Pathology

Sheet Slide

number

5

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Intracellular accumulation

Accumulation of abnormal amounts of various substances , either in the cytoplasm within organelles (typically lysosome) or in the nucleus .

These substances can be either produced by the affected cell or from outside it.

These substances can also be harmless (can stay in the cell for many years without causing any damage) , or harmful (causing varied degree of injury) .

Examples of intracellular accumulation:

Protein, triglyceride , cholesterol , carbon , hemosiderin , glycogen , lipofuscin , infectious organisms .

The general pathway or mechanisms of accumulation

1- Abnormal metabolism of substances: as in fatty liver occurs by (lipid deposition).
2- Accumulation of abnormal endogenous substances as a result of genetic or acquired defects in its folding, packaging, transport, or secretion, as with certain mutated forms of α1-antitrypsingenetic or acquired lack of enzymes.
3- Genetic or acquired lack of enzyme: Failure to degrade a metabolite due to inherited enzyme deficiencies. The resulting disorders are called *storage diseases. (complex substances that should be metabolites but the enzyme which is responsible for this defectes so the substances will accumulate inside the cell)*

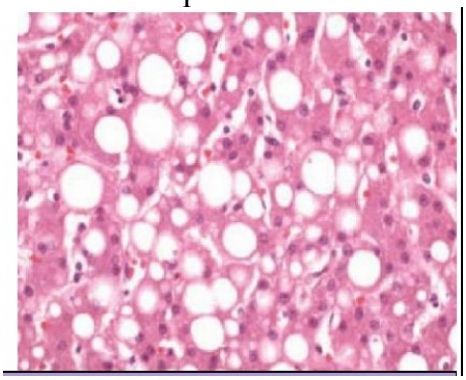
4- Accumulation of exogenous indigestible material : Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulation of carbon or silica particles is an example for this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

Fatty changes : steatosis

Is Fatty change refers to any abnormal accumulation of triglycerides within parenchymal cells. It is most often seen (exclusively) in the liver (hepatocyte), since this is the major organ involved in fat metabolism, but it may also occur in heart, skeletal muscle, kidney, and other organs.

When we talk about reversible cell injury , we detect two morphological changes :
>> 1-swelling 2- fatty change
So fatty changes are reversible .

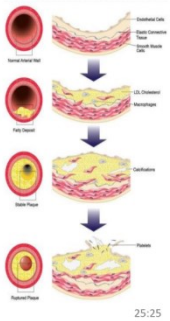
Steatosis may be caused by 1) toxins : the most common cause (alcohol toxicity) , 2) protein malnutrition : lack of proteins that transport lipids from the liver (decrease in the synthesis of lipoproteins) ,3) diabetes mellitus : because it usually gets increased in fat production) ,4) obesity (large amounts of lipids), or anoxia and starvation .
Alcohol abuse and diabetes associated with obesity are the most common causes of fatty change in the liver (fatty liver) in industrialized nations.
Because of all these causes , we will have abnormality in lipid metabolism (either by increase in the production of lipids or defect in transportation of lipids) result in accumulation of triglycerides inside the hepatocytes , due to this the mass and the size of the liver will be larger and the color of the liver will turn into yellow and becomes shiny due to triglycerides and also soft , under the microscope we will see empty vacuole inside the hepatocyte which is rich with lipids , but because the lipid is not taken either by hematosilen or eosin , the color of the lipid vacuole will be White.



Section in the Liver

Notice : the large droplets push the nucleus to the peripheral “similar to adipose tissue”

An example for accumulation disease which is very significant and dangerous is accumulation of cholesterol and cholesterol esters in the tissue (the most significant site is blood vessel wall) …. (atherosclerosis.. reduces the lumen) , because of this there will be an ischemia (reduction in the blood flow) .
If this atherosclerosis undergoes an injury , it gets development into clotting (thrombosis).



