What’s New in Surgical Restoration of Articular Cartilage

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Articular Cartilage

- Allows Nearly Frictionless Motion
- Lubrication of Joint
- Transmits & Distributes Forces

Articular Cartilage Composition

- Water (65 – 80 %)
- Collagen Type II (10 – 20 %)
- Aggrecan (5 %)
Articular Cartilage

- Avascular
- Aneural
- No Lymphatics

Because of this, articular cartilage has a limited capacity for intrinsic healing and repair.

Is This True ???
Cartilage Injury

Typically Trauma

- Rotational force in direct trauma is the most common cause of injury
- In most cases, injury is in weight-bearing area of articular cartilage
- Usually in the medial compartment (4X – lateral side)
- More often seen with other traumatic injuries to the knee, such as ligamentous or meniscal damage
Goals of Cartilage Repair

- Restore smooth articular cartilage surface
- Relieve patient's symptoms and improve function
- Match biomechanical and biochemical properties of normal hyaline cartilage
- Prevent or slow progression of focal chondral injury to end-stage arthritis
The objective of Microfracture is to bring marrow–derived stem cells into the lesion to create a repair tissue.

Articular Chondrocytes are not the primary repair cell
Microfracture repair tissue is predominantly fibrocartilage (Type I collagen)
Repair tissue often lacks long-term durability, since it does not have the appropriate mechanical or biological properties
Repair tissue begins to deteriorate after about 1 year
ACI

Objectives of ACI is to deliver viable chondrocytes to regenerate cartilage tissue in a lesion.

Two surgical procedures are required; a harvesting surgery and an implantation surgery following cell culture for cell count expansion.

- Suture fixation of membrane is technically demanding.
- High cost (~$25,000)

OATS
Objective of OATS/Mosaicplasty technique is to restore the articulating surface with a more or less normal osteochondral structure.

Harvest site morbidity can be extensive, especially with mosaicplasty.

Procedure can be technically demanding.

Repair tissue in the spaces between plugs is fibrocartilage.

Emerging Competitive Products
Juvenile Cartilage

- Particulated Juvenile Cartilage
- 1 Month shelf life
- $4,500 per unit
- Refrigerated Product

Freeze-Dried Cartilage

- Augment to Microfracture
- Mix with PRP and Seal with Fibrin Glue
- Collagen mostly Type II
Allograft Disc

- Cartilage Bone Disc
- Frozen Product
- Two year shelf life
- Cut to Size
- $5,000 per piece

What's New ???
One Step Stem Cell Procedure

- Use Bone Marrow Concentrate for Stem Cells
- With or Without Membrane
- Covered with Tisseel
One Step Stem Cell Procedure

Cartilage Processor

Point-of-Care Cartilage Autograft Processor
Cartilage Processor

- Conveniently Powered by Surgical Drill

Cartilage Processor

- Precision in Size Reduction and Separation

Cartilage Processor

- Rapid Increase in Surface Area and Chondrocyte Exposure
Cartilage Processor

- Creates autologous cartilage particles smaller than 1mm in size
- Can produce a volume of cartilage graft sufficient to apply to a 4cm squared defect
- Graft produced in 2 minutes
- Utilizes standard surgical drill
- Maintains a high degree of cell viability & bioactivity
- Sterile, disposable

One Year Post-op

Viable Allograft Cartilage
Viable Allograft Cartilage

- Allograft cartilage particles <1mm
- Provides viable chondrocytes capable of migrating, proliferating and producing neocartilage tissue matrix components
- Enzyme exposure during processing to improve diffusion of factors and increase chondrocyte exposure
- Cryopreserved to increase shelf life

Scientific Rationale

- ARE WE CRAZY ?????
Scientific Rationale

What is driving this sudden appearance of viable cell allograft products?

