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## Post-mortem proteolysis: Emerging link between Myostatin, Oxidative stress and Autophagy

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► **To cite this version:**

Rim Nassar. Post-mortem proteolysis: Emerging link between Myostatin, Oxidative stress and Autophagy. 8ème congrès du club français Autophagie CFATG, Oct 2018, La Grande Motte, France. hal-02940611

**HAL Id: hal-02940611**

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Submitted on 16 Sep 2020

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Université Libanaise

Ecole Doctorale  
Sciences et Technologie



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# ***Post-mortem* proteolysis: Emerging link between Myostatin, Oxidative stress and Autophagy**

Presented by  
**Rim Nassar**



National Council for Scientific Research

**DMeM**

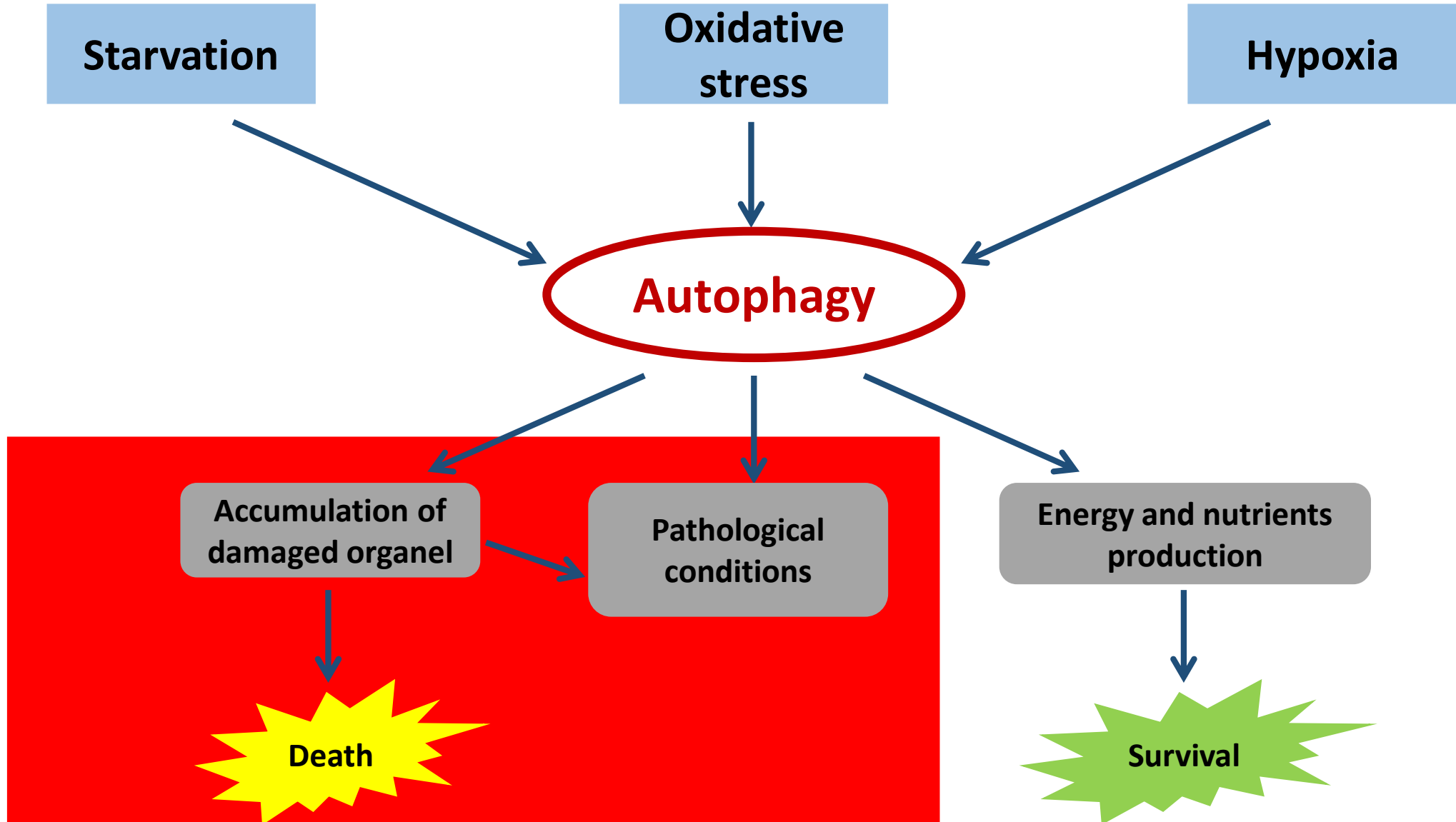
Dynamique Musculaire et Métabolisme

**LIT**

Laboratoire d'Innovation Thérapeutique

# Role of autophagy

Crucial process that is involved in the degradation and recycling of damaged components within the cell



# Autophagy is required to maintain muscle mass and function

## ➤ Constitutive conditions *Masiero et al 2009:*

The inhibition of autophagy



1. muscle atrophy
2. loss of force production
3. muscle weakness

## ➤ Pathological muscle conditions associated to autophagy dysregulation

Pompe disease (*C. Nascimbeni et al 2012*)

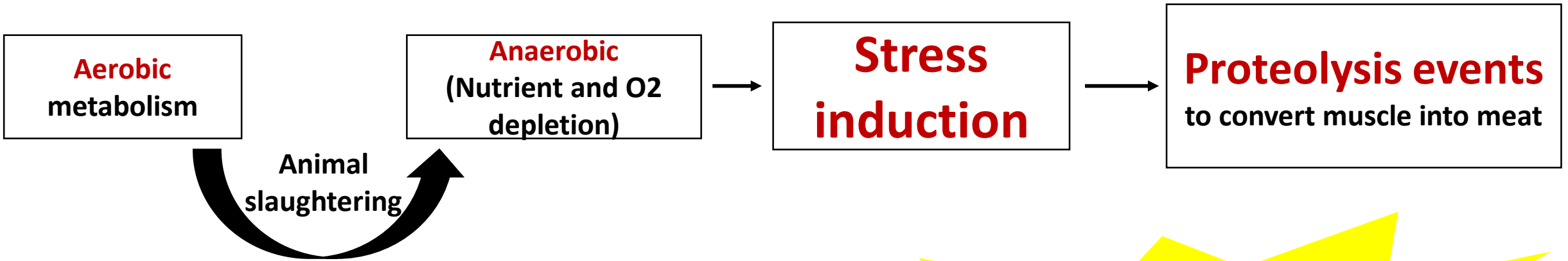
Vici syndrome (*Cullupe et al 2013*)

Duchenne Muscular Dystrophy (*De Plame et al 2012*)



Down-regulation of autophagy  
(accumulation of damaged  
organelles)

# Muscle post-mortem maturation



Autophagy 10:1, 137–143; January 2014; © 2014 Landes Bioscience

## Autophagy during beef aging

Marina García-Macia,<sup>1,†</sup> Verónica Sierra,<sup>1,2,†</sup> Ana Palanca,<sup>1</sup> Ignacio Vega-Naredo,<sup>1</sup> David de Gonzalo-Calvo,<sup>1</sup> Susana Rodríguez-González,<sup>1</sup> Mamen Oliván,<sup>2</sup> and Ana Coto-Montes<sup>1\*</sup>

Quid of **Autophagy** regulation in PM ?

