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

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INRA, UMR866 Dynamique Musculaire Et Métabolisme, UFR STAPS, Université Montpellier 1, 34000 Montpellier, France.

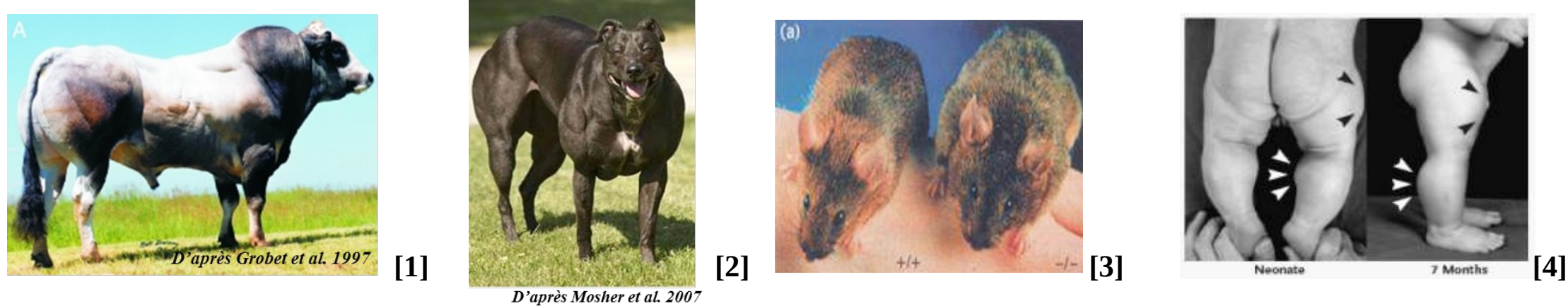
Background

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.



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 muscles

Muscles Membranes (Maintain architecture of the muscle fiber)

and

Mitochondrial Membranes (Contain respiratory chain)

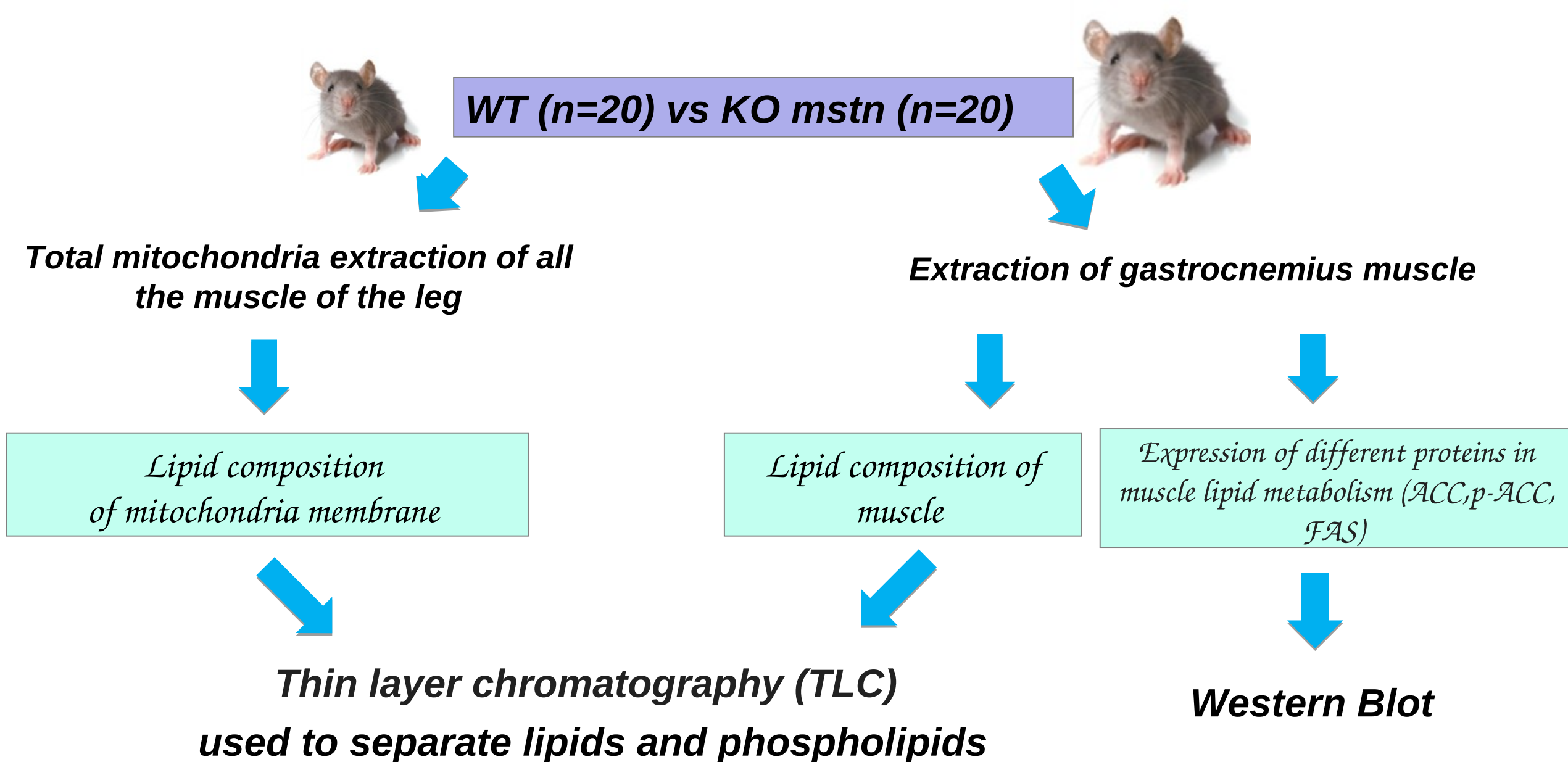
Consisted mainly lipids and phospholipids

