CONNECTIVE TISSUE PROPER
CONNECTIVE TISSUE WITH THE SPECIAL PROPERTIES
CONNECTIVE TISSUES

- Connective tissue proper
- Connective tissue with special properties
  - Mucous tissue
  - Elastic tissue
  - Adipose tissue
- Blood and bone marrow
- Supporting connective tissues
  - Cartilage
  - Bone
CONNECTIVE TISSUES

- They have the same origin – mesenchyme and the same structure (cells and extracellular matrix)
- Unlike epithelial cells, connective tissue cells are widely separated by components of extracellular matrix

Cells of connective tissue + extracellular matrix [ECM]

- Connective tissue proper
- Connective tissue with special properties
  - Mucous tissue
  - Elastic tissue
  - Adipose tissue

Closely aggregated polyhedral cells and very little extracellular matrix
Epithelia are derived from all germinal layers.
Connective tissue is composed of two elements:
- Cells
- Extracellular matrix [ECM]
  - Fibers – collagen fibers, elastic fibers, reticular fibers
  - Ground substance

Extracellular matrix = Fibers + ground substance

Cells of connective tissues (CTs)
- Connective tissue proper – fibroblasts, fibrocytes
- Adipose tissue – adipoblasts, adipocytes
- Cartilage – chondroblasts, chondrocytes
- Bone – osteoblasts, osteocytes
- Blood – formed elements (erythrocytes, leukocytes)
ORIGINS OF CT CELLS

Mesenchymal cell

- Mast cell
- Fibroblast
- Chondroblast
- Osteoblast
- Osteocyte
- Fibrocyte
- Hematopoietic stem cells
  (Hematopoiesis)

Adipocyte (white adipose tissue)

Adipocyte (Brown adipose tissue)
The function of connective tissues

- Providing structural support
- Serving as a medium for exchange
- Aiding in the defense and protection of the body
- Forming a site for storage of fat

The function of connective tissue proper

- Forms the capsules encasing organs
- Stroma forming the structural framework within organs
- Medium for exchange of metabolic waste, nutrients and oxygen between the blood and many of cells in the body
Cells of Connective Tissue (CT) proper

- The cells spend all their live in the tissue
  - Fibroblasts – originate from undifferentiated mesenchymal cells, produce ECM components, can proliferate
  - Fibrocytes – quiescent fibroblasts

Two stages of activity

- The active cells
  - Fibroblasts
- The quiescent cells
  - Fibrocytes
**Fibroblasts**
- the most common cells in connective tissue
- cells responsible for the synthesis of ECM components
- branched cytoplasm
- ovoid, large and pale staining nucleus with nucleolus
- rich in RER and well developed Golgi complex
- produce the growth factors → influence growth and cells differentiation
- proliferate when the additional fibroblasts are required

**Fibrocytes**
- smaller than fibroblasts
- fewer processes
- smaller, darker, elongated nucleus
- small amount of RER
Myofibroblasts

- The cells with features of fibroblasts – produce ECM and smooth muscle cells (SMC) – contain actin and myosin filaments
- They are observed during wound healing
- The activity of myofibroblasts is responsible for wound closure after tissue injury – *wound contraction*
The cells which reside in the tissue

- Macrophages
- Mast cells
- Plasma cells
- Leukocytes
- Melanocytes
Macrophages → the Mononuclear Phagocyte System

- Morphological features reflect functional activity of macrophages:
  - they have pseudopodia, only in macrophages
  - irregular surface with protrusions – pinocytotic and phagocytic activity
  - oval or kidney-shaped nucleus located centrally
  - well-developed Golgi complex, many lysosomes, prominent rough endoplasmic reticulum (RER)

- Macrophages derive from monocytes of blood
- Monocytes cross the wall of venules and capillaries to penetrate the connective tissue
- They mature and acquire morphological features of macrophages

