Coordinated regulation of autophagy by energy-sensing machineries

AMPK and mTORC1 regulate autophagy through direct phosphorylation

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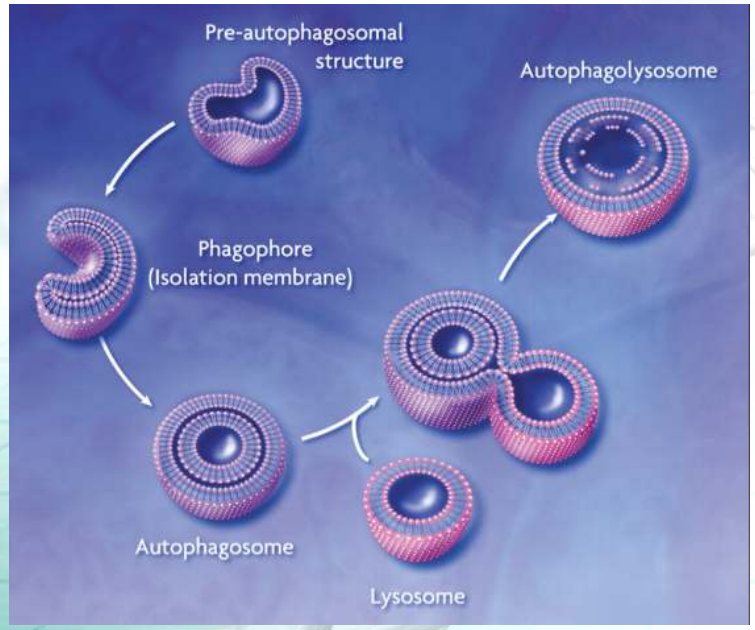
Autophagy (macroautophagy)

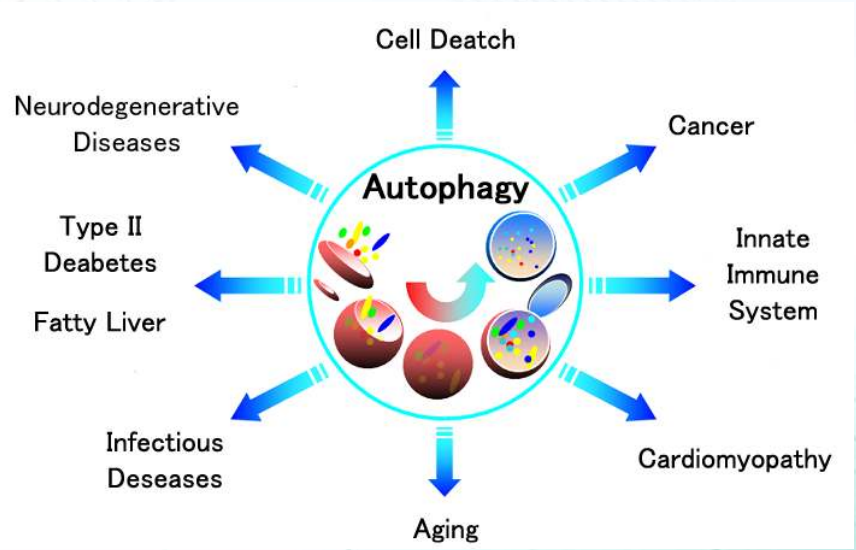
: A bulk degradation process to maintain cellular homeostasis in response to cellular stresses

: Double-membrane vesicles, “autophagosome”

: Recycle cellular contents to provide energy or new building blocks

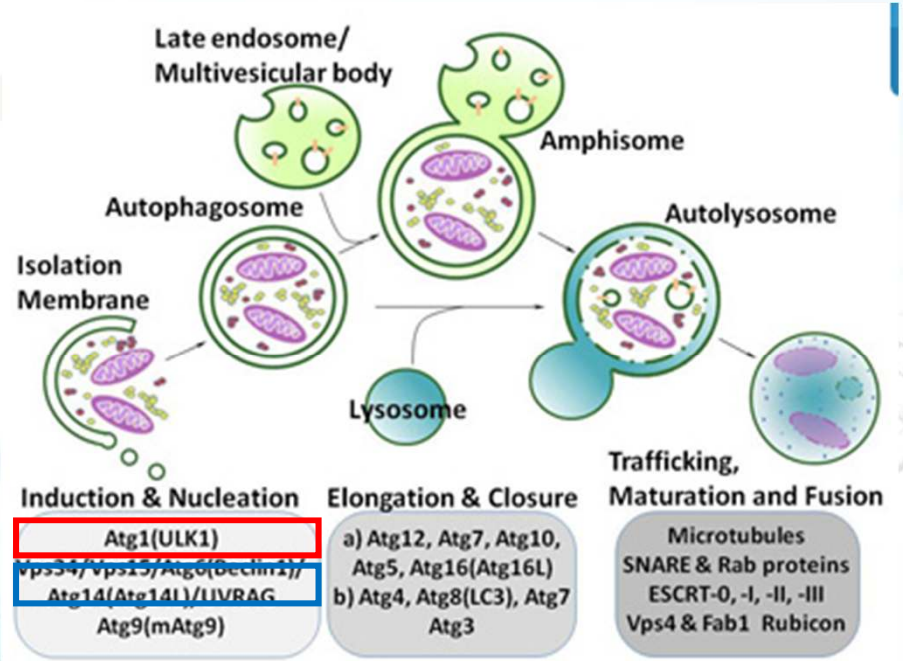
: Remove the damaged or long-lived proteins/organelles, or pathogens





