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Pathology

Doctor 2018 | Medicine | JU

Sheet Slides

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- In the previous lectures we discussed cell injuries, their causes and their morphological changes, in this sheet we're going to discuss the mechanisms of cell injuries.

But before we start with the mechanisms, there are some principles we should know about (they were mentioned in the previous lecture)

Principles of cell injury: -

- The cellular response to injury depends on: -
  1)The duration of the injury
  2)The severity of the injury

- The consequences of the injury depend on:-
  1)type of the tissue :- The response of the cardiac muscle against ischemia is different from the response of brain cells to ischemia and is also different from the response of skeletal muscles to ischemia.

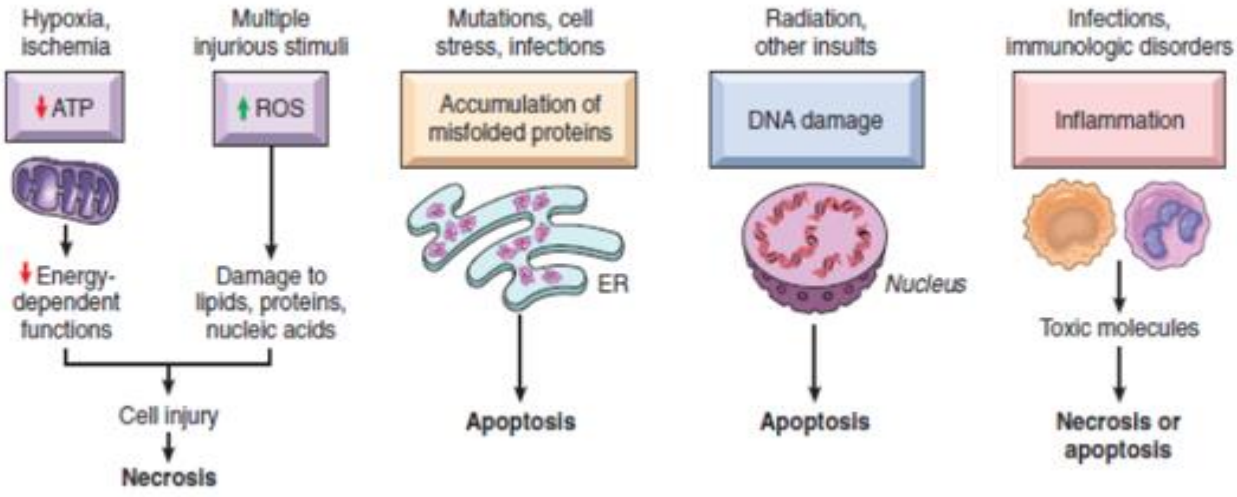
  2)The status of the tissue before the injury :- is it a healthy or diseased tissue.

  3)The adaptability of the tissue :- it is different from cell to cell ,from tissue to tissue and from organism to organism.

  4) the genetic makeup of the injured cell :- for example if someone took a drug in a toxic dose he may be affected with its toxicity and the other one may need a larger dose to be affected with its toxicity.

There are so many mechanisms of cell injury, the mechanism depends on the cause of the cell injury , but most of these mechanisms are interrelated to each other (more than one mechanism can apply or take place at the same time)

- As we all know the cell is made of a cell membrane (phospholipid bilayer containing proteins) , the cytoplasm and it contains organelles , mitochondria, ER , ribosomes, lysosomes and the nucleus . So the mechanisms of cell injury are different according to <u>which part of the cell is affected</u> and to <u>what is the cause of the cell injury</u>



Mechanisms of cell injury

- Hypoxia and ischemia are the most common causes of the cell injury, the mechanism of their damage is mainly **<u>decreasing ATP synthesis</u>**

ATP is needed for most functions of the cell such as (Ion transport, phosphorylation, protein synthesis and other functions)

- <u>Generation of reactive oxygen species</u> (Free radicals) which can be caused by radiation injury, UV light, sun exposure and other causes, they make their damage on the proteins, membranes and the nucleus which leads to cell necrosis
- <u>Inflammation</u> as a response to microbes and pathogens
- <u>Accumulation of misfolded proteins</u> (mainly involved in cell death by apoptosis)
- DNA damage

Hypoxia and Ischemia

We defined hypoxia as a decrease in oxygen and its main cause is ischemia(reduced blood supply caused by blockage of an artery)

Oxygen is needed by the cell for the oxidative

Phosphorylation in the mitochondria

so if there is no oxygen there will be a defective oxidative phosphorylation which leads to a failure of ATP generation which will turn off any function that depends on ATP such as the sodium potassium pump (sodium will end up in the cytosol → water entering the cell → cell swelling)and this causes cell swelling reversible injury we mentioned in one of the previous lectures.