- Macrophages are long-living cells, can proliferate locally and may survive for months in tissues.
- The cells are distributed throughout the body, and in certain regions have special name:
  - histocytes – the connective tissue proper
  - Kupffer cells – the liver
  - microglia cells – the central nervous system
  - osteoclasts – the bone
  - dust cells in the lung
Macrophages function

- phagocytosis of foreign substances and bacteria
- antigen processing and presentation to other cells (Antigen Presenting Cells – APC)
- secretion of cytokines and other molecules
  - enzymes, e.g. collagenase
- removing cell debris and damaged extracellular components

- Macrophages when stimulated
  - may increase in size and are arrangement in clusters forming epithelioid cells;
  - may fuse to form multinuclear giant cells
- Epithelioid cells and giant cells are found only in pathological conditions.
Mast cells

derive from stem cells of the bone marrow

- Oval to round connective tissue cells
- The cytoplasm is filled with basophilic secretory granules
- Small, spherical nucleus, situated centrally

- Secretory membrane-bound granules of mast cells
  - they contain biological active substances:
    - histamine - promotes an increase in vascular permeability
    - heparin - (sulfated glycosaminoglycan is blood anticoagulant)
    - neutral proteases
    - chemotactic factor for eosinophils and neutrophils

- substances not stored in the granules:
  - leukotriens (C₄, D₄, E₄), tromboxanes, platelet-activating factor, interleukins…..
Mast cells

- The connective tissue mast cells
  - skin and peritoneal cavity

- The mucosal mast cells
  - the connective tissue of the intestinal mucosa and lungs

- The surface of mast cells contains specific receptors for immunoglobulin E (IgE), a type of immunoglobulin produced by plasma cells
Leukocytes

or white blood cells

- the wandering cells of the connective tissue
- they migrate through the walls of capillaries and postcapillary venules from the blood to connective tissue (diapedesis)

- Granulocytes
- B and T Lymphocytes
Plasma cells

- large, ovoid cells with basophilic cytoplasm, very well developed RER
- the Golgi complex occupy pale region in histological slides
- spherical nucleus, placed excentrically containing compact, coarse heterochromatin and lighter areas
- Average of plasma cells live is short, 10 – 20 days.
- B lymphocyte → plasma cell → synthesis of immunoglobulin
Adipose cells

- Adipose cells, adipocytes, fat cells
  - the connective tissue cells for storage of neutral fats or for the production of heat.

Melanocytes

- origin - neuroectoderm of neural crest
- function – synthesis and accumulation of the melanin
Fibroblasts – The extracellular matrix

- **Fibers**
  - Collagen fibers
  - Elastic fibers
  - Reticular fibers

- **Ground substance**
  - Glycosaminoglycans (GAGs)
  - Proteoglycans
  - Multiadhesive glycoproteins

The connective tissue fibers are formed by proteins that polymerize into elongated structures.

- **Collagen fibers**
  - Are formed by protein collagen
  - The collagen is the most abundance protein in the human body (30% of dry weight)
  - The collagens belong to a family of more than 25 members

  - The cell type responsible for collagen synthesis
    - Fibroblasts, chondrocytes, osteoblasts
    - Odontoblasts
    - Endothelial cells
    - Vascular smooth muscle cells
The collagen profile
• the principal amino acids – glycine (33.5%), proline (12%), hydroxyproline (10%)
• amino acids that are characteristic of the collagen – hydroxyproline and hydroxylysine

Collagen types

- Type I – the abundant: skin, tendon, bone, dentin, cementum
- Type II – cartilage, vitreous body
- Type III – reticular fibers: skin, muscle, blood vessels
- Type IV – all basement membranes (lamina densa of the basal lamina)
- Type V – fetal tissue, skin, bone, placenta
- Type VII – epithelia – anchors skin epidermal basal lamina to underlying stroma (anchoring fibrils)
Collagen is a protein polymer composed of monomeric units of the protein Tropocollagen.

