Dokumenttyp: journal article

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Abstract: Cell therapy would be favorably performed immediately after nucleotomy, to restore intervertebral disc functionality and to slow down disc degeneration. Promising results were reported from small animal models but remaining problems, especially in larger animals, include loss of vital cells due to annular damage at the injection site and detrimental intradiscal conditions. The aim of the present study was to optimize cell-based disc therapy using a new albumin-hyaluronan hydrogel together with bone marrow-derived mesenchymal stem cells in a large porcine disc model. Luciferase cell labeling was evaluated to follow-up stem cells metabolically up to 7 days in 3D cell cultures mimicking the harsh disc environment with low oxygen and glucose concentrations. As a pilot in vivo study, the implant was injected into porcine discs after removal of ~10% of nucleus volume and animals were killed immediately after surgery (n = 6) and 3 days later (n = 6). 24 discs were analyzed. Implant persistence and cell activity (luciferase + WST assay) were observed simultaneously. In vitro cell culture with reduction of glucose (20, 5, 0.5, 0 mM) and oxygen (21, 5, 2%) significantly decreased metabolic cell activity and luciferase activity after 3 days, with no recovery and a further decrease after 7 days, establishing luciferase activity
as a metabolic sensor. During 3 days of 3D culture with disc-like conditions, luciferase activity decreased to 8%. In vivo, initial implant volume shrank to 61% at day 3 with evidence for hydrogel compression. Luciferase activity in vivo at day 3 was 2% without referencing but 23% after referencing to in vitro cell adaptation, and 38% after additional consideration of detected implant volume loss. In vitro analysis up to 7 days established for the first time luciferase activity as a metabolic sensor for mesenchymal stem cells used in regenerative disc therapy. Under the present protocol, short-term in vivo analysis after 3 days suggests improved implant retention inside the disc and persistence of metabolically active cells; however, further studies will have to prove long-term in vivo outcome.

Zeitschriftentitel / Abkürzung:
Eur Spine J

Jahr: 2014

Band: 23

Heft / Issue: 9

Seiten: 1837-47

Sprache: eng


Print-ISSN: 0940-6719

TUM Einrichtung:
Institut für experimentelle Onkologie und Therapieforschung

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Experimentelle Onkologie und Therapieforschung > 2014

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