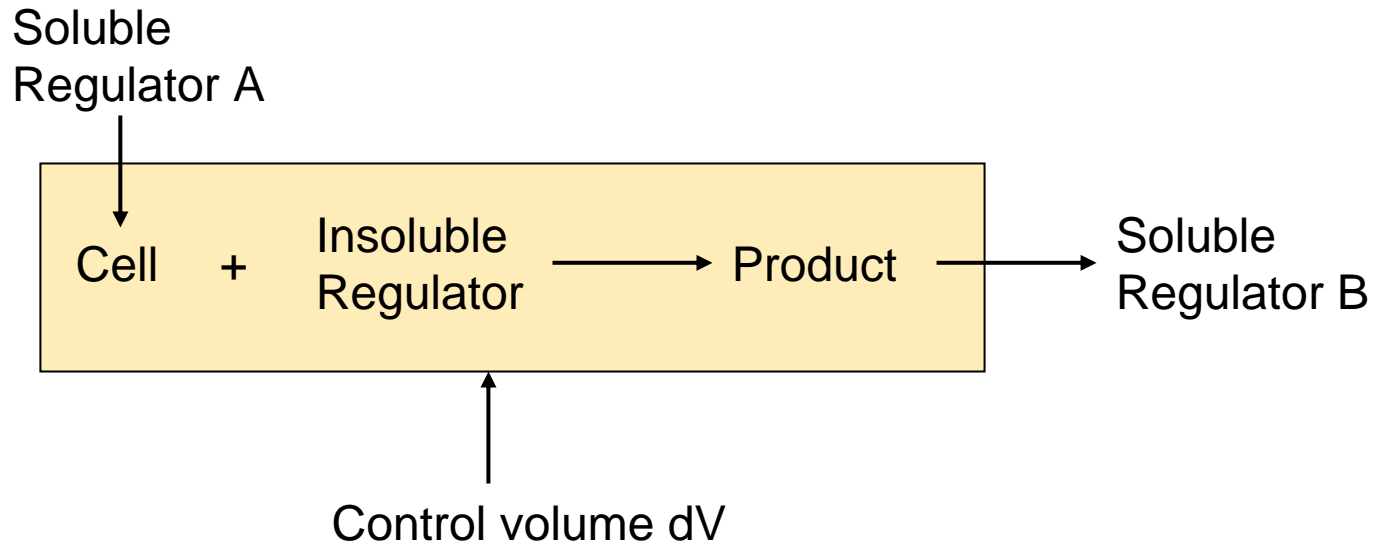


2.79J/3.96J/20.441J/HST522J
Biomaterials-Tissue Interactions

**Structure and function of
naturally occurring extracellular
matrices (ECMs).**