"How does cellular stresses trigger autophagy reaction?"

Autophagy machinery (Executors)



Nat Cell Biol (2011)

Autophagy (2011)

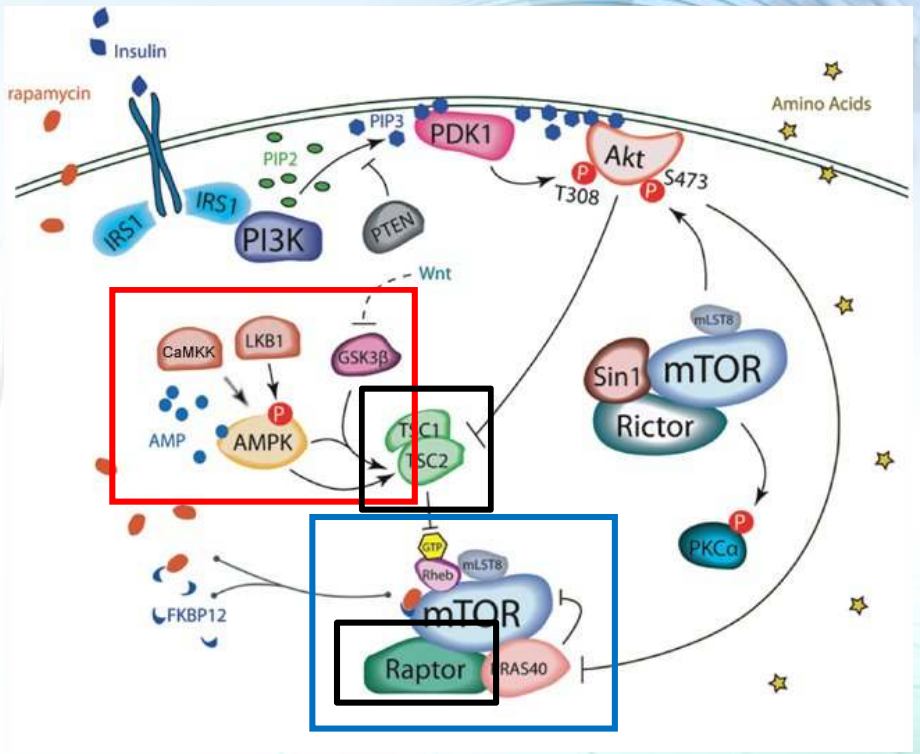
Cell cycle (2011)

Annu Rev Pharm Toxicol (2012)

Cell (2013)

Autophagy (2013)

Cellular energy-sensing pathways



AMPK (AMP-activated protein kinase)

mTORC1

In low energy status

: active in low E

: active in high E

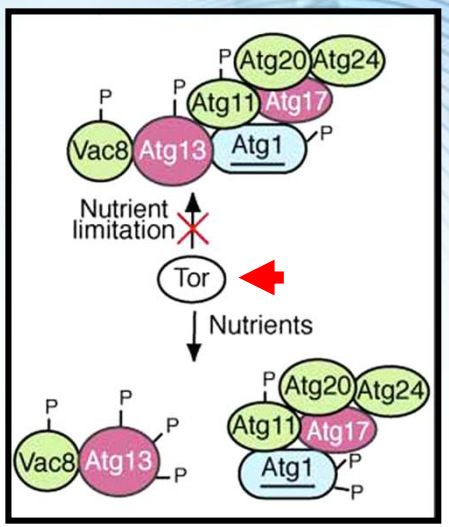
AMPK inhibits mTORC1

: simulates E-producing pathways and simultaneously inhibits E-consuming pathways

: simulates protein synthesis to promote cell growth

ULK1 (a mammalian homologue of yeast ATG1)

ATG1 complex



ATG1 (Yeast)

