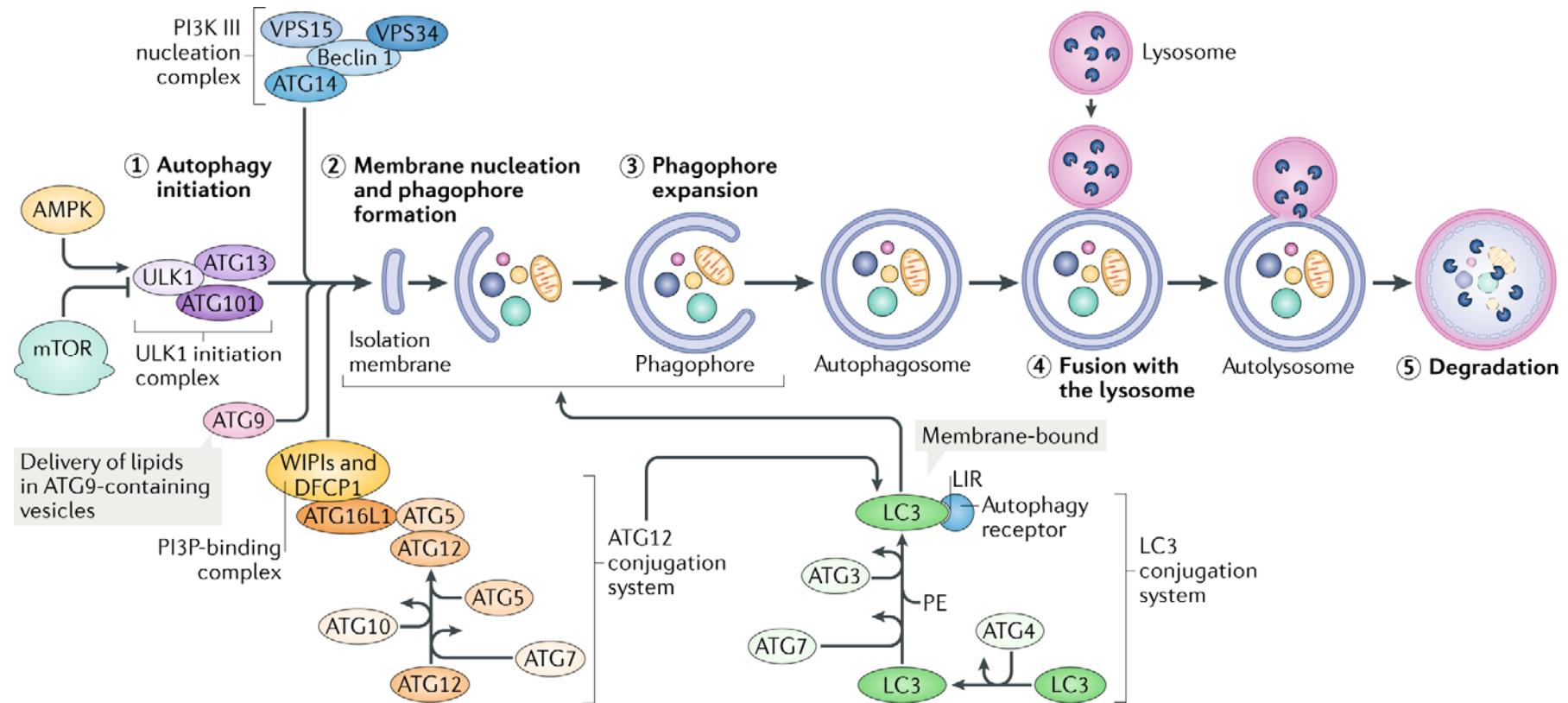
Dysfunctional organelles

Defective enzymes



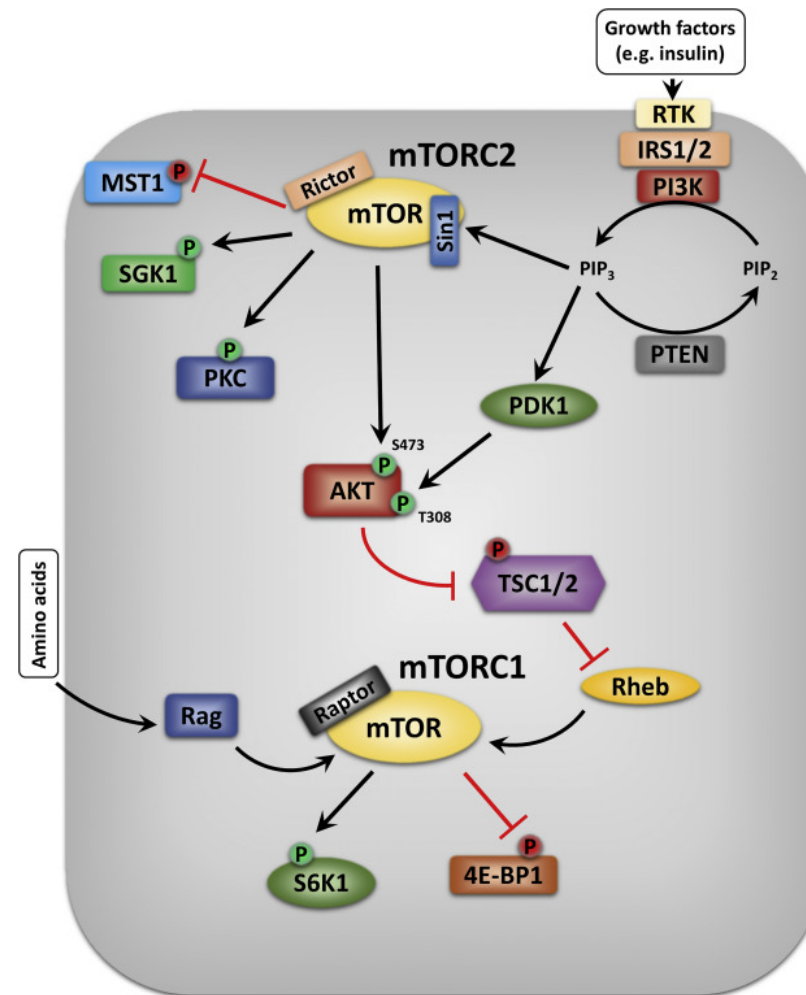
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Autophagy