- Some cells can respond to hypoxia by generating ATP without oxidative phosphorylation we call it anaerobic glycolysis, such as liver cells but brain cells can't do anaerobic glycolysis …. (the response of the tissue to the injury is different in this case, it is according to the cell type)

- Brain cells can't do anaerobic glycolysis so immediately when someone is infected with hypoxia or ischemia , one or two minutes → cell death , but in the liver it takes longer time because it can do anaerobic glycolysis

Hypoxia effects

- ✓ Reduced activity of membrane ATP dependent sodium pumps → cell swelling
- ✓ Lactic acid accumulation→ decreased PH → failure of enzymes (such as the enzymes needed for DNA replication, protein synthesis)
- ✓ Disruption of ribosomes :- ribosomes are bound to the ER , when the cell swells that means that the organelles of the cells are also going to swell such as mitochondria and ER , so the ribosomes will detach from the ER and the ribosomes main function is protein synthesis → reduction of protein synthesis
- ✓ Accumulation of ROS :- hypoxia leads to reduction of oxygen supply so the oxidative phosphorylation will be affected so the mitochondria will use

The oxygen in an insufficient way which leads to ROS generation and also leads to defects in the **mitochondrial membranes**→ depletion of ATP, and **lysosomal membranes** (leakage of lysosomal enzymes to the cytoplasm and then to the outside)

- ✓ Necrosis is the end result

Ischemia-reperfusion Injury

- When the blood goes back to its ischemic tissue (when the blockage of the artery is removed) that doesn't mean restoration of normal functions because in some cases we might face paradoxical cell injury (reper-fusion injury) , mostly happens after myocardial infarction or after cerebral infarction , so what causes the paradoxical cell injury ?

  - **The blood that floods back makes further damage by the generation of ROS** , the retaining blood contains large amount of oxygen so the tissue must have advantage of this oxygen for oxidative phosphorylation to generate ATP ☺ but the problem is that the tissue is still damaged form the previous ischemia and the mitochondria is also damaged and despite the presence of O2 from the restored blood supply → the oxidative phosphorylation will be defective(damaged mitochondria) → generation of ROS

- The increased generation of ROS is from :-
  1. Injured cells with damaged mitochondria & defective antioxidant mechanisms
  2. Infiltrating new leukocytes, the blood is loaded with RBCs , oxygen and white blood cells (leukocytes) , the leukocytes can generate free radicals that will add to the process .

So we'll have free radicals coming from the ischemic tissue (as a result of repair-fusion) and free radicals from the infiltrating new leukocytes → paradoxical injury

Another mechanism by which the damage of the reperfusion injury occurs is Inflammation, as we said the retained blood is loaded by RBCs, leukocytes, complementary proteins, inflammatory mediators, they're all going to initiate in inflammatory reaction.

Generating ROS + Inflammation = damage of the tissue in repair-damage injury.

Oxidative stress

It means the formation of free radicals (ROS), the ROS are characterized by one single unpaired electron on their outer shell, this unpaired electron makes their energy very high (they are high energy molecules with highly damaging effect, making them very unstable), so whatever they react with (DNA, membranes, proteins) , they damage it and transform it into free radicals in a chain of reactions that results in necrosis.

ROS are generated in: -

1) Chemical injury (CCL4)
2) Radiation injury (UV, X ray)
3) Hypoxia
4) Cellular aging
5) Inflammation (inflammatory cells such as microphages and neutrophils have the ability to generate ROS to kill the microbe or the pathogen that caused the inflammation)
6) Ischemia-reperfusion injury

*Note: - Free radicals (ROS) are produced normally in our cells but in **small amounts** during the redox reactions in the mitochondria and they are removed immediately before they exert their damage, but in the cases we mentioned above, (ROS) are produced in **large amounts (high damage capacity)**

✓ Normally the oxygen is reduced to produce water in our cells by certain steps through which to produce free radicals, but those radicals are produced in small amounts which can be removed immediately, but what are those certain steps?

