Cell injury “2”

Editing File

Objectives:

- Understand the concept of cell and tissue adaptation to environmental stress including the meaning of hypertrophy,hyperplasia,aplasia, hypoplasia and metaplasia with there clinical manifestations.
- Awareness of the concept of hypoxic cell injury and its major causes.
- Understand the definition and mechanisms of free radical injury.

Color Code:

Female’s Notes
Male’s Notes
Important
Extra

Pathology Team 441

MED441 KING SAUD UNIVERSITY

Revised & Reviewed by: Abdulaziz & Bahammam Faye Wael Sendi

Lecture outline

Adaptation to environmental stress/cell injury:
Hypertrophy, hyperplasia, atrophy, squamous metaplasia, osseous metaplasia and myeloid metaplasia.

Cell injury:
- Hypoxic cell injury
- Free radical injury
- Reversible & irreversible cell injury

Adaptation to environmental stress

Cells are constantly adjusting their structure and function to accommodate changing demands. When cells face physiological (not disease)or pathologic stress /stimuli (change) they undergo adaptation .
The principal adaptive responses are

- Hypertrophy
- Hyperplasia
- Atrophy
- metaplasia.

If the adaptive capability of the cell is exhausted or if the external stress is too harmful,
cell injury develops.
Within certain limits injury is reversible and cells return to normal.
But, in severe or persistent stress the injury becomes irreversible and leads to cell death.

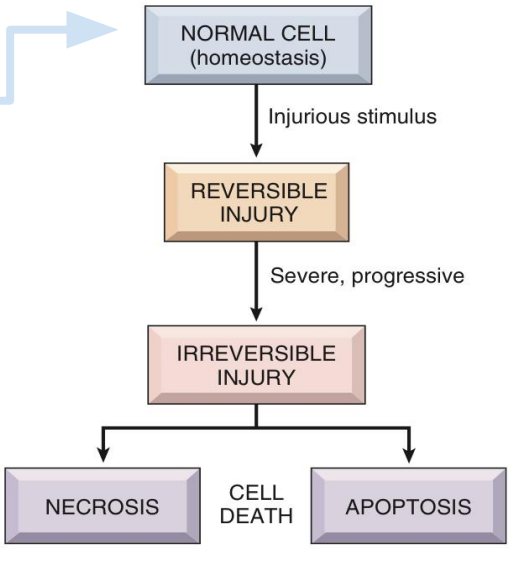
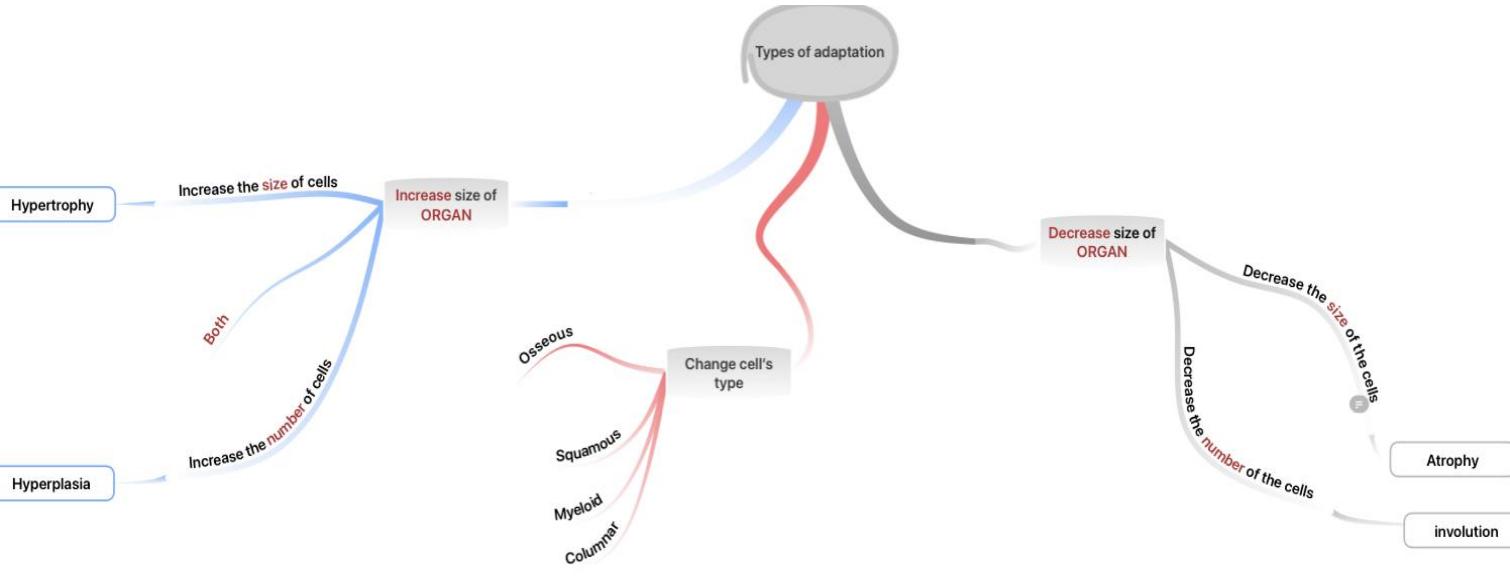


