Winter Quarter 5:1;2011

e-news

Comparative Orthopaedic Lab

"Finding a joint solution"

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Current Projects

- Intra-Articular Therapy for OA
- Subchondral Bone in OA
- Optimizing Allograft Tissue Preservation
- Biomarkers for Osteoarthritis
- Relationship of Vascular Disease with OA
- Pedicle Screw Fixation in Osteoporosis
- Clinical Evaluations of ACP
- Multiscale Modeling of OA
- *In vitro* Model of Traumatic Arthritis
- On-field Diagnosis of Meniscal Pathology
- Comparison of Suture Anchors
- Biologic Total Joint Arthroplasty

Last quarter's "top 5"

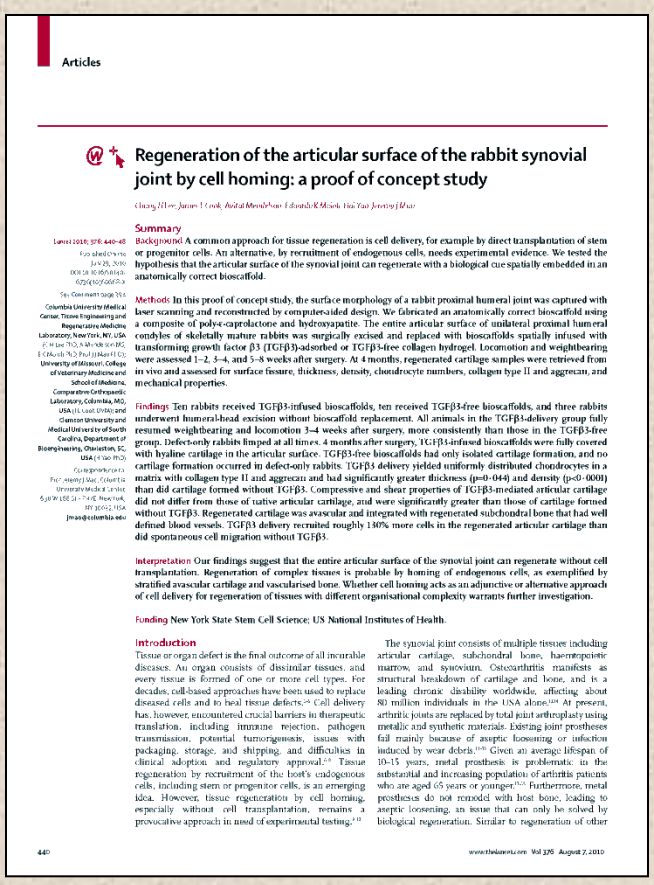
1. We received a very generous financial gift from ACell, Inc that will support our personnel
2. Dr. Vladimir Bobic visited the COL to work on our *Subchondral Bone in OA* collaboration
3. Dr. Steven Arnoczky visited the COL to give the Niemeyer Lecture and DOS Grand Rounds
4. Our *Biologic Joint Replacement* research made international news
5. Drs. Cook and Bal were selected for the One Health Initiative Advisory Board

Biologic Joint Replacement work published in *The Lancet*

The COL participated as part of a research team that created complete joint surfaces in rabbits using a biological "scaffold". The study was led by Jeremy Mao of Columbia University.

The scaffold was implanted using the surgical technique currently used for shoulder replacement in humans. The scaffolds are infused with a growth factor, which encourages the host's own cells to make new cartilage and bone. This is the first time this type of cartilage regeneration has ever been reported using this type of scaffold.

The study found that the rabbits given the infused scaffolds resumed weight-bearing and functional use of their limbs faster and more consistently than those without. Four months later, cartilage had formed in the scaffolds creating a new, functional cartilage surface for the humeral head. The team observed no complications or adverse events after surgery; the new tissue regeneration was associated with excellent limb use and shoulder health, indicating the procedure is both safe and effective. The next step toward FDA approval and clinical use is to study the technique in larger animals.



Articles

Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study

Summary

Background A common approach for tissue regeneration is cell delivery, for example by direct transplantation of stem or progenitor cells. An alternative, by recruitment of endogenous cells, needs experimental evidence. We tested the hypothesis that the articular surface of the synovial joint can regenerate with a biological cue spatially embedded in an anatomically correct bioscaffold.

Methods In this proof of concept study, the surface morphology of a rabbit proximal humeral joint was captured with laser scanning and reconstructed by computer-aided design. We fabricated an anatomically correct bioscaffold using a composite of poly-ε-caprolactone and hydroxyapatite. The entire articular surface of unilateral proximal humeral condyles of skeletally mature rabbits was surgically excised and replaced with bioscaffolds spatially infused with transforming growth factor β3 (TGFβ3)-adsorbed or TGFβ3-free collagen hydrogel. Locomotion and weightbearing were assessed 1–2, 3–4, and 5–8 weeks after surgery. At 4 months, regenerated cartilage samples were retrieved from in vivo and assessed for surface fissure, thickness, density, chondrocyte numbers, collagen type II and aggrecan, and mechanical properties.