- Tropocollagen 8.6 nm
- Three α chains
- Elongated protein 280 nm in length and 1.5 nm in width

Structural arrangement of collagen:
1) Collagen is arranged into microfibrils.
2) Microfibrils are arranged into fibrils.
3) Fibrils are grouped into a fiber.
4) Fibers are grouped into a collagen bundle.
Collagen synthesis

- **Procollagen** (3\(\alpha\) chains) synthesis
  - Registration peptides on both amino-terminal and carboxy-terminal ends
  - Precursor of tropocollagen

- Hydroxylation of proline and lysine
  - Peptidyl proline hydroxylase
  - Peptidyl lysine hydroxylase
  - Co-factors: \(\text{O}_2\), Fe, vit. C

- Glycosylation of hydroxylysine
  - Transferases
  - Mn

- Removing of registration peptides
  - Procollagen peptidases
  - Tropocollagen

- Formation of covalent cross-links between tropocollagen molecules
  - Lysyl oxidase
  - Cu and \(\text{O}_2\) ions
Vitamin C (ascorbic acid) deficiency leads to the scurvy, disease characterized by the degeneration of connective tissue. Lack of vit. C → abnormal hydroxylation of procollagen → synthesis of defective collagen
Reticular fibers

- consist mainly of type III collagen
- extremely thin
- they form extensive network in certain organs
- stain black by impregnation with silver salts – *agyrophylic fibers*

**Localization**
- are particularly abundant in smooth muscle tissue
- endoneurium
- spleen, lymph nodes, bone marrow
- constitute a network around the cells of parenchymal organ, eg. liver, endocrine glands
- the wall of arteries
Elastic fibers

- Elastin – the main component
- Precursor of elastin - proelastin
- Elastin is hydrolyzed by pancreatic elastase
- Elastin is rich in glycine and proline
- Contains two unusual amino acids – desmosine and isodesmosine formed between four lysines
- Has rubberlike qualities

- Elastoblasts
  - Fibroblasts
  - Chondrocytes
  - Vascular SMC
  - Endothelial cells
The elastic fibers system

- **Oxytalan fibers**
  - zonule fibers of the eye
  - dermis
  - do not contain elastin
  - consist of a bundle of 10nm microfibrils composed of glycoproteins: fibromodulin I and II, and fibrillin.

- **Elaunin fibers**
  - around sweet glands
  - dermis
  - irregular deposits of elastin between the microfibrils

- **Elastic fibers**
  - the wall of large arteries
  - connective tissues
  - elastin located centrally and thin sheath of microfibrils
  - the most numerous component of the system
Ground substance

- highly hydrated, colorless and transparent complex mixture of macromolecules
- it fills the space between cells and fibers
- it is viscous and acts as lubricant and barrier to the penetration of invaders

- Glycosaminoglycans (GAGs)
- Proteoglycans
- Multiadhesive glycoproteins
Glycosaminoglycans (GAGs)

- called mucopolysaccharides
  - dermatan sulfate
  - chondroitin sulfate
  - keratan sulfate
  - heparan sulfate
  - hyaluronic acid

- with the exception of hyaluronic acid GAGs are bound covalently to a protein core, forming proteoglycans
- with the exception of hyaluronic acid all other GAGs are sulfated
- GAGs are intensely hydrophilic and act as polyanions
Proteoglycans

- are composed of a protein core associated with the four main GAGs (without hyaluronic acid)
- proteoglycan (monomer) is three-dimensional structure (can be pictured as test tube brush)

Proteoglycans of extracellular matrix (ECM)

- **aggrekan** – the most important, the dominant in cartilage
- **syndecan, fibroglycan**

Functions:
- structural component of ECM
- anchoring cells to the ECM
- as extracellular and surface proteoglycans bind many protein growth factors (TGF-β → transforming growth factor)

- Proteoglycans are degraded by several cell types (lysosomal enzymes). The lack of lysosomal enzymes causes several disorders in humans
Multiadhesive glycoproteins

