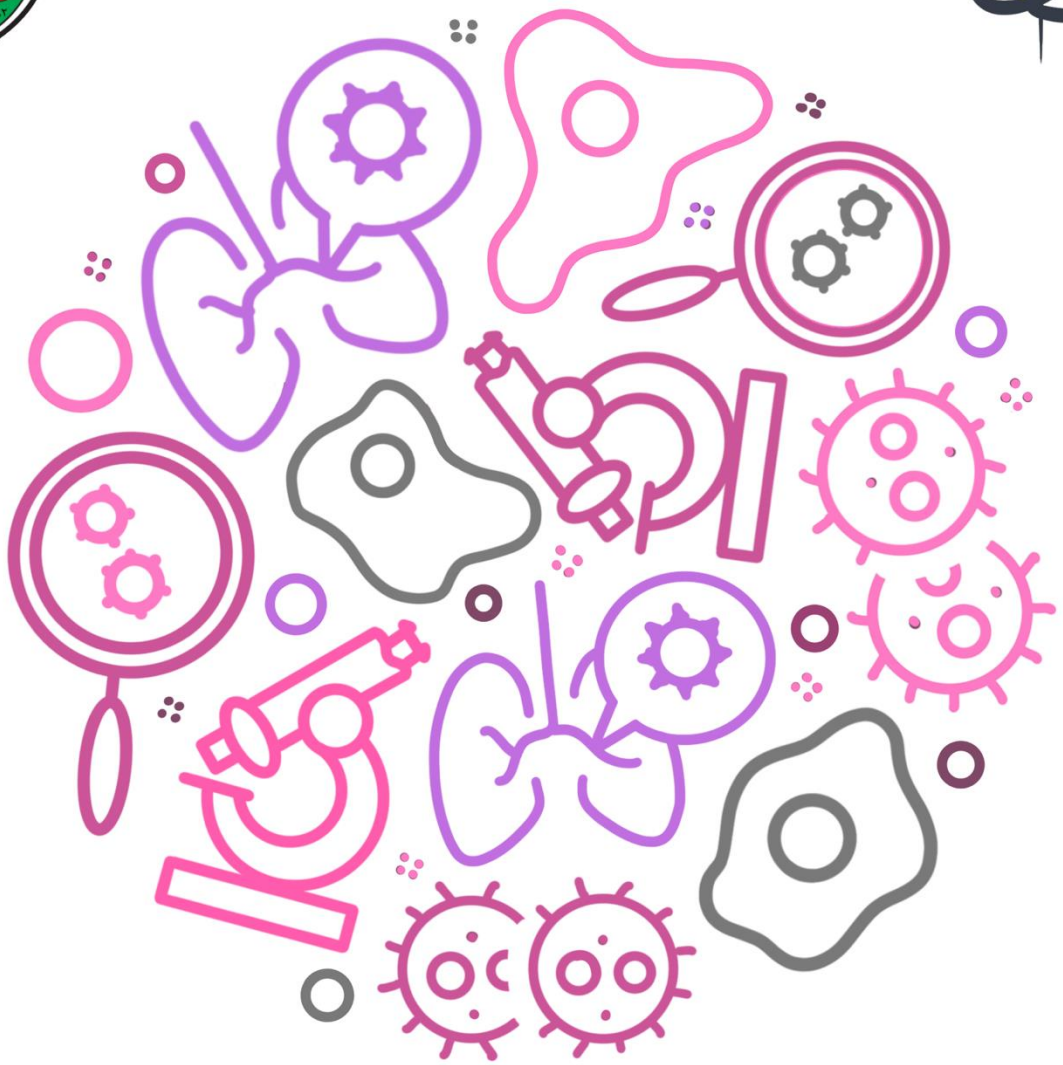
SHEET NO. 5



PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

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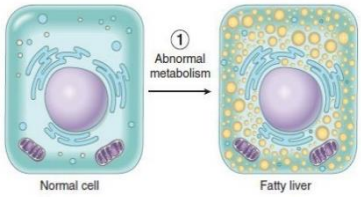
In the previous lectures, we discussed cell injuries, their causes, their mechanisms, and the differences between Apoptosis and Necrosis. In this lecture, we will discuss the intracellular accumulation of different substances, calcification, and cellular aging.

