PATHOLOGY

◉ Sheets ○ Slides

Number: 5

Done by: Noor m'abreh

Corrected by: Bayan Almajali

Subject: Cell injury, death and adaptations

Doctor: Dr.Mazen

00/00/0000

Autophagy:

Autophagy is a survival mechanism that recycles materials in case of energy deprivation or nutrients deprivation. It is lysosomal digestion of cell's own components in order to provide nutrients and energy again for the cell.

Autophagy is initiated by multi-protein complexes that sense nutrient deprivation.

→ First the cell creates a membrane-bound vesicle around certain organelles and proteins (targets of autophagy to be recycled) to create what is known as **autophagic vacuole**, which is hypothesized to be formed from ribosome-free regions of ER. This is stimulated by the protein complexes.

→Then the vacuole fuses with a lysosome, forming an **auto-phagolysosome,** so the lysosomal hydrolases will digest the contents of the vacuole.

It can also be used for organelle turn-over:

Why would we turn-over organelles? → Organelles are either no longer need them OR because of the aging factor -that leads to damage or dysfunction of it so it must be replaced- .

Autophagy plays it role in:

1. Adaptation failure:

If there is adaptation failure where the atrophic tissue can no longer adapt to the stress, it undergoes autophagy. It will signal a unique type of cell death (neither apoptosis nor necrosis), it is a type that is not fully understood –the book says it signal apoptosis but it's not accurate.

2. Clear misfolded proteins:

What diseases are related to misfolded proteins?

→Alzheimer's, Parkinson's, CJD, DN 2 (type 2 diabetes), etc. Mostly neurodegenerative diseases.

Misfolded proteins are related to inflammatory bowel disease (IBD) →as the name implies it is inflammation of the bowel (أمعاء).

→When activating the immune system, collateral damage occurs and when activating it improperly we got more damage, causing patient of IBD to suffer from mucus diarrhea, bleeding and other symptoms.

→IBD is divided to two major diseases:

1-Crohn

2-Ulcerative colitis (UC)

Because autophagy is related to IBD, it is an active area of research –thinking this way: can we modify the cell to make it to eat its own material (autophagy) or inhibit it depending on its activity?-.

Autophagy is also has a role in cancer → if you have a chronic inflammation, it is a risk factor for cancer.

Intracellular accumulations:

Four major groups:

→Lipids accumulation

→Proteins accumulation

→Glycogen accumulations

→Pigments accumulations

Lipids accumulation

Fatty accumulation: (Steatosis)

CCl_4 is the toxin that mainly causes it (generally any material that damages the liver cells but mainly CCl_4).

The mechanism → inability to package lipids, cholesterol and fatty materials in the cell so it becomes unable to produce proteins because:

- the ER is damaged
- the mitochondria is damaged (means NO ATP)

It is easily observed in the liver tissue because liver cells are responsible for transporting all these fats, lipids, cholesterol to the periphery and receiving back from the periphery because the liver synthesizes cholesterol and metabolizes all the fats got from the diet. If they CAN'T export, fat accumulates.

This fat change can also occur in heart, kidney and muscles.

The heart, kidney & muscles can (and do) use lipids as energy source → in this case rather than burning lipids to produce energy they accumulate.

Fatty accumulation is caused by toxins (e.g. CCl_4), obesity, diabetes, protein malnutrition, alcohol abuse & anoxia.

The most common causes of fatty liver are alcohol abuse (comes first in western countries), obesity & diabetes.

Atherosclerosis:

→Cholesterol can accumulate on the wall of the arteries.

-Sclerosis: hardening due to formation of plaques (calcium deposits) caused by the affinity of phospholipids.

Calcium accumulates between the cells NOT in the membrane of the cells.

Calcium likes to deposits in damaged tissues & membranes and because calcium accumulates there, it attracts microphages that can ingest the accumulated cholesterol and become *foam cells* (fat-laden macrophages seen in atherosclerosis) then the microphages will attract fibroblasts that are going to deposit excess collagen.

