BIOMATERIALS-TISSUE INTERACTIONS:
“Tools” for Understanding the Molecular, Cellular, and Physiological, Bases of the Tissue Response to Implants

M. Spector, Ph.D. and I.V. Yannas, Ph.D.

Tissue* + Biomaterial**
Cell + Matrix**

* Structure comprising cells of the same type
** Solid surface
CELL-MATRIX INTERACTIONS

**In Tissue**
Cell + Extracellular Matrix

**In Tissue Engineering Scaffolds**
Cell + Biomaterial Scaffold

CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

- Control Volume
- Unit Cell Processes
- Types of Tissues
- Tissue Formation and Remodeling *In Vitro*
- Wound Healing *In Vivo*
Cell

Matrix

Extracellular

Articular Cartilage

40min

Chondrocytes (P2 Canine) in a Type I Collagen-GAG Scaffold

Image removed due to copyright considerations.

Source: B. Kinner
UNIT CELL PROCESSES
Concept of a “Control Volume” around a Cell

Soluble Regulator A

Cell + Matrix (Regulator) → Product + Soluble Regulator B

“Control Volume”

UNIT CELL PROCESSES
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“Control Volume”

Mechanical Loading (Strain)
CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

- Control Volume
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UNIT CELL PROCESSES

- Mitosis
- Migration
- Synthesis
- Contraction
- Endocytosis
- Exocytosis
COLLAGEN-GAG MATRICES: MODEL BIOMATERIALS
(ANALOGS OF EXTRACELLULAR MATRIX)
Investigation of cell interactions (UCPs) \textit{in vitro}

- Type I (bovine and porcine)
- Type II (porcine)
- Chondroitin 6-sulfate

\textbf{IV Yannas, et al.} PNAS, 1989

\begin{itemize}
  \item Freeze-dried
  \item Dehydrothermally cross-linked
  \item Additional cross-linking
\end{itemize}

\begin{center}
\begin{tabular}{|c|c|}
\hline
1mm & 500\,\mu m \\
\hline
\end{tabular}
\end{center}

CELL –MATRIX INTERACTIONS WITH
COLLAGEN-GAG MATRICES \textit{IN VITRO}

\begin{itemize}
  \item Can provide insights into interrelationships among cell processes.
    \begin{itemize}
      \item How do mitosis and synthesis interrelate?
      \item How do mitosis and synthesis relate to contraction?
      \item How does migration relate to contraction?
    \end{itemize}
  \item Can provide insights into cell behavior \textit{in vivo}.
  \item Can provide insights into scaffold composition and structure for improved performance in regenerative medicine.
\end{itemize}
Chondrocytes (Passage 2 Canine) in a Type I Collagen-GAG Matrix

Live cell imaging for a period of 5 hours.

Image removed due to copyright considerations.

J. Cheng

CELL–MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction
Chondrocyte (P2 Canine) in a Type I Collagen-GAG Matrix: Mitosis

<table>
<thead>
<tr>
<th>Day</th>
<th>DNA (ug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

**Effects of Cross-Linking on Chondrocyte Proliferation in Collagen-GAG Matrices**

CELL - MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction

40min  
Chondrocytes (P2 Canine) in a Type I Collagen-GAG Matrix: Migration and Contraction

B. Kinner
CELL –MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction

Effects of Cross-Linking on Chondrocyte Biosynthesis in Collagen-GAG Matrices

CELL –MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction

Chondrocytes (P2 Canine) in a Type I Collagen-GAG Matrix: Contraction

Image removed due to copyright considerations.

40 min

B Kinner
**Cell-Mediated Contraction**

Non-Seeded: 8 days  
Cell-Seeded: 8 days

**Non-Seeded and Cell-Seeded Collagen-GAG Scaffolds**

Mean ± SEM

Adult canine articular chondrocytes (passage 3) contract a type I collagen-GAG matrix, reflected in the decrease in diameter.


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Human Articular Chondrocytes in Monolayer Culture
IH - Green: \( \alpha \)-smooth muscle actin; Orange: type II collagen

Image removed due to copyright considerations.

Chondrocytes express the gene for \( \alpha \)-smooth muscle actin and this enables them to contract

B. Kinner, et al., JOR 2001;19:233

\( \alpha \)-Smooth Muscle Actin Immunohistochemistry of Human Articular Cartilage

Image removed due to copyright considerations.

