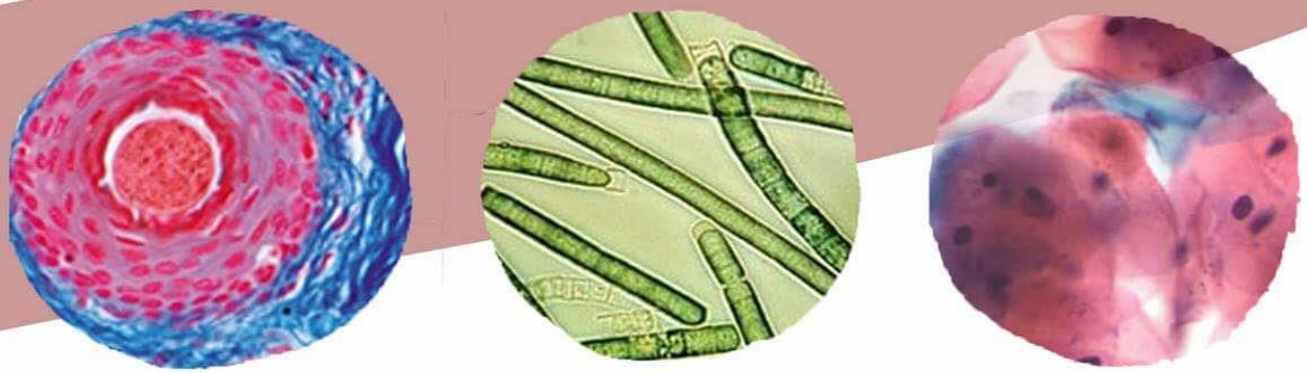
INTRODUCTION TO PATHOLOGY



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Sheet# 5

In this lecture you will be able to understand the following topics:

1. Autophagy

2. Intracellular Accumulations

3. Pathologic Calcification

4. Cellular Aging

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1. AUTOPHAGY

We have previously discussed autophagy in adaptive cell responses, specifically in our discussion of cell atrophy. Here we will discuss it in more detail.

Where we see autophagy before? In adaptor cellular process (ATROPHY)

What is autophagy ("self-eating")?

Lysosomal digestion of the cell's own components.

How does autophagy occur? (mechanism)

The process is initiated by multi-protein complexes that sense nutrient deprivation and stimulate the formation of a double membrane. The membrane begins to elongate until it completely encloses the cytoplasmic organelles that need to be recycled. This is called the autophagic vacuole, or the autophagosome. The autophagosome then fuses with lysosomes to form the autophagolysosome. Finally, the lysosomal degradative enzymes will produce the building blocks (refer to the figure). We can synthesize something new or use them for energy. This is a survival mechanism.

- If adaptation fails (i.e. if the starved cell can no longer cope by eating itself), autophagy will signal cell death by a means that is neither apoptosis nor necrosis and is not well-understood. (In the book it says apoptosis but that is false. Please fix it).

- There's a link between autophagy and inflammatory bowel disease, but it is not well-understood. It is also linked to cancer, and we will discuss this later in the course.

Why does autophagy occur?

1. Organelle turnover

Sometimes the cell needs to recycle its own organelles (organelle turnover) due to dysfunction, damage and beyond repair.

2. Clearance of misfolded protein

Autophagy is used for clearance of misfolded proteins if they are present in large quantities in the cell. It can be found in diseases related to neurons and hepatocytes (refer to table in the book). It degrades all of the misfolded proteins.

2. INTRACELLULAR ACCUMULATIONS

There are **four main pathways** of abnormal intracellular accumulations (accumulations inside the cell):

• Inadequate removal of a normal substance secondary to defects in mechanisms of packaging and transport, as in fatty change in the liver

• Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion, as with certain mutated forms of α1-antitrypsin

• Failure to degrade a metabolite due to inherited enzyme deficiencies. The resulting disorders are called storage diseases.

• Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulation of carbon or silica particles is an example of this type of alteration.

a. Fatty change (steatosis):

An abnormal accumulation of Triglycerides / Triacyl glycerol (TAG). This happens mostly in the liver but can occur in the heart, kidney or skeletal muscles or any other organ that is involved in fatty acid metabolism. They use lipids as a source of energy. Toxins, protein malnutrition, diabetes, obesity, or anoxia can all lead to fatty change. Alcohol abuse and diabetes associated with obesity are the most common causes of fatty change in the liver in industrialized nations. In Jordan the most common cause is diabetes associated with obesity. Different regions have different diseases /incidences. CCl_4 (carbon tetrachloride) which is an example of how an indirect toxin can affect the liver. Why does it cause fatty acid deposition in the liver? By forming CCl_3 free radical that can cause a reduction in production of apoproteins which are important in the metabolism and trafficking of lipids. And if we cannot export lipids outside the liver, fatty acids will accumulate.

b. Cholesterol and cholesterol esters:

Atherosclerosis is the most important example, where lipid accumulation happens on the walls of arteries. The normal arterial wall begins to get fatty deposits and you eventually make this fibrous cap from fibrin around it and you have some macrophages that start to take up the fatty acids and produce what are called foam cells. It can cause local inflammatory reaction & collateral damage (damaged cells). It will attract calcium. You eventually get some kind of calcification with age and if you're unlucky if this fibrous cap can rupture, releasing fat and calcium in these cells into the blood stream, which causes thrombosis (formation of a clot in a blood vessel) that will decrease elasticity of blood vessels and leads to ischemia, stroke, and heart attack. This will be discussed later in details in the cardiovascular system. Xanthomas is the deposition of cholesterol and cholesterol esters with macrophages under the skin (to the places that normally not for fat deposition). They form in the case of high levels of cholesterol due to either acquired or hereditary hyperlipidemia.

