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Commentary

Mechanobiology to repair the herniated disc

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Herniation of the intervertebral disc (IVD) is a painful event that occurs in up to 2% of the general population at some point in life, usually in the fourth or fifth decade. It essentially is the extrusion of the core of the IVD, the gel-like Nucleus Pulposus (NP), through the ruptured collagenous layers of the Annulus Fibrosus (AF). The pain results from the compression or inflammation of the nearby spinal nerves. Removal of the remaining NP material (discectomy) is the most rapid and effective therapy for neurological decompression. Current procedures, however, are not directed to repair the herniated IVD and in fact aggravate the damage, predisposing the IVD to further degeneration. The reason is that the remaining cells of the IVD, both in the NP and the AF, undergo severely changed loading conditions, more particular a (higher) deviatoric shear stress instead of an all-sided hydrostatic pressure that was imposed by the osmotic NP. Mechanical overloading is an established factor that induces degeneration of the NP [1], characterized by an increased expression of cytokines and matrix-degrading enzymes, and a downregulation of their inhibitors. Cytokines known to have a detrimental effect are tumor necrosis factor alpha (TNFα) and interleukin-1β (IL-1β); these generate local inflammation in the NP and an upregulation of extracellular matrix (ECM)-degrading enzymes: matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). Simultaneously, a downregulation of their inhibitors (tissue inhibitor of metalloproteinases, TIMPs) occurs. All these effects together push the ECM in a vicious cycle of degeneration [2].

In order to address this problem, tissue engineers have extensively studied biomaterials that could be used as a substitute for the NP, either or not enriched with growth factors or cells [3]. In this issue of *EBioMedicine*, Tsujimoto and coworkers present an acellular bioresorbable ultra-purified alginate (UPAL) gel implantation system [4]. Alginate, a natural polymer derived from brown seaweed, is very biocompatible and friendly to cells from the IVD: endplate-, AF- and NP-derived stem cells proliferate and effectively produce ECM, which could in time replace the degrading alginate [5,6]. Furthermore, in the concentration used in this study (2 wt%), alginate closely resembles the rheological properties of the healthy NP [7], thus mimicking the natural mechanical environment. Finally, alginates are open structures and thus facilitate the migration of cells from the host-tissue; this allows for an acellular regenerative therapy without the labor-intense and expensive use of (stem) cells. Alginates usually contain a concentration of endotoxins considered too high for clinical applications. Tsujimoto and colleagues developed an ultra-purified alginate (UPAL) with an endotoxicity less than 0.0001 compared to conventional alginate. In an *in vitro* starvation model, UPAL showed higher cell viability and a lower percentage of apoptotic cells as compared to regular alginate, thereby showing benefit in biocompatibility. It is unfortunate that the regular alginate was not considered as a control in the subsequent *in vivo* studies; this would have allowed a conclusion on the need and perhaps benefits of the ultra-purification of alginate.

An outstanding feature of the tissue engineering strategy presented here, not to be underestimated for its clinical relevance, is the closure of the AF that contains the highly-pressurized NP. In humans, pressures in the NP can be as high as 2.0 MPa under external loading conditions, which is about ten times the pressure in a car tire. Reherniation of an injected hydrogel thus is a serious clinical risk and techniques that deal with the damaged annulus fibrous are increasingly recognized as mandatory [8]. The solution presented by Tsujimoto and colleagues stands out by its simplicity and efficacy: an *in situ* rapid cross-linking by coverage with $CaCl_2$. None of the discs injected and closed with UPAL showed extrusion of the hydrogel under mechanical loading, *in vitro* nor *in vivo*. The exclusion of reherniation obviously is a necessary condition for safe clinical usage. However, the *in vivo* studies show another benefit: in the UPAL gel group, the percentage of collagen type I positive NP cells was lower, and the percentage of collagen type-II positive cells was higher than in the aspirated or discectomy groups. Furthermore, the percentage of GD2+Tie2+ cells, indicating NP progenitor cells, increased significantly at 2 and 4 weeks after UPAL implantation. These observations confirm that NP progenitor cells migrate into the originally cell-free hydrogel and strongly suggest that the appropriate mechanobiological conditions are created for NP regeneration.

Tsujimoto and colleagues present a tissue engineering strategy for IVD repair that is safe and clinically feasible: they rightly point out that matrix-based medicine offers crucial benefits over cell-based therapies in terms of immunology, the risk of disease transmission, and the cost and duration of the procedure. Whether the proposed procedure is also efficacious, however, is an outstanding question: all biomechanical, radiological and histological results presented indicate a partial rather than a full repair of the IVD after 24 weeks in sheep. Given the safety of the material and the procedure and the unmet clinical need, longer-term studies in patients are presumably more in place than follow-up studies in large animals. One concern for a clinical trial may be that the discectomy model in sheep is not quite representative for the situation in patients: instead of one, well-defined defect in the AF, the AF of

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the patient may show multiple hidden lesions that are not closed by the cross-linking hydrogel. A preliminary *in vitro* study addressing this particular risk would be recommendable.

Conflict of interest

Dr. Smit has nothing to disclose.

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