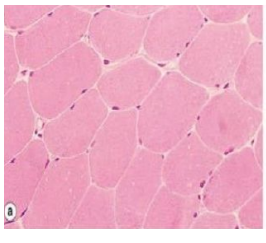
Fig. 2.2 Sequence of reversible cell injury and cell death. Necrosis and apoptosis are the two major pathways of cell death and are discussed in detail later.

Types of Adaptation



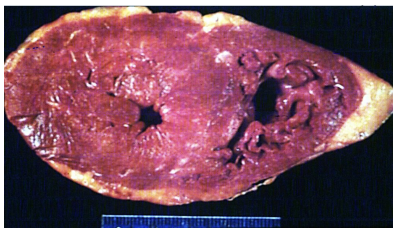
Increase the size of the ORGAN

	Hypertrophy	Hyperplasia
definition	an increase in the size of the cells.	increase in the number of cells
demand	increased	increased
cells' type	not capable of dividing/replication	capable of replication.
example cell	striated muscles.	---------
Physiological	1- breast during lactation (الرضاعة) 2- pregnant uterus 3- the skeletal muscles by exercise.	**1- Hormonal hyperplasia:** the proliferation of the glands of the female breast at puberty and during pregnancy **2-Compensatory hyperplasia** :when a portion of liver is partially resected, the remaining cells multiply and restore the liver to its original weight.
Pathologic	Cardiomyocytes (myocardium) in heart failure . (e.g. in hypertension or aortic valve disease)	excessive stimulation by hormones or growth factors excess estrogen hormone leads to endometrial hyperplasia in the uterus which causes abnormal menstrual bleeding حيض. Sometimes pathologic hyperplasia acts as the platform from which cancer can develop.



skeletal muscles at rest

Skeletal muscle at exercise



Myocardial Hypertrophy
Left ventricle is thicker than normal

The difference between smooth muscle layer (myometrium) during Pregnancy and normal one

Usually hyperplasia occurs together with hypertrophy (both) examples :

1- Uterus during pregnancy: in smooth muscle of the uterus.this is physiological NOT disease

2- Prostate in elderly: in the prostate gland and stroma. This condition is called "benign nodular prostatic hyperplasia" so excess urination and hard urination occurs due to prostate hyperplasia and hypertrophy because of high levels of testosterone in males.

3- Because of the High Demand on heart in hypertension patients, they may show Heart Hypertrophy in X-ray

Decrease the size of the ORGAN

shrinkage in the size of cells because of the reduced demand on the organ .
Atrophic cells are not dead but have diminished function.
In atrophic cells there is decreased protein synthesis and increased protein degradation.