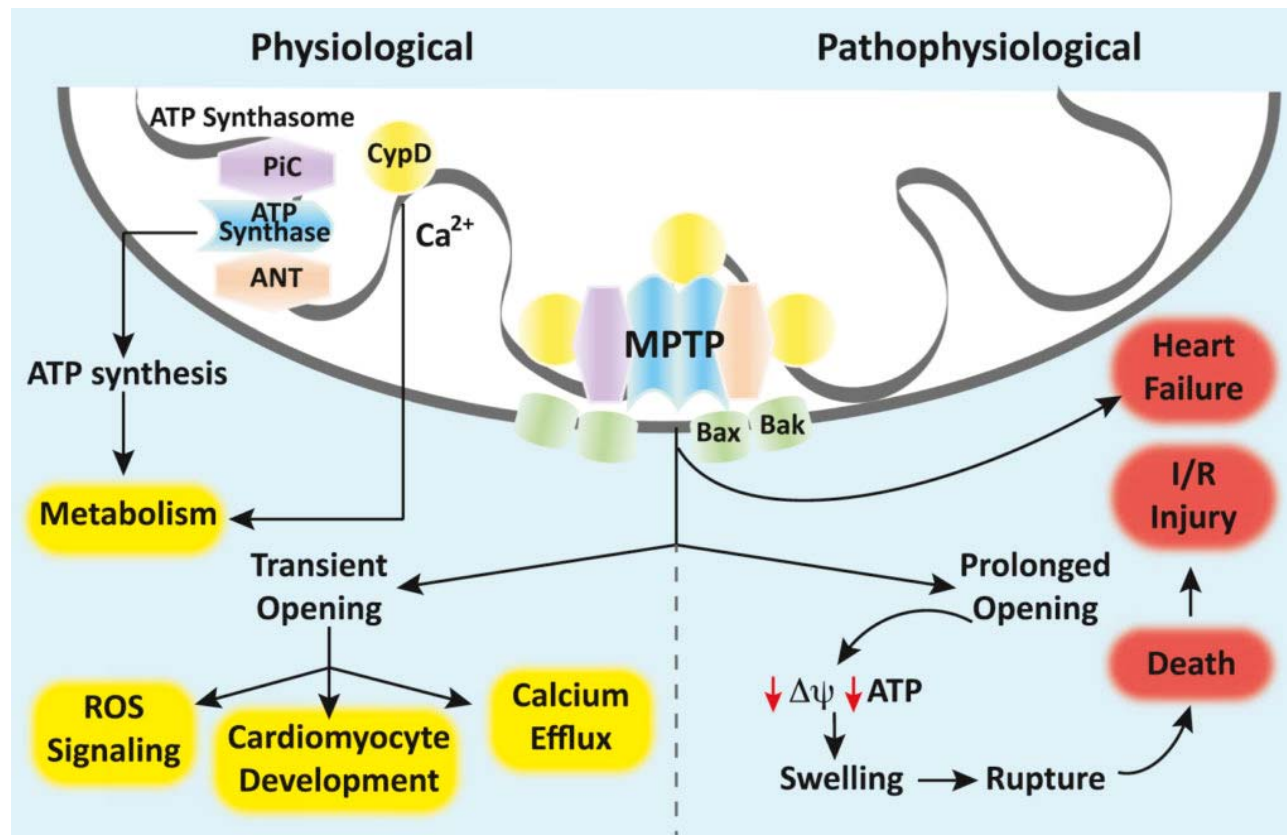
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mTorC1/2

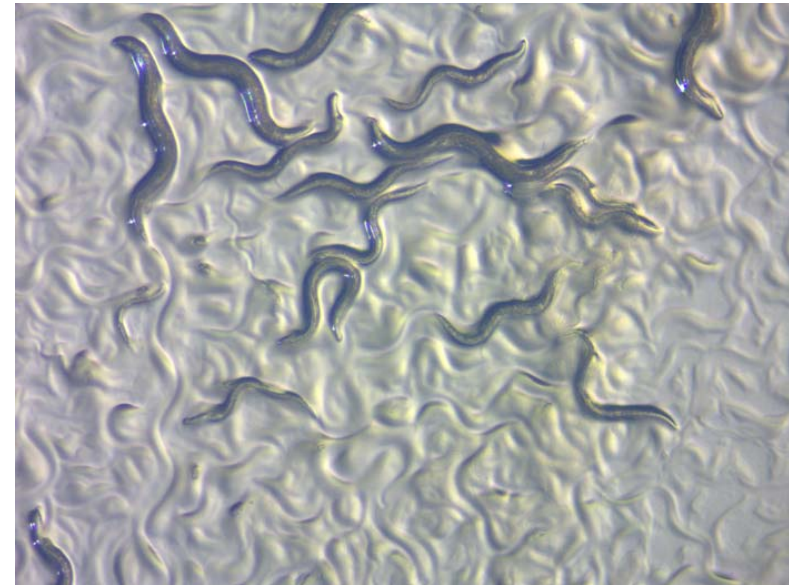
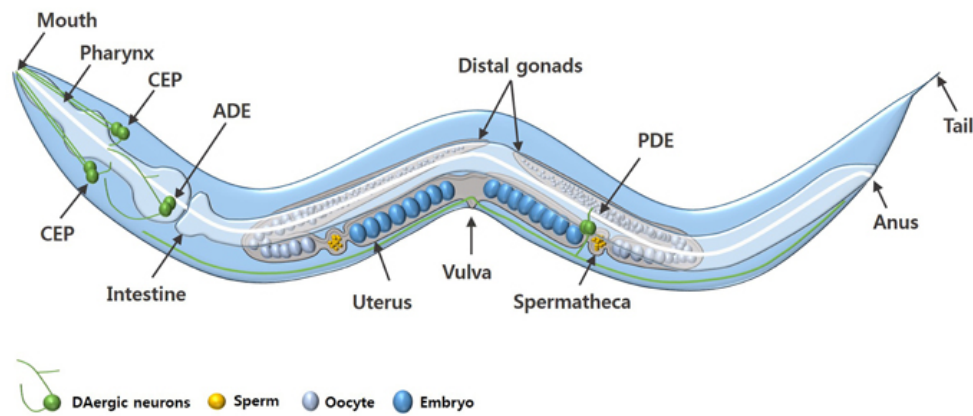


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Mitochondrien



Caenorhabditis elegans (C.elegans)

