# Central role of AMPK in the regulation of skeletal muscle protein turnover

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# Central role of AMPK in the regulation of protein skeletal muscle turnover

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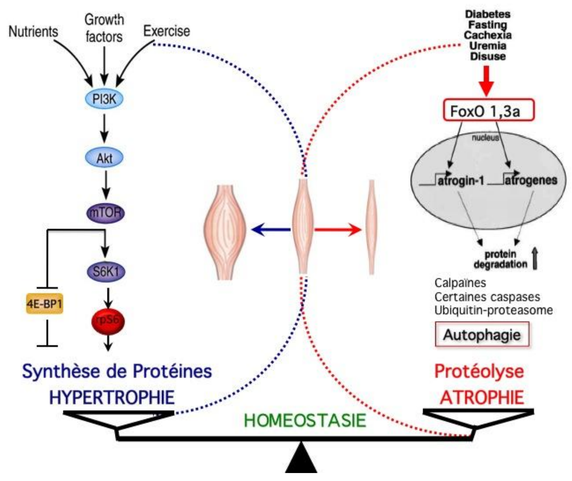
**INTRODUCTION:**

Skeletal muscle mass is depending upon a dynamic balance between anabolic and catabolic processes. At a cellular level, two major signaling pathways are involved: the transcription factors FoxO related pathway, implicated in the control of protein breakdown systems (ubiquitin-proteasome system and autophagy), and the IGF-1/Akt/mTORC1 pathway associated with the canonic pathway of protein synthesis and hypertrophy (3, 4). The aim of this study is to better understand the role played by the metabolic sensor system AMPK in the regulation of protein synthesis and breakdown. We show in muscle cells that the AMP-activated protein kinase (AMPK) decreases the mTORC1 pathway activity and simulates ubiquitin-proteasome and autophagy systems in a FoxO3-dependant manner. Furthermore, we identify Ulk1 as a new interacting partner of AMPK, which plays a major role in the autophagy induction.

## Regulation of muscular mass

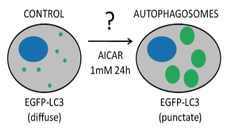
### Signaling pathways:




AMPK = metabolic sensor activated by AICAR

Regulates FoxO3a (1, 4)

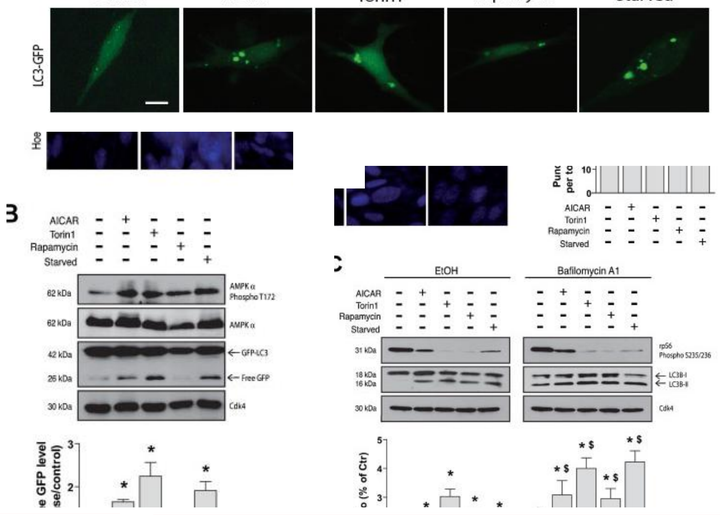
FoxO3a = transcription factor of genes implicated in autophagyl(2)




