Connective Tissue-2

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Fibers of connective tissue

- The fibrous components of connective tissue are elongated structures formed from proteins that polymerize after secretion from fibroblasts.
- The three main types of fibers include collagen, reticular, and elastic fibers.
- Collagen and reticular fibers are both formed by proteins of the collagen family, and elastic fibers are composed mainly of the protein elastin.
Collagen

- The **collagens** constitute a family of proteins
- Collagen is the most abundant protein in the human body, representing 30% of its dry weight
- Produced mostly by fibroblasts
Collagen subtypes

- **Fibrillar collagens**, such as collagen types I, II, and III, have polypeptide subunits that aggregate to form large fibrils clearly visible in the electron or light microscope.

- **Network or sheet-forming collagens**, such as type IV collagen, have subunits produced by epithelial cells and are major structural proteins all epithelial basal laminae.

- **Linking/anchoring collagens** are short collagens that link fibrillar collagens to one another (forming larger fibers) and to other components of the ECM. **Type VII collagen** binds type IV collagen and anchors the basal lamina to the underlying reticular lamina in basement membranes.
<table>
<thead>
<tr>
<th>Type</th>
<th>Synthesizing cell</th>
<th>Function</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibroblast, osteoblast, odontoblast, cementoblast</td>
<td>Resist tension</td>
<td>Dermis, tendons, ligament, capsules, bone, dentin, cementum</td>
</tr>
<tr>
<td>II</td>
<td>chondroblasts</td>
<td>Resists pressure</td>
<td>Hyaline and elastic cartilage</td>
</tr>
<tr>
<td>III</td>
<td>Fibroblasts, reticular cells, smooth muscle, hepatocytes</td>
<td>Form structural framework of organs</td>
<td>Reticuloendothelial system, lung, skin</td>
</tr>
<tr>
<td>IV</td>
<td>Epithelium, muscle, Schwann cells</td>
<td>Meshwork of the lamina densa</td>
<td>Basal lamina</td>
</tr>
<tr>
<td>VII</td>
<td>Epithelial cells of epidermis</td>
<td>Anchoring fibrils between the lamina densa and reticularis</td>
<td>Derma-epidermal junction</td>
</tr>
</tbody>
</table>
Collagen Fibers

- Type I collagen is the most abundant and widely distributed collagen.
- Collagen type I subunits assemble to form extremely strong fibrils.
- Fibrils bundle together further by other collagens into much larger structures called collagen fibers.
- Collagen fibers form structures such as tendons, organ capsules, and dermis.
Collagen fibers in LM

- Collagen I fibers appear as large eosinophilic bundles
- They may fill the extracellular space.
- Subunits for these fibers were secreted by the fibroblasts associated with them.
Collagen fibers in TEM

- In longitudinal sections, fibrils display alternating dark and light bands.
- In cross section, the cut ends of individual collagen molecules appear as dots.
Collagen Synthesis

- **Collagen synthesis** occurs in many cell types but is a specialty of fibroblasts.
- The initial *procollagen α chains* are polypeptides made in the RER.
- In the ER three α chains are selected, aligned, and stabilized by disulfide bonds at their carboxyl terminals, and folded as a **triple helix**
- The triple helix undergoes exocytosis and is cleaved to a *procollagen molecule*
- Procollagen is the basic subunit from which the fibers are assembled.
**Intracellular environment**

- Formation of mRNA for each type of a chain.
- Synthesis of procollagen a chains with propeptides at both ends. Clipping of signal peptide.
- Hydroxylation of specific prolyl and lysyl residues in the endoplasmic reticulum. Vitamin C dependent.
- Attachment of soluble galactosyl and glucosyl sugars to specific hydroxyllysyl residues.
- **Assembly of procollagen molecules (triple helix).**
- Nonhelical propeptides.
- Transport of soluble procollagen to Golgi complex.
- Packaging of soluble procollagen in secretory vesicles.
- Secretory vesicles assisted by microtubules and microfilaments transport soluble procollagen molecules to cell surface.
- **Exocytosis of procollagen molecules to extracellular space.** Procollagen peptidases cleave most of the N-terminal propeptide transforming procollagen into insoluble collagen molecules, which aggregate to form collagen fibrils.
- **Fibrillar structure is reinforced by the formation of covalent cross-links between collagen molecules.** Catalyzed by the enzyme lysyl oxidase.
Reticular Fibers

- **Reticular fibers** consist of collagen type III
- Collagen III forms an extensive network of thin fibers
- They are found in delicate connective tissue of many organs such as liver, spleen, lymph nodes
- Reticular fibers are not visible in hematoxylin and eosin (H&E) preparations
- They stain black after impregnation with silver salts, and are thus termed **argyrophilic**
- Reticular fibers contain up to 10% carbohydrate and are therefore periodic acid-Schiff (PAS) positive
Reticular fibers-Silver stain
Elastic Fibers

- **Elastic fibers** are thinner than the type I collagen fibers
- They are found between collagen bundles
- Mainly found in organs subject to regular stretching or bending, such as the stroma of lungs
- They have rubber-like properties that allow tissue containing these fibers to be stretched and return to their original shape
- In the wall of large blood vessels, especially arteries, elastin also occurs as fenestrated sheets called elastic lamellae.
- Elastic fibers and lamellae stain poorly with H&E
- They are stained more darkly than collagen with orcein and aldehyde fuchsin
Elastic Fibers
Ground substance
Definition