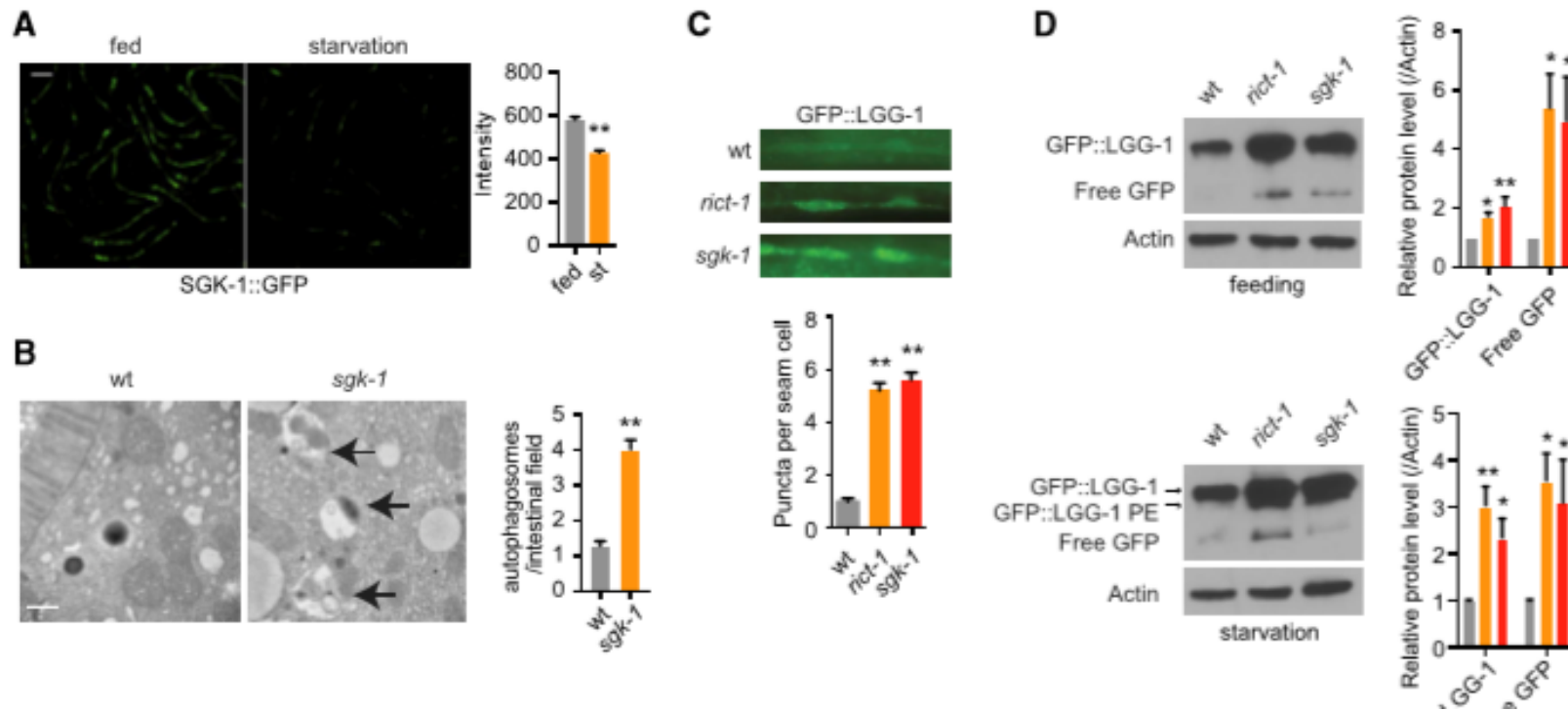


Methods

- Sgk1 Knockout AML12 Cells
- Transmission Electron Microscopy (TEM)
- Measuring Autophagy Levels in *C. elegans* and Cells
- Chloroquin *C. elegans* Treatment
- Western Blotting
- Longevity Assay
- RNA Interference (RNAi)
- Quantitative RT-PCR
- Brood Size
- Developmental Timing
- Nile-Red Staining
- SGK-1-GFP Co-IP for Mass Spectrometry
- Oxygen Consumption
- ATP Measurement
- Creation of the VDAC-1::FLAG *C.elegans* Transgenic Lines
- VDAC1 in Vitro Pull-Down Assay and Ubiquitination Assay
- mtDNA Copy Number
- Mitochondrial Ca²⁺ Uptake
- Paraquat Treatment
- Identification of the VDAC1 Phosphorylation Site by Mass Spectrometry
- Hepatic Ischemia/Reperfusion Model

