Connective Tissue

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Features

- Originates from the mesenchyme
- Composed of cells and extracellular matrix
- Highly vascular
- Variable regenerative power
Functions

• Support:
• Defense and protection:
• Storage:
• Transport:
Cells of the Connective Tissue

**Fixed cells:**
- Fibroblasts.
- Adipose cells
- Mast cells.
- Macrophages.

**Transient cells:**
- Plasma cells.
- White blood cells (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes).
- Macrophages.
Fibrocyte

(Fiber producing cell)

Fibroblast
Fibroblast

• The most numerous cells of connective tissue.
• Occur in active and inactive forms (fibrocyte).
• Originate from undifferentiated mesenchymal cells.
• Capable of some movement.
• Rarely undergo division (in adults).
Fibroblasts/ histological features

- Closely associated with collagen bundles.
- Elongated, fusiform, and have many processes.
- Cytoplasm is pale and difficult to be differentiated from near by tissue.
- Nucleus is large (ovoid) euchromatic, prominent nucleolus
- E.M: prominent Golgi, mitochondria, rER, actin and myosin.
Fibrocytes/histological features

• Smaller and spindle-shaped.
• The nucleus is smaller and darker (heterochromatic).
• Few processes.
• E.M: few rER.
• When stimulated, it may revert to fibroblast.
Myofibroblasts

- Has features of both smooth muscles and fibroblasts.
- Their contraction is responsible for wound contraction.
Mast cell
Mast cell

• Large cell ~ 7-20 μm.
• Derived from precursors in the bone marrow.
• Nucleus: central ovoid.
• Cytoplasm highly granular, metachromatic.
• Granules contain:
  – Heparin
  – Histamin
  – Leukotriens
  – Eosinophil chemotactic factor.
  – Neutrophil chemotactic factor.
  – Platelet activating factor.
  – Bradykinin.
  – Thromboxane A₂

Perivascular mast cells
Mucosal mast cells
Plasma cell
LYMPHOCYTES AND PLASMA CELLS
(Agents of the immune response)

Lymphocytes → differentiation stimulated by immune activation → Plasma Cells (produce immunoglobulins - antibodies)
Plasma cell

- Derived from B lymphocytes following exposure to an antigen.
- Present at portal of entry of organisms and sites of chronic inflammation.
- Life span ~ 10-20 days.
- Large ovoid cells ~ 20 µm.
- Nucleus: eccentric with clusters of heterochromatin ➔ cart-wheel or clock-face nucleus.
• **Cytoplasm:**
  – Intensely basophilic.
  – Well developed supranuclear Golgi apparatus (-ve image).
  – Well developed rER.

• **Functions:** secretion of specific antibodies.
Negative Golgi stain
Macrophage
Macrophage

• Derived from monocyte.
• Large cells ~10-30 μm.
• Surface shows many projections.
• Nucleus: eccentric, oval or indented (kidney-shaped).
• Cytoplasm: well developed Golgi, prominent rER, many lysosomes.
• They are part of the MPS.
• Multinuclear giant cells
Macrophage eating bacteria
Monocytes and macrophages are the same cells at different stages of maturation.
Dust cells
Mononuclear phagocyte system

• Is a part of the immune system that consists of the phagocytic cells

• The macrophage like cells have been given different names in different organs

• also called Reticuloendothelial System or Macrophage System
MONONUCLEAR PHAGOCYTIC SYSTEM
(reticuloendothelial system)

Monocyte

Mononuclear wandering cell → coalescence → Giant Cell

- Macrophages
  - bone marrow
  - connective tissue
- Osteoclasts
  - bone resorption
- Kupffer Cells
  - liver sinusoids
- Microglial Cells
  - central nervous system
- Dendritic cells
  - Lymph node
  - spleen
  - Langerhans cells
  - epidermis

(All characterized by phagocytic activity)
Extracellular Matrix

- Extracellular Matrix = ground substance + fibers.
  - Resists compression and stretching forces.
  - The water content allows rapid exchange of metabolites.
Ground substance

• Composed of:
  – **Glycosaminoglycans:**
    • Sulfated: keratan sulfate, chondroitin sulfate, dermatan sulfate and heparin.
    • Non-sulfated: hyaluronic acid
  – **Proteoglycans:** Responsible for the gel state of the extracellular matrix.
  – **Adhesive glycoproteins:** laminin, chondronectin, osteonectin and fibronectin.
Proteoglycan
b Proteoglycans linked to hyaluronan

hyaluronidase
A typical glycoprotein
Functions of proteoglycans

• Resistance of compression.
• Retardation of movement of microorganisms.
• Act as a filter.
<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, basal lamina</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>
</tbody>
</table>
Connective Tissue Fibers