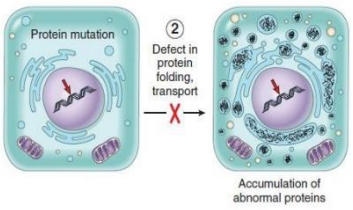
Intracellular Accumulation

Substances can accumulate inside the cell due to different mechanisms, it may accumulate in the cytoplasm, organelles (lysosomes, nucleus) depending on the type of the material that is deposited.
There are mainly four mechanisms for the deposition of these materials:

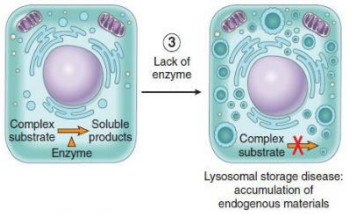
1. **Inadequate removal of a normal substance**
   When the material is normal endogenous material but it is inadequately removed or degraded from the cell.
   Ex. **fatty change** that occurs in the liver.



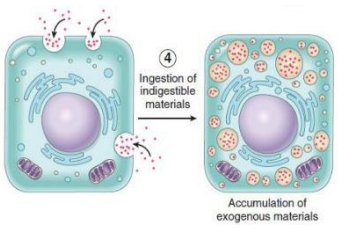
2. **Accumulation of an abnormal endogenous substance**
   Defects in the folding of this protein leading to the accumulation of misfolded protein in the endoplasmic reticulum. Ex. **α1-antitrypsin deficiency disease.**



3. **Failure to degrade a metabolite due to inherited enzyme deficiencies**
   Accumulation of substances due to deficiency of the enzyme needed to degrade this metabolite.
   Ex. **Lysosomal storage diseases,** substances accumulate inside the lysosomes due to a lack of certain lysosomal enzymes due to a genetic mutation.

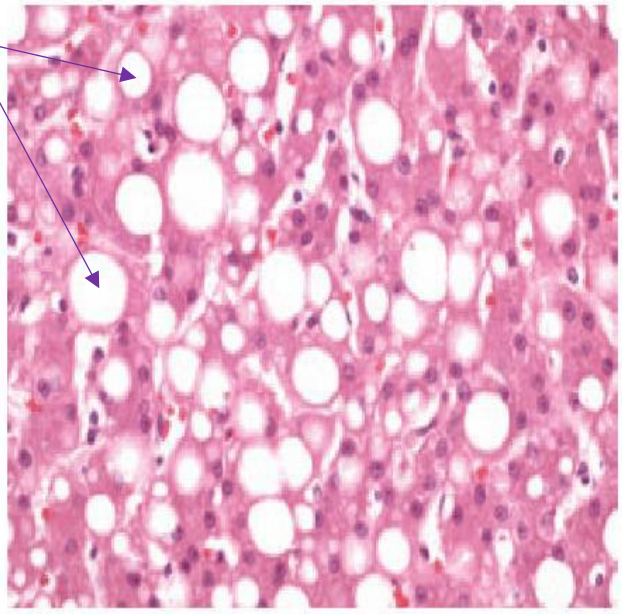


4. **Deposition and accumulation of an abnormal exogenous substance**
   extracellular exogenous material that comes from outside and get deposited in the cell. Ex. **Carbon deposition in the lung and selica deposition**.



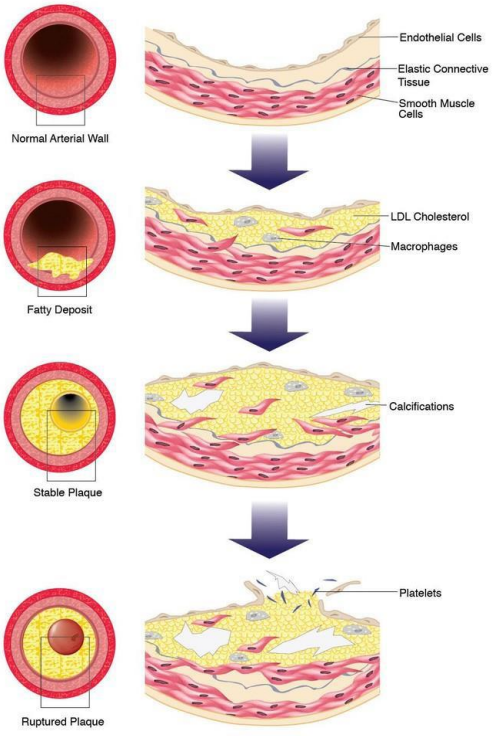
Fatty change (steatosis):

