Myostatin deficiency in skeletal muscle alters the lipid composition of mitochondrial membranes

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Background

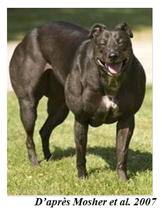
Myostatin (Mstn) is a negative regulator of skeletal muscle growth

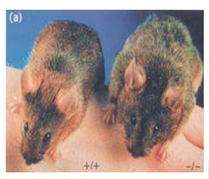
Natural mutation or targeted inhibition in mstn gene

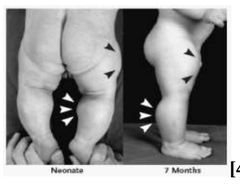
⇒*results in twofold increase in skeletal muscle mass (**hypertrophic phenotype**) in some species*

⇒*is considered as a promising treatment for various muscle-wasting disorders.*

[1]


D'après Mosher et al. 2007 [2]


[3]



[4]

Beyond muscle hypertrophy, mstn knock-out mice (KO) showed

- **Increased muscle Fatigability [5]**
- **Decreased in number of mitochondria and mitochondrial respiratory function [6]**
- **A loss of fat mass [7]**

In skeletal mucles

Muscles Membranes (Maintain architecture of the muscle fiber) **and** Mitochondrial Membranes (Contain respiratory chain) { **Consisted mainly lipids and phospholipids**

"Does exist an alteration of the lipid composition of muscle and mitochondrial membranes in KO mstn mice that could participate in the metabolic and contractile alterations observed in this model ?"

Aim of the study

To Characterize the lipid composition and the lipid metabolism in muscle and mitochondrial membranes in KO mstn mice.

Methodology


WT (n=20) vs KO mstn (n=20)

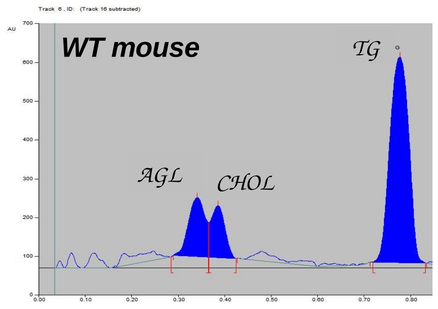

Total mitochondria extraction of all the muscle of the leg

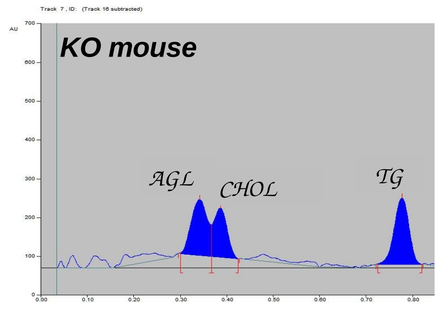
Extraction of gastrocnemius muscle

- *Lipid composition of mitochondria membrane* → ***Thin layer chromatography (TLC) used to separate lipids and phospholipids***
- *Lipid composition of muscle* → ***Thin layer chromatography (TLC) used to separate lipids and phospholipids***
- *Expression of different proteins in muscle lipid metabolism (ACC,p-ACC, FAS)* → ***Western Blot***

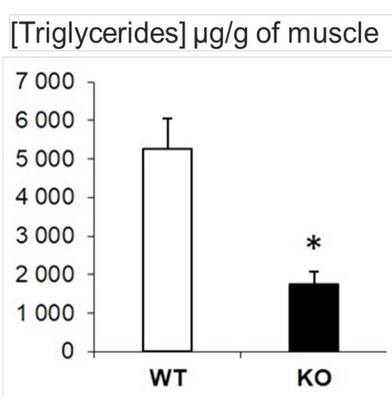
Results

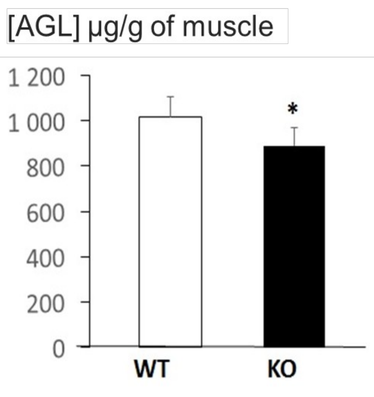
Lack of Mstn led to an alteration of the lipid composition in gastrocnemius muscle





