# **CELL ADAPTATION, CELL INJURY AND CELL DEATH**

# PATHOLOGY

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LEC 1

# PATHOLOGY

**Greek word means:** Pathos (suffering) Logos(study) Study of diseases

## PATHOLOGY BRIDGES CLINICAL PRACTICE AND BASIC SCIENCE



# PATHOLOGY It involves investigation of the:

- Undelying <u>causes (etiology</u> of the diseases)
- Mechanism(<u>pathogenesis</u>) that results in the presenting <u>signs</u> and patient symptoms.
- The pathologist identify changes in <u>Morphology</u> of cells and tissue (gross and microscopical appearance)

# PATHOGENESIS.

- Definition :
- the sequence of <u>cellular</u>, <u>biochemical</u>, and <u>molecular</u> events that follow the exposure of cells or tissues to an injurious agent
- Mechanism that results in the presenting signs and patient symptoms



# GENERAL SYSTEMIC

## HOMEOSTASIS

When the cell is functioning properly it's said to be in a "**steady state**" i.e. it can handle normal

physiological demands



# **AETIOLOGY (CAUSES OF INJURY)**

- 1. Ischemia / hypoxia
- 2. Physical agents
- 3. Chemical agents
- 4. Infections
- 5. Immune reactions
- 6. Gene defects
- 7. Nutritional imbalances
- 8. Aging

- Although there are large number of factors that cause disease, they can all be grouped into two classes:
- <u>genetic</u> (e.g., inherited mutations and disease-associated gene variants, or polymorphisms)
- and <u>acquired</u> (e.g., infectious, nutritional, chemical, physical).
- Most of the diseases are Multifactorial
- arise from the effects of various external triggers on a genetically susceptible individual
- like atherosclerosis and cancer.

## **ARE ALL INJURIOUS STIMULI LETHAL?**

The answer is "No" Injury of <u>limited severity</u> and <u>short duration</u> allows the cells to come back to their normal functional levels Survival of the cell to injury depends on its ability to respond and adapt to injury

## Response to injury depends on:

- Type of injury
- Duration
- Severity / extent
- For e.g low dose of toxins or a brief duration of ischemia may lead reversible cell injury
- While larger toxin doses or longer ischemic intervals may result in irreversible injury and cell death

## Consequences of an injurious stimulus depend on

- cell type ,
- <u>status</u>,
- <u>adaptability</u> and
- <u>genetic makeup</u> of the injured cell

 cell type: <u>Neurons</u> are highly susceptible to anoxia (5min)
 <u>Cardiac muscle</u> dies after only 20-30 minutes
 whereas <u>skeletal muscle</u> can withstand for a very long time (2-3 hours ).

2. pre-existing state: e.g: nutritional or hormonal state, age of the person etc. e.g. glycogen rich hepatocyte can tolerate ischemia much better than other cells.

# TYPES OF RESPONSE TO INJURY OR STRESS

- <u>Recovery</u> to normal status(morphologically and functionally): when the injurious agent is removed.
- <u>Adaptations</u>: when stressful condition persist but the cell adapt itself to the new stressful condition
- Cell injury: when the cell damage occur.
- Which is either reversible or
- irreversible cell death :( Apoptosis or Necrosis)

# **ADAPTATIONS**

## Adaptations:

• are <u>reversible changes</u> in the <u>size</u>, <u>number</u>, <u>phenotype</u>, <u>metabolic</u> <u>activity</u>, or <u>functions</u> of cells in response to changes in their environment

# Cellular Adaptation to cell injury:

- Cellular adaptations could be physiological or pathological adaptations.
- Physiological Adaptations usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g. the enlargement of breast)
- 2. Pathological Adaptations usually represent the pathways by which the cells escape the cell injury.