- Most commonly seen in the **liver** since it is the most common organ involved in fat metabolism, but also it can be seen in the heart, kidney, muscles, and other tissues.
- It is due to the deposition of **Triglycerides** in the cells, as you see here the fatty position is manifested by white fatty droplets inside the cells which vary in their sizes (some of them are macro and others are micro).
- The cases of this deposition can be the
  - toxins (ex. Carbon tetrachloride)
  - Protein malnutrition
  - Diabetes mellitus (DM)
  - Obesity
  - anoxia
- Alcohol abuse and **DM +obesity** are the most common causes of fatty liver disease in industrialized countries.



Cholesterol and Cholesteryl Esters

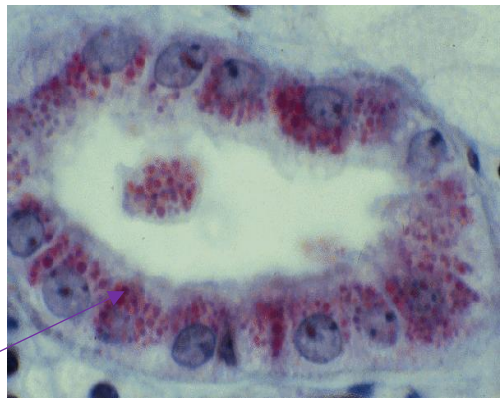
- The most common site for deposition is in the **walls of the blood vessels.**
- Phagocytes and macrophages in the walls of the blood vessels uptake the fat, then they become overloaded with these lipids (triglycerides, cholesterols, and cholesterol esters).
- The cause is either **increased intake** or **decreased catabolism** of these cholesterol and cholesterol esters.
- The best example is **Atherosclerosis** which can predispose to coronary heart disease or cerebrovascular accidents.



Proteins

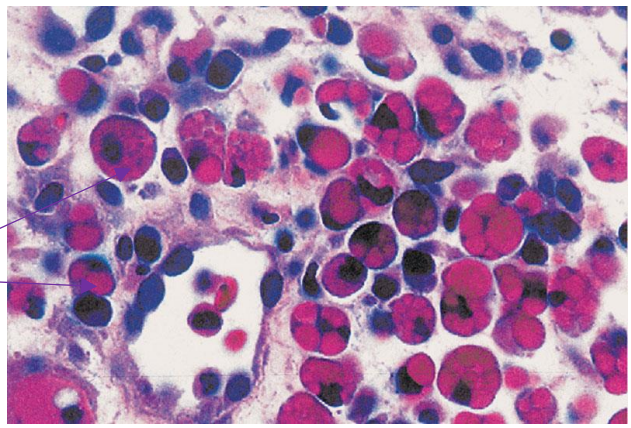
- Depositions of the protein much less common than lipid depositions.
- Proteins can be either **produced inside** the cell or **derived from outside** the cell.
- Examples :

a) Nephrotic syndrome



Normally, when a trace amount of albumen excreted, they are reabsorbed by the kidney tubules then return to the blood. But People with **nephrotic syndrome** lose large amounts of their albumin in the urine with increased reabsorption by the kidney, which causes deposition of proteins in the proximal convoluted tubules in the kidney.
These pinkish droplets inside the epithelial cells of the renal tubules are proteins that are reabsorbed from the urine in order to return them to the blood but because the protein amount is high, they will accumulate in cells giving this color.

b) Russell bodies in plasma cells



excessive amounts of immunoglobulin production in the plasma cells, so they get deposited inside the endoplasmic reticulum of these cells as pinkish droplets.

c) Alcoholic hyaline in liver

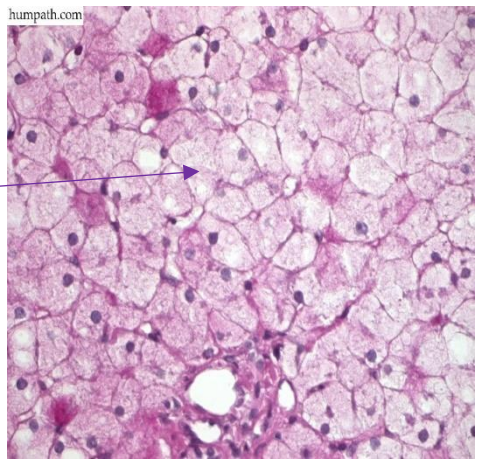
In the liver cells of alcoholic patients.

d) Neurofibrillary tangles in neurons

In the neurons of patients with Alzheimer's disease.

Glycogen

- Glycogen accumulated due to a defect or abnormality in the glucose or glycogen metabolism.
- Examples:
  a) **Diabetes mellitus (DM):** In which glycogen and glucose are deposited in the renal tubular cells, heart cells, or vessel cells of the pancreas.
  b) **Glycogen storage disease:** An inherited abnormality in the metabolism of glycogen which causes deposition of glucose and glycogen.
- This pic is from the liver, notice that the faint pink color indicates the glycogen.

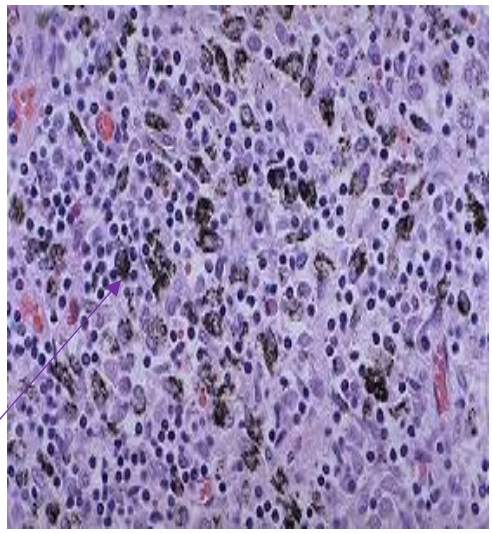


Pigments

pigments are colored materials that can be either **endogenous** or **exogenous**.

a) Exogenous pigments :

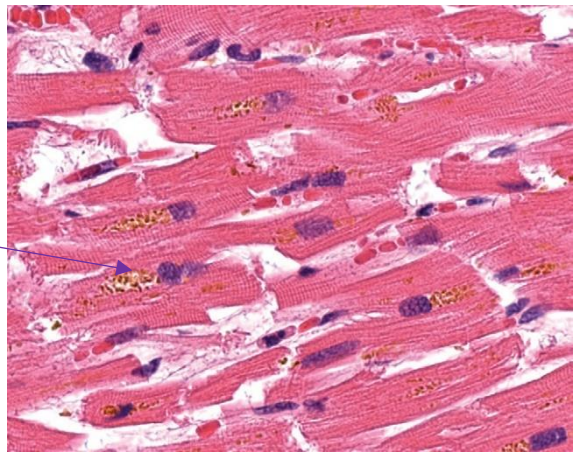
- The most common exogenous pigment is **carbon** which we get it from air pollution or coal dust.
- When the Carbon enters the lungs, it ingested by alveolar macrophages then it is carried to the lymphatic canals into trachea bronchial lymph nodes giving them blackish discoloration (Alveolar macrophages → lymphatic channels → tracheobronchial LN)
- Under the microscope we can see the carbon pigment (black granular pigment inside the macrophages), we call this in lung **Anthracosis.**



b) Endogenous pigments:

1. lipofuscin pigment

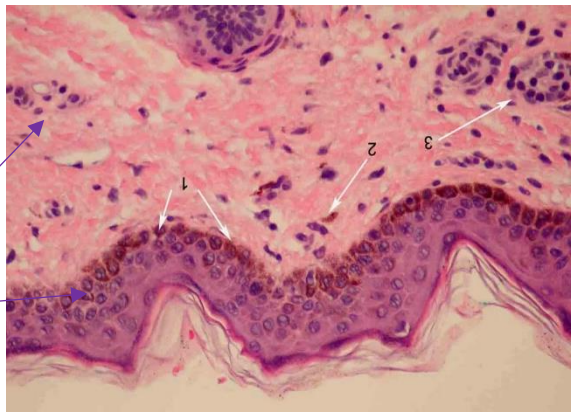
- It is considered the **wear-and-tear pigment** due to the case of its deposition.
- It is accumulated in cases of **aging** and **atrophy** of the cells.
- The tissues that develop a lipofuscin deposition are the **heart**, **liver**, and **brain** cells.
- Lipofuscin material is composed of lipids and proteins, this material usually has **brown-yellow** discoloration granular pigment.



