eIF3f depletion impedes mouse embryonic development, reduces adult skeletal muscle mass and amplifies muscle loss during disuse

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To cite this version:
Aurélie Docquier, Laura Pavlin, Audrey Raibon, Christelle Bertrand, Chamroeun Sar, et al.. eIF3f depletion impedes mouse embryonic development, reduces adult skeletal muscle mass and amplifies muscle loss during disuse. 5. International Congress of Translational Research in Human Nutrition (ICTRNH 2019), Jun 2019, Clermont-Ferrand, France. hal-02737500
**INTRODUCTION**

Muscle mass homeostasis is controlled by protein synthesis and degradation. Eukaryotic initiation factor 3f (eIF3f), a subunit of eIF3 complex, is a fundamental element of MTORC1 pathway, allowing physical interaction between S6K1 and MTOR. Phosphorylation of downstream effectors of MTORC1 pathway like S6 leads to enhanced translational capacity and myotubes hypertrophy. Despite its important role in protein synthesis regulation shown in vitro, its physiological role in skeletal muscle is poorly described. Generation of mice carrying a mutation in the eIF3f gene allows to further define in vivo eIF3f roles in muscular homeostasis.

**MATERIAL & METHODS**

Embryonic death occurs at early stage of development

**Embryo phenotype**

<table>
<thead>
<tr>
<th>Embryo phenotype</th>
<th>Normal</th>
<th>Necrotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (n=136)</td>
<td>78.7</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Any homozygous eIF3f-/- embryo was recovered

<table>
<thead>
<tr>
<th>Embryo genotype</th>
<th>WT+/+</th>
<th>+/f</th>
<th>f/f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage (n=136)</td>
<td>25.8</td>
<td>30.3</td>
<td>44.0</td>
</tr>
</tbody>
</table>

Reduced eIF3f expression mainly impacts skeletal muscles mass

**Fiber size is smaller without any change in fiber number in skeletal muscles of eIF3f-/- mice**

**PROTEIN SYNTHESIS ACTIVITY AND EFFICIENCY ARE ALTERED IN eIF3f-/- MICE**

**MTORC1 downstream effectors activity is decreased in skeletal muscles of eIF3f-/- mice**

**HINDLIMB IMMOBILIZATION STUDY**

Decrease of muscle mass and CSA is larger in eIF3f-/- mice

Induction of eIF3f expression is decreased in eIF3f-/- mice

Activities of S6K1 and S6 are reduced in eIF3f-/- mice

Reduced eIF3f expression level exacerbates protein synthesis decrease

**CONCLUSION**

Embryonic death suggests an essential role of eukaryotic Initiation Factor 3f for mice development. Whole body partial depletion allows normal growth despite a body mass reduction without change in body size. Mass lowering concerns only lean mass, skeletal muscles of heterozygous mice displaying a smaller fiber size, eIF3f mRNA and protein expressions are reduced in muscles of eIF3f-/- mice, as well as protein synthesis and MTORC1 pathway activity. During immobilization, reduction of eIF3f induction results in a stronger atrophy, with a larger decrease in muscle mass and CSA in eIF3f-/- mice. Protein synthesis is also reduced and associated with a lower MTORC1 pathway activity in eIF3f-/- mice. These results confirm in vivo the essential role of eIF3f in development, muscular growth and muscle mass homeostasis.