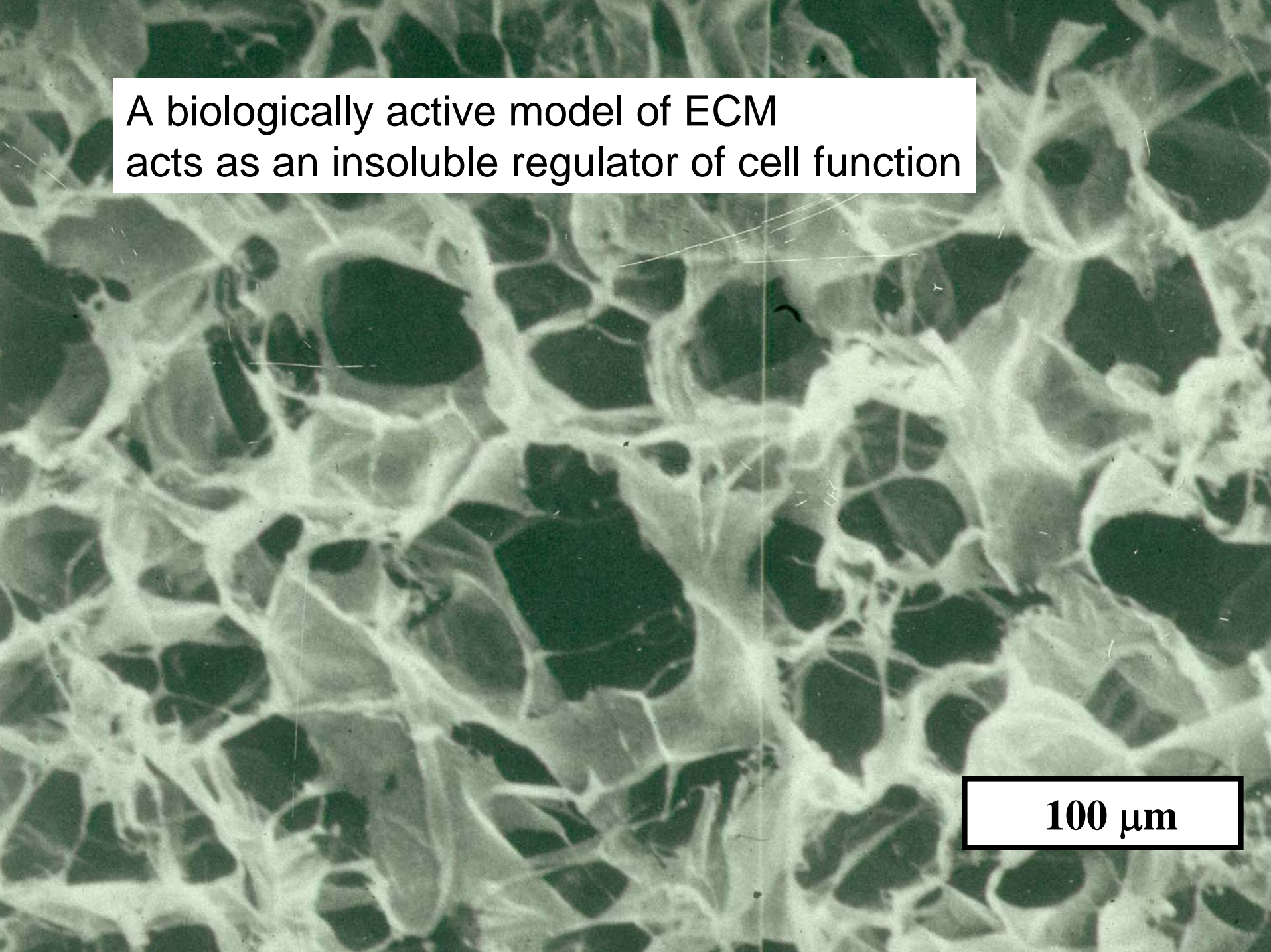
The insoluble regulator in a unit cell process is part of an ECM macromolecule



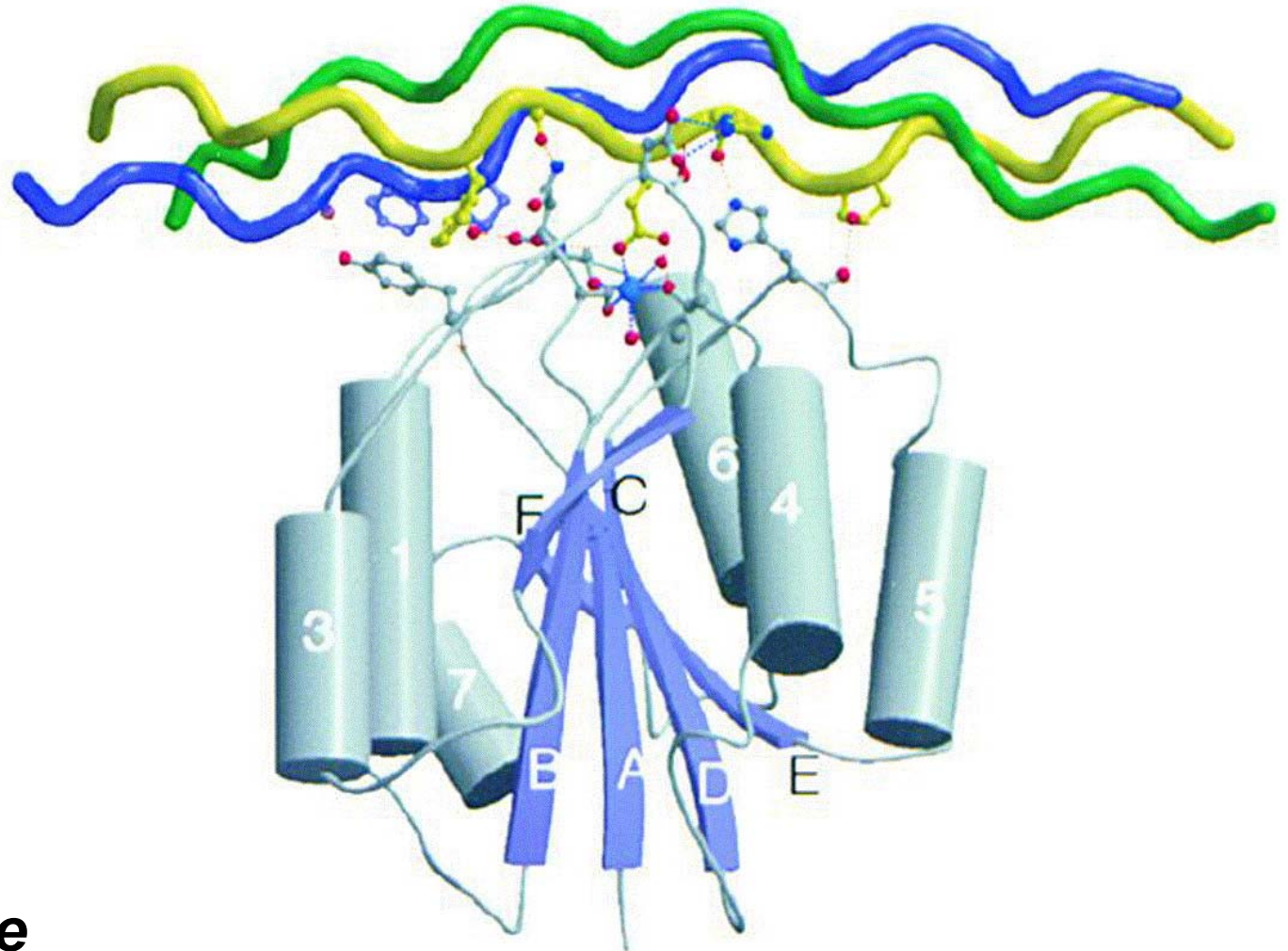
Unit cell process confined conceptually in a control volume dV

