Lectures of Ultrastructure of Cell

(Master's Stage)
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Anatomy and Histology Department

By

Prof. Dr. Khulood Naji Rasheed

The Inclusions

They are minor cytoplasmic structures that are not usually surrounded by a membrane. They consist of such diverse materials like: stored cellular products, glycogen granules, pigment granules, fat droplets and crystals, stored waste products, as well as foreign bodies, viruses, intracellular bacteria, dust particles. Inclusions differ in nature in different types of cells. They are non-living structures incapable of growth and multiplication and do not possess metabolic activity (transitory structures, accumulated metabolites or other substances). Important and commonly seen inclusions include:

1. **Lipids:** accumulations of triglycerides droplets in storage form as common form of inclusions, are not only stored in specialized cells (adipocytes) but also located as individuals' droplets in various cell types, especially hepatocytes. These are fluid at body temperature and appear in living cells as spherical droplets. On demand, they serve as a local store of energy and a potential source of short carbon chains that are used by the cell in its synthesis of membranes and other lipid-containing structural components or secretory products (lipid droplets are usually nutritive inclusions that provide energy for cellular metabolism). Lipid droplets may appear in a cell for a brief time (as in intestinal cells) or may reside for a long period (as in adipocytes). Most solvents used in histological preparations extract triglycerides from cells, leaving empty spaces indicative of lipids locations. However, with the use of osmium and glutaraldehyde, the lipids may be fixed in position as gray-to black intracellular droplets.

2. **Glycogen:** aggregates of the carbohydrate polymer in which glucose is stored, visible as irregular clumps or granules in several cell types notably abundant in liver and muscle. It appears in electron micrograph as clusters, or rosette of β particles (and larger α particles in the liver) that resemble ribosomes, located near the smooth endoplasmic reticulum. Glycogen is an important energy source of the cell; therefore, it will be available on demand. The enzymes responsible for glycogenolysis degrade glycogen into individual molecules of glucose and can be utilized by multiple organs of the body.

3. Pigments: are deposits of naturally colored material, including:

- melanin, dark brown granules which serve in skin to protect cells from ultraviolet radiation.

- lipofuscin is a brownish-gold pigment. It is easily seen in nondividing cells such as neurons and cardiac muscle cells. Lipofuscin accumulates during the years in most eukaryotic cells because of cellular senescence (aging). Lipofuscin is a conglomerate of oxidized lipids, phospholipids, metals, and organic molecules that accumulate within the cells because of oxidative degradation of mitochondria and lysosomal digestion. Phagocytotic cells such as macrophages may also contain lipofuscin, which accumulates from the digestion of bacteria, foreign particles, dead cells, and their own organelles. Recent experiments indicate that lipofuscin accumulation may be an accurate indicator of cellular stress.

- hemosiderin is an iron-storage complex found within the cytoplasm of many cells. It is most likely formed by the indigestible residues of hemoglobin, and its presence is related to phagocytosis of red blood cells. Hemosiderin is most easily demonstrated in the spleen, where aged erythrocytes are phagocytosed, but it can also be found in alveolar macrophages in the lung tissue, especially after pulmonary infection accompanied by small hemorrhage into the alveoli. It is visible in light microscopy as a deep brown granule, indistinguishable from lipofuscin. Hemosiderin granules can be differentially stained using histochemical methods for iron detection.

4. Crystals: believed that these structures are crystalline forms of certain proteins. Such inclusions are found in the Sertoli cells (crystals of Charcot Böttcher) and Leydig cells (crystals of Reinke) of the testis, and occasionally in macrophages. With the TEM, crystalline inclusions have been found in many cell types and in virtually all parts of the cell, including the nucleus and most cytoplasmic organelles. Although some of these inclusions contain viral proteins, storage material, or cellular metabolites, the significance of others is not clear.

Vesicles

Small, spherical compartments that are separated from the cytosol by membrane. Many vesicles are made in the Golgi apparatus and the endoplasmic reticulum or made from parts of the cell membrane. Because they are separated from the cytosol, the space inside the vesicle chemically different from the cytosol. Vesicles are basic tools of the cell for organizing metabolism and as chemical reaction chambers. They can be classified according to their contents and function into several types, more common are lysosomes and peroxisomes.

