Establishment of a model for skeletal muscle injury via mechanical and oxidative stress and elucidating the role of reactive oxygen species in repair and regeneration

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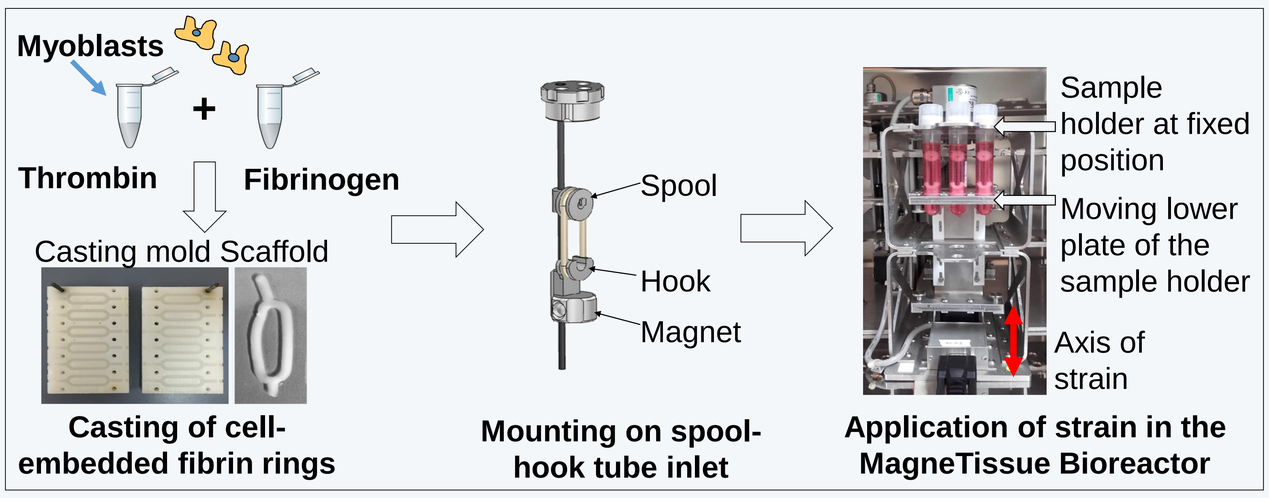
INTRODUCTION

Skeletal muscle tissue engineering presents a promising tool to study muscle development and diseases. While a small number of 3D systems investigating myogenic diseases have been published, there is still a lack of models for myogenic injuries [1,2]. The involvement of reactive oxygen species (ROS) in numerous processes of skeletal muscle has been considered a merely detrimental one. New evidence, however, suggests that ROS are not only toxic agents, but also required effectors for regenerative processes. Whether ROS triggers positive or negative effects is, amongst others, regulated by their concentration and duration of oxidative stress [3].

Figure 1: MagneTissue bioreactor schematic



PRELIMINARY RESULTS

With our custom-made bioreactor system – MagneTissue – we are able to rapidly engineer biomimetic tissue constructs resembling native tissues in terms of structure, gene expression profile and maturity through the application of various types of tensile stress profiles (fig1, fig2) [2]. Furthermore, we established a bioreactor system that builds up non-injurious loads of hydrostatic pressure, leading to increased ROS levels in the medium (fig3) [4].

