

Preparation of Tissues for Study

- Chemical fixatives such as formalin are used to preserve tissue structure by cross-linking and denaturing proteins, inactivating enzymes, and preventing cell autolysis or self-digestion.
 - Dehydration of the fixed tissue in alcohol and clearing in organic solvents prepare it for embedding and sectioning.
 - Embedding in paraffin wax or epoxy resin allows the tissue to be cut into very thin sections (slices) with a microtome.
 - Sections are mounted on glass slides for staining, which is required to reveal specific cellular and tissue components with the microscope.
 - The most commonly used staining method is a combination of the stains hematoxylin and eosin (H&E), which act as basic and acidic dyes, respectively.
 - Cell substances with a net negative (anionic) charge, such as DNA and RNA, react strongly with hematoxylin and basic stains; such material is said to be “basophilic.”
- *Cationic substances, such as collagen and many cytoplasmic proteins react with eosin and other acidic stains and are said to beacidophilic .

Light Microscopy

- **Bright-field microscopy**, the method most commonly used by both students and pathologists, uses ordinary light and the colors are imparted by tissue staining.
- **Fluorescence microscopy** uses ultraviolet light, under which only fluorescent molecules are visible, allowing localization of fluorescent probes which can be much more specific than routine stains.
- **Phase-contrast microscopy** uses the differences in refractive index of various natural cell and tissue components to produce an image without staining, allowing observation of living cells.
- **Confocal microscopy** involves scanning the specimen at successive focal planes with a focused light beam, often from a laser, and produces a 3D reconstruction from the images.

Autoradiography

- This process localizes cell components synthesized using radioactive precursors by detecting silver grains produced by weakly emitted radiation in a photographic emulsion coating the tissue section or cells.
- With either light microscopy or TEM, autoradiography permits unique studies of processes such as tissue growth (using radioactive DNA precursors) or cellular pathways of macromolecular synthesis.

Cell & Tissue Culture

- Cells can be grown in vitro from newly **explanted tissues** (primary cultures) or as long-established cell lines and can be examined in the living state by phase-contrast light microscopy

Enzyme Histochemistry

- **Histochemical** (or cytochemical) techniques use specific enzymatic activities in lightly fixed or unfixed tissue sections to produce visible products in the specific enzyme locations.
- Fixation and paraffin embedding denatures most enzymes, so histochemistry usually uses frozen tissue sectioned with a cryostat.
- Enzyme classes for which histochemical study is useful include phosphatases, dehydrogenases, and peroxidases, with peroxidase often conjugated to antibodies used in immunohistochemistry.

Visualizing Specific Molecules

■ Some substances specifically bind certain targets in cells.

■ **Immunohistochemistry** is based on specific reactions between an antigen and antibodies labeled with visible markers, often fluorescent compounds or peroxidase for light microscopy and gold particles for TEM.

■ If the cell or tissue antigen of interest is detected by directly binding a labeled **primary antibody** specific for that antigen, the process is considered **direct immunohistochemistry**.

***Indirect immunohistochemistry** uses an unlabeled primary anti- body that is detected bound to its antigen with labeled secondary **antibodies**.

*The indirect immunohistochemical method is more commonly used because the added level of antibody binding amplifies the signal detected and provides greater technical flexibility.

Specific gene sequences or mRNAs of cells can be detected microscopically using labeled complementary DNA (cDNA) probes in a technique called in situ hybridization (ISH).

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Interpretation of Structures in Tissue Sections

Many steps in tissue processing, slide preparation and staining can introduce minor **artifacts** such as spaces and precipitates that are not normally present in the living tissue and must be recognized.

■ Sections of cells or tissues are essentially 2D planes through 3D structures, and understanding this fact is important for their correct interpretation and study

The Cell

Many cells show polarity, meaning different areas of the cell have different structures

The most-studied polarity is in epithelial cells, they have

1-Apical domain

2-Basal (basolateral) domain

The Plasma Membrane

The plasma membrane (**cell membrane or plasmalemma**) that envelops every eukaryotic cell.

It functions as a **selective barrier** regulating the passage of materials into and out of the cell and facilitating the transport of specific molecules.