* Lysosomes

Are small principal sites of intracellular digestion (Fig.1), may be spherical, rounded, elliptical or highly irregular in shape. They are membrane-limited vesicles that contain different enzymes. Lysosomes, which are usually spherical, range in diameter from (0.05 to 0.5)μm and present a uniformly granular, electron- dense appearance in the electron microscope. Lysosomal hydrolases are synthesized and segregated in the RER and then transferred to the Golgi apparatus, where the enzymes are further modified and packaged in vacuoles that form lysosomes.

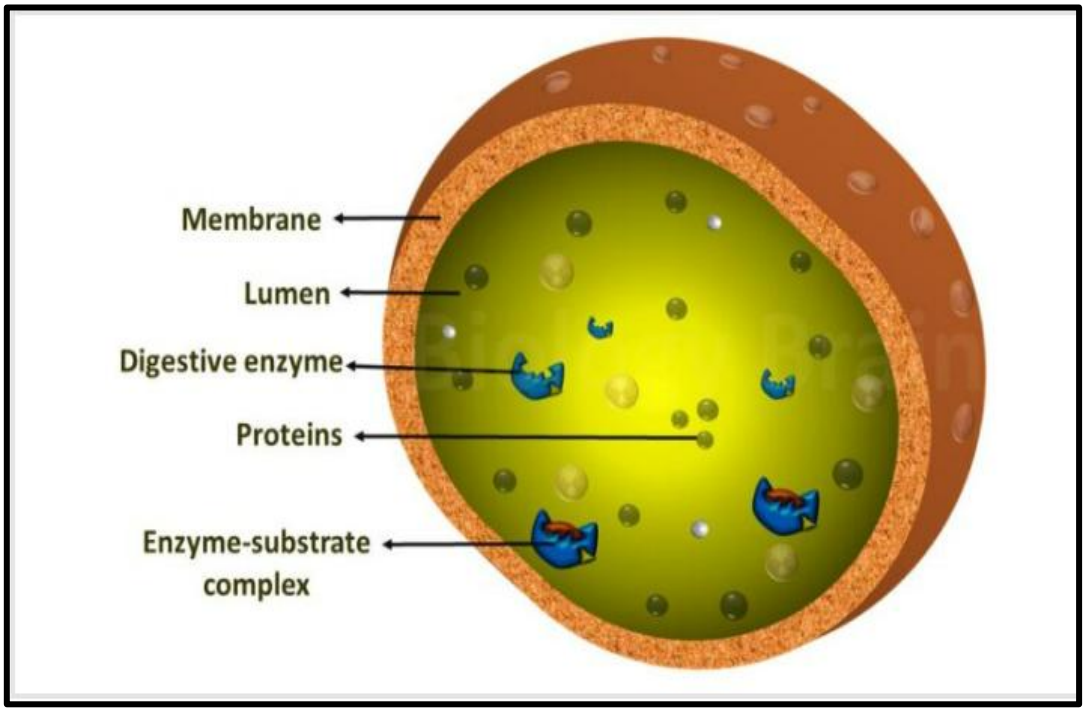

Fig. 1: Diagram of Lysosome.

Structure of Lysosomes

Lysosomes are round tiny bags filled with dense material rich in acid phosphatase (tissue dissolving enzymes) and other hydrolytic enzymes (Fig.2). They consist of two parts:

(1) Limiting membrane: This membrane is single and is composed of lipoprotein.

(2) Inner dense mass: This enclosed mass is made up of very dense contents. Lysosomes are of various types, and they help in intracellular digestion. Their contents vary with the stage of digestion.