*Sclerosis (hardening)

*Fibrous tissue is a connective tissue.

c. Protein accumulation:

Happens due to one of two reasons:

1. Overproduction of proteins by cells themselves (ex. Russell bodies)

Russell bodies: happen in cells that produce immunoglobulins, where accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells, forming rounded, eosinophilic Russell bodies.

2. Excess protein is presented to the cells from the outside (ex. Nephrotic syndrome). Nephrotic syndrome: too much protein is escaping from the kidneys. Normally in the kidney, proteins (such as albumin) are reabsorbed at the proximal convoluted tubules by pinocytosis. In nephrotic syndrome, too much protein is escaping through the kidney into the urine and there is also a much larger reabsorption of the protein, which later accumulates in the kidney tubules. The tubules will develop abnormal pink droplets and will gain an abnormally pink appearance(eosinophilic).

d. Glycogen accumulation:

This typically occurs due to an abnormality in glucose or glycogen metabolism (e.g. Diabetes). Abnormal glucose levels in the blood lead to deposition of glycogen in the heart, kidney, and pancreas (islets of Langerhans). A group of hereditarily related glycogen storage diseases are called glycogenosis or glycogen storage diseases. G-6-phophatase deficiency is an example that causes glycogen accumulation in the liver. A **mosaic pattern** develops in the liver (picture in the slide).

e. Pigments accumulation (Endogenous & Exogenous):

Pigments can be **exogenous** (coming from outside the body) such as **carbon** or **endogenous** (synthesized within the body itself) such as **lipofuscin and melanin**. The most common exogenous pigment is carbon (depending on where you live). It is indigestible. Alveolar macrophages try to clear it and send them to lymphatic channels and your tracheobronchial lymph nodes will also turn black. If you have so much deposition in your lungs that causes anthracosis. Another type of carbon deposition are tattoos. Dermal macrophages take up the pigment and that's how a tattoo stains the skin.

- **Lipofuscin** (wear-and-tear-pigment) is an endogenous pigment. As cells age, lipofuscin gets deposited in them. This happens in the heart, live and brain. This is a combination of lipids and proteins. It is not injurious on its own, but is an indication of a past free radical injury, it indicates a previous lipid peroxidation. Also called brown atrophy because of its color. Grossly, it can be seen as small, shrink, brown organ (during surgery). These depositions are perinuclear , and can be seen using the electron microscope.

- Another example of an endogenous pigment **is melanin** which is produced by melanocytes. Melanin protects against UV light, which can cause cancer by damaging the DNA of the cells. Melanin accumulates in the dermal microphages and adjacent keratinocytes. This is what gives the skin a tan. Also, certain polymorphisms can cause the formation of freckles. Albino doesn't produce melanin.

f. **Hemosiderin**

It is a hemoglobin-derived pigment. The way we store iron in the blood is using apoferritin. When apoferritin has iron in it, it's called holoferritin (or just ferritin). We expect physiological (as opposed to pathological) accumulation of hemosiderin in areas where aging red blood cells degraded (bone marrow, spleen, and liver). The colors seen in a bruise are the different stages of iron, depending on how oxidized it is. Deposition of hemosiderin is pathologic in the case of hemosiderosis, which is systemic pathological deposition of hemosiderin, such as hemochromatosis, hemolytic anemia (due to active degradation of RBC) or repeated blood transfuses anything that causes excess destruction of RBCs (or excess iron production). (Check slides for pictures). It may look like lipofuscin accumulation, but the main difference is that hemosiderin looks more defused (not perinuclear) and iron is stained with the Prussian blue stain.

*apoferritin – without iron

*holoferritin – with iron

3. PATHOLOGIC CALCIFICATION

- The abnormal deposition of calcium salts (calcium phosphate) together with smaller amounts of iron, magnesium, and other minerals.

Two types:

a. Dystrophic Calcification:

Happens in dead or dying tissues. Typically calcium homeostasis is normal. Although if you have hypercalcemia, that will make it worse. But hypercalcemia is not the cause of dystrophic calcification (it is the main cause of metastatic calcification). Traumatic fat necrosis causes calcification. In this, you can have calcium accumulations in heart valves which is an important cause of stenotic aortic valve, a dangerous condition.

