Systemic Mesenchymal Stem Cell Transplantation for the Treatment of Skeletal Muscle Trauma

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Introduction
Skeletal muscle trauma leads to severe functional deficits. Present therapeutic treatments are unsatisfying and insufficient posttraumatic regeneration is a problem in trauma and orthopaedic surgery. Mesenchymal stem cell (MSC) therapy is a promising tool in the regeneration of muscle function after severe trauma. Our group showed increased contraction forces compared to a non-treated control group 3 weeks after MSC transplantation (TX) into an injured skeletal muscle. In addition we demonstrated a dose-response relationship of the amount of injected MSC and force enhancement. We furthermore investigated the fate of the transplanted MSC labelled with very small iron oxide particles using 7 Tesla-MRI. Histological analyses revealed fusion events between existing myofibers but only to a low amount. The increase of muscle force can not be explained by these events only. Before further steps are taken the impact of paracrine effects and the homing to the site of trauma of the MSC has to be evaluated. Experimental studies about the functional regeneration of traumatized skeletal muscle after systemic MSC-TX do not exist.

Materials and Methods
36 female SD-rats received an open crush injury of the left soleus muscles. One week after trauma 2.5 x 10^6 autologous MSC, harvested from tibial biopsies, were transplanted intraarterially (i.a., femoral arteria, group 1) or intravenously (i.v., tail vein, group 2) (n=18). Control animals received saline (i.a.: group 3; i.v.: group 4) (n=18). Histological analysis and biomechanical evaluation by in vivo muscle force measurement was performed 3 weeks after TX.

Results
Twitch stimulation of the healthy right soleus muscles resulted in a contraction force of 0.52±0.14 N. Forces of tetanic contraction in the uninjured muscles reached 0.98±0.27 N. The i.a. MSC-TX improved the muscle force of the injured soleus significantly compared to control (fast twitch: 82.4%, p=0.02, tetany: 61.6%, p=0.02). Contraction forces of muscles treated i.v. (MSC vs. saline) showed no functional improvement. The histological analysis showed no differences in the amount of fibrosis.

Discussion and Conclusions
The presented study demonstrates the effect of systemic MSC-TX in the treatment of severe skeletal muscle injuries. Interestingly, the functional regeneration could only be increased by i.a. application. The entrapment of MSC in the lungs and the dilution effect in the circulation, when injecting the MSC i.v. could be the reason. For possible future therapeutic approaches a systemic application is considered to be favourable compared to local injections due to the better distribution of the cells in the target muscle.

Disclosures
Authors have nothing to disclose.