Corso di Dottorato di Ricerca in Scienze della Vita e dell'Ambiente - Ciclo XXXIX

SIDE EFFECTS OF STATINS ON EARLY-DIFFERENTIATING AND MATURE MURINE SKELETAL MUSCLE MYOTUBES

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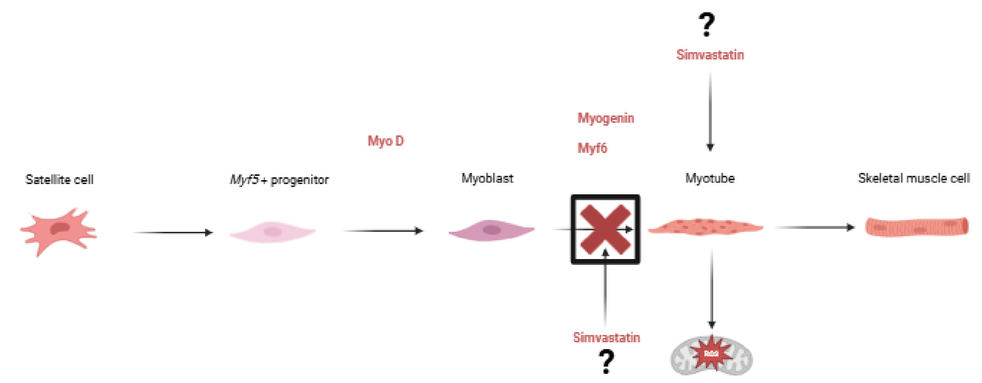
INTRODUCTION

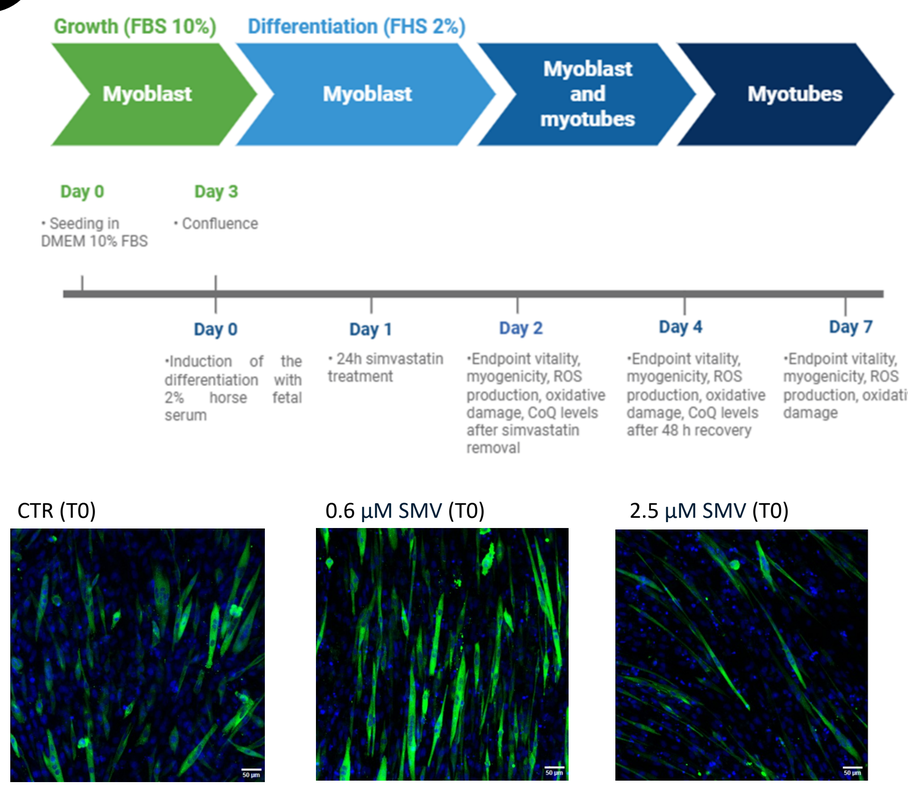
Skeletal muscle represents one of the most quantitatively significant organs in the body, involved in a lot of processes such us locomotion and energy metabolism. For this reason, the loss of physiological functions during aging can generate the onset of severe disabilities. Evidence indicates that, although statins reduce mortality and morbidity from cardiovascular diseases in patients with high LDL-cholesterol levels, they may also induce adverse effects such as myopathy, ranging from myalgia to rhabdomyolisis[1]. The processes leading to statin-associated muscle symptoms are currently not fully elucidated. In this context, impairment of muscle regeneration could partially explain statin-associated muscle symptoms[2]. Myogenesis is a closely regulated process which starting from satellite cells (stem cells) lead to the formation of new functional muscle fibers. Some authors[3] have already showed that myoblasts are more susceptible to the toxic effects of statins with compromising mitochondrial function and reducing markers of cell proliferation, differentiation and fusion, leading to impaired myotube formation. In this scenario, the aim of this study was to deepen the role of statins on early differentiating and differentiated myotubes of murine skeletal muscle cells (C2C12), reproducing an *in vitro* model of Coenzyme Q deprivation by simvastatin (SMV) treatment and analysing its effect in terms of oxidative stress and morphological impact.