Causes of atrophy

1. decreased workload or disuse (e.g. immobilization of a limb in fracture),
2. loss of innervation (lack of neural stimulation to the peripheral muscles caused by injury to the supplying nerve causes atrophy of that muscle
3. diminished blood supply
4. inadequate nutrition
5. loss of endocrine stimulation (e.g. the loss of hormone stimulation in Menopause (عمر انقطاع الدورة)
6. aging: senile atrophy of brain can lead to dementia

- Some of these stimuli are physiologic (the loss of hormone stimulation in menopause) and others pathologic (denervation)

Physiotherapy is the treatment for Disuse Atrophy

Involution: it is the reduction in the cell number.

Metaplasia

A Reversible change of the one cell type to another. By the cell itself

Certain types of cells are extra sensitive to a particular toxic agent or environment.

When they get exposed to that agent or environment they get replaced by another type of cell which is better able to tolerate that toxic agent or environment. This is known as metaplasia.

In metaplasia the cells adapt by changing (or differentiating) from one type of cell into another type of cell

Metaplasia is usually a reversible provided the causative toxic agent is removed.

Squamous

columnar cells → Squamous cells.

Location : the respiratory tract: (bronchus)following chronic injury in **smokers.**

Reason : The squamous epithelium is able to survive under the toxicity of tobacco better than the columnar epithelium.

The problem : the protective functions of columnar epithelium are lost mucus secretion and ciliary action.

The cervix following chronic irritation and inflammation. where?

If the causative agent persists, it may predispose to provide a platform for cancer to develop squamous metaplasia and later squamous cell cancer arise from it.

squamous cell carcinoma of cervix may arise from the squamous metaplasia of cervix.

Myeloid

(Extramedullary hematopoiesis): is the proliferation of hematopoietic tissue in sites other then the bone marrow such as : liver of spleen

Metaplasia

Osseous

It's the formation of new bone at sites of tissue injury.

Cartilaginous metaplasia may also occur

Columnar

squamous cells → columnar cells.

Location : In the esophagus in chronic gastro-esophageal acid reflux disease.

Because : The normal stratified squamous epithelium of the lower esophagus cannot handle the acidity of reflux disease (this change is called **Barrett's oesophagus**)

It can be precancerous and lead to development of adenocarcinoma of esophagus

E.g. In females columnar epithelium could transfer into squamous in uterus because of high concentration of acids during reproductive ages.

Dysplasia

Is the enlargement of an organ or tissue by the proliferation of cells of an abnormal type. Note that dysplasia isn't cancer but maybe progress to cancer

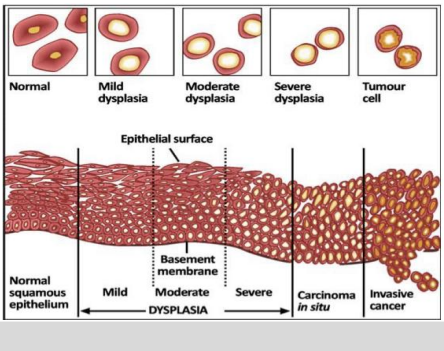
In some cases, metaplasia can transport into dysplasia as a sequence of event of cellular adaptation.

Ex. a man who smokes a lot for a while

His Columnar ciliated epithelium has transport to squamous cells as a result of irritation, doctor advise him to stop smoke but he hasn't stopped, then he comes to the hospital with a cancer in his lung because the metaplasia has developed into Dysplasia .

summary:

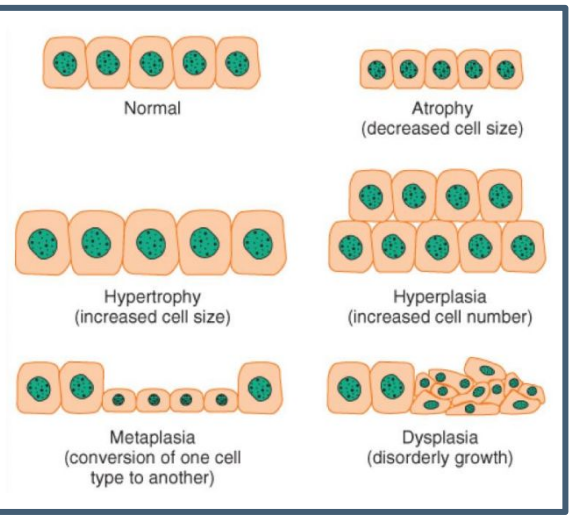
Cell injury→irritation→squamous metaplasia affect the respiratory epithelium→metaplasia→haven't stop smoking→Dysplasia