- It is an indication of a previous free radical injury to the tissue with resultant peroxidation of the membranes and damage to the lipids in these membranes.
- **brown atrophy:** When the tissue deposits an excessive amount of lipofuscin pigment and turns brown in color which illustrates **atrophy**. (lipofuscin deposited in the case of **atrophy**).

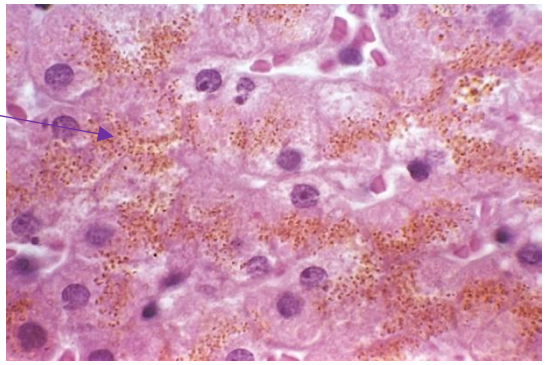
2. Melanin pigment

- Melanin is produced by melanocyte which presents in the skin, it gives the skin its color.
- If melanin is produced in a large amount in the skin the person has deep colored skin and if it present in a small amount the person has fair colored skin.
- In addition to the color, Melanin offers protection against UV light.
- If melanin present in a large amount it accumulates in the dermal macrophages giving them this brown discoloration and in the adjacent keratinocytes at the basal cell layer of the skin as in this microscopic pic.

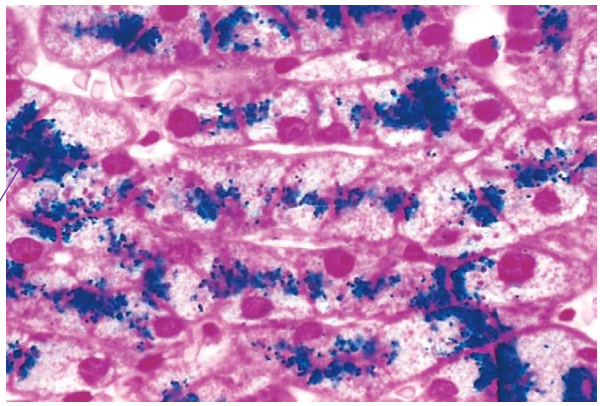


- The deposition of this pigment characterizes the **Freckles** that we see in fair-colored skin people after exposure to sunlight.

3. Hemosiderin pigment



- Hemoglobin derived granular pigment, **brown** in color with a granular appearance.
- **Iron** is usually stored in tissues by binding to **apoferritin** to form **ferritin micelles** **(Iron + apoferritin = ferritin micelles)**
  So, when we have excessive deposition of iron, we have excessive deposition of these ferritic micelles in the tissues.
- Iron can be deposited either in physiologic or pathologic ways :
  - → **Physiologic**: in the tissues that have a rabid red blood cell turn over like in macrophages or the phagocytes of the bone marrow, spleen, or in the liver.
  - → **Pathologic**: can be localized in cases of :
    1. **Bruise**: local pathologic deposition from hemorrhage (after a localized hemorrhage).
    2. **Hemosiderosis**: systemic pathologic deposition of hemosiderin. can result from :
    - hemochromatosis (genetic disease)
    - certain hemolytic anemias (thalassemia, sickle cell anemia)
    - In patients taking repeated blood transfusions



- How can we make sure that the brown pigment in the liver is an iron pigment, not lipofuscin pigment or melanin pigment for example?