: A protein kinase triggering autophagy as a most ups tream regulator in yeast

: ATG1 complex formation is required for the kinase a ctivity and sensitive to rapamycin or nutrient level

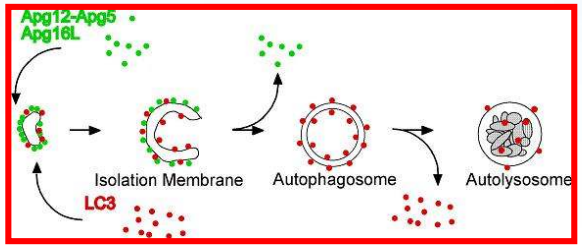
ULK1 (Mammals)

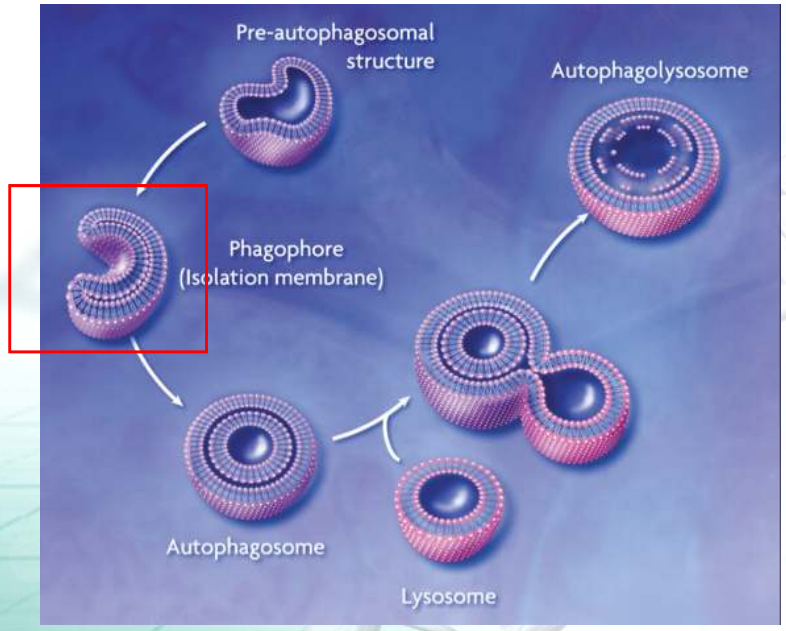
: mammalian homologue of yeast Atg1, a protein kinase activity

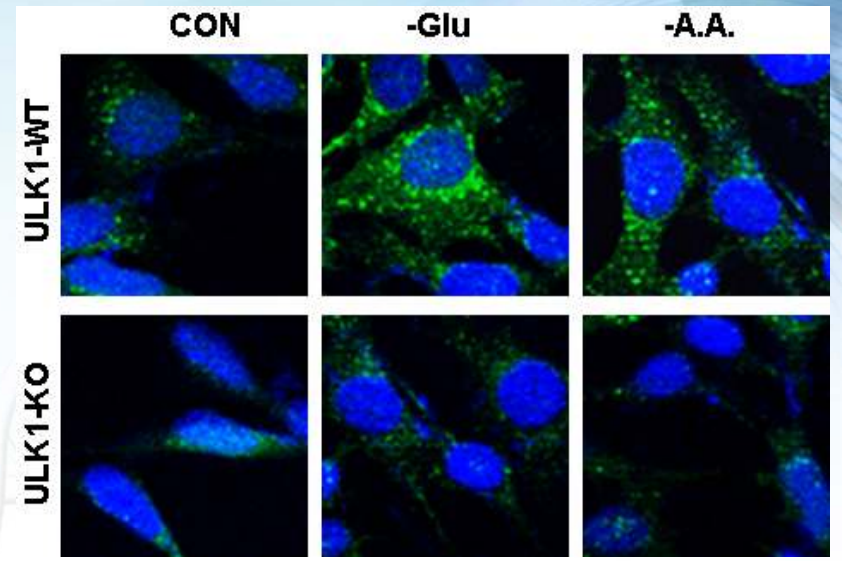
: Corresponding mammalian counterparts are identified (Atg13 – mAtg13; Atg17 – FIP200)

