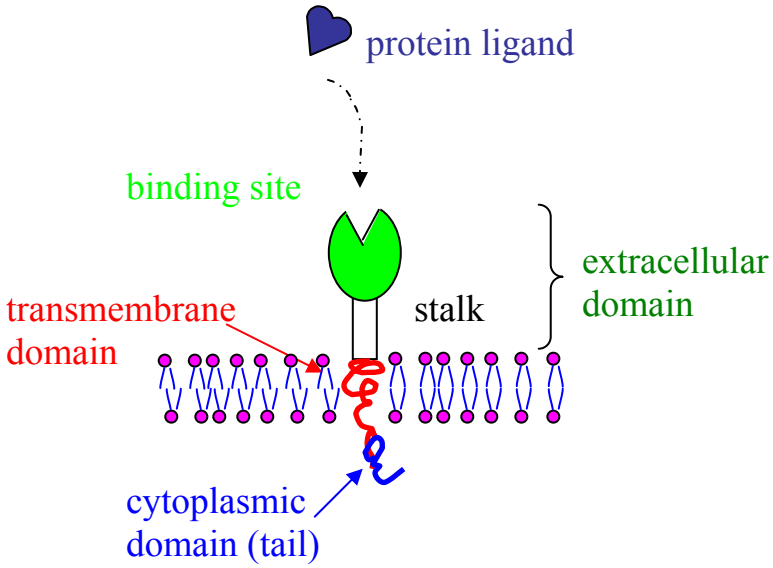
Lecture 7:
Cell-Surface Interactions: Host Responses to Biomaterials

Synthetic surfaces exposed to biological fluids adsorb proteins— how does this mediate the body's ultimate response to a biomaterial?

Protein-Cell Interactions

proteins (in solution or on a surface) bind with cell "receptors"
⇒ *physiological response*



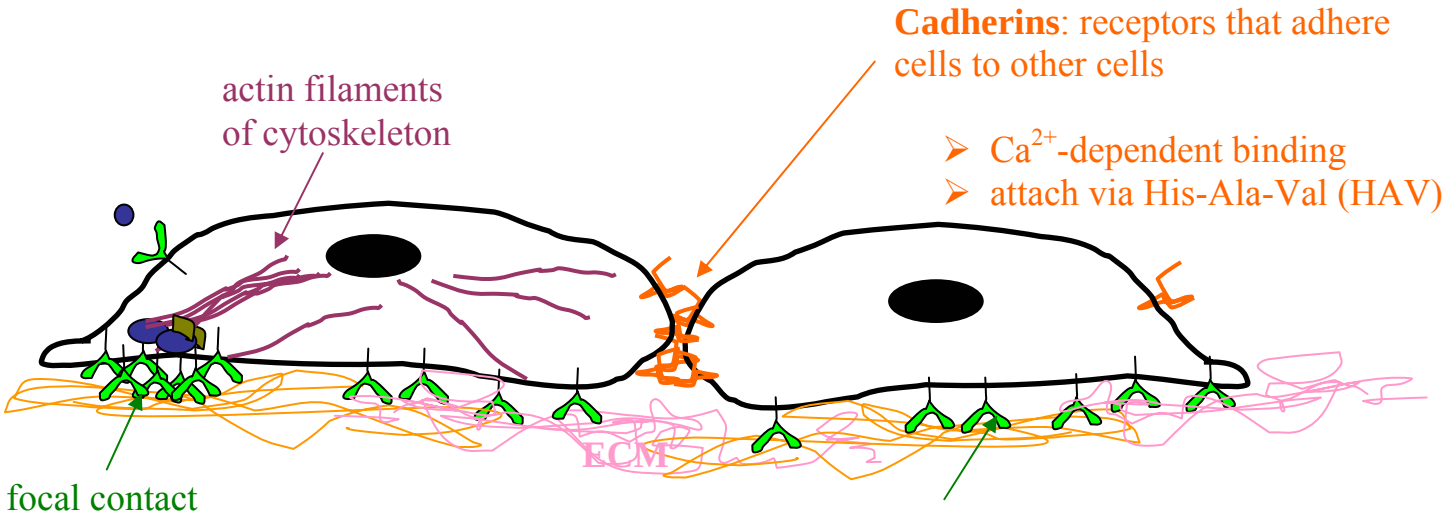
Cell surface receptors: membrane-embedded proteins or glycoproteins that control signal transduction and cell adhesion (~100 types/cell!)

