

## Extracellular matrix



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- Network of proteins and carbohydrates that binds cells together
- Supports and surrounds cells
- Regulates cells activities
- Lattice for cell movement

## Extracellular matrix molecules



- Only 5 classes of macromolecules
    - Collagens
    - Elastic fibers
    - Proteoglycans
    - Hyaluronan
    - Adhesive glycoproteins
- Insoluble – can not be hydrated
- Soluble – easily hydrated
- They can be mixed up in different proportions for different functions

## Functions



- Mechanical support
- Embryonic development
- Pathways for cellular migration
  - Wound healing
- Management of growth factors

## Collagen

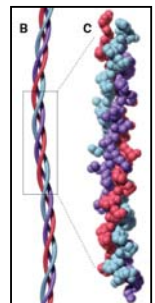


- Major **insoluble** fibrous protein of the extracellular matrix and connective tissue
- Most abundant protein in animals
- Made by fibroblasts and some epithelial cells

## Collagen – molecular structure



- Triple helix of polypeptides
- Each polypeptide is a left-handed helix too



## Types of collagen

- Fibrillar
  - Forms structures such as tendon or cartilage
- Sheet forming
- Connecting
  - Supports and organizes fibrous collagen
- Transmembrane

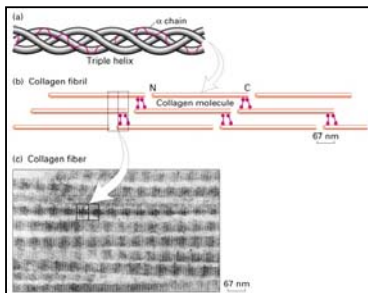


## Fibrillar collagen I

- Basic unit – triple helix 300 nm long
- 2  $\alpha_1$  and 1  $\alpha_2$  molecules
- Collagen fibrils form by lateral interactions of triple helices
  - Stabilized by covalent bonds
  - Displacement by 67 nm (gives the striated look)

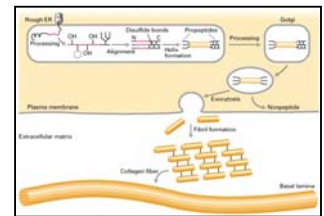


## The basic structural unit of collagen



## Assembly of collagen fibers

- Synthesized in secretory pathway as procollagen
- Glycosylation in ER and Golgi
- Helix formation in ER
  - Disulfide bonds that are cleaved later
- Assembly outside !



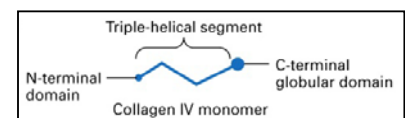
## Sheet forming collagen

- Polymerizes into sheets
- Forms basal membranes – collagen IV
- Collagen VIII – Descemet's membrane of cornea



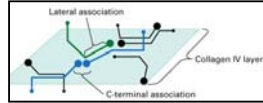
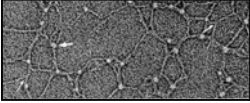
## Collagen IV

- A helix interrupted about 24 times by segments that can not form a helix
- Globular domains at both C- and N-termini



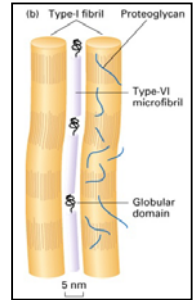
## Collagen IV

- Nonhelical domains introduce flexibility
- C-terminus globular domains associate with each other
- Helical domains associate laterally to form branching strands



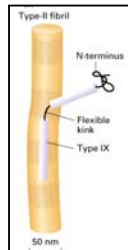
## Connecting collagens

- Link fibrillar and sheet forming collagens to into networks and connect them to other structures
- Collagen VI – short helices interspersed with globular domains
  - Align collagen I into parallel structures



## Connecting collagens

- Collagen IX has two rigid helices connected by the flexible kink
- The globular N-terminus binds to proteoglycans in the extracellular matrix
  - Links collagen II to glycosaminoglycans (provides cushion for compression as in cartilage)



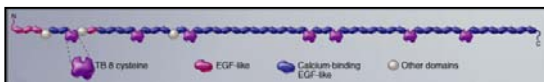
## Elastic fibers

- Found throughout the body
- Most prominent in skin
- Composite of fibrillin fibrils and elastin
- Synthesized only by fetal and juvenile fibroblasts
  - Whatever is made by puberty has to last until the end
  - Loss is responsible for wrinkles



## Fibrillin

- Tread like protein
- Forms 10 nm microfibrils
- Found in elastic fibers and basal lamina
- Linear molecule with independently folded domains



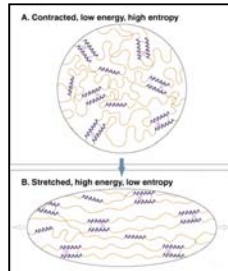
## Elastin

- A polymer of tropoelastins
- Tropoelastins form a family of closely related proteins
- Products of a single gene and alternative splicing



## Elastin

- Continuous random network of elastin polypeptides
- Helical domains separate random chains rich in hydrophobic residues



## Soluble components of extracellular matrix

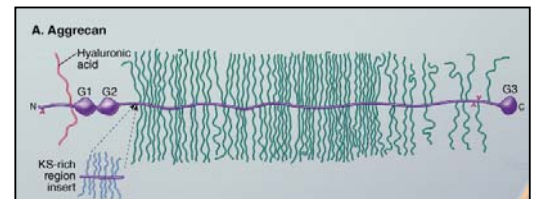
- Proteoglycans
  - Form highly hydrated gel responsible for volume of extracellular matrix
- Hyaluronan
  - Hydrated polysaccharide
  - Makes matrix resilient to compression
- Multiadhesive matrix proteins
  - Long flexible molecules that bind other matrix components and cells