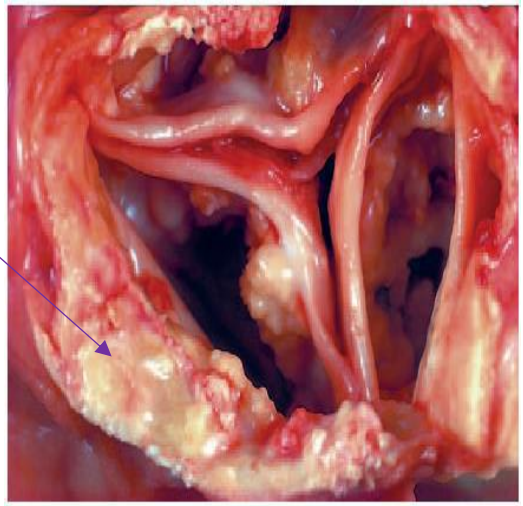
  We use **Prussian blue stain**, Prussian blue stain gives these granules the blue color if it contains iron, but if it is lipofuscin or melanin it will not take the stain.

Pathologic Calcification

- Abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals.
- Two types of calcifications (Dystrophic Calcification and Metastatic Calcification)

1. Dystrophic Calcification

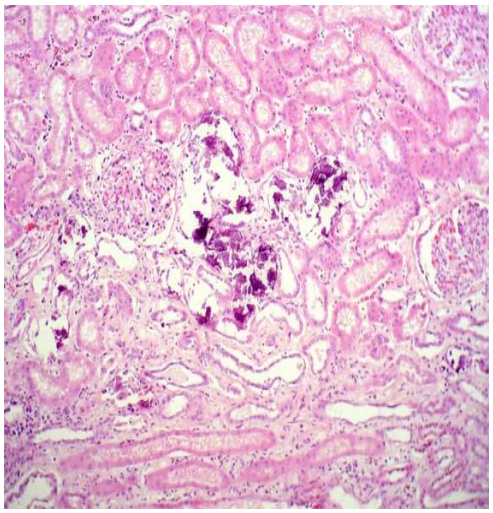
- The deposition of calcium in tissues with necrosis or in damaged tissues of any type.
- It is usually associated with a normal calcium level in the blood and normal calcium metabolism.
- It is exacerbated by hypercalcemia but it is not associated with it.
- Examples:
  - Deposition in the walls of blood vessels affected by atherosclerosis
  - Aging or damaged heart valves, like deposition of the calcium in the aged aortic valve leading to aortic stenosis.
  - Deposition of calcium in the area of inflammation like tuberculosis
  - Incidental finding dystrophic calcification indicates insignificant past cell injury.



- If the dystrophic calcification deposition is excessive it can be associated with organ dysfunction but if it is of a minimal amount it cannot be associated with organ dysfunction.

2. Metastatic Calcification

- It has nothing to do with the metastasis or malignancy BUT it is a **misnomer**.
- It indicates the deposition of calcium in **normal tissues** and it is always associated with an abnormal calcium metabolism that is hypercalcemia.



- Under the light microscope, calcium can be seen purple in color but grossly it gives a whitish chalky color like in the aortic valve above.
- It is surrounded by normal tissue, not damaged, aged, injured or necrotic ones.
- Any causes that are associated with **Hypercalcemia** can cause Metastatic calcification. Examples :
    - Hyperparathyroidism (whether it is primary or secondary) which can occur in renal failure OR the production of parathyroid hormone-related protein like what occurs with certain malignancies.
    - Bone destruction of any causes (metastasis, Paget's disease of the bone, multiple myeloma (MM)(a tumor of the plasma cells of the bone), leukemias, immobilization)
    - Vit-D intoxication also can result in hypercalcemia.
    - Sarcoidosis is an autoimmune disease associated with hypercalcemia.
    - Renal failure with 2ry hyperparathyroidism.
- Deposition of calcium occurs in different tissues like **vessels**, **lung**, and **kidney** but always in normal tissues.

Cellular Aging

- Age is one of the strongest independent risk factors for many chronic diseases, such as **cancer**, **Alzheimer's disease**, and **ischemic heart disease**.
- Aging is associated with a Progressive decline in the life span and functional capacity of cells.
- There are several mechanisms for cellular aging :

1. Accumulation of mutations in DNA.

- Mutations usually accumulate due to exposure to radiation, UV light, toxins, and other different causes.
- The normal cell can repair any damage that occurs in its DNA, but with the aging of the cell, this capacity is decreased, which lead to accumulation of different mutation that will lead to decreased the functional capacity of the cell and its ability to replicate.