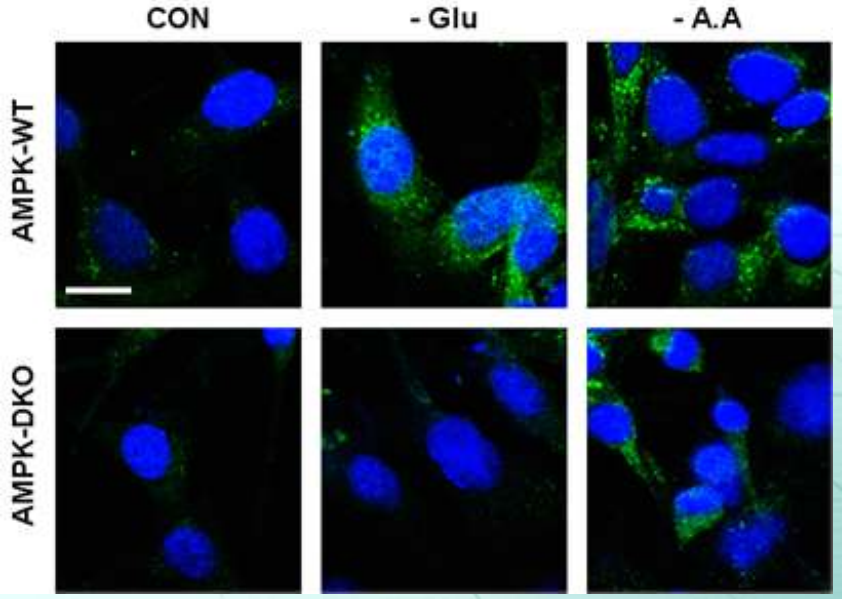
: However, ULK1 complex, is shown to be a stable complex insensitive to nutrient level

ULK1 and AMPK is required for starvation-induced autophagy

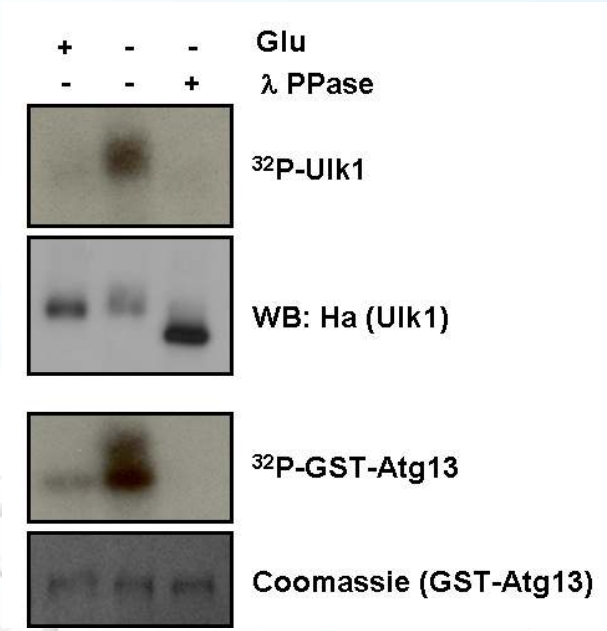




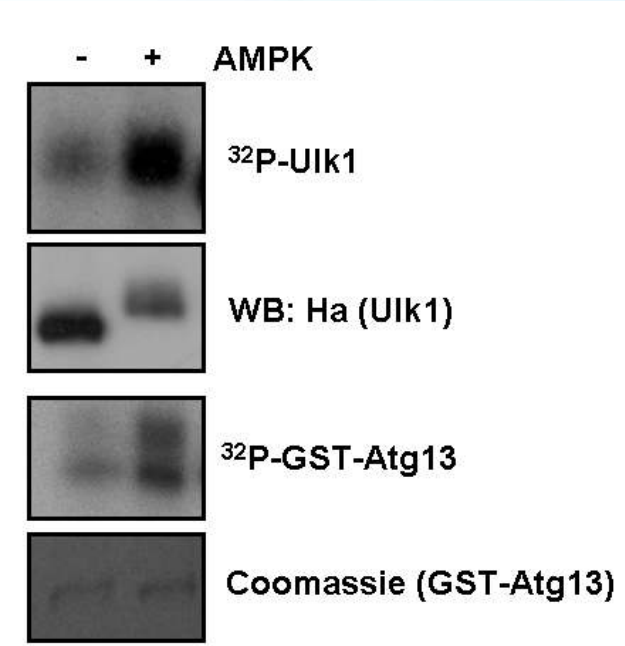




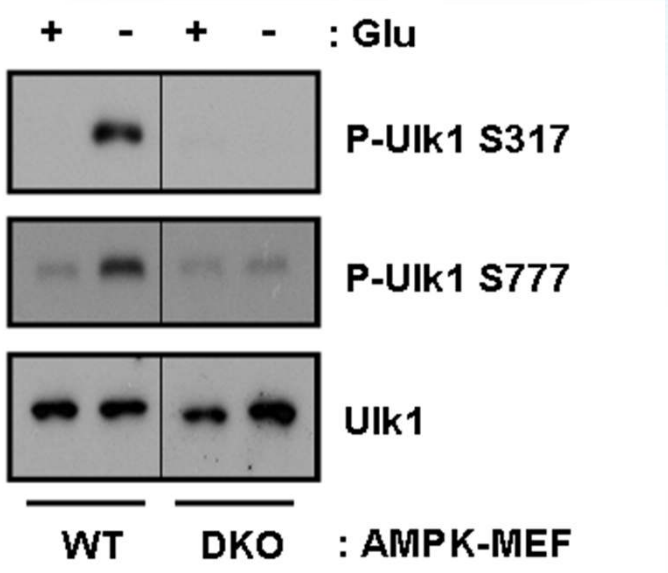
Glucose starvation activates ULK1 by phosphorylation