**PM maturation depends on:**

- Biochemical factors: stress, pH, pathway signaling
- Physical factors: animal breeding and slaughtering
- **Genetic factors**

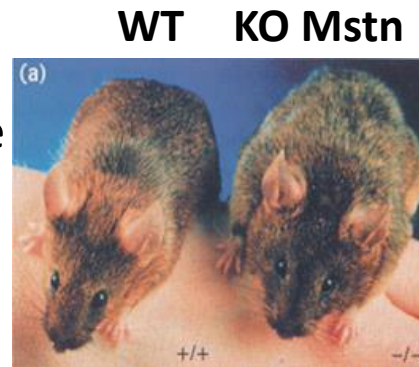
# Myostatin: Negative regulator of muscle mass

## => Protein synthesis/degradation balance

- **Absence** (KO Mstn) => Hypertrophy => increase of the muscle fiber number and size
- **Conserved function** among species



Grobet et al 1997



## => Redox balance

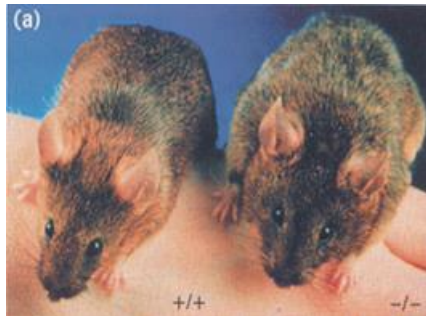
- **Absence** (Ploquin et al 2012) => **Antioxidant status enhancement**
- (Sriram et al 2011) => Addition of Mstn => increase the ROS production



**Is the autophagic process involved in the post-mortem maturation of muscle into meat??**

**How this mechanism is regulated??**

# Experimental design: Pilot study

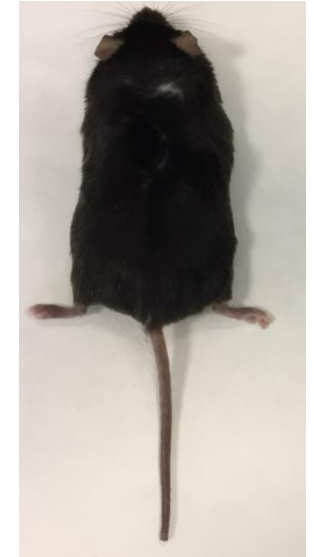
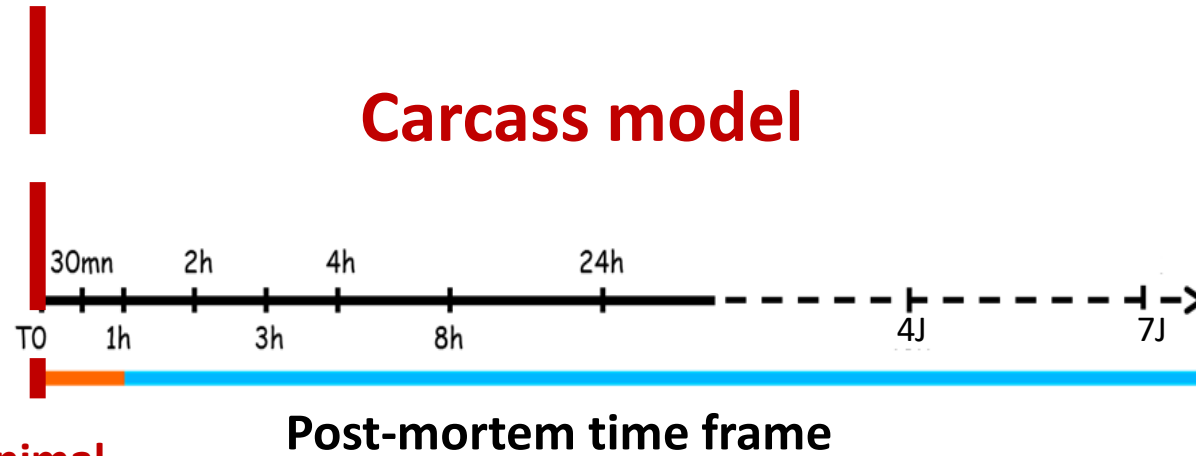