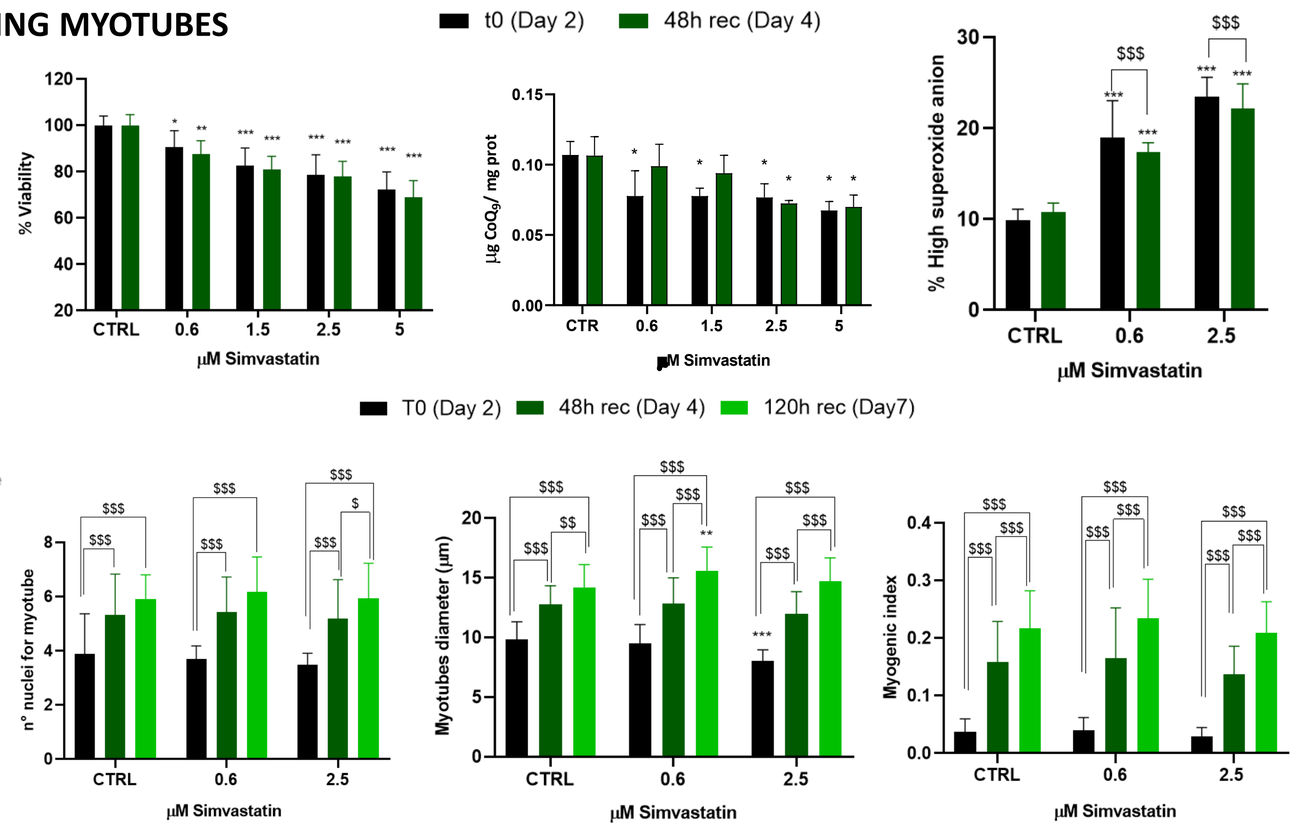
DISCUSSION

The preliminary data of this study confirm the established finding that statins induce intracellular Coenzyme Q deprivation in both early differentiated (myoblasts) and mature myotubes, starting from 0.6 µM of SMV. Additionally, increased oxidative stress was noted as mitochondrial superoxide anion in early myotubes and lipid peroxidation (nmol MDA) in mature myotubes, particularly at 2.5 µM after 24 hours and 48 hours of SMV treatment, respectively, highlighting higher susceptibility in myoblasts. Confocal images showed