“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

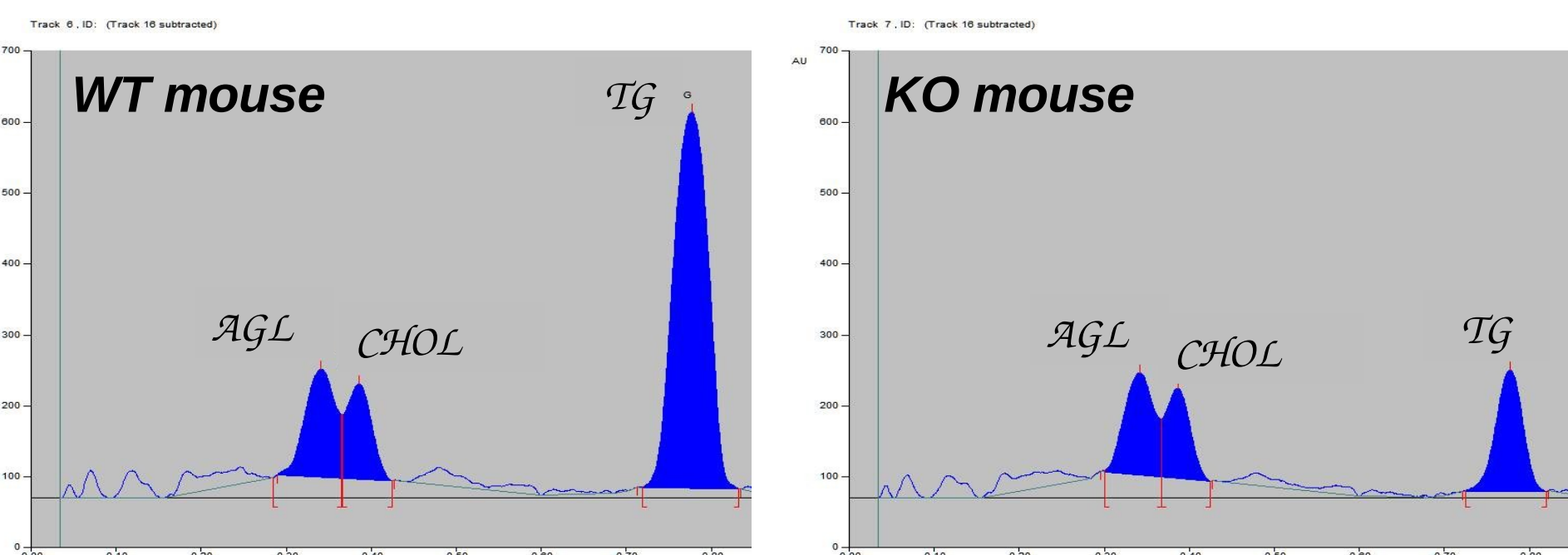
To Characterize the lipid composition and the lipid metabolism in muscle and mitochondrial membranes in KO mstn mice.