ligand-receptor binding mediates:

- Adhesion
- Contraction
- Motility
- Secretion
- Proliferation

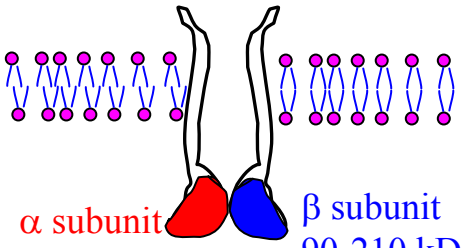
Cell adhesion mechanisms

Cells attach to other cells and to extracellular matrix (ECM) through adhesion receptors that bind specific peptide sequences of other proteins



Cadherins: receptors that adhere cells to other cells

- Ca^{2+}-dependent binding
- attach via His-Ala-Val (HAV)



Integrins: bind cells to adhesion proteins in ECM

- Ca^{2+}/Mg^{2+}-dependent binding
- attach to Arg-Gly-Asp (RGD), Leu-Asp-Val (LDV), & other

- 2 associated subunits— ~22 α/β combinations having different ligands
- adhere to fibronectin, vitronectin, tenascin, collagen, laminin in ECM, & cell counter-receptors (ICAMs: intracellular cell-associated matrix proteins)
- adhere to plasma proteins fibrinogen, factor X (coagulation), C3bi
- typical receptor/ligand $K_D \sim 10^{-6}$-10^{-7} mol/L
- 2D diffusion in cell membrane $D \sim 10^{-10}$ cm^2/s
- integrin clustering: i) recruits cytoskeletal proteins (talin, vinculin, actin) ⇒ mediates traction (focal contacts)

  ii) recruits cytoplasmic signaling molecules (e.g. tyrosine kinase) ⇒ mediates cell secretions, etc.

Extracellular matrix houses adhesion proteins that bind to cell receptors

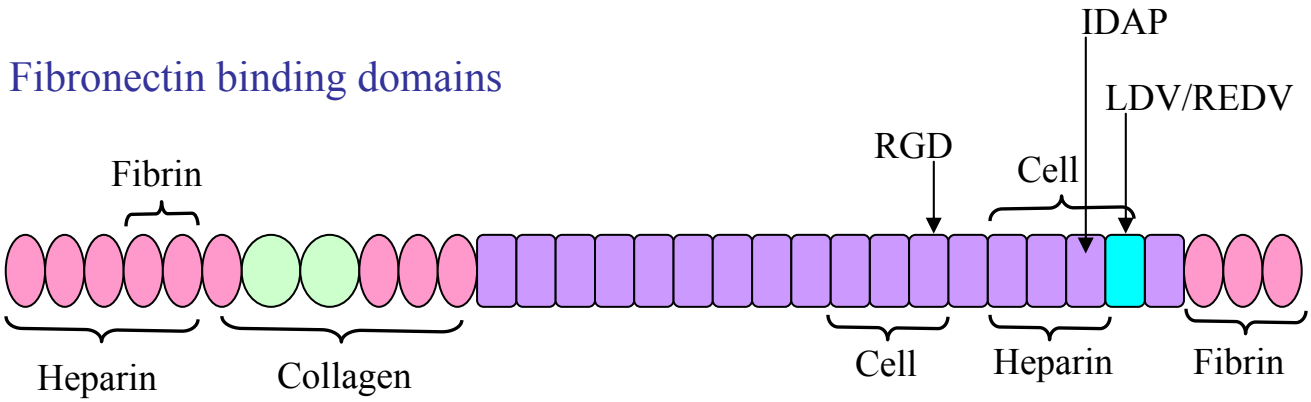
ECM functions:

- anchor cells
- control cell orientation
- regulate cell growth
- maintain cell differentiation
- provide scaffolding for tissue renewal

ECM components:

- fibrous proteins: collagen (strength), elastin (elasticity)
- intrafibrillary matrix: proteoglycans (GAG-protein molecules)
- adhesive glycoproteins: fibronectin, laminin, etc.
- calcified in formation of bones, teeth
- can be "remodeled": broken down and regenerated

Adhesion proteins exhibit domains for binding cell integrins, other ECM molecules & plasma proteins



Adhesion proteins play a primary role in the body's response to injury and introduction of foreign materials.

