2.79J/3.96J/BEH.441J/HST522J
Biomaterials-Tissue Interactions

Outline of three lectures on ECMs

A. Irreversible healing of ECMs in different organs.

B. Structure and function of naturally occurring ECMs.

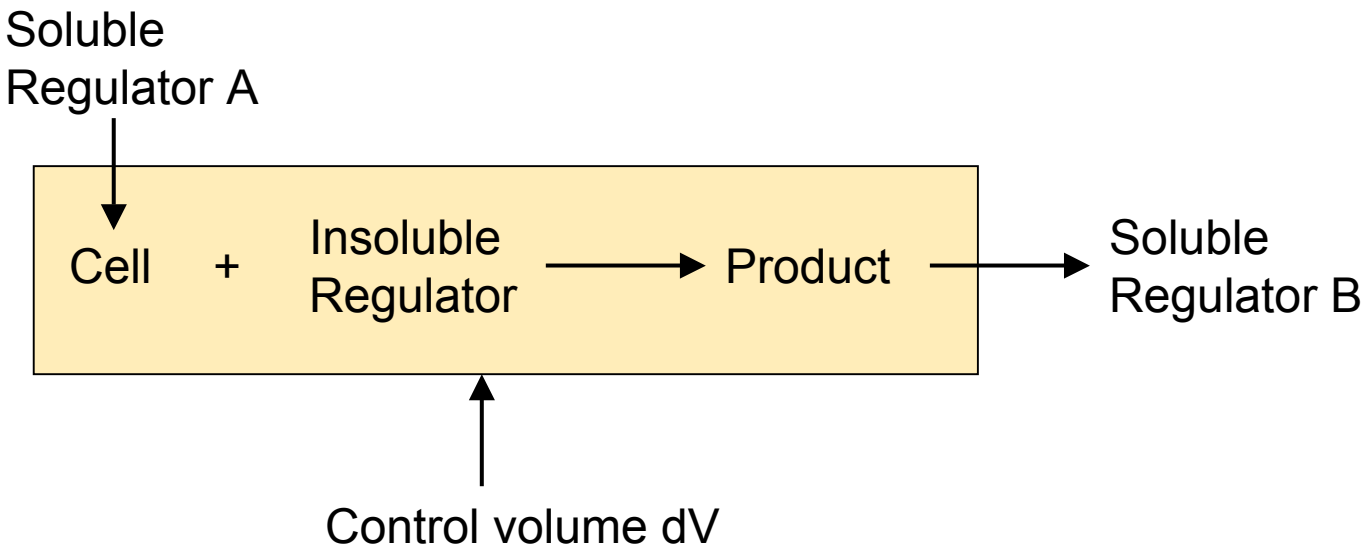
C. Synthesis of biologically active ECM models.

B. Structure and function of naturally occurring ECMs

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

image removed due to copyright considerations

Definition of unit cell process



Unit cell process confined conceptually in a control volume dV

The Extracellular Matrices (ECMs) Part I.

(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. Part II.