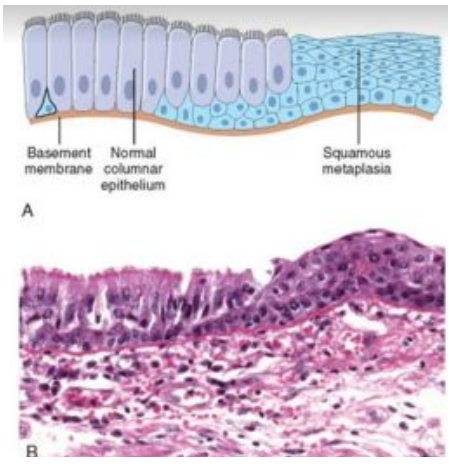


Summary ;
Change in size of cells
Atrophy : Decrease in the size or number of cells
Hypertrophy : Increase in the size of cells

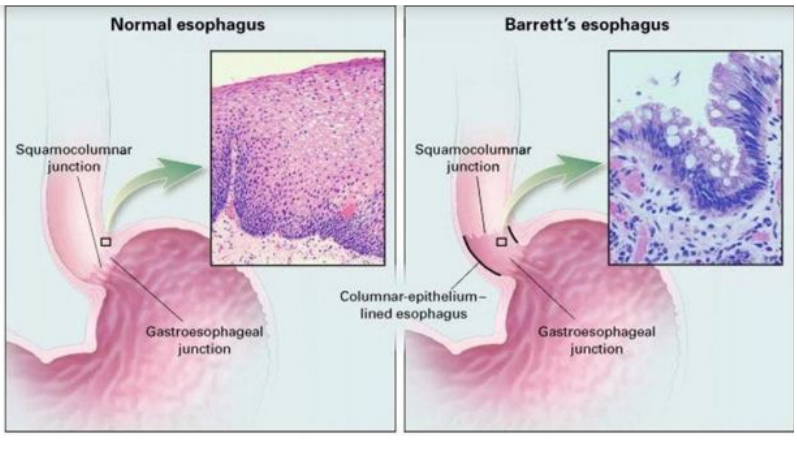
Change in number of cells
Involution : Decrease in the number of cells
Hyperplasia : Increase in number of cells

Change in type of cells :
Metaplasia : Stable change to another cell type
Dysplasia : Change that could cause cancer





Columnar cells → Squamous



Squamous cells →Columnar

Examples of metaplasia

Original tissue	Stimulus	Metaplastic tissue
Ciliated columnar epithelium of bronchial tree	Cigarette smoke	Squamous epithelium
Transitional epithelium of bladder	Trauma of bladder calculus	Squamous epithelium
Columnar epithelium in gland ducts	Trauma of calculus	Squamous epithelium
Fibrocollagenous tissue	Chronic trauma	Bone (osseous) tissue
Esophageal squamous epithelium	Gastric acid	Columnar epithelium
Columnar glandular epithelium	Vitamin A deficiency	Squamous epithelium

Stevens et al: Core Pathology, 3rd Edition.

NOTE: the term "hypoplasia" and "aplasia" are not adaptations

- Hypoplasia refers to an organ that does not reach its full size. It is a developmental disorders and not an adaptive response.
- Aplasia is the failure of cell production and it is also a developmental disorders e.g. during fetal growth aplasia can lead to agenesis of organs.

Cell injury

When the cell is exposed to an injurious agent , stress stimulus and it leads to injury of the cell

When cell injury occur ?

