

## Abstract

Intervertebral disc (IVD) herniation is a common spinal condition that causes pain, disability, and a socioeconomic burden on patients. Surgical discectomy is the current standard of care, but it is unsuccessful in preventing recurrent herniation because it fails to address the IVD's poor healing capacity and repair annulus fibrosus (AF) defects. Therefore, there is an unmet clinical need to develop therapeutic strategies that promote endogenous AF repair. Mesenchymal stem cell-derived exosomes are shown to promote regenerative tissue repair, but research on their application within the IVD is still in its infancy. The current study aimed to: (1) successfully characterize mesenchymal stem cell-derived exosomes and evaluate their ability to promote regenerative AF repair, and (2) develop a biodegradable delivery system consisting of hydrogel-embedded poly(lactic-co-glycolic) acid (PLGA) microspheres for the controlled release of encapsulated exosomes. AF cells were treated with exosomes preconditioned in either hypoxic or normoxic culture conditions. Experimental results showed that hypoxic exosomes led to greater proliferative and migratory responses and were therefore utilized in downstream applications. Hypoxic exosome pre-treatment protected AF cells from inflammatory and catabolic damage induced by an *in vitro* biochemical challenge. In parallel, a PLGA microsphere delivery system was successfully fabricated and integrated with an injectable interpenetrating network hydrogel system to allow for controlled exosome delivery. Short-term and long-term studies revealed that the composite hydrogel system did not significantly increase herniation risk or decrease pH to levels that would be associated with a degenerative microenvironment. Finally, a proof-of-concept study showed that exosomes could be successfully encapsulated within the microspheres and released from the composite hydrogel system over three weeks. These results suggest that targeted delivery of exosomes is a promising therapeutic strategy for regenerative AF repair.