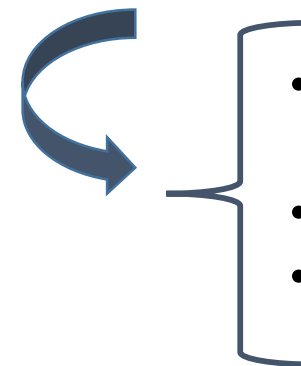
WT

KO Mstn

**Animal  
slaughtering**  
By cervical  
dislocation

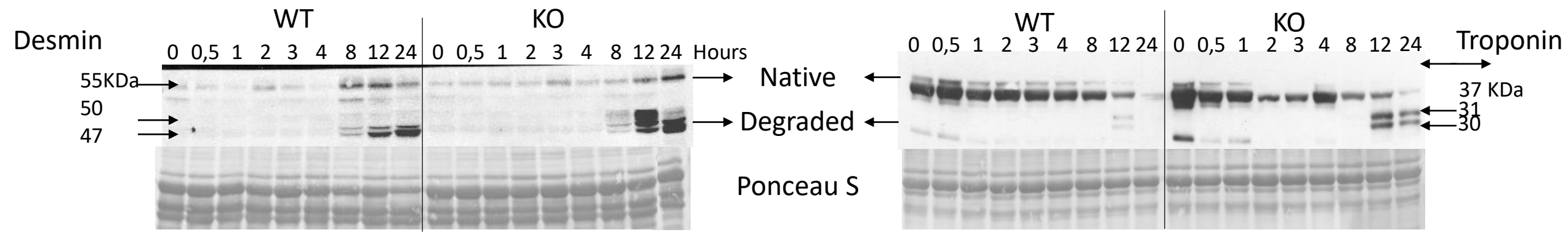
## Carcass model



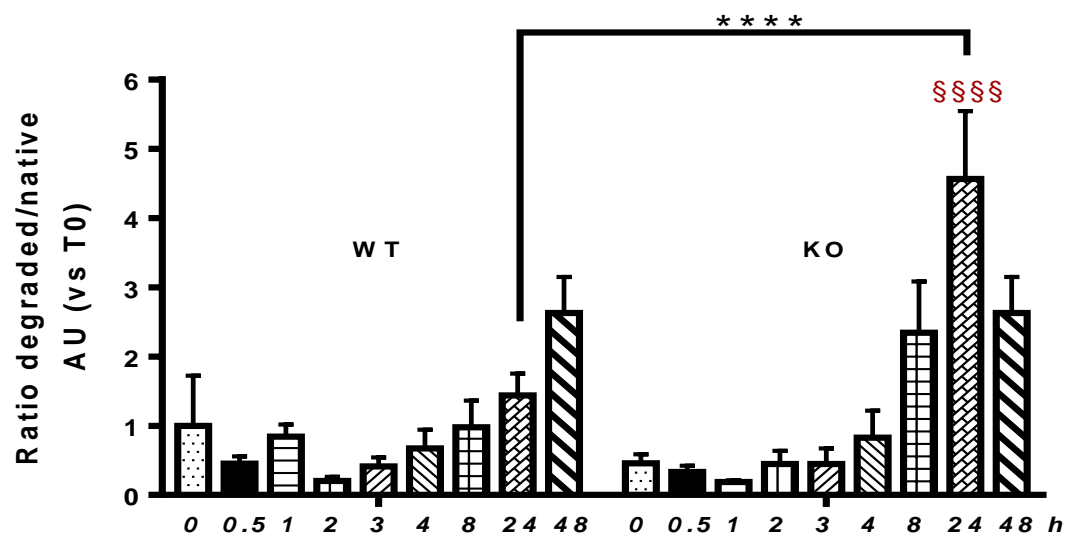
- 
- Myofibrillar protein degradation (Troponin T- Filamin C - Desmin)
  - Oxidative stress markers
  - Autophagic flux



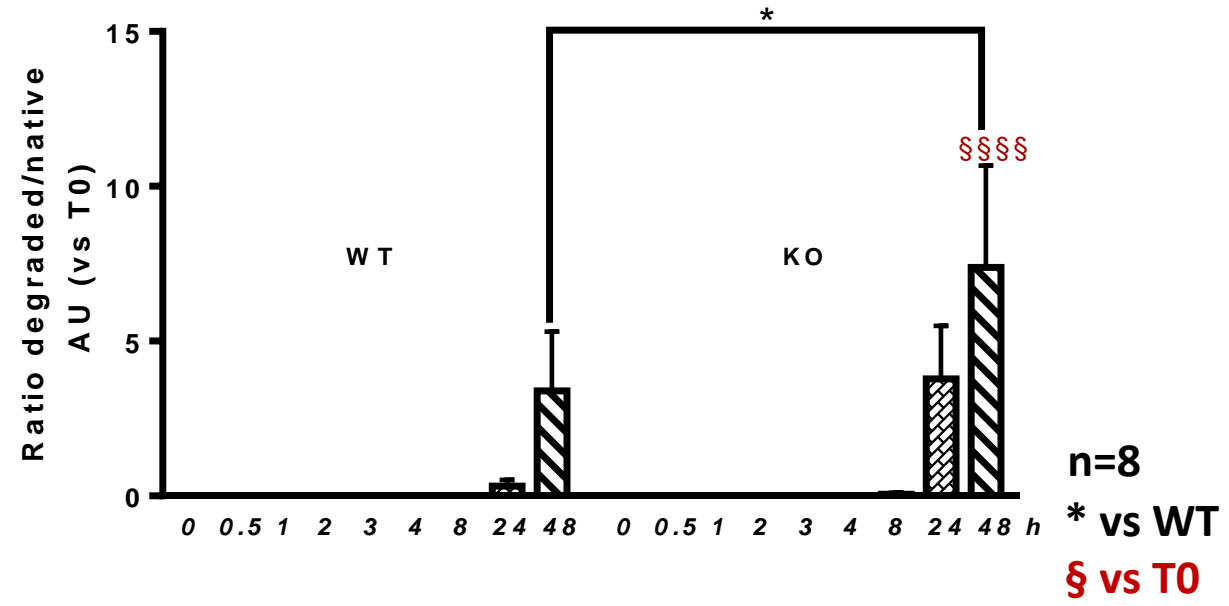
# Post-mortem myofibrillar protein degradation is more pronounced in KO Mstn



