جامعة الملك سعود
King Saud University

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MED439
KING SAUD UNIVERSITY

CELL INJURY

Lecture 1

Objectives:

- Understand the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical manifestations.
- Be aware of the concept of hypoxic cell injury and its major causes.
- Understand the definitions and mechanisms of free radical injury.

Lecture 1 outline:

> Adaptation to environmental stress/cell injury:
Hypertrophy, hyperplasia, atrophy, Metaplasia (and its types)

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

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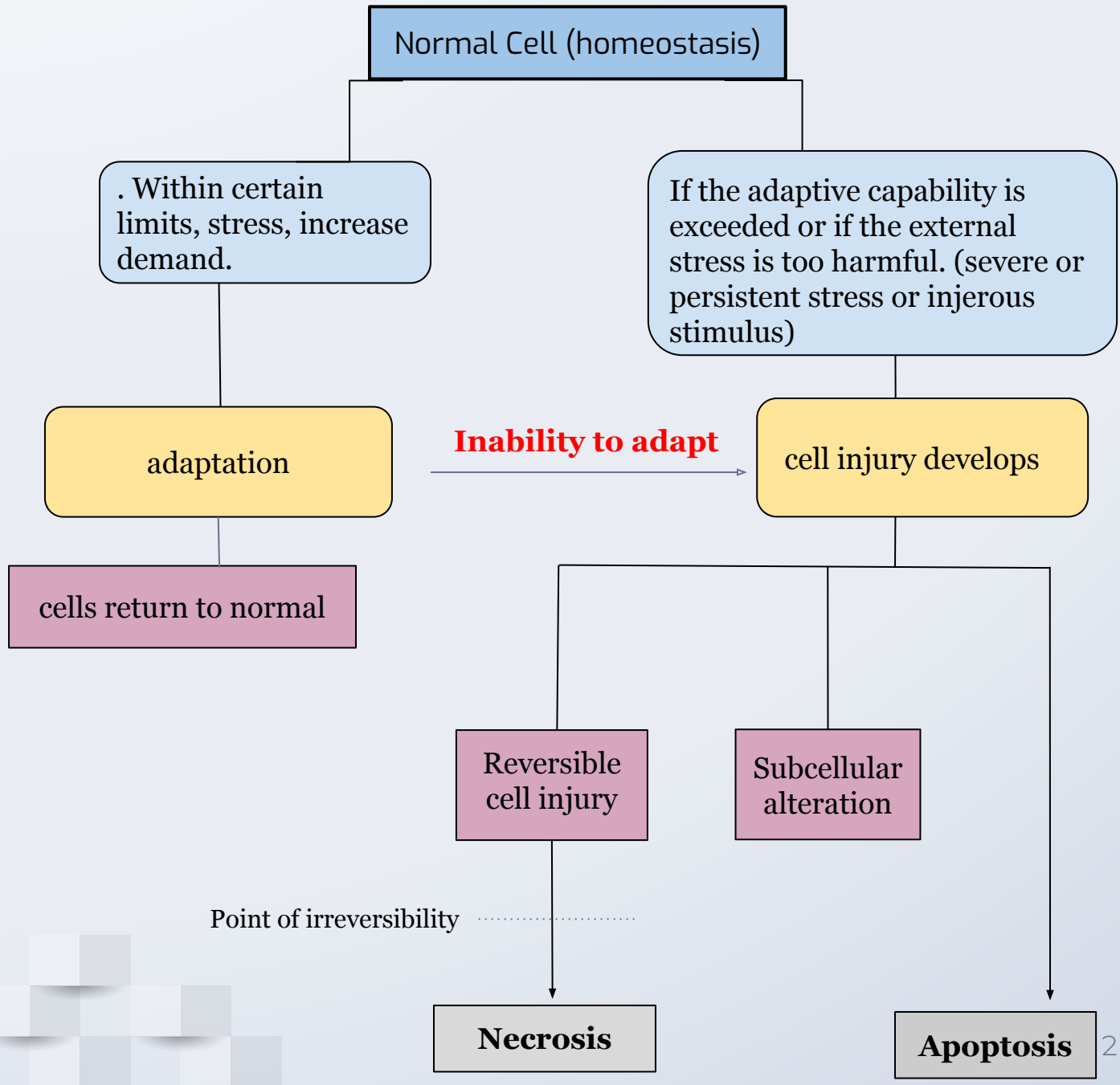
Adaptation to environmental stress

› Cells are constantly adjusting their structure and function to accommodate changing demands i.e. they adapt within physiological limits.

› Adaptation is not necessarily bad, it is a form of adjusting.

› As cells encounter physiologic stresses or pathologic stimuli, they can undergo adaptation. The principal adaptive responses (forms of adaptation the cell takes when there is Environmental changes) are:

- **Hypertrophy**
- **Atrophy**
- **Hyperplasia**
- **Metaplasia**



Hypertrophy

›Is an **increase in size** of cells ⟶ can lead to Increase in size of tissue/organ
›An increased demand on cells ⟶ can lead to hypertrophy.
›Takes place in: cells that are **not capable of dividing** e.g. striated muscles.