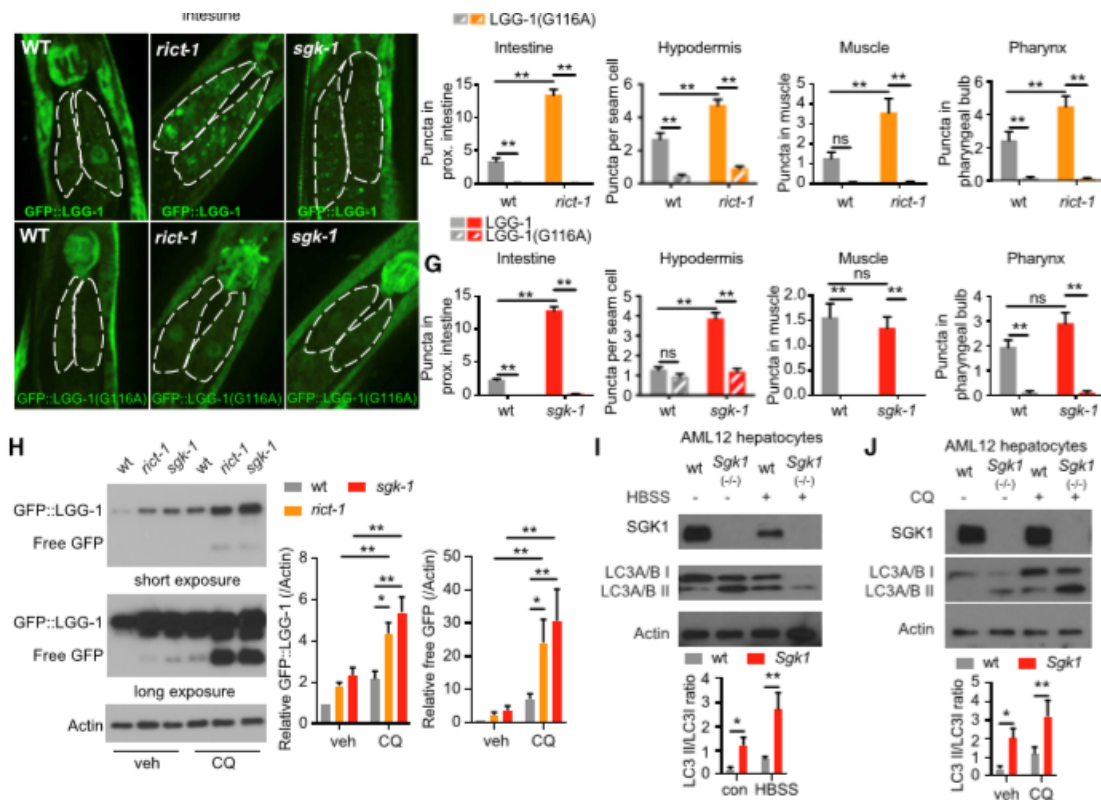
Results

mTorC2 Pathway Members RICT-1 and SGK-1 Negatively Regulate Autophagy



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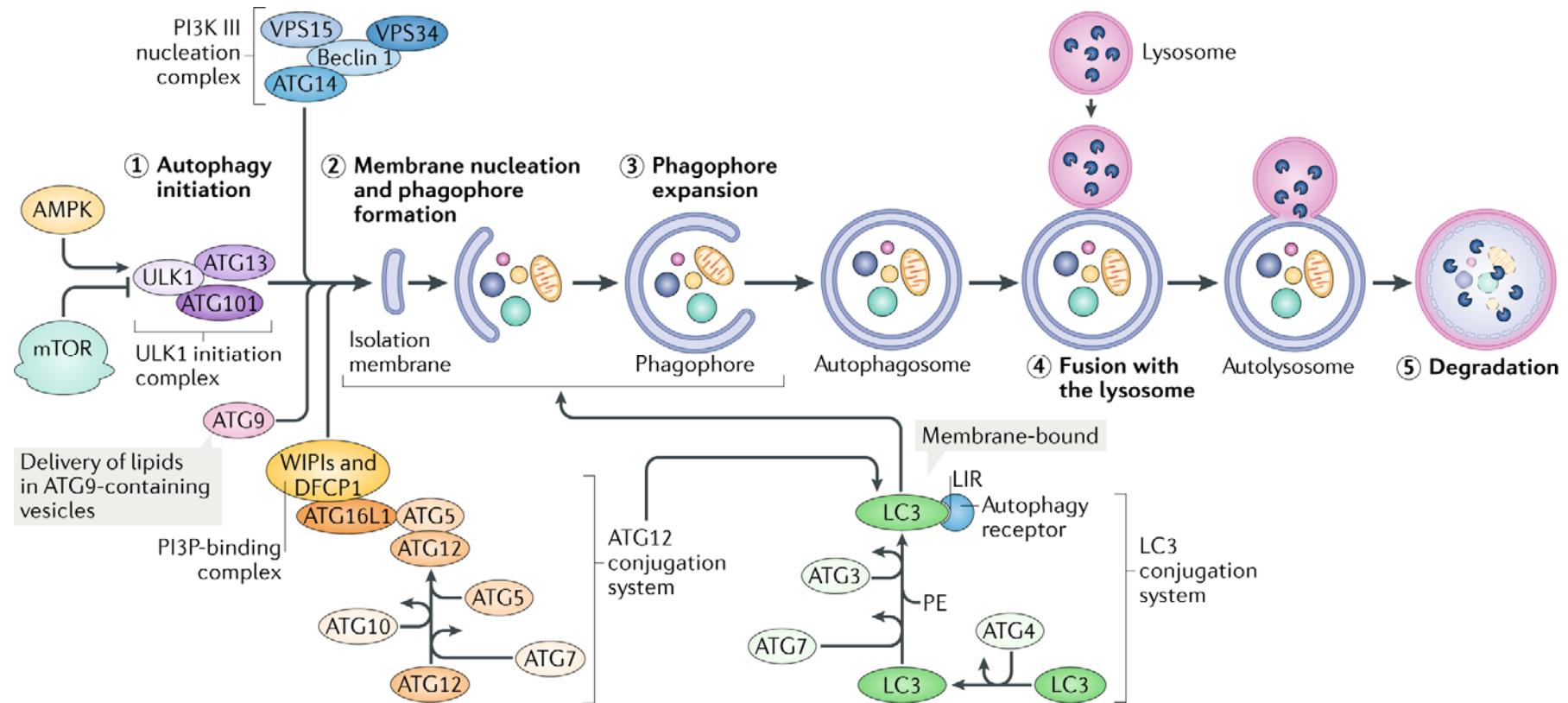
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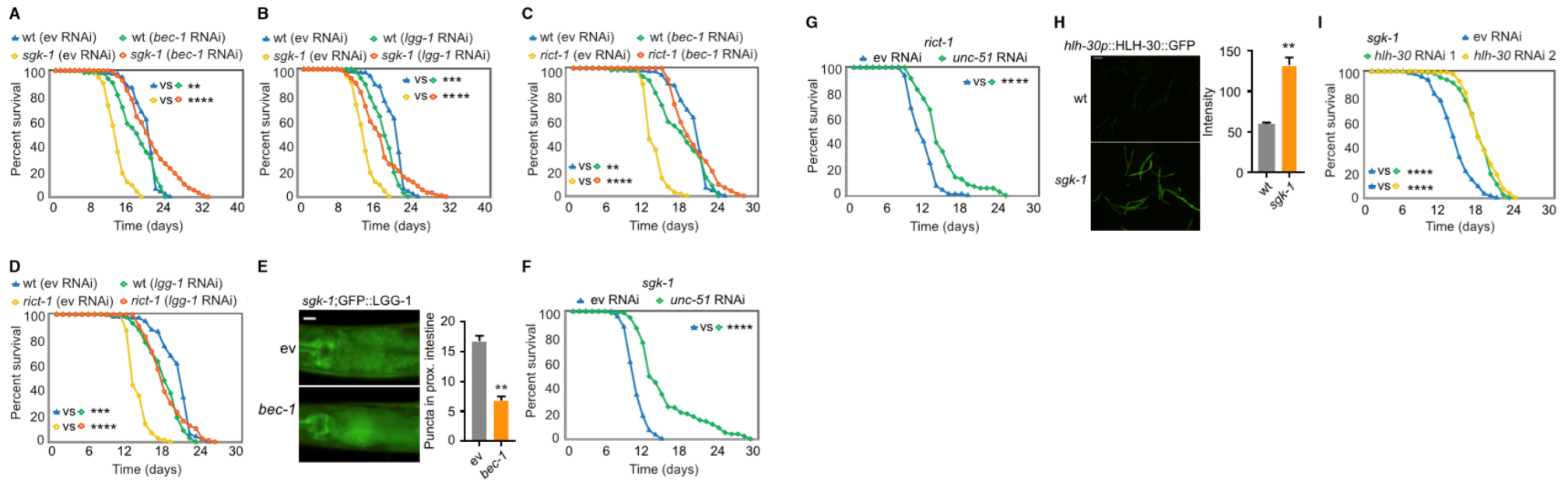
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Inhibition of Autophagy Restores Normal Lifespan in Short-Lived mTorC2 Mutants