# Adaptive changes in cell growth & differentiation are include:

Atrophy (decrease in cell size)
 Hypertrophy (increase in cell size).
 Hyperplasia (increase in cell number).
 Metaplasia (change in cell type).
 PLASIA = GROWTH





Atrophy (decreased cell size)



#### Hyperplasia (increased cell number)



Metaplasia (conversion of one cell type to another)



Dysplasia (disorderly growth)



#### Hypertrophy (increased cell size)

## Adapted Cell

# Types of cellular adaptations to stress

- 1. Atrophy (smaller cells)
- 2. Hypertrophy (bigger cells)
- 3. Hyperplasia (more cells )
- 4. Metaplasia (different types of cells)

# Normal



# Atrophy



Hypertrophy



Hyperplasia



Metaplasia

# Atrophy means Shrinkage in the size of the cell by loss of cell substance,

when a sufficient number of cells are involved, the entire tissue or organ diminishes in size, or becomes atrophic.

• atrophic cells may have diminished function,

they are <u>NOT dead</u>.

 reduction in the structural components of cell, e.g. reduction of mitochondria, endoplasmic reticulum, & myofilaments of atrophic skeletal muscles to balance the decrease in nutrition supply.

## Examples of clinical significance

#### of atrophy

#### Loss of innervation

• In polio virus ----- loss of innervation ----- atrophy of limb



Atrophy may progress to the point at which cells are injured and die.
mechanism of atrophy,

- due to loss of balance between protein synthesis and degradation.
- Increased protein degradation probably plays a key role in atrophy.

Atrophy can be physiologic or pathologic.
 <u>A- Physiologic atrophy</u>

- Atrophy of thyroglossal duct & notochord (during embryonic & fetal life)
- Decreases the size of uterus after labor.
- <u>**B- Pathologic atrophy</u>**. Depends on the underlying cause and can be local or generalized.</u>

# The common causes of atrophy are the following:

- 1) <u>Decreased workload (atrophy of disuse</u>), e.g. immobilized limb in plaster cast, or a patient with complete bed rest, skeletal muscle atrophy which is initially reversible but with more restriction of activity, there are decrease in size.
- 2) Loss of innervation (denervation atrophy), e.g. atrophy of skeletal muscles due to loss of their nerve supply.
- 3) <u>Diminished blood supply</u>, e.g. progressive brain atrophy due to ischemia.
- **4)** <u>Inadequate nutrition</u>, e.g. protein calories malnutrition (Marasmus), there is marked muscle wasting due to loss of fat & protein stores in the body.

5) Loss of <u>endocrine stimulation</u>, e.g. loss of <u>estrogen</u> stimulation after menopause results in physiologic atrophy of the <u>endometrium</u>, vaginal epithelium, and breast.

6) Aging (senile atrophy), e.g. atrophy of the brain & heart with aging.

7) Pressure, Tissue compression for any length of time can cause atrophy. An enlarging benign tumor can cause atrophy in the surrounding compressed tissues.



#### **Brain atrophy**

A, Normal brain of a young adult. B, Atrophy of the brain in an 82-year-old male with atherosclerotic disease. Atrophy of the brain is due to aging and reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the right half of each specimen to reveal the surface of the brain.

## Hypertrophy:

- Hypertrophy refers to an increase in the size of cells, resulting in an increase in the size of the organ.
- It is NOT due to cellular swelling but to the synthesis of more structural components.

Cells capable of division may respond to stress by undergoing both hyperplasia and hypertrophy, whereas in **nondividing cells** (e.g.,myocardial fibers), hypertrophy occurs.

- Hypertrophy can be <u>physiologic or pathologic</u>:
- **Physiological hypertrophy**.e.g. hypertrophy of skeletal muscles of bodybuilders due to increased workload.
- Pathological hypertrophy: Cardiac muscles hypertrophy in patient with chronic hypertension or cardiac valve diseases.
- In hypertrophy of both skeletal & cardiac muscles, there is increased synthesis of proteins & myofilaments per cells to achieve balance between the demands & the cell functional capacity.

#### Skeletal muscle hypertrophy in weightlifter

 In response to increased workload during weightlifting and exercise, the individual skeletal muscle cell will undergo hypertrophy



## <u>Mechanisms of hypertrophy</u>.

- In hypertrophy of cardiac muscles, there is re-stimulation of genes (that are normally present during fetal life),
- these genes resulting increased synthesis of <u>growth factors</u> (Insulin like growth factor IGF, fibroblast growth factor FGF),
- these growth factors are responsible for increased production of cellular proteins & result in hypertrophy of cardiac muscles.