## Proteoglycans

- Diverse group of proteins with multiple polysaccharide chains
- Found in connective tissues and extracellular matrix
  - Also attached to the surface of many cells
- Responsible for volume of extracellular matrix
  - Highly hydrated

## Proteoglycans

- Consist of multiple glycosaminoglycans (GAGs) posttranslationally added to a core protein



## Proteoglycans

- Very diverse
  - Different type of core protein (aggrecan, syndecan)
  - Different composition of GAGs (chondroitin sulfate, heparin, heparan sulfate)
  - Different lengths

## GAG synthesis

- GAGs are posttranslational modifications of a core protein
- Core protein is synthesized in secretory pathway
- Polysaccharides are added in ER by glycosyl transferases
- Elongated and modified in Golgi

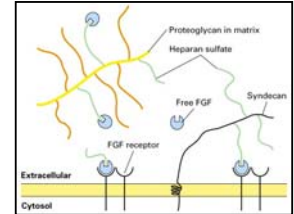
## Functions of proteoglycans

- Structural – elastic space fillers
- Limit diffusion of macromolecules
- Impede passage of microorganisms
- Act as lubricants in the joints
- Regulate cell motility and adhesion



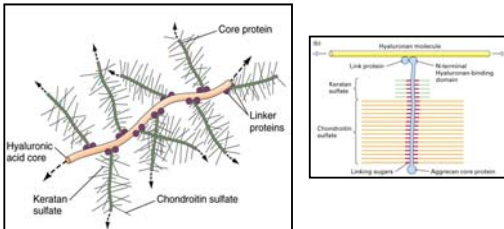
## Other (nonstructural) functions of proteoglycans

- Sequestration of growth factors
- Present hormones to cell-surface receptors



## Proteoglycans

- Assemble into aggregates with hyaluronan as a core of the aggregate



## Hyaluronan a.k.a. hyaluronic acid, hyaluronate

- Major component of proteoglycans
- Extremely long, negatively charged polysaccharide
- Resists compression
  - Swollen gel creates turgor pressure
- Forms viscous, hydrated gels
  - Large number of anionic residues on the surface bind water



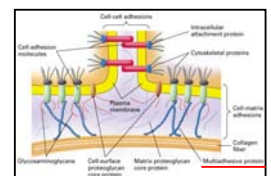
## Hyaluronan

- Hyaluronan keeps cells apart from one another
  - Facilitates cell migration
  - Surrounds migrating and proliferating cells
  - Inhibits cell-cell adhesion



## Adhesive glycoproteins

- Long flexible molecules with domains for binding
  - Collagen
  - Other matrix proteins
  - Polysaccharides
  - Cell surface molecules
  - Signaling molecules



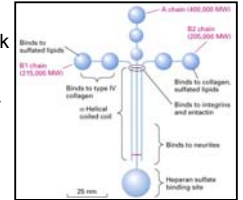
## Adhesive glycoproteins

- Attach cells to the extracellular matrix
  - Regulate cell attachment
  - Migration
  - Cell shape
- Organize components of the matrix
- Most bind to integrins – cellular adhesion receptors



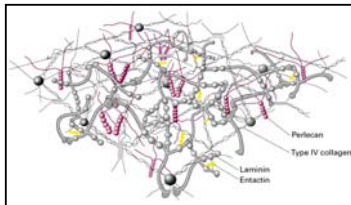
## Laminins

- Adhesive glycoproteins present in basal lamina
- Basal lamina guides cells during development
  - Cells migrate along laminin containing surfaces
- Cross-shaped proteins
  - As long as basal lamina is thick
- 3 subunits
- High affinity binding sites for
  - Heparan sulfate
  - Collagen IV
  - Cellular adhesion receptors



## Basal lamina

- A thin planar assembly of extracellular matrix proteins
- Basis is formed by collagen IV and laminin



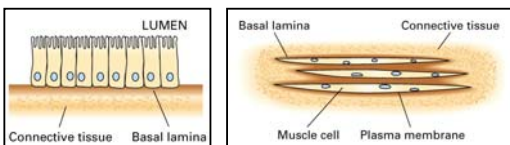
## Interaction of the basal lamina with adjacent cells

- Collagen IV and laminin interact with cell surface integrins and bind adjacent cells to basal lamina
- Basal lamina guides cells during development
  - Cells migrate along laminin containing surfaces



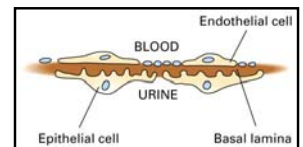
## Basal lamina is structured differently in different tissues

- Polarized cells
  - Filter that regulates passage of nutrients
- Smooth muscle
  - Maintenance of integrity



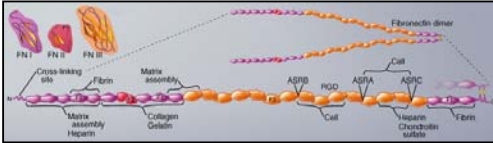
## Basal lamina is structured differently in different tissues

- Kidney glomerulus
  - Separates two cell layers
  - Double thickness lamina – both layers produce the basal lamina
  - Filters blood to form urine



## Fibronectins

- Attach cells to matrices that contain fibrous collagen
- Essential for migration and cellular differentiation



## Tenascin

- Expressed in embryonic tissues, wounds and tumors
- Plays a role in development
- Modular protein with 6 arms
- Binds to cells via integrins