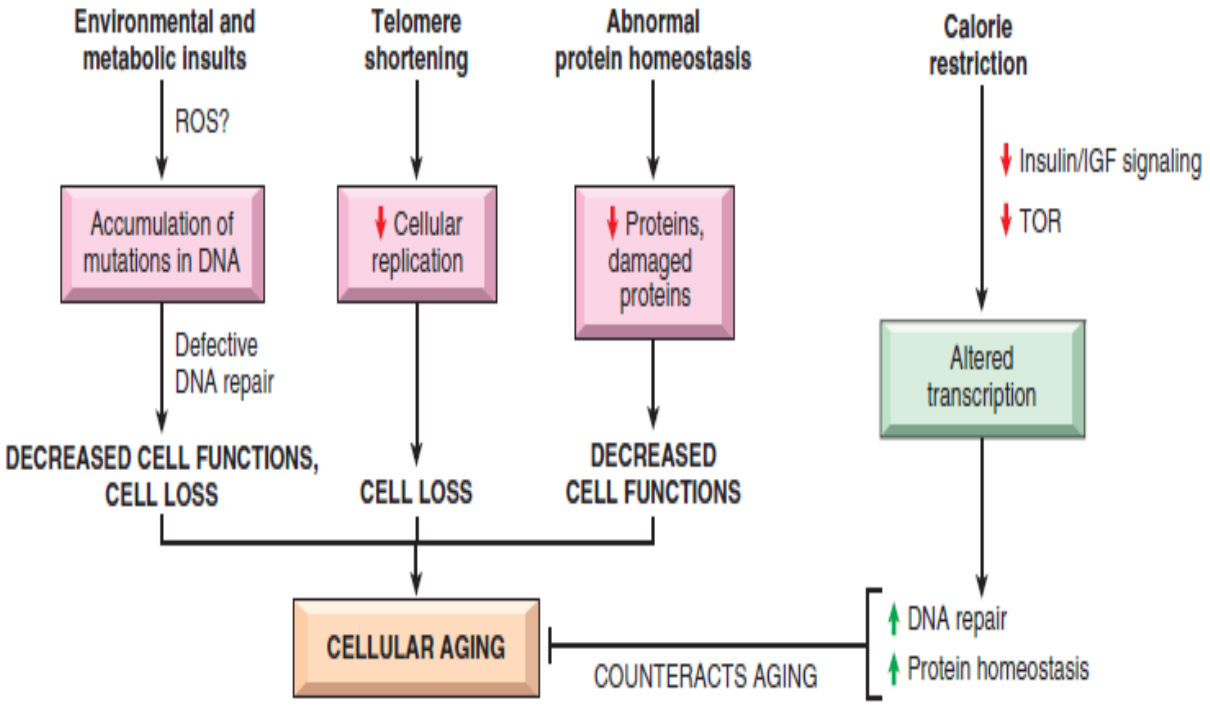
2. Decreased cellular replication (replicative senescence)

- Somatic cells can proliferate for a certain number of times before they enter into cell cycle arrest.
- **replicative senescence:** It is a progressive decrease in the number of divisions that a cell can undergo.
- Every somatic cell has a certain number of times for dividing…why? because they have **telomers**.
- **Telomers:** short repeats of DNA at the end of the chromosomes, which protect the coding material of chromosome at both ends. These telomeres are usually kept at their normal length by an enzyme called **telomerase**.
- But In the case of cell aging the activity of the telomerase enzyme decreases, so the length of the telomers at both ends of the chromosomes will be shorter, this will let the cell sense that the DNA at both ends of the chromosome is exposed which might prevent further replication and let the cell go into cell cycle arrest, we call it **replicative senescence.**

3. Defective protein homeostasis

With aging, the cell's ability to produce proteins and chaperones(needed to fold the protein) decreases, and protein degradation increases which results in a decrease in the number of proteins in the cells.

✓ **To sum up the previous:**



Now … Let's talk in more details about **Telomeres**:

Please, take a minute to watch this >> https://youtu.be/U0fRAr-ZHCo

- Short repeated sequences of DNA at both ends of chromosomes.
- They are present to ensure complete replication of the chromosome without damaging to the coding DNA material at both ends, so protect them.
- Telomeres get progressively shortened upon the replication of the cell, with bouts of replications like in the aging process. The shorting of these telomers will signal the cell to enter into cell cycle arrest.
- Telomere length is maintained by the telomerase enzyme. Telomerase enzyme expressed in a high level in germ cells, low level in stem cells but absent in most somatic cells → that's why the somatic cells enter the replicative senescence very early, after few divisions.
- Telomerase is reactivated in cancer cells, so they continue to divide in a limitless number of divisions.