→Calcium depositing is a signal of inflammation and tissue damage and leads to loss of some elasticity of the vessels.

In blood vessels, elastin provides elasticity whereas collagen provides strength and is important for integrity.

In scurvy: bleeding occurs due to lose of the ability to cross-link collagen.

Xanthoma:

Cholesterol can accumulate in the sub-dermis too →Xanthoma.

Atherosclerosis & Xanthoma are associated with hereditary or acquired hyperlipidaemia.

Proteins accumulations:

Are much less common than lipid accumulations.

The amount of albumin that is lost in urine is absorbed back in the proximal tubule of the kidney via pinocytosis.

Protein (albumin) accumulates in case of nephrotic syndrome, in which large amounts of proteins are found in urine, but why? Because cells are going to absorb as much as they can by pinocytosis however they can only export a limited amount. If they absorb more than what they export, protein will accumulate.

Immunoglobulins are antibodies secreted from B-cells (plasma cells). → The secretion of them can be physiological or pathological (details are not required).

Glycogen accumulation:

Glucose & glycogen metabolism abnormalities.

Glucose abnormalities→ diabetes.

Glycogen accumulation due to glycogen pathway abnormalities→glycogen storage diseases, *glycogenoses*.

Glycogen-6-phosphatase (G6P) deficiency will be shown as a typical mosaic pattern (empty vacuoles) when you sample it in the liver.

Pigments accumulation:

Exogenous pigment accumulation:

These pigments stick around because they are indigestible materials→ no enzymes available (or functionally can) digest.

The most common exogenous pigment is carbon-depigmentation.

Anthracosis→if there is too much carbon deposition→staining microphages black. When carbon is inhaled, alveolar macrophages phagocytoses the carbon and transported through lymphatic channels to the regional tracheobronchial lymph nodes and stain it black.

→Most common among smokers.

Tattoo is another example of having indigestible material in cell (tattoo inks are mainly carbon based) →injecting those into the skin and dermal microphages will eat them.

The only way to get rid of tattoos is laser or surgery.

Endogenous pigment accumulation

Lipofuscin ''wear and tear pigment''

- related to aging

→A sign of past free radical damage (lipid peroxidation /protein damage /DNA damage).

⇨ Lipofuscin is lipid and proteins accumulation due to past free radical damage that occurs in many organs but typically in the heart (having brown atrophy), kidney & brain. Brown pigment sometimes accumulate in large amounts to produce an appearance of *brown atrophy*. In electron microscopes, they appear as granules.

Melanin (another endogenous pigment) is produced in melanocytes.

Melanin protects our skin from the UV radiation and determines skin color, causes tan.

Accumulates in dermal macrophages and adjacent keratinocytes, which is related to the presence of freckles.

Hemosiderin:

- A hemoglobin-derived granular pigment that accumulates in tissues where there is excess of iron. Also represent large aggregates of the ferritin micelles.

Iron is not free to run in the blood but rather normally stored within cells in association with the protein apo-ferritin, forming ferritin micelles.

Micelles without iron→apo-ferritin.

Micelles with iron→holo-ferritin.

Hemosiderosis: systemic pathologic deposition of hemosiderin (due to hemochromatosis, hemolytic anemias, repeated blood transfusions).
Where can we find Hemosiderosis accumulation? In other than these physiological areas: (the liver /bone marrow/phagocytes of the spleen).

- Blood doping is the practice of boosting the number of red blood cells in the bloodstream in order to enhance athletic performance (by blood transfusion).--> can be detected

–Sometimes-by systemic deposition of hemosiderin.

Another example of hemosiderin deposition that is not related to a diseased condition (ask yourself why would blood accumulate and being destroyed in non-diseased conditions?)
→ Bruise.
Bruises range in color (blue, black, purple, etc) →the amount of blood determines the intensity of the color, where the hue of it is determined by the oxidation state of the iron (un-oxidized iron →gray / oxidized iron →red).

