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Joint resurfacing possibilities loom large

An advanced textile weaving process has been used in combination with gene therapy technology to fabricate large, anatomically relevant tissue-engineered cartilage constructs with the ability to deliver anticytokine therapy. The material properties of the constructs, produced *in vitro*, permit load-bearing immediately upon implantation and, by expressing the anti-inflammatory molecule IL-1 receptor antagonist (IL-1Ra), the implant counters the inflammatory milieu associated with joint degeneration in osteoarthritis (OA).

“We have developed an engineered cartilage replacement that has the functional properties and anatomy of a human hip,” reports corresponding author Farshid Guilak. “This implant could be used to completely resurface an arthritic joint, beyond repair of small focal cartilage defects.”

The development of biological resurfacing techniques to repair large cartilage lesions remains a major unmet need in the treatment of OA. “While we have good algorithms for treatment of focal cartilage defects, little has been attempted

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with the concept of whole-joint surfacing,” comments Daniel Grande of the Feinstein Institute of Medical Research, who was not involved in the study. Joint resurfacing could offer an alternative to total joint arthroplasty for patients with end-stage OA, particularly young, active individuals, for whom few therapeutic options are available.

In the current study, functional cartilage constructs that mimic the shape of hip joint surfaces were produced by seeding human adipose-derived stem cells (ASCs) onto a hemispherically shaped 3D orthogonally woven scaffold, which was created using poly(ϵ -caprolactone) fibre, an FDA-approved biomaterial. “The scaffold consists of hundreds of biocompatible and resorbable fibres, giving it the flexibility and toughness needed to withstand loading in the joint as cartilage forms within the pores of the scaffold,” Guilak explains.

Furthermore, the ASCs within the scaffold were genetically modified using a doxycycline-inducible lentiviral vector to enable tunable biosynthesis of IL-1Ra. “These cell-seeded

constructs had the anatomy and properties of normal cartilage, but with the added ability to deliver anti-inflammatory therapy on-demand,” says Guilak.

The scaffolds maintained their original size and anatomical shape over 38 days in chondrogenic culture, during which time the seeded ASCs synthesized extracellular matrix that accumulated uniformly over the inner and outer surfaces of the hemispheres and filled the internal pores. Total DNA, sulfated glycosaminoglycan and collagen content in the engineered cartilage hemispheres all increased significantly over time in culture.

The addition of doxycycline to the culture medium induced the expression of IL-1Ra by the constructs at concentrations of nearly 1 $\mu\text{g/ml}$. This controlled expression of IL-1Ra was sufficient to prevent IL-1-induced matrix metalloproteinase activity.

As Grande points out, questions remain about how well the construct will work *in vivo*, how the engineered joint surfaces will interact with the host, and how one might fine-tune the release of IL-1Ra to counter the variable amounts of IL-1 present in the joint. “These questions are important to the successful translation of this technology to the clinic,” says Grande. “The continued development of this significant paradigm-shifting work includes *in vivo* testing of the cartilage construct and the ability to allow feedback-controlled release of the IL-1Ra.”

Guilak and colleagues are currently performing animal studies to test the efficacy of the implants *in vivo*.

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ORIGINAL ARTICLE Moutos, F. T. et al. Anatomically shaped tissue-engineered cartilage with tunable and inducible anticytokine delivery for biological joint resurfacing. *Proc. Natl Acad. Sci. USA* <http://dx.doi.org/10.1073/pnas.1601639113> (2016)

FURTHER READING Smith, B. D. & Grande, D. A. The current state of scaffolds for musculoskeletal regenerative applications. *Nat. Rev. Rheumatol.* **11**, 213–222 (2015)