Methodology



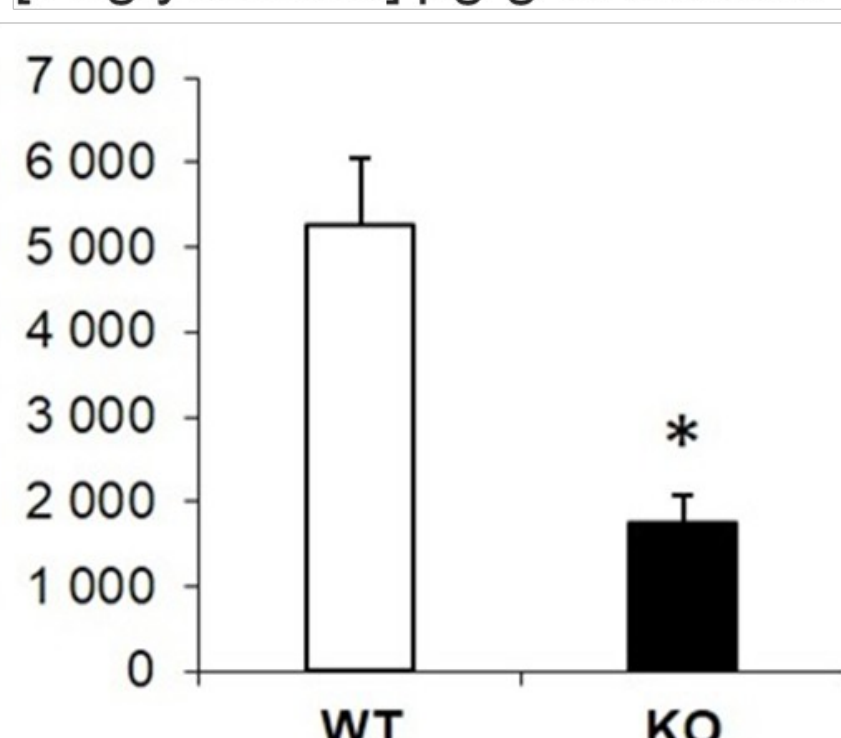
Results

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

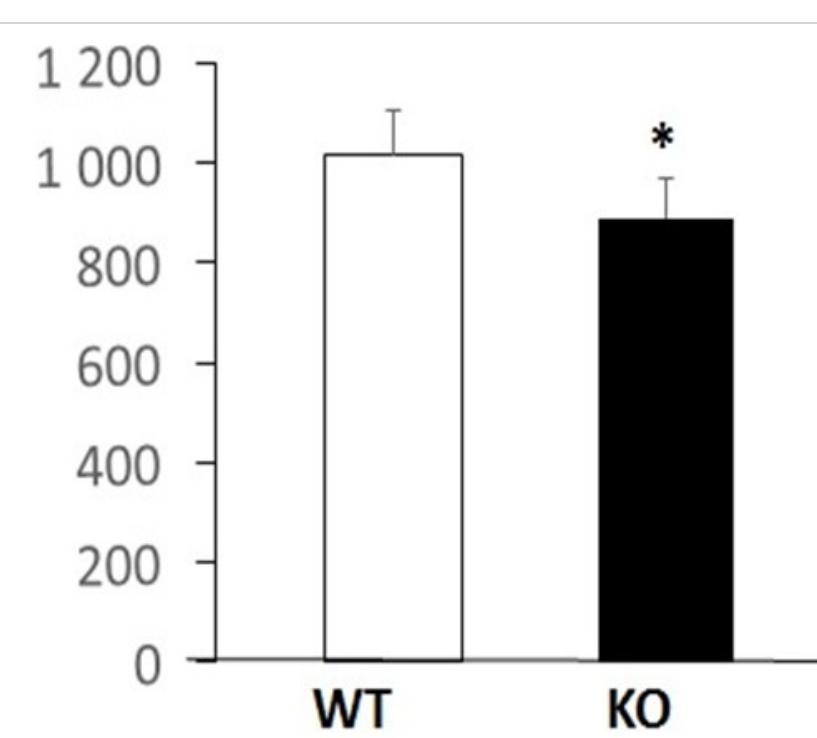


Lipids chromatographic profiles of gastrocnemius muscle

[Triglycerides] µg/g of muscle



[AGL] µg/g of 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-oxidation in gastrocnemius muscle