- Collagen
- Elastic
- Reticular
Collagen fibers

• Gives the extracellular matrix strength to resist tensile forces.
• Formed of protein collagen (30% of all proteins of the body).
• H & E: long, wavy pink bundles.
• Birefringent
• E.M: cross banding at 67 nm.
• Fibers are formed of aggregation of fibrils.
• Fibrils are formed of tropocollagen.
• Tropocollagen is formed of 3 helical polypeptide chains.
• α-chains possess 1000 amino acids.
• Every 3rd amino acid is glycine.
  – Other amino acids: proline, hydroxyproline, hydroxylysine.
• The sequence of amino acids determines the type of collagen.
  – There are 28 types of collagen.
### Major Types of Collagen

<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, ligaments, capsules, bone, dentin, cementum</td>
</tr>
<tr>
<td>II</td>
<td>chondroblasts</td>
<td>Resists pressure</td>
<td>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>V</td>
<td>Fibroblasts, mesenchymal cells</td>
<td>Associated with type I.</td>
<td>As in type I and placenta</td>
</tr>
<tr>
<td>VII</td>
<td>Epidermal cells</td>
<td>Anchoring fibrils between the lamina densa and reticularis</td>
<td>Derma-epidermal junction</td>
</tr>
</tbody>
</table>
Formation of mRNA for each type of a chain.

Synthesis of procollagen α 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 hydroxylysyl 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 nonhelical terminal peptides, 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.
Collagen bundle

↓↓

Fibers

↓↓

Fibrils

↓↓

Tropocollagen

↓↓

3 Helical polypeptide chains, \( \alpha \)-chains.

8.6 nm
**Intracellular**

* Transcription (Nucleus).
* Translation (rER).
* Hydroxylation (rER).
* Glycosylation (rER & Golgi).
* Formation of the triple helix.
* Secretion of procollagen (trans Golgi network and microtubules).

*** Vit. C is essential

**EXTRA CELLULAR**

Cleavage and assembly
Clinical applications

- Keloid
- Vitamin C deficiency (Scurvy)
- Ehlers–Danlos syndrome
Keloids
Ehlers–Danlos syndrome – Type with Hypermobility
Elastic fibers

• Composed of:
  1- Elastin
  2- Fibrillin
    • Elasticity is due to elastin.
    • Stability is due to fibrillin microfibrils (resistant to boiling).
  – Appears yellow in fresh tissue (if large amount is present)
    • Digested by pancreatic enzyme elastase
Elastic fibers consist of individual microfibrils (fibrillin) which are embedded in an amorphous matrix (90% of the fiber and composed of elastin).

Elastic material is found in certain ligaments (elastic ligaments), some cartilage (called elastic cartilage) and in large arteries (elastic arteries).
Elastin molecules are crosslinked by desmosine
Reticular fibers

- Consist mainly type III collagen.
- Short, thin and branching.
- High sugar content
- Give PAS +ve reaction.
- Stain with Silver Nitrate (*Argyrophyllic*).
- Found mainly in reticular lamina of basement membrane, RES organs (supporting stroma)
## Connective Tissue Fibers

<table>
<thead>
<tr>
<th>Fiber</th>
<th>Properties</th>
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<tbody>
<tr>
<td>Collagen</td>
<td>Undulating course of longitudinally striated bundles, form meshwork of variable texture, stain pink-red in H&amp;E. Nonextensible.</td>
</tr>
<tr>
<td>Elastic</td>
<td>Forms sheets or lamina, Unstained in H &amp; E. Reversibly extensible. Stains brown-black in Orcein or Resorscin Fuchsin.</td>
</tr>
<tr>
<td>Reticular</td>
<td>Delicate network, Unstained in H &amp; E. Reversibly extensible. PAS +ve, stains black in AgNO₃ (Argyrophilic).</td>
</tr>
</tbody>
</table>
Classification of Connective Tissue

- **Connective tissue proper:** dense and loose
  - Loose (areolar)
  - Dense regular
  - Dense irregular

- **Special connective tissue:**
  - Reticular
  - Elastic
  - Adipose
  - Bone
  - Cartilage
  - Blood

- **Embryonic connective tissue:**
  - Mesenchymal connective tissue
  - Mucous connective tissue
Loose connective tissue

- Called also areolar connective tissue
- Typically contains cells, fibers and ground substance in equal amounts (more cells and ground substance than fibers)
- Supports epithelium (superficial layer of dermis and lamina propria)
- Surrounds small blood vessels
- Fills spaces between muscle and nerve cells
- Mesentery
- Its flexible but not very resistant to stress
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 of digestive tract
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, tendons, aponeuroses
- Tendons are poorly vascularized and repair of damaged tendons is very slow
Collagen

Tendons (collagen)
Reticular connective tissue

• consists of reticular cells (modified fibroblasts) and the network of reticular fibers formed by them

• forms the structural framework (stroma) in certain organs

• 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 with slender cell processes.
- Mesenchymal cells have stem cell properties, i.e. they are able give rise to other cell and tissues types.
- The extracellular matrix is mainly ground substance, which can be stained with dyes that also stain mucin - hence the alternative name of this tissue type: mucoid connective tissue.
Mesenchymal connective tissue

- Mucoid connective tissue also forms a compliant cushion around the vessels of the umbilical cord, where it is also called Wharton's jelly.
- In adult humans, mesenchymal connective tissue is only found in the dental pulp.