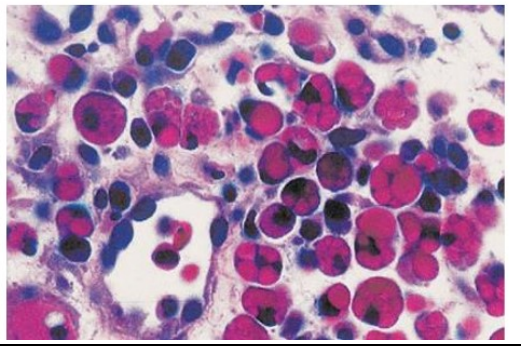
herosclerosis

Sometimes cholesterols accumulate in subcutaneous tissue under the skin and cause Skin xanthomas :(focal accumulations of cholesterol) sometimes appear, the result of hyperlipidemia and impaired excretion of cholesterol , when these xanthoma are found under the eyes we call it (xanthelasma).

Proteins accumulation :

may occur when excesses are presented to cells or if the cells synthesize excessive amounts.

1) In the kidney, for example, trace amounts of albumin filtered through the glomerulus are normally reabsorbed by pinocytosis in the proximal convoluted tubules. However, in disorders with heavy protein leakage across the glomerular filter **(e.g., nephrotic syndrome**), there will be much larger reabsorption of protein, and vesicles containing this protein accumulate, giving the histologic appearance of pink, hyaline cytoplasmic droplets. The process is reversible: If the proteinuria abates, the protein droplets are metabolized and they will disappear .
2) accumulation of newly synthesized immunoglobulins that may occur in the RER of some plasma cells (due to some causes it produce large amount of antibodies and they will remain inside the cell not secreted by it) forming rounded, eosinophilic Russell bodies (accumulation in the cytoplasm) , and sometimes the protein will penetrate the nucleus so we call it (dutcher body)



Russell bodies

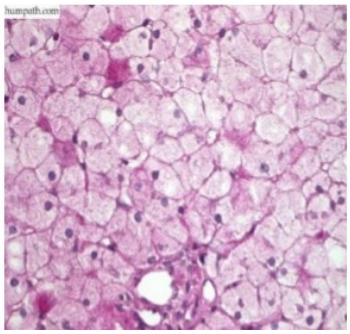
3) Mallory bodies or “alcohol hyaline “: alcohol damages the cytoskeletal proteins in hepatocyte , and when it damages the protein , the protein will be missfolded (abnormal shape of the protein) and it will accumulate inside the hepatocyte .

4) Neurofibrillary tangle : found in the brain in alzheimer disease , damage of cytoskeletal proteins and they accumulate inside the neuron

Glycogen accumulation :

It will occur in two situations :

1) In diabetes mellitus
2) In children (inborn metabolism errors) .. absence of the enzyme which is responsiple for metabolism of glycogen so that causes glycogen storage diseases .



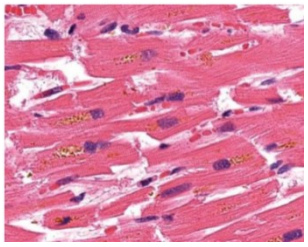
Liver hepatocytes filled with glycogen

Accumulation of pigments :

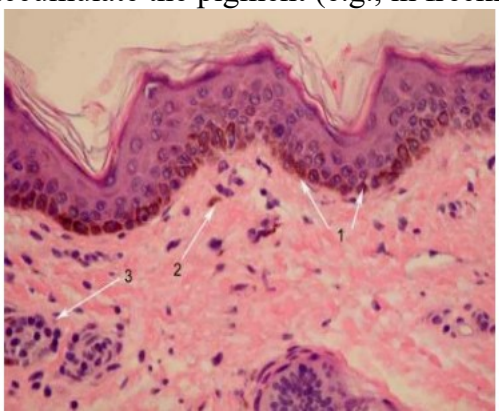
Pigments are colored substances that are either exogenous, coming from outside the body, such as carbon, or endogenous, synthesized within the body itself, such as lipofuscin, melanin, and certain derivatives of hemoglobin.