## AICAR induces autophagy in proliferating C2C12 cells and primary myotubes

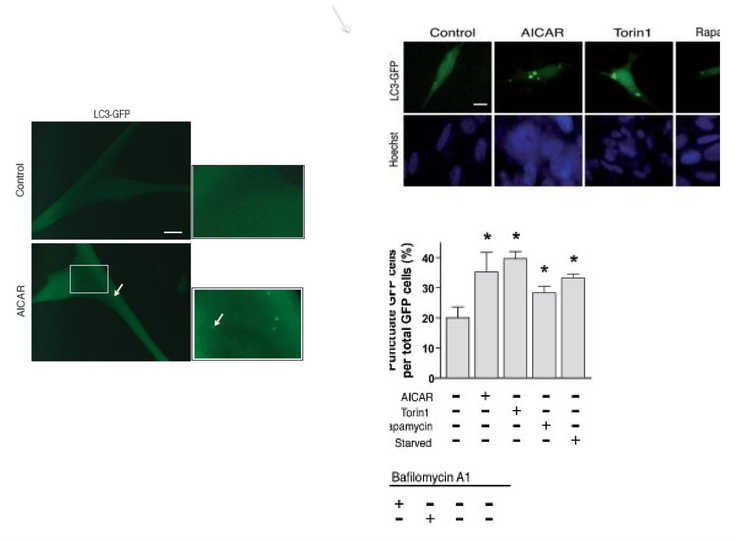
*C2C12 myoblasts, prolifération (J3)*

**AMPK activation increases autophagic fluxes in proliferating cells**




*Primary myotubes, différentiation (D4)*

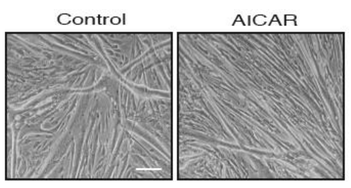
**AMPK activation increases autophagic fluxes in primary myotubes**

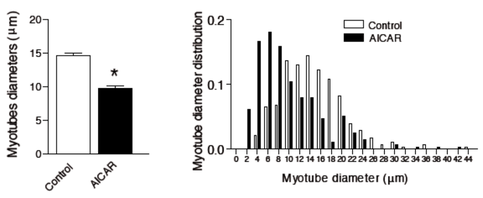


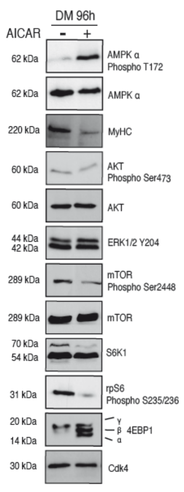

## AICAR inhibits protein translation and induces protein ubiquitination

*Primary myotubes, différentiation (D4)*

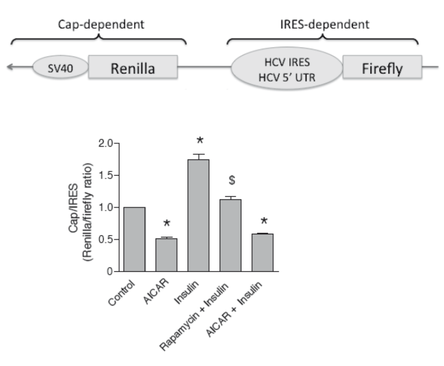
**AMPK inhibits protein translation and induces primary myotubes atrophy**