Pathologic calcification:

Damaged tissue (like in *atheromas*) and dead tissue as well attracts calcium.

The type of necrosis associated with calcium is *caseous necrosis.*

Dystrophic calcification (DC) is the calcification occurring in degenerated or necrotic tissue.

Normal calcium metabolism allows calcium to deposit however hypercalcemia will allow more and may cause damage.

Metastatic calcification
→Deposition of calcium in normal tissue.
→In this case calcium metabolism is abnormal (having hypercalcemia for example).
→Similar to calcification of bone.
→Micelles that we use in ossification centers attract calcium.

*Calcification can occur intracellular or extracellular.

*The aortic valve (related to the hypertrophy of the heart discussed earlier) is a site of calcification.

Causes of Metastatic calcification:

→ **Hyperparathyroidism** (1ry/2ry).

Parathyroid hormone increase Calcium levels in the blood.

Over-active parathyroid gland causes excess hormone secretion. This is primary hyperparathyroidism.

If something else induce the parathyroid gland to produce parathyroid hormones: secondary hyperparathyroidism (e.g. renal failure).

→ **Bone destruction** (metastasis, MM, leukemia, Paget's).
More calcium to the blood ->hypercalcemia.
The only type of cancer that causes extra bone formation around the metastasis –and not destruction- is prostate cancer.

→ **Vitamin-D intoxication, Sarcoidosis.**
Too much Vit-D ->hypercalcemia.

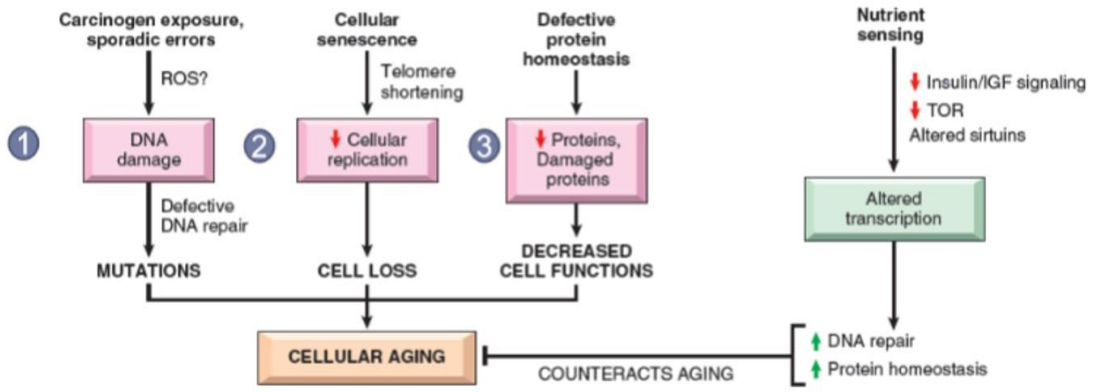
Cellular aging

Increases the risk factor of a lot of diseases.

ROS, exposure to chemicals & reactions ….etc. → lead to DNA damage.
As we grow older the ability to repair the damage decrease.

<u>Mechanisms:</u>

Mechanisms



Cellular senescence: no cellular replication

→Why? Because telomeres get shorter with time so it is not coding.

→Circular DNA replicates easily while linear DNA it is longer process …the tips of the DNA can't be replicated so every time the cell replicates, it lose a part of the telomere.

→The only way to add those tips is by using an enzyme (telomerase that uses its own RNA template in a certain way to add them).

Not all cells have telomerase (germ cells/ stem cells have it, whereas somatic cells don't).

So somatic cell will replicate and lose a part of the telomere until reaching a point at which one more replication will make you lose the last gene on the chromosomes (cause DNA damage).

***So certain signal will tell the cell then to stop replicating.

→This don't happen in cancerous cells. Cancer cells reactivate telomerase so they continue replicating beyond

the “stop point”. (80% of cancer cells have telomerase reactivated).

*if you use telomerase to extend life, you could possibly induce cancer cells.

Depriving yourself and fasting will help you to live longer life and free of diseases.