- In the mitochondria the oxygen turns into superoxide (superoxide is a free radical) this superoxide is reduced into hydrogen peroxide (H_2O_2) by an enzyme called Superoxide dismutase(H_2O_2 is also a free radical with high damage capacity) then H_2O_2 is reduced into H_2O by the action of either by glutathione peroxidase enzyme or by catalase

In certain cases H_2O_2 can't be reduced to water in case of some injuries which produces more free radicals are produced which gives us hydroxyl radicals (OH) it is also a free radical with damaging capacity

The other scenario of producing free radicals as we mentioned is Inflammation , the main goal of inflammation reactions is to get rid of the microbes that cause inflammation by the inflammatory cells , by a process called phagocytosis by (neutrophils and macrophages) the phagocytic vacuole binds to lysosomal enzymes , and at the same time it generates free radicals by an enzyme called **myeloperoxidase** (this enzyme is found in neutrophils and macrophages) to kill the microbe or the pathogen that caused the inflammation , the questions is.. How can these free radicals kill the microbes?

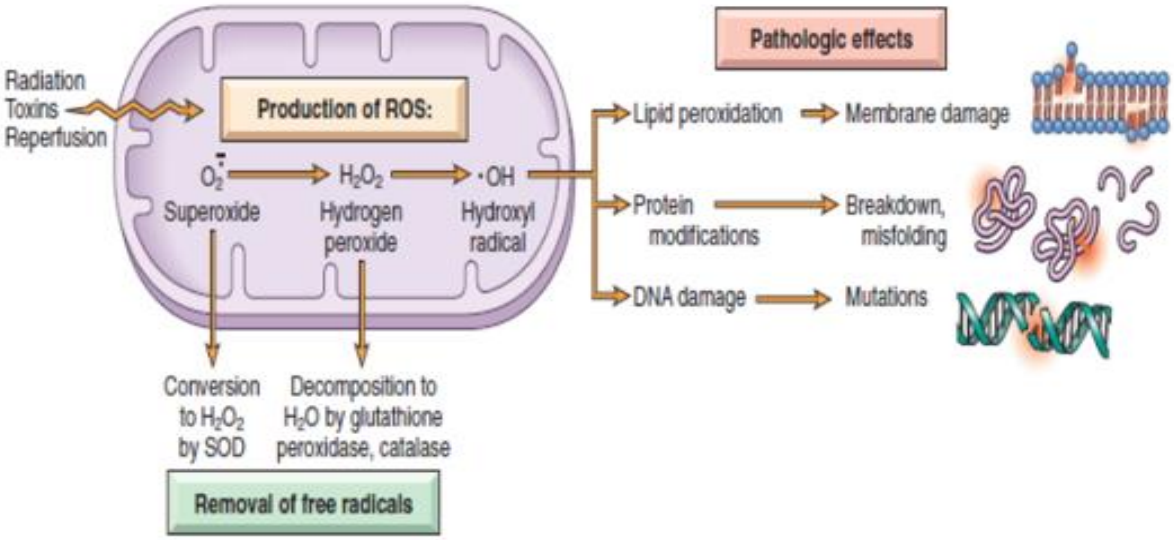
- Oxygen turns into superoxide
- Superoxide turns into H_2O_2
- H_2O_2 turns into **Hypochlorite** by the enzyme myeloperoxidase (hypochlorite is found in the cleaning materials, and it's a free radical that kills microbes).

Removal of free radicals

- Spontaneous decay (immediately removed), we said that if the free radical reacts with anything it turns it into free radical , but if the free radical didn't react with anything it is immediately removed
- Superoxide dismutase (superoxide → H_2O_2)
- Glutathione peroxidase and catalase(most active enzyme) (H_2O_2 → water)
- Endogenous or exogenous anti-oxidants (vitaminsA, C, E and B-carotene) they naturally protect our bodies from the effects of free radicals

Effects of ROS

- Lipid peroxidation of membranes (plasma , lysosomal , mitochondrial membranes) which causes damage and disruption of those membranes
  - Damage of plasma membrane → all the cell contents will get outside
  - Damage of mitochondrial membrane → depletion of ATP
  - Damage of lysosomal membrane → leakage of lysosomal enzymes
- Protein modification , by the crosslinking of the proteins which makes these proteins
  - Nonfunctional
  - Ready for degradation and fragmentation
  - Loss of enzymatic activity
  - Misfolding
- DNA damage , by making a single strand break which leads to a mutation
- Killing of microbes



Cell injury caused by toxins

Toxins are the environmental chemicals and substances produced by infectious pathogens and they mediate damage by two ways:-

- Direct-acting toxins.
- Indirect-acting toxins (latent toxins).