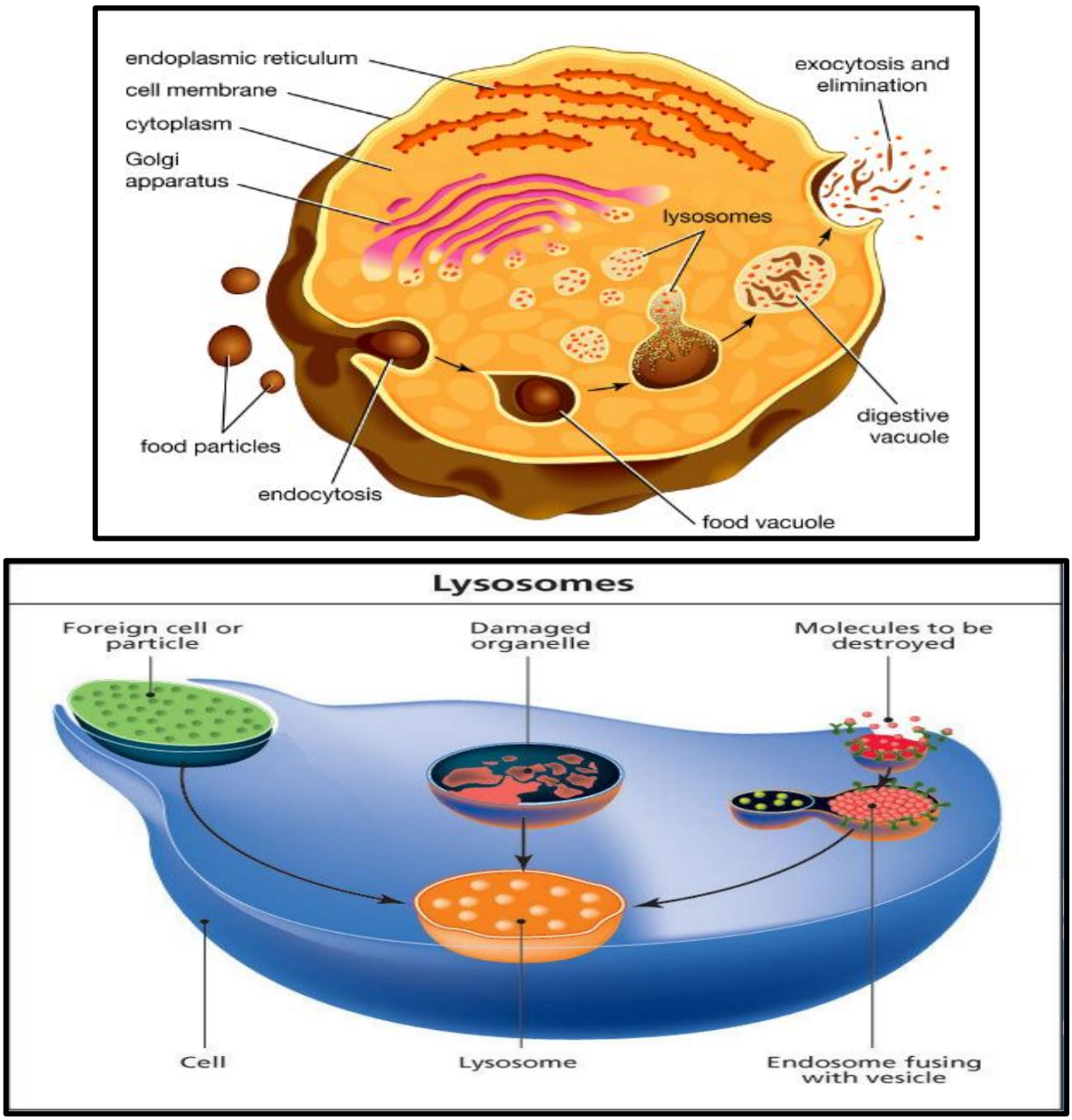

Fig. 2: Diagram of digestion within lysosome.

Kinds of Lysosomes

(1) primary lysosome (protolysosome, storage granule): a small sac-like body. Its enzymatic contents are synthesized by ribosomes and accumulated in ER. From there, they enter Golgi region, where acid phosphatase reaction takes place. Acid phosphatase rich region of Golgi maturing face is thought to be involved in production of lysosomes. As primary lysosomes formed 'recently' they considered virgin, because their enzymes haven't taken place their role in hydrolysis yet.

(2) secondary lysosome (digestive vacuole or heterophagosome): these are produced either from phagocytosis or pinocytosis of foreign material by the cell. Within the cell, after phagocytosis or pinocytosis, the foreign bodies or extra-cellular substances are enclosed within the membrane and these membranes bound structures are known as phagosome or pinosomes. These ultimately fuse with primary lysosomes, thus forming secondary lysosome. This body having engulfed material within membrane has also full complements of acid hydrolases (hydrolytic enzymes). The digested material of these lysosomes passes through the lysosomal membrane and is incorporated into the cell so that they may be reused in metabolic pathways.

(3) residual body (dense body, telolysosome): these are formed in case the digestion is incomplete. Hence, lysosomes having undigested material or debris are called residual bodies. These bodies are formed due to lack of certain enzymes in lysosomes. These are rejected from the cell by exocytosis and sometime in certain cells these bodies remain in cells for long time, so they referred to ageing. These residual bodies also cause diseases such as fever, hepatitis, polynephritis, hypertension, and congested heart failure.

