For immediate release: 30 May 2015

Okayama University research: Compound-protein combination shows promise for arthritis treatment

(Okayama, 30 May) Screening over 700 compounds reveals a steroid hormone with the capability to promote the repair of 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 and Takuo Kaboki and colleagues at Okayama University Graduate School of Medicine, the National Institutes of Health in the US and Harvard School of Dental Medicine identify a steroid hormone that could help cartilage development - ‘chondrogenesis’ – thereby regenerating the damaged joint tissue.

The researchers screened cultures of cartilage stem cells with over 700 compounds for substances associated with chondrogenesis, and identified enhancements to these substances in the presence of the steroid hormone fluocinolone acetonide (FA). The researchers then studied cultures of the stem cells that develop into bone and cartilage cells in cultures of FA and transforming growth factor beta 3 (TGF-β3). Previous studies have reported that TGF-β3 plays an important role in chondrogenesis, but antagonistic effects on the development and proliferation of cartilage cells have also been observed, particularly in the presence of certain other bioactive proteins.

In experiments in vitro the researchers found that both TGF-β3 and FA inhibit chondrogenesis, but when present together they upregulate both a key marker and a regulator for chondrocytes. Further experiments 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 some combination 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 to study the effects of different combinations of these proteins revealed antagonistic effects on chondrogenesis.

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. They checked the cultures of the compounds for the presence of the promoter for a gene of a type of collagen that makes up the majority of the cartilage protein in joints (Col2a1 promoter), as well as a known marker (Acan) and a known regulator of chondrocytes (Sox9).

They found 86 compounds that enhance Col2a1 promoter, 8 that regulated Acan but just one that upregulated Sox9 as well, that is, FA. FA is a glucocorticoid, a type of hormone that takes its name from its steroid structure, its role in glucose metabolism, and because it is synthesised in the adrenal cortex and plays an important.
Clinical use of glucocorticoids

Glucocorticoids are already used for clinical applications. FA is currently mainly used for dermal, dental and ophthalmological prescriptions and TA and DEX, which have similar structures, have already been used in injections for the management of joint diseases. While glucocorticoid injections are widely used to treat in rheumatoid arthritis and other joint diseases, they have been recognised as harmful to cartilage over prolonged use, possibly due to inhibiting effects on the development of cartilage cells from stem cells. Investigation of alternative glucocorticoids may decrease cartilage damage from long-term use.

The researchers found that FA/TMFB3 enhanced chondrogenesis by enhancing the activity of the mTORC1/AKT pathway. As AKT inhibitors have been used as a chemotherapeutic treatment for tumors, exploitation of these effects to treat arthritis will require caution.

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


DOI: 10.1002/jbmr.2502


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Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place 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.