Kim and Spector, JOR 2000;18:749
MUSCULOSKELETAL CELLS THAT CAN EXPRESS $\alpha$-SMOOTH MUSCLE ACTIN AND CAN CONTRACT

- Articular chondrocyte
- Osteoblast
- Meniscus fibroblast and fibrochondrocyte
- Intervertebral disc fibroblast and fibrochondrocyte
- Ligament fibroblast
- Tendon fibroblast
- Synovial cell
- Mesenchymal stem cell


POSSIBLE ROLES FOR $\alpha$-SMOOTH MUSCLE ACTIN-ENABLED CONTRACTION

Musculoskeletal Connective Tissue Cells

- Tissue engineering: Contracture of scaffolds
- Healing: Closure of wounds (skin wounds and bone fractures)
- Disease processes: Contracture (Dupuytren’s)
- Tissue formation and remodeling: Modeling of ECM architecture (e.g., crimp in ligament/tendon?)
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TYPES OF TISSUES

Which Tissues Can Regenerate Spontaneously?

<table>
<thead>
<tr>
<th>Connective Tissues</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articular Cartilage, Ligament, Intervertebral Disc, Others</td>
<td>v</td>
<td></td>
</tr>
<tr>
<td>Epithelia (e.g., epidermis)</td>
<td>v</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac, Skeletal</td>
<td></td>
<td>v</td>
</tr>
<tr>
<td>Smooth</td>
<td>v</td>
<td></td>
</tr>
<tr>
<td>Nerve</td>
<td></td>
<td>v</td>
</tr>
</tbody>
</table>
BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

Connective Tissue
Epithelia
Muscle
Nerve

UNIT CELL PROCESSES
Concept of a “Control Volume” around a Cell

Cell + Matrix + Product

Soluble Regulator A
Mechanical Loading (Strain)

“Control Volume”

Soluble Regulator B
BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

Connective Tissue Epithelia Muscle Nerve Adhesion Protein Collagen Biomaterial

Integrin
“UNIT CELL PROCESSES”

Cell + Matrix

Connective Tissue Epithelium Muscle Nerve

Mitosis Synthesis Migration Contraction Endocytosis Exocytosis

Cell + Matrix

Connective Tissue Epithelium Muscle Nerve

Mitosis Synthesis Migration Contraction Endocytosis Exocytosis

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"UNIT CELL PROCESSES"

Regulator

UCP

Cell + Matrix → Product + Regulator

Connective Tissue Epithelia Muscle Nerve Adhesion Protein Collagen Biomaterial Integrin Mitosis Synthesis Migration Contraction Endocytosis Exocytosis Cytokines (Growth Factors)

"UNIT CELL PROCESSES"

Regulator

Mechanical Force (Strain)

UCP

Cell + Matrix → Product + Regulator

Connective Tissue Epithelia Muscle Nerve Adhesion Protein Collagen Biomaterial Integrin Mitosis Synthesis Migration Contraction Endocytosis Exocytosis Cytokines (Growth Factors)
"UNIT CELL PROCESSES"

Regulator **Mechanical Force (Strain)**  

Cell + Matrix → Product + Regulator

- Connective Tissue
- Epithelia
- Muscle
- Nerve
- Adhesion Protein Collagen Biomaterial Integrin

- Mitosis Synthesis Migration Contraction Endocytosis Exocytosis

- Cytokines (Growth Factors)

- Integrin

- Matrix strain (contracture/shrinkage)

- Cytokines (Growth Factors)
“UNIT CELL PROCESSES”

TGF-β1

Contraction

Fibroblast + Collagen → Contracture + Reg.

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TISSUE FORMATION AND REMODELING

IN VITRO

Canine chondrocytes grown in a type II collagen-GAG scaffold for 2 weeks. (Safranin O stain for GAGs)

N. Veilleux

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WOUND HEALING
Roots of Tissue Engineering

- Injury
- Inflammation (Vascularized tissue)
- Reparative Process
  - Regeneration*
    - CT: bone
    - Ep: epidermis
    - Muscle: smooth
  - Repair (Scar)
    - CT: cartilage
    - Nerve
    - Muscle: cardiac, skel.

4 Tissue Categories
- Connective Tissue
- Epithelium
- Nerve
- Muscle

RESPONSE TO IMPLANTS: WOUND HEALING

- Surgical Implantation
- Acute Inflammation
  - Vascular Response
    - Clotting
    - Phagocytosis
    - Neovascularization
    - New Collagen Synthesis
  - Granulation Tissue
- Tissue of Labile and Stable Cells
- Framework Intact
- Regen. (incorp. of implant)
- Chronic Inflammation
- Tissue of Permanent Cells
- Framework Destroyed
- Scarring (fibrous encapsulation; synovium)
- Chronic Inflammation
- Scarring (fibrous encapsulation; synovium)

Chronic Inflammation