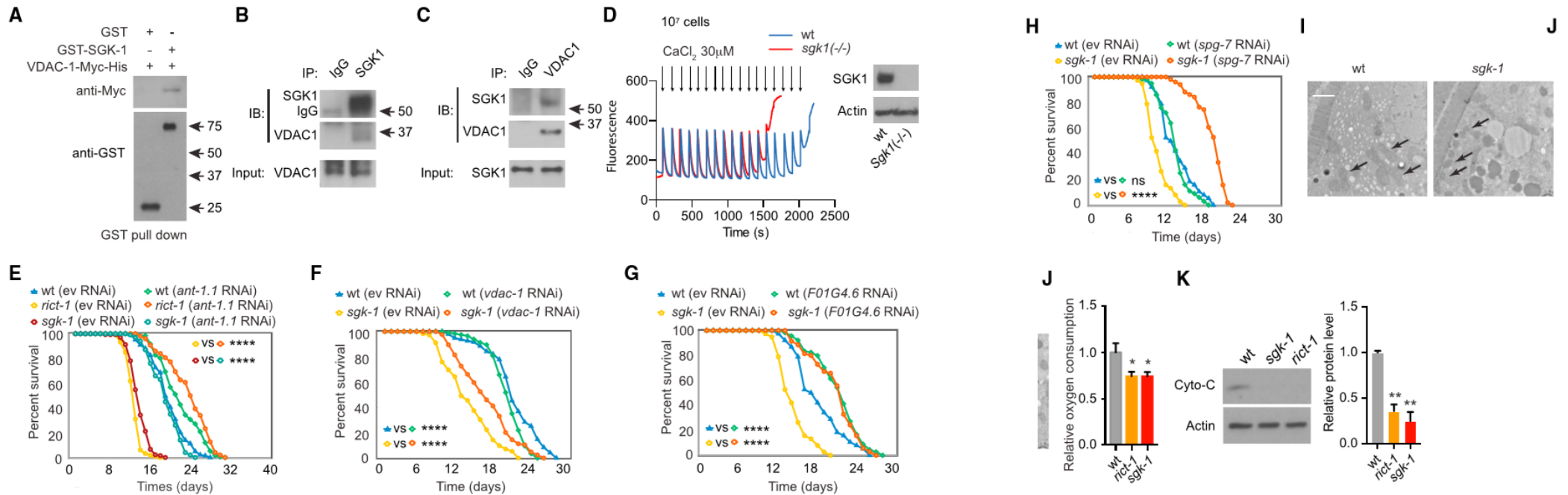


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SGK-1 Regulates mPTP Opening

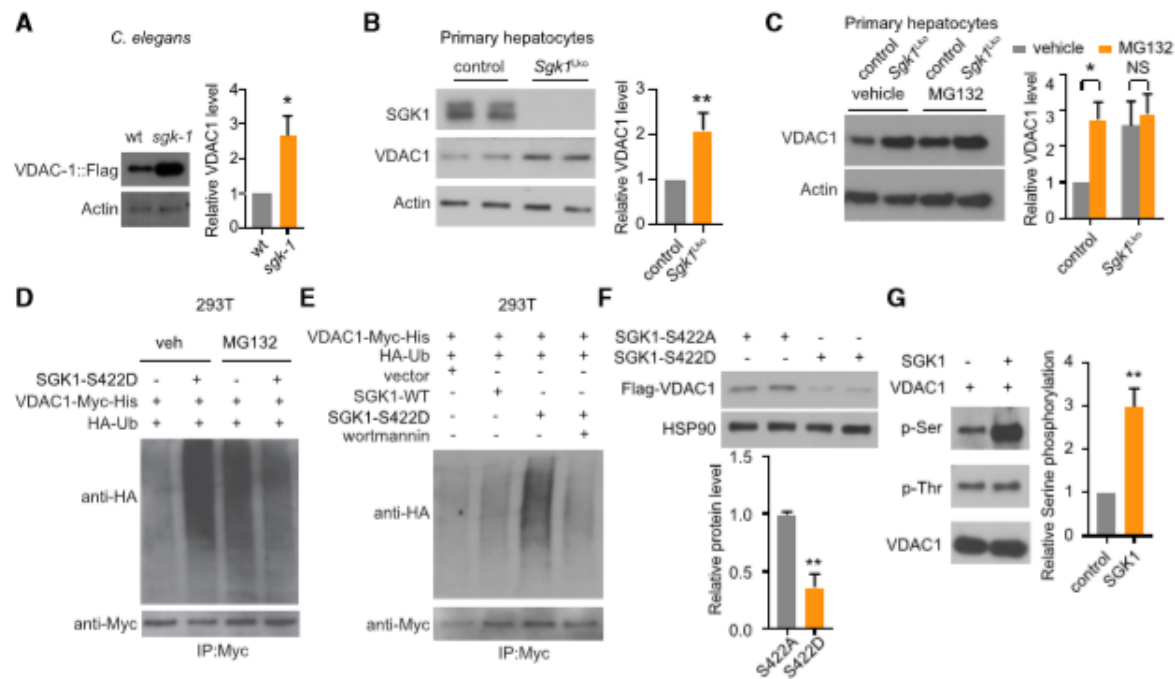


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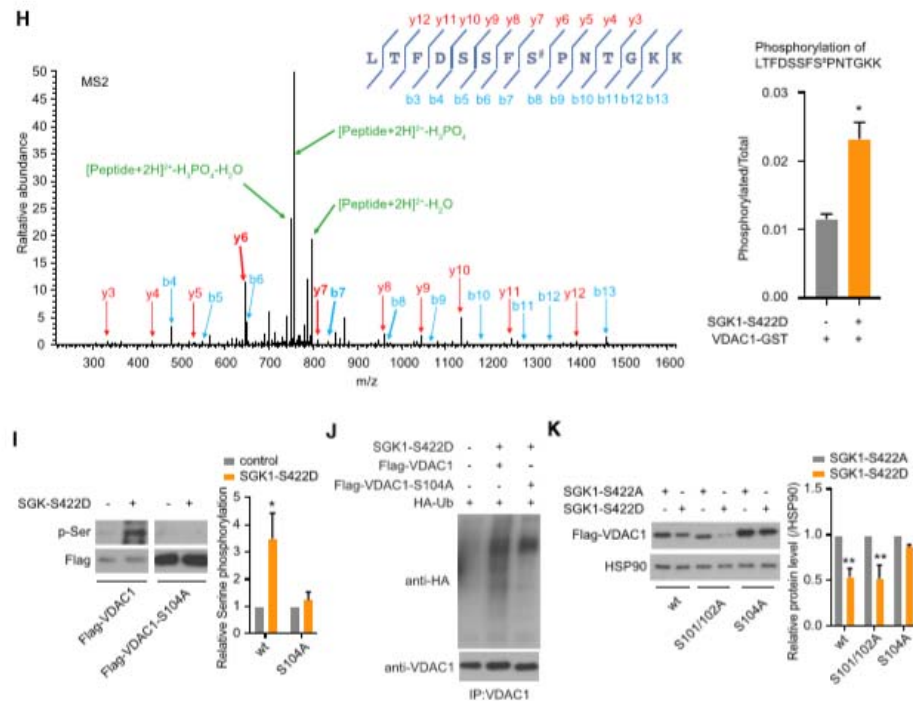
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SGK-1 Negatively Regulates mPTP Function by Decreasing VDAC-1 Protein Levels



