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

Rim Nassar

► **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

<https://hal.inrae.fr/hal-02940611v1>

Submitted on 16 Sep 2020

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Université Libanaise

Ecole Doctorale
Sciences et Technologie



INRA
SCIENCE & IMPACT



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

Presented by
Rim Nassar



National Council for Scientific Research

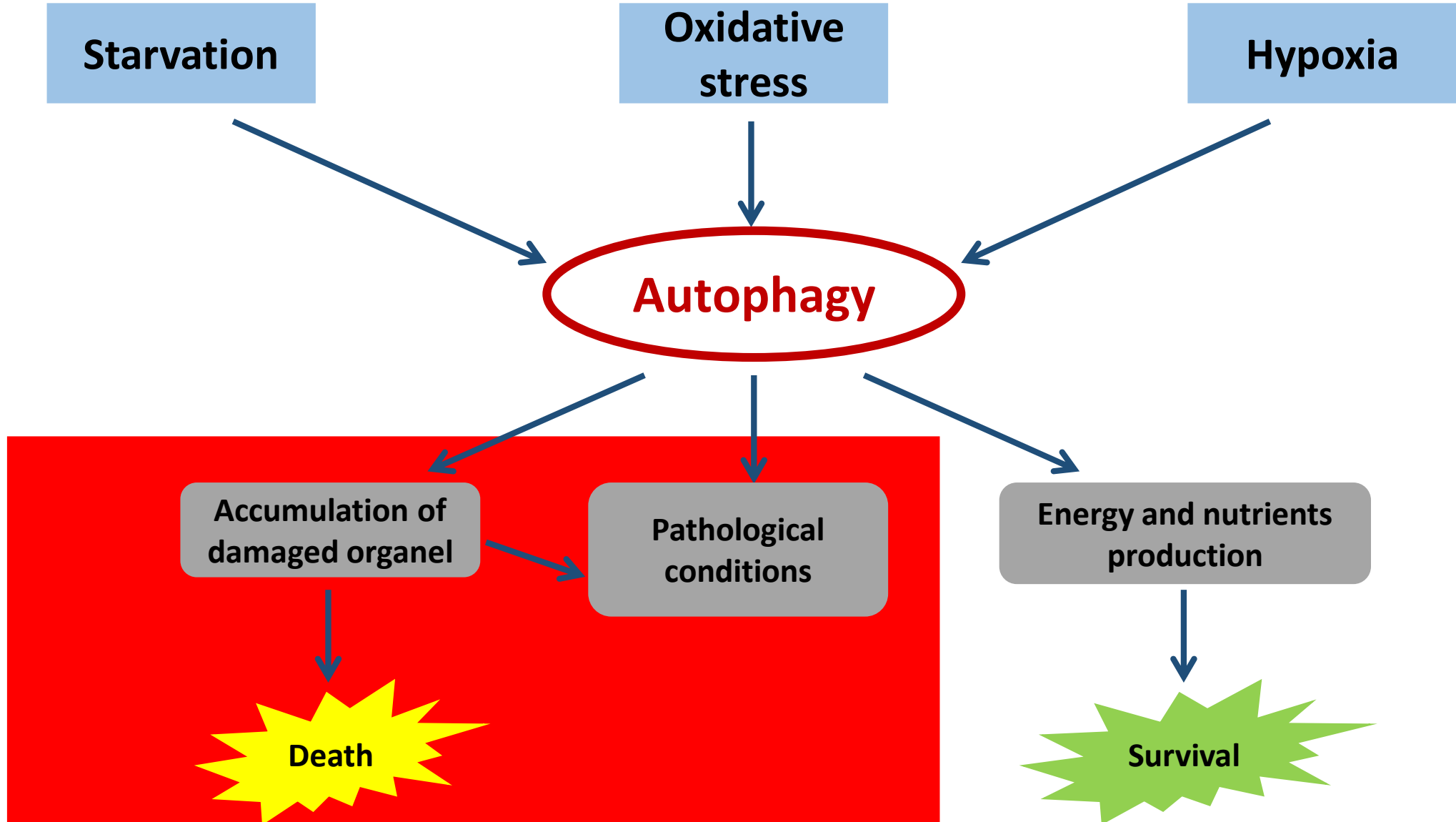
DMeM
Dynamique Musculaire et Métabolisme

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*)

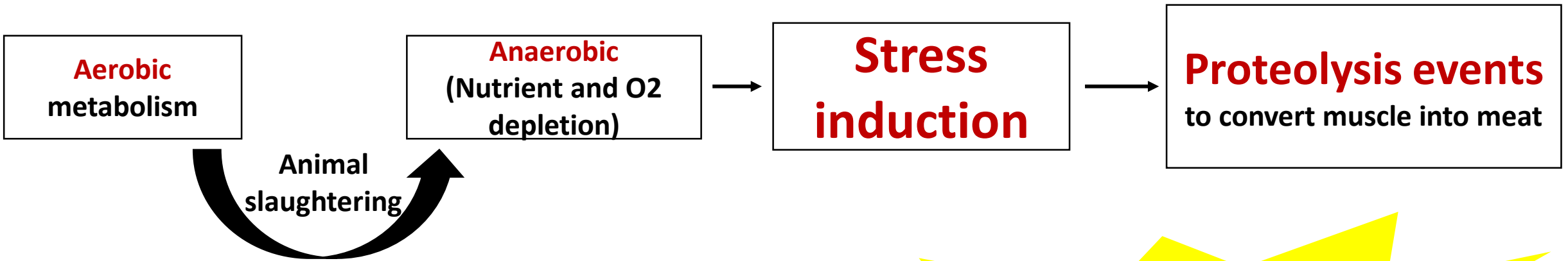
Vici syndrome (*Cullupe et al 2013*)

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,^{1,†} Verónica Sierra,^{1,2,†} Ana Palanca,¹ Ignacio Vega-Naredo,¹ David de Gonzalo-Calvo,¹ Susana Rodríguez-González,¹ Mamen Oliván,² and Ana Coto-Montes^{1*}

Quid of **Autophagy** regulation in PM ?

