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Stromal Vascular Fraction Regenerative Potential in a Muscle Ischemia/Reperfusion Injury Mouse Model

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Abstract : Ischemia/reperfusion (IR) injury induces muscle fiber atrophy and skeletal muscle fiber death with subsequently functionality loss. The heterogeneous pool of cells, especially mesenchymal stem cells, contained in the stromal vascular fraction (SVF) of adipose tissue could promote muscle fiber regeneration. To prevent SVF dispersion, it has been proposed the use of injectable biopolymers that work as cells carrier. A significant element of the extracellular matrix is hyaluronic acid (HA), which has been widely used in regenerative medicine as a cell scaffold given its biocompatibility, degradability, and the possibility of chemical functionalization. Connective tissue micro-fragments enriched with SVF obtained from mechanical disaggregation of adipose tissue were evaluated for IR muscle injury regeneration using low molecular weight HA as a scaffold. IR induction. Hindlimb ischemia was induced in 9 athymic nude mice through the clamping of the right quadriceps using a plastic band. Reperfusion was induced by cutting the plastic band after 3 hours of ischemic period. Contralateral (left) muscular tissue was used as healthy control. Treatment. Twenty-four hours after the IR induction, animals (n=3) were intramuscularly injected with 100 µl of SVF mixed with HA (SVF-HA). Animals treated with 100 µl of HA (n=3) and 100 µl saline solution (n=3) were used as control. Treatment monitoring. All animals were in vivo monitored by magnetic resonance imaging (MRI) at 5, 7, 14 and 18 days post-injury (dpi). High-resolution morphological T2 weighed, quantitative T2 map and Dynamic Contrast-Enhanced (DCE) images were acquired in order to assess the regenerative potential of SVF-HA treatment. Ex vivo evaluation. After 18 days from IR induction, animals were sacrificed, and the muscles were harvested for histological examination. At 5 dpi T2 high-resolution MR images clearly reveal the presence of an extensive edematous area due to IR damage for all groups identifiable as an increase of signal intensity (SI) of muscular and surrounding tissue. At 7 dpi, animals of the SVF-HA group showed a reduction of SI, and the T2relaxation time of muscle tissue of the HA-SVF group was 29±0.5ms, comparable with the T2relaxation time of contralateral muscular tissue (30±0.7ms). These suggest a reduction of edematous overflow and swelling. The T2relaxation time at 7dpi of HA and saline groups were 84±2ms and 90±5ms, respectively, which remained elevated during the rest of the study. The evaluation of vascular regeneration showed similar results. Indeed, DCE-MRI analysis revealed a complete recovery of muscular tissue perfusion after 14 dpi for the SVF-HA group, while for the saline and HA group, controls remained in a damaged state. Finally, the histological examination of SVF-HA treated animals exhibited well-defined and organized fibers morphology with a lateralized nucleus, similar to contralateral healthy muscular tissue. On the contrary, HA and saline-treated animals presented inflammatory infiltrates, with HA slightly improving the diameter of the fibers and less degenerated tissue. Our findings show that connective tissue micro-fragments enriched with SVF induce higher muscle homeostasis and perfusion restoration in contrast to control groups.

Keywords : ischemia/reperfusion injury, regenerative medicine, resonance imaging, stromal vascular fraction
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