- The **ground substance** of the ECM is a highly hydrated (with much bound water), viscous, transparent, complex mixture of three major kinds of macromolecules, filling the space between cells and fibers in connective tissue.
Composed of:

- Glycosaminoglycans (GAGs)
- Proteoglycans: Responsible for the gel state of the extracellular matrix.
- Adhesive glycoproteins
GAGs

- Also called mucopolysaccharides
- Long polymers of repeating disaccharide units, usually a hexosamine and uronic acid.
- The hexosamine can be glucosamine or galactosamine, and the uronic acid can be glucuronate or iduronate.
- They have a high negative charge
- GAGs have an extended conformation
- They have space-filling, cushioning, and lubricant functions.
Other types of GAGs

<table>
<thead>
<tr>
<th>GAG</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid</td>
<td>Most connective tissue, cartilage, dermis, synovial fluid.</td>
</tr>
<tr>
<td>Keratan sulfate</td>
<td>Cartilage, cornea, intervertebral disc.</td>
</tr>
<tr>
<td>Heparan sulfate</td>
<td>Blood vessels, lung, <strong>basal lamina</strong></td>
</tr>
<tr>
<td>Chondroitin 4-sulfate</td>
<td>Cartilage, bone, blood vessels</td>
</tr>
<tr>
<td>Chondroitin 6-sulfate</td>
<td>Cartilage, blood vessels, umbilical cord.</td>
</tr>
<tr>
<td>Dermatan sulfate</td>
<td>Skin, heart valves, blood vessels</td>
</tr>
<tr>
<td>Heparan sulfate (Heparin)</td>
<td>Mast cell granules, basophils, liver lung, skin.</td>
</tr>
<tr>
<td>Glycosaminoglycan</td>
<td>Distribution</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Umbilical cord, synovial fluid, vitreous humor, cartilage</td>
</tr>
<tr>
<td>Chondroitin 4-sulfate</td>
<td>Cartilage, bone, cornea, skin, notochord, aorta</td>
</tr>
<tr>
<td>Chondroitin 6-sulfate</td>
<td>Cartilage, umbilical cord, skin, aorta (media)</td>
</tr>
<tr>
<td>Dermatan sulfate</td>
<td>Skin, tendon, aorta (adventitia)</td>
</tr>
<tr>
<td>Heparan sulfate</td>
<td>Aorta, lung, liver, basal laminae</td>
</tr>
<tr>
<td>Keratan sulfate</td>
<td>Cartilage, nucleus pulposus, annulus fibrosus</td>
</tr>
</tbody>
</table>
Proteoglycans consist of a core protein to which are covalently attached various numbers and combinations of the sulfated GAGs.

Like glycoproteins, they are synthesized on RER, mature in the Golgi apparatus, where the GAG side-chains are added, and secreted from cells by exocytosis.

Unlike glycoproteins, proteoglycans have attached GAGs which often comprise a greater mass than the polypeptide core.
After secretion proteoglycans become bound to the hyaluronan by link proteins and their GAG side-chains associate further with collagen fibers and other ECM components.
Hyaluronan

- The largest and most ubiquitous GAG is **hyaluronan** (also called hyaluronate or hyaluronic acid)
- Hyaluronan forms a viscous, pericellular network which binds a considerable amount of water
- It has an important role in allowing molecular diffusion through connective tissue and in lubricating various organs and joints.
Adhesive Glycoproteins

- The adhesive glycoproteins are large molecules with branched oligosaccharide chains and allow adhesion of cells to their substrate.
- They have multiple binding sites for cell surface integrins and for other matrix macromolecules.
- Examples: Laminin, chondronectin, osteonectin and fibronectin.
Glycoprotein

Proteoglycan

GAG

Protein core
Classification of Connective Tissue
Connective tissue proper:
• Loose (areolar)
• Dense regular
  • Dense irregular
  • Dense regular

Special connective tissue:
• Reticular
• Elastic
• Adipose
• Bone
• Cartilage
• Blood

Embryonic connective tissue
• Mesenchymal (mucoid) connective tissue
Loose Connective Tissue

- Also called areolar connective tissue
- Typically contains cells, fibers and ground substance in equal amounts
- Supports epithelium (lamina propria)
- Surrounds small blood vessels
- Fills spaces between muscle and nerve cells
- Mesentery
- It is flexible but not very resistant to stress
Dense Regular Connective Tissue

- Parallel bundles of collagen fibers with few fibrocytes aligned with collagen and separated by very little ground substance
- Provides resistance to prolonged or repeated stresses exerted in the same direction
- Ligaments and tendons
Collagen Fibers

Fibroblasts
Dense Irregular Connective Tissue

- Bundles of collagen fibers are randomly interwoven with no definite orientation
- Provides resistance to stress from all directions
- Dermis of skin, organ capsules, submucosa
Reticular Connective Tissue

- Consists of reticular cells (modified fibroblasts) and the network of reticular fibers formed by them
- Forms the structural framework in which the cells of the organ are suspended
- In the liver, bone marrow, lymph nodes and the spleen
Mesenchymal Connective Tissue

- Mesenchyme forms the undifferentiated "filling" of the early embryo.
- It consists of mesenchymal cells, which interconnect by slender cell processes.
- Mesenchymal cells have stem cell properties, i.e. they are able give rise to other cell and tissues types.
- The wide extracellular space between the mesenchymal cells is occupied by ground substance.