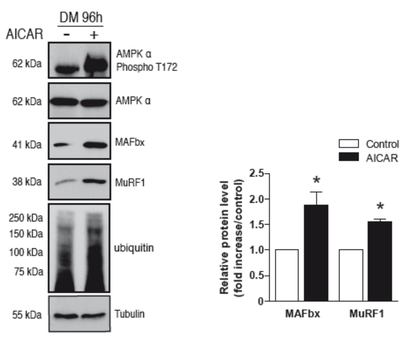



**AMPK increases protein polyubiquitination**

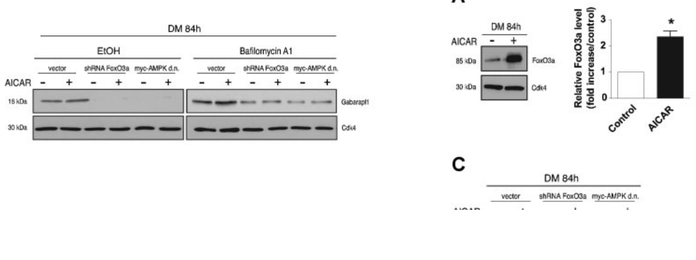


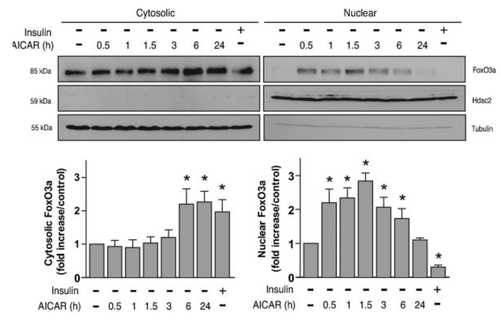

## FoxO3a-dépendent regulation of autophagy induced by AMPK activation

**AMPK induces the expression of autophagic proteins in a Foxo3-dependant manner**

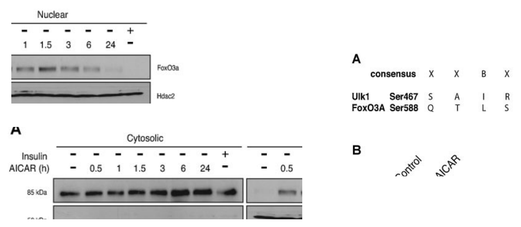
*Primary myotubes, différentiation (D4)*



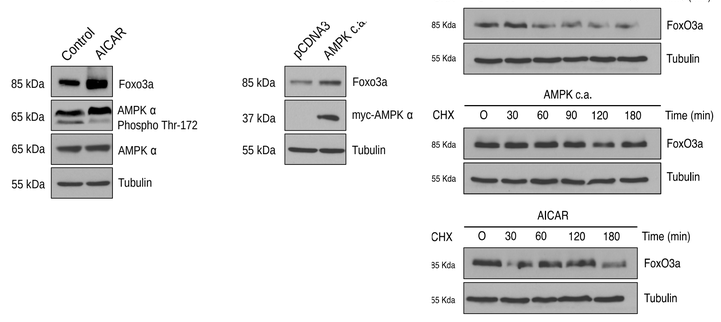

**AICAR induces a transient FoxO3a nuclear localization**




**AMPK interacts with FoxO3a and induces Ser-588 phosphorylation**



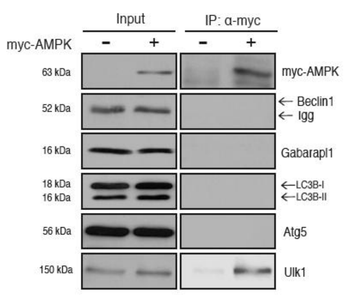

**AMPK stabilizes FoxO3a**

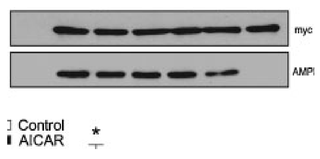



## Ulk1 : A new target of AMPK

*Proliferating myoblasts*

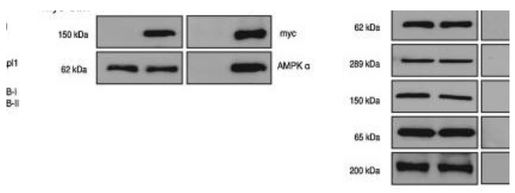
**AMPK interacts with Ulk1 and induces Ser467 phosphorylation**



