Universität Basel

Research Project

Improving human muscle engineering by PGC-1alpha expression and molecular imaging using positron emission tomography (PET)

Third-party funded project

Project title Improving human muscle engineering by PGC-1alpha expression and molecular imaging using positron emission tomography (PET)
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The ability to regenerate muscle tissue from patients own cells would have profound impact on many human diseases. Cell therapy is within reach as a novel treatment option for incontinence, reflux, vocal cord dysfunction and other muscle-related pathologies. Muscle precursor cells (MPCs) are quiescent adult
stem cells and are located under the membrane surrounding the muscle fibers. After trauma or damage, MPCs participate in tissue regeneration by proliferating and differentiating into myoblasts and later fuse to
form new myofibers. The majority of MPCs is committed to the myogenic lineage and MPCs are therefore
most suitable for muscle engineering.
Despite the progress in the field of muscle tissue engineering, one of the main problems is the decreased capacity and growth of MPCs in the aged population since many clinical conditions for which muscle tissue engineering will be useful are commonly found in the elderly patients. Importantly, even in these individuals, the ability of MPCs to regenerate muscle fibers can be improved by exercise and therapeutic regulation of gene expression.
The transcriptional coactivator peroxisome proliferator-activated receptor ã coactivator 1á (PGC-1á) is a key integrator of neuromuscular activity in skeletal muscle and plays an important role in exercise-mediated adaptations. PGC-1alpha expression is regulated proportionally to the amount of exercise in
a muscle and protects skeletal muscle from atrophy. PGC-1alpha is also involved in the muscle fiber-type switch towards oxidative muscle fibers that are capable to sustain long-term contractions.
Many different cellular therapies are on the door step into clinics. Therefore, a method to track transplanted cells and to determine the functional outcome of these interventions in a non-invasive manner
is of key interest. Specifically, the ability to monitor these cells in “real time” would allow us to better understand tissue reconstruction and effectiveness of the cell-based therapies elucidate homing process,
distribution, local retention and functional integration of transplanted stem cells in vivo. Positron Emission
Tomography (PET) using radioactively labeled molecules is a highly sensitive, quantitative imaging modality which provides information on functional physiologic or biochemical changes in vivo. We

hypothesize that human MPCs supplemented with PGC-1alpha are able to form new functional muscle tissue
with improved functional properties. Our project thus aims at the generation and validation of viral vectors
for ectopic expression of PGC-1alpha in MPCs, assess the therapeutic potential of these engineered MPCs in
two mouse models in vivo, longitudinally track these injected mouse muscle precursors non-invasivelywith PET. In the past, while most effort was put on reporter system development and evaluation in the past, less attention was paid to the possibility of PET monitoring of the functionality of the engineered tissues. Besides using the dopamine D2 receptor as a reporter gene, we will follow features such as glucose metabolic state, oxygenation status, VEGF release and/ or the vascularisation level of the transplanted MPCs over time with established PET tracers with the aim to finally establish new PET-based protocols to non-invasively assess the therapeutic efficacy of the cellular treatment. The PET analysis will be combined with a thorough functional characterization of engineered MPCs in culture in order to define cellular parameters that are predictive for a high therapeutic efficacy in subsequent application in vivo. Hopefully, these data will provide insights into novel approaches to overcome the limitations of autologous stem cell treatment of single muscles in elderly patients.

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