that SMV treatment slowed myogenesis in early myotubes and reduced the diameter of mature myotubes, compromising muscle cell morphology and likely their functionality. The next step of this study will investigate SMV's impact on oxidative stress by analyzing endogenous antioxidant defence levels and muscle fiber contractility using electrical pulse stimulation (EPS), replicating an *in vitro* model of physical exercise.

1 EFFECT OF STATINS ON A MODEL OF EARLY DIFFERENTIATING MYOTUBES

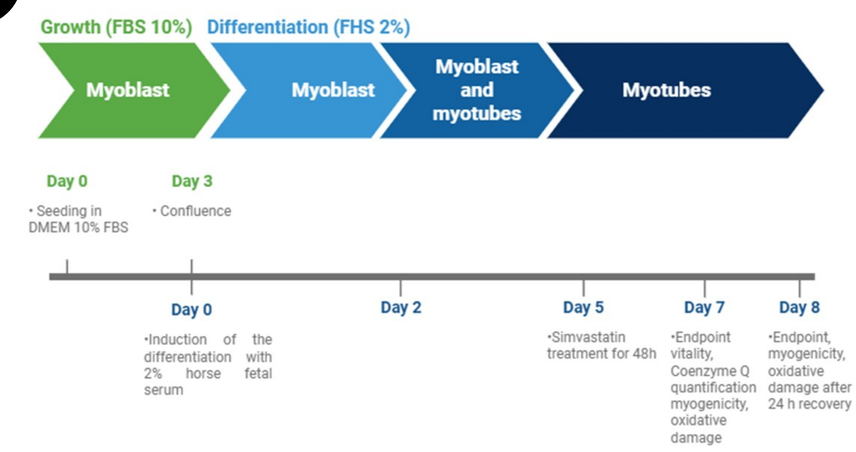


CTR (T0) | 0.6 µM SMV (T0) | 2.5 µM SMV (T0)