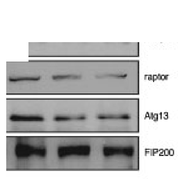



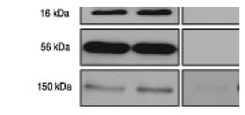


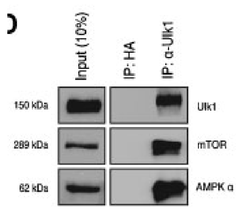
**Dynamique du complexe ???**

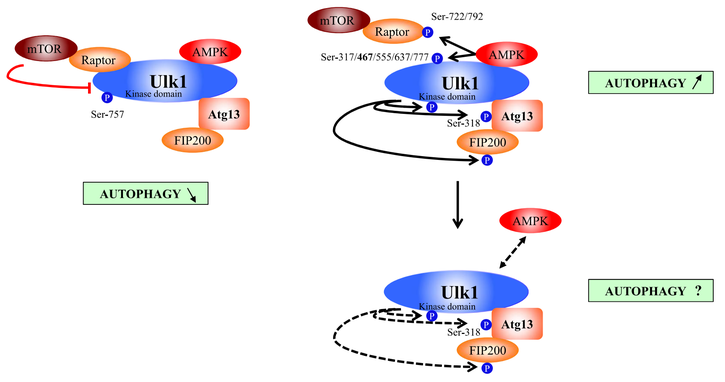



**Complex AMPK/Ulk1/mTOR/raptor/Atg13/FIP200 formation**



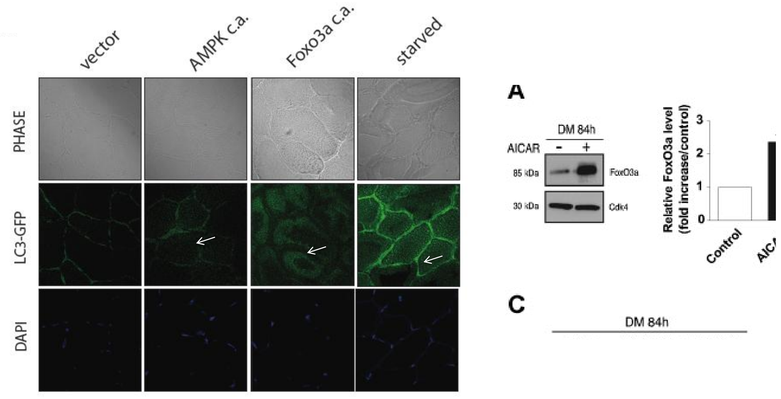



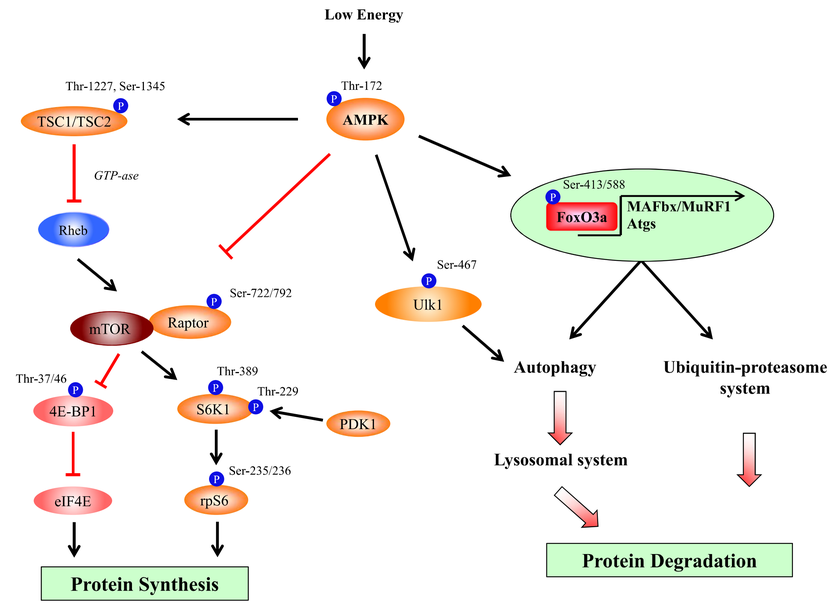




## Conservation des résultats *In vivo* ???

**Formation de vésicules autophagiques dans les fibres électroporées avec des formes activées de l'AMPK ou de FoxO3a**




## In summary




## CONCLUSION :

In this study, we identified AMPK-associated signaling pathways implicated in the muscular mass regulation. The characterization of a new interacting partner of AMPK, essential to the autophagy process suggests novel therapeutic perspectives in the treatment of myopathies associated to an increase of proteolysis.

## *REFERENCES* :

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*(2) Mammucari C, Milan G, Romanello V, Masiero E, Rudolf R, Del Piccolo P, Burden SJ, Di Lisi R, Sandri C, Zhao J, Goldberg AL, Schiaffino S, Sandri M (2007). Cell Metab. 6(6):458-71.*
*(3) Rivas DA, Lessard SJ, Coffey VG (2009). Appl Physiol Nutr Metab, 34(5):807-16, pour revue.*
*(4) Sanchez AMJ, Candau RB, Csibi A, Pagano AF, Raibon A, Bernardi H. (2012). Am J Physiol Cell Physiol, 303(5):C475-85 for review.*