The most common exogenous pigment is carbon (an example is coal dust), an ubiquitous air pollutant of urban life. When inhaled, it is phagocytosed by alveolar macrophages and transported through lymphatic channels to the regional tracheobronchial lymph nodes of the pigment blacken the draining lymph nodes and pulmonary parenchyma **(anthracosis).**

Lipofuscin, or "wear-and-tear pigment," is an insoluble brownish-yellow granular intracellular material that accumulates in variety of tissues (particularly the heart, liver, and brain) because of aging or atrophy. Lipofuscin represents complexes of lipids and proteins that are derived from the free radical–catalyzed peroxidation of polyunsaturated lipids of subcellular membranes. It is not injurious to the cell but it is a marker for a past free radical injury. when presents in large amounts, imparts an appearance to the tissue which is called brown atrophy (converts organ color into brown).



Melanin is an endogenous, brown-black pigment that is synthesized by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation. Although melanocytes are the only source of melanin, adjacent basal keratinocytes in the skin can accumulate the pigment (e.g., in freckles).



Hemosiderin is a hemoglobin-derived granular pigment that is golden yellow or brown and accumulates in tissues when there is a local or systemic excess of iron. Iron is normally stored within cells in association with the protein apoferritin, forming ferritin micelles. Hemosiderin pigment represents large aggregates of these ferritin micelles, readily visualized by light and electron microscopy; the iron can be unambiguously identified by the Prussian blue .

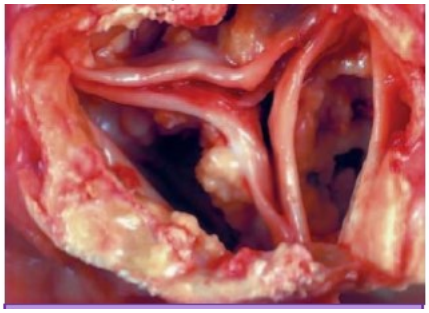
(عشان اميز بين ال melanin and hemosiderin under the microscope بستخدم ال Prussian blue في حالة
صار لونها ازرق مع الصبغة معناها هي hemosiderin و اذا اي لون تاني غير الازرق معناها melanin)

Pathological calcification :

Two types :

1) dystrophic calcification : occurs in necrosis , **in dead or dying cell,** they attract calcium ions (calcification) , regardless of the level of calcium ions in the blood

(يعني شو ما يكون مستوى الكالسيوم بالدم مرتفع منخفض طبيعي .. مش مهم , المهم انو وين ما يكون عندي خلية ميتة رح يصير ال calcification) وفي معظم الحالات بكون مستوى الكالسيوم طبيعي



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2- Metastatic calcification : deposition of calcium in **normal tissue** in the presence of hypercalcemia . … usually can be harmless (does not affect the function) , but in some cases when the calcium level is very high and lasts for long duration it leads to tissue damage and cell injury which affect the function

- an example of harmful metastatic : nephrocarsinoma

- It is associated with tumoral carcinosis .

Metastatic calcification presents in hypercalcemia , and one of the causes of hypercalcemia is:

1- presence of a tumor in the patient and the tumor metastasis the bone , and break the bone and release calcium ion and transport it into the blood so the result is (hypercalcemia), then the metastatic calcification of the liver will occur .

2- increased secretion of parathyroid hormone : when parathyroid increase (activation of osteoclast) , the resorption of calcium ions from bone increases .

3- renal failure .

4- vitamin-D related disorders : increases the resorption of calcium from kidney and intestine .

Inflammation

Inflammation is a physiologic protective response involving host cells, blood vessels, and proteins and other mediators that **is intended to eliminate the initial cause of cell injury**, as well as the necrotic cells and tissues resulting from the original insult, **and to initiate the process of repair .**

Inflammation occurs in the vascularized connective tissue .

Sometimes inflammation causes damage (cell injury) when it becomes out of control .