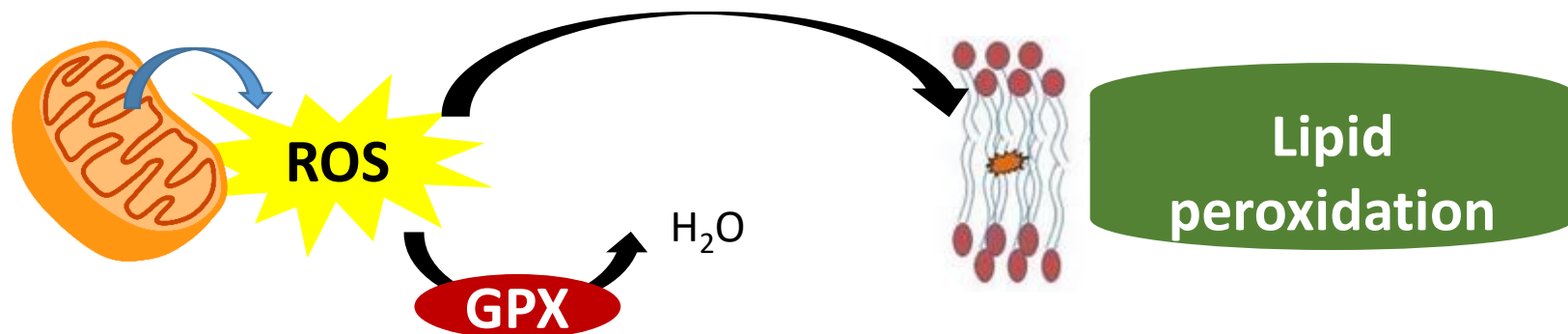
**Desmin Degradation**



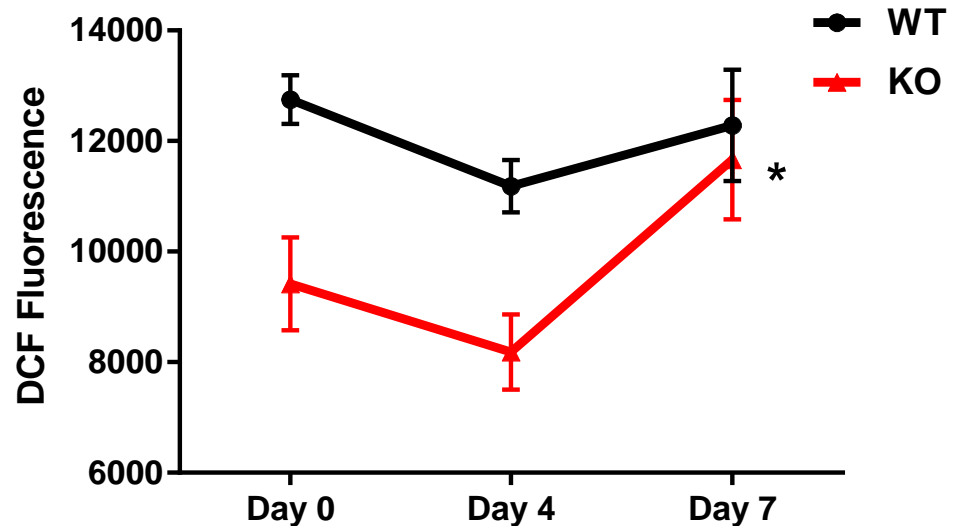
**Troponin T Degradation**



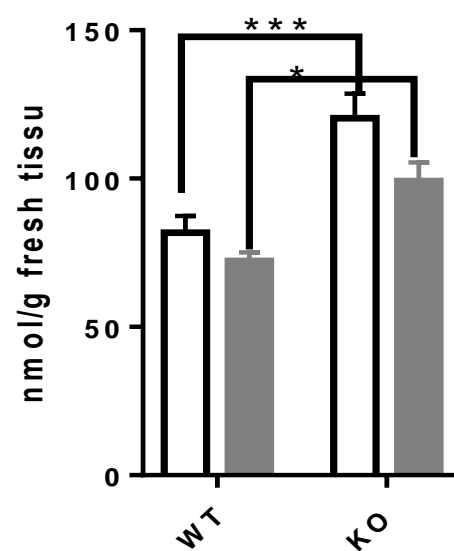
# The oxidative stress was not induced during the PM maturation in WT and KO *Mstn* mice