- contain protein moiety with carbohydrates
- play an important role in the interaction between neighboring adult and embryonic cells
- play role in the adhesion of cells to their substrate

- **Fibronectin**
  - the product of fibroblasts and epithelial cells
  - has sites to bind cells, collagen and GAGs, the interactions help to mediate normal cell adhesion and migration

- **Laminin**
  - the adhesion of epithelial cells to basal lamina

- **Matrix receptors** are cell-surface molecules. Cells bind to collagen, fibronectin, laminin
  - **Integrins** – transmembrane linker proteins, interact with the cytoskeleton

- Intracellular proteins – the interaction between integrins, ECM, cytoskeleton elements
  - **Paxilin**
  - **Vinculin**
  - **Talin**
Types of connective tissue

Connective Tissue

- Connective tissue proper
  - Loose
  - Dense
    - Regular
    - Irregular
  - Mucous tissue

- Connective tissue with special properties
  - Adipose tissue
  - Elastic tissue
    - Hematopoietic (lymphatic and myeloid)

- Supporting connective tissues
  - Cartilage
  - Bone
Mesenchymeme

- The precursor embryonic tissue for all types of connective tissue
- Stellate undifferentiated cells and ground substance
- The lack of fibers
- Under specific stimuli the cells differentiate into the cells of connective tissue - fibroblasts, adipoblasts, chondroblasts, osteoblasts, blood cells
The connective tissue proper

- **Loose connective tissue**
  - the very common type of connective tissue
  - fills spaces between groups of muscle cells, supports epithelial tissue, forms layer around lymphatic and blood vessels.
  - is found in dermis, hypodermis, mucous membranes
  - has delicate consistency, it is flexible, well vascularized, not very resistant to stress
Dense connective tissue (CT)

- is adapted to offer resistance and protection
- there are fewer cells than loose connective tissue and high amount of collagen fibers

**Dense irregular CT**
- the collagen fibers are arranged in bundles without a definite orientation
- provide resistance to stress from all directions
- is found in dermis
Dense regular CT

- the collagen bundles are arranged in the definite pattern
- it is found in tendons

- the collagen fibers have parallel, closely packed bundles of collagen separated by a small quantity of intracellular ground substance
- fibrocytes have elongated nuclei parallel to the fibers
- the cytoplasm of fibroblasts stains the same color as the fibers
The connective tissue with special properties

- **Elastic tissue**
  - is composed of bundles of thick parallel elastic fibers
  - the spaces between the fibers are occupied by thin collagen fibers and flattened fibroblasts
  - is found in yellow ligaments of the vertebrates column

- **Reticular tissue**
  - consists of reticular fibers (type III collagen) and specialized fibroblasts named reticular cells
  - reticular tissue create the special microenvironment for hematopoietic organs and lymphoid organs
The connective tissue with special properties

- **Mucous connective tissue**
  - has a abundance of ground substance rich in hyaluronic acid
  - is jellylike tissue containing very few collagen fibers type I and type III
  - the cells – mainly fibroblasts
  - is found in umbilical cord and is referred to as Wharton’s jelly
  - is found in the pulp of young teeth

![Umbilical cord images]
Adipose tissue
- Special type of the connective tissue with predomination of adipose cells (adipocytes, fat cells)

✓ Adipocytes
  - as isolated cells, in small aggregates (adipose tissue)

Adipose tissue is found in a variety of places:
1] the hypodermis
2] surrounding and protecting certain organs
3] the medullary cavity of long bones

Functions:
1] stores energy
2] contributes to the thermal insulation of the body
3] protects delicate organs from mechanical trauma

- Unilocular adipose tissue (common or yellow)
- Multilocular adipose tissue (brown)
Unilocular (common or yellow) adipose tissue