Two mechanisms of repair depend on type of cells :

can the cell divide or not :

1- if it divides it can regenerate
2- if not it doesn't it will replace it by fibrous tissue (scar) ,
note that : even if the cell can divide and the injury is very large it will replace it by fibrous tissue , in skin as an example .

causes of inflammation :
are the causes of cell injury note that **the most common that is countered in inflammation is infection .**

patterns of inflammation :
Inflammation can be acute or chronic
1)acute : its immediate (short duration) (minutes to few day)
Predominant cell type is :neutrophil cells
Fluids and plasma protein accumulation
2)chronic : it is delayed and lasts for longer duration (more than one week)
By Macrophages , lymphocytes and plasma cells
Vascular proliferating and scarring

Components of inflammation :
1) The vascular wall cell : including endothelial cells and smooth muscles in the vessels
2) The circulating cell : white blood cells and platelets

3) Circulating proteins (chemical mediators) :there are two families of chemical mediators
the first type is synthesized in the liver and released in the blood and then it reaches the side of inflammation, it is called (plasmic derived or systemic chemical mediator)
the second type is synthesized in the site of injury by the participating cell , it is called (cellular derived or local mediator)
4) Connective tissue cell : include fibroblast (the most common) , its responsible for production of extra cellular matrix and produce mediators to participate in inflammation process , and mast cell is important in inflammation process(it produces histamine) .
5) connective tissue (extra cellular matrix)

Cardinal (local)…at the site of injury .. signs of acute inflammation :

1- Warm /heat
2- Redness
3- Pain
4- Swelling
5- Loss of function

(suffix- itis .. present inflammation)
Inflammation can not occur in cartilage .

Acute inflammation

Acute inflammation has two major components

• **Vascular changes:** alterations in vessel caliber resulting an increase in the blood flow (vasodilation) which will increase the **hydrostatic pressure** , and changes in the vessel wall that permit plasma proteins to leave the circulation (**increased vascular permeability**) it will result a tumor or swelling . In addition, endothelial cells are activated, resulting increase in the adhesion of leukocytes and migration of leukocytes through the vessel wall.

• **Cellular events:** emigration of leukocytes from the circulation and accumulation in the site of injury (cellular recruitment), followed by an activation of leukocytes, enabling them to eliminate the offending agent.

chemical mediator is the responsible for this process .

Mechanism of acute inflammation :

- **Vasodilation**

- **Exudation-edma**
- **Emigration of cell**
- **Mediator release**
- **Phagocytosis : to clean the damaged cell and to do regeneration or healing.**

The most common chemical mediator produced by the cell is cytokines

- **About increased vascular permeability in inflammation :**

When some chemicals affect the blood vessel and induce it to be relaxed (vasodilation) this will increase the blood flow , after this process , hydrostatic pressure occur >>>

(لما يزيد ال hydrostatic pressure لحالو ما بسمح للسوائل تطلع من جوا ال blood vessel لبرا .. في كمان عوامل تانيه .. رح نحكي عنها بعدين)

At the normal situation in our circulatory system :

At the level of capillaries there is no out flow or in flow , the force that maintains this process is hydrostatic force and osmotic pressure (equal) .

At the level of arteriole the net force is hydrostatic pressure so the nutrients flow out .

At the level of venules the net force is osmotic pressure so the nutrients inflow .

In inflammation :

All net forces become hydrostatic pressure (in arteriole and venule and capillary) so all nutrients will be out , (edema will occur) .

Note : any fluid that presents outside the blood vessels between the cells in the tissue is called edema .

If the edema contains larg amount of protein its called exudate .

And if the edema contains low amount of protein it is called transuded .

بالبداية الكمية الاكبر يلي بتطلع عبارة عن fluid وكمية قليلة من البروتين (transudation) بس بعدها لما تزيد ال permeability بصير يطلع بروتين اكتر وبوقتها بسميها exudate .

Increased vascular permeability mechanisms :

1- **Endothelial cell contraction : (junction) .. if one of the endothelial cells contracts ,the space will increase and the liquid will flow out through the space .**
2- **Direct endothelial cell injury : immediate sustained response**
3- **leukocyte dependent endothelial injury :**
4- **Increased transcytosis**
5- **Leakage from new blood vessels : tissue repair involves new blood vessel formation (angiogenesis). These vessels sprouts remain leaky until proliferation of the endothelial cells and to be mature sufficiently to form intercellular junctions.**