- ✓ Direct acting toxin is any toxin enters the body and directly does the damage, whereas the latent toxins our body must turn them into active metabolites and those active metabolites will mediate the damage

Direct acting toxins

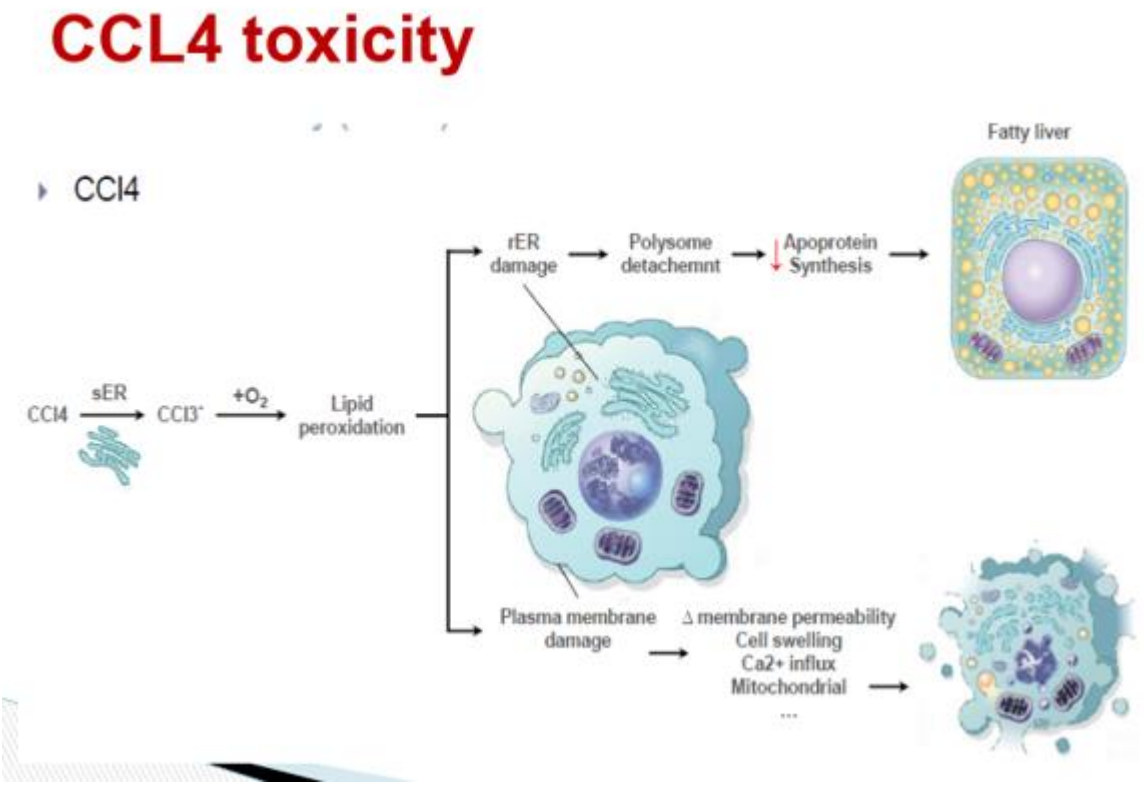
- They act directly by combining with a critical molecular component or cellular organelle.
- such as Mercuric chloride poisoning
- Mercuric chloride poisoning is found in the contaminated seafood (contaminated means impured by the addition of poisonous or polluting substances)
- Another example of direct acting toxins is chemotherapeutic agents

Now the question is .. what is the direct acting toxins acting mechanism?

- The toxin binds to sulfhydryl groups of membrane proteins which leads to disruption of the cell membrane (as we took in biochemistry) and it makes damage to membrane proteins , and some proteins are ATP dependent channels (sodium potassium pumps) → depletion of ATP → cell swelling (because of the accumulation of sodium ions inside the cell) → cell death

Latent toxins

- Those toxins must be turned into active metabolites by the enzyme **cytochrome p-450 in the sER of the liver** then they start their damage by the **generation of free radicals** such as (CCL4 and acetaminophen) they exert their damage by turning into active metabolites those active metabolites are free radicals



- In the case of CCL4, CCL4 turns into CCL3, CCL3 is a free radical and it starts doing its damage .. lipid peroxidation, DNA damage and protein crosslinking ☹ so we will face a decrease in the protein synthesis such as the apoproteins.

- The apoproteins are important for the transport of lipids and when we face a decrease in their synthesis, lipids transport will be defected.

- In this way, lipids will accumulate inside the cells which leads to **Fatty liver**

Don't waste your time buddy,someone will steal the grade you're aiming for