Basic Tissue Cell Types and Functions

Cell type	Tissue Function	Example
epithelial	covers external (ex, skin) & internal (ex, intestine, blood vessel) organ surfaces	endothelial cells
connective	supports other body tissues; houses nerves & blood vessels	fibroblasts (ECM generation), cartilage, bone
muscle	specialized for contraction;	smooth, skeletal, cardiac
nerve	generate electrical signals & secrete neurotransmitters	brain cells, peripheral nerve

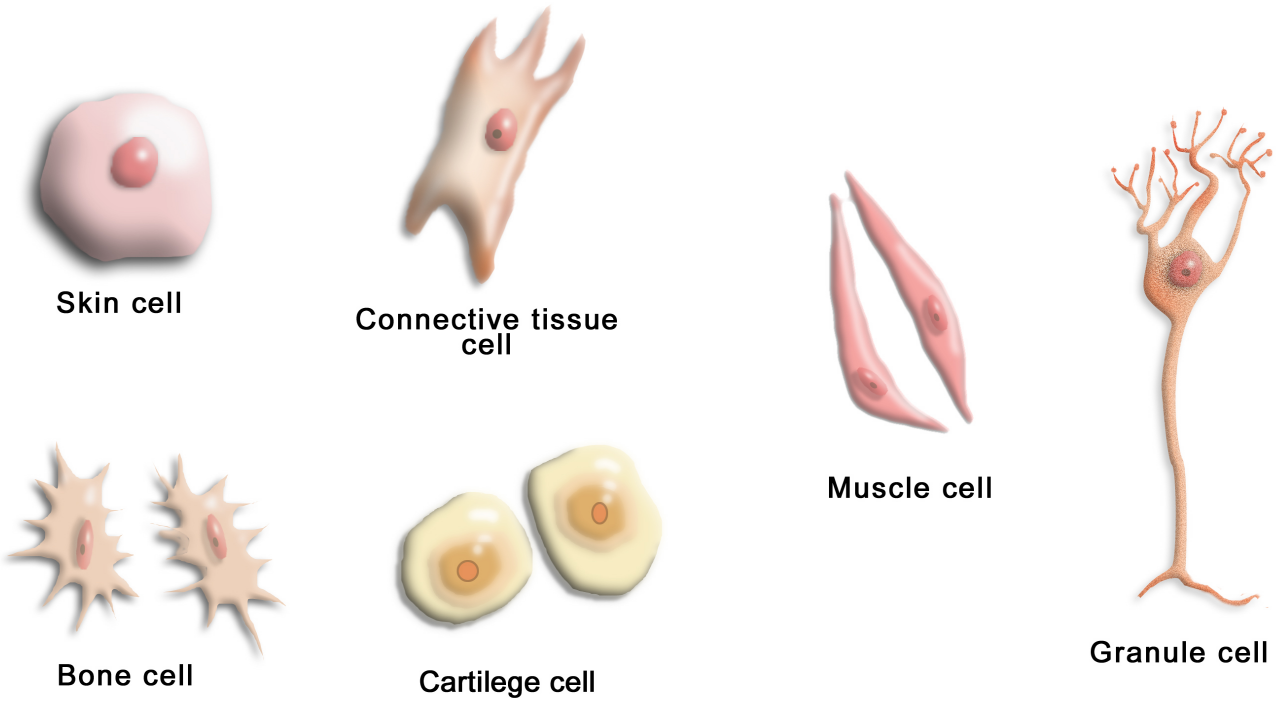


Figure by MIT OCW.