# HYPER-TROPHY IN-CREASE IN SIZE OF CELLS











Comparison between normal heart (above) & hypertrophied heart (below)



#### Lt. ventricular hypertrophy

This is cardiac hypertrophy. The number of myocardial fibers never increases, but their size can increase in response to an increased workload, leading to the marked thickening of the left ventricle in this patient with hypertension. Note: normal Lt. ventricular wall thickness is 1.2 cm. to 1.5 cm

 Cardiac hypertrophy eventually reaches a limit beyond which enlargement of muscle mass is no longer able to compensate for the increased burden,

 and <u>cardiac failure</u> ensues (degenerative changes occur in the myocardial fibers), & of myocyte death can occur by either apoptosis or Necrosis. On the left is a normal uterus showing the normal mass of smooth muscle in its wall. On the right is a uterus from a pregnant women, in which the striking increase in mass of smooth muscle is evident. At cellular level this is due to both hyperplasia and hypertrophy of uterine smooth muscle.

Uterine hypertrophy in pregnancy





Lt. small spindle-shaped uterine smooth muscle cells from a normal uterus. Compare this with (Rt) large, plump hypertrophied smooth muscle cells from a gravid uterus (same magnification).

## Hyperplasia:

- Hyperplasia is an increase in the number of cells in an organ or tissue, usually resulting in increased volume of the organ or tissue.
- Hyperplasia & hypertrophy are closely related & develop concurrently in tissues, (e.g. gravid uterus)
- Hyperplasia could be <u>Physiological or</u>
   <u>Pathological</u>

## <u>Physiological hyperplasia</u>: which include

## • Hormonal hyperplasia,

- like proliferation of the glandular epithelium of the female breast at puberty and during pregnancy
- And the physiologic hyperplasia that occurs in the pregnant uterus.
- <u>Compensatory hyperplasia</u>, this hyperplasia occurs when portion of the tissue is removed or diseased
- e.g. <u>partial hepatectomy</u>, in which the remaining hepatocytes start mitotic activity after 12 hours & eventually restore the normal size of liver.

## Example

When some portion of liver is removed in the process of transplantation, the remaining portion of liver starts replication and eventually the normal weight of liver will be restored.



- The massive physiologic growth of the uterus during pregnancy is a good example of hormone-induced increase in the size of an organ that results from:
- both <u>hypertrophy and hyperplasia</u> (due to estrogen stimulation),

• similarly, prolactin and estrogen cause hypeplasia of the breasts during lactation.

## Mechanism of hyperplasia.

- <u>Hyperplasia is generally caused by:</u>
- 1-increased local production of growth factors, or increased levels of growth factor receptors on the responding cells.
- 2- in some cases, by increased
- output of new cells from tissue stem cells

## Pathological hyperplasia.

Pathologic hyperplasias are caused by excessive hormonal stimulation or growth factors acting on target cells.

**Examples** of pathological hyperplasia

#### **1.Endometrial hyperplasia**

- abnormal hormone-induced hyperplasia,
- due to disturbance of balance between estrogen and progesterone (absolute or relative increases in the amount of estrogen),
- It is a common cause of abnormal menstrual bleeding.
- 2<u>. Benign prostatic hyperplasia</u>
- is another common example of pathologic hyperplasia induced by responses to hormones(androgen),

#### **Endometrial hyperplasia**



The prominent folds of endometrium in this uterus (opened to reveal the endometrial cavity) are an example of hyperplasia. The hyperplasia involves both endometrial glands and stroma.

# Cellular adaptations in disease Nodular hyperplasia of

prostate

From a young man showing uniform texture of gland Stevens & Lowe 1999

Normal



From an elderly man showing irregular hyperplastic nodules. This would cause obstruction 3. Hyperplasia that is associated with certain viral infections, such as papillomaviruses, which cause skin warts and a number of mucosal lesions composed of masses of hyperplastic epithelium.