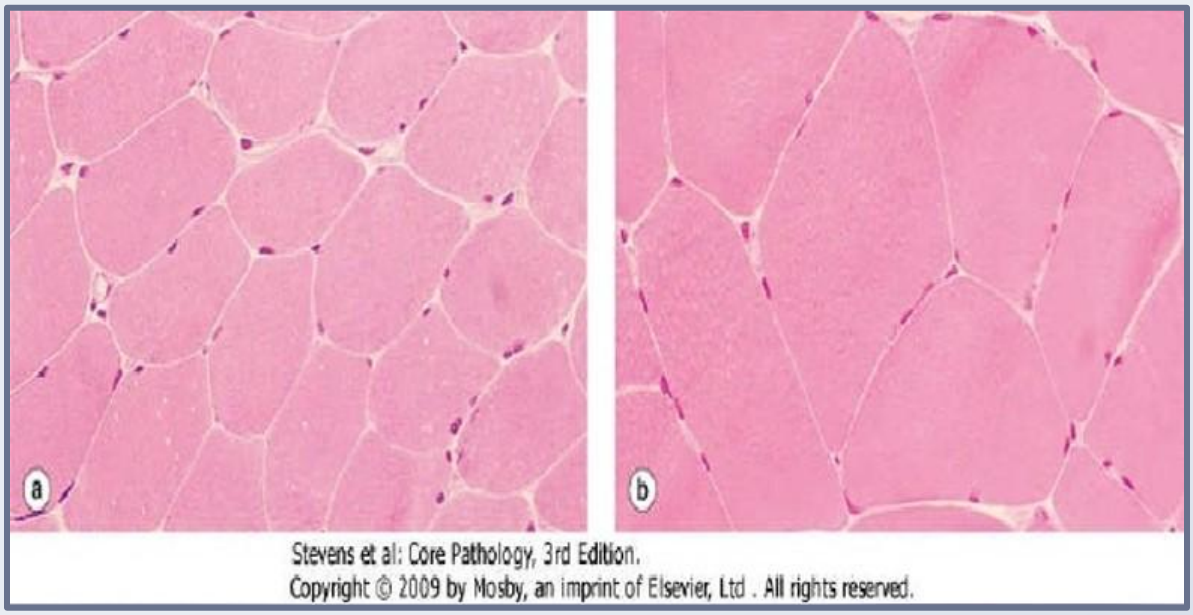
- Hypertrophy can be:

- **Physiological** (Normal):
  - breast during lactation.
  - pregnant uterus. (Undergoes Hypertrophy AND Hyperplasia)
  - the skeletal muscles undergo only hypertrophy in response to increased demand by exercise (see Image below).

- **Pathologic** (Abnormal):
  - the cardiomyocytes (muscle cells of the heart i.e. myocardium) undergo hypertrophy in heart failure (Disease cause an increase of Demand) (e.g. hypertrophy in hypertension or aortic valve disease).

> left ventricular hypertrophy that is caused by chronic uncontrolled hypertension.

> muscular hypertrophy can be caused by misuse of anabolic steroids.



›Hypertrophy of skeletal muscle in response to exercise. Taken at the same magnification, **(a)** shows muscle fibers in the transverse section from the soleus muscle of a **normal** 50 year old man, and **(b)** shows fibers from the same muscle in a veteran **marathon runner.**

Hyperplasia

Hypertrophy = Enlarge
Hyperplasia = Multiply
They depend on cell nature i.e. if it's capable of dividing or not

increased demand on cells.

increase in the **number** of cells → increase in the size of an organ/tissue

Takes place in the cells **capable of replication.**

- Hyperplasia can be:

Physiologic, two types:

1. Hormonal hyperplasia e.g. the proliferation of the glands of the female breast at puberty and during pregnancy
2. Compensatory (loss) hyperplasia e.g. when a portion of liver is partially resected, the remaining cells multiply and restore the liver to its original weight.

Pathologic:

caused by abnormal excessive stimulation of cells, be it by hormones or growth factors. e.g. excess estrogen (there will be excess stimulation of the uterus) leads to endometrial hyperplasia which causes abnormal menstrual bleeding. Sometimes pathologic hyperplasia acts as the base/platform for cancer to develop from. Thus, patients with hyperplasia of the endometrium are at increased risk of developing endometrial cancer.

