Role of PPARδ in satellite cells and muscle development

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Introduction

•Skeletal muscle is the most abundant tissue in the body and its proper function is critical for motor performance and human health[3].

•Mature muscle cells (fibers) can be classified as either slow or fast fibers based on differences in metabolism and rate of fatigue[2]

•Slow muscle fibers (type 1) use oxidative metabolism to produce energy and are resistant to fatigue[2]

•Fast muscle fibers (type 2; including 2a, 2b, and 2x) are mainly glycolytic and much less resistant to fatigue[2]

•Satellite cells are muscle progenitor cells that are responsible for the growth and maintenance of adult skeletal muscle[1]

•PPARδ is a member of the peroxisome proliferation activated receptor (PPAR) family nuclear receptors and has been shown to be important in the maintenance of the slow fiber types[2,3]; however, the function of *Pparδ* in satellite cells is still unknown.

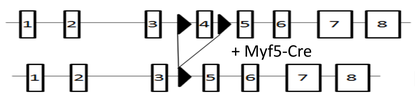
Objectives

•Establish a mouse model for conditional mutation of PPARδ in the myogenic progenitor cells

•Investigate the effect of *Pparδ* mutation on satellite cells

•Determine the role *Pparδ* in muscle differentiation and function

Materials and Methods



•A mouse model was created which has a conditional mutation of the *Pparδ* gene restricted to the myogenic progenitor cells in the embryo and later restricted to the muscle and brown fat lineage in the adult using myf5-cre mediated recombination of loxP sites.

•Quantitative real-time (RT)-PCR was performed to confirm tissue-specific knockdown of *Pparδ*.

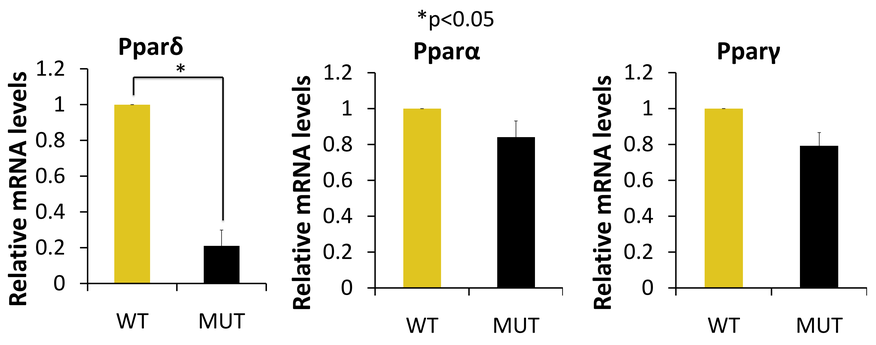
•Representative slow (Soleus; SOL) and fast (EDL) muscles were analyzed for fiber type composition using myosin heavy chain isoform specific monoclonal antibodies

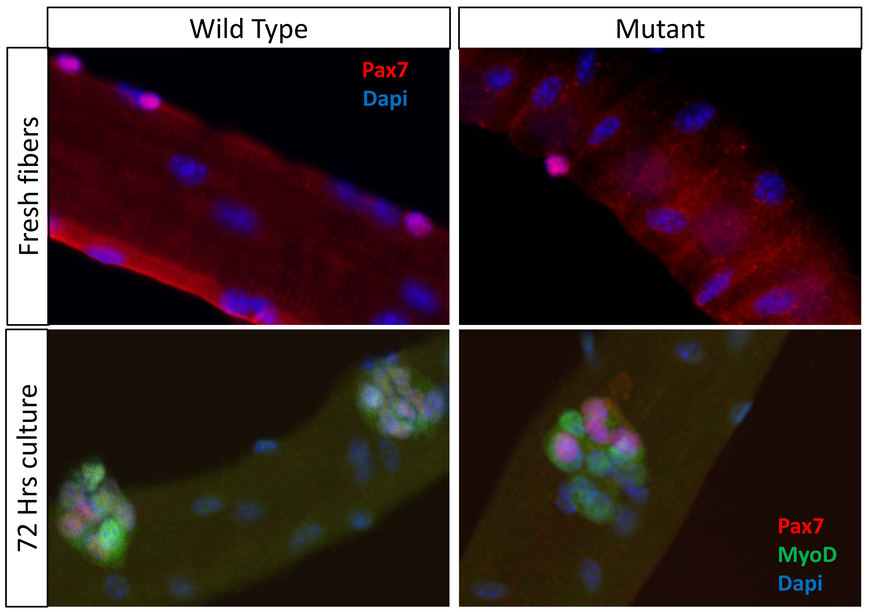
•Single fibers were isolated from the EDL using collegenase B digestion and the number of satellite cells per fiber determined

