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REGENERATIVE MEDICINE

Dishing up functional human cartilage

Tissue engineers have found a way to grow functional human cartilage from human mesenchymal stem cells (MSCs) *in vitro,* without the use of scaffold, using a cellular self-assembly method that mimics cartilage formation during embryonic development.

Mesenchymal condensation is a key stage in the formation of cartilage, whereby cells form dense cellular bodies and set boundaries that define their growth and differentiation. Previous studies have shown that human MSCs can be induced *in vitro* to aggregate and form condensed mesenchymal cell bodies (CMBs), but the team of investigators led by Gordana Vunjak-Novakovic of Columbia University have now used this method to engineer functional cartilage.

They first established that after 5 days in culture CMBs develop boundaries, characterized by the presence of tenascin on their outer surfaces and expression of mesenchymal condensation genes, and lose their ability to fuse. "We discovered that if we fuse these small cellular bodies together prior to their boundary setting, a larger homogenous cellular body can be formed," explains Vunjak-Novakovic.

> "The capacity of CMBs for cartilage repair was demonstrated *in vitro*..."

The next step involved developing a method for using CMBs to form articular cartilage on bone substrate. Anatomically shaped cartilage was grown *in vitro* by pressing CMBs onto porous human condyle-shaped scaffolds created from decellularized trabecular bone, which caused the CMBs to fuse into a dense cellular region and penetrate into the bone matrix. Over 5 weeks of cultivation, this cellular layer developed into a thick (>1 mm) layer of cartilage that covered the condylar surface. "We were surprised to see that the cartilage layer became physiologically stiff and stratified," Vunjak-Novakovic recounts, "and that a functional interface formed between the cartilage and bone tissues."

The capacity of CMBs for cartilage repair was demonstrated *in vitro* in a cartilage-defect model. After 5 weeks of cultivation under chondrogenic conditions, CMBs fused and filled the defect, forming cartilage tissue that integrated mechanically and structurally with the surrounding native tissue. The next step will be to test the stability of the engineered tissue in animal models.

The investigators contend their simple 'biomimetic' approach might extend to the bioengineering of other tissues originating from mesenchymal condensation.

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Original article Bhumiratana, S. *et al.* Large, stratified, and mechanically functional human cartilage grown *in vitro* by mesenchymal condensation. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1324050111