Specialized Connective Tissue (cartilage, bone,)

Dr. Samina Hyder Haq
Cartilage

- Three types
  1. Hyaline Cartilage: present in growth plate, larynx, trachea and bone. Contain Type II collagen and a high % of PGS
  2. Fibro- Cartilage: Knee and annulus fibroses of inter vertebral disc. Has type 1 collagen and less PGS
  3. Elastic Cartilage: Ear and epiglottis contain Elastic fibres
FIBROCARTILAGE

LOCATIONS:
- Intervertebral discs separating vertebrae along spinal column
- Pads within knee joint
- Between pubic bones of pelvis

FUNCTIONS:
- Resists compression
- Prevents bone-to-bone contact
- Limits relative movement

LM × 750
(c) Fibrocartilage

Collagen fibers in matrix
Lacuna
Chondrocyte
ELASTIC CARTILAGE

LOCATIONS: Pinna of external ear; auditory canal; epiglottis

FUNCTIONS: Provides support, but tolerates distortion without damage and returns to original shape.

Chondrocyte

Elastic fibers in matrix

LM × 358

(b) Elastic cartilage
HYALINE CARTILAGE

LOCATIONS: Between tips of ribs and bones of sternum; covering bone surfaces at synovial joints; supporting larynx (voicebox), trachea, and bronchi; forming part of nasal septum

FUNCTIONS: Provides stiff but somewhat flexible support; reduces friction between bony surfaces

LM × 500 (a) Hyaline cartilage
### Tissue Composition

<table>
<thead>
<tr>
<th>Component</th>
<th>Cartilage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells</td>
<td>5</td>
</tr>
<tr>
<td>Matrix</td>
<td>95</td>
</tr>
<tr>
<td>Water</td>
<td>70</td>
</tr>
<tr>
<td>Mineral</td>
<td>-</td>
</tr>
<tr>
<td>Organic</td>
<td>30</td>
</tr>
<tr>
<td>Collagen</td>
<td>60</td>
</tr>
<tr>
<td>Proteoglycan</td>
<td>25</td>
</tr>
<tr>
<td>Protein</td>
<td>15</td>
</tr>
</tbody>
</table>

### Articular Cartilage Structure

- No nerves
- Pain-free use
- Non-perception of injury
- No blood vessels
- No bruising
- Nutrition from synovial fluid
- Hydration from synovial fluid
- Source of repair absent
- Viable after death
CARTILAGE TURNOVER

Chondrocyte

Degradation
Collagenases
Gelatinases
Stromelysins
Aggreccanases
TIMPs

↑ cytokines, IL-1 α
↑ TNF

↓ glucocorticoids
↓ NSAIDs

Synthesis
Collagens
Proteoglycans
Proteins

↑ growth factors, IGF-1
↑ TGFβ

↓ cytokines
↓ NSAIDs
Growth plate Cartilage

- **Reserve Zone**
- **Proliferative Zone**
- **Zone of Maturation**
- **Upper Hypertrophic Zone**
- **Lower Hypertrophic Zone**
- **Metaphysis**

Calcification of cartilage:
- Osteoid
- Calcified trabecula
- Osteoblast
- Capillary
- **reserve or resting zone** composed of small round chondrocytes.

- **proliferative zone**, composed of columns of flattened cells lying parallel to the axis of the long bone.

- At the base of these columns, the cells mature and enlarge to form the **hypertrophic zone**. It is in the lowermost portion of the hypertrophic zone that matrix calcification begins in the **longitudinal septa** separating the columns of cells. Calcification does not occur in the **transverse septa** between cells in the same column. Under the calcified cartilage of the lower hypertrophic zone lies the newly formed spongy woven bone of the metaphysis. Increase in bone length occurs within the cartilage in the proliferative zone.
New bone formation in the growth plate

- The cells within the deepest region of the calcified cartilage die and their lacunae are invaded by capillaries from the metaphysis. Migrating osteoblasts from the metaphysis settle on the spicules of calcified cartilage and produce a layer of osteoid on its surface, which subsequently calcifies to form a woven bone. As growth continues, the woven bone of the metaphysis is modeled by osteoclasts and osteoblasts into the mature trabecular and later compact bone of the diaphysis.
## Comparison of Bone and Cartilage

<table>
<thead>
<tr>
<th>Structural Features</th>
<th>Cartilage</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Ground substance</td>
<td>2. PG + H2O</td>
<td>2. Ca and P mineral</td>
</tr>
</tbody>
</table>
## Comparison of Bone and Cartilage

