Okayama University Research: Compound-Protein Combination Shows Promise for Arthritis Treatment

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(Okayama, 29 May 2015) Screening over 700 compounds identified a steroid hormone with a strong capability to promote the repair of damaged cartilage in joints.

Damaged cartilage leads to pain and reduced joint mobility in millions of arthritis sufferers worldwide, yet there remains a lack of effective treatments. Now Emilio Satoshi Hara and Takuo Kuboki and colleagues at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, the National Institutes of Health in the US and Harvard School of Dental Medicine have identified a steroid hormone that could help cartilage formation - 'chondrogenesis' – thereby regenerating the damaged joint tissue.

The researchers screened over 700 compounds with a chondrogenic cell line for substances that could induce chondrogenesis, and identified enhanced chondrogenesis in the presence of the steroid hormone fluocinolone acetonide (FA). The researchers then studied cultures of mesenchymal stem/progenitor cells (MSCs) that develop into bone and cartilage cells in the presence of FA and transforming growth factor beta 3 (TGF-β3).

In in vitro experiments, the researchers found that FA could strongly potentiated TGF-β3-associated chondrogenesis of MSCs, compared to the group stimulated only with TGF-β3. But FA alone suppressed chondrogenesis. In further experiments, the researchers highlighted the cellular pathways for the enhanced activity.

In addition, the researchers confirmed the effects of the combined compounds in experiments with mice. “The in vivo cartilage repair model confirmed that FA/TGF-β3 is uniquely able to promote cartilage repair,” report the researchers. They add that the combination could have potential for clinical applications based on the development of stem cells into cartilage cells.

Background
Chondrogenesis
The only cells that exist in healthy cartilage are chondrocytes. Previous efforts to promote chondrogenesis using growth factors, gene therapy and compounds have had limited success as the cartilage does not readily regenerate. Harnessing the ability to develop cartilage cells from stem cells offers a promising approach to aiding cartilage regeneration but has not yet been achieved.

Previous research has pointed towards transforming growth factor beta and insulin-like growth factors as the main contributors towards chondrogenesis. This suggests that combinations of some of these proteins would
enhance differentiation of human bone marrow stem/progenitor cells (hBMSCs) - the stem cells that develop into bone and cartilage cells. However, previous experiments that studied the effects of different combinations of these proteins revealed antagonistic effects on chondrogenesis. In order to overcome these antagonistic effects, in this investigation, the researchers hypothesized that small chemical compounds could enhance the activity of these growth factors, and therefore performed a screening of more than 700 compounds.

The screening tests
The researchers screened a Food and Drug Administration (FDA)-approved drug library containing 640 compounds and an orphan ligand library containing 84 compounds using a chondrogenic cell line. After adding the drugs to the cell cultures, they checked the activity of the gene promoter for collagen type II, which makes up the majority of the cartilage protein in the joints (Col2a1), as well as the activity of a marker gene of chondrocytes (Aggrecan), and an important regulator of chondrogenesis (Sox9).

In the first screening, they found 86 compounds that enhanced Col2a1 promoter, then they found 8 that regulated Aggrecan, but just one that upregulated Sox9 as well, that is, FA. FA is a glucocorticoid, a type of steroid hormone that takes its name from its steroid structure. Unlike some natural steroid hormones synthesised in the adrenal cortex, FA is a synthetic glucocorticoid, and was shown to have stronger effects in activating the cellular receptor for glucocorticoids.

Clinical use of glucocorticoids
Glucocorticoids are already used for numerous clinical applications. FA is currently mainly used for dermal, dental and ophthalmological prescriptions and triamcinolone acetonide (TA) and dexamethasone (DEX), which have similar molecular structures, have already been used in injections for the management of joint diseases. While glucocorticoid injections are widely used to treat rheumatoid arthritis and other joint diseases, they have been recognised to be harmful to cartilage over prolonged use, possibly due to inhibiting effects on the development of cartilage cells from stem cells. Since the researchers found that glucocorticoids with similar molecular structure have different effects on chondrogenesis, these results open new venues for further investigation of alternative glucocorticoids that may decrease cartilage damage even in long-term use.

Figure caption
Among glucocorticoids, FA/TGF-β3 is uniquely able to promote articular surface regeneration. Substantial cartilage repair of the knee joints in mice was observed only in the group transplanted with hBMSCs treated with FA/TGF-β3. Arrowheads show the borders of the surgical defect. The asterisk shows the regenerated superficial layer of the articular cartilage only in FA/TGF-β3 group. Arrows indicate articular surface damage in the groups that received TA/TGF-β3-treated hBMSCs.

Reference
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About Okayama University
Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Education House sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 14,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences. Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.
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