The Molecular Switch: Targeting AMPK–mTOR Signaling to Drive Stress Adaptation Across Tissues

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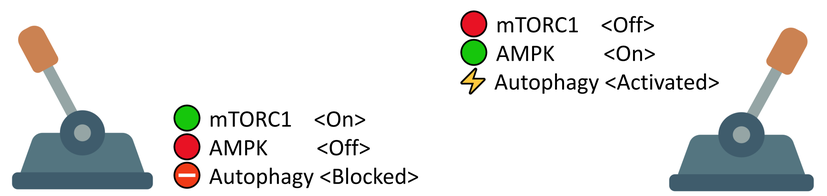
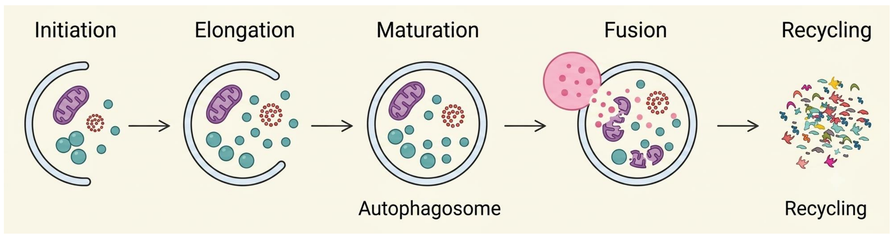
- Fasting triggers a conserved cellular clearance program (autophagy) by turning the AMPK and mTOR "molecular switch".
- AMPK acts as the energetic accelerator during nutrient scarcity (On switch), while mTOR suppression lifts the inhibitory brake (off switch)
- Both pathways converge at the ULK1 complex (site), driving adaptive stress responses in all types of tissues





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Introduction

- Cellular Homeostasis: Autophagy degrades damaged organelles and macromolecules during metabolic stress
- Dual Nutrient-Sensing Switch:

- mTORC1: Growth-promoting kinase that suppresses autophagy when nutrients are plentiful (Sengupta et al., 2010; Mizushima et al., 2004).

- AMPK: Cellular energy sensor activated during high AMP/ATP ratios during fasting (Egan et al., 2011; Hardie et al., 2012)

- ULK1 Convergence: AMPK phosphorylates ULK1 to initiate autophagy, whereas mTORC1 phosphorylates ULK1 to block it (Kim et al., 2011; Egan et al., 2011)

Objective

- Determine whether AMPK activation and mTOR suppression are mechanistically required for fasting-induced autophagy (Egan et al., 2011; Kim et al., 2011)
- Compare activation kinetics and functional outcomes across skeletal, neuronal, and cardiac tissues (Xinyan et al., 2025; Alirezaei et al., 2010; Zhao et al., 2021)
- Evaluate the translational potential of nutrient-sensing pathways for human clinical applications (Dethlefsen et al., 2018; Espinoza et al., 2025)

Methods

- Literature Search: Evaluated primary studies across cell culture, mouse knockout models, and clinical trials (e.g., Mizushima et al., 2004; Bujak et al., 2015; Dethlefsen et al., 2018)
- Comparative Parameters: Analyzed autophagic flux markers (LC3B-II turnover, p62, ULK1 phosphorylation) across skeletal muscle, brain, and heart tissues under varied fasting regimens (Xinyan et al., 2025)

RESULTS

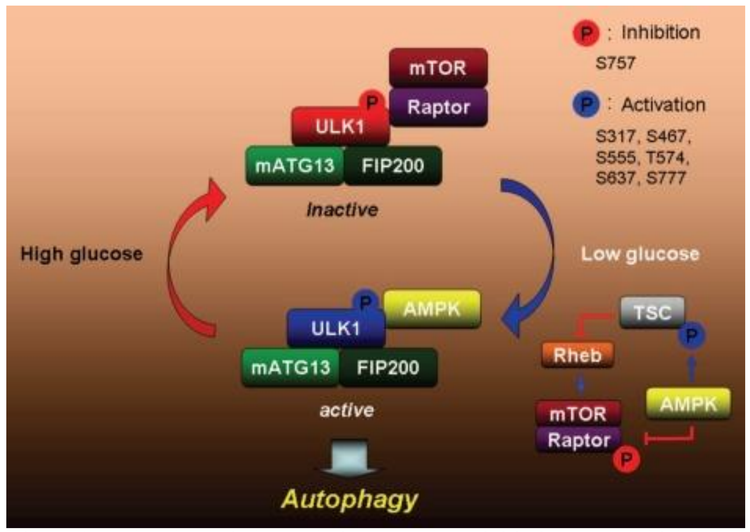

Figure 1. Molecular switch regulating autophagy initiation. Under high glucose, mTORC1 phosphorylates ULK1 (Ser757) to inhibit autophagosome formation. Under low glucose (fasting), AMPK directly activates ULK1 (Ser317/Ser555) and suppresses mTORC1 via TSC2/Rheb [Kim et al. (2011)].