IMPORTANT

Membranes range from 7.5 to 10 nm in thickness and consequently are visible **only in the electron microscope** (can NOT be resolved by the light microscope). They appear as a trilaminar unit in TEM.

The line between adjacent cells sometimes seen faintly with the light microscope consists of plasma membrane proteins plus extracellular material, which together can reach a dimension visible by light microscopy.

Components of plasma membrane

1-Phospholipids

2- Cholesterol

3- Proteins:

A) Integral: incorporated directly within the lipid bilayer

B) Peripheral: bound to one of the two membrane surfaces, particularly on the cytoplasmic side

4-Oligosaccharide (carbohydrate) chains linked to many of the phospholipid (to form glycolipids) and protein (to form glycoproteins) molecules.

Functions of Plasma Membrane

1. **Physical barrier:** Establishes a flexible boundary, protects cellular contents, and supports cell structure.

Phospholipid bilayer separates substances inside and outside the cell.

2. **Selective permeability:** Regulates entry and exit of ions, nutrients, and waste molecules through the membrane

3. **Electrochemical gradients:** Establishes and maintains an electrical charge difference across the plasma membrane.

4. **Communication:** Contains receptors that recognize and respond to molecular signals.

The Cytoplasm

Inside the cell membrane, the fluid cytoplasm (or cytosol) bathes metabolically active structures **called organelles**, which may be **membranous** (such as mitochondria) or **nonmembranous** protein complexes (such as ribosomes).

Most organelles are positioned in the cytoplasm by movements along the polymers of the **cytoskeleton**, which also determines a cell's shape and motility.

Ribosomes

Ribosomes are macromolecular machines, about 20×30 nm in size, which assemble polypeptides (proteins) from amino acids in a sequence specified by mRNA.

They can be free in the cytosol or bound to the rough endoplasmic reticulum.

During protein synthesis many ribosomes typically bind the same strand of mRNA to form larger complexes called **polyribosomes, or polysomes**

Differences between free and bound ribosomes

Free ribosomes synthesize cytosolic and cytoskeletal proteins and proteins for import into the nucleus, mitochondria, and peroxisomes.

Bound ribosomes synthesize proteins that are to be incorporated into membranes, stored in lysosomes, or eventually secreted from the cell.

Note that: The proteins produced by these ribosomes are segregated during translation into the interior of the ER's membrane cisternae.

Endoplasmic Reticulum (ER)

The endoplasmic reticulum is an **anastomosing network** of intercommunicating channels or cisternae formed by a continuous membrane network.

two types:

Rough endoplasmic reticulum (rER)

Smooth endoplasmic reticulum (sER)

Functions of ER

1-Synthesis: Provides a place for chemical reactions.

sER is the site of lipid synthesis and carbohydrate metabolism

rER synthesizes proteins for secretion, incorporation into the plasma, membrane, and as enzymes within lysosomes.

2-Transport: Moves molecules through cisternal space from one part of the cell to another, sequestered away from the cytoplasm

3-Storage: Stores newly synthesized molecules, sER stores C

4-Detoxification: sER detoxifies both drugs and alcohol.

Histological appearance

rER:

Light microscopy: Intense basophilia (blue to purple on H &E)

Electron microscopy: Appears as interconnected flat cisternae and tubules associated with ribosomes

sER:

Light microscopy: can not be seen under LM

Electron microscopy: Appears as interconnected tubules with various shapes and sizes and not stack of flattened cisternae not associated with ribosomes

Golgi Apparatus

Golgi apparatus, or Golgi complex, completes posttranslational modifications of proteins produced in the rER and then packages and addresses these proteins to their proper destinations.

Material moves from the rER cisternae to the Golgi apparatus in small, membrane-enclosed carriers called **transport vesicles**.

Has two sides (ends):

Receiving end (cis): receives transport vesicles

Shipping end (tran): ships secretory vesicles

Histological appearance

Golgi cannot be seen in H & E staining.