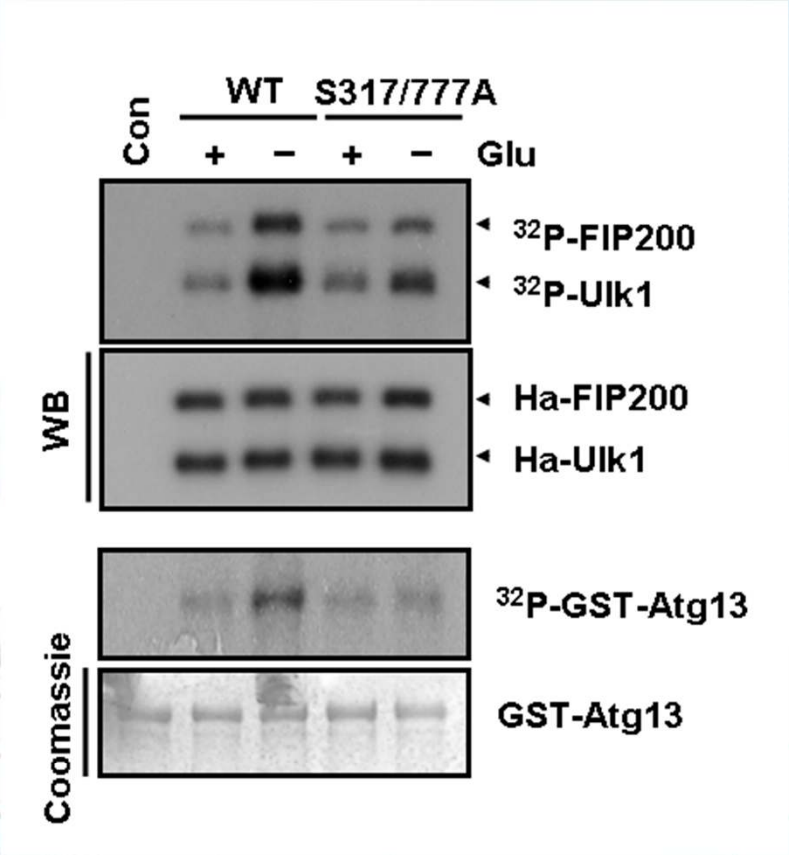
AMPK can directly activate ULK1



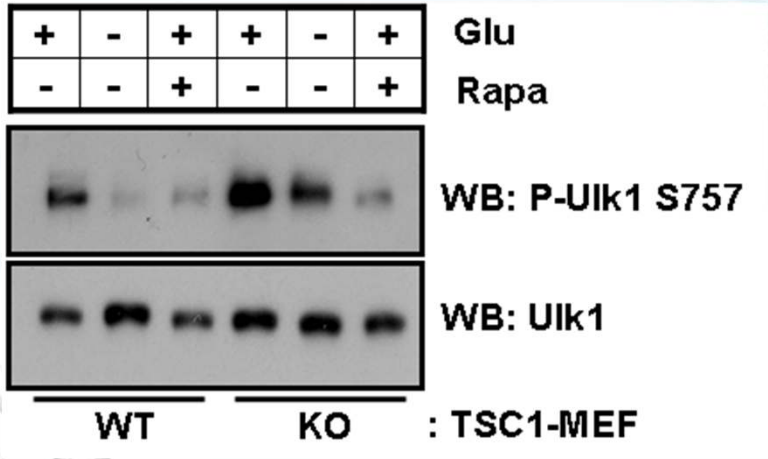
AMPK phosphorylates ULK1 at S317/S777 in response to glucose starvation



