Regulation of muscle stem cells by ERRgamma

Sprawozdania

Informacje na temat projektu

MUSTEMERR

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Final Report Summary - MUSTEMERR (Regulation of muscle stem cells by ERRgamma)

Skeletal muscle stem cells called the satellite cells are localised within the myofibre basal lamina and are activated upon muscle injury, they then proliferate and differentiate to replace the damaged muscle. Satellite cells play a crucial role in maintaining skeletal muscle homeostasis and repair and are the key rate-limiting step for successful regeneration. Recent evidence has improved our understanding of the mechanisms underlying skeletal muscle metabolic reprogramming and its ability regenerate after damage.

In particular, Estrogen Related Receptors (ERR α, β and γ) are a sub-family of orphan nuclear hormone receptors that have been identified as major regulators of cellular and mitochondrial metabolism. In 2012/13 the fellow reported that skeletal muscle-specific over-expression of ERRγ drives metabolic and angiogenic muscle reprogramming that was beneficial in both health and disease.
The MUSTEMERR project tests the hypothesis that targeting ERRγ in skeletal muscle will improve the myofibre regenerative capacity via satellite cell recruitment and growth factor secretion. ERRγ–driven metabolic and angiogenic myofibre remodelling will be protective to muscle subjected to stimuli that cause damage and are followed by regeneration. The project is focused on the following main objectives: (1) To establish the satellite cell proliferation and differentiation profiles in ERRγ transgenic muscles at baseline and in response to acute eccentric exercise. (2) To investigate the effect of ERRγ on satellite cell recruitment in response to muscle injury. (3) To determine the interplay between muscular revascularisation and reparative myogenesis by ERRγ. (4) To determine whether an AAV-mediated ERRγ delivery increases satellite cell recruitment and improves muscle integrity and function.

Phase I (2014-2016) progress report
In the past two years we have made great progress towards the completion of objectives (1) and (2) and some effort has taken place addressing objective (3). During the project we found that ERRγ transgenesis does not result in an increase in skeletal muscle satellite cells. To our surprise the satellite cell pool of this mouse model is significantly lower compared to wild type mice. When this mouse is crossed with the hyper-muscular myostatin null mouse -that is known to have a satellite cell deficit-, the satellite cell number is further reduced and a large number of fibres has a single satellite cell. Fibre cultures revealed lower cells per cluster and fewer clusters compared to control despite a proportional increase in satellite cell progeny. Remarkably, when challenged with injury, ERRγ overexpression in myostatin deficient mice lead to accelerated muscle regeneration highlighting the importance of microcirculation during regeneration. This work challenges the dogma of an inverse relationship between muscle fibre size and oxidative capacity and was published recently (Matsakas et al. Elife. 2016;5. pii: e16940).

Phase II (2016-2018) progress report
In the past two years we addressed objectives (3) and (4). During the second phase of the project we generated strong evidence linking the growth factors that can be isolated from blood with skeletal myogenesis in cellular and experimental studies (i.e. in vitro, ex vivo and most importantly in vivo). Strikingly, we found that growth factors contained in the releasate from platelets promoted muscle stem cell commitment-to-differentiation and accelerate skeletal muscle regeneration in response to acute injury. These results provided important mechanistic evidence that can be exploited in regenerative medicine and have been published recently (Scully et al. Acta Physiol. 2018, e13207).
We also found that the levels of dystrophin-glycoprotein complex (DGC) proteins at the sarcolemma differ in highly glycolytic muscle compared to wild-type and that these changes can be normalised by the super-imposition of an oxidative metabolic programme by ERRγ. Importantly we showed that the metabolic properties of the muscle do not impact on the total amount of DGC components at the protein level. Our work showed that the metabolic property of a muscle fibre is a key determinant in regulating the expression of DGC proteins at the sarcolemma. We provided novel evidence that the DGC complex is a highly adaptable structure that responds to the metabolic nature of the fibre.
In addition, we used adeno-associated viral gene delivery to epigenetically induce ERRγ expression in the mouse. We found that administration of AAV8-ERRγ into the tibialis anterior muscle resulted in increased

succinate dehydrogenase and lower central nucleation in muscles of dystrophic mice in an age-specific manner. These findings were independent of muscle stem cell proliferation and differentiation profiles.

We identified a novel role for a key transcriptional regulator of skeletal muscle mass and function in the context of skeletal muscle stem cell function and regeneration. The findings of this project have the potential to make a fundamental change to scientific knowledge, and lead to novel pathways to support skeletal muscle angiogenic and metabolic remodelling. These findings may be of significant interest to biomedical or pharmaceutical industry. A large amount of research is being conducted by industry on developing drugs and cell based regimes that reverse the effects of metabolic de-regulation in skeletal muscle in the context of ageing or impaired regeneration. Our work provides a greater understanding of the angiogenic and metabolic regulation of the skeletal muscle and a new target for research that could be developed with the aim of promoting muscle regeneration. Therefore, our work has the potential to generate new drug-testing platforms.

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