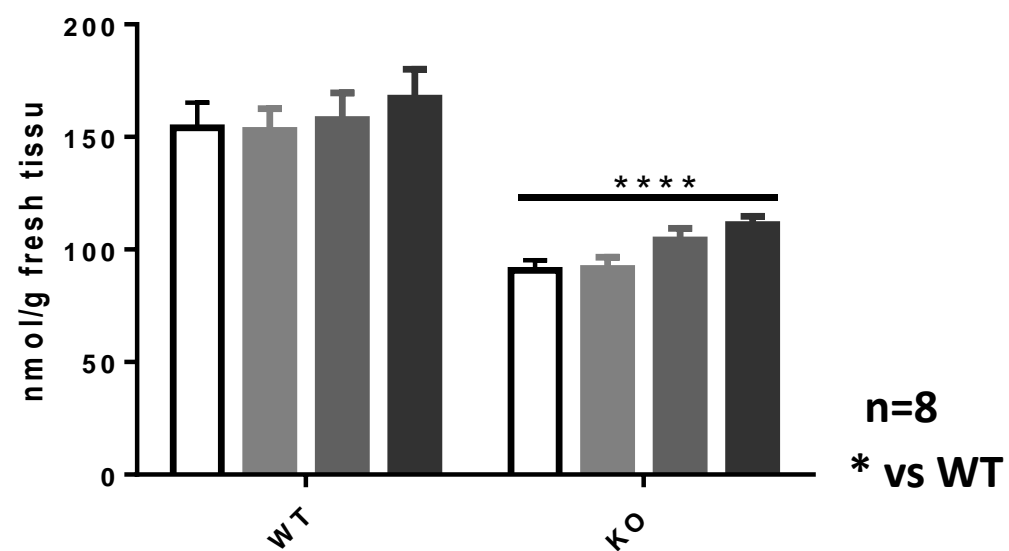
### ROS measurement



### GPx activity



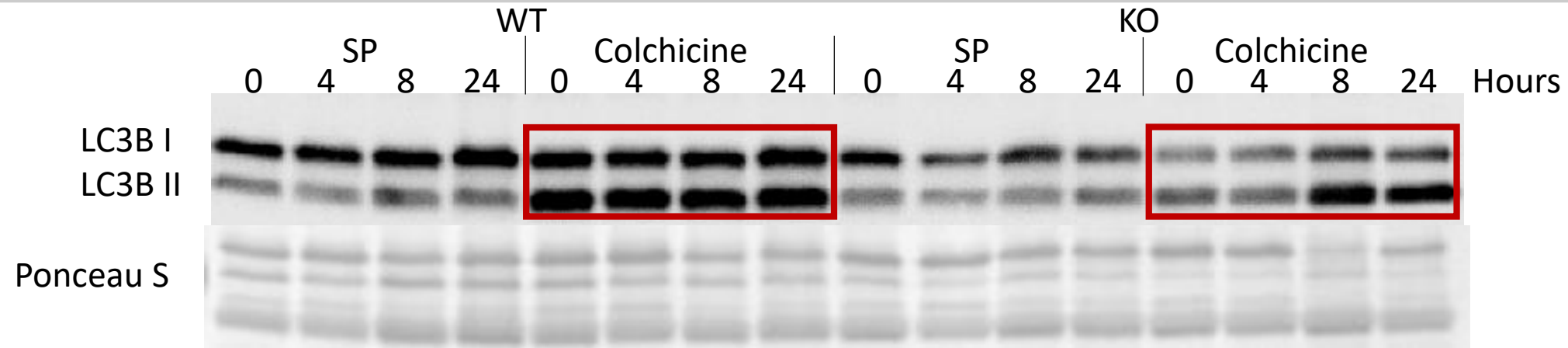
### Lipid peroxidation



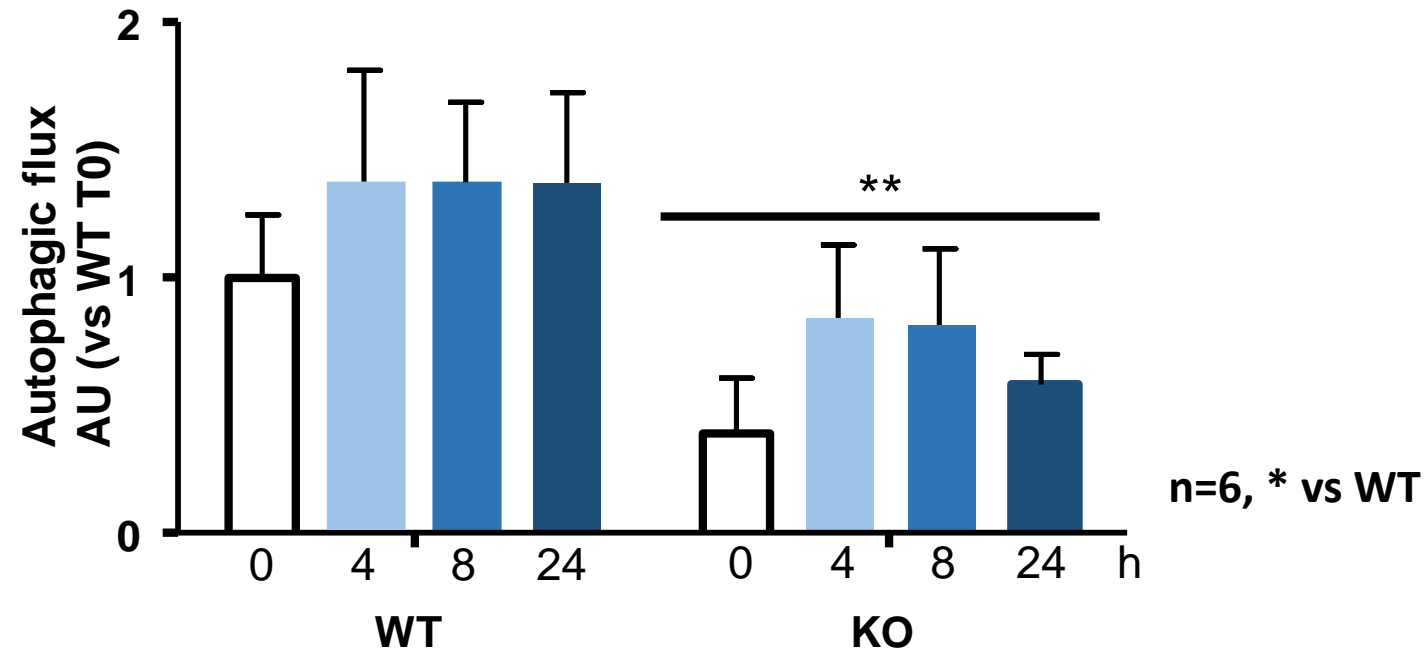
Legend for bar graphs: Day 0 (white), Day 1 (light grey), Day 4 (medium grey), Day 7 (dark grey)

n=8  
\* vs WT

# The autophagy was not induced during the PM maturation in WT and KO Mstn mice



Autophagic flux (LC3BII<sub>COL</sub> – LC3BII<sub>SP</sub>)



## In our PM model (muscle on carcass):

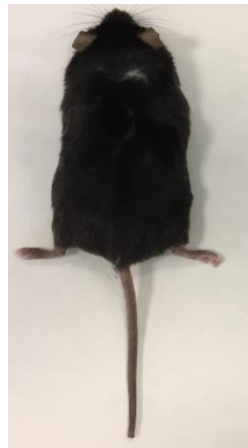
*Absence of ROS production  
alteration*