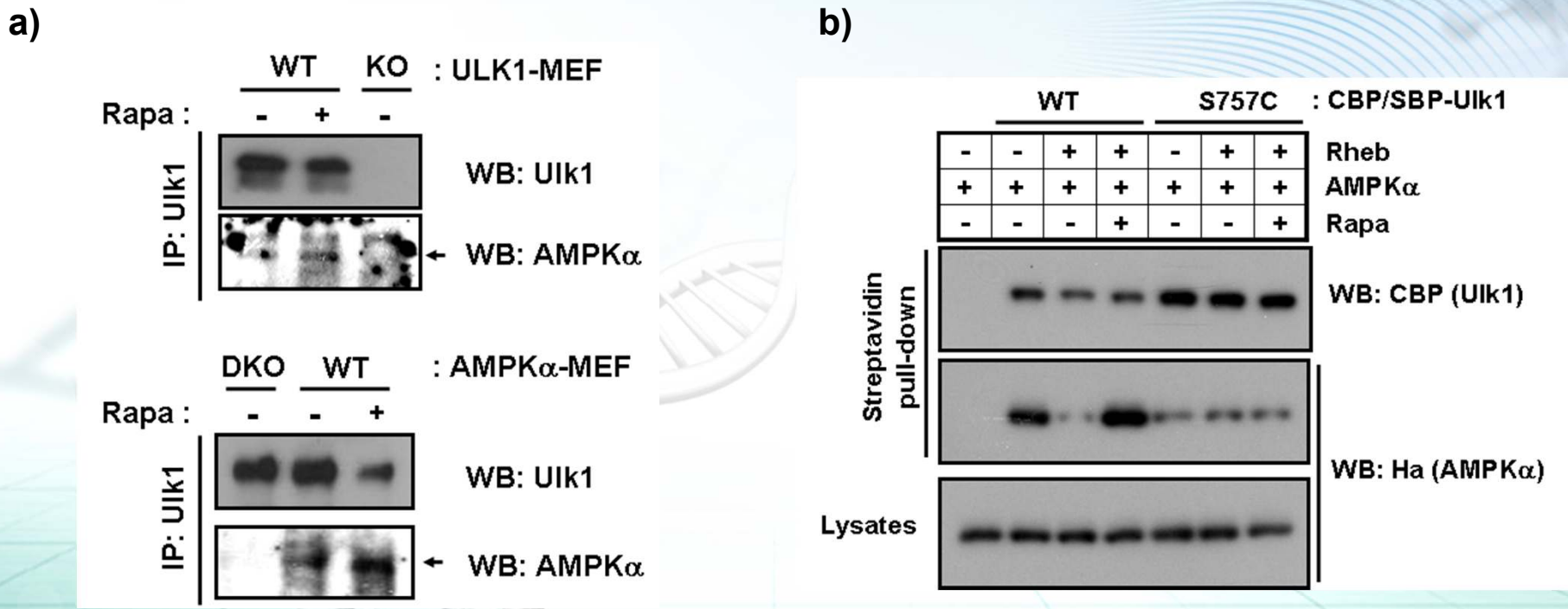
Phosphorylation of S317/S777 is required for ULK1 activation in response to glucose starvation



mTORC1 directly phosphorylates ULK1 at S757

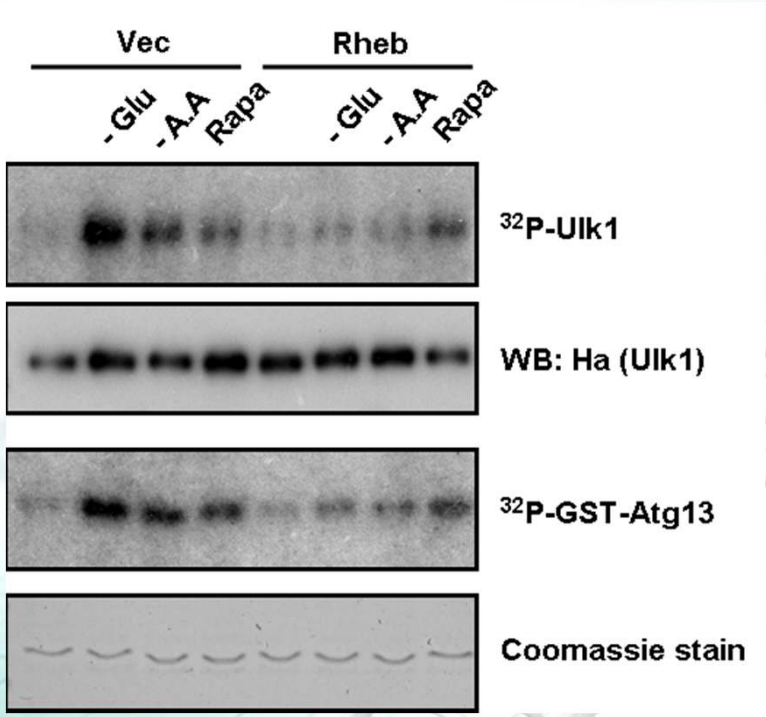


mTORC1-mediated ULK1 S757 phosphorylation suppresses AMPK-ULK1 interaction



Inhibition of mTORC1 is required for ULK1 activation by AMPK

a)