<table>
<thead>
<tr>
<th>Metabolic Features</th>
<th>Cartilage</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oxygen</td>
<td>1. Relatively low</td>
<td>1. Relatively high</td>
</tr>
<tr>
<td>2. Nutrition</td>
<td>2. By diffusion through matrix</td>
<td>2. By diffusion through cytoplasm</td>
</tr>
<tr>
<td>3. Repair capability</td>
<td>3. Limited ability</td>
<td>3. Extensive ability</td>
</tr>
</tbody>
</table>
Structure of Bone
Structure of Bone

- Bones are heterogeneous in their organization and may be divided into distinct structural regions.
- At the outer surface is the periosteum, which is the source of the cells responsible for growth in bone width.
- Adjacent to this is cortical bone, and on the inner surface of the bone, adjacent to the marrow cavity, is trabecular bone.
- The inner surfaces of the bone are covered by cells that form the endosteum. Both trabecular and cortical bone are made of calcified lamellae in which osteocytes are entombed. The osteocytes are linked by a network of uncalcified channels termed canaliculi.
Two components of the bone

- **Compact** = cortical Bone
  Runs the length of the long bones, forming a hollow cylinder

- **Spongy** = trabecular bone
  Has a light, honeycomb structure
  Trabeculae are arranged in the directions of tension and compression
  Occurs in the heads of the long bones
  Also makes up most of the bone in the vertebrae
Bone Forming Cells

- Osteocytes
- Osteoblasts and osteoclasts derived from osteioprogenitor cells.
Osteocytes

- Trapped osteoblasts
- Keep bone matrix in good condition and can release calcium ions from bone matrix when calcium demands increase
- Connected to each other by long filopodia that run through narrow channels in calcified matrix – canaliculi
Osteoblast

- Make collagen – well developed secretory organelles
- Activate crystallization of hydroxyapatite onto the collagen matrix, forming new bone
- As they become enveloped by the collagenous matrix they produce, they transform into osteocytes
Osteoclasts

- Resorbe bone matrix from sites where it is deteriorating or not needed
- Multinucleated giant cells
- Focal decalcification and extracellular digestion by acid hydrolases and uptake of digested material
- Attach to the surface of the bone via integrins
- Absorption by production of HCl by proton pump and chloride channels
Extracellular matrix of the bone - osteoid

- Collagen type I arranged in a mesh
- Layers of various orientations (add to the strength of the matrix)
- Other proteins 10% of the bone protein
- Direct formation of fibers
- Enhance mineralization
- Provide signals for remodeling
Mineral

- A calcium phosphate/carbonate compound resembling the mineral hydroxyapatite
  - $\text{Ca}10(\text{PO}_4)_6(\text{OH})_2$
  - Hydroxyapatite crystals
  - Imperfect
  - Contain Mg, Na, K
Mineralization of the Bone

- Calcification occurs by extracellular deposition of hydroxyapatite crystals
- Trapping of calcium and phosphate ions in concentrations that would initiate deposition of calcium phosphate in the solid phase, followed by its conversion to crystalline hydroxyapatite
- Mechanisms exist to both initiate and inhibit calcification
Bone formation

- Osteoblast synthesize and secrete type I collagen
- Collagen molecules form fibrils
- Fibrils stagger and overlap themselves
- Mineral deposition
- Fibers join to form the framework
INTRAMEMBRANOUS BONE FORMATION

Progenitor cells
  ↓
Osteoblasts
  ↓
Osteoid
  ↓
Woven bone
  ↓
Lamellar bone

Suture lines Periosteum

ENDOCHONDRAL BONE FORMATION

Chondrocytes
  ↓
Cartilage
  ↓
Calcified cartilage
  ↓
Osteoid
  ↓
Woven bone
  ↓
Lamellar bone
  ↓
Growth plate End plate

Matrix synthesis

Calcification

Chondrocyte hypertrophy Matrix calcification

Vascular invasion Osteoblast recruitment

Resorption and reformation

Resorption and reformation
Bone remodeling

- Remodeling is the replacement of old bone tissue by new bone tissue which mainly occurs in the adult skeleton to maintain bone mass. This process involves the coupling of bone formation and bone resorption.