In highly active cells, with prominent golgi apparatus, it gives a negative image (as if an empty space)

Secretory Granules

The granules are surrounded by membrane and contain a concentrated form of the secretory product

Histologically

Light microscopy: they cannot be resolved, but in cells active in protein synthesis, they give apical cytoplasm intense eosinophilic appearance (pink)

Electron microscopy: homogenous electron dense structures near the apex of the cell

Lysosomes

Lysosomes are sites of intracellular digestion and turnover of cellular components.

Under electron microscopy, we can distinguish between primary and secondary lysosomes:

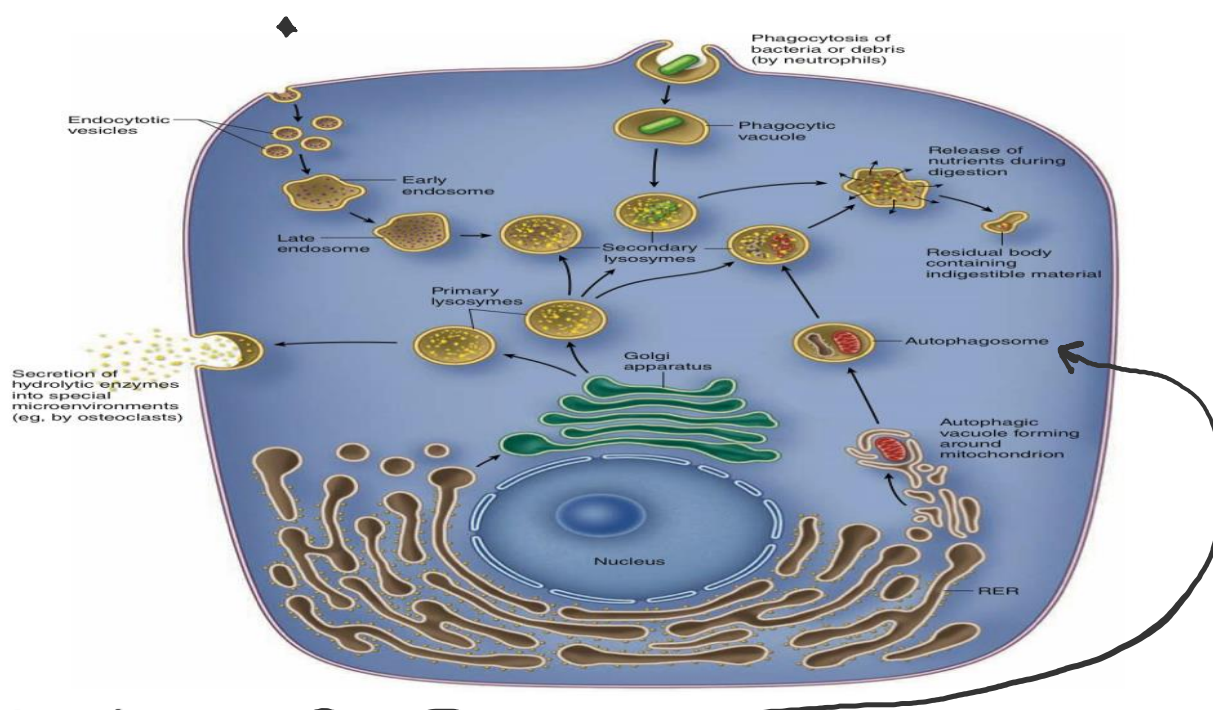
Primary: Uniformly granular electron dense appearance

Secondary: Larger with heterogenous appearance (particulate content)

Lysosomes are not well shown on H&E-stained cells but can be visualized by light microscopy after staining with **toluidine blue**.

Synthesis of lysosomal enzymes occurs in the RER, with packaging in the Golgi apparatus. Endocytosis produces vesicles that fuse with **endosomes** before merging with **lysosomes**.

Phagocytic vacuoles (or phagosomes) fuse with **primary lysosomes** to become **secondary lysosomes** (or heterolysosomes), in which ingested material is degraded.



Autophagosomes: are formed after nonfunctional or surplus organelles become enclosed with membrane and the resulting structure fuses with a lysosome.

The products of lysosomal digestion are recycled to the cytoplasm, but indigestible molecules **remain in a membrane-enclosed residual body**, which may accumulate in long-lived cells as lipofuscin. In some cells, such as osteoclasts, the lysosomal enzymes are secreted into a restricted extracellular compartment.

Mitochondria

Mitochondria are membrane-enclosed organelles with arrays of enzymes specialized for aerobic respiration and production of **adenosine triphosphate (ATP)**, which supplies energy for most cellular activities.

The number of mitochondria is related to the cell's energy needs: cells with a high-energy metabolism (eg, cardiac muscle, cells of some kidney tubules) have abundant mitochondria, whereas cells with a low-energy metabolism have few mitochondria.

Under the TEM each mitochondrion is seen to have two separated and very different membranes that together create two compartments: the innermost matrix and a narrow intermembrane space

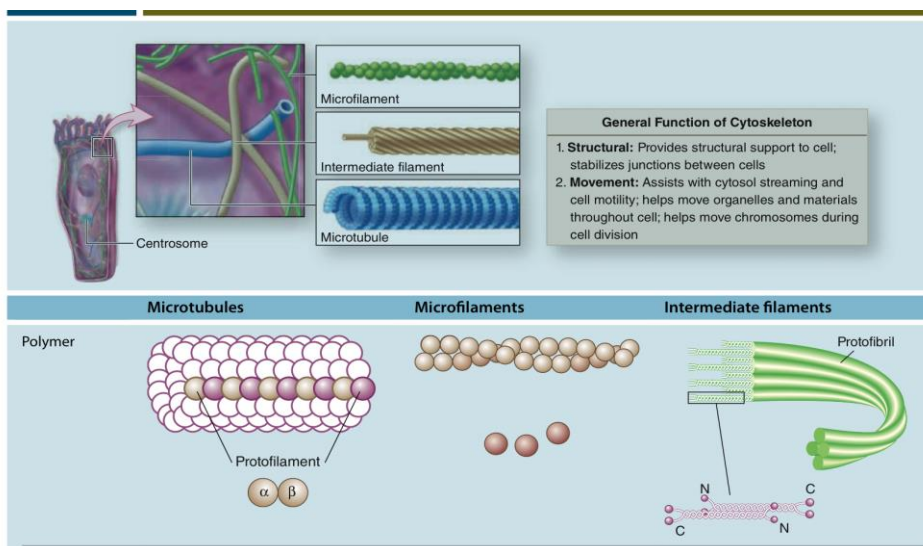
The **outer membrane** contains many transmembrane proteins **called porins** that form channels through which small molecules such as pyruvate and other metabolites pass from the cytoplasm **to the intermembrane space**.

The **inner membrane** has many long folds **called cristae**, which project into the matrix and greatly increase the membrane's surface area.

The cytoskeleton

The cytoplasmic cytoskeleton is a complex array of:

- (1) Microtubules.
- (2) microfilaments (also called actin filaments).
- (3) intermediate filaments.



General Function of Cytoskeleton

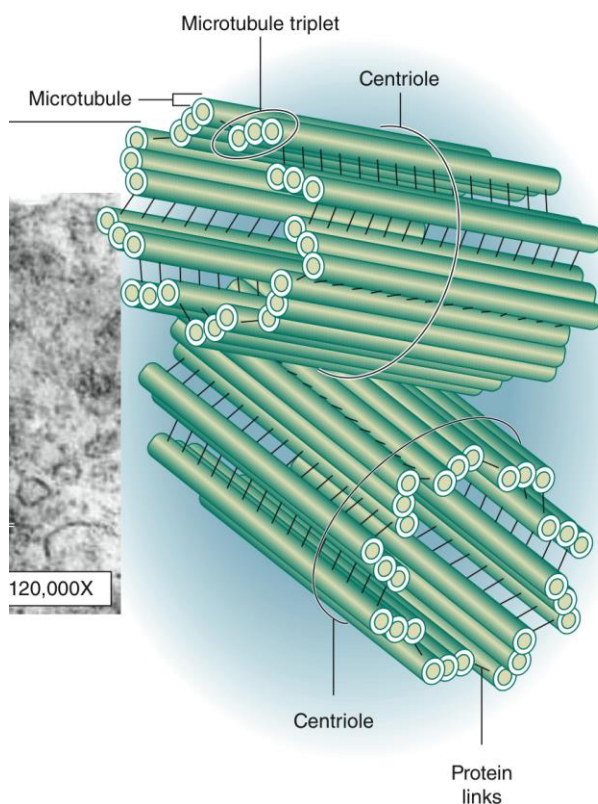
- 1. Structural**: Provides structural support to cell; stabilizes junctions between cells.
- 2. Movement**: Assists with cytosol streaming and cell motility; helps move organelles and materials throughout cell; helps move chromosomes during cell division