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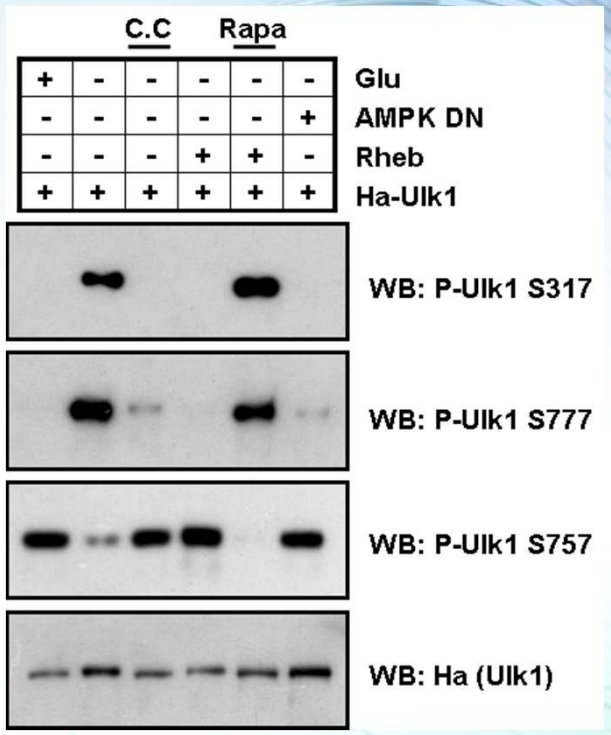
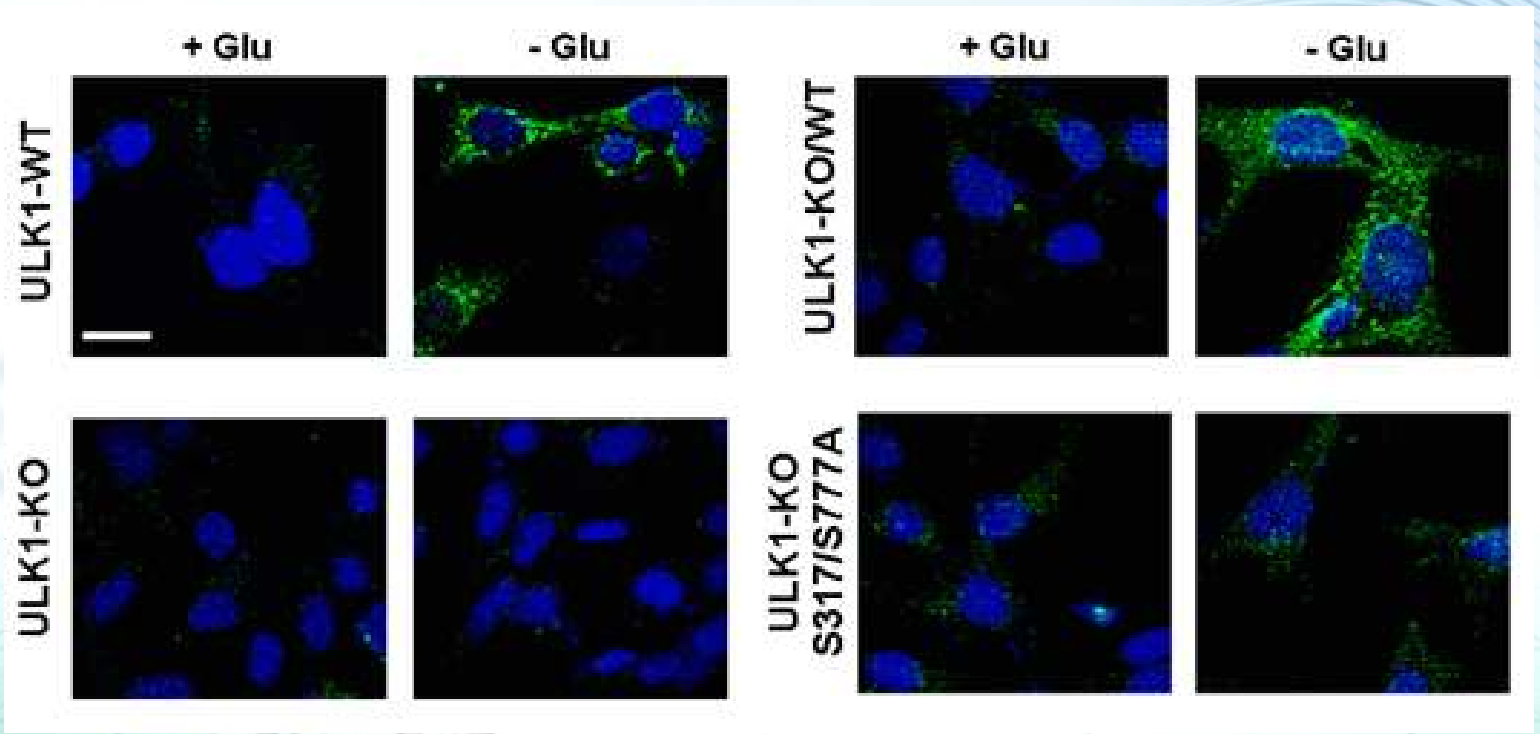