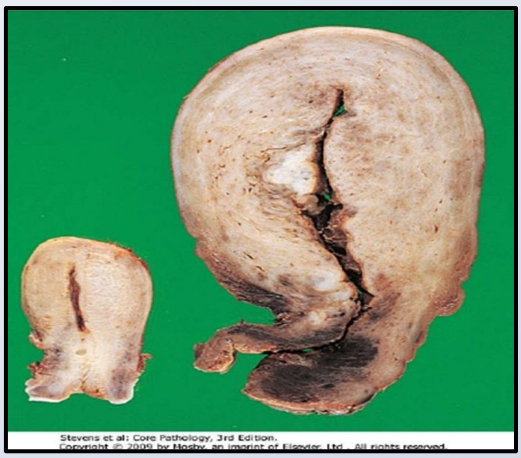
Another example is the nodular hyperplasia of the prostate.

›Hypertrophy and hyperplasia **can occur together**, e.g.

–Benign prostatic hyperplasia: a common disease with symptoms like the inability to urinate, or having multiple, more than normal, urination sessions and dribbling at end of urination. Because of the hormonal actions, especially testosteron)

–The uterus during pregnancy (smooth muscles).

On the left is a normal uterus normal smooth muscle wall. On the right is the uterus of a recently pregnant woman in which there is marked increase in the smooth muscle wall thickness. This is due to the hypertrophy and hyperplasia of uterine smooth muscle.



Atrophy

Atrophic cells are not dead but have diminished function. In atrophic cells there is decreased protein synthesis and increased protein degradation.

is shrinkage in the **size** of cells → the entire organ decreasing in size

reduced demand on cells

It is the opposite of hypertrophy

Atrophy is also a decrease in the number of cells, but mainly refers to the shrinkage in size

Causes of atrophy include:

- **decreased workload or disuse** (e.g. immobilization of a limb in fracture)
- **loss of innervation** (lack of neural stimulation to the peripheral muscles caused by injury to the supplying nerve causes atrophy of that muscle)
- ***Physiological e.g.*** loss of endocrine stimulation (e.g. the loss of hormone stimulation in menopause, uterus endometrium lining will undergo Atrophy)
- **misuse of anabolic steroids**. (can cause testicular atrophy over time that can affect liver function)
- **aging:** senile atrophy of brain can lead to dementia.
- **diminished blood supply**
- **inadequate nutrition**
- ***pathological e.g.*** Denervation

Involution

-It is the reduction in the cell number, back to its normal size. (opposite of hyperplasia)

> it is a type of atrophy.

The term “hypoplasia” and “aplasia” are not adaptation responses to environmental stress

Hypoplasia refers to an organ that does not reach its full size. It is a developmental disorders and not an adaptive response. E.g. very small finger or femur

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.
Cause: Embryogenesis, e.g. being born with no arm.

Metaplasia

the cells adapt by changing (differentiating) from one type of cell into another type of cell, I.e. Cell completely changes appearance, morphology (phenotype)

Here the cells are sensitive to a particular causative/toxic agent are replaced by another cell types better able to tolerate the difficult environment.

Metaplasia is usually reversible provided the causative agent is removed.

The problem is that the function of the original cell is lost and you are left with a new cell that doesn't have the same function as the original

It is NOT precancerous but can be a platform for cancer to start unlike dysplasia, which is a precancerous condition

Examples include:

1- Squamous metaplasia

(can handle injury but doesn't function like the original)

columnar cells → Replaced by → squamous cells

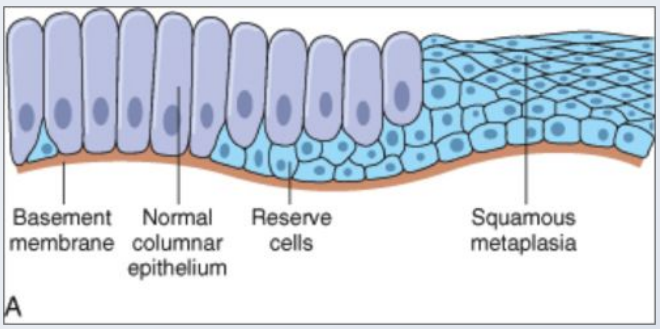
It is seen in:

In respiratory tract: the columnar epithelium of the bronchus is replaced by squamous cell following chronic injury in chronic smokers. The squamous epithelium is able to survive better under circumstances that the more fragile columnar epithelium would not tolerate. But the important protective functions of columnar epithelium are lost, such as mucus secretion and ciliary action.

In cervix: replacement takes place at the squamocolumnar junction.

If the causative agent persists, it may provide the base for (or predispose to) malignant transformation. In fact, it is thought that cigarette smoking initially causes squamous metaplasia and later squamous cell cancers arise from it.

Similarly squamous cell carcinoma of cervix also arises from the squamous metaplasia in the cervix.