Table 1. Examples of autophagy-dependent life span extension

Genetic/pharmacologic intervention	Species	Anti-aging phenotype
Loss of IGF signaling due to mutated *daf-2*	*C. elegans*	Elevated autophagy levels and dauer formation, life span extended by 70%
CR mutant *eat-2*	*C. elegans*	Enhanced autophagy, life span extended by 28%
Null-mutant of *cnb-1* (calcineurin)	*C. elegans*	Enhanced autophagy, mean life span extended by 31%
Overexpression of HLH-30	*C. elegans*	Increased autophagic activity, life span extended by up to 20%
Resveratrol treatment	*C. elegans*	Elevated autophagy levels, life span extended by 11%
Spermidine treatment	*C. elegans*	Elevated autophagy levels, life span extended by 15%
Muscle-specific transgenic expression of FOXO	*D. melanogaster*	Autophagy partially enhanced proteostasis, life span extended by 21%
Brain-specific overexpression of Atg8a	*D. melanogaster*	Enhanced neuronal autophagy, life span extended by >50% in female flies
Rapamycin treatment	*D. melanogaster*	Increased autophagy levels, decreased translation, median life span extended by 22%
Spermidine treatment	*D. melanogaster*	Elevated autophagy levels, mean life span extended by <30%
Transgenic overexpression of ATG5	Mouse	Enhanced autophagy, improved insulin sensitivity and motor function, life span extended by 17%
CR	Mouse	Life span extended by 51%

Table 1. Summary of cross-species evidence demonstrating that genetic or pharmacologic activation of autophagy (e.g., spermidine, CR, mTOR inhibition) extends lifespan and enhances proteostasis [Madeo et al. (2015)].

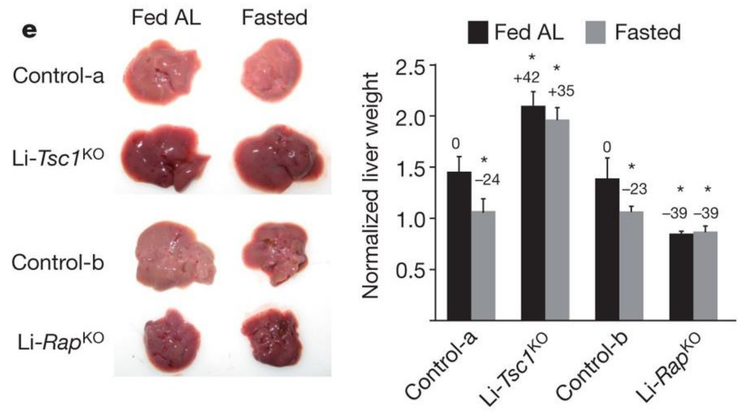

Figure 2. Genetic knockout of AMPK or autophagy-related genes in rodents blocks fasting-induced adaptation, establishing key regulatory nodes in tissue remodeling [Bujak et al. (2015) / He et al. (2012)].

Key Takeaways

- Mechanics Required:
  - AMPK activation, which acts as the energetic accelerator
  - mTORC1 suppression, which lifts the brake
  - fasting-induced autophagy at the ULK1 node.
- Tissue-Specific Kinetics: Autophagic flux varies across organs;
- Ex.
  - Neurons show rapid induction during acute fasting (Alirezaei et al., 2010),
  - Skeletal muscle needs sustained methods for structural remodeling (Xinyan et al., 2025).
- Translational Gap: Animal models compared to human trials/ models show stronger flux activation, in comparison to the modest flux changes in humans (Dethlefsen et al., 2018; Espinoza et al., 2025).

REFERENCES

ACKNOWLEDGEMENTS

Special thanks to my faculty mentor, Dr. Jutta B. Heller, for her guidance, feedback, and support throughout the development of my capstone project. I would also like to acknowledge the University of Washington Tacoma TBIOMD Capstone Program for the opportunity to conduct and present this research.