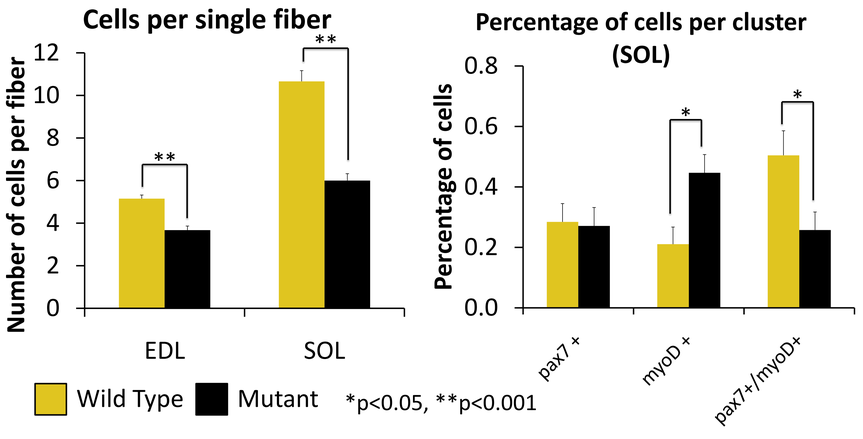
•Satellite cells were harvested from the hind limbs of wild type and mutant littermates and cultured for proliferation and differentiation assay

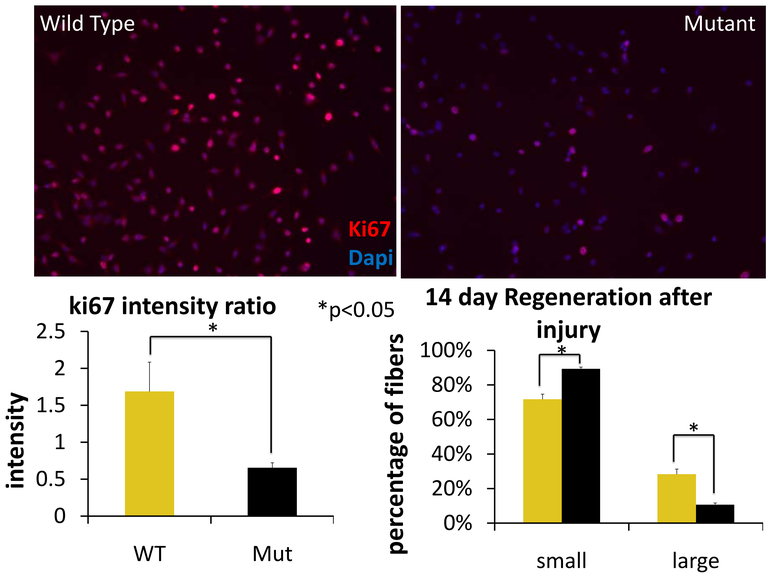
•Glucose tolerance was tested to confirm the insulin sensitivity in wild type and mutant littermates 8-9 months of age

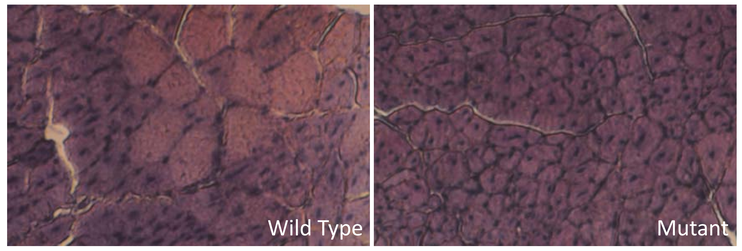
Results











Conclusions

•*Pparδ* expression has been reduced in the skeletal muscle, while the expression of *Pparα* and *Pparγ* remain unchanged, suggesting that there is no compensation from other PPAR isoforms.

•Fibers from slow and fast muscles have fewer satellite cells per fiber in the mutant animals compared to wild type animals.

•Cultured fibers from the soleus had more differentiating satellite cells (MyoD+) and fewer proliferating satellite cells (Pax7+/MyoD+)in the mutant animals

•Satellite cells from mutant animals showed less proliferation in vitro

•The expression of known *Pparδ* target genes was reduced in the skeletal muscle of mutant animals

•Satellite cell mediated muscle regeneration after injury is delayed in mutant animals

References

1. Kuang S, et al. Cell. 2007; 129(5):999-1010.
2. Wang YX, et al. PLoS Biol. 2004; 2(10):e294.
3. Schuler M, et al. Cell Metab. 2006; 4(5):407-14.

Acknowledgement

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