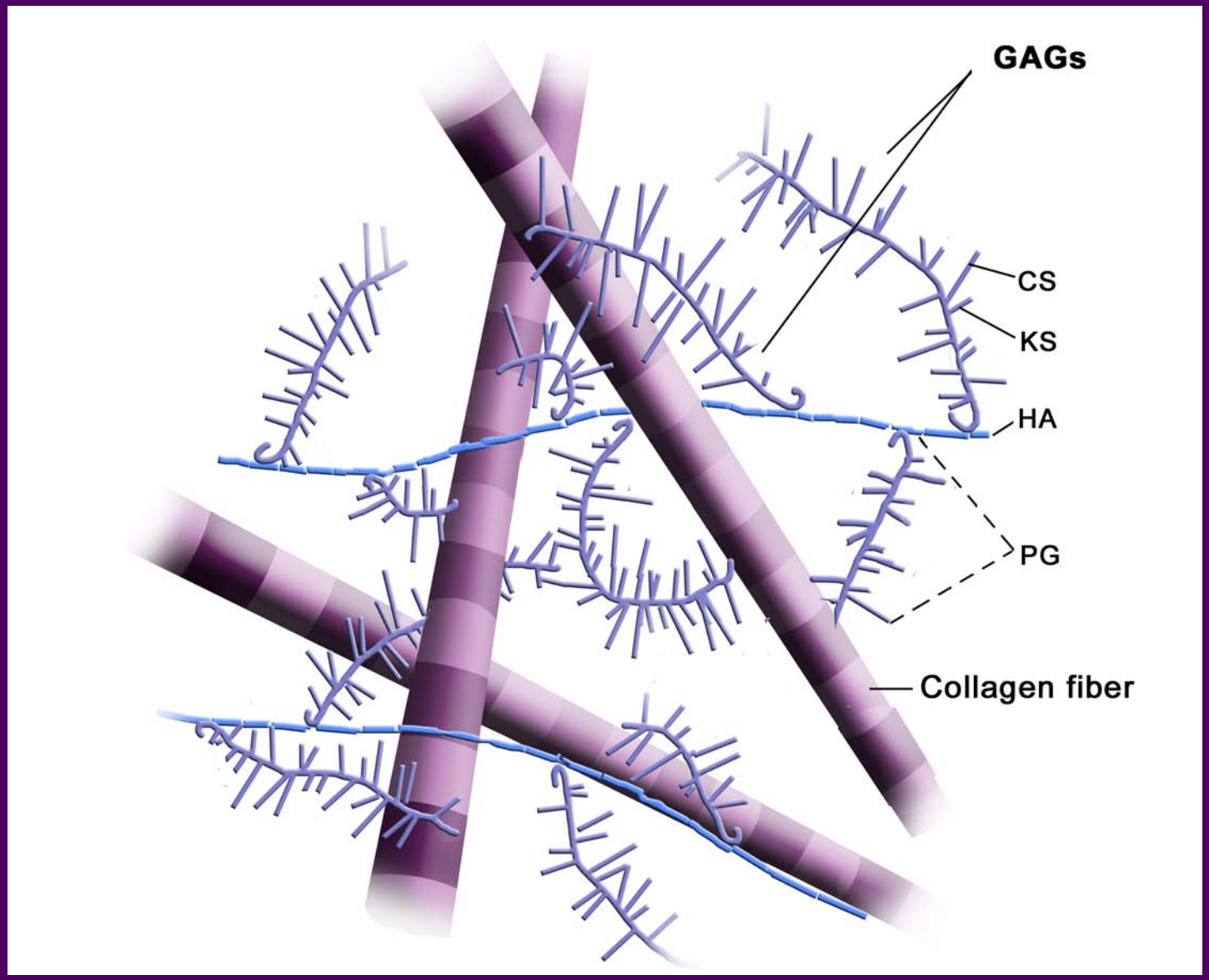
(summary of structure and function)

- **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.**
- **<u>Recently, certain synthetic ECM models have induced organ regeneration in adults</u>.**

The major ECM molecules

1. Collagens.
2. Elastin.
3. Proteoglycans and glycosaminoglycans (GAGs).
4. Cell-adhesion molecules (fibronectin, laminin, others).
5. Water (about 65%).

Schematic view of ECM



Hierarchy of structural order in proteins

<u>Primary structure</u>: the complete sequence of amino acids (AA) in the polypeptide chain. Scale: 1 nm.
<u>Secondary structure</u>: the local chain configuration (sequence of 3 - 5 AA). Scale: 10 nm.
<u>Tertiary structure</u>: the configuration of the entire macromolecule. Scale: 100 nm.

Hierarchy of structural order in proteins (cont.)

<u>Quaternary structure</u>: The packing pattern of several identical molecules that characterizes a crystalline fiber. Scale: 1000 nm = 1 μm.

<u>Architecture</u>: 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)

<u>Primary structure</u>: 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.

<u>Secondary structure</u>: 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.

COLLAGEN STRUCTURE

Images removed due to copyright considerations

Cross-linking of collagen molecules

Image removed due to copyright considerations

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.**