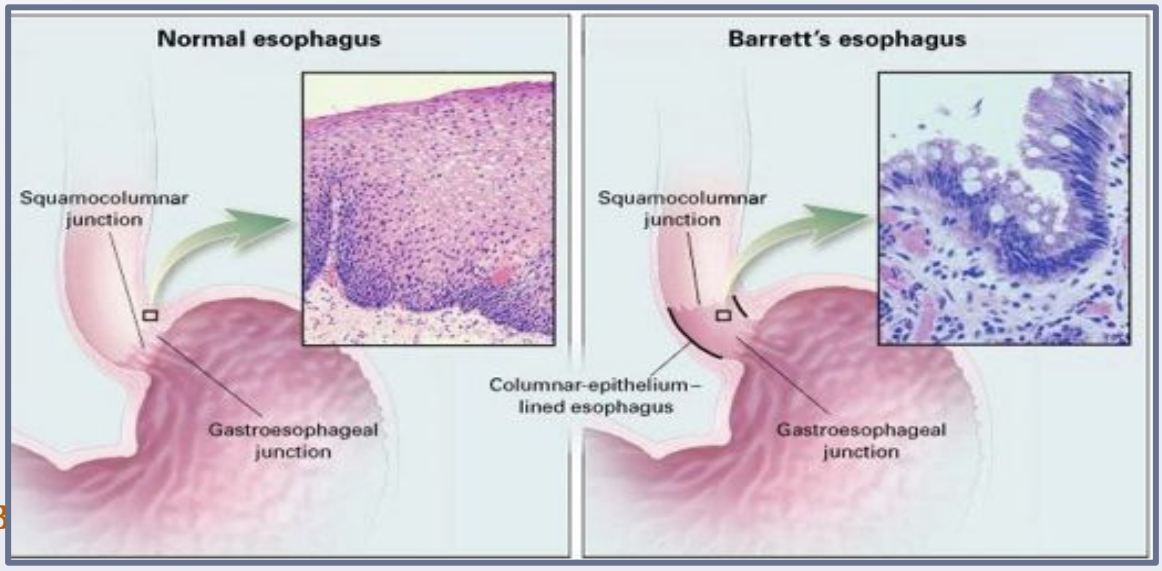
Metaplasia is not considered a disease itself, but as a phenomenon. The inflammation accompanied by it is the disease

Squamous and columnar metaplasia are the most common, and can be dangerous

2-Columnar cell metaplasia:

squamous cells → Replaced by → columnar cells

It is seen in the esophagus in chronic gastroesophageal reflux disease (rise of stomach acidity to esophagus). The normal stratified squamous epithelium of the lower esophagus (can't handle acidity) undergoes metaplastic transformation to columnar epithelium (which can handle acidity but causes irritation). This change is called as **Barrett's oesophagus** and it can be precancerous and lead to development of adenocarcinoma of esophagus.



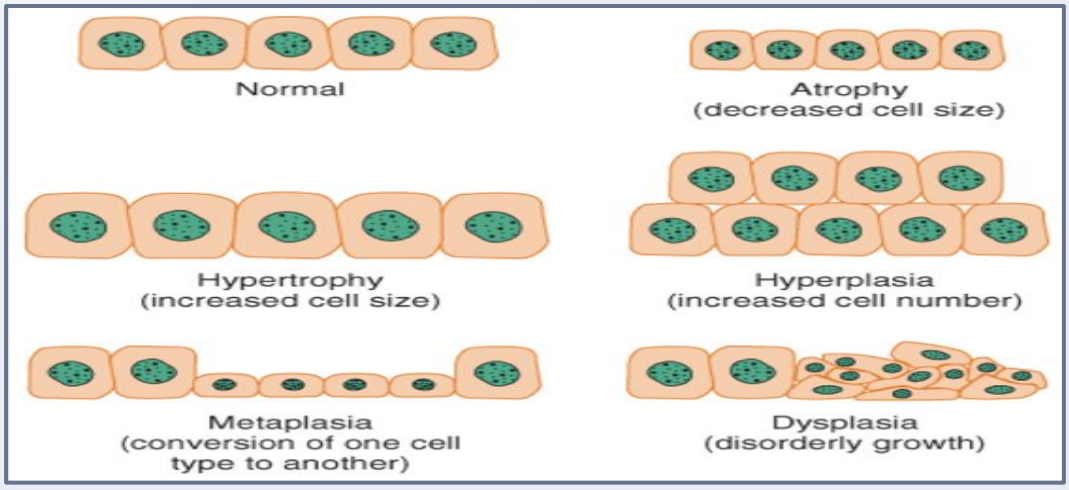
* B

3- Osseous metaplasia: it is the formation of new bone at sites of tissue injury. Cartilaginous metaplasia may also occur. E.g. someone with bad muscle injury may experience bone growth in site of injury

4- Myeloid metaplasia (extramedullary hematopoiesis): is the proliferation of hematopoietic tissue in sites other then the bone marrow such as liver or spleen.