Centrosome

The centrosome is the microtubule-organizing center for the mitotic spindle and consists of paired centrioles.

The TEM reveals that the two centrioles in a centrosome exist at right angles to each other.

Each centriole consists of **nine microtubular triplets** peripherally arranged, and **no** microtubules in the center (arrangement: 9+0).



The Nucleus

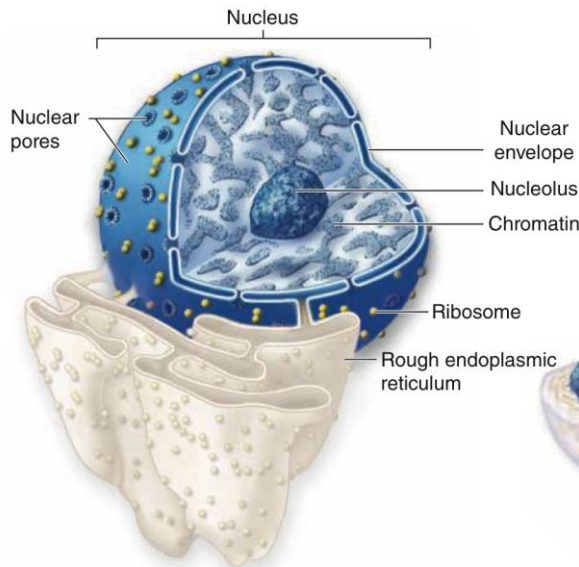
The nucleus contains the code for all of a cell's enzymes and other proteins. It also contains the molecular machinery to replicate the DNA and to synthesize and process all types of RNA.

The nucleus usually appears as a large rounded or oval structure, often near the cell's center.

It consists of a **nuclear envelope** containing **chromatin**, with one or more specialized regions of chromatin called **nucleoli**.

Functions of the Nucleus

- 1. Cellular regulation:** Houses genetic material, which directs all cellular activities and regulates cellular structure
- 2. Production:** Produces ribosomal subunits in nucleolus and



Chromatin

- *The mass of DNA and its associated proteins
- *Microscopically two categories of chromatin can be distinguished:

1-*Euchromatin* is visible as finely dispersed granular material in the electron microscope and as lightly stained basophilic areas in the light microscope.

→ associated with active cells

2-*Heterochromatin* appears as coarse, electron-dense material in the electron microscope and as intensely basophilic clumps in the light microscope.

→ associated with inactive cells

Nucleolus

The nucleolus is a spherical, highly basophilic subdomain of nuclei in cells actively engaged in protein synthesis

It is the location of ribosomal subunit assembly and transcription of ribosomal RNA (rRNA).

*The intense basophilia of nucleoli is due not to heterochromatin but to the presence of densely concentrated rRNA.

The Nuclear Envelope

The nuclear envelope is a double set of membranes with a narrow perinuclear space, which separates the cytoplasm from nucleoplasm.

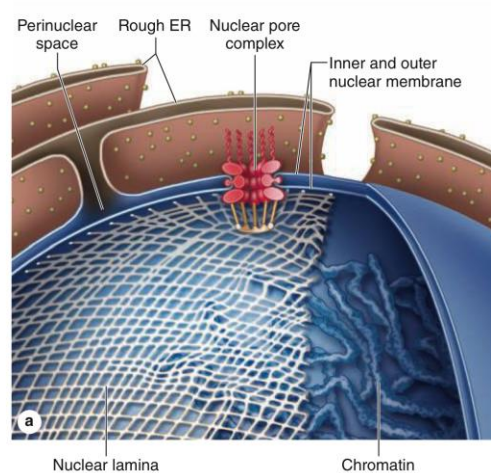
*The outer membrane binds ribosomes and is continuous with the RER.