A biologically active model of ECM
acts as an insoluble regulator of cell function

100 μm



Phenotype change: fibroblast $\alpha 2\beta 1$ integrin binds to collagen ligand GFOGER (hexapeptide)



***Integrin
adhesion to
collagen at the
GFOGER ligand***

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**Emsley et al., 2000₄
Knight et al., 2000**

The Extracellular Matrices (ECMs)

(summary of structure and function)

- **Insoluble macromolecular networks.**
- **Structure varies with organ; but different ECMs comprise few types of macromolecules (mostly collagen, elastin, proteoglycans) plus water (65%).**
- **ECM does not migrate, proliferate, synthesize proteins or contain DNA!**
- **Give and take of signals with cells. Ligands on ECM surface interact specifically with cell receptors (integrins).**
- **Partly determine the state of differentiation of cells.**

The Extracellular Matrices...

(summary of structure and function)

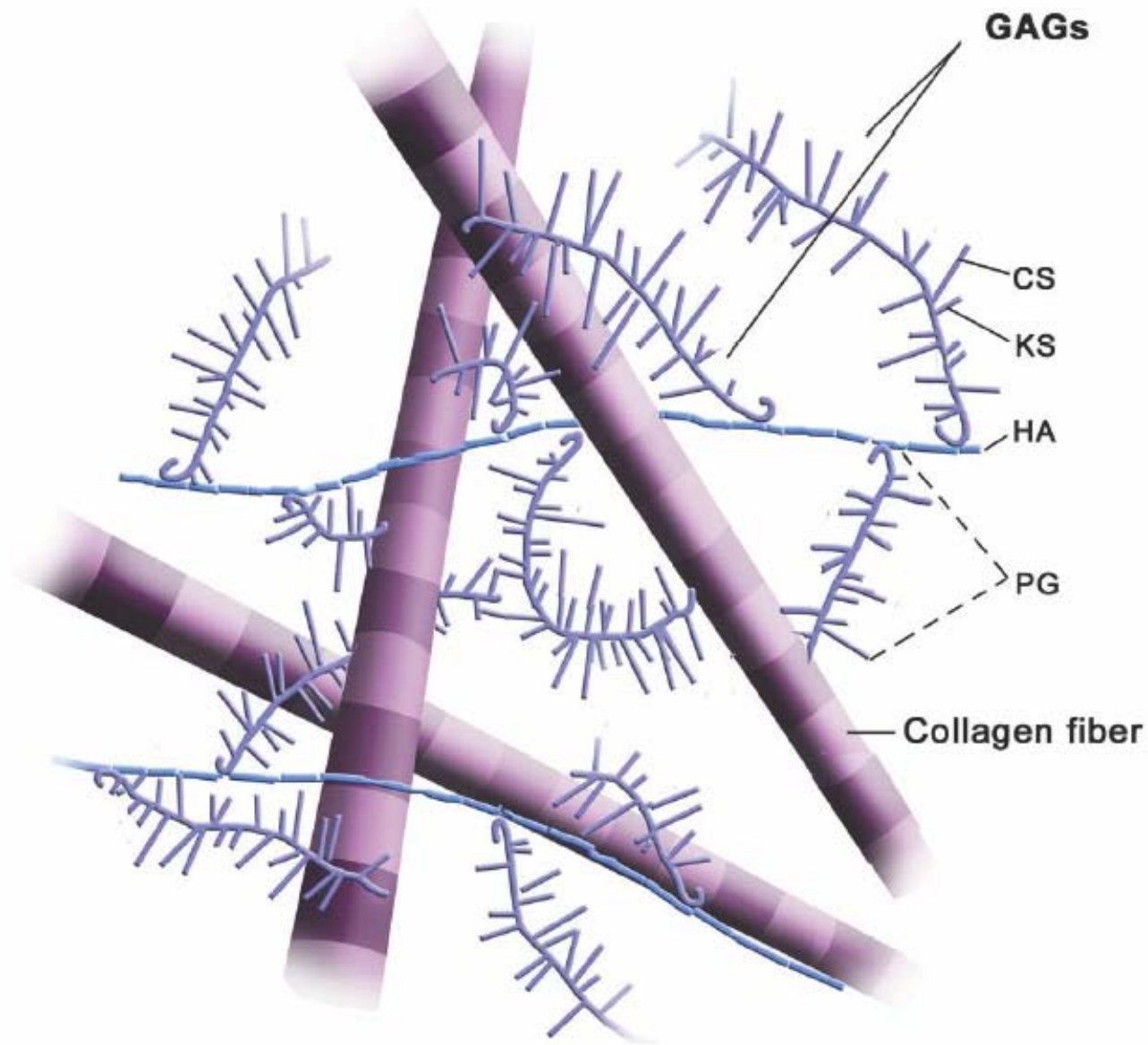
- Possibly play role of memory storage device which is used to record events (e.g., a recent cell migration), thereby informing cells of what has already been done and acting as “arrow” in a kinetic process.
- Often bind cytokines and growth factors and act as reservoirs of such molecules.
- Loss of cell-matrix contact characterizes tumor cells just prior to spreading of cancer from one organ to another (metastasis).
- Determines the shape of animals and maintains positional homeostasis of organs.
- Recently, certain synthetic ECM models have induced organ regeneration in adults.