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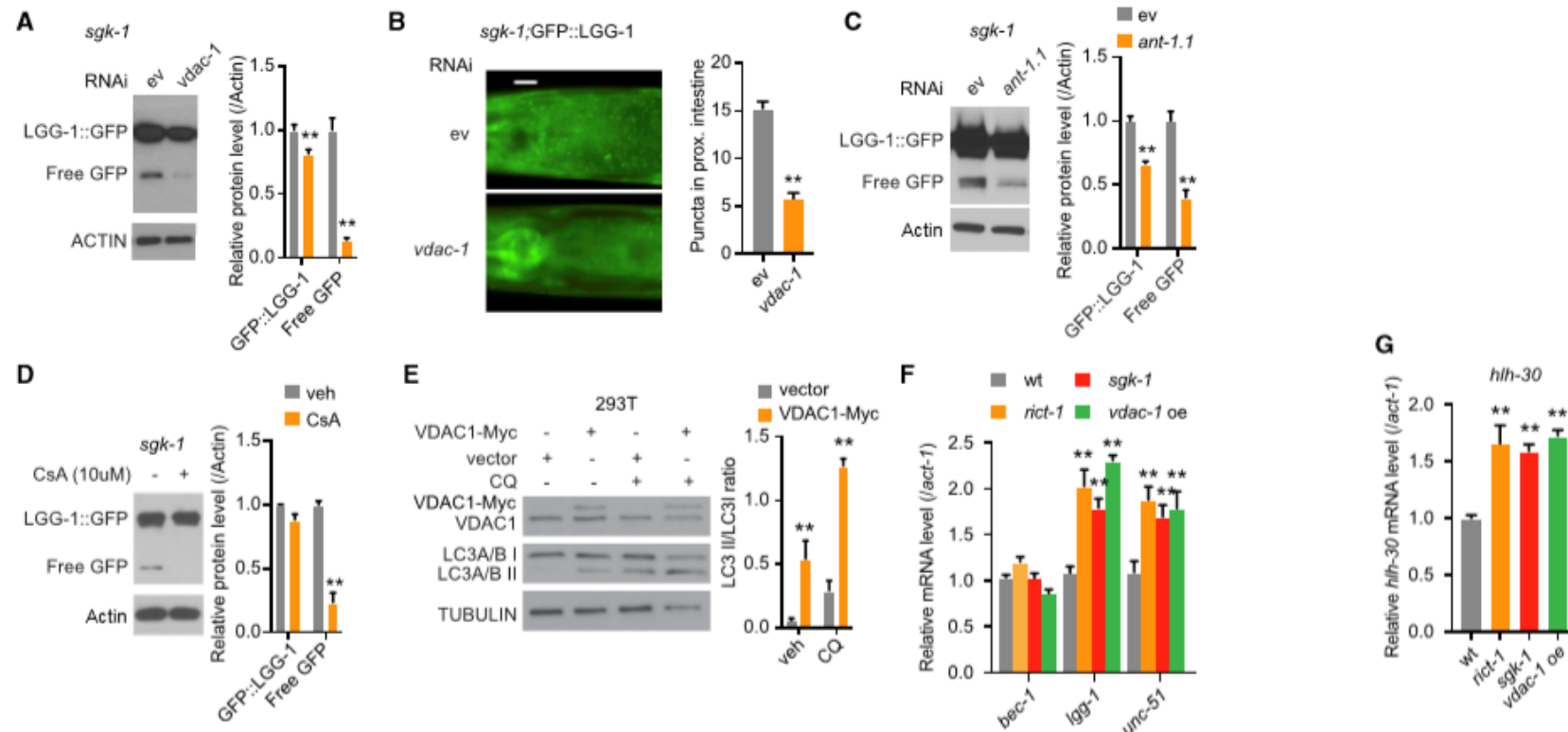


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Accumulation of VDAC-1 Protein Induces Autophagy

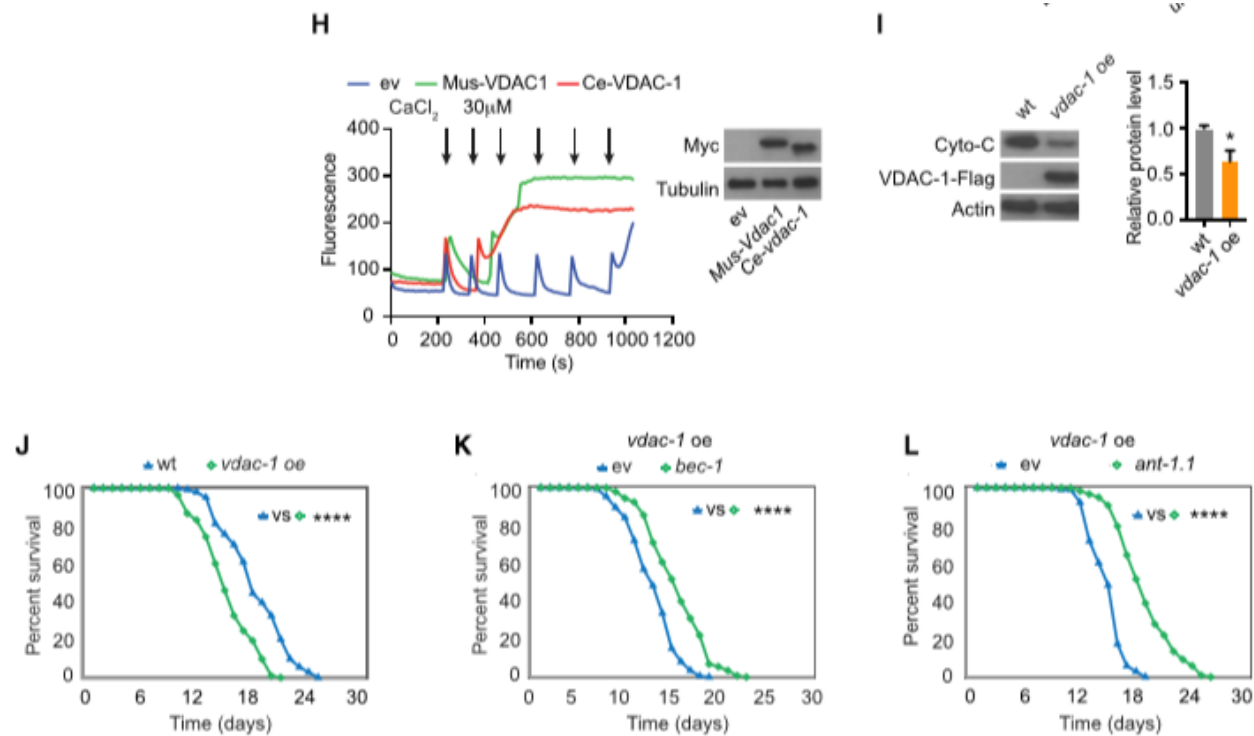


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Increased Mitochondrial Permeability Is Detrimental to Longevity and Organismal Health