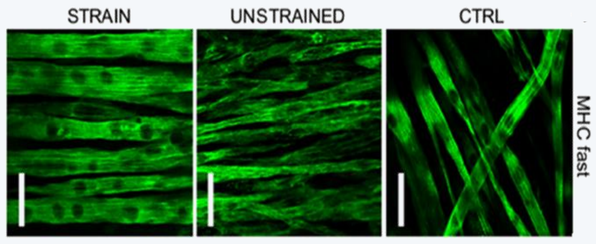


Figure 2: Biomimetic tissue constructs created with the MagneTissue bioreactor

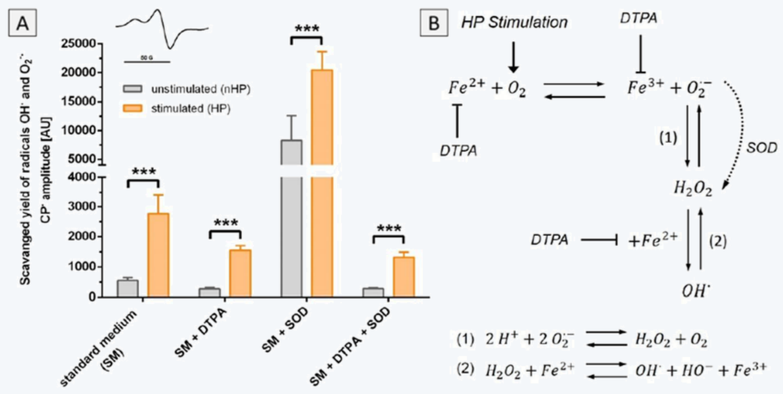


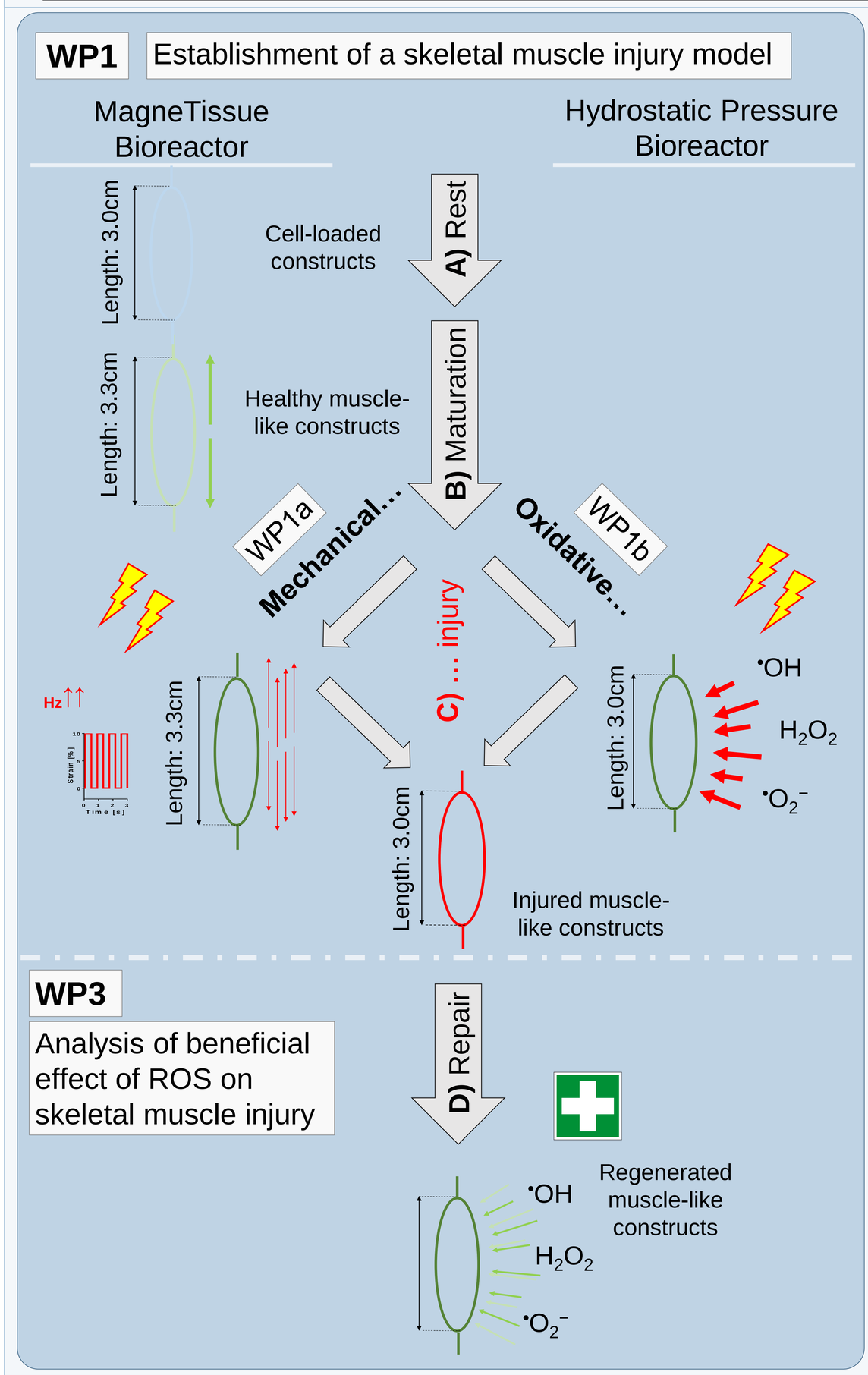
Figure 3: Acellular ROS formation by hydrostatic pressure stimulation

Project Outline

WP1: Establishment of a skeletal muscle injury model:
- Creation of healthy muscle-like constructs (A-B)
- Induction an injury (C) by
  - **WP1a:** mechanical overstimulation with high-frequency tensile strain using the MagneTissue bioreactor
  - **WP1b:** oxidative stress by applying defined ROS levels with the hydrostatic pressure bioreactor

WP2: Elucidating the effect of ROS in skeletal muscle development:
- Assessment of the effect of different ROS levels during myogenesis (E-G)
- Establishment of an optimal ROS level that might enhance skeletal muscle development (G).

WP3: Analysis of beneficial effects of ROS for skeletal muscle recovery:
- Generation of injured skeletal muscle
- Treatment of harmed tissue with identified beneficial ROS levels to initiate tissue recovery and repair (D).



CONCLUSION

Overall, further insights into underlying mechanisms and importance of ROS signaling in skeletal muscle injury will be results of this thesis. In addition, this work may also help to identify new therapeutic entry points for pharmacologic targeting of oxidative/metabolic stress response signaling cascades with antioxidants.

References:
[1] H.H. Vandenburgh, S. Hatfaludy, P. Karlisch, J. Shansky, Am. J. Physiol. - Cell Physiol. 256 (1989). [2] P. Heher, B. Maleiner, J. Prüller, A.H. Teuschl, J. Kollmitzer, X. Monforte, S. Wolbank, H. Redl, D. Rünzler, C. Fuchs, Acta Biomater. 24 (2015) 251–265. [3] E. Barbieri, P. Sestili, J. Signal Transduct. 2012 (2012) 982794. [4] B. Rieder, A.M. Weihs, A. Weidinger, D. Szwarc, S. Nürnberger, H. Redl, D. Rünzler, C. Huber-Gries, A.H. Teuschl, Sci. Rep. 8 (2018) 17010.

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