*It is penetrated by nuclear pore complexes.

*It is supported internally by a meshwork, the nuclear lamina, composed of intermediate filament subunits called lamins.

Nuclear pore complexes

Nuclear pore complexes (nuclear pores) contain more than 30 core proteins (nucleoporins), span both membranes of the nuclear envelope, and regulate the bidirectional transfer of macromolecular complexes between the nucleus and cytoplasm.



Epithelial Tissue: SUMMARY OF KEY POINTS

- An epithelium is a tissue in which cells are bound tightly together structurally and functionally to form a sheetlike or tubular structure with little extracellular material between the cells.
- Cells in epithelia each have an **apical side** facing the sheet's free surface and a **basal side** facing a basement membrane and underlying connective tissue.
- Epithelia are often specialized for absorption or **transcytosis**, pinocytosis of material at the apical side and exocytosis at the basolateral side (or vice versa).
- Cells of most epithelia exhibit continuous renewal, with the locations of stem cells and rates of cell turnover variable in various specialized epithelia.

Basement Membrane.

- The **basement membrane** of all epithelia is a thin extracellular layer of specialized proteins, usually having two parts: a basal lamina and a more fibrous reticular lamina.
- The **basal lamina** is a thin meshwork of type IV collagen and laminin produced by the epithelial cells.
- The reticular lamina contains type III collagen and anchoring fibrils of VII collagen, all secreted by cells of the immediately adjacent connective tissue.

■ **Together**, these components attach epithelia to connective tissue, regulate (filter) substances passing from connective tissue into epithelia, provide a guide or scaffold during tissue regeneration after injury, and compartmentalize epithelial cells from other tissues.

Intercellular Junctions

■ Intercellular junctions are well developed in epithelia and consist of three major types, with different functions.

■ **Tight or occluding junctions** are formed by interacting trans- membrane proteins such as **claudin** and **occludin**; linear arrangements of these linked proteins surround the apical ends of the cells and **prevent paracellular passage** of substances (between the cells.)

■ **Adherent or anchoring junctions**, formed by interacting proteins of the **cadherin** family, are points of strong attachment holding together cells of the epithelium.

■ Adherent junctions may form ***zonula adherens*** that encircle epithelial cells just below their tight junctions or scattered, spot-like attachment sites called **desmosomes** or ***maculae adherens***, both of which are attached to cytoplasmic keratins.

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■ Hemidesmosomes composed of transmembrane **integrins** attach cells to proteins of the basal lamina.

■ **Gap or communicating junctions** are points of cell contact where both plasma membranes have numerous hexameric complexes of transmembrane connexons, each forming a channel allowing passage of small molecules from one cell to the other.

Apical Structures of Epithelial Cells

■ **Microvilli** are small membrane projections with cores of **actin filaments** that generally function to increase epithelial cells' apical surface area for **absorption**.

■ **Stereocilia** are long microvilli with specialized mechanosensory function in cells of the inner ear and for absorption in tissues of the male reproductive tract.

■ **Cilia** are larger projecting structures with a well-organized core of microtubules (in a 9 + 2 arrangement called the axoneme) in which restricted, dynein-based sliding of microtubules causes ciliary movement that propel material along an epithelial surface.

Morphological Types of Epithelia

■ An epithelium in which the basement membrane has one cell layer is **simple**; the cells of different simple epithelia range widely in height, from very thin or **squamous**, to roughly **cuboidal**, to very tall or **columnar**.

■ *Epithelia* with two or more layers of cells are **stratified** and almost all such epithelia are **stratified squamous**, in which the outer cell layers are thin and flattened.

■ Cells of stratified squamous epithelia move gradually from the basal to the surface layers, changing shape and becoming filled with **keratin** intermediate filaments.

■ Stratified squamous epithelia such as the epidermis cover the body surface, **protecting underlying tissues from excess water loss** (dehydration) and microbial invasion.

■ **Pseudostratified epithelia** are thick and appear to have several cell layers; all cells attach to the basal lamina but not all extend to the free epithelial surface.