The major ECM molecules in tissues

- 1. Collagens.**
- 2. Elastin.**
- 3. Proteoglycans and glycosaminoglycans (GAGs).**
- 4. Cell-adhesion molecules (fibronectin, laminin, others).**

[Water (about 65% of tissue weight).]

Schematic view of ECM



The Extracellular Matrices.

Part I. Collagens

Hierarchy of structural order in proteins

Primary structure: the complete sequence of amino acids (AA) in the polypeptide chain. Scale: 1 nm.

Secondary structure: the local chain configuration (sequence of 3 - 5 AA). Scale: 10 nm.

Tertiary structure: the configuration of the entire macromolecule. Scale: 100 nm.

Hierarchy of structural order in proteins (cont.)

Quaternary structure: The packing pattern of several identical molecules that characterizes a crystalline fiber. Scale: 1000 nm = 1 μ m.

Architecture: Pattern comprising several fibers of a protein that constitute a macroscopic tissue. Often contains fibers of two different proteins (collagen and elastin) and one or more proteoglycan molecules. Scale: 1-10 mm.

Collagens

(most fibrous collagens)

Primary structure: Glycine “hinge” every third AA makes polypeptide chains capable of rotation. Hydroxyproline (25% of total AA content) stiffens polypeptide chains. Varies with organ; several such “collagens” have been identified. Fibrous collagens to be discussed here only.

Secondary structure: Combination of hinge-like glycine and stiff hydroxyproline units, leads to helical macromolecule with sharp pitch.

Collagens (cont.)

(most fibrous collagens)

Tertiary structure: Three helical polypeptide units twist to form a triple-helical collagen molecule: a molecular “rope” which has some bending stiffness and does not undergo rotation.

Quaternary structure: Several collagen molecules pack side-by-side in a highly specific register to give a crystalline fiber with a 64-nm periodicity (collagen banding pattern).

The architectural structure of collagen is uniaxial orientation in tendon, biaxial orientation in the dermis, etc. It determines the mechanical behavior of the tissue.

Primary

Secondary

Diagram removed due to
copyright restrictions.

Tertiary

Quaternary

COLLAGEN STRUCTURE

banding

Electron microscopy

Images removed due to
copyright restrictions.

Collagen structure

Cross-linking of collagen molecules

Diagram removed due to copyright restrictions.
Formation of intramolecular and intermolecular cross-links in type I collagen.

Collagen structure-function relations

- The primary structure of collagen is tissue-specific. Type I in tendon, type II in cartilage, etc.
- The secondary and the tertiary structures are specific substrates for the metalloprotein enzyme collagenase that degrades collagen fibers. Remodeling of tissues during wound healing by collagenase. Melting of collagen to gelatin (loss of tertiary structure) spontaneously follows such degradation.
- The banding (quaternary structure) of collagen fibers determines the blood clot-forming properties of collagen (primarily through induction of platelet aggregation).

