Pathophysiology

PHCL 324

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Cellular adaptation, injury and death

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Objectives

- Cellular Adaptation and Response to Stress
- What are the Cellular adaptations?
- What is Atrophy, Hypertrophy, hyperplasia, dysplasia, metaplasia? *What causes and types of each on?*
- General Principles of Cell Injury
- Possible Biochemical Mechanisms of Cell Injury. Causes and effects of each one
- Define and study apoptosis and necrosis and morphological changes in each one
- Differentiate between apoptosis and necrosis

Further Reading:
- Essentials of Pathophysiology for pharmacy Martin M. Zdanowicz.
- Pathophysiology Made Incredibly Easy! *Springhouse*, 2nd edition
Cellular Adaptation and Response to Stress

When a cell is exposed to damaging stressors (like changes in; Oxygenation, Temperature, Molecular toxins, and Electrolytes), it will respond either by

1- Adaptation by Atrophy, Hypertrophy, Hyperplasia, Metaplasia, Dysplasia
   - If the cell is unable to adaptation → cell injury
   OR

2- Cell injury when it exposed to injurious stimulus.
   - If mild and transient injury → reversible injury
   - If severe and progressive injury → irreversible injury (cell death)

Necrosis        Apoptosis
1) What are the Cellular adaptations?

It is the different changes that take place in the cell to adapt it to the environment By:

- Atrophy
- Hypertrophy
- Hyperplasia
- Dysplasia
- Metaplasia
What is Atrophy?

– It is the *shrinkage and decrease in the size of cells or organs*.

– **What causes atrophy?**

  • decreased use (Disuse atrophy)
  • decreased blood supply (Ischemia)
  • decreased nutrition
  • Change hormones (estrogen in menopause)
  • Lose innervate (as, paralysis in limbs)
What is Hypertrophy

• Means *increase in the size of the cell or organ to*

• **What causes or types of hypertrophy?**

1- **Physiological hypertrophy:**
   • – due to increased protein synthesis within the cell, or decreased protein breakdown
   • Occurs when a cell or tissue is exposed to an increased workload (exercise)
   • NOT due to increased cell volume or fluid

2- **Compensatory hypertrophy:** When one kidney is removed, for example, the remaining kidney hypertrophies to increase its functional capacity.

3- **Pathological hypertrophy in:**
   • **Cardiac hypertrophy** in prolonged hypertension)
What is Hyperplasia?

- **Increase in cell or tissue number**

- **What causes hyperplasia?**
  - Due to increased rate of cells division faster than the rate of their death.
  - Can only occur in cells capable of mitosis (therefore, not Cardiac muscle or nerve cells).
What are the types or causes of hyperplasia?

- **Physiological hyperplasia:** Breast and uterine hyperplasia that occurs during pregnancy
- **Compensatory hyperplasia:** When a portion of the liver is surgically removