Lecture 5

- Some injuries result in reversible cell injury. Some cause cell death. It all depends on the injury's nature.
- Some cells can withstand harsher injuries, avoiding necrosis.
- Main cell necrosis causes:
  ATP deplition.
- Main ATP depletion causes:
  Reduced O_2 supply, nutrients
  Increase in toxins like cyanide (blocks O_2 usage, no ATP generation)

- in hypoxia, mitochondria's (where oxidative phosphorylation takes place) sodium-potassium pumps will stop working. They are ATP driven pumps. When sodium is expelled, water passes passively into and out of the cell (mitochondria?). If there is no ATP, sodium is not pumped outside and stays inside, water follows and stays inside as well. Leading to inflammation/swelling. If the cell has microvilli, they end up becoming flattened. Cytoplasmic bleps occur (reversible injury). The ER swells as well. Ribosomes on the RER detach due to RER swelling so protein synthesis stops.

- In cases of hypoxia, cells carry out anaerobic respiration. ATP is produced. So is lactic acid. Lactic acid decreases the pH. For a limited time, the cell functions without O_2.

If lactic acid accumulates, enzymes, proteins cannot function anymore. This causes them to lose their normal structure (denaturation). If these cells are given O_2 they will go back to normal. If not, it turns into an irreversible injury.

- In hypoxia, calcium accumulates inside the cell. Calcium activates proteases which breakdown proteins. Calcium activates endonucleases which start the process of DNA degradation. Calcium causes release of lysosomal enzymes, which cause more destruction.
All these = CELL LYSES
Calcium activates phospholipases which breakdown the membrane and lead to pore formation = Irreversible Injury

ATP depletion ⇒ Pumps stop ⇒ Excess water ⇒ failure of calcium pump ⇓ Excess calcium ⇓ irreversible injury

- due to mitochondrial damage
- excess toxins
- ischaemia

Mitochondrial damage:

- Leads to mitochondrial permeability. Mitochondria contains ions, enzymes, cytochrome c. Cytochrome c is released into the cytosol due to increased permeability. This causes apoptotic cascade.

- Initiates both, apoptotic pathway and necrotic pathway.

Accumulation of oxygen-derived free radicals:

What are they?

- Oxygen gains an electron. It develops the ability to kill cells. Its unstability causes it to initiate a cascade of series.
- Sometimes we need it for reduction for ATP production. That is physiological.
- Sometimes it happens pathologically. Neutrophils use them to aid in harmful agents killing like bacteria.
- They are harmful to the liver, cell membrane, (try to take an electron from it, causing lipid pereoxidation) proteins, DNA.
- They can cause cancer.
- Normally, they are produced in small amounts.

Lecture 6

Intracellular Accumulation :

- Accumulation of:
  exogenous materials — cellular components
- in: Cytoplasm, in lysosomes, in nucleus
- The degree of harm (harmless → severe)

- What causes the accumulation?
  - Some cells have certain amount of substance, like, liver cells. If there is shitty removal of fatty droplets, accumulation takes place. This can be inside hepatocytes.

- Substance (exogenous) is synthesized by a unique pathway or it is deposited due to other conditions. Alpha-1-tryptin deficiency causes the accumulation of abnormal proteins inside.

- Failure to degrade a metabolite. An intermediate is formed, lysosomes cannot get rid of them and they accumulate inside the lysosomes. This causes lysosomal storage diseases.

- Exogenous (carbon, silicon) enters, cannot be removed.

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- Cholesterol and esters might accumulate in the blood vessels walls due to diet. This happens in the muscle layer. Causes lumen narrowing. Usually injury to the endothelium lining takes place, leading to accumulation.

- Excessive proteins inside the cells. Tubules in kidney accumulates protein if there is leakage in the glomerulus. This causes the tubules to absorb proteins. "loss of protein in urine".

- Excessive immunoglobulins in plasma cells.

- Glycogen accumulation in diabetic people or people with glycogen storage diseases.

- Accumulation of pigment. Carbon material deposits in the lungs in smokers, causing them to turn black. Anthracoses.

- Lipofusion pigment accumulation in aging cells. Or injury due to O_2 free radicals.

Calcification:

- deposition of calcium

dystrophic	metastatic
• blood calcium level is normal. mostly deposited in empty tissue	• hyper calcimia • calcium in blood is deposited in normal tissues

- can be due to aging process
- can happen in valves, aorta, compromises blood flow
- whitish in colour
- parathyroid hormone immobilizes calcium from bone. deficiency causes calcium depositing.

Cellular aging:

- risk factor for multiple diseases
- cell accumulate DNA damage → might → apoptosis
  → might not
- they lose their normal function
- decrease in cells entering replicative stage
- telomeres shorten