■ **Transitional epithelium or urothelium**, found **only** in the lining of the urinary system, is stratified, with large rounded surface cells protective against urine.

Epithelial Secretion/Glands

■ *The major function in many epithelial cells is synthesis and secretion of specialized products; organs composed primarily of such epithelia are called **glands**.*

■ **Exocrine glands** have epithelial ducts carrying secretions to specific sites; the ducts of simple glands are unbranched and those of compound glands are branched.

■ *The secretory portions of exocrine glands may form round, saclike **acini** (also called **alveoli**) or elongated **tubules**; both types of secretory units may themselves branch.*

■ **Endocrine glands** lack ducts; secreted substances are hormones carried throughout the body by the interstitial fluid and blood, with specificity produced by the hormone receptors of target cells.

■ Glands have three basic secretory mechanisms: **merocrine**, which uses exocytosis; **holocrine**, in which terminally differentiated cells filled with lipid product are released; and **apocrine**, in which apical, product-filled areas of cells are extruded.

■ Exocrine glands producing mucus, or similar individual cells called goblet cells, are called **mucous glands**; oligosaccharide components of mucus stain poorly with routine dyes but stain well with PAS stain.

■ Exocrine glands producing largely enzymes (proteins) are called serous glands and stain darkly with H&E due to the cells' content of RER and secretory granules.

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Connective Tissue

- Connective tissue is specialized to physically **support** and **connect** other tissues and maintain the water required for metabolite diffusion to and from cells.
- Connective tissues all consist primarily of **extracellular** material rather than cells.
- Within most organs connective tissue proper form the supportive **stroma**, which supports the organ's unique functional components or parenchyma.
- The **extracellular matrix (ECM)** of connective tissue proper usually consists of both large protein fibers and nonfibrous areas of unstained **ground substance** rich in various GAGs and water.
- All adult connective tissues are derived from an embryonic form of connective tissue called **mesenchyme**, which contains uniformly undifferentiated **cells** scattered in a gel-like matrix.

Cells of Connective Tissue

- **Fibroblasts** (fibrocytes), the major cells of connective tissue proper, are elongated, irregularly shaped cells with oval nuclei that synthesize and secrete most components of the ECM.
- **Adipocytes** (fat cells) are very large cells specialized for storage of triglycerides; they predominate in a specialized form of connective tissue called adipose tissue.
- **Macrophages** are short-lived cells that differentiate in connective tissue from precursor cells called monocytes circulating in the blood; they function in ECM turnover, phagocytosis of dead cells and debris, and antigen presentation to lymphocytes.
- **Mast cells** also originate from blood cell precursors and are filled with granules for the release of various vasoactive agents and other substances during inflammatory and allergic reactions.
- **Plasma cells** are short-lived cells that differentiate from B lymphocytes and are specialized for the abundant secretion of specific anti- bodies (immunoglobulins).
- **Besides** macrophages and plasma cells, other leukocytes normally wander through all types of connective tissue proper, providing surveillance against bacterial invaders and stimulating tissue repair.

Fibers of Connective Tissue

- The most important and abundant fibers of connective tissue are composed of the protein **collagen**, of which there are some 20 related types.
- Synthesis of collagen by fibroblasts and certain other cells involves posttranslational modifications in the RER, notably **hydroxylation** of the numerous prolines and lysines, and formation of helical trimeric subunits of procollagen.

- Upon exocytosis, the nonhelical ends of the procollagen subunits are removed , forming trimeric collagen molecules that aggregate and become covalently bound together in large collagen fibrils.
- The highly regular assembly of collagens in the fibrils produces a characteristic pattern of crossbanding visible ultrastructurally along the fibrils of some collagen types.
- Fibrils of type I collagen are bundled together by other forms of non- fibrillar, linking collagens to produce large collagen bundles.
- Collagen fibrils are degraded by collagenase enzymes classified as matrix metalloproteinases (MMPs), produced primarily by macrophages.
- Type III collagen produces a network of delicate reticular fibers, which stain very dark with silver stains and are abundant in immune and lymphoid tissues.
- Elastic fibers, or sheets called elastic lamellae, are composed of the proteins elastin and fibrillin, which exist in a stretchable conformation that provides elastic properties to connective tissues rich in this material.