*Absence of autophagy induction*

***Is the model carcass representative of livestock  
slaughtering condition?***



**Carcass model Vs isolated muscle**

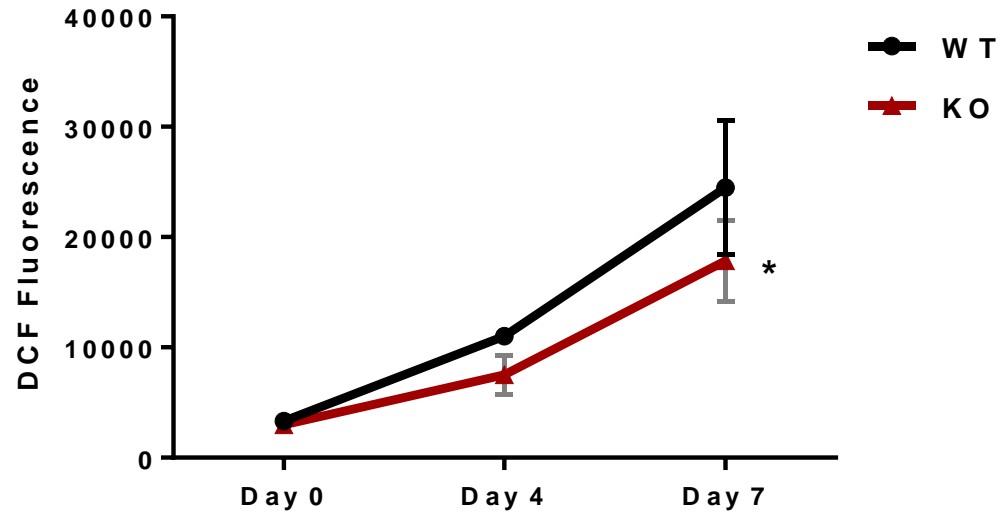


# The oxidative stress markers were increased during the PM maturation

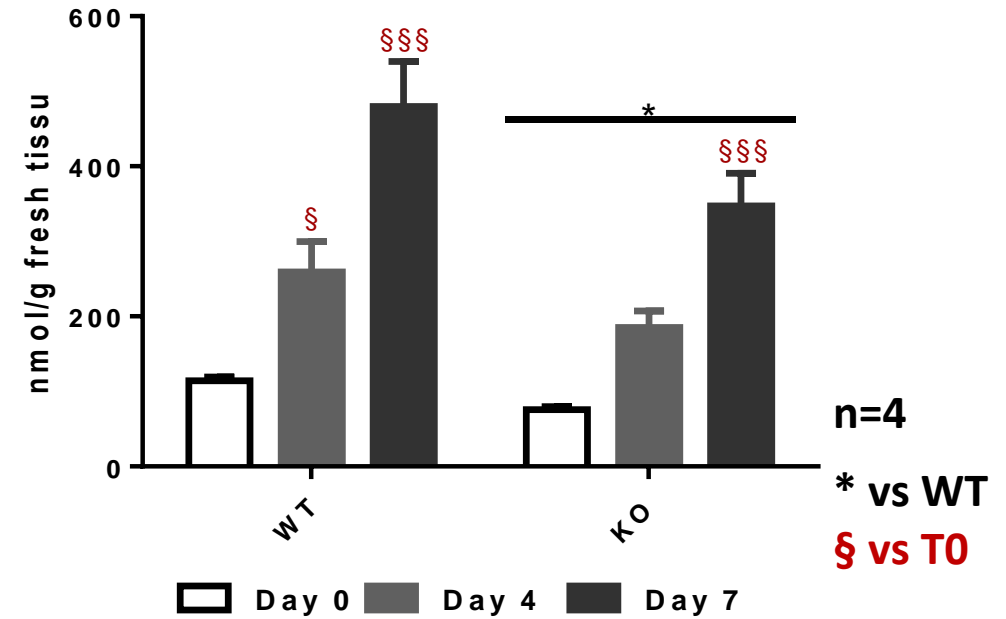
Isolated muscle



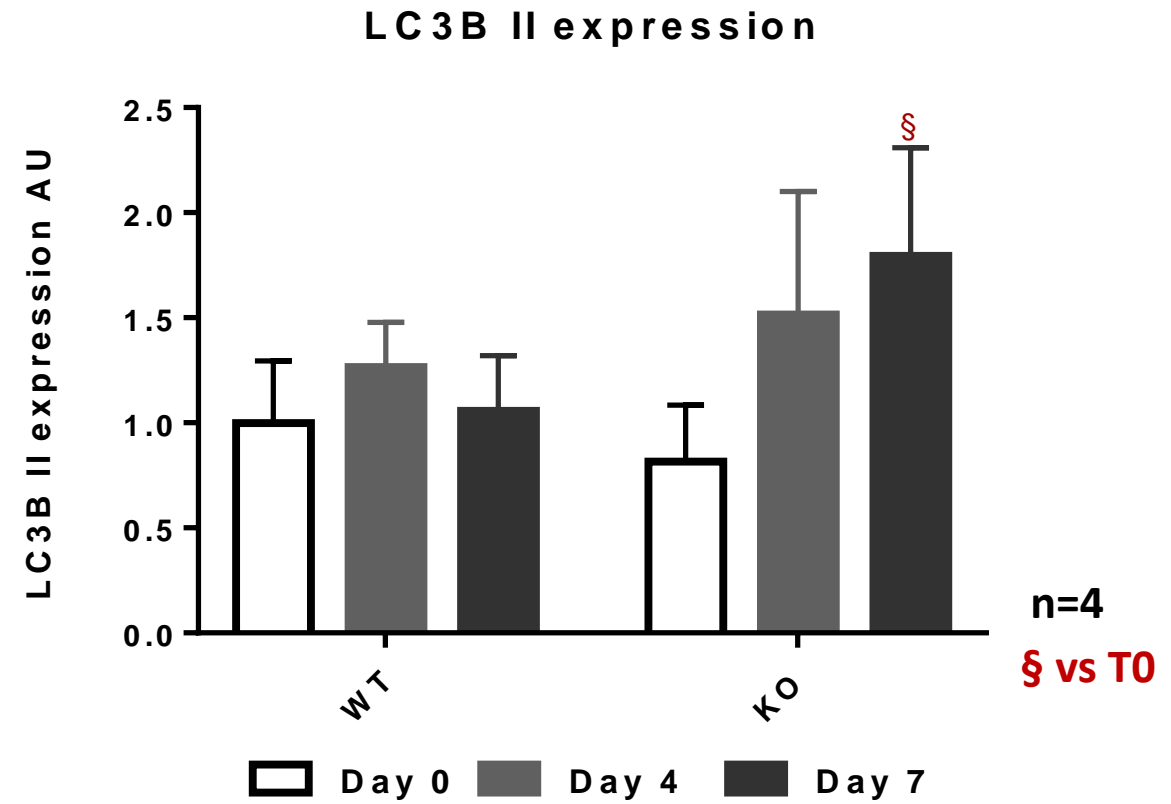
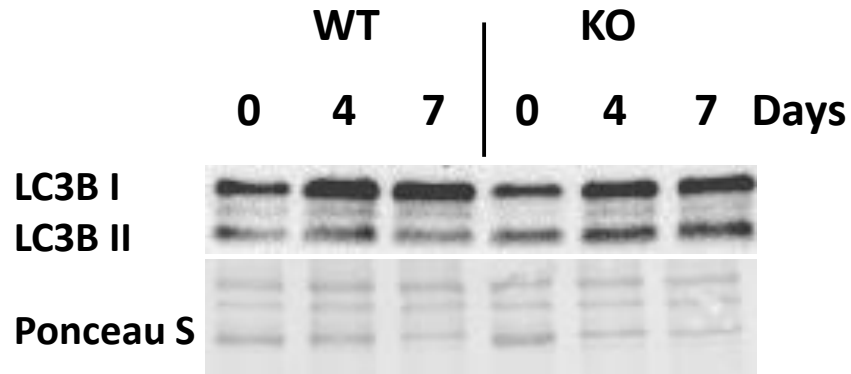
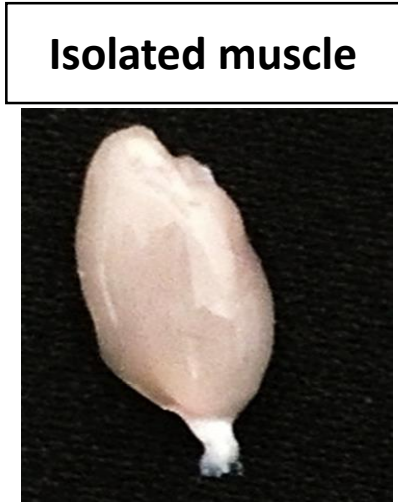
ROS measurement



Lipid peroxidation



# Increasing of LC3 expression during PM in the absence of myostatin



# Conclusion



***Our pilot model on isolated muscle suggested:***

- 1. The involvement of autophagic process in PM**
- 2. The PM autophagy could be correlated to an oxidative stress and may depend on genotype**
  - **Increasing the « n » number of animal**
  - **Measurement of the autophagic flux**



**Via which mechanism the myostatin could regulates proteolysis??**

# Acknowledgment

## Participants

### UMR DMeM INRA- Montpellier

Anne Bonnieu  
Béatrice Chabi  
Arnaud Chatonnêt  
Barbara Vernus  
François Casas  
Lionel Tintignac



Christelle Bertrand-Gaday  
Sylvain Cerda  
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Mélanie Macart