PM maturation depends on:

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

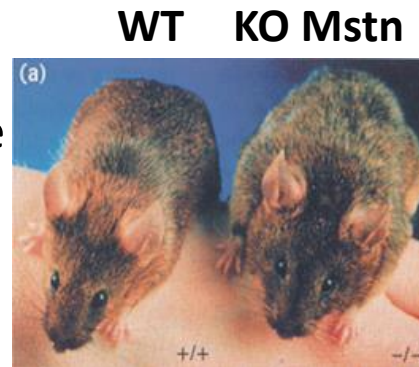
Myostatin: Negative regulator of muscle mass

=> 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

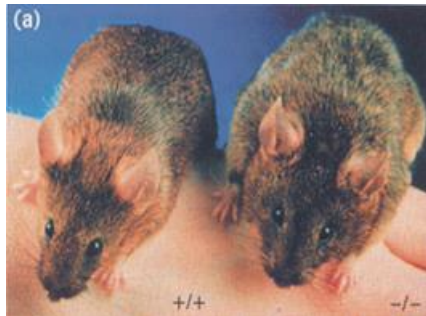
- **Absence** (Ploquin et al 2012) => **Antioxidant status enhancement**
- (Sriram et al 2011) => Addition of Mstn => increase the ROS production



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

How this mechanism is regulated??

Experimental design: Pilot study

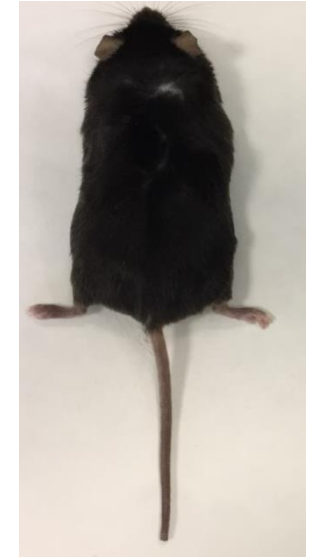
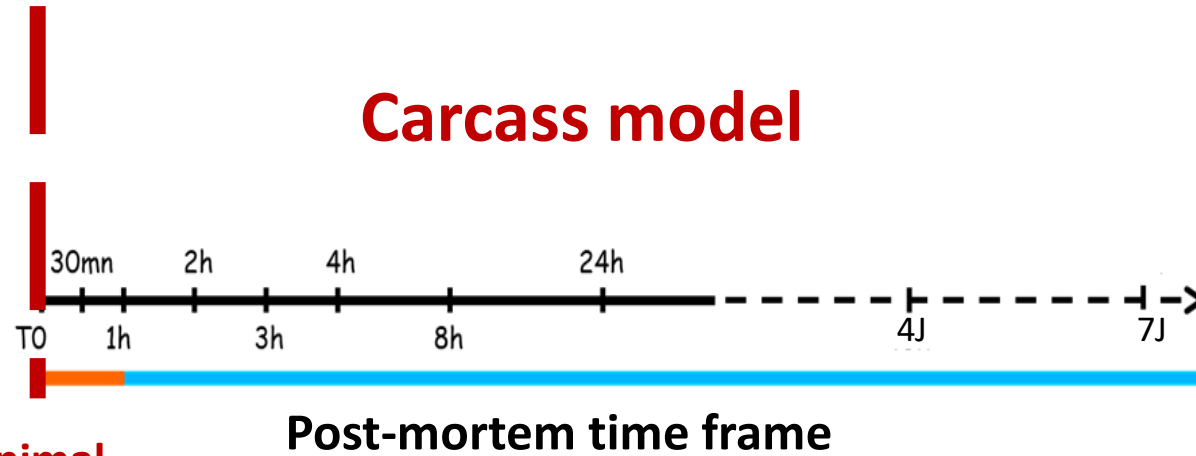



WT

KO Mstn

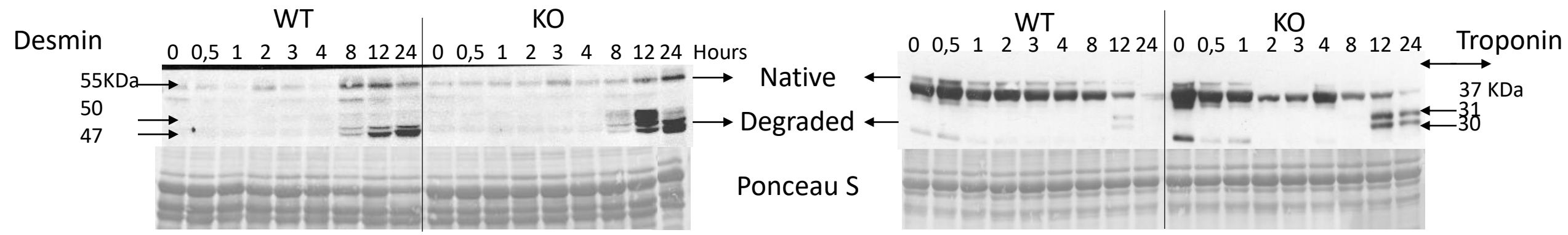
**Animal
slaughtering**
By cervical
dislocation