Ground Substance

- **Ground substance** is the watery, largely unstained extracellular material that is more abundant than fibers in some types of connective tissue proper.
- Ground substance is rich in **hydrated glycosaminoglycans (GAGs)**, **proteoglycans**, and **multiadhesive glycoproteins**.
- The major types of GAGs are **hyaluronan** (hyaluronic acid), which is a very long polymer of the disaccharide glucosamine-glucuronate, and various shorter chains of **sulfated GAGs** composed of other disaccharide polymers.
- Sulfated GAGs such as **chondroitin sulfate** and **keratan sulfate** have various sizes and compositions, but they are all bound to the core proteins of proteoglycans and are produced in the Golgi apparatus before secretion.
- Proteoglycans attach to polymers of HA via **linker proteins** to form huge complexes in ground substance that bind water and other sub- stances, including certain polypeptide growth factors that help regulate fibroblast proliferation.
- **Multiadhesive glycoproteins** such as fibronectin and laminin have binding sites for collagens and for integrin proteins in cell membranes, thus allowing temporary attachments between cells and the ECM required for cell migration and positioning.

Types of Connective Tissue

- **Connective tissue proper** is usually classified as loose or dense according to the amount of collagen and ground substance present.
- **Loose connective tissue** (or areolar tissue) has relatively more ground substance than collagen, and it typically surrounds small blood vessels and occupies areas adjacent to other types of epithelia.
- **Dense irregular connective tissue** is filled primarily with randomly distributed bundles of type I collagen, with some elastic fibers, providing resistance to tearing from all directions as well as some elasticity.
- **Dense regular connective tissue**, prominent in tendons and ligaments, features bundles of essentially parallel type I collagen, providing great strength (but little stretch) in binding together components of the musculoskeletal system.
- **Reticular tissue** consists of delicate networks of type III collagen and is most abundant in certain lymphoid organs where the fibers form attachment sites for lymphocytes and other immune cells.
- **Mucoid tissue** is a gel-like connective tissue with few cells found most abundantly around blood vessels in the umbilical cord.

Adipose Tissue

- The defining cells of adipose tissue (fat), **adipocytes**, are very large cells derived from mesenchyme and specialized for energy storage in lipid droplet(s) with **triglycerides**.
- Adipocytes store lipids from three sources: from dietary fats packaged as **chylomicrons** in the intestine; from triglycerides produced in the liver and circulating as **very-low-density lipoproteins** (VLDLs); and from fatty acids synthesized locally.
- Lipids are mobilized from adipocytes by **hormone-sensitive lipase** activated by **norepinephrine** released from the adrenal gland and various peptide hormones.
- Cells of adipose tissue are supported by reticular fibers, with connective tissue septa dividing the tissue into lobules of various sizes.
- There are two types of adipose tissue: **white fat and brown fat**

White Adipose Tissue

- **White adipose tissue** is found in many organs throughout the body, typically forming about 20% of the body weight in adults.
- Adipocytes of white fat are typically very **large cells**, ranging in diameter from 50 to 150 μm
- These cells each contain primarily **one large lipid droplet** (they are **unilocular**), causing the nucleus and remaining cytoplasm to be pushed against the plasmalemma.
- Fatty acids are released from white adipocytes by **lipase** activity when nutrients are needed and carried throughout the body on plasma proteins such as albumin.
- **Leptin** is a polypeptide hormone with target cells in the hypothalamus that is released from white adipocytes and helps regulate eating behavior.

Brown Adipose Tissue

- **Brown fat** comprises up to 5% of the newborn body weight but smaller amounts in adults .
- Adipocytes of this tissue are typically smaller than those of white fat and contain primarily **many small lipid droplets** (they are multi-locular) in cytoplasm containing many mitochondria and a central nucleus.
- Fatty acids released in adipocytes of brown fat are metabolized in mitochondria of these cells for **thermogenesis** rather than ATP synthesis, using **uncoupling protein-1**.

Good luck in your first mid exam

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