### Laboratoire d'Innovation Thérapeutique Beyrouth

Fadia Najjar  
Aline Hamade

## Collaborations

### UMRH Theix

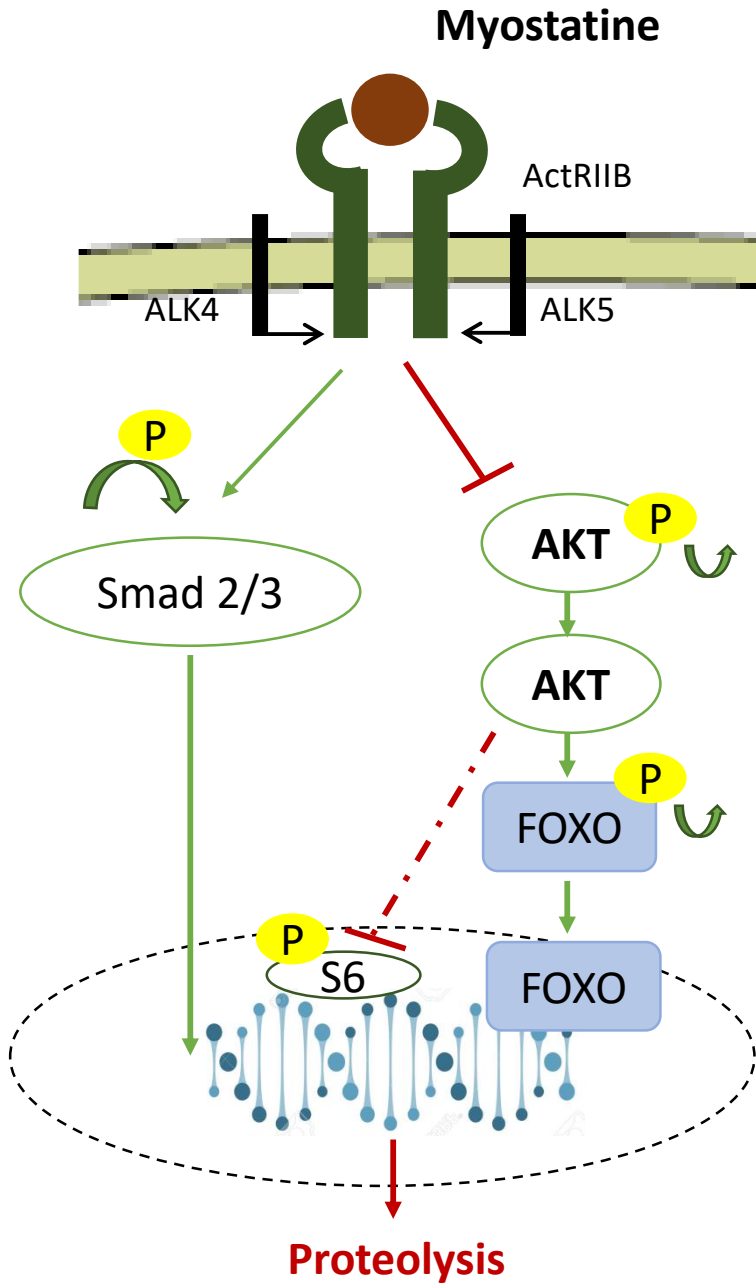
Brigitte Picard  
Isabelle Cassar-Malek

### INSERM, ERI25-Muscles et Pathologies, Montpellier

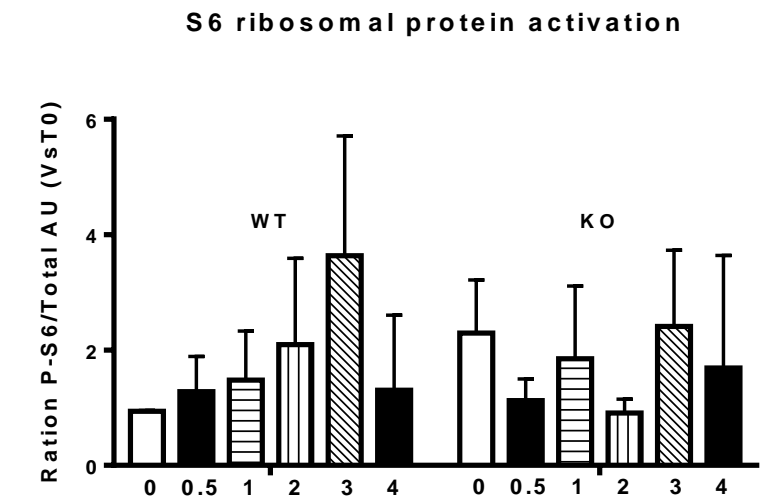
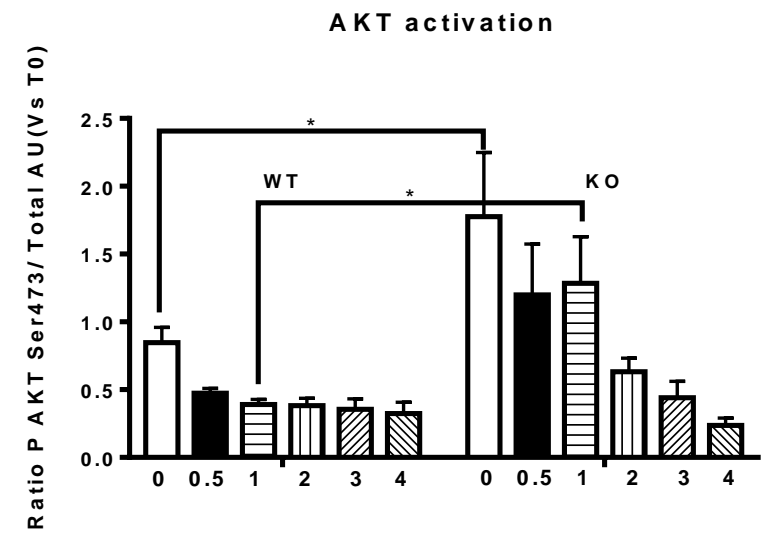
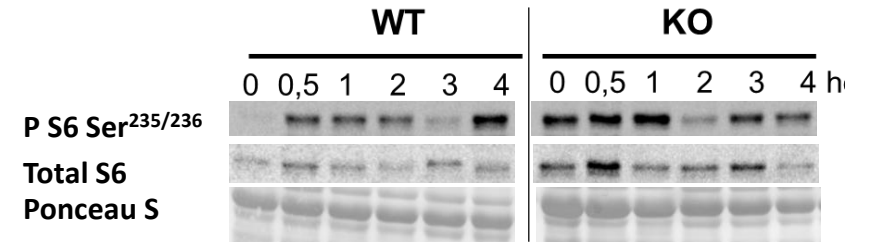
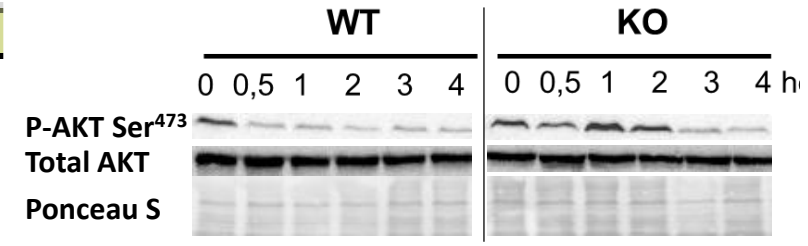
Gilles Carnac