(4) autophagic vacuole (cytolysosome or autophagosome): in this case, lysosome digests a part of cell (e.g., mitochondria or portion of ER) by the process of autophagy. For example, liver cells show numerous autophagosome during starvation. This is a mechanism by which the cell can achieve degradation of its own constituents without irreparable damage. Autophagy of organelles, cell, or tissue during the process of growth and differentiation or cell death is important and necessary (Fig.3).

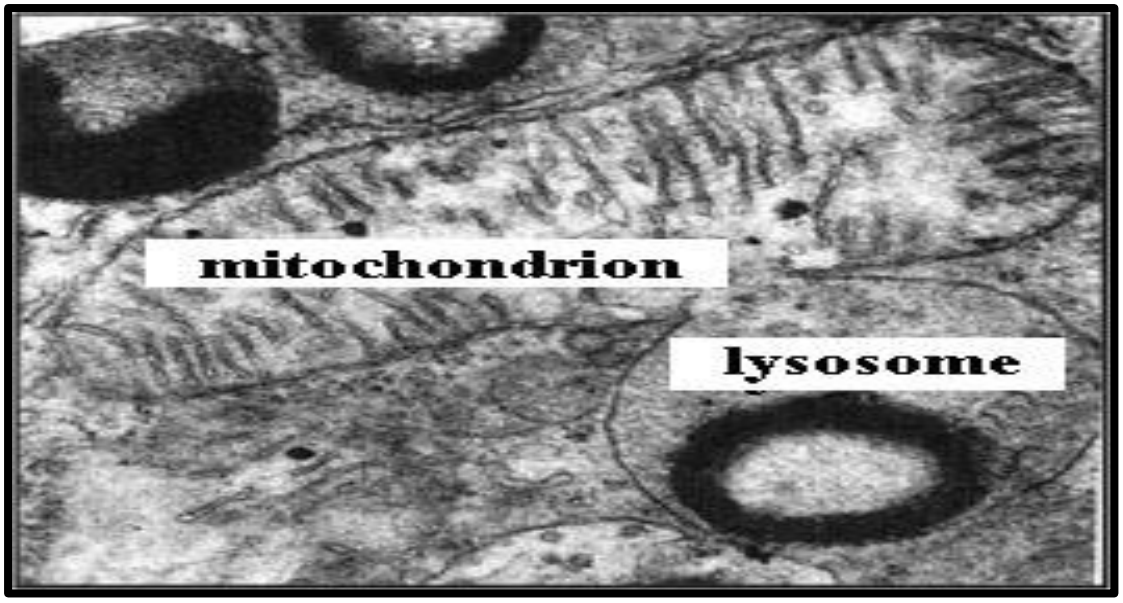

Fig. 3: Mitochondrion digested by lysosome (electron microscope).

Chemical Nature of Lysosomes

Chemically, lysosomes are defined as a body rich in acid hydrolases. Lysosomal enzymes can break down all major biological macromolecules present in the cells or entering the cells from outside into their building blocks subunits. The common enzymes in the lysosomes are about 40 different enzymes (powerful enzymes, capable of digesting all kinds of materials inside or outside the cell, could break down/digest even the cell). Lysosomes are particularly abundant in cells with great phagocytic activity like macrophages.

Functions of Lysosomes

1. digestion of useful materials: organic substances (food particles) taken up by the cells in vacuoles (pinocytosis or phagocytosis) from the environment are digested.

2. digestion of harmful materials: foreign particles, such as viruses, bacteria, and toxic molecules, are disposed of by hydrolyzing them in certain leucocytes and macrophages. This is called natural defense of the body.

3. digestion of unwanted materials: dead cells and debris that accumulate at the sites of injury are destroyed in some WBC. This is called natural scavenging of the body (lysosomes break down harmful cell products, waste materials, and cellular debris).

4. autolysis: plays a role in normal developmental changes in animals, e.g., in the breakdown and absorption of tail during the metamorphosis of frog's tadpole (removal of excess or nonfunctional organelles i.e., no longer required, then, digested products from autophagosomes are reused in the cytoplasm.). In autolysis, lysosome membrane ruptures and releases the enzymes into the surrounding cytoplasm, this kills and lyses the cell (lysosomes break down cells that are ready to die i.e., cell destroys itself if needed, thus lysosomes called suicidal bags).