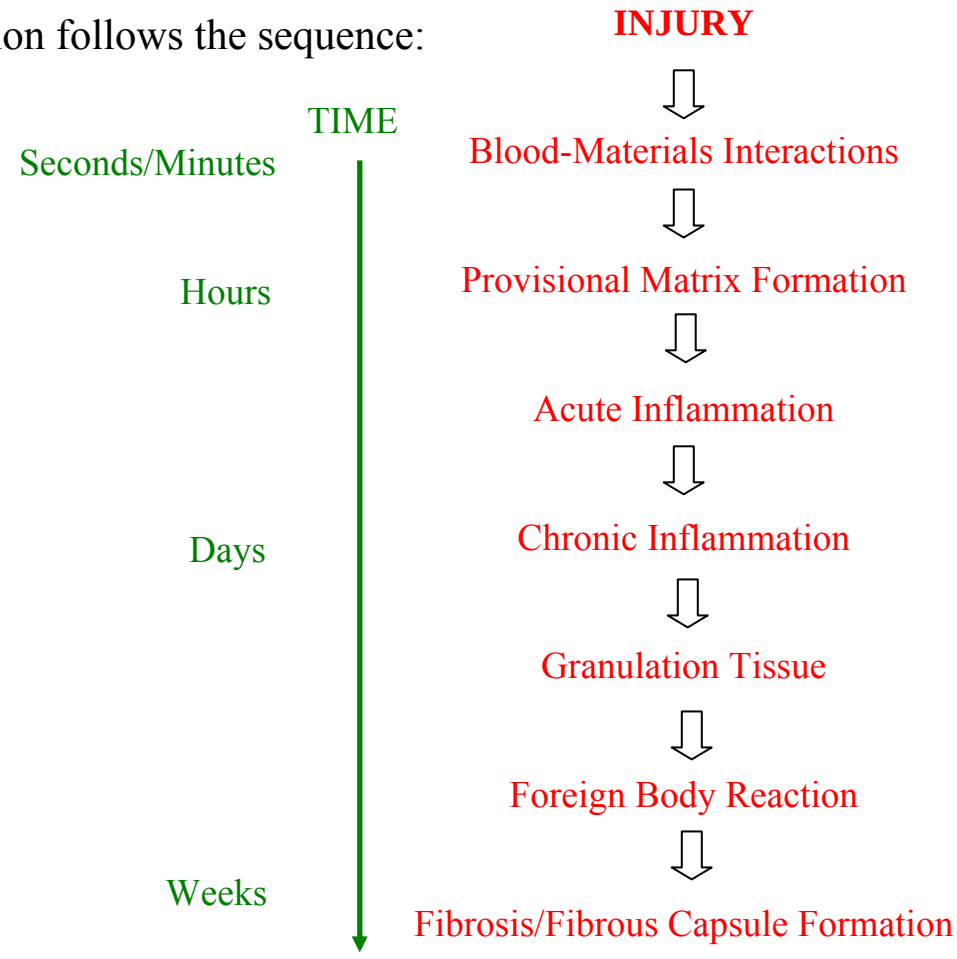
Injured tissue response: known as inflammatory response

goal: to destroy or inactivate foreign entity, initiate healing
mechanism: signal "cascades" from plasma & cells

Implantation of biomaterials activates two cooperative signaling cascades:

1) **Coagulation Cascade**—involves ~12 proteins
2) **Complement Alternative Pathway**—involves >20 proteins

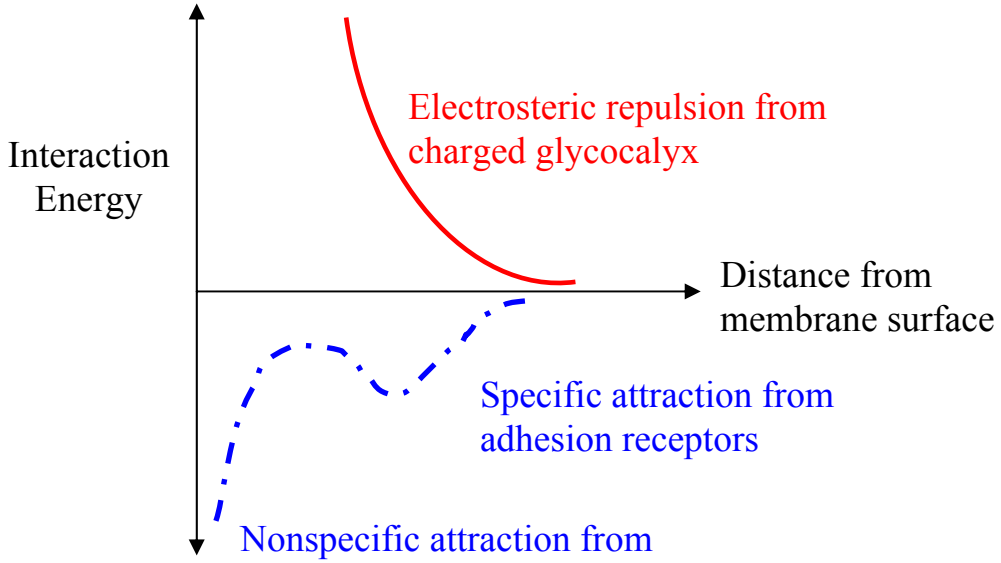
The host reaction follows the sequence:

