[A QUICK SUMMARY]

[pathology, 5th lec]

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INTRACELLULAR ACCUMULATION MECHANISMS:

Inadequate removal of a normal substance

Normal endogenous material

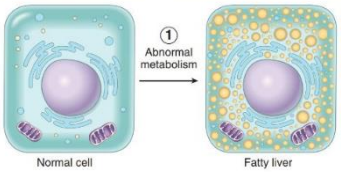
↓

Inadequately removed

↓

accumulate

E.g: fatty change ➡ liver



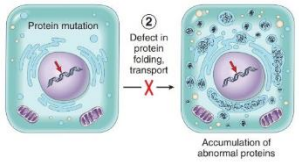
Accumulation of an abnormal endogenous substance

misfolding protein

↓

accumulated in the ER

E.g: α1-antitrypsin deficiency disease



Failure to degrade a metabolite due to inherited enzyme deficiencies

genetic mutation

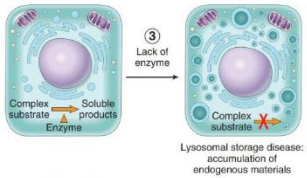
↓

enzymatic deficiency

↓

accumulate of metabolites

E.g : Lysosomal storage diseases



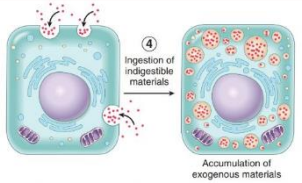
Deposition and accumulation of an abnormal exogenous substance

abnormal exogeneous substances

↓

deposition in the cell

E.g: carbon deposition in the lung



FATTY CHANGE (STEATOSIS)

Causes: toxins (ex. Carbon tetrachloride)/Protein malnutrition/Diabetes mellitus (DM) /Obesity/anoxia

Where: in the **liver** (organ involved in fat metabolism) **heart, kidney, muscles**

Mechanism: deposition of Triglycerides in the cells

E.X: Alcohol abuse and DM +obesity >>>fatty liver disease.

CHOLESTEROL AND CHOLESTERYL ESTERS DEPOSITION

Causes: increased intake or decreased catabolism of these cholesterol and cholesterol esters.

Where: walls of the blood vessels

Mechanism: Phagocytes and microphages uptake the fat >>> overloaded with lipids (triglycerides, cholesterols, and cholesterol esters).

E.X: **Atherosclerosis** predispose to: coronary heart disease **or** cerebrovascular accidents.

GLYCOGEN DEPOSITION

Causes: abnormality in the glucose or glycogen metabolism

E.X: Glycogen storage disease:

Where: liver

Mechanism:

inherited abnormality in the metabolism of glycogen >>>deposition of

E.X: Diabetes mellitus (DM):

Where: renal tubular cells, heart cells, or vessel cells of the pancreas

E.g:

PROTEINS DEPOSITION

Nephrotic syndrome	Russell bodies in plasma cells	Alcoholic hyaline in liver	Neurofibrillary tangles in neurons
Lose large amount of **albumin** in the urine >>> increase reabsorption by the kidney >>> deposition of proteins in the **proximal convoluted tubules** -Pinkish color droplets	excessive amounts of immunoglobulin production in the **plasma cells** >> deposited in the **ER of the plasma cells** -pinkish color droplets	In the **liver** cells of alcoholic patients.	In the neurons of patients with Alzheimer's disease.

PIGMENTS

EXOGENOUS

carbon

Causes: air pollution or cool dust.
Mechanism: alveolar macrophages ingest the Carbon → lymphatic channels → tracheobronchial LN
Color under the L.M : black granular pigment [inside the macrophages]
Diseases: Anthracosis [in lung]

lipofuscin pigment
wear-and-tear pigment

Causes: aging and atrophy
Where: heart, liver, and brain cells.
Color under the L.M : brown-yellow granular pigment
E.X: brown atrophy: excessive amount of lipofuscin pigment>>> cells turn brown in color (atrophy)
Others: It is an indication of a previous free radical injury [peroxidation of the membranes and damage to the lipids]

Melanin pigment

Causes: melanocyte in the skin
Where: in the dermal macrophages & adjacent keratinocytes at the basal cell layer of the skin
Color : large amount in the skin>> deep colored skin /small amount >> fair colored skin
E.X: Freckles
Others: Melanin offers protection against UV light & colorize the skin.