5. aid in fertilization: lysosome of sperms releases their enzymes to dissolve the egg membranes for the entry of sperm into ovum in fertilization. This is called extracellular digestion.

Lysosomes and Disease

Loss of one or more hydrolysis enzymes because of genetic mutation will certainly affect the metabolic activity of the body. This phenomenon is considered an embryonic disease that occurs because of a genetic defect in the genes responsible for producing these enzymes, where the enzymes are defective and ineffective. As a result of these cases, substrates accumulate in the cells, which leads to the emergence of pathological symptoms such as the appearance of symptoms of Pompe disease and Gout disease, where the first is caused by the accumulation of glycogen, while the second is caused by the accumulation of uric acid.

* Peroxisomes

- Small membrane-bounded organelle (membrane-enclosed), presents in all cell type, provide a safe environment for a variety of reactions to inactivate toxic molecules. Like lysosome but less dense and contain several types of oxidases and catalases enzymes (Fig. 4).

- Named for their enzymes which are degrading hydrogen peroxide H2O2 that is harmful to cell (break down into water and oxygen molecules).

- They break down a variety of molecules, including toxins, alcohol, and fatty acids.

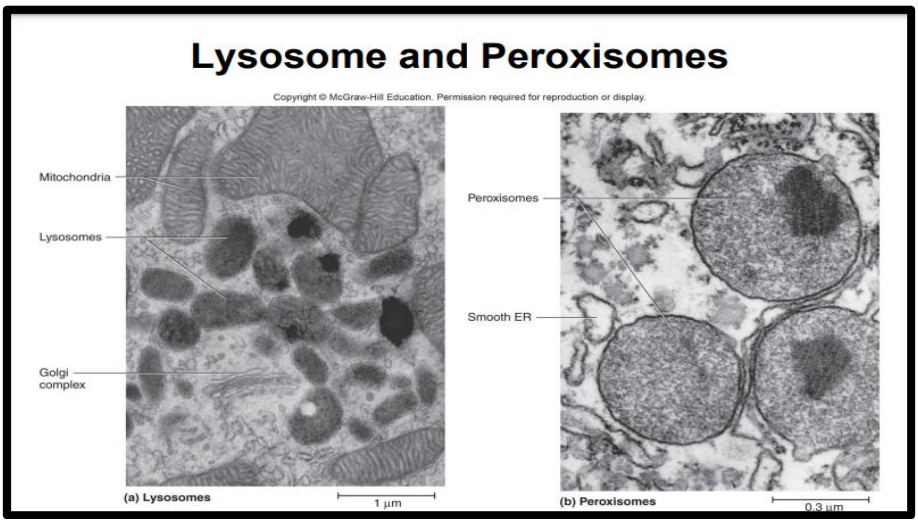

Fig. 4: Lysosome and Peroxisomes.

Peroxisomes and Disease

These organelles underappreciated for proper cell function and health of organism. The most severe peroxisomal disease called Zellweger Syndrome is caused by mutations that block peroxisomal protein import.

Zellweger syndrome: is called peroxisome biogenesis disorders, which are caused by defects in any one of 13 genes, required for the normal formation and function of peroxisomes. Zellweger disorders result from dysfunctional lipid metabolism, including the over-accumulation of very long-chain fatty acids, defects of bile acids and specialized lipids found in cell membranes and myelin sheaths of nerve fibers. Symptoms of these disorders include an enlarged liver; characteristic facial features such as a high forehead, underdeveloped eyebrow ridges, wide-set eyes; and neurological abnormalities such as cognitive impairment and seizures. Infants with Zellweger syndrome also lack muscle tone, sometimes to the point of being unable to move, and may not be able to suck or swallow, retinal degeneration, and impaired hearing. Jaundice and gastrointestinal bleeding also may occur. Prognosis for infants with Zellweger syndrome is poor. Most infants do not survive past the first 6 months, and usually succumb to respiratory distress, gastrointestinal bleeding, or liver failure. There is no cure for Zellweger syndrome, nor is there a standard course of treatment. Since the metabolic and neurological abnormalities that cause the symptoms of Zellweger syndrome are caused during fetal development, treatments to correct these abnormalities after birth are limited. Most treatments are symptomatic and supportive.