Lipids chromatographic profiles of gastrocnemius muscle



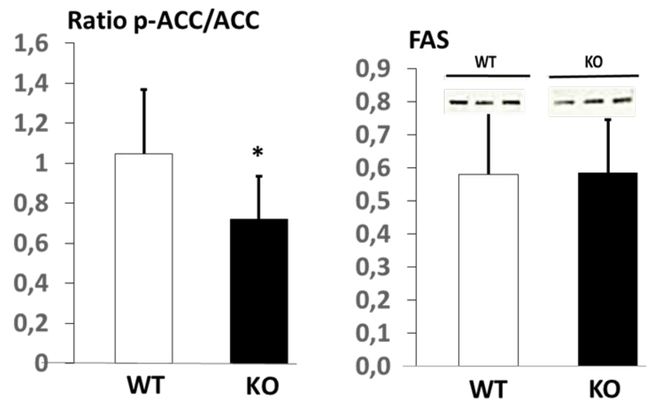


Mstn skeletal muscles showed a decrease of TG concentration (70 %) and AGL concentration (12%) compared to WT muscle.

No changes observed at the other lipids (DG , Cholesterol, MAG ...)

=> suggests a decrease in muscular lipogenesis in gastrocnemius KO mstn mice

Lack of Mstn led to an inhibition of lipid beta-oxydation in gastrocnemius muscle

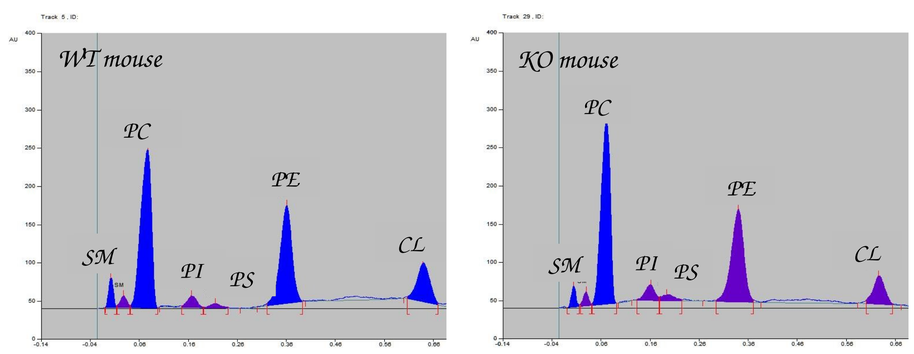


*=> The WB shows that the ratio p-ACC/ACC <1 showed a significant decrease in KO mstn mice compared to WT mice (** p<0,05)* (n=8)

*This can indicate that the **b-oxydation is inhibited**. This result can join the previous result and confirm the lipogenesis reduction and the alteration of the mitochondrial function observed in KO mstn mice*

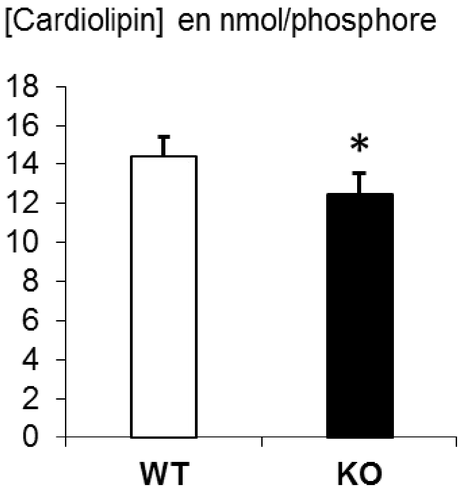
Figure 3: The protein expression of lipids synthesis pathways

Lack of Mstn induced an alteration of the lipid composition of mitochondrial membranes in KO mstn mice



Chromatographic profiles of membrane phospholipids composition of mitochondria: .

PC:,Phosphatidycholin
PE: Phosphatidylethanolamine,
PS: Phosphatidylserine,
SM: Sphingomyelin
CL: Cardiolipin