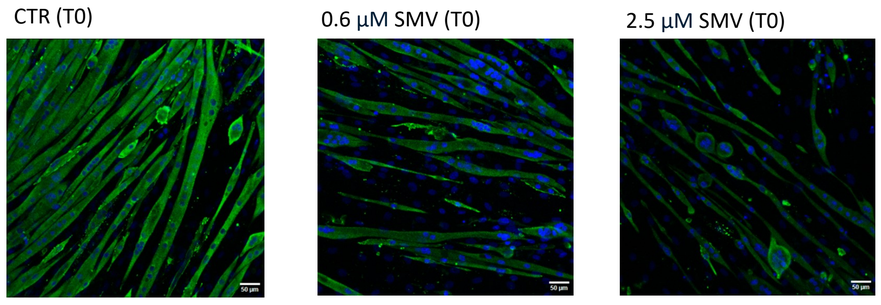


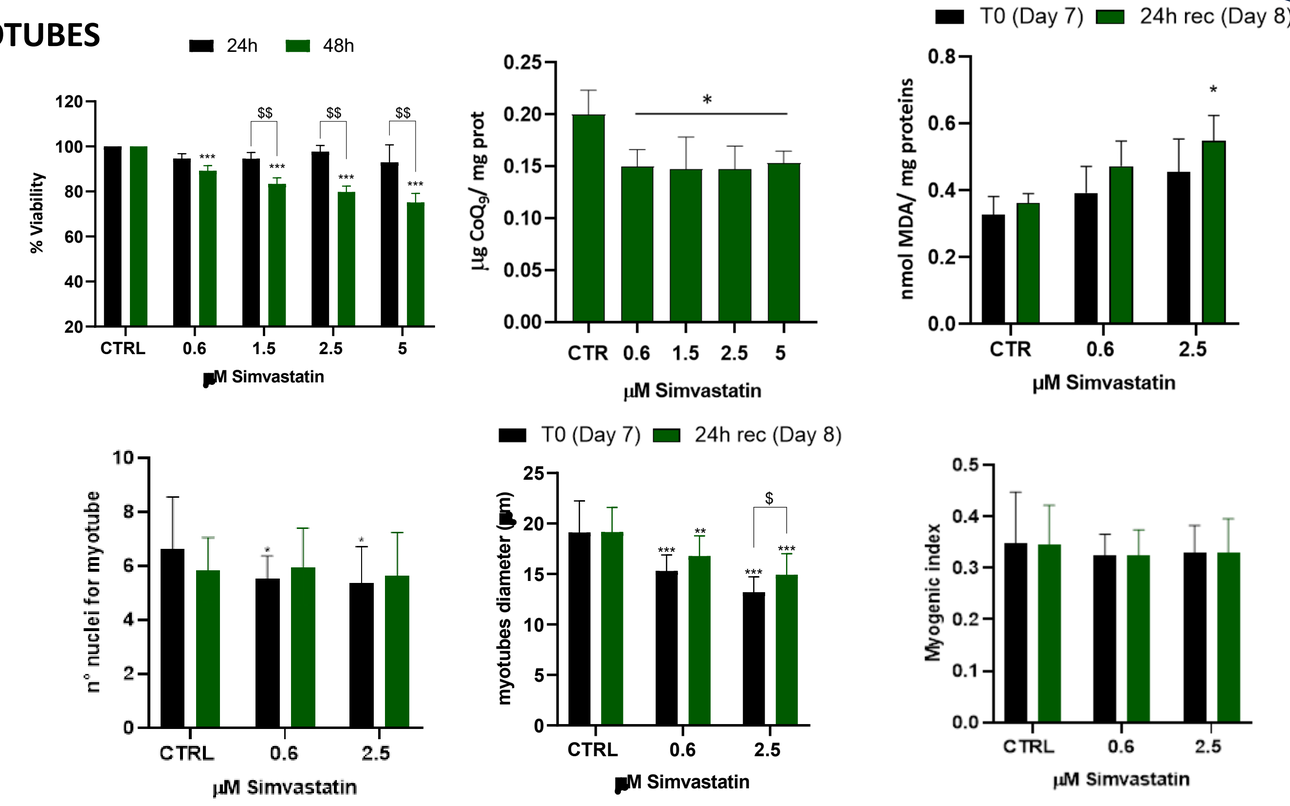
ANOVA *p<0.05,**p<0.01,***p<0.001 *vs* Ctrl; $ p<0.05, $$ p<0.01, $$$ p<0.001, T0 *vs* 48 hours recovery

2 EFFECT OF STATINS ON A MODEL OF DIFFERENTIATED MYOTUBES



CTR (T0) | 0.6 µM SMV (T0) | 2.5 µM SMV (T0)





ANOVA *p<0.05,**p<0.01,***p<0.001 *vs* Ctrl; $ p<0.05, $$ p<0.01, $$$ p<0.001, T0 *vs* 48 hours recovery

BIBLIOGRAPHY

1) Schweitzer *et al.* The impact of statins on physical activity and exercise capacity: an overview of the evidence, mechanisms, and recommendations. *Eur J Appl Physiol*
2) Gerda M. *et al.* C2C12 myoblasts are more sensitive to the toxic effects of simvastatin than myotubes and show impaired proliferation and myotube formation,Biochemical Pharmacology 2021.
3) Vinci P *et al*. Statin-Associated Myopathy: Emphasis on Mechanisms and Targeted Therapy. Int J Mol Sci. 2021

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