Stress/increased demand → Adaptation e.g. hypertrophy → Unable to adapt → Cell injury

Injurious stimuli e.g. hypoxia → Cell injury

Cell injury

- **Reversible**
  - Cell injury is reversible up to a certain point , No more injurious stimuli complete repair Cells , tissue back to normal Restoration of normal organ function
- **Irreversible**
  - Persistent or strong injurious stimuli
  - **Tissue repair**
    - with diminished capacity impaired cell function
  - **Cell death**
    - Necrosis
      - occurs due to disease, injury, or failure of the blood supply (ischemia) and it is always **pathologic**
    - apoptosis
      - when a cell dies through activation of an internally controlled suicide program

type of injury
time duration of injury
severity of injury

→ **What determine the extent of damage (reversible or not)**

Cause of cell injury

Immunologic agents
thyroid damage caused by autoantibodies

Physical Agents
mechanical trauma, burns and deep cold, sudden change in atmospheric pressure, radiation,electric shock

Chemical Agents +Drugs
oxygen in high concentrations, poisons, pollutants, insecticides, industrial and occupational hazards, alcohol and narcotic drugs and therapeutic drugs.

Nutritional Imbalances
Nutritional imbalance can cause cell injury

Genetic Derangement
E.g sickle cell anemia

Infection agent
Bacteria +virus or fungus

Oxygen Deprivation (hypoxia)

common cause
, Hypoxia can be due to:
i. **Ischemia** (obstruction of arterial blood flow), E.g. in myocardial infarction and atherosclerosis.
ii. **Inadequate oxygenation of the blood** e.g. lung disease and carbon monoxide poisoning
iii. **Decreased oxygen-carrying capacity of the blood** e.g. anemia
iv. **Inadequate tissue perfusion due to cardiorespiratory failure**, hypotension, shock etc

Depending on the severity of the hypoxia, cells may adapt, undergo injury or die

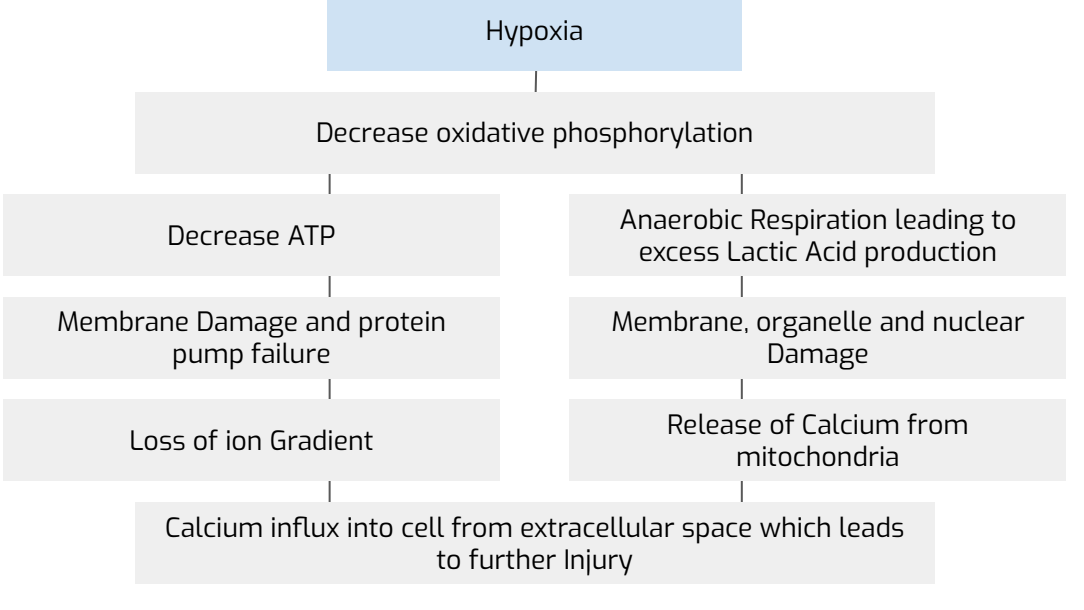
vulnerability of cell to hypoxic injury From most vulnerable to least