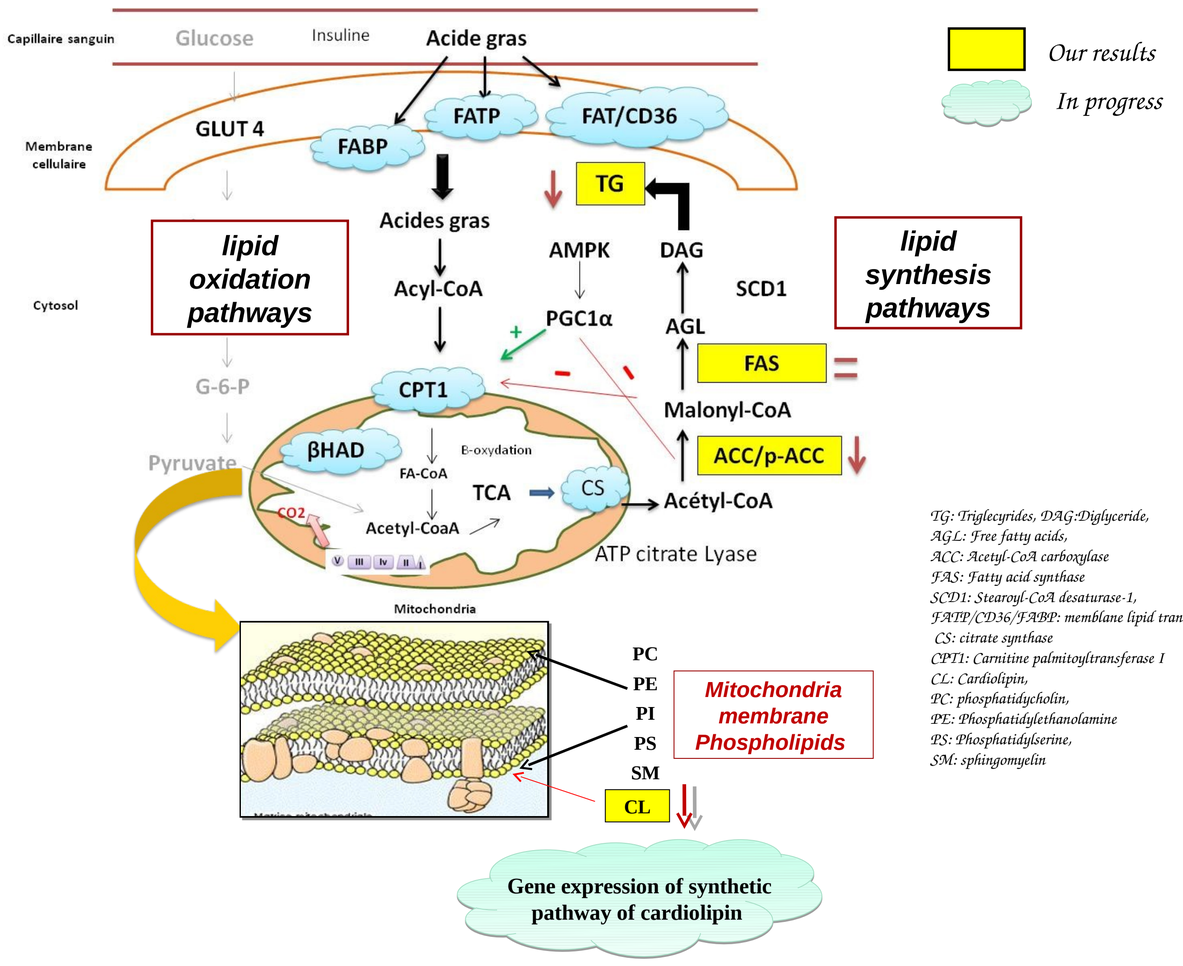


No change in the concentrations of major phospholipids PC and PE.

⇒***We showed a significant reduction (13%) of Cardiolipin in mstn KO mitochondria.***

Likely linked to the alteration in the mitochondria function observed in KO mstn mice., as cardiolipin plays a fundamental role in the stabilization of the respiratory chain and thus in mitochondria function.

Discussion/Conclusions



TG: Triglecyrides, DAG:Diglyceride,
AGL: Free fatty acids,
ACC: Acetyl-CoA carboxylase
FAS: Fatty acid synthase
SCD1: Stearoyl-CoA desaturase-1,
FATP/CD36/FABP: memblane lipid transporter
CS: citrate synthase
CPT1: Carnitine palmitoyltransferase I
CL: Cardiolipin,
PC: phosphatidycholin,
PE: Phosphatidylethanolamine
PS: Phosphatidylserine,
SM: sphingomyelin

*In this study, we suggest that **Myostatin deficiency reduced muscular lipogenesis and oxidation lipids** and **alters the lipid composition of mitochondrial membranes, with a decrease in cardiolipin mitochondrial** content.*

*Further analysis are in progress to bring out **new perspectives on the relationship between mitochandrial signaling pathways of cardiolipin or muscle lipid metabolism and the mitochondrial or muscle function.***

1 Grobet et al., 1997, Nat Gene ,17(1):71-4.
2 Mosher et al., 2007, PLoS Genet. 2007;3(5):79
3Mcpherron et al.,1997, Nature, 387, 83-90.
4Shuelke et al., 2004, N Engl J Med ;350(26):2682-8.
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ACKNOWLEDGEMENTS
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