### Verruca vulgaris

Multiple papules with rough, pebble-like surfaces at infection sites

- Although these forms of hyperplasia are abnormal, the process remains controlled, because the hyperplasia regresses if the hormonal stimulation is eliminated.
- Pathologic hyperplasia, however, constitutes a fertile soil in which cancerous proliferation may eventually arise,
- <u>like hyperplasia of the endometrium are at</u> increased risk for developing <u>endometrial</u> <u>cancer</u>

Metaplasia: is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.

Metaplasia is cellular adaptation whereby cells sensitive to a particular stress are replaced by other cell types better able to withstand the adverse environment,

## TYPES OF METAPLASIA.

- A- Epithelial metaplasia: which include
- Epithelial metaplasia from columnar to squamous, as occurs in the respiratory tract of the cigarette smoker, the normal ciliated columnar epithelial cells of the trachea and bronchi are often replaced focally or widely by stratified squamous epithelial cells.
- These metaplastic squamous cells in the respiratory tract represent an undesirable change result in <u>reduced functions</u>. Moreover, the influences that predispose to metaplasia, if persistent, may induce <u>malignant transformation</u> in metaplastic epithelium and called <u>squamous cell</u> <u>carcinoma</u>.



### **Epithelial Metaplasia**

Metaplasia of normal columnar (left) to squamous epithelium (right) in a bronchus, shown (above) schematically and (down) histologically.

- 2. <u>Metaplasia from squamous to</u> columnar type may also occur, as in Barrett esophagus, in which the esophageal squamous epithelium is replaced by <u>intestinal-like columnar</u> cells under the influence of refluxed gastric acid.
- Cancers may arise in these areas, and these are typically glandular (adeno)carcinomas.

#### **Columnar (intestinal) metaplasia esophagus**



Metaplastic transformation (arrow) of the normal esophageal stratified squamous epithelium (Lt) to mature columnar epithelium (Barrett esophagus)

## • <u>3-metaplasia from transitional</u> <u>epithelium to squamous epithelium:</u>

• This occur in urinary bladder from stone or schistosomiasis infection (bilharziasis) due to chronic irritation with the spine of Schistosoma hematobium egg. May progress to squamous cell carcinoma.

 Urothelial Squamous Metaplasia - The urothelium lining the urinary bladder can undergo squamous metaplasia due to chronic injury from urinary stones and from granulomatous chronic inflammation associated with an infection due the worm Schistosoma hematobium. With time these can progress to squamous cell carcinoma.





- <u>B-Connective tissue metaplasia</u> is the formation of cartilage, bone, or adipose tissue (mesenchymal tissues) in tissues that normally do not contain these elements.
- For example, bone formation in muscle after trauma, designated as myositis ossificans

## MECHANISMS OF METAPLASIA.

- Metaplasia does NOT result from a change in the phenotype of an already differentiated cell type;
- Instead it is the result of a
   reprogramming of stem cells
   that are known to exist in normal tissues, or
   of undifferentiated mesenchymal cells
   present in connective tissue.

- In a metaplastic change, these precursor cells differentiate along a new pathway.
- The differentiation of stem cells to a particular lineage is brought about by signals generated by cytokines, growth factors, and extracellular matrix components in the cells' environment.
- These external stimuli promote the expression of genes that drive cells toward a specific differentiation pathway.

# •KEY CONCEPTS

### Cellular Adaptations to Stress

• Atrophy: decreased cell and organ size, as a result of decreased nutrient supply or disuse; associated with decreased synthesis of cellular building blocks and increased breakdown of cellular organelles.

<u>Hypertrophy</u>: increased cell and organ size, often in

response to increased workload; induced by growth factors produced in response to mechanical stress or other stimuli; occurs in tissues incapable of cell division

• Hyperplasia: increased cell numbers in response to hormones and other growth factors; occurs in tissues whose cells are able to divide or contain abundant tissue stem cells

• Metaplasia: one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type, often in response to chronic irritation, that makes cells better able to withstand the stress; usually induced by altered differentiation pathway of tissue stem cells; may result in reduced functions or increased propensity for malignant transformation