Carcass model

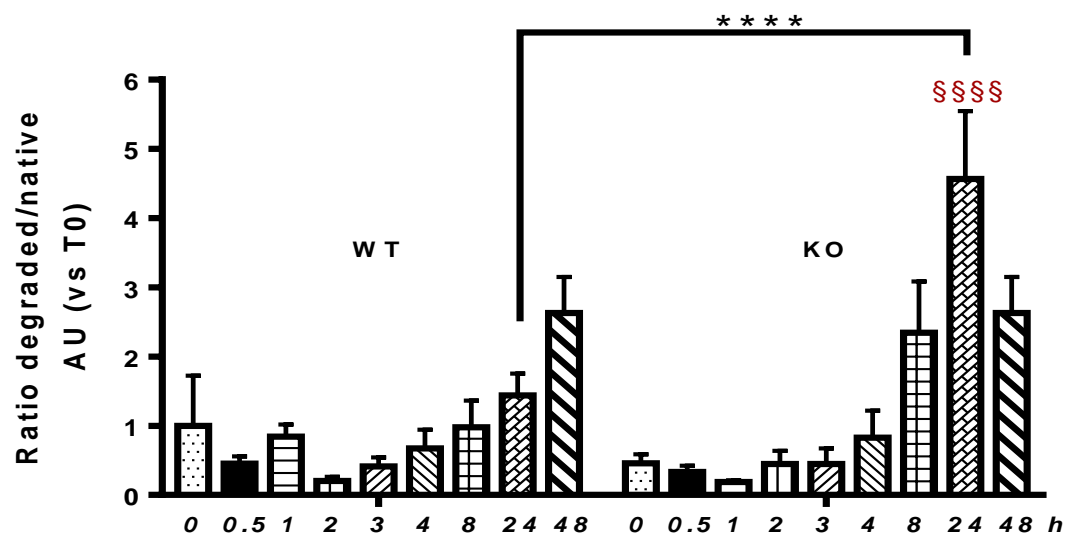


- 
- Myofibrillar protein degradation (Troponin T- Filamin C - Desmin)
 - Oxidative stress markers
 - Autophagic flux

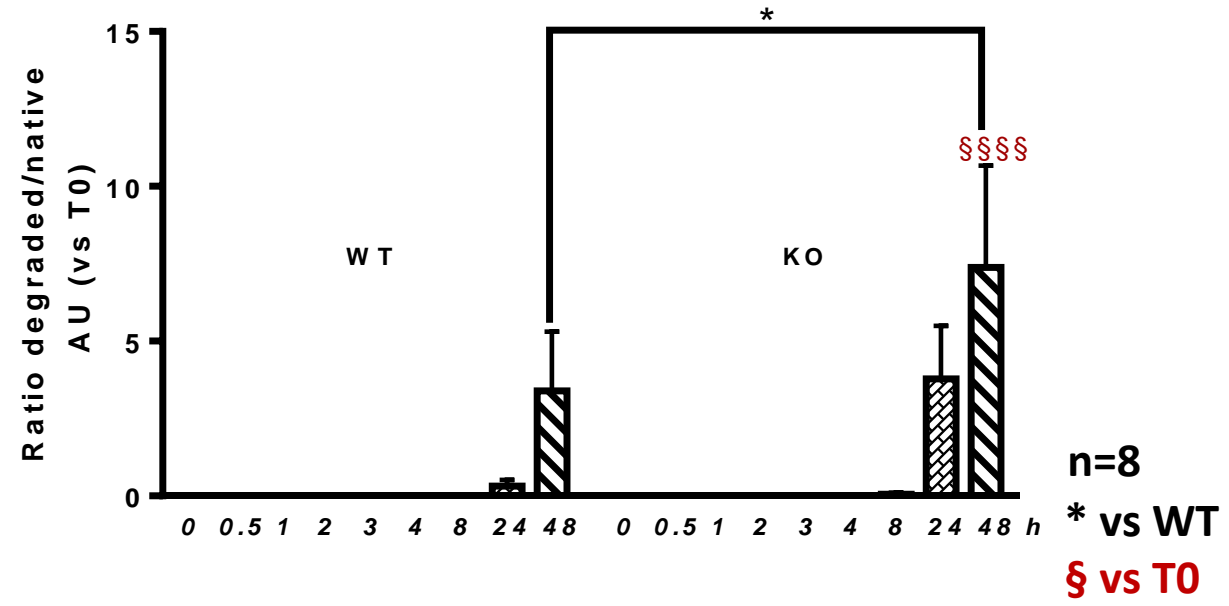
Post-mortem myofibrillar protein degradation is more pronounced in KO Mstn