Collagen structure-function relations (cont.)

- The architectural structure of collagen determines the function of collagen fibers as mechanical reinforcements of connective tissues (tendon, skin, bone, arteries etc.). Tendon fibers are bundles of uniaxially aligned fibers that are crimped. Skin (dermis) is a random planar array of crimped collagen fibers. Bone is a ductile ceramic (hydroxyapatite) which is reinforced by collagen fibers. Large blood vessels (aorta, large arteries) are interpenetrating networks of elastin fibers and collagen fibers.

No enzyme

Exposed to collagenase

Three photos removed due to copyright restrictions.

Exposed longer

Effect of exposure of collagen fibers to collagenase

collagen

Diagram removed due to
copyright restrictions.

**Degradation of
collagen
molecule by
collagenase
(Gross)**

spontaneous melting
to gelatin following degradation

Enzyme attacks only 775-776 AA link

Diagram removed due to
copyright restrictions.

Cleavage site of collagen molecule by collagenase is within the fibronectin binding region (766-786)

Diagram removed due to copyright restrictions.

The Extracellular Matrices

Part II.

- 2. Elastin fibers.**
- 3. Proteoglycans (PG) and glycosaminoglycans (GAG).**
- 4. Cell-adhesion molecules (CAM).**

Elastin fibers

- **A network of randomly coiled macromolecules. No periodicity. Highly extensible chains.**
- **Rubber-like elasticity is complicated by hydrophobic bonding effects.**
- **Interaction of hydrophobic (nonpolar) AA with water leads to hydrophobic bonding. Primarily entropic, not energetic, bonding between molecules. It forces nonpolar macromolecules, such as elastin, to adopt a compact, rather than extended, shape in hydrated tissue.**
- **Stretching of elastin fibers leads to large entropy loss due to reduction in chain configurations and increased “ordering” of water molecules against nonpolar AA. Spontaneous retraction.**
- **Elastic ligament of neck. Blood vessel wall.**

The Hydrophobic bond

$$\Delta G = \Delta H - T\Delta S$$

Equilibrium when $\Delta G = 0$. G is Gibbs' free energy, the enthalpy is $H = E + PV$, T is absolute temperature and S is the entropy. The process goes spontaneously from left to right when $\Delta G < 0$. Find the position of thermodynamic equilibrium for a well-known example of insolubility:



The experimental data show (all units in calories per mol):

$$\begin{aligned}\Delta G &= \Delta H - T \Delta S \\ +2600 &= -2800 - 298(-18) \\ +2600 &= -2800 + 5400\end{aligned}$$

Conclusion: Insolubility of paraffin in water due to entropy loss, not to enthalpy change! (Kauzmann)

Diagram removed due to copyright restrictions.

Models of (a) Goldup, Ohki and Danielli (b) Singer and Nicolson (c) Lenard and Singer (d) Lucy (e) Kreutz (f) Vanderkooi and Green.

Historical models of cell membrane structure

Cell membrane showing bilayer structure

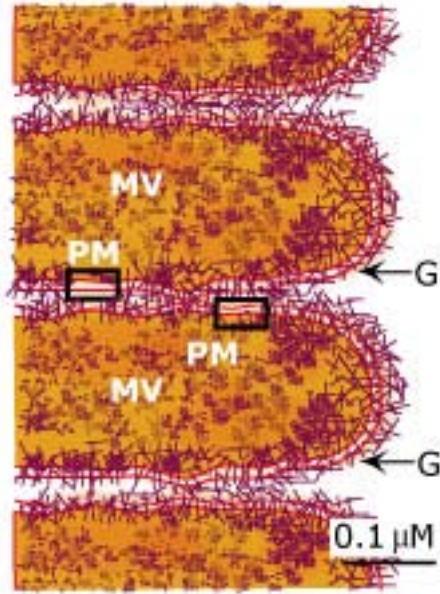


Figure by MIT OpenCourseWare.