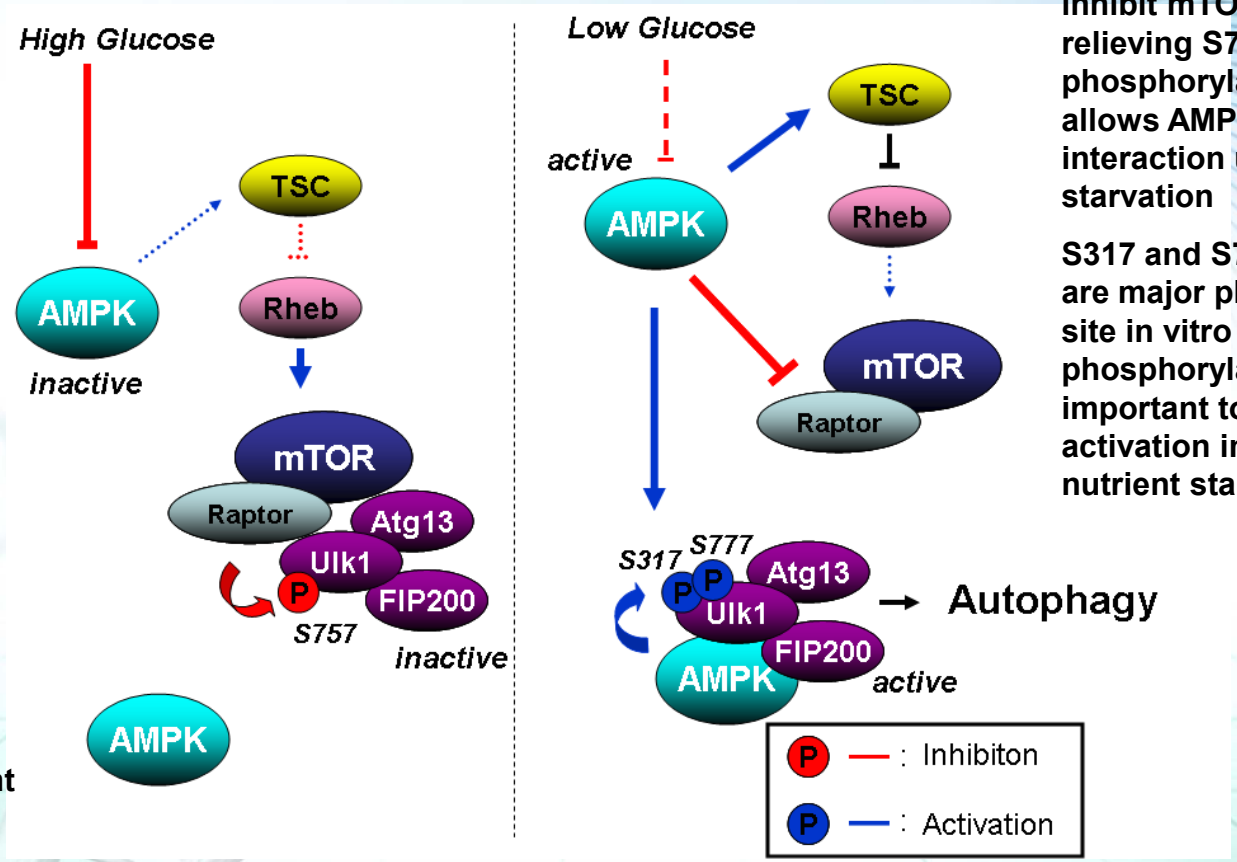
AMPK-dependent ULK1 phosphorylation is important for autophagy in response to glucose starvation



Proposed model

mTORC1 complex interacts with and phosphorylates ULK1 at S757

This phosphorylation inhibits AMPK-ULK1 interaction under nutrient rich condition



AMPK phosphorylates to inhibit mTORC1, thereby relieving S757 phosphorylation, which allows AMPK-ULK1 interaction upon glucose starvation

S317 and S777 of mULK1 are major phosphorylation site in vitro and this phosphorylation is important to ULK1 activation in response to nutrient starvation

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