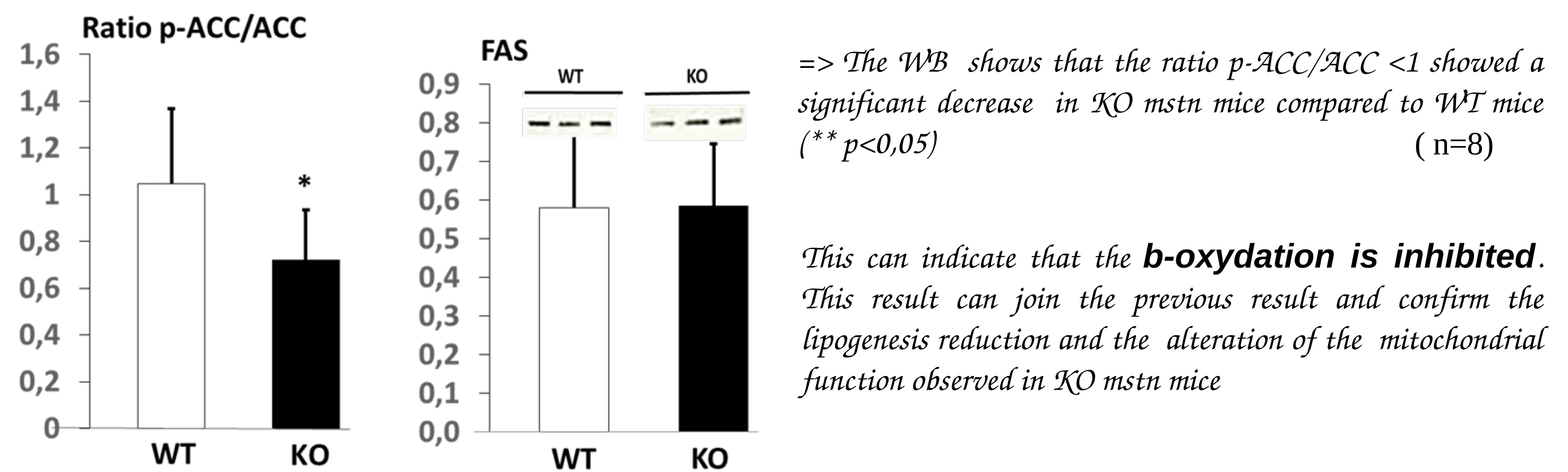
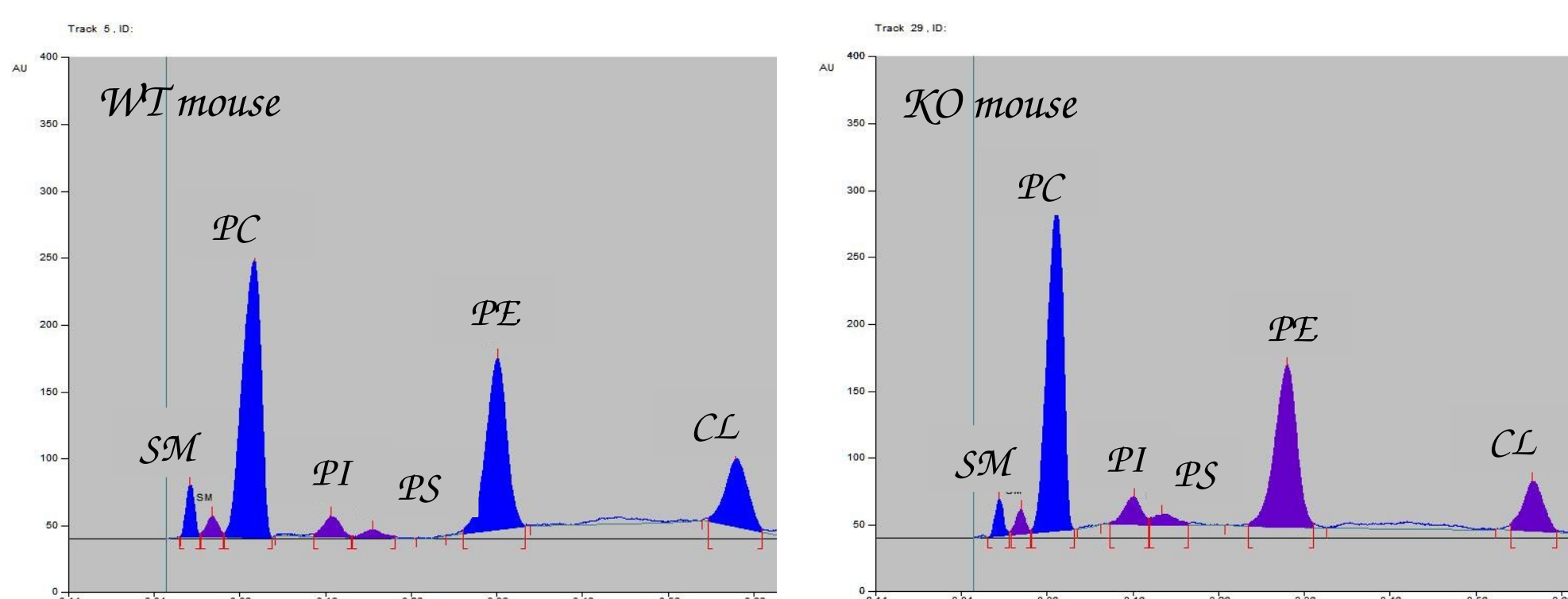