Findings Ten rabbits received TGFβ3-infused bioscaffolds, ten received TGFβ3-free bioscaffolds, and three rabbits underwent humeral-head excision without bioscaffold replacement. All animals in the TGFβ3-delivery group fully resumed weightbearing and locomotion 3–4 weeks after surgery, more consistently than those in the TGFβ3-free group. Defect-only rabbits limped at all times. 4 months after surgery, TGFβ3-infused bioscaffolds were fully covered with hyaline cartilage in the articular surface. TGFβ3-free bioscaffolds had only isolated cartilage formation, and no cartilage formation occurred in defect-only rabbits. TGFβ3 delivery yielded uniformly distributed chondrocytes in a matrix with collagen type II and aggrecan and had significantly greater thickness (p=0·044) and density (p<0·0001) than did cartilage formed without TGFβ3. Compressive and shear properties of TGFβ3-mediated articular cartilage did not differ from those of native articular cartilage, and were significantly greater than those of cartilage formed without TGFβ3. Regenerated cartilage was avascular and integrated with regenerated subchondral bone that had well defined blood vessels. TGFβ3 delivery recruited roughly 180% more cells in the regenerated articular cartilage than did spontaneous cell migration without TGFβ3.

Interpretation Our findings suggest that the entire articular surface of the synovial joint can regenerate without cell transplantation. Regeneration of complex tissues is probable by homing of endogenous cells, as exemplified by stratified avascular cartilage and vascularised bone. Whether cell homing acts as an adjunctive or alternative approach of cell delivery for regeneration of tissues with different organisational complexity warrants further investigation.

Funding New York State Stem Cell Science; US National Institutes of Health.

Introduction

Tissue or organ defect is the final outcome of all incurable diseases. An organ consists of dissimilar tissues, and every tissue is formed of one or more cell types. For decades, cell-based approaches have been used to replace diseased cells and to heal tissue defects.[1–3] Cell delivery has, however, encountered crucial barriers in therapeutic translation, including immune rejection, pathogen transmission, potential tumorigenesis, issues with packaging, storage, and shipping, and difficulties in clinical adoption and regulatory approval.[2,3] Tissue regeneration by recruitment of the host's endogenous cells, including stem or progenitor cells, is an emerging idea. However, tissue regeneration by cell homing, especially without cell transplantation, remains a provocative approach in need of experimental testing.[4–11]

The synovial joint consists of multiple tissues including articular cartilage, subchondral bone, haemtopoietic marrow, and synovium. Osteoarthritis manifests as structural breakdown of cartilage and bone, and is a leading chronic disability worldwide, affecting about 80 million individuals in the USA alone.[12,13] At present, arthritic joints are replaced by total joint arthroplasty using metallic and synthetic materials. Existing joint prostheses fail mainly because of aseptic loosening or infection induced by wear debris.[14,15] Given an average lifespan of 10–15 years, metal prosthesis is problematic in the substantial and increasing population of arthritis patients who are aged ≤5 years or younger.[14,15] Furthermore, metal prostheses do not remodel with host bone, leading to aseptic loosening, an issue that can only be solved by biological regeneration. Similar to regeneration of other

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Recent Pubs

1. Cook JL, et al. Proposed definitions and criteria for reporting time frame, outcome, and complications for orthopaedic studies. Vet Surg 2010
2. Lee CH, Cook JL, et al. Regeneration of articular surface of a synovial joint by cell homing. The Lancet 2010
3. Kuroki K, et al. Expression of Toll-like receptors 2 and 4 in stifle joint synovial tissues of dogs with or without OA. Am J Vet Res 2010
4. Cook JL, et al. The OARSI histopathology initiative – Histopathological assessments of osteoarthritis in the dog. OA & Cartilage 2010
5. Breshears LA, et al. The effect of uniaxial cyclic tensile load on gene expression in canine CCL ligamentocytes. Vet Surg 2010
6. Bian L, et al. Dynamic mechanical loading enhances functional properties of tissue engineered cartilage. Tissue Eng 2010
7. Arnoczky SP, Cook JL, et al. Translational models for studying meniscal repair and replacement. Tissue Eng 2010
8. Bal BS, et al. In vivo outcomes of tissue engineered osteochondral grafts. J Biomed Mater Res 2010
9. Breshears LA, et al. Detection and evaluation of MMPs involved in cruciate ligament disease in dogs. Vet Surg 2010.
10. Fox DB, et al. Effects of growth factors on synovial fibroblasts seeded on synthetic scaffolds for meniscal engineering. Res Vet Sci. 2010