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


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

Collagen printed on an agarose gel substrate:

Formability of hydrogels for tissue engineering


Poly(methyl methacrylate) microspheres

Hydrogel precursor

Dissolve microspheres

Ordered porous structure

Tissue engineering

Scaffolds with ordered, highly interconnected porosity

PEG hydrogel scaffolds

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

Swelling behavior of dex-HEMA (---), dex-lactate-HEMA (----) and dex-lactate2-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.
Tissue barriers/conformal coatings
Conformal coatings

Applications: tissue barriers

Tissue barriers and conformal coatings

1) Blood vessel
   - Adsorbed layer of photoinitiator
   - Photoinitiator solution

2) Green laser
   - PEG-diacrylate 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
Interactions of cells with their environment

Signals from extracellular environment:
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:
The insoluble surroundings of the cell:
Functions of the native extracellular matrix (ECM):
Collagen and Adhesions Proteins: Structure and Function

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

Controlling cell attachment and migration

Actin filaments (cytoskeleton)

integrin

\[ \alpha \quad \beta \]

\[ \text{Ca}^{++} \quad \text{Ca}^{++} \quad \text{Ca}^{++} \quad \text{Ca}^{++} \quad \text{Ca}^{++} \quad \text{Ca}^{++} \]

(Extracellular space)

ECM fiber

Adhesion protein

Structure of integrins:

Figure by MIT OCW.
Adhesive interactions can play multiple roles simultaneously: supporting adhesion, delivery of biochemical signals, or delivering biomechanical signals.
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
Control of cell attachment by mechanical properties of substrate

Polyelectrolyte multilayers (Rubner lab MIT):

Biomacromolecules | No cell attachment | Strong cell spreading

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>
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<tr>
<td>RGD</td>
<td>Laminin α-chain, fibronectin, collagen</td>
<td>Multiple integrins</td>
<td>Cell-ECM adhesion</td>
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<tr>
<td>YIGSR</td>
<td>Laminin β1-chain</td>
<td>α₁β₁ and α₃β₁ integrins</td>
<td>Cell-ECM adhesion</td>
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<td>RNIAEIKDI</td>
<td>Laminin γ-chain</td>
<td>unknown</td>
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<td>HAV</td>
<td>N-cadherin</td>
<td>N-cadherin</td>
<td>Cell-cell adhesion</td>
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<td>DGEA</td>
<td>Type I collagen</td>
<td>α₂β₁ integrin</td>
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<td>VAPG</td>
<td>Elastase</td>
<td>Elastase receptor</td>
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<tr>
<td>KQAGDV</td>
<td>Fibrinogen γ-chain</td>
<td>β₃ integrins</td>
<td>Cell-ECM adhesion</td>
</tr>
</tbody>
</table>
Cell responses to RGD

Fraction Seeded Cells Adhere

GRGDSP

GRGESP

Tethered RGD

+ soluble RGD
Cells respond to control of ligand density at the surface


Cells respond to control of ligand density at the surface

![Graph showing the relationship between ligand density and cell speed. The graph illustrates that cells have optimal speed at a medium ligand density. At very low ligand density, cells are too weakly adherent and do not extend filopodia. At very high ligand density, cells are too strongly adherent and release for mechanical forces.]
Further Reading