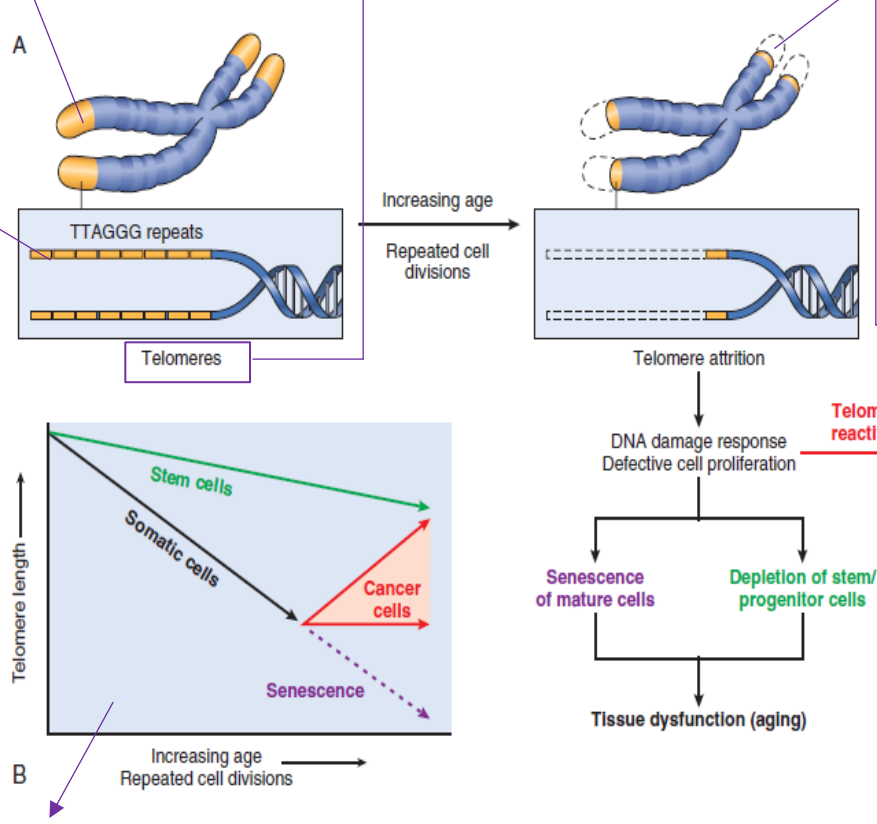
Don’t worry!! Nothing new

The yellow color short repeat of DNA at both ends of the chromosome is called the **telomers.**

Telomerase enzyme is important for maintaining the telomers.

If we have reduced the amount or the activity of the telomerase enzyme, these telomers will be shortened in every division cycle. With repeated cell division and with aging, we will get very short telomers that signal the cell to go into cell cycle arrest.

A short repeats of nucleotides



Telomerase activation will be seen in **cancer** cases in which the replicated ability will be maintained forever

You can see here that telomerase enzyme is expressed in high levels in germ cells and in low level in stem cells but is absent in most somatic cells, that why the somatic cells with increasing age and repeated few cell divisions they will enter the cell cycle arrest while stem cells take more time because they have a much higher amount of telomerase enzyme .but if the cell is transformed into a cancer cell, the telomerase activity is turned on and the cell will continue to replicate unendlessly.

Defective protein homeostasis (we discussed this topic before)

Defective protein homeostasis which occurs with aging is due to :

- Increased turnover
- Decreased synthesis
- The defective activity of chaperones and proteasomes
- The overall decrease in intracellular proteins
- Accumulation of misfolded proteins can trigger apoptosis

Anti-aging- slowing of aging (elixir of youth)

Calorie restriction

Improve immunity

reduce IGF

Physical activity

Stress accelerates aging

Precise mechanisms underlying these effects remain to be defined

Persistent inflammation, chronic metabolic diseases, accelerates aging

IF IT WAS EASY EVERYBODY WOULD DO IT !

HAVE FUN ♥