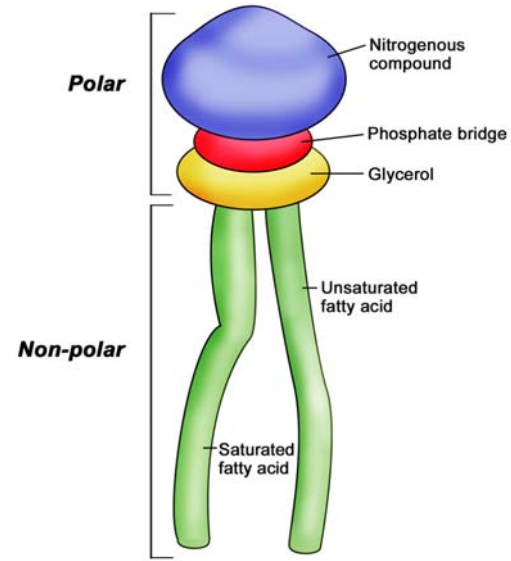


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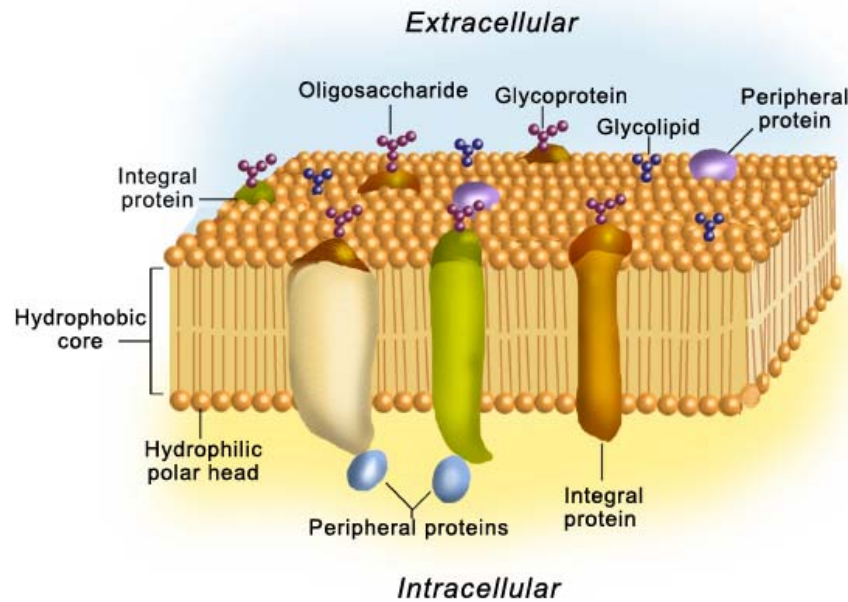


Figure by MIT OpenCourseWare.

**Elastin fibers
in the relaxed aorta.
Elastin
macromolecules
are random coils tied
together to form
a 3-dimensional
(insoluble) network.**

Two histology photos removed
due to copyright restrictions.

**Macromolecules
coil upon
themselves due to
high content of
nonpolar
(hydrophobic)
amino acids that
mediate
withdrawal from
polar medium
(aqueous buffer)
and promote
bonding within
chains.
These networks
stretch extensively
like all rubbers.**

Proteoglycans (PGs) and glycosaminoglycans (GAGs)

- **A proteoglycan is a polypeptide chain (proteo) with polysaccharide (glycan or GAG) side chains.**
- **Primary structure modeled as an alternating copolymer of two different glucose-like units, one of them an acidic sugar-like molecule, the other an amino sugar with a negatively charged sulfate group (except hyaluronic acid that is not sulfated).**
- **Electrostatic interactions between charged groups in GAG side chains of PG responsible for about 50% of stiffness of articular cartilage (Grodzinsky et al.).**

Proteoglycans (PGs) and glycosaminoglycans (GAGs)

PG

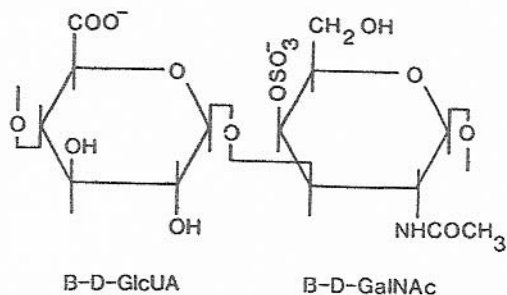
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Structures of four subpopulations of cartilage proteoglycans.

GAG side chains of PG

PG

FIGURE 8.1 continued.

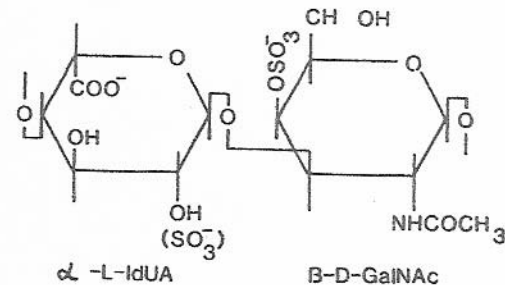
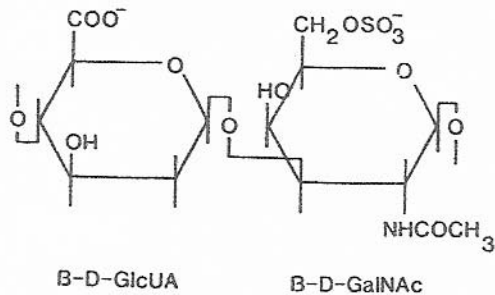
CHONDROITIN 4-SULFATE
(n 20-60)