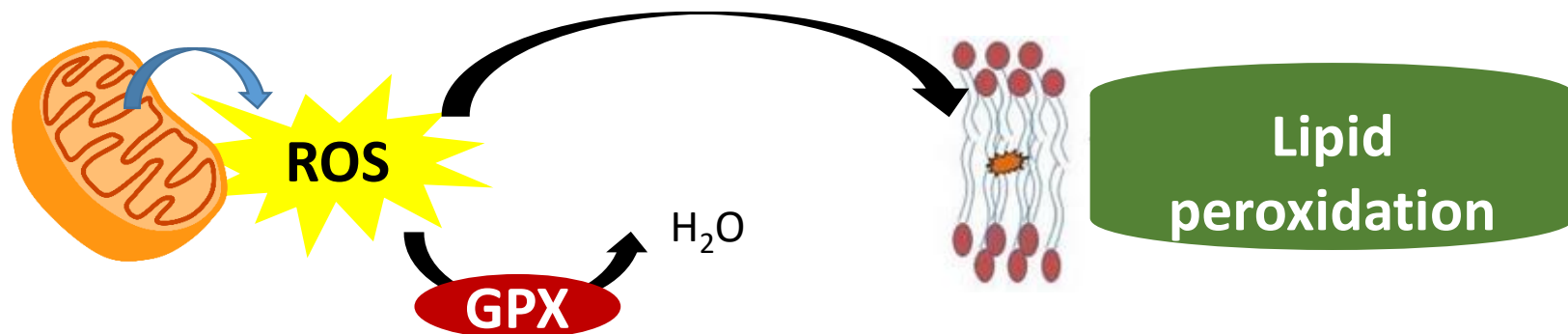
Desmin Degradation



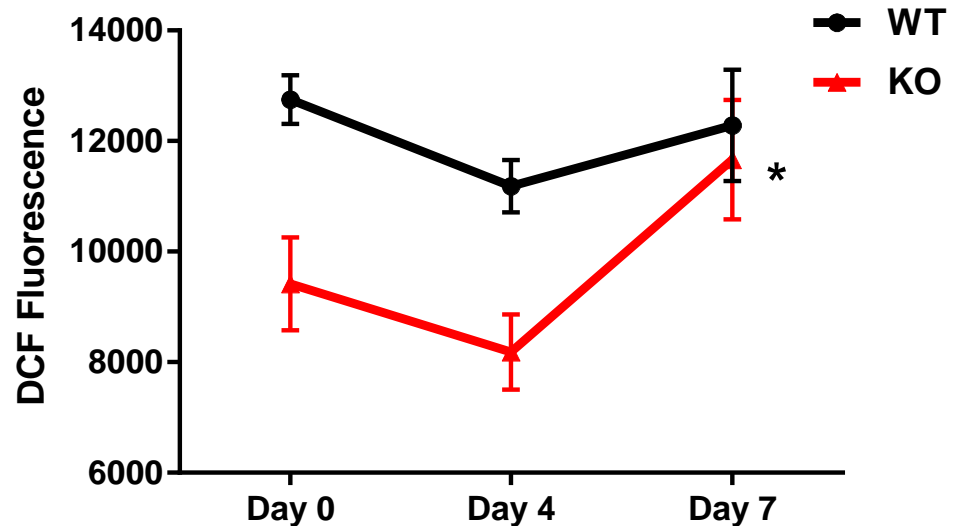
Troponin T Degradation



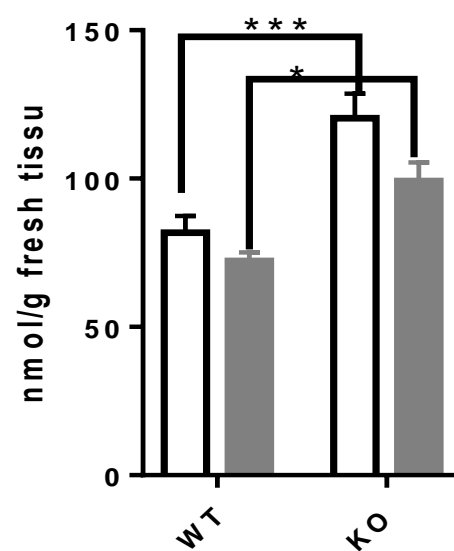
The oxidative stress was not induced during the PM maturation in WT and KO *Mstn* mice