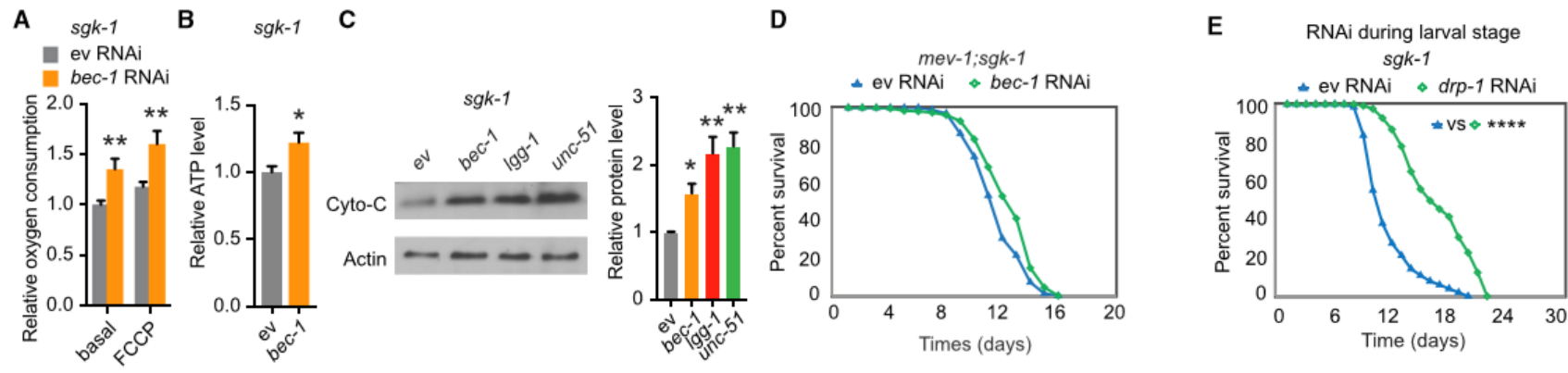


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Inhibition of Autophagy Restores Lifespan by Enhancing Mitochondrial Function in *sgk-1* Mutant Worms

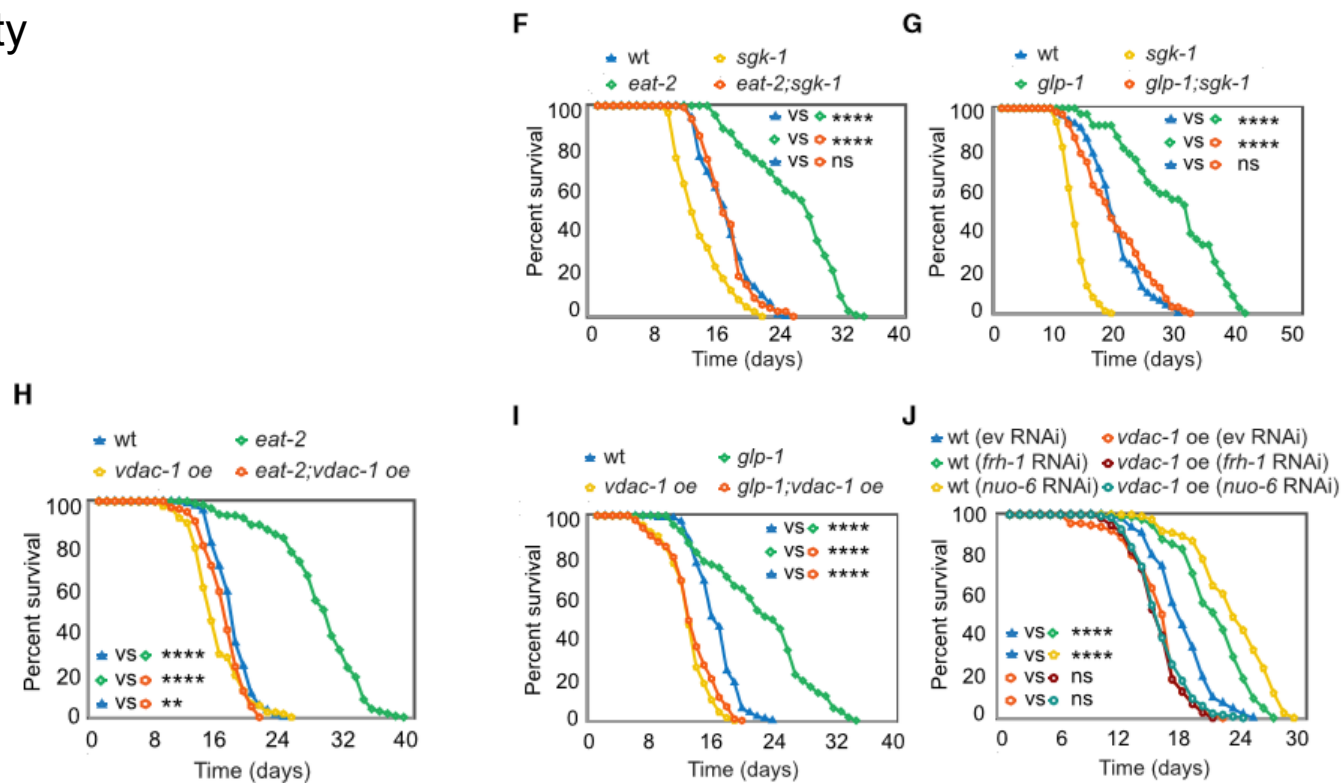


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Enhanced Autophagy Is Not Beneficial for Lifespan Extension with Increased Mitochondrial Permeability

