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Commentary

Gel and cells: A promising reparative strategy for degenerated intervertebral discs

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One of the most common causes of physical disability is lower back pain, which affects overall well-being and work performance, with recent reports indicating a lifetime prevalence as high as 85% in industrialized countries [1]. The recent *Global Burden of Disease* study states that lower back pain is the most common musculoskeletal disorder and imposes the highest disability burden of all specific conditions in developed countries [2]. There are currently no disease-modifying therapies for lower back pain and, although there are several known risk factors, such as obesity, psychological factors, age and sex, and genetic variants, the underlying cellular and molecular cause(s) of back pain remain unclear [3].

While the exact aetiology of lower back pain is unknown, a frequently associated pathology is the degeneration of the intervertebral disc (IVD), a specialized joint of the axial skeleton that serves to absorb and disperse compressive forces, to confer tensile and torsional strength, and to provide flexibility to the spine [4]. The mature IVD is a multi-component structure consisting of three distinct, yet interdependent specialized tissues: a gelatinous central nucleus pulposus (NP), encased by the outer fibrous annulus fibrosus (AF), that together are sandwiched between the cartilage endplates that anchor the IVD to the adjacent, rostral and caudal vertebral bodies. IVD herniation is a common pathology of sciatica and is often treated by discectomy to remove IVD materials compressing the nerve root. As IVD has inherently poor self-repair capability, such procedures do not address the potential for further tissue degeneration, thus leading to severely disabling lower back pain and necessitating additional surgery [5].

In an article in *EBioMedicine*, Ukeda and co-workers report the development of a novel regenerative therapeutic strategy that involves the application of bone marrow-derived mesenchymal stem cells (BMSCs) combined with a hydrogel [6]. The bioresorbable hydrogel consisted of ultra-purified alginate (UPAL), a polysaccharide derived from the brown seaweed, *Phaeophyceae*, which gelates via calcium ion-mediated crosslinking. BMSCs were chosen by virtue of their known multi-lineage differentiation ability as well as trophic effects, such as immunomodulation, on immune cells as well as other tissue-specific cells [7]. UPAL was used based on the investigators' previous finding that introduction of UPAL alone prevented post-discectomy IVD degeneration by facilitating extracellular matrix (ECM) production and deposition [8]. In this study, the researchers aimed to test whether implantation of a combination of BMSCs encapsulated in UPAL could act to stimulate disc regeneration, specifically via the activation of endogenous NP cells (NPCs). First, isolated NPCs were co-cultured with fluorescently pre-labelled BMSCs in 3D hydrogel. After 7 days of culture, the cells were differentially sorted based on fluorescence and analysed. The results showed that co-culturing BMSC with NPCs led to BMSC differentiation into NPCs, which in turn led to a mutual activation effect between NPCs and BMSCs, resulting in enhancement of ECM production in both cell types. This is consistent with various reported findings that exposure to cells of the NP stimulates BMSC differentiation into an NPC phenotype [e.g., 9]. Using a rabbit puncture mediated model of IVD degeneration followed by discectomy, the researchers observed that implantation of BMSCs encapsulated in 2% UPAL into the degeneration site promoted IVD regeneration, evidenced by MRI and histological findings. Specifically, at a 12-week time point the typical oval-shaped NP tissue was restored, accompanied by the appearance of more collagen type II-producing cells, but fewer collagen type I-producing cells in the BMSCs + Gel group, compared to the discectomy control and the Gel alone groups. Of particular interest is the finding that the implanted BMSCs appeared to have been stimulated to differentiate into NPCs, identified based on expression of the NP cell markers, HIF-1α, GLUT-1, and Brachyury, and increasing in number with time. Taken together, these findings suggest the potential utility of the "Gel and Cells" BMSCs + UPAL combination as a tissue-engineered construct for IVD regeneration and repair.

While there have been previous reports on the application of BMSCs in various hydrogel biomaterial scaffolds for IVD repair [e.g., 10], a particularly intriguing finding reported here is the apparent, mutually enhancing interaction between BMSCs and NPCs, resulting in both BMSC differentiation into NPCs and activation of NPCs. Notochordal cells, which are developmental precursors of NPCs have previously been shown to stimulate BMSC differentiation towards a young NPC phenotype [9], thought to be mediated by secreted factors. However, it is not known that BMSCs have a reciprocal stimulatory effect on NPCs. The

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encapsulation of BMSCs by Ukeda et al. [6] likely enhanced the retention of BMSC-secreted factors, resulting in enhancement of NPC bioactivity observed in the 3D *in vitro* cultures, as well as activation of resident NPCs in the site of IVD degeneration *in vivo*. The absence of osteophyte formation also indicated that the rapid curing of the UPAL hydrogel prevented leakage of BMSCs. In this manner, the "Gel-Cells" approach may function as a means to efficiently capture the trophic activity of the BMSCs, although it is unknown whether the immunomodulatory activity of the BMSCs also played a role in the observed effects.

There are, however, some remaining hurdles for successful and practicable translation of the technology described by Ukeba et al. [6]. These include: (1) effective repair of the AF, the outer fibrous structure of the IVD, which is often compromised in degenerative disc diseases; (2) achieving material properties in the regenerated tissue that are comparable to those of the native NP, a critical requirement for its mechanical function; and (3) functional integration of the regenerated NP with the other components of the IVD, i.e., the AF and the cartilage endplates, for structural integrity and mechanical stability. Finally, given the continuous mechanically "pressing" need of the loaded environment of the IVD, it is essential that production of the new ECM in the "regenerated" IVD must be optimally matched, in time and scale, to biodegradation of the non-native alginate hydrogel scaffold, to achieve biocompatible and structural stability.

Disclosure

None

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