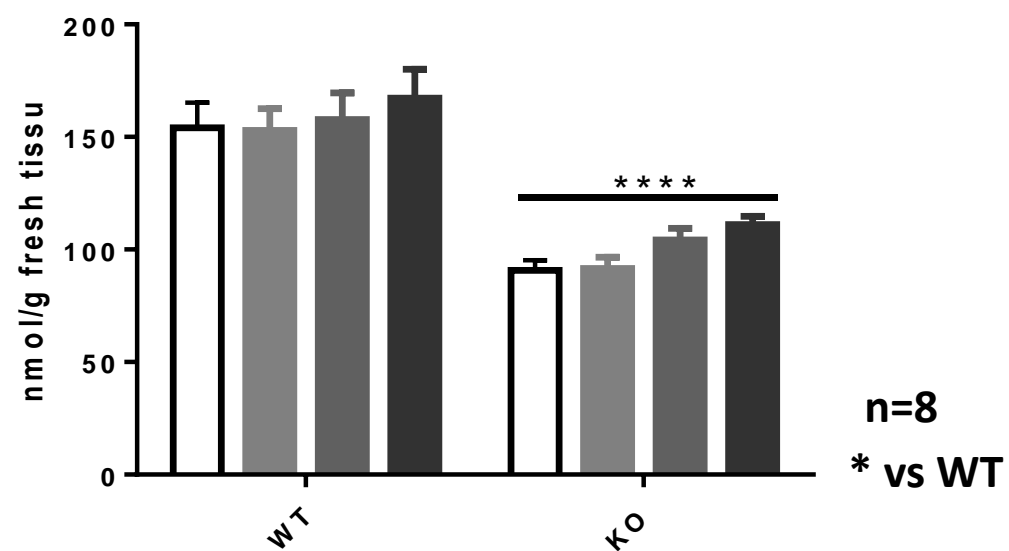
ROS measurement



GPx activity



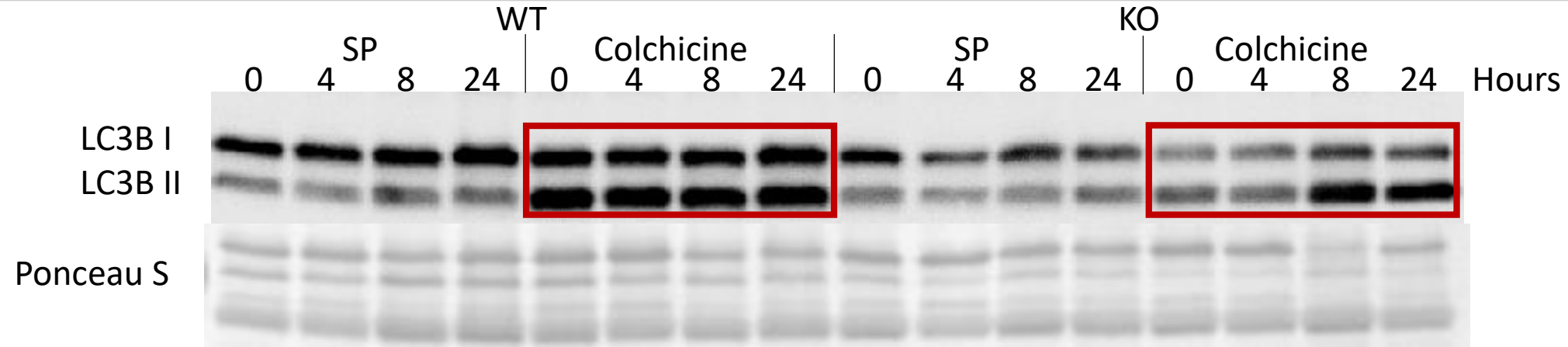
Lipid peroxidation



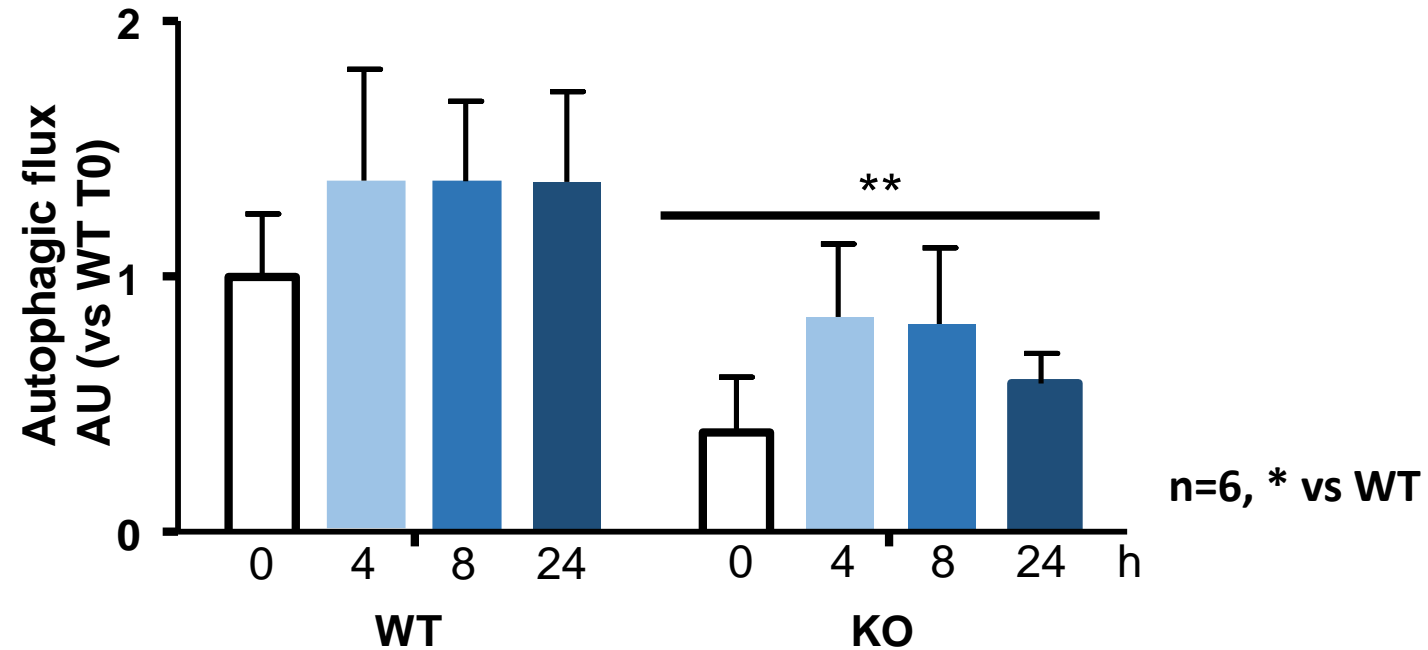
Legend for GPx activity and Lipid peroxidation: □ Day 0, ■ Day 1, ■ Day 4, ■ Day 7

n=8
* vs WT

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



Autophagic flux (LC3BII_{COL} – LC3BII_{SP})



In our PM model (muscle on carcass):