- In the normal adult about 3% of the cortical bone is remodeled per year, whereas about 25% of trabecular bone is remodeled.
Bone remodelling

- It consists of five phases:
  1. **activation**: preosteoclasts are stimulated and differentiate under the influence of cytokines and growth factors into mature active osteoclasts
  2. **resorption**: osteoclasts digest mineral matrix (old bone)
  3. **reversal**: end of resorption
  4. **formation**: osteoblasts synthesize new bone matrix
  5. **quiescence**: osteoblasts become resting bone lining cells on the newly formed bone surface
Bone remodelling Cycle

1. **Resorption**
2. **Reversal**
3. **Formation**
4. **Resting Phase**

The bone remodelling cycle involves the processes of resorption, reversal, formation, and resting phase, which are interlinked to maintain bone health and structure.
Calcium Homeostasis

- The bone of the skeleton serves two major functions: in providing a supporting structure for the other tissues and organs, and in providing a reservoir whereby calcium homeostasis can be maintained.

- Maintenance of calcium homeostasis is essential, as both hypocalcemia and hypercalcemia are physiologically deleterious. For example, hypocalcemia can result in tetany and hypercalcemia can result in calcification in tissues that do not normally calcify. Plasma calcium levels can be affected by the action of parathyroid hormone, vitamin D and calcitonin.
## Calcium Homeostasis

<table>
<thead>
<tr>
<th>Parathyroid hormone (parathyroid)</th>
<th>Released by low plasma calcium Stimulates bone resorption Prevents calcium excretion by kidneys Stimulates calcitriol synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol (1,25-diOH-Vit.D) (Vit. D in diet)</td>
<td>25-hydroxylation in liver 1-hydroxylation in kidney Stimulates bone resorption Stimulates intestinal calcium absorption</td>
</tr>
<tr>
<td>Calcitonin (thyroid)</td>
<td>Released by high plasma calcium Inhibits bone resorption</td>
</tr>
</tbody>
</table>
Phosphate level in serum

- The kidneys help control the amount of phosphate in the blood. Extra phosphate is filtered by the kidneys and passes out of the body in the urine. The amount of phosphate in the blood affects the level of calcium in the blood. Calcium and phosphate in the body react in opposite ways: As blood calcium levels rise, phosphate levels fall. But this relation between calcium and phosphate may be disrupted by some diseases or infections.
# Rickets (Deficiency in Ca and P04)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Calcium (high turnover)</td>
<td>Ca deficiency in diet Vitamin D deficiency in diet 1,25 diOH Vitamin D deficiency (1 hydroxylase defect) Organ resistance to Vitamin D (receptor defect)</td>
</tr>
<tr>
<td>↓ Phosphate (low turnover)</td>
<td>PO4 deficiency in diet Impaired kidney reabsorption Impaired kidney reabsorption Organ availability (alkaline phosphatase defect)</td>
</tr>
</tbody>
</table>
Structure of Teeth

- Enamel
- Dentine
- Pulp
- Gum
- Cementum
- Bone
- Blood vessel
- Nerve
Enamel

- In a set of teeth, the visible part is the white or yellowy enamel. This is the hardest material in the human body, consisting of calcium phosphate, fluorine, protein and water. Thanks to this combination, the enamel optimally protects the interior of each tooth from temperature differences, bacteria and acids, as well as from the pressure required to chew food.
Dentine

- The largest component of the tooth is comprised of dentine—the second barrier for protecting the dental pulp. In contrast to the enamel, it is made up of less compacted material and is thereby more susceptible to acids and bacteria. Dentine contains many tiny canals, through which run the nerve fibers. When a tooth is carious, the nerve fibers send impulses to the brain. We feel pain and go to the dentist.
Pulp

The pulp lies in a hollow chamber that is surrounded on all sides with dentine. It is comprised of blood vessels, connective tissue and cells. Appendages of the cells and nerves rise into the dentine; they supply it with nourishment, deposit dentine and transfer impulses.

The pulp is also responsible for the highly complex process of tooth formation. Before baby teeth or permanent teeth break into the oral cavity, pulp cells form dentine and enamel.
Cementum

- In the jaw bone, the root is surrounded by cementum. It is interspersed with tiny connective fibers, (collagen type I) which anchor the tooth into its socket with some degree of flexibility. The tooth is actually suspended from fibers which connect the bone to cementum. It is, therefore, not directly attached to the bone.
Dental Caries

- **Dental caries**, also known as **tooth decay** or **cavity**, is a disease wherein bacterial processes damage hard tooth structure (enamel, dentin and cementum. These tissues progressively break down, producing dental cavities (holes in the teeth). Tooth decay is caused by specific types of acid-producing bacteria that cause damage in the presence of fermentable carbohydrates such as sucrose, fructose, and glucose. The mineral content of teeth is sensitive to increases in acidity from the production of lactic acid.
Role of Fluoride in preventing dental Caries

