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Stem cell-induced regeneration of skeletal muscle tissue: characterization of a glycerol-induced muscle damage model

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Skeletal muscle is an important tissue in the organism, critical for movement and thermoregulation. Muscle tissue has a remarkable ability to regenerate, provided mainly by a subpopulation of muscle cells, referred to as satellite cells. A better knowledge of this recovery mechanism could help researchers and medical practitioners to develop therapeutic approaches to treat muscle-related diseases by pharmacological or stem-cell based means. Besides muscle cells and structure, also efficient neural transmission is critical for the organ function. This is provided by the neuromuscular junctions (NMJs), which are formed by the alignment of a motor neuronal pre-synaptic compartment and its muscular post-synaptic counterpart. In this thesis a glycerol-induced muscle degeneration/regeneration model was characterized and applied to address the regeneration of muscle and NMJs in the absence and presence of mesenchymal stem cells derived from adipose tissue (ASCs). In the absence of ASCs, glycerol injection led to early fiber necrosis, fibrotic tissue deposition and loss of actin and dystrophin. Between five and eight days after the glycerol injections, regeneration became evident with center-nucleated fibers and the expression of eMHC. Regarding the NMJs, their amount was diminished throughout the entire observation time of eleven days, with a slight recovery at five days post-injection. Notably, presynapses appeared to be more susceptible to glycerol damage than postsynapses and a complete recovery was not achieved within the observation window. In the presence of ASCs, the initial glycerol-induced damage was reduced compared to the glycerol-only model, but a recurrent inflammation and fibrosis was detected eleven days after the injection and the amount of regenerating fibers was higher. Further, in the presence of ASCs, early NMJs recovery was increased, but this was followed by a deterioration eleven days after the treatment. Those findings suggest that, while ASCs exert a beneficial effect in the first days after the treatment, a later inflammatory phase inflicts secondary muscle and NMJ degeneration. Since ASCs could not be detected in the affected muscles, it is likely that their effects on this tissue were rather due to release of signaling molecules than to direct engraftment in the muscle.
In conclusion, a glycerol-based regeneration/degeneration paradigm was successfully established that allows to test properties of skeletal muscle and NMJs in the absence and presence of therapeutic means. This showed a differential sensitivity of pre- and postsynaptic portions to glycerol, as well as transient beneficial and latent inflammatory effects of systemic ASC application on skeletal muscle.