Figure 3: The protein expression of lipids synthesis pathways

⇒ 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-oxidation 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

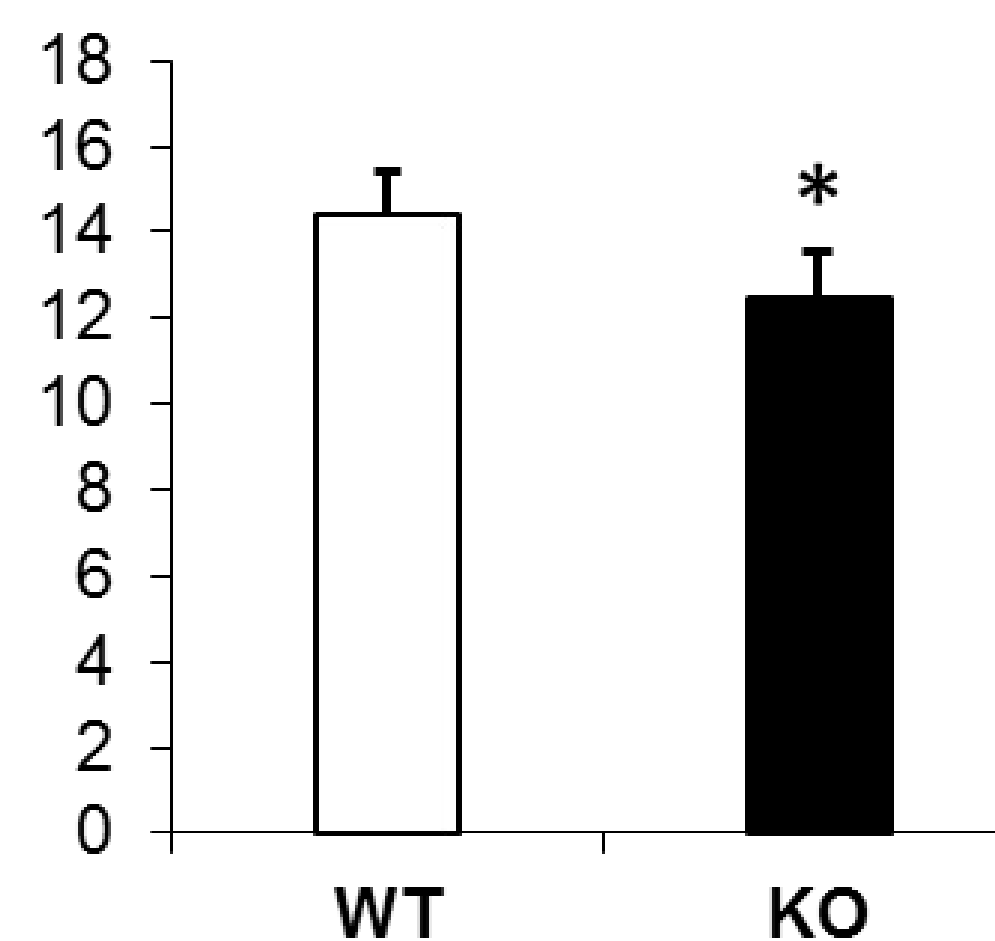
Lack of Mstn induced an alteration of the lipid composition of mitochondrial membranes in KO mstn mice