- Calcium, as found in milk and green vegetables are often recommended to protect against dental caries. It has been demonstrated that Calcium and fluoride supplements decrease the incidence of dental caries. Fluoride helps prevent decay of a tooth by binding to the hydroxyapatite crystals in enamel. The incorporated Calcium makes enamel more resistant to demineralization and, thus, resistant to decay.
Mammalian Collagenase

- **Collagenases** are enzymes that break the peptide bonds in collagen. They belong to a family of extracellular metalloproteases. Collagenase production can be induced during an immune response, by cytokines that stimulate cells such as fibroblasts and osteoblasts, and cause indirect tissue damage. They play an important role in:
  - Bone Remodeling
  - Wound Healing
  - Resorption of uterine lining
  - Cancer
Bacterial Collagenase

- Certain Gram positive bacteria produce collagenase which is used in cell culture studies to isolate cells. Unlike animal collagenases that split collagen in its native triple-helical conformation, bacterial collagenase is unique because it can degrade both water-insoluble native collagens and water-soluble denatured ones. It can attack almost all collagen types, and is able to make multiple cleavages within triple helical regions.
Difference in action of Mammalian and bacterial collagenase
Gas gangrene

**Gas gangrene** (also known as "Clostridial myonecrosis" is a bacterial infection that produces gas within tissues in gangrene. It is a deadly form of gangrene usually caused by Clostridium gram positive bacteria. It is a medical emergency. Bacteria may enter the muscle through a wound and go on to proliferate in necrotic tissue and secrete powerful toxins. These toxins destroy nearby tissue, generating gas at the same time."
Gas gangrene

(a) (b)

Muscle fibers

Clostridium

Gas-filled spaces
Matrix metalloproteinase (MMPs)

- They are zinc-dependent endopeptidases;
- Collectively they are capable of degrading all kinds of extracellular matrix proteins, but also can process a number of bioactive molecules. They are known to be involved in the cleavage of cell surface receptors, the release of apoptotic ligands.
- The MMPs play an important role in associated with various physiological and pathological processes such as morphogenesis, angiogenesis, cirrhosis, arthritis and metastasis. MMP-2 and MMP-9 are thought to be important in metastasis. MMP-1 is thought to be important in rheumatoid and osteo-arthritis
Elastin

- In contrast to collagen, which forms fibers that are tough and have high tensile strength, elastin is a connective tissue protein with rubber-like properties. Elastic fibers composed of elastin and glycoprotein microfibrils are found in the lungs, the walls of large arteries, and elastic ligaments. They can be stretched to several times their normal length, but recoil to their original shape when the stretching force is relaxed.
Structure of Elastin

- Elastin is an insoluble protein polymer synthesized from a precursor, tropoelastin, which is a linear polypeptide composed of about 700 amino acids that are primarily small and nonpolar (for example, glycine, alanine, and valine. Elastin is also rich in proline and lysine, but contains only a little hydroxyproline and no hydroxylysine.
TropoElastin

- Tropoelastin is secreted by the cell into the extracellular space. There it interacts with specific glycoprotein microfibrils, such as fibrillin, which function as a scaffold onto which tropoelastin is deposited. Some of the lysyl side chains of the tropoelastin polypeptides are oxidatively deaminated by lysyl oxidase, forming allysine residues. Three of the allysyl side chains plus one unaltered lysyl side chain from the same or neighboring polypeptides form a desmosine cross-link
Cross linking of Elastin

Figure 4.12 Desmosine cross-link in elastin.
Elastic Fibres

Stretching a network of elastin & fibrillin molecules.

- The molecules are joined together by covalent bonds with fibrillin proteins (red) to generate a cross-linked network. In this model, each elastin molecule in the network can expand and contract as a random coil, so that the entire assembly can stretch and recoil like a rubber band.
Figure 4.13 Elastin fibers in relaxed and stretched conformations.
Role of α1-Antitrypsin

- In the normal lung, the alveoli are chronically exposed to low levels of neutrophil elastase released from activated and degenerating neutrophils. This proteolytic activity can destroy the elastin in alveolar walls if unopposed by the inhibitory action of α1-AT, the most important inhibitor of neutrophil elastase. Because lung tissue cannot regenerate, emphysema results from the destruction of the connective tissue of alveolar walls.
Destruction of alveolar tissue by elastase