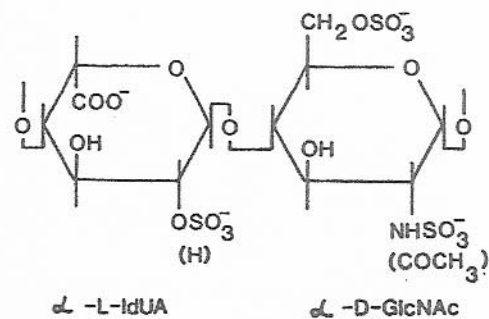
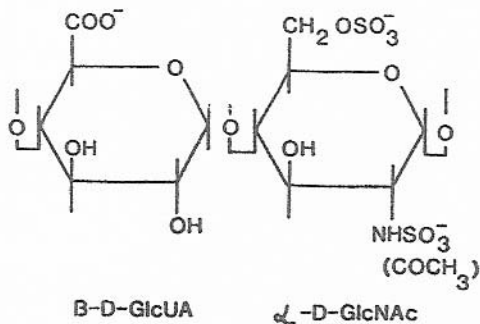
Glycosaminoglycans

disaccharide repeat unit

DERMATAN SULFATE
(n 30-80)



HEPARAN SULFATE
(Heparin)



Proteoglycans and glycosaminoglycans

repeat unit of chondroitin 6-sulfate

Diagram removed due to
copyright restrictions.

a proteoglycan

Image removed due to
copyright restrictions.

Electron microscopic view of a
proteoglycan
from bovine nasal cartilage

Cell-adhesion molecules

- **Cell-matrix interactions involve binding of transmembrane proteins (integrins) on specific sites (ligands) in ECM molecules such as fibronectin, laminin and collagen. Example: integrins of contractile fibroblasts bind to fibronectin molecules that are attached to collagen fibers (fibronexus).**
- **Integrins connect with proteins in the cell cytoplasm and a signal is transmitted to or from the nucleus.**

An integrin “connects” the interior of the cell (cytoplasm) with the ECM outside it

