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Myostatin deficiency in skeletal muscle alters the lipids 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 and is considered as a promising treatment for various muscle-wasting disorders.

"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?"*

**Lack of Mstn led to decreased oxidative pathway of lipids in KO mstn muscle**

**Modification of lipids composition of muscle and mitochondrial membrane in KO mstn**

**Phospholipids composition of mitochondrial membrane**

- We showed a significant reduction (13%) of Cardiolipin in mstn KO mitochondria.
- This result could be associated with the alteration of mitochondrial function observed in KO mstn. Indeed, cardiolipin plays a fundamental role in the stabilization of the respiratory chain and thus in mitochondria function.

**Fatty acids composition of muscle**

- We evaluated fatty acid synthase (FAS) and phosphatidylethanolamine (PE) activity in KO mstn muscle.
- Mitochondria from KO mstn muscle had a reduced fatty acid synthase (FAS) activity.

**Synthetic Pathways of cardiolipin**

- We observed a decrease in cardiolipin synthetic pathway.
- The decrease in the transcription of major phospholipids (PC, phosphatidylethanolamine and PE) could be secondary to the decrease in cardiolipin synthesis.

**Discussion/Conclusion**

In this study, we demonstrated a decrease in mitochondrial cardiolipin content, in relation with a decrease in FAS and cardiolipin synthetic genes expression. Overall, results demonstrate that myostatin deficiency reduces lipid synthesis and alters the lipid composition of muscle and mitochondrial membranes, with a decrease in cardiolipin mitochondrial content. This new knowledge suggests the possibility to modulate the phospholipids composition in muscle mitochondria using endurance training, and evaluate its consequences on mitochondrial function.

*Figure 1: Reduction of Cardiolipin synthase quantity evaluated by Western Blot. KO mstn muscle had a reduced Cardiolipin synthase activity compared to Wild type muscle.

Figure 2: Reduction of Cardiolipin synthase gene expression evaluated by qPCR. KO mstn muscle had a reduced Cardiolipin synthase gene expression compared to Wild type muscle.

Figure 3: Changes in triglyceride pathway in KO mstn muscle. A) Fatty acid synthase (FAS) activity was evaluated by gas chromatography. Increase of FAS in KO mstn muscle compared to Wild type muscle. B) Synthesis of fatty acids (FAS) activity was evaluated by gas chromatography. Increase of FAS in KO mstn muscle compared to Wild type muscle.

Figure 4: Changes in mitochondrial membrane of mstn KO muscle. A) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle. B) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle.

Figure 5: Changes in mitochondrial membrane of mstn KO muscle. A) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle. B) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle.

Figure 6: Changes in mitochondrial membrane of mstn KO muscle. A) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle. B) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle.

Figure 7: Changes in mitochondrial membrane of mstn KO muscle. A) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle. B) Changes in phospholipids composition of mitochondrial membrane in KO mstn muscle compared to Wild type muscle.