Interactions of cells with their environment;
Engineering materials with biological recognition

Last time:
Polyelectrolyte hydrogel swelling thermodynamics
Applications of polyelectrolyte hydrogels: BioMEMS and drug delivery

Today:
Biological recognition in vivo
Engineering biological recognition of biomaterials: controlling cell adhesion, migration, and cytokine signaling

Reading:


Supplementary Reading:

ANNOUNCEMENTS:
In situ formability: example: ‘printable’ gels

Collagen printed on an agarose gel substrate:

Formability of hydrogels for tissue engineering

Hydrogel precursor

Dissolve microspheres

Poly(methyl methacrylate) microspheres

Colloidal crystal template

Filling of the interstices with a solidifying matrix or with nanoparticles

Structured porous replica

Ordered porous structure

Tissue engineering

Scaffolds with ordered, highly interconnected porosity

Brightfield image:

PEG hydrogel scaffolds

Confocal fluorescence:

Degradable hydrogels: degradation by hydrolysis of cross-links (mechanism I)

1. Most common route to degradable gels:

2. Physical gels:
   - Thermal breakdown of noncovalent junctions
   - (Usually relatively rapid)
Dextran-based degradable hydrogels: degradation by hydrolysis of cross-links

Swelling behavior of dex-HEMA (—), dex-lactate-HEMA (—–) and dex-lactate$_2$-HEMA (—–) hydrogels in aqueous solution (pH 7.2, 37°C). The initial water content of the hydrogels was 80%, the degree of methacryloyl substitution was approximately 6.

Figure by MIT OCW.
Tissue barriers/conformal coatings
Applications: tissue barriers

Tissue barriers and conformal coatings

1) Blood vessel

2) Photoinitiator solution

3) Vessel

Two Layers of Hydrogel Formed in Situ

Figure by MIT OCW.

(After An and Hubbell 2000)
Engineering Biological Recognition in Synthetic Materials
Signals from extracellular environment:

1. **Insoluble factors**
   - e.g., adhesion proteins + receptors on other cells

2. **Mechanical props of local environment**

3. **Soluble factors**
   - e.g., cytokines, chemokines

**Cell integrates total signaling inputs for decisions about fate**

**Enzyme/cytokine secretion**
Incorporation of ECM signals in biomaterials

1. Cell adhesion/migration
2. Matrix remodeling
3. Cytokine signaling

Peptides or proteins tethered to biomaterial surface, examples of (1) and (3)

(2) Matrix remodeling:

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The insoluble surroundings of the cell:
Functions of the native extracellular matrix (ECM):

- **Mechanical support**
- **Cues for cell survival/function**
  - Anchorage-dependent cell growth
  - Differentiation cues
- **Organization of tissue**
Collagen and Adhesions Proteins: Structure and Function

• Lodish et al. *Molecular Cell Biology*
Cell adhesion

Controlling cell attachment and migration

Structure of integrins:

Actin filaments (cytoskeleton)

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Adhesive interactions can play multiple roles simultaneously: supporting adhesion, delivery of biochemical signals, or delivering biomechanical signals.

Signaling may be regulated by physical distribution of adhesion receptors.
Cells sense and respond to the stiffness of their substrate

(Discher, Janmey, Wang *Science* **310** 1139-1143 (2005))
Cell adhesion on biomaterials:
Cell responses to non-biological, synthetic biomaterials

1. Protein adsorption
2. Denaturation (unfolding)?
3. Cell responses to expected and unexpected epitopes
4. Reorganization?
   - Vroman effect: protein exchange

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Control of cell attachment by mechanical properties of substrate

Polyelectrolyte multilayers (Rubner lab MIT):

Biomacromolecules

No cell attachment

Strong cell spreading

Cell must be capable of generating traction

Figure by MIT OCW.
Controlling cell response to biomaterials by building in ECM cues on a ‘blank slate’ background
Design of protein adsorption-resistant surfaces
Design of protein adsorption-resistant surfaces
Limiting nonspecific cell adhesion

Methyl methacrylate

Poly(ethylene glycol) methacrylates

PMMA
Tailoring cell adhesion on biomaterials via immobilized ligands

**Peptide**  integrin-binding GRGDSP sequence

**PEO**  short 6-9 unit side chains for protein resistance

**PMMA**  backbone anchors hydrophilic side chains
Peptides used to modulate cell adhesion on biomaterials

<table>
<thead>
<tr>
<th>Peptide sequence</th>
<th>Derived from</th>
<th>Conjugate receptor</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKVAV</td>
<td>Laminin α-chain</td>
<td>LBP110 (110 KDa laminin binding protein)</td>
<td>Cell-ECM adhesion</td>
</tr>
<tr>
<td>RGD</td>
<td>Laminin α-chain, fibronectin, collagen</td>
<td>Multiple integrins</td>
<td>Cell-ECM adhesion</td>
</tr>
<tr>
<td>YIGSR</td>
<td>Laminin β1-chain</td>
<td>α₁β₁ and α₃β₁ integrins</td>
<td>Cell-ECM adhesion</td>
</tr>
<tr>
<td>RNIAEIIKDI</td>
<td>Laminin γ-chain</td>
<td>unknown</td>
<td>Cell-ECM adhesion</td>
</tr>
<tr>
<td>HAV</td>
<td>N-cadherin</td>
<td>N-cadherin</td>
<td>Cell-cell adhesion</td>
</tr>
<tr>
<td>DGEA</td>
<td>Type I collagen</td>
<td>α₂β₁ integrin</td>
<td>Cell-ECM adhesion</td>
</tr>
<tr>
<td>VAPG</td>
<td>Elastase</td>
<td>Elastase receptor</td>
<td>Cell-ECM adhesion</td>
</tr>
<tr>
<td>KQAGDV</td>
<td>Fibrinogen γ-chain</td>
<td>β₃ integrins</td>
<td>Cell-ECM adhesion</td>
</tr>
</tbody>
</table>

- Peptides more robust than intact proteins
- $K_D$ of R-L binding usually significantly reduced:
  - e.g. RGD vs.
  - FN $K_D$ 1000-fold lower for peptide
Cell responses to RGD

Fraction Seeded Cells Adhere

0 0.1 0.2 0.3 0.4 0.5

GRGDSP

GRGESP

ADHESION NOT MEDIATED BY PROTEIN FROM SERUM BINDING TO PEPTIDE (CONTROL)

COMPETITION FOR RECEPTORS LEADS TO CELL DETACHMENT

Tethered RGD

soluble RGD

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Cells respond to control of ligand density at the surface


Cells respond to control of ligand density at the surface

Cells too strongly adherent to release and extend filipodia

Cells too weakly adherent; no traction for mechanical forces
Further Reading