# Ongoing work



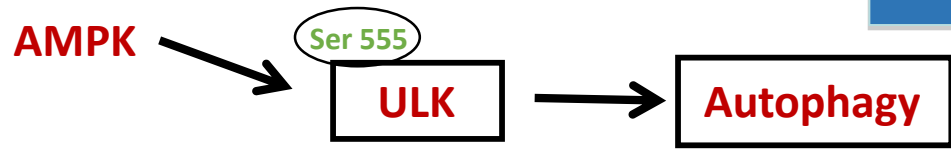
(H.Q.Han et al 2013)



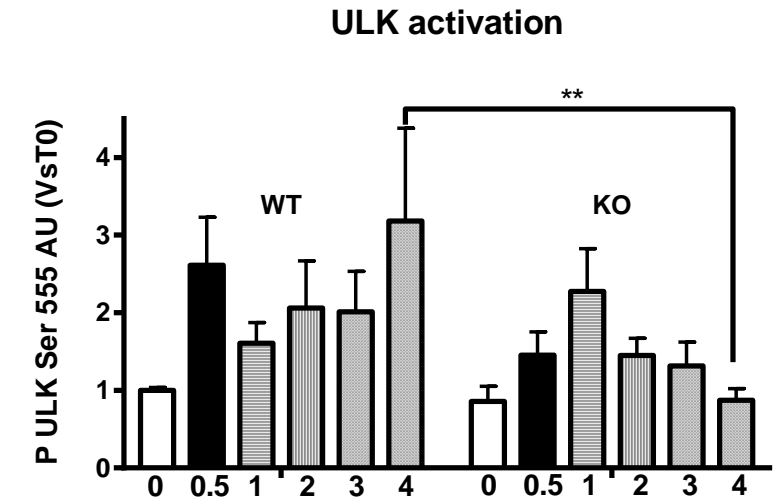
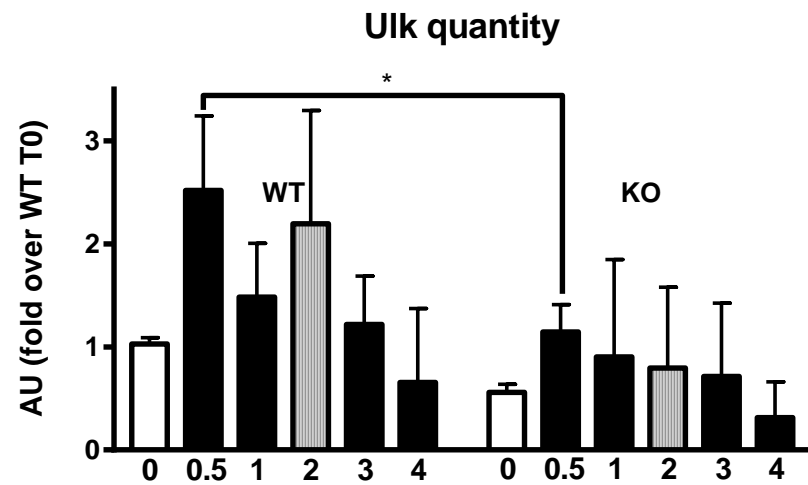
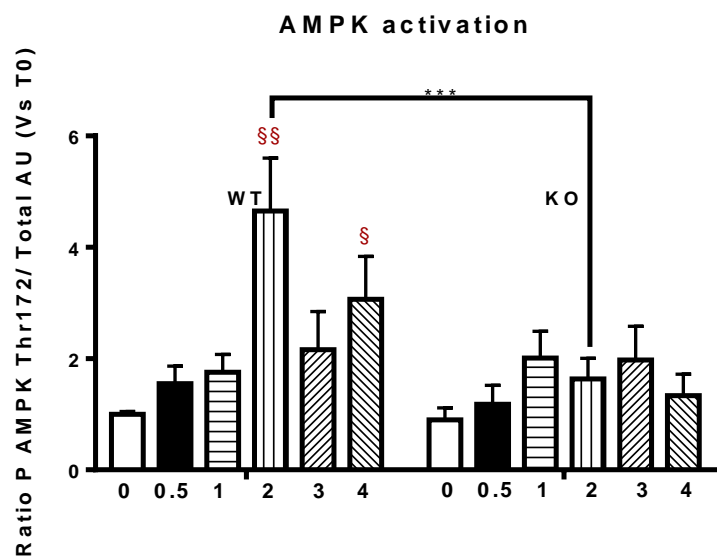
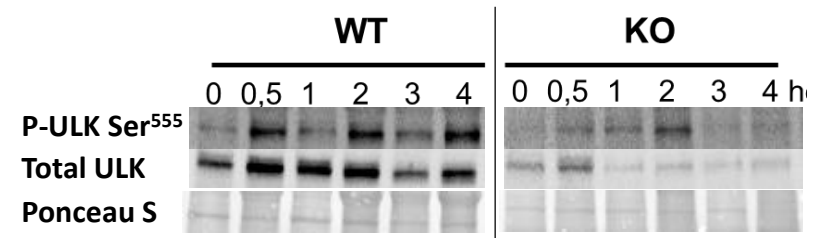
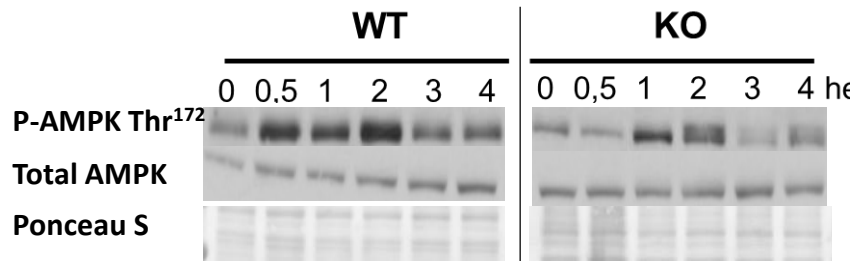
n=8\* p ≤ 0.01 Vs WT

**KO Mstn enhances the activation of AKT correlated with S6 activation at basal level**

# Ongoing work



n=8\* p ≤ 0.01 Vs WT, § p ≤ 0.01 Vs T0



**KO Mstn reduces AMPK activation and total ULK synthesis => reduced ULK activation during PM maturation**

# Stress induction at 7 days post-mortem in an isolated muscle correlated with autophagic induction

Isolated muscle



Carcasse