- Existing technologies
  - High cost (ACI)
  - Technically difficult (OATS)
  - Patient improvements degrade over time and bridges may be burned (MFx)
- The regulatory hurdle for products needing FDA approval is high
- New science has challenged conventional wisdom regarding cartilage tissue, cartilage grafting, and cryopreservation

Scientific Rationale

- The conventional notion
  - Cartilage is a structural, non-dynamic tissue in which chondrocytes are “trapped”.
  - Limited regenerative capacity – as if chondrocytes are not looking for something to do, they’re looking for a reason to die
  - This conclusion seems reasonable given that lesions on articular surfaces are not expected to heal, but rather to progress to chronic degeneration

Scientific Rationale

- The historically dominant cartilage repair technologies are consistent with the conventional notion
  - Debridement/Chondroplasty
    - Clean up and smoothen out the articular surface to improve sliding, while disturbing the chondrocytes as little as possible
  - ACI (autologous chondrocyte implantation)
    - Liberates the chondrocytes entirely from their pericellular “prison”, so they can proliferate, migrate, regenerate
  - Microfracture (marrow stimulation)
    - Get the chondrocytes out of the way entirely, and let stem cells do the work
  - OATS
    - Replace the articular surface with undisturbed, fully formed articular cartilage; no need for the chondrocytes to do anything
Scientific Rationale

- The new paradigm
  - Cartilage tissue is suitable for void filling and provides scaffolding and growth factors
  - Chondrocytes are capable of migrating, proliferating, and producing neo-cartilage tissue matrix components
- If you...
  - Position the chondrocytes near the tissue surface (or vice versa)
    - Reduces the distance needed to migrate out of the tissue, and increases exposure to external stimulating factors
  - Provide progenitor cells and/or growth factors (BMAC, PRP) as part of the surgical technique
    - To provide additional stimulus for neo-cartilage matrix component (e.g., GAG) production by chondrocytes

Cartilage Processor

- Following Particulation:
  - Chondrocyte Viability Remains high
  - Chondrocytes Can Produce Matrix Components
  - Chondrocytes Can Proliferate and Occupy the New Matrix

Scientific Rationale

- Chondrocyte viability remains >90%
  - Qualitative Live/Dead Assay (Green = live cell)

SEM showing cells at fragment surface
Scientific Rationale

- Chondrocyte viability remains >90%
- Quantitative cell viability assay

![Graph showing cell viability before and after mincing]

Scientific Rationale

- Chondrocytes produce matrix components
- Quantitative GAG assay during 4 weeks culture

![Graph showing GAG concentration over weeks]

Scientific Rationale

- Chondrocytes proliferate and occupy new matrix
- Fluorescent microscopy showing chondrocyte outgrowth and particle fusion

![Images showing outgrowth and particle fusion]
Viable Allograft Cartilage

- The enzyme exposure process...
  - Promotes earlier, more robust chondrocyte bioactivity
  - Following cryopreservation...
    - The chondrocytes rapidly recover to bioactivity levels comparable to non-cryopreserved fresh allograft tissue
Viable cartilage allograft...
  - Is immunologically safe to implant

Scientific Rationale

- Enzyme exposure process
  - Improves chondrocyte outgrowth from the fragments
  - Improves particle fusion
- Cryopreservation
  - Chondrocytes demonstrate robust outgrowth from fragments following cryopreservation
  - Outgrowth from enzyme exposed tissue occurs faster than from non-exposed tissue (both cryopreserved)
  - Bioactivity of cryopreserved tissue is low initially after thawing, but rapidly recovers

Scientific Rationale

Outgrowth results with human tissue

![Unsorted and treated human cartilage fragments embedded in fibrin glue](image)
(A) Unsorted cartilage fragment at 0. (B) Unsorted cartilage fragment at 6 wk of culture. (C) Treated cartilage fragment at 0. (D) Treated cartilage fragment at 6 wk of culture. The f corresponds to fibrin. The arrow shows cellular outgrowth.
Scientific Rationale
Cryopreservation can be utilized to increase the shelf life of enzyme-exposed allograft tissue.

Chondrocytes demonstrate robust outgrowth from enzyme-treated fragments following cryopreservation.

Scientific Rationale
Human cartilage fragments can be cryopreserved up to at least 6 months and still demonstrate robust outgrowth and matrix production similar to non-cryopreserved cells.

Histological section of adult human cartilage fragments stained with H&E. (A) Fresh fragments-uncultured. (B) Fresh fragments-8 weeks of culture. (C) 12 weeks cryopreserved-8 weeks of culture. (D) 24 weeks cryopreserved-8 weeks of culture.

Where Do We Go From Here?
Maybe Cartilage Is Repairable?

On The Horizon

Bioscaffolds & Gene Therapy
Thank You !!!!