Osseous and Myeloid Metaplasia are usually not dangerous or of much consequences

Change in size of cells	
Atrophy	Reduction in the size of cells (and reduction number of cells).
Hypertrophy	Increase in the size of cells
Change in number of cells	
Involution (a type of atrophy)	Decrease in the number of cells
Hyperplasia	Increase in the number of cells
Change in differentiation of cells	
Metaplasia	Stable change to another cell type



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*

CELL INJURY

When the cell is exposed to an injurious agent or stress, a sequence of events follows that is loosely termed cell injury.

As all diseases start at a cellular level
cell→ tissues→ organs

›Cell injury is *reversible* up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell reaches a point of no return and suffers irreversible cell injury and ultimately cell death. (although reversible, some functions may be altered)

› Cell Injury is either **Gradual** or **Sudden (intense)**, if the cell is not given time to adapt it goes straight into cell injury

›Cell death, is the ultimate result of (irreversible) cell injury.

Two principal patterns of cell death:

Necrosis is the type of cell death that occurs after ischemia and chemical injury, and it is always **pathologic**

Apoptosis occurs when a cell dies through activation of an internally controlled suicide program.

General idea of cell injury:

Normal cell

stress/increased demand → Adaptation e.g. hypertrophy

Unable to adapt

Injurious stimuli e.g. hypoxia

Persistent or strong injurious stimuli

Cell Injury

No more injurious stimuli → Injury is reversible → Complete repair → cells/tissue back to normal and restoration of normal organ function

2 possibilities:
1- tissue repair but with diminished capacity → impaired function E.g. Limb
2- injury becomes irreversible → cell death (necrosis or apoptosis)

*atherosclerosis is a disease of the arteries characterized by the preposition of plaques of fatty material on their inner walls

Causes of cell injury

(For Both reversible and irreversible)

1) Oxygen Deprivation (hypoxic cell injury)

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

Depending on the severity of the hypoxia, cells may adapt, undergo injury or die. Also some cell types are more vulnerable to hypoxic injury then others e.g. neurons are most susceptible followed by cardiac muscle, hepatocytes and then skeletal muscles.

2) Physical Agents e.g. mechanical trauma, burns and deep cold, sudden changes in atmospheric pressure, radiation, and electric shock

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

4) Infectious Agents

5) Immunologic agents e.g thyroid damage caused by autoantibodies

6) Genetic Derangements e.g sickle cell anemia.

7) Nutritional Imbalances

8) failure of membrane structural integrity. E.g. failure of sodium pump causing electrolyte imbalance

9) metabolic pathway blockage: like GAUT, purine metabolism deficiency (which causes uric acid increment and crystal formation in joints

10) Deficiency of certain substances (metabolites): by atherosclerosis, glucose deficiency (hypoglycaemia > diabetes mellitus) and hormones deficiency.

histopathology is responsible for Biopsy: a piece of tissue taken for diagnostic purpose

MECHANISM OF CELL INJURY

1

Depletion of ATP

It is the most important part. and is caused by mitochondrial damage Or ischemic and toxic injuries

2

Cell membrane damage\defects in membrane permeability

3

Mitochondrial damage:

It is seen specially in hypoxic injury and cyanide poisoning.

4

Ribosomal damage:

It is seen in alcohol damage of liver cells and with antibiotic use

5

Nuclear and DNA damage

6

Free radical injury

Free Radicals are always looking for a reaction

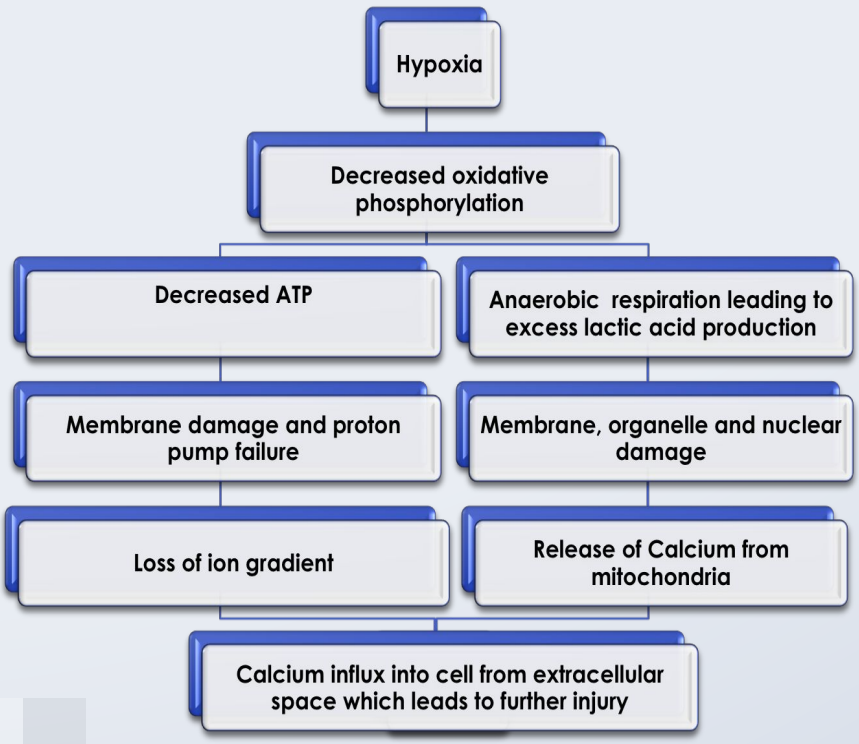
7

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.