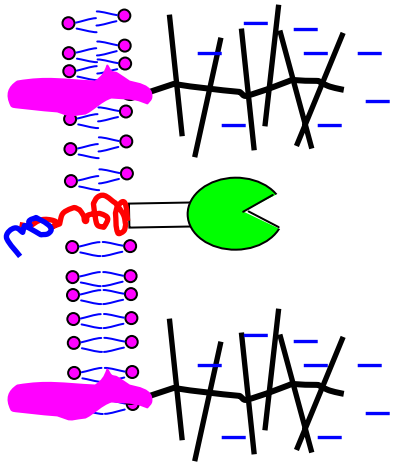


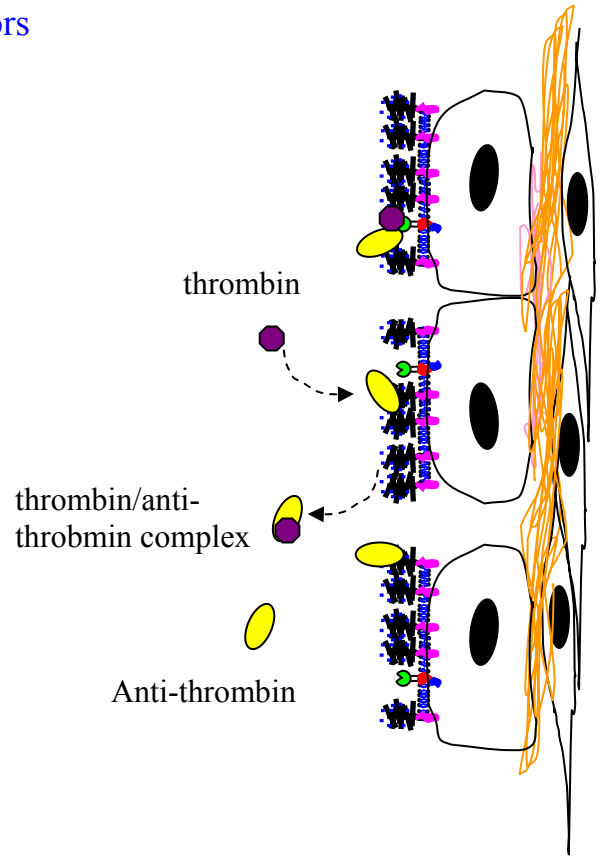
1. Coagulation Cascade

In absence of injury or foreign materials, clotting is prevented by the endothelial cell lining of blood vessels which exhibit heparan sulfate proteoglycans on their surface

Heparan sulfate: - polysaccharide w/ SO_3^- and COO^- charges
- provides electrosteric repulsion
- binds anti-thrombin → deactivates thrombin



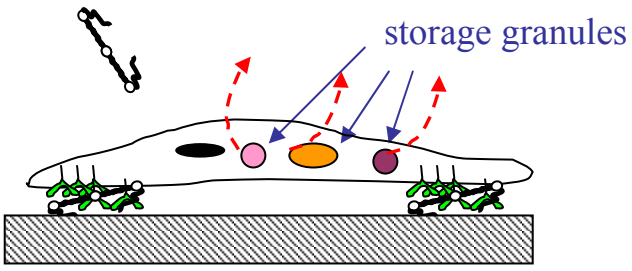




INJURY ⇒ release of fluids, proteins & blood cells from vascularized connective tissues at site

- Vasodilation ⇒ redness & swelling
- Adsorption of plasma proteins (esp. fibrinogen) on foreign surfaces & injured tissues

- platelets (250M/cc, 0.3 vol%) bind to adsorbed plasma proteins (FGN, VN, FN) via αIIb/β3 (gpIIb/IIIa) receptors (~40,000/cell) and exposed collagen via α1/β1(gpIb) receptors (~15,000/cell)
- platelet binding triggers release of storage granule contents to extracellular environment (mediated by focal contacts)