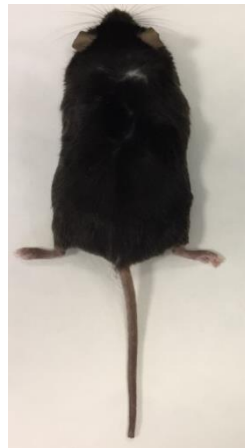
*Absence of ROS production
alteration*

Absence of autophagy induction



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

Carcass model Vs isolated muscle

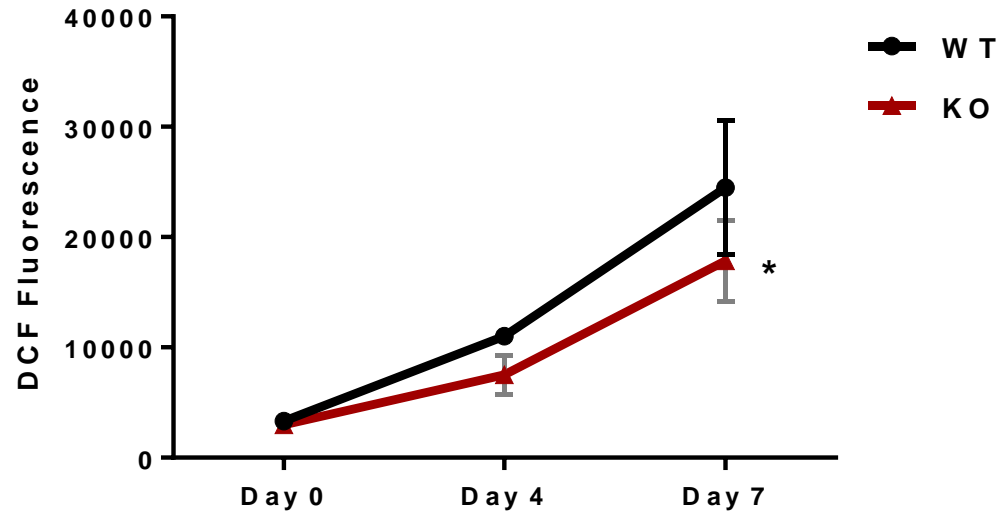


The oxidative stress markers were increased during the PM maturation

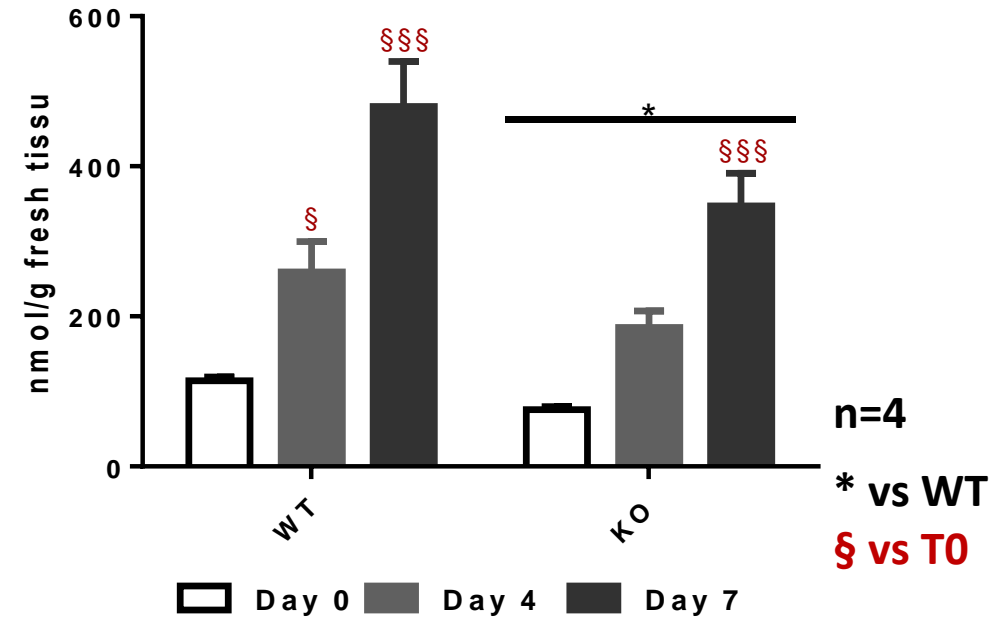
Isolated muscle



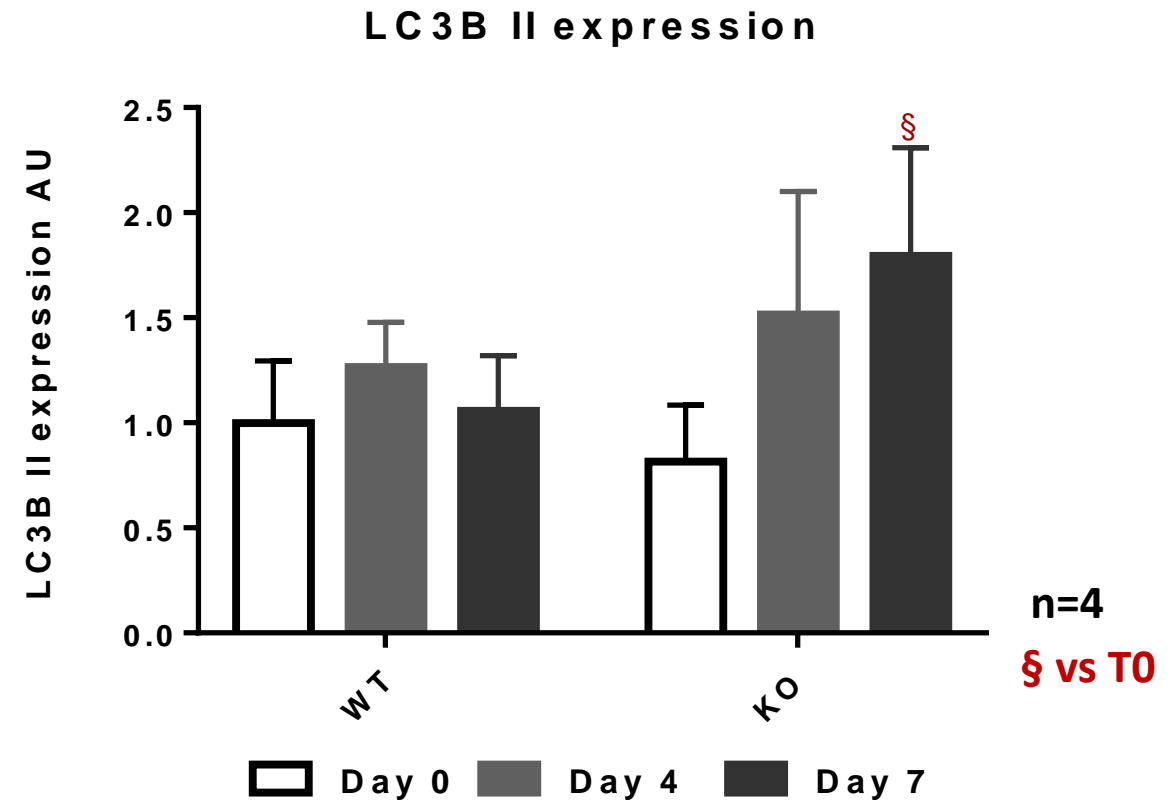
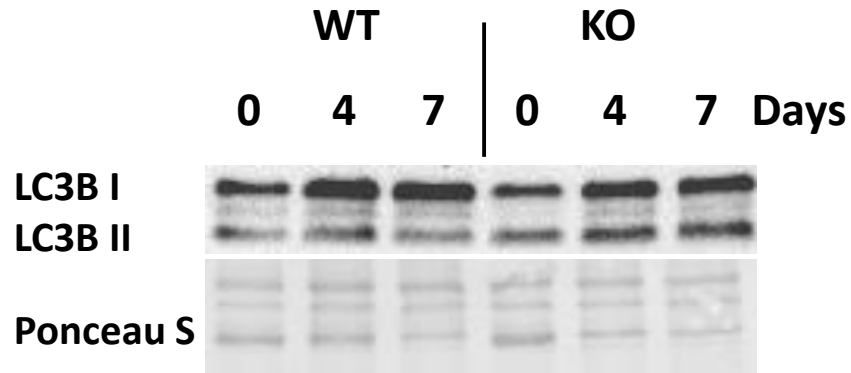
ROS measurement



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
Romain Godoye
Mélanie Macart