Neuron → **Cardiac muscle** → **hepatocyte** → **Skeletal muscle**

mechanism of cell injury

1. **Depletion of ATP**
2. **Cell membrane damage/defects in membrane permeability**
3. **Nuclear and DNA damage**
4. **Mitochondrial damage:** specially in hypoxic injury and cyanide poisoning
5. **Ribosomal damage** in alcohol damage of liver cells and with antibiotic use
6. **Free radical injury**
7. **Influx of intracellular calcium leading to loss of normal calcium balance** ischemia causes an increase in intracellular calcium concentration. Increased Ca2+ in turn activates a number of enzymes which cause damage

mechanism of hypoxic cell injury

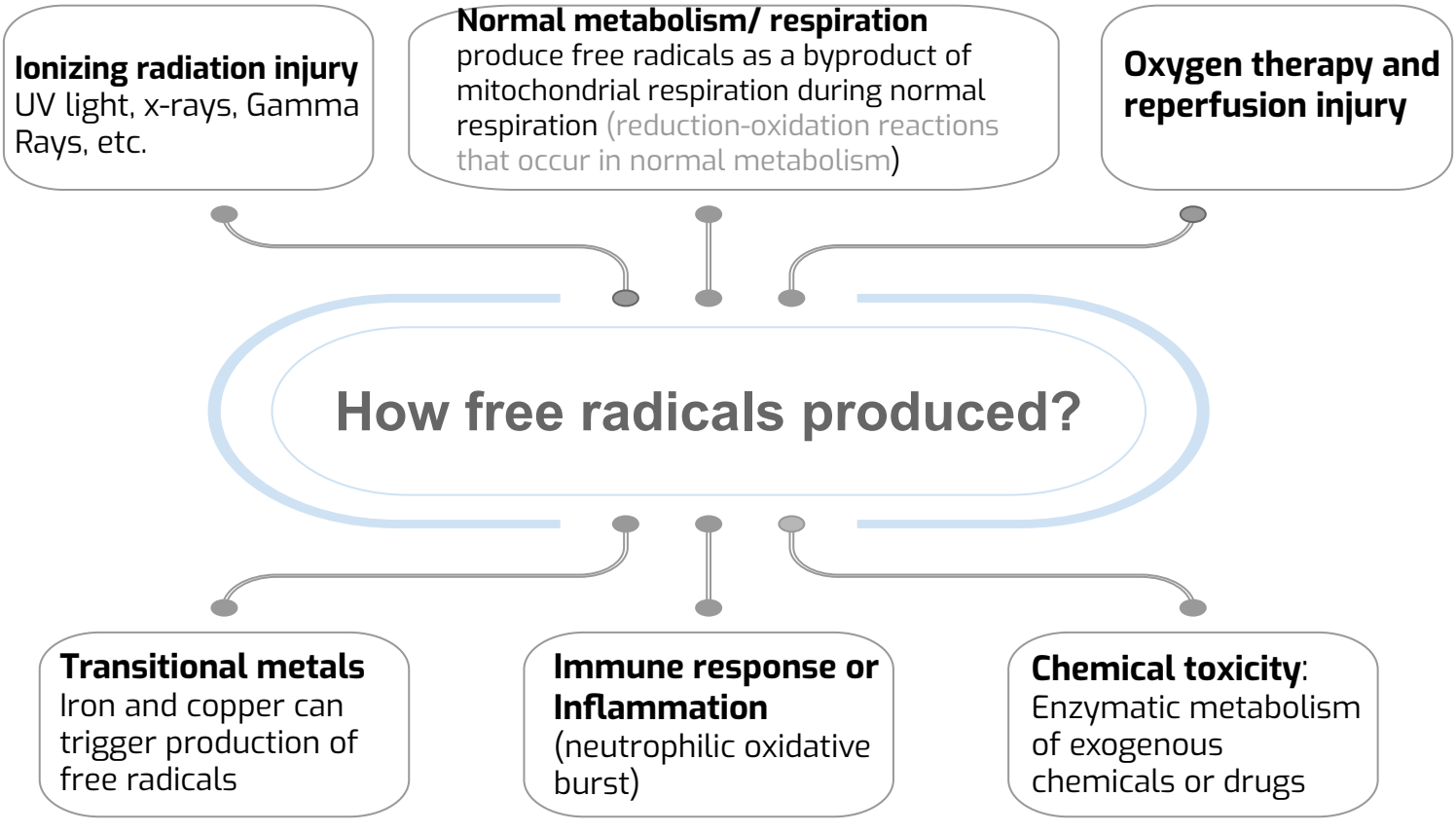


Free radice injury

Click here

Free radical injury(oxidative stress): is due to excess accumulation of oxygen-derived free radicals.

Free radicals: are highly reactive and harmful atoms that have a single unpaired electron in the outer orbit. These atoms are called reactive oxygen species/free radicals