- The color varies from white to dark yellow (depends on diet – carotenoids)
- It is found throughout the human body except:
  - eyelids, the penis, the scrotum, the entire auricle of the external ear (without the lobule)
- The distribution is determined by age and sex:
  - in the newborn has uniform thickness in the body
  - its distribution is partly regulated by sex hormones and adrenocortical hormones (different distribution in male and female body)

Spherical, isolated cell

- Lipid droplet
- Nucleus
- Cytoplasm

Signet ring cells

- Lipids are removed in routine histological techniques
- Sudan III

Polyhedral cells in adipose tissue
Unilocular (common or yellow) adipose tissue

- Cytoplasm
  - Golgi complex
  - mitochondria
  - poorly developed RER
  - SER
  - free polyribosomes
  - pinocytotic vesicles

- Basal lamina

- Vimentin intermediate filament

- Adipose tissue
  - Is richly vascularized
Unilocular (common or yellow) adipose tissue

- Large depot of energy for organism
- Lipids in adipose cells – triglycerides, glycerol
- Adipose cells can synthesize fatty acids from glucose \( \rightarrow \) insulin
- Metabolism of adipose tissue is regulated by hormones
  - The autonomic nervous system plays important role in mobilization of fats

Adipose tissue as a secretory organ

- enzymes – lipoprotein lipase
- leptin – peptide hormone (\( ob \) gene, acts on receptors in the hypothalamus of the brain where it inhibits appetite)
- adiponectin – protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism
- adipsin - serine protease that is secreted by adipocytes into the bloodstream.
- \( \text{TNF}_\alpha \) (Tumor Necrosis Factor \( \alpha \))
- source of estrogens in postmenopausal women (cytochrome P450 aromatase)
Obesity in adults

The disorders of energy, when energy intake exceeds energy expenditure.

- Adipose tissue (the largest organ in the body)
  - in men of normal weight represents 15 – 20% of the body
  - in women of normal weight = 20 – 25% of the body

- Hypertrophic obesity
- Hyperplastic obesity
- Genetic influences

There is no question that profound genetic influences affect weight regulation.

Leptin (its discovery in 1994), an appetite-suppressing hormone secreted by adipocytes. Leptin receptors - in neurons of the hypothalamus (target organ). Complex leptin/receptor: the appetite-stimulating neuropeptide Y (NPY) is suppressed by leptin.
Multilocular adipose tissue (brown fat)

- Multilocular tissue cells are polygonal and smaller than unilocular adipose cells
- The cytoplasm contains:
  - great number of lipid droplets of various sizes
  - spherical and central nucleus
  - numerous mitochondria with abundant long cristae (containing colored cytochromes)
- The cells receive direct sympathetic innervation
- The tissue is rich in capillaries
Distribution of multilocular adipose tissue

- In humans the tissue is important mainly in the first postnatal life (produces heat and protects the newborn against cold)
- It is greatly reduced in adulthood
- The tissue is more abundant in hibernating animals – hibernating gland

In human newborn the multilocular adipose tissue constitutes 2 - 5% of the body weight

- Mainly around the shoulder blades and kidneys
Function of the multilocular adipose tissue

- The main function is to produce heat
- The production is stimulated when human newborn or animals are exposed to the cold environment
- Nerve impulses release epinephrine → the stimulation of lipase in adipocytes → the release of fatty acid, that are metabolized → heat production (temperature of tissue is elevated)
- Mitochondria of multilocular adipocytes contain transmembrane protein – thermogenin (known as uncoupling protein 1, or UCP1)
- The energy is not used to synthesize ATP but is dissipated as heat
- Warmed blood circulates throughout the body
Slides

- Mesenchyme

Embryo head
- Mucous tissue

The umbilical cord - Warthon’s jelly

Vein

Arteries
Loose connective tissue

- Nuclei of fibrocytes and others cells
- Collagen fibers
- Elastic fibers
- Dense connective tissue
  - Dense regular CT
  - Dense irregular CT

Tendon

Skin
- Adipose tissue

Signet ring cells