Laboratoire d'Innovation Thérapeutique Beyrouth

Fadia Najjar
Aline Hamade

Collaborations

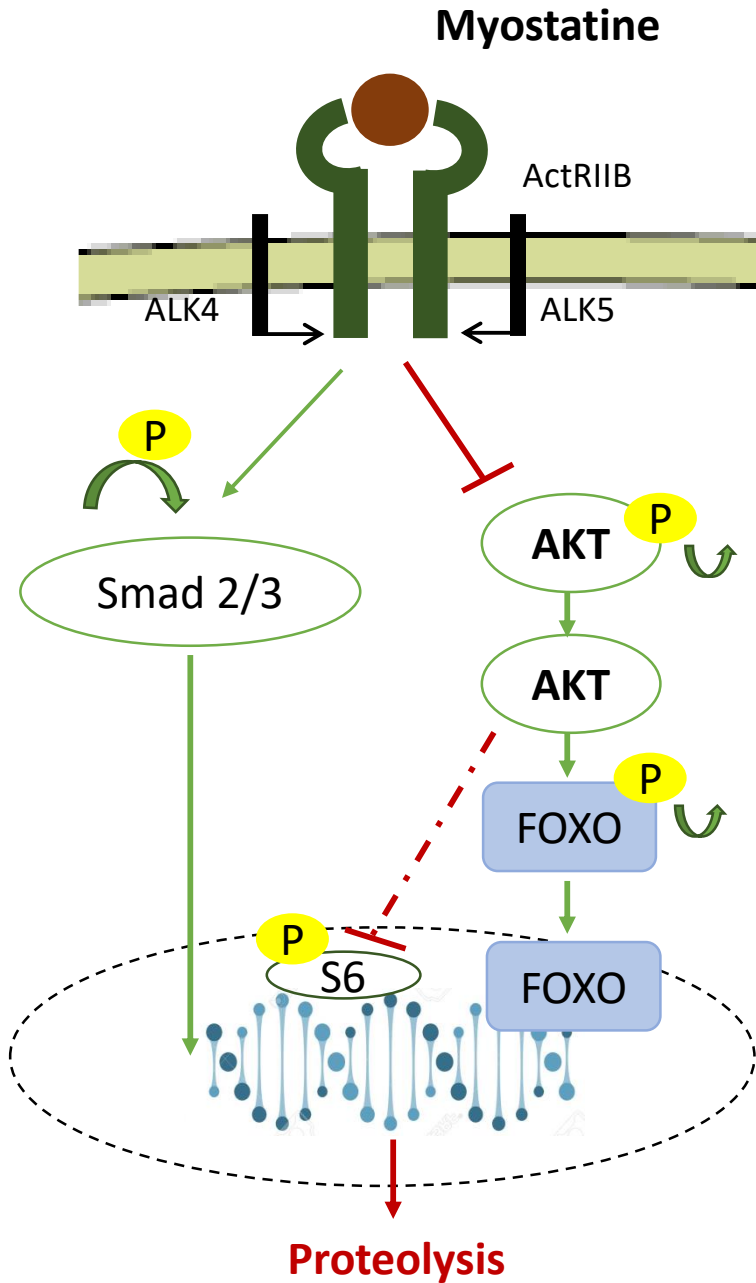
UMRH Theix

Brigitte Picard
Isabelle Cassar-Malek

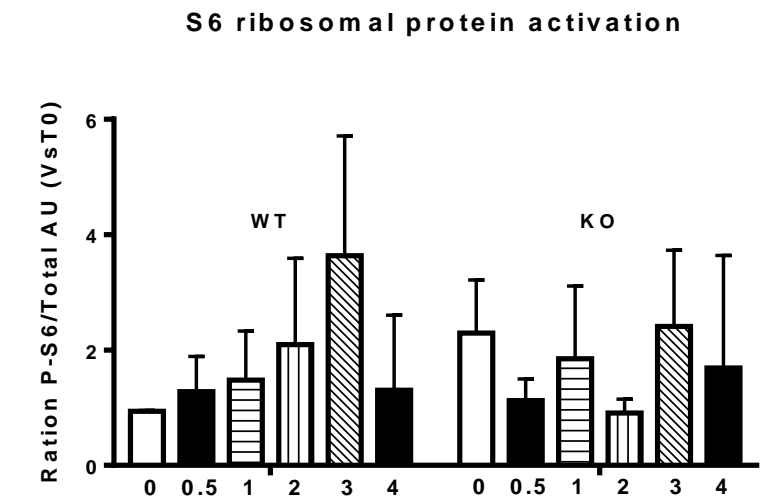
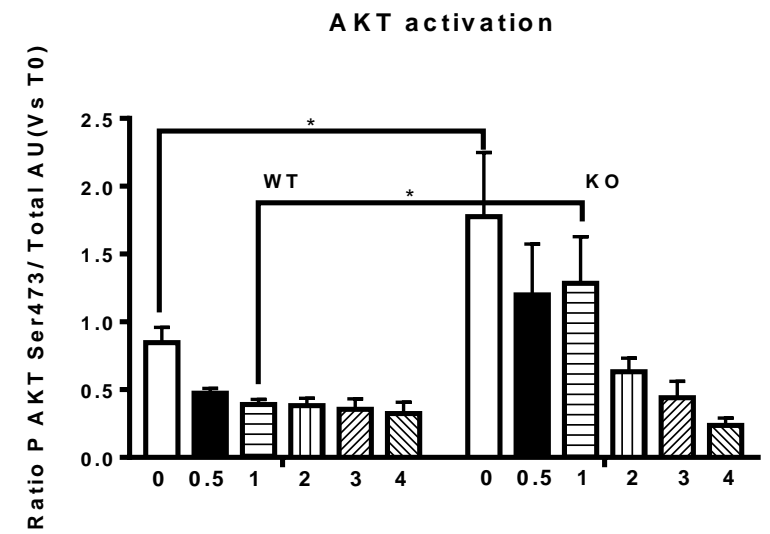
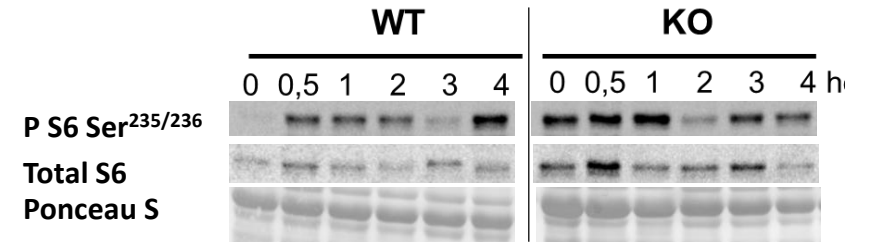
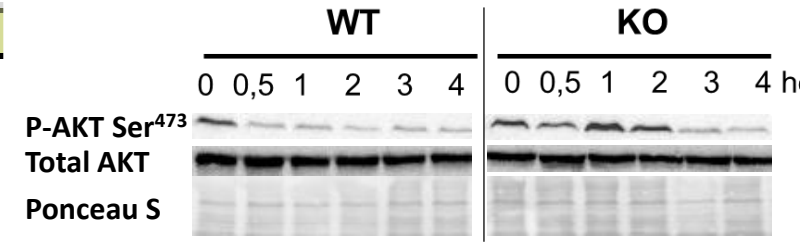
INSERM, ERI25-Muscles et Pathologies, Montpellier