*Ischemia: is a regional low blood circulation due to clot and causes free radicals. Due to the poor circulation it results in hypoxemia

Mechanism in hypoxic cell injury



Free Radical Injury

Free radical injury is due to excess accumulation of oxygen-derived free radicals (oxidative stress). Free radicals are highly reactive and harmful atoms that have a single unpaired electron in the outer orbit. They are referred to as reactive oxygen species/free radicals. The free radicals are produced in our cells through several ways, called as the free radical generating systems. (they cause damage to membranes)

Free radicals are produced via

1- **Normal metabolism/ respiration:** Small amounts of harmful reactive oxygen is produced as a by-product of mitochondrial respiration during normal respiration (reduction-oxidation reactions that occur in normal metabolism).

2- **Ionizing radiation injury** e.g. UV light, x-rays result in production of free radicals.

3- **Chemical toxicity:** enzymatic metabolism of exogenous chemicals or drugs.

4- **Oxygen therapy** and reperfusion injury (Myocardial Infarction complication)

5- **Immune response or inflammation** (neutrophilic oxidative burst)

6- **Transition metals** such as iron and copper can trigger production.

The names of the common free radicals (reactive oxygen species, ROS) **(important)**

- **superoxide anion radical (O2-)**
- **hydrogen peroxide (H2O2)**
- **hydroxyl ions (OH)**
- **Peroxynitrite (ONOO-)**

***Peroxynitrite** is formed by the interaction of **superoxide (O2-)** and **Nitric oxide (NO)** is an important chemical mediator generated by various cells and it can also act as a free radical.

Free radicals cause damage to:

1. Lipids: lipid peroxidation of membranes → damage of cell membranes & organelles etc.

2. Proteins: oxidative modification of proteins → protein fragmentation.

3. Nucleic acid: DNA damage → cell aging & malignant transformation of cells

How does our body fight the free radicals?

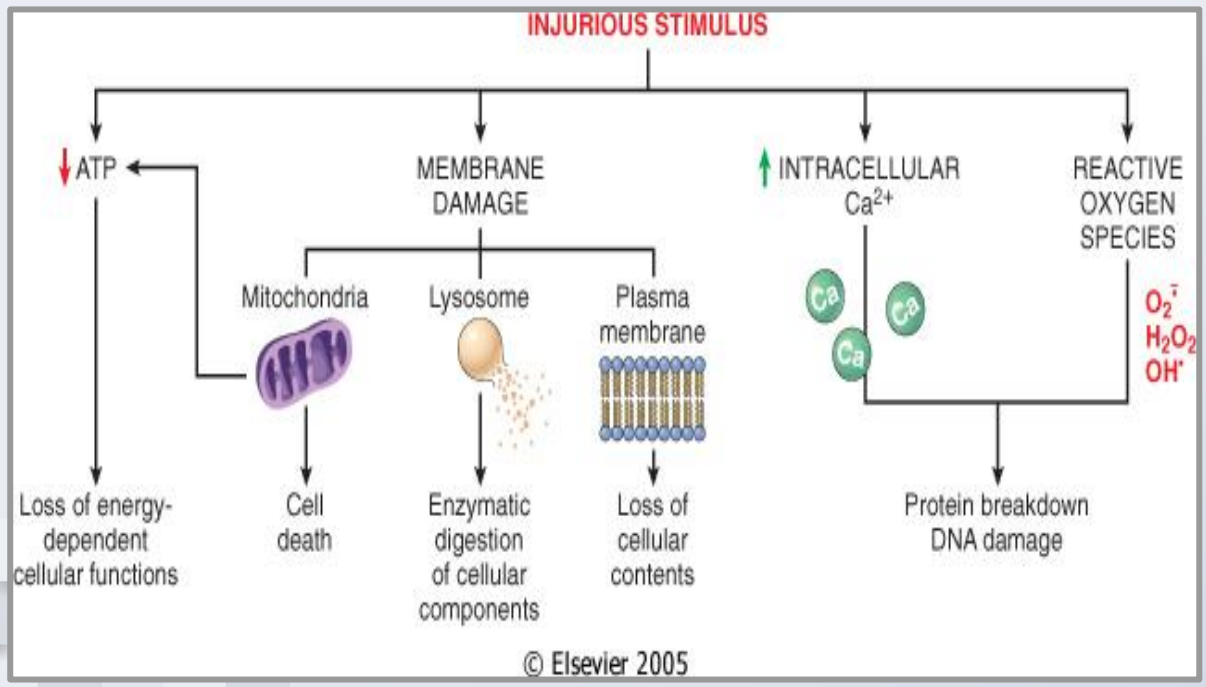
Certain substances in the cells remove or inactivate the free radicals in order to minimize injury caused by them. They form the free radical scavenging system.