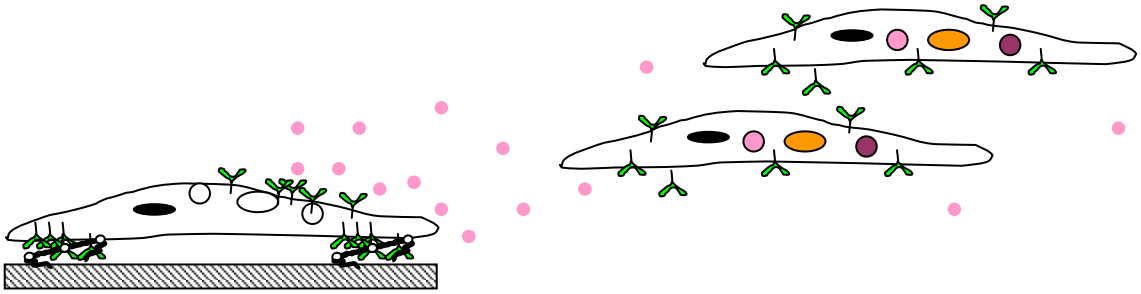
- platelet-specific proteins
- plasma proteins
- coagulation factors

- ADP, Ca^{2+}, serotonin (neurotransmitter)

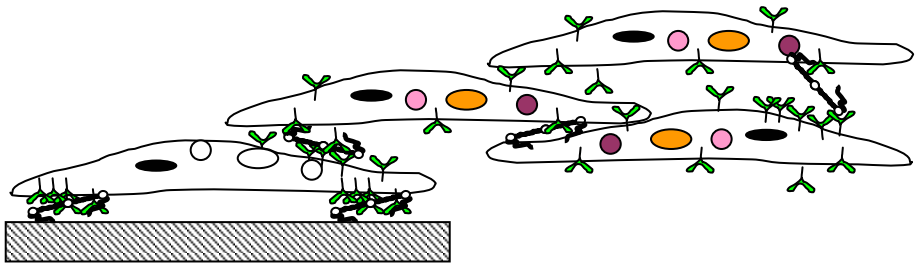
- enzymes (acid hydrolases)

- granule release increases receptor expression on surface & recruits other platelets to site

  chemotaxis: cell migration along a chemical gradient

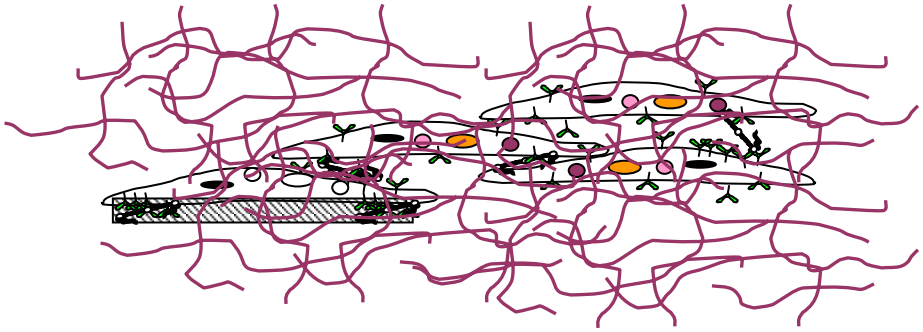


- platelet aggregation via fibrinogen bridges, forms a "plug" that initially reduces blood flow



- complex cascade of enzymatic activity on platelet surface culminates with factor X conversion of plasma protein prothrombin (~100 μg/ml) to thrombin

- thrombin cleaves fibrinogen to form insoluble fibrin which crosslinks around platelet plug to form the thrombus or clot



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See "The Coagulation Cascade" at http://labtestsonline.org/images/coag_cascade.pdf

Copolymer film surface after incubation in whole blood for 2h. Platelets and red blood cells are observed in fibin matrix.

R. Barbucci et al., *J. Biomed. Mater. Res*. **1999**, *46*, 186.

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Platelets on modified PE surface from platelet-rich plasma

J.H. Lee and H.B. Lee, *J. Biomed. Mater. Res*. **1998**, *41*, 304.

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Fibrin matrix created by addition of thrombin to fibrinogen.

A.V. Cooper et al., *Blood* **2003**, *102*, 535.

Photos removed for copyright reasons.

Endothelial lining of rat carotid artery before (top) and after (bottom) photochemical damage. Bottom image shows formation of thrombosis.

Y. Kim et al., *Acta Neurochirurgica* **2004**, *146*, 45.