Common free radicals (important)

1) superoxide anion radical ($O2^{-}$) important
2) hydrogen peroxide ($H2O2$)
3) and hydroxyl ions (OH^{-})
4) Nitric oxide (NO)
   (an important chemical mediator generated by various cells and it can also act as a free radical)

Free radicals cause damage to:

Proteins

Nucleic acid

Lipids

oxidative modification of proteins lead to protein fragmentation.

DNA damage causes cell aging & malignant transformation of cells

lipid peroxidation of membranes will damage cell membranes & organelles

How does our body fight the free radicals?

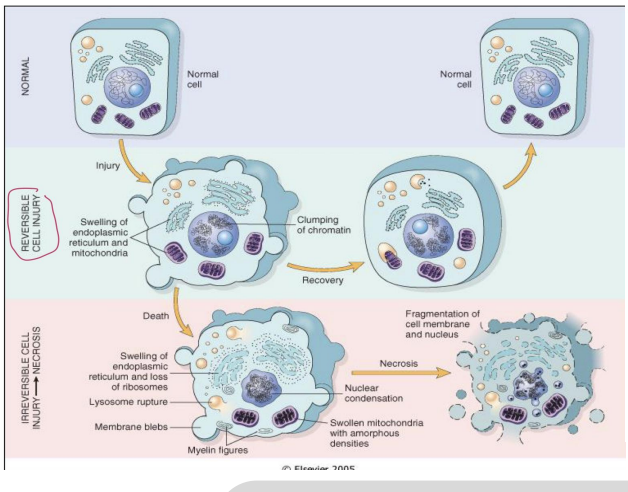
Certain substances in the cells remove or inactivate the free radicals in order to minimize injury caused by them .they are called "free radical scavenging system" these substance :

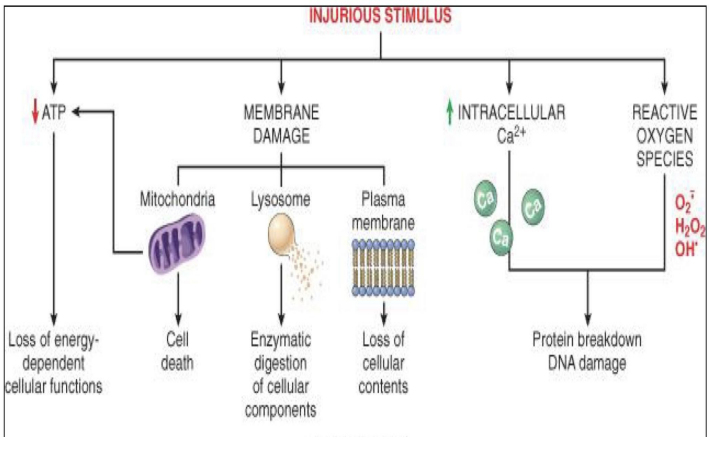
1-Antioxidant : e.g. vitamin A, E, C (ascorbic acid)

2-Enzyme : which break down hydrogen peroxide and superoxide anion كيف نتذكرها ؟ وين توجد الانزيمات؟
<جسمك=GSMC> في

- **Glutathione peroxidase**
- **Superoxide dismutases**
- **mannito**
- **Catalase**

NOTE: Any imbalance between free radical-generating and radical-scavenging systems results in oxidative stress causing cell injury





Reversible Cell Injury

- Fatty change: appearance of small or large lipid vacuoles in the cytoplasm
- Swelling+vacuolization of cytoplasm"hydropic/vacuolar degeneration"
- Mild mitochondrial swelling
- Mild rough endoplasmic reticulum and plasma membrane damage
- Defect in protein synthesis
- **Mild** eosinophilia of cytoplasm. Why? (due to decrease RNA in cytoplasmic) Appears red under microscope

Irreversible Cell Injury

- **severe** mitochondrial damage with the appearance large, amorphous densities in mitochondria
- **Severe** plasma/cell membrane damage
- **Increased** eosinophilia
- Numerous myelin figures
- Rupture of lysosomes leakage and enzymatic digestion of cellular contents
- Nuclear damage
  1-pyknosis (shrinkage)
  2-karyolysis (dissolution)
  3-karyorrhexis (break down or fragmentation

MCQs

1- the proliferation of hematopoietic tissue in sites other than bone marrow is

A)Osseous metaplasia	B)Myeloid metaplasia	C)Columnar metaplasia	D) Squamous metaplasia

2-If the causative agent persists , squamous cells may be

A)Replaced to cancer	B)Platform for fungi	C)Replaced again to squamous	D)Platform for cancer

3-When the hepatocyte multiply to restore its original weight . this is called....

A)cancer	B)hypertrophy	C)hypoplasia	D)hyperplasia

4- all of these are changes associated with reversible cell injury except

A)Hydropic	B)Vacuolar degeneration	C)Rupture of lysosomes	D)mitochondrial swelling

5) the most common cause of cell injury

A)nutritional imbalance	B) oxygen deprivation	3)chemical agents	4) genetic degeneration

6)Which one of this cells is the most susceptible to hypoxic injury

A)Hepatocyte	B) cell of skeletal muscle	C) cell of cardiac muscle	D)neuron

SAQs

1- what are the physiological types of hyperplasia?
Slide 3
2- where do hyperplasia and hypertrophy occur simultaneously?
Slide 3
3)what's the antioxidants of the free radical scavenging system

1)B 2)D 3)D 4)C 5)B 6)D

CASES

1) When the cast is removed, the patient notices that his right leg is weak and visibly smaller than the left leg. Which of the following terms best describes this change in the patient's leg muscle?

A) Hyperplasia	B) Metaplasia	C) Atrophy	D) Ischemic necrosis

2) A five-year-old boy suffers blunt trauma to the leg in an accident. Six months later, bone trabeculae have formed within the striated skeletal muscle at the site of tissue injury. Which of the following morphology adaptation happened to injury?

A) Metaplasia	B) Dysplasia	C) Atrophy	D) Hypertrophy

3) A 70 years-old went to hospital and complained of hypertension, doctors investigated. X-Rays showed that the left ventricle of the heart is very thick. What type of adaptation happened to the heart?

A) Metaplasia	B) Dysplasia	C) Atrophy	D) Hypertrophy

Boys Questions

1)C 2)A 3)D

Leaders:
Lama Al-Jamili
Salem Abokhanjar

Sub-Leader:
Manar Al-Abdullah

Organizer:
Aya Alhossain

Members:

Lama Bin Salamh
Rahmah Alzahrani
Noyer Awad
Rahaf alamri
Layan Alhelal
Taif alshehri
Renad Aldawayan
laila almeshariy
Alanoud Albawardi
Reema Alrashedi
Shouq Alhathal
Tarfa albaz
Jumana AL-qahtani
Lama Alrumaih
Ayah Sayed
Shahad Helmi
Norah Alsewailem
Leen Alhadlaq
Arwa Alenzi
Reem Al Kulaibi

Mohammed Alwahibi
Sultan Alosaimi
Rakan alobaid
Abdullah Abdulrazaq

Pathology
Team 441