Chromatographic profiles of membrane phospholipids composition of mitochondria :

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

[Cardiolipin] en nmol/phosphore

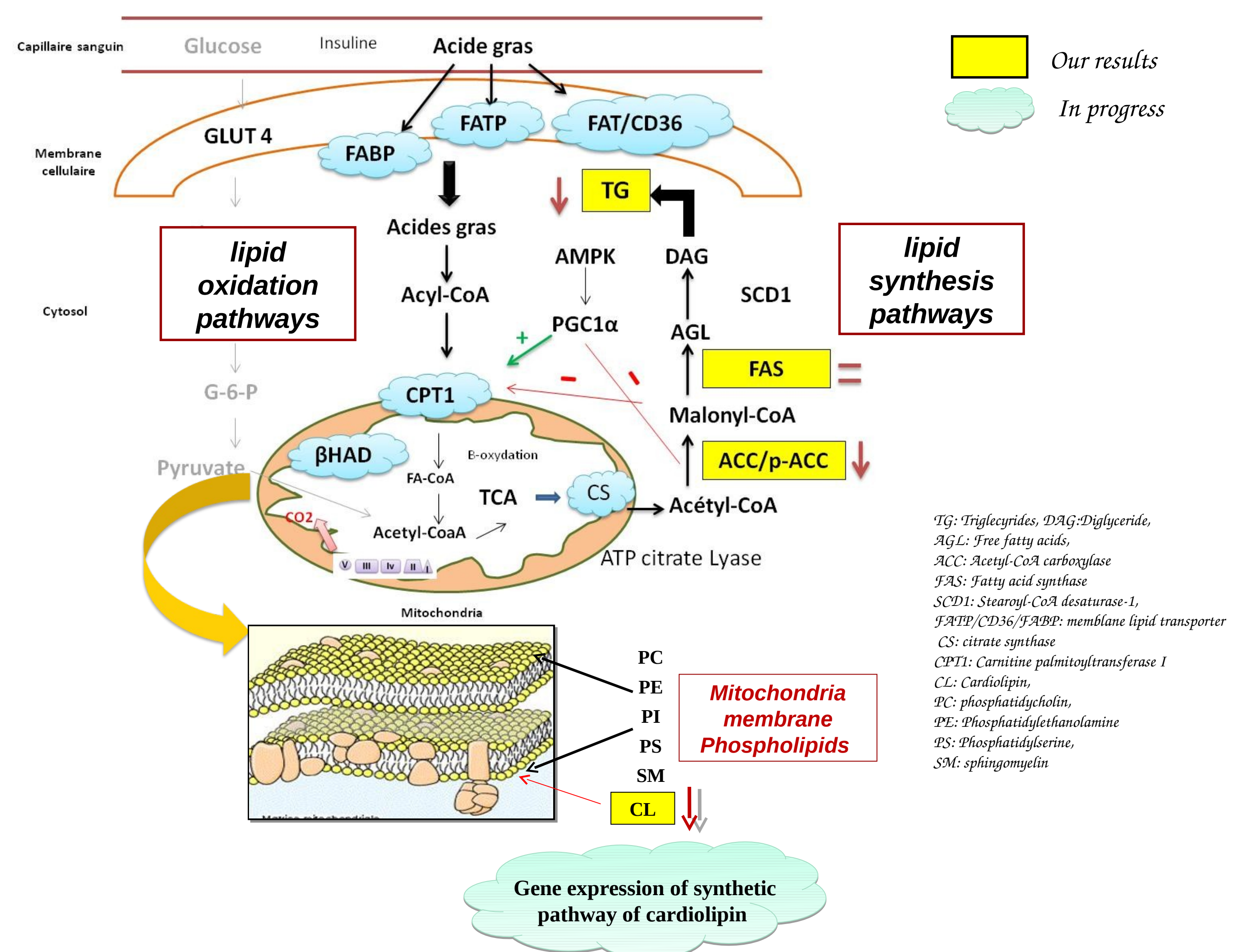


No change in the concentrations of major phospholipids PC and PE.

⇒ 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



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 mitochondrial signaling pathways of cardiolipin or muscle lipid metabolism and the mitochondrial or muscle function.

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