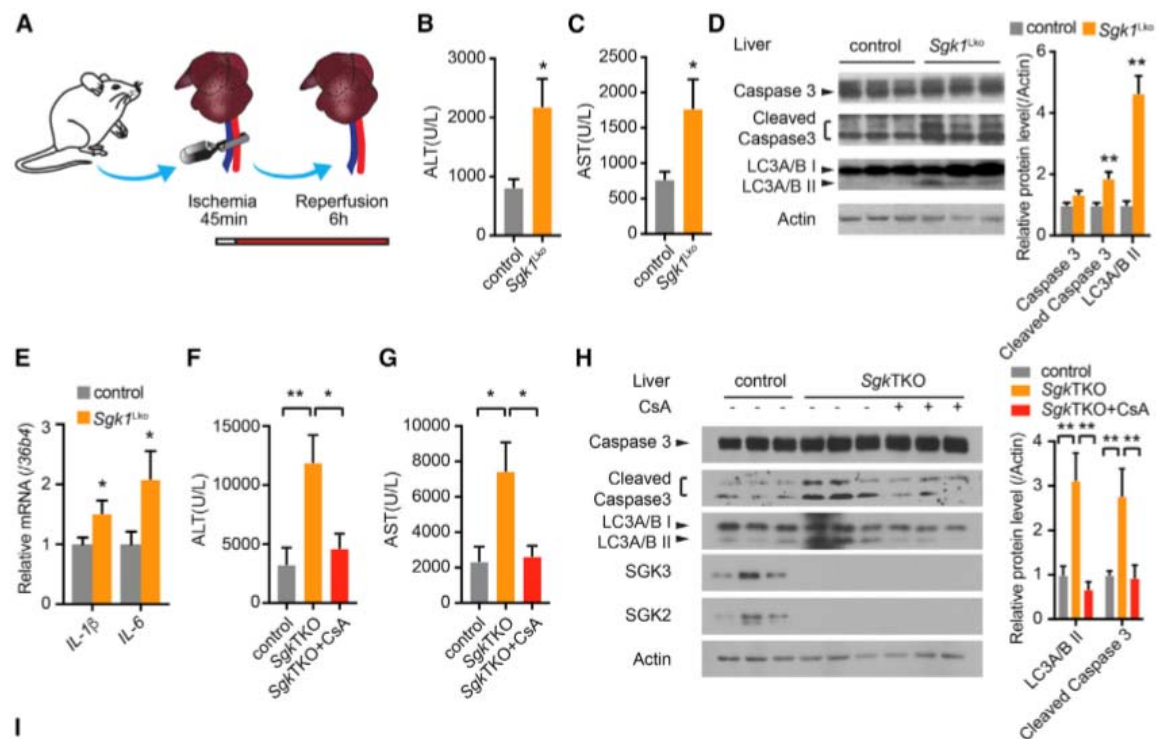


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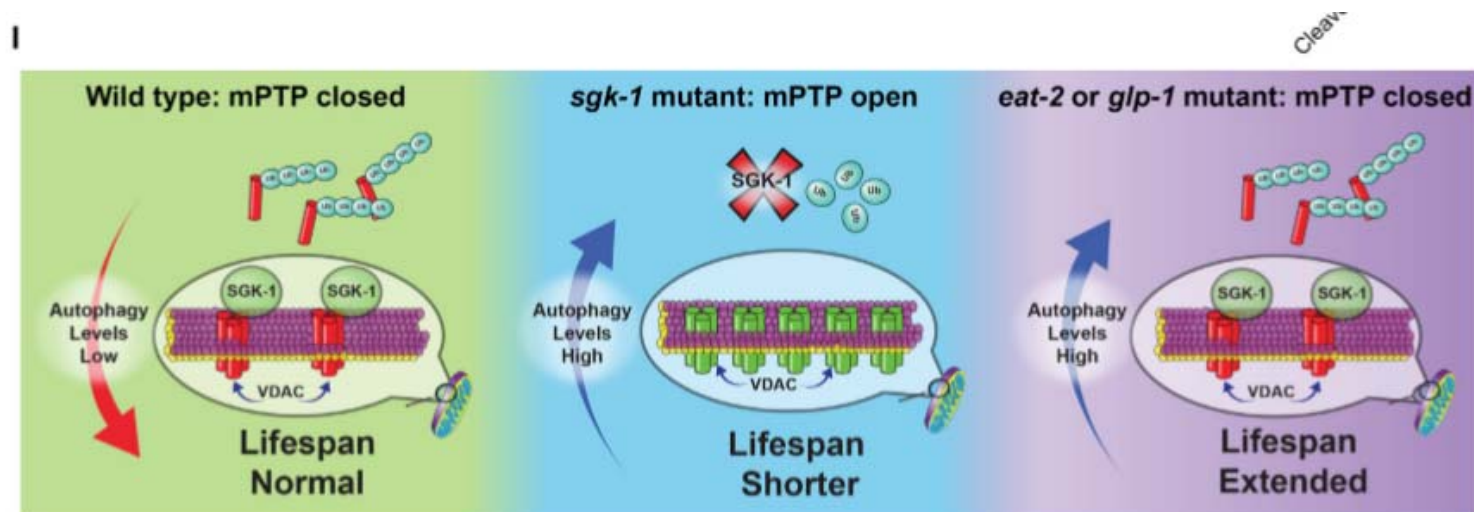
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Liver-Specific Sgk Knockout Mice Are More Sensitive to Hepatic I/R-Induced Injury



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9. Liver-Specific *Sgk* Knockout Mice Are More Sensitive to Hepatic I/R-Induced Injury

Discussion

mTorC2 and SGK1 Maintain Mitochondrial Homeostasis

- mTorC2 deficiency-> accumulation of VDAC-1 -> mPTP open
 - >compromise oxidative capacity, Cytochrom C and ATP directly
 - > progeria as direct consequence
-
- mTorC2 and SGK1 regulate mitochondrial permeability through physical association with mPTP regulatory molecules -> VDAC1 abundance

Discussion

mTorC2 and SGK-1 Suppress Maladaptive Autophagy

- increased intestinal autophagic flux -> negative consequence for longevity
- additional tissues???
- Spatiotemporal effect???
- non-cell autonomous regulation of autophagy ???
- additional mechanism- mTorC1 (suppression of autophagy)

Discussion

mPTP Opening Negatively Modulates Longevity and Health

- increased opening of mPTP drives mitochondrial dysfunction and increased autophagy -> devastating, shortening lifespan, I/R injury chance increased
- caloric restriction protects mitochondria from mPTP opening in rat heart (Hofer et al. 2009)
- Metformin (anti-aging properties) inhibits mPTP

->low mitochondrial permeability as obligate step to extend lifespan

Discussion

Autophagy as a Double-Edged Sword in I/R Injury

- Autophagy beneficial in I/R injury through improved cellular homeostasis, decreased expression of inflammatory genes (MA et al. 2015)
- excessive autophagy -> pressure overload-induced cardiac remodeling, heart failure in cardiac I/R injury (Gottlieb and Mentzer, 2010)
- widespread mPTP opening shortly after reperfusion -> autophagy to be detrimental
- inhibition of autophagy in early reperfusion reduces injury

-> mPTP as major governing influence on the autophagy effect in I/R Injury

Discussion

Resolving the Paradox: How Inhibition of Autophagy Restores Lifespan in mTORC2 Mutants

- Increased autophagy is general thought to be beneficial for longevity
- autophagy is detrimental when coupled with increased mitochondrial permeability
- mitochondrial permeability -> mitochondrial fragmentation, initiates autophagy-> excessive, non-selective mitochondrial clearance and failure to replace

defect in ATP synthase activity vs. Mitochondrial permeability

mitochondrial permeability -> lifespan, aging, many disease states

Autophagy -> harmful during I/R injury if accompanied with mPTP opening

Conclusion