Gilles Carnac

Ongoing work



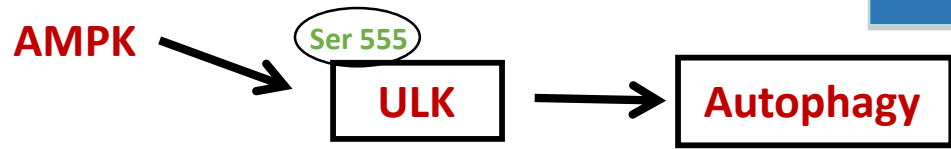
(H.Q.Han et al 2013)



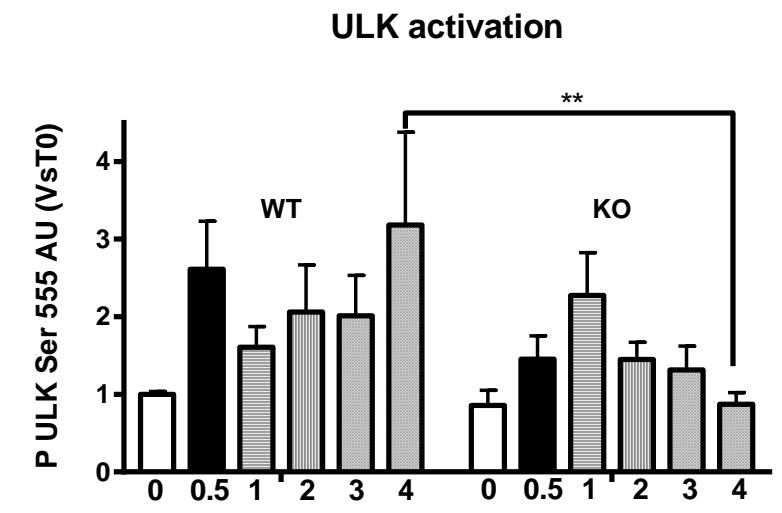
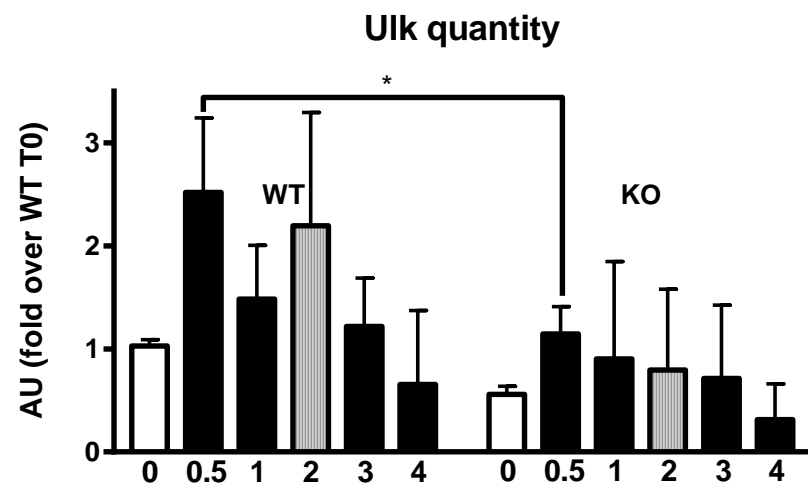
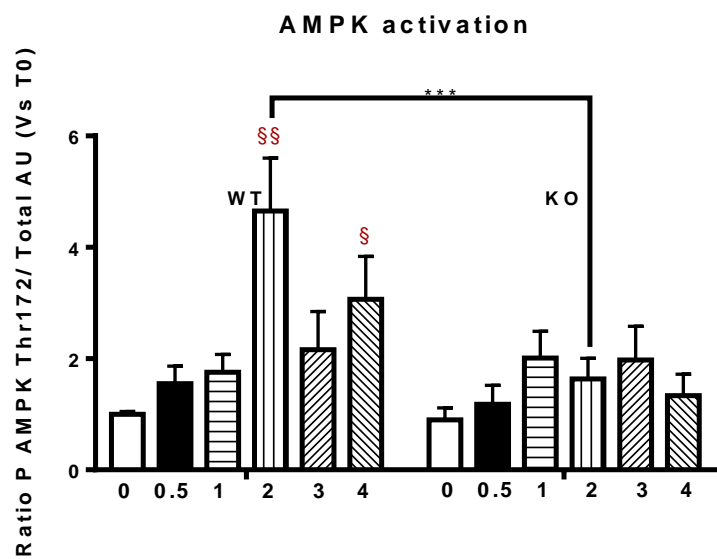
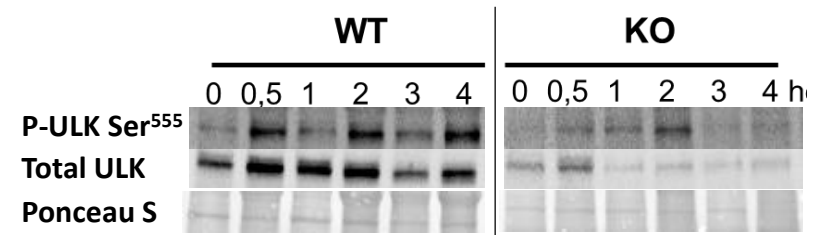
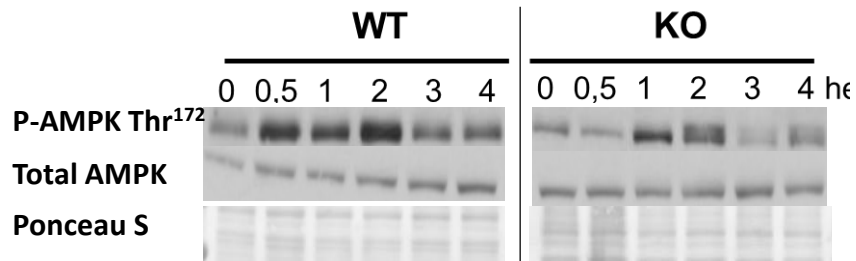
n=8* p ≤ 0.01 Vs WT

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

