Overview of Module 3, Part I

Module 3, Lecture 6

20.109 Spring 2008

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Topics for Lecture 6

• First, a presentation from Atissa Banuazizi
• Review of big picture:
  – brief module 3 overview
  – cartilage tissue engineering concepts
• What does each day of module 3 contribute?
  (start today, finish next time)
Overall goals of Module 3

• Design experiment to study effects of local environment on cell de-differentiation
  – cell: primary chondrocytes, \textit{in vitro} culture
  – local environment: material properties, cell density, culture medium composition
  – effects: viability, morphology, collagen II:I ratio

• Grander purpose: discovering factors that maintain chondrocyte phenotype has utility for cartilage tissue engineering
  – conditions for \textit{ex vivo} cell expansion
  – conditions for bulk cartilage production
Therapies for damaged tissue

• All tissues have limited regeneration
  – e.g., skin: shallow vs. deep cuts

• Replace with tissue graft
  – donor tissue: limited supply, immune response
  – autologous tissue: donor site damage

• Replace with permanent synthetic substitute (not strictly speaking TE)
  – inflammatory response (chronic)
  – mis-match with natural tissue properties
  – multiple replacements/surgeries

• A new strategy: promote regeneration of ~native tissue = tissue engineering
Potential components for cartilage TE

**scaffold/matrix**
- usually degradable, porous
- hydrogel (e.g., alginate)

**soluble factors**
- TGF, BMP, others

**cells**
- stem cells, or
- chondrocytes

integrated implantable
or injectable device
Roles of components in cartilage TE

• Cells
  – contribute to tissue reconstruction (secrete matrix)

• Cytokines
  – stimulate chondrocyte production of fresh matrix
  – simulate stem cell differentiation to chondrocytes
  – attract stem cells to wound site (chemokines)

• Scaffold
  – retain cells and cytokines in needed location
  – provide mechanical support and structure for new tissue

• Any component may be engineered!
  – cells: genetically engineered to express a needed protein
  – cytokine proteins: engineered to have longer half-lives
  – scaffold: engineered to have specific chemical, mechanical, and biological properties that mimic cartilage
    e.g., cell-adhesive peptide sequences
Cartilage structure and growth

• Cartilage structure
  – chondrocytes make collagen (CN), proteoglycans (PG)
  – CN forms covalently cross-linked fibers
  – PG promote influx of water/ions

• Natural cartilage growth
  – very slow turnover of collagen in absence of damage
  – even if damaged, little new extracellular matrix forms
  – atypical wound healing partly because avascular
Cartilage replacement

• Specific requirements for replacement
  – sustain compressive loads (done by PG, water)
  – lubricate joint (done by PG, synovial fluid)
  – sustain tensile stresses (done by collagen)

• Ideal replacement has collagen/proteoglycan balance of native tissue
  – option 1: promote native tissue regeneration *in vivo*
  – option 2: grow native tissue-like construct *in vitro*, implant it
  – either option may involve cells and/or scaffold and/or cytokines


What can we learn from culture models?

- What cell/cytokine/scaffold/culture combinations stimulate or sustain the chondrocyte phenotype?
- Knowledge can feed into multiple kinds of therapies:

**Cell transplantation therapy**

1. Biopsy: a few chondrocytes
2. Inject many cells into patient
3. Grow fresh tissue *in vivo*

**Cartilage replacement therapy**

1. Put together cells, scaffold, cytokines
2. Grow cartilage-like tissue *in vitro*
3. Directly implant into patient

... and many other potential alternatives!