cell membrane

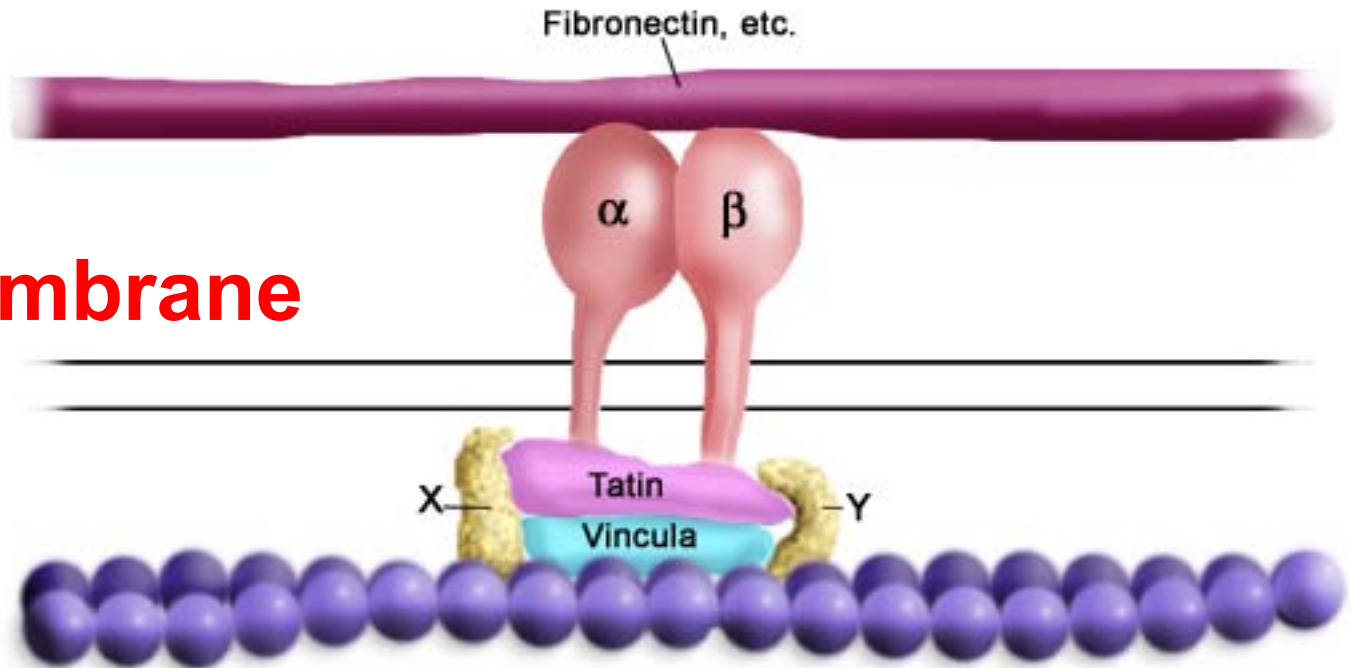


Figure by MIT OpenCourseWare.

Figure from (Hynes, 1990)

Bilayer structure of cell membrane viewed by electron microscopy

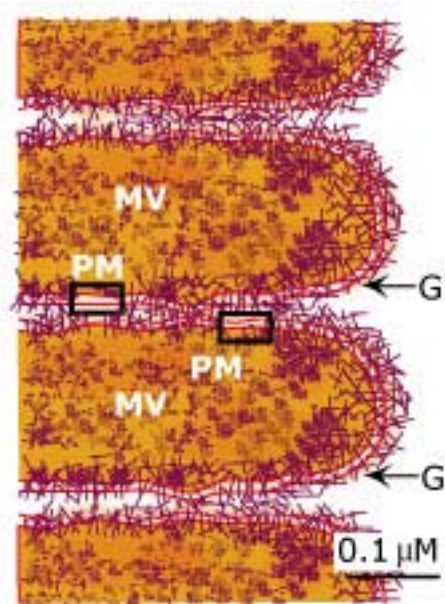


Figure by MIT OpenCourseWare.

Phospholipid molecule

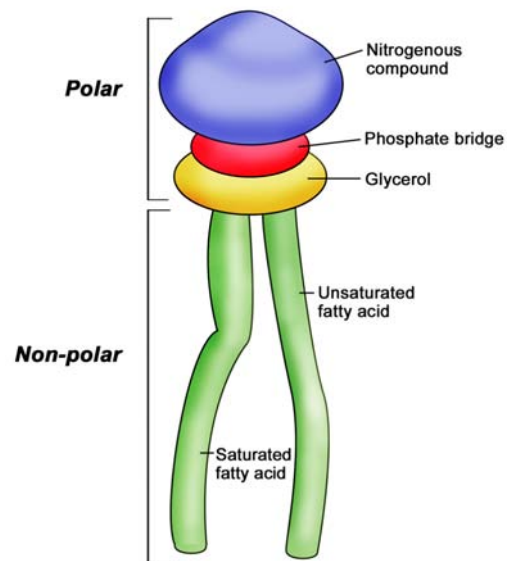


Figure by MIT OpenCourseWare.

Cell membrane showing cell surface receptors (integrins)

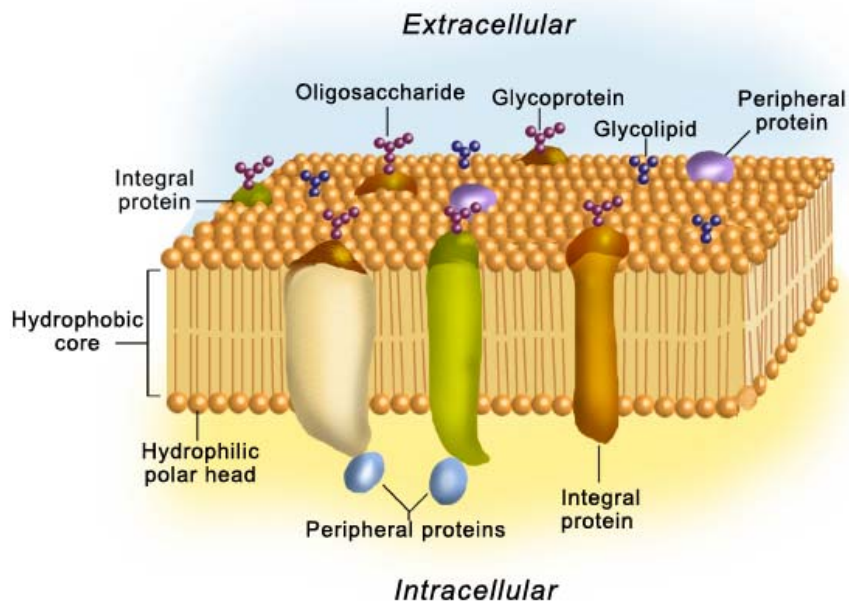


Figure by MIT OpenCourseWare.

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