Pathogenesis of dystrophic calcification:

-Initiation: In extracellular sites: normally in our bones, there are small matrix vesicles that are rich in phospholipids and phosphatases that allow the deposition of calcium into them because calcium is attracted to phospholipids and phosphatases allow local calcium accumulation and crystal formation. In damaged tissue, the cellular membrane bursts leaving little vesicles (the vesicles will spontaneously form) of cellular membrane that are similar to matrix vesicles in bone, and this allows calcium accumulation along with attraction of phosphate by membrane-associated phosphatases and formation of crystalline calcium phosphate. In intracellular sites: typically happens inside mitochondria, because the cell can no longer regulate its calcium homeostasis. Calcium enters the cell and it'll deposit in phospholipid rich membranes, mainly in the mitochondria because they have lots of calcium.

- Propagation: Depends on how much calcium and how much phosphate is available. Which means if you have hypercalcemia, while it is not the cause of dystrophic calcification, it can accelerate propagation. Also, depending on the presence of mineral inhibitors and how much collagen you have.

Increased collagen is a fertile ground for calcification. As in atherosclerosis, the thick fibrous cap causes calcification.

b. Metastatic Calcification:

Happens in normal tissues and is almost always caused by abnormal calcium metabolism (hypercalcemia). Causes of hypercalcemia include: Primary hyperparathyroidism which increases production of parathyroid hormone leading to calcification. Secondary hyperparathyroidism which is caused by renal failure due to accumulation of phosphate which stimulates the parathyroid, causing hyperparathyroidism and calcification. Destruction of bone due to the effects of accelerated turnover also causes hypercalcemia, as in Paget's disease, leukemia & multiple myeloma. Finally, vitamin-D related disorders including vitamin D intoxication and sarcoidosis (in which macrophages activate a vitamin D precursor). Excess vitamin D can cause hypercalcemia. Metastatic calcification can accumulate in lungs or kidneys (forming stones) or gastric mucosa. It is normally not problematic, unless it is excessive and in certain organs.

4. CELLULAR AGING

Aging is the strongest independent risk factor for a lot of diseases (Alzheimer's, ischemic heart disease, cancer…). The older you are the more at risk you are at getting a disease (Murphy's law – anything that can go wrong, will go wrong).

Three mechanisms that lead to cellular aging:

1. DNA damage: we have previously discussed this.

2. Reduction in cellular replication: human chromosomes are linear, not circular (i.e. they have ends). When the cell sees these ends of exposed DNA, it considers them foreign. So the cell uses an enzyme called telomerase, which is an RNA associated protein, which adds a little extra length to the end of a chromosome to protect it from degradation. As you age, telomerase activity is reduced. As the cell replicates, the telomeres

(chromosome ends) get shorter and shorter to a point where more replication will cause the exposition of the DNA, which could cause DNA degradation, damage and mutations, so the cell stops replicating. So you only have a certain number of cell cycles as you age. For example Werner Syndrome, in which patients prematurely age. Patients are age of 6 or 7 but they could look 50. If we compare Werner-syndrome cells to normal ones that have the same age along with baby cells, and we isolate them, they will die much faster than normal cells and the longest to survive are the baby cells (have the longest telomeres).

3. Damage to proteins: such as: mutations, free radical injury, that all lead to cellular aging. There are things that counteract aging:

- DNA repair and enhancing our protein homeostasis (getting rid of damaged proteins).

- Recent studies have shown that certain pathways have an effect on cellular aging. In particular a) insulin and insulin growth factor signaling pathway and b) Target of Rapamycin TOR pathway (a signaling molecule that is targeted by the drug rapamycin (inhibits its action)). What these two control is the metabolism of your cell. By inhibiting these pathways that ultimately leads to improved DNA repair and protein homeostasis and enhanced immunity, all of which inhibit aging. A cell that has faster metabolism will use up itself and age quicker. Sirtuinsdeacytelate DNA specifically activating DNA repair, so if you affect these to make them further deacytelate DNA, you may survive longer.

- Telomerase activity is expressed in germ cells and is present at low levels in stem cells, but it is absent in most somatic tissues. Therefore, as most somatic cells age their telomeres become shorter and they exit the cell cycle, resulting in an inability to generate new cells to replace damaged ones. Conversely, in immortalized cancer cells, telomerase is usually reactivated and telomere length is stabilized, allowing the cells to proliferate indefinitely. Telomere shortening may also decrease the regenerative capacity of stem cells, further contributing to cellular aging.

USMLE Time ☺

Try to solve these questions :

1- A CT scan of 43-year-old woman with a parathyroid adenoma and hyperparathyroidism revels extensive calcium deposits in the lungs and kidney parenchyma .These radiologic findings are best explained by which mechanism of disease ?

2- A 24-yeaar-old woman contracts toxoplasmosis during her pregnancy and delivers a neonate at 37 weeks of gestation with a severe malformation of the central nervous system , MRI studies of the neonate reveal porencephaly and hydrocephalus . An X-ray film of the head shows irregular densities in the basal ganglia . These X-ray findings are best explained by which mechanism of disease ?

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