ENDOGENOUS

Hemosiderin pigment

Causes: excessive deposition of **iron** either in physiologic or pathologic ways
Where: → **Physiologic**: tissues have a rabid red blood cell turnover like in macrophages & phagocytes **of** the bone marrow, spleen or liver. → **Pathologic:** check below
Color under the L.M : brown granular pigment
E.X: *Pathologic deposition*: **1. Bruise**: after a localized hemorrhage **2. Hemosiderosis**: **causes**: hemochromatosis, hemolytic anemias, repeated blood transfusions
Others: Iron + apoferritin = **ferritin micelles**

PATHOLOGIC CALCIFICATION

DYSTROPHIC

Where: injured/necrotic dead tissues.

*Not associated with hypercalcemia but exacerbated by it

*usually associated with a normal calcium level in the blood & normal calcium metabolism

E.X: • **Atherosclerosis** (deposition of calcium in the walls of blood vessels)

• **Aging or damaged heart valves** (**aortic stenosis**, which is the deposition of calcium in the aged aortic valve)

•**tuberculosis** (deposition of calcium in the area of inflammation)

• **insignificant past cell injury is the indication of incidental finding of dystrophic calcification**

If the dystrophic calcification deposition is excessive it can be associated with organ dysfunction

METASTATIC CALCIFICATION

Where: normal tissues (like **VESSELS, LUNG, KIDNEY)**

*associated with hypercalcemia

* associated with an abnormal calcium metabolism

Causes: • **Hyperparathyroidism -whether it is primary or secondary- (occur in renal failure *OR* the production of parathyroid hormone related protein** (like in certain malignancies)

• **Bone destruction** (metastasis, Paget's disease of the bone, multiple myeloma (MM),leukemias, immobilization)

• **Vit-D intoxication**

• **Sarcoidosis** [autoimmune disease]

• **Renal failer with 2ry hyperparathyroidism.**

Grossly: whitish chunky color / under LM: purple

Pathologic calcification = Abnormal deposition of calcium salts + smaller amounts of Iron, magnesium & other minerals.

CELLULAR AGING

➢ **Aging is associated with a Progressive decline in the life span and functional capacity of cells**

*Due to less activity of the telomerase enzyme

Causes: radiation, UV light, toxins, ROS

Environmental and metabolic insults → ROS? → Lowering Cell's capacity to repair any damage → **Accumulation of mutations in DNA** → Defective DNA repair → **DECREASED CELL FUNCTIONS, CELL LOSS**

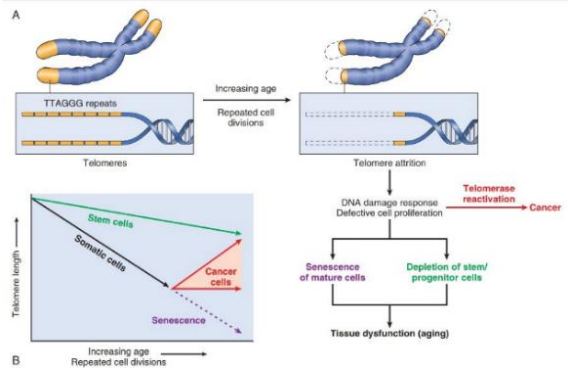
Telomere shortening → ↓ **Cellular replication** → the cell go into cell cycle → **CELL LOSS**

Abnormal protein homeostasis → ↓ **Proteins, damaged proteins** → less **chaperones** → more **proteins degradation** → less # of proteins → **DECREASED CELL FUNCTIONS**

Due to:

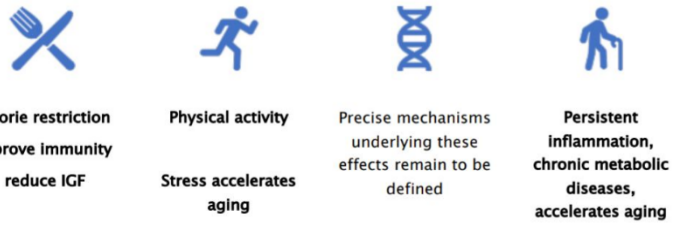
- Increased **turnover**
- Decreased **synthesis**
- Defective activity of **chaperones and proteasomes**
- Overall decrease in **intracellular proteins**
- Accumulation of **misfolded proteins** can trigger apoptosis

CELLULAR AGING



*replicative senescence: It is a progressive decrease in the number of divisions that a cell can undergo.

Anti aging– slowing of aging (elixir of youth)



➢ **Telomers**: short repeats of DNA at the end of the chromosomes, which protect the coding material of chromosome at both ends & ensure complete replication of them

➢ Progressively shortened upon replication (aging)

➢ Telomere length is maintained by telomerase enzyme.

➢ Telomerase expressed in **germ cells**, low levels in **stem cells**, but absent in most **somatic cells**.

➢ Telomerase is reactivated in cancer cells.