These substances are:

•**Antioxidants**: e.g. vitamins E, A and C (ascorbic acid).

•**Enzymes** (IMPORTANT): which break down hydrogen peroxide and superoxide anion and destroy free radicals e.g. Catalase, Superoxide dismutases, Glutathione peroxidase and mannitol.

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



Reversible Cell Injury

The time duration of injury and the severity of injury will determine the extent of cell damage i.e. whether the injury is reversible or irreversible.

*initially cell injury is reversible.

Ultrastructural (electron microscopic) changes associated with reversible cell injury are:

Swelling & vacuolization of cytoplasm called hydropic/ vacuolar degeneration.

Mild mitochondrial swelling/Injury.
the rough endoplasmic reticulum and plasma membrane damage.

Mild eosinophilia (Pinkness) of cytoplasm (due to decrease in cytoplasmic RNA)

Defect in protein synthesis.

Note that: it is important that the nucleus doesn't change much (it would be irreversible if it did)

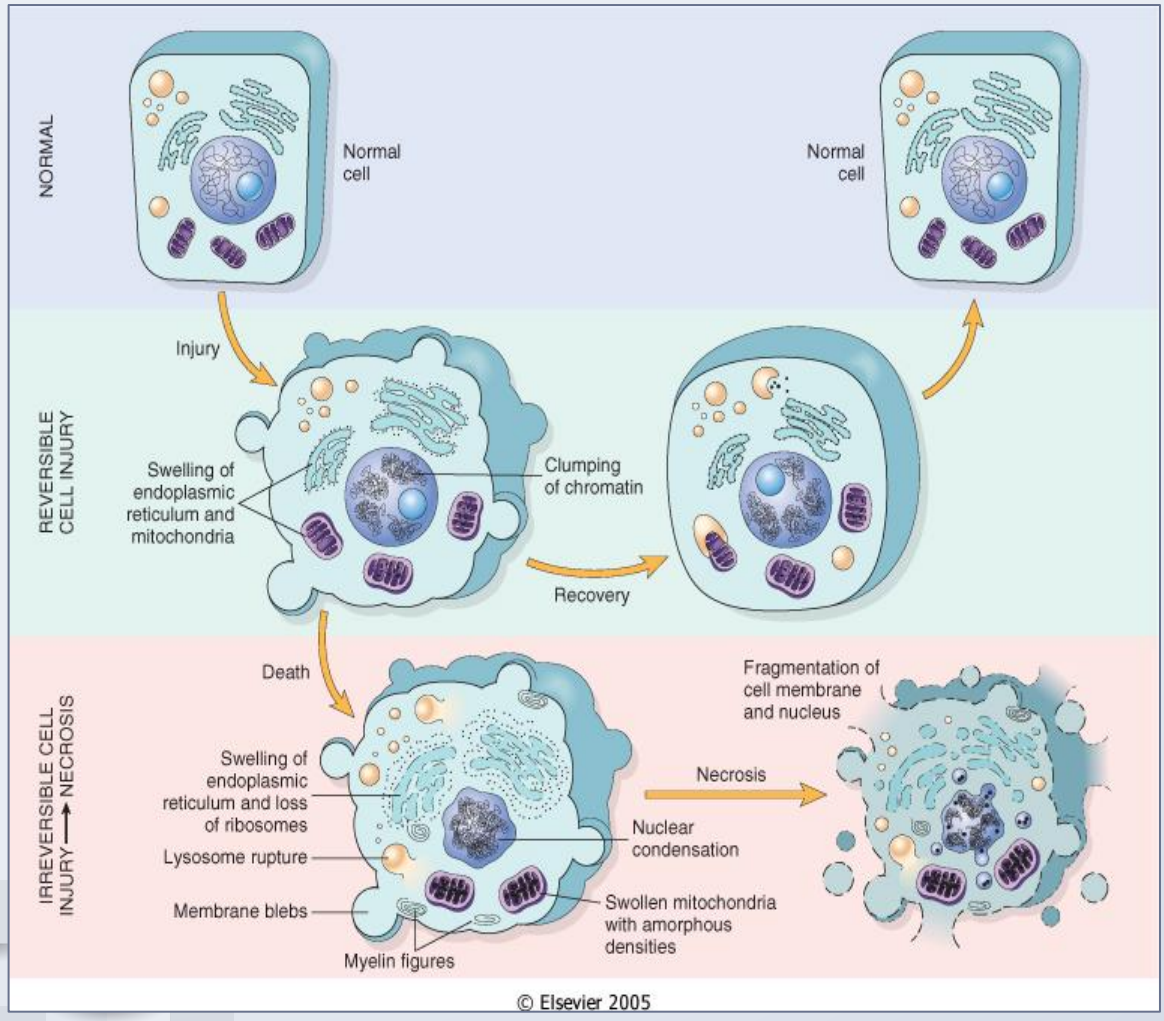
Within limits, the cell can compensate for these derangements and, if the injurious stimulus is removed the damage can be reversed.

Irreversible Cell Injury

Persistent or excessive injury causes cells to pass into irreversible injury.

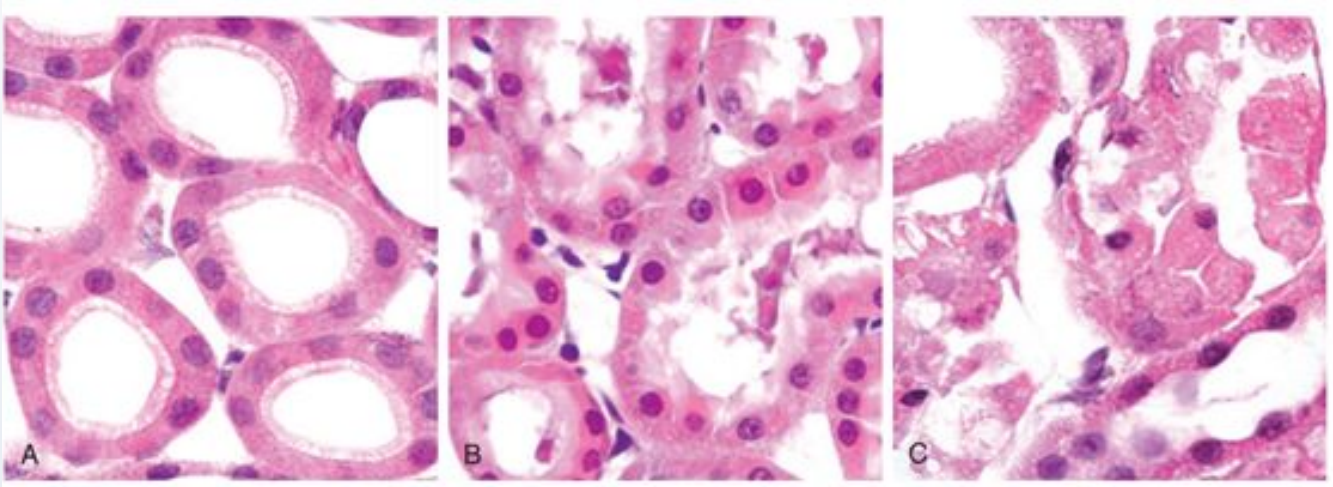
Irreversible injury is marked by:

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



General example

Acute renal failure: after the kidney “shuts down” the cellular damage is either reversible or irreversible depending on the severity and time) on the renal tubules. It is reversible when there are blebs and swelling in the cells. Reversible by I.V. and electrolytes (depending on the cause of failure.



necrosis here: A) showing normal kidney tubules with viable epithelial tissues. B) early, reversible ischemic injury showing surface blebs, increased eosinophilia and swelling. C) Necrotic (irreversible) injury of epithelial cells with loss of nuclei.

1- A 4-D
2- C 5-B
3- D 6-A

MCQs

Q1: Atrophy is:			
A) Shrinkage in size	B) Decrease in number of cells	C) Increase in size	D) Increase in number of cells
Q2: Low O2 supply to cell results in:			
A) Pyknosis	B) Nuclear lysis	C) ATP depletion	D) Hypotrophy
Q3: All of the answers below are ROS except:			
A) Nitric oxide	B) Superoxide	C) Hydroxyl ions	D) Carbon trioxide
Q4 :Which is not a sign of irreversible cell injury:			
A) Lysosomal rupture	B) Severe membrane rupture	C) Pyknosis	D) None of the above
Q5: The most common cause of cell injury:			
A) Physical agents	B) Hypoxia	C) Chemical injury	D) Infections
Q6: A decrease in ATP will cause which of the following cellular effects:			
A) Influx of calcium	B) Influx of potassium	C) Increased pH	D) Shrinkage of cell size

SAQs

Q1: Name Enzymes of the free radical Scavenging system.

Q2: Name organs where Hypertrophy and Hyperplasia happen at the same time.

Q3: Name the common Free radicals.

Q4: What is the mechanism of cell injury?

Helpful videos

Cell adaptation:

https://www.youtube.com/watch?v=-OB7SwKR4iI

- غادة العثمان
- ماجد العسكر

- مها فهد
- منى العبدلي
- شعاع خضري
- غيداء العسيري
- بنان القاضي
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- بدر الريس
- عبد العزيز الكريدا
- حمود القاضب
- فراس القايدي
- فيصل الفاضل
- يزيد القحطاني
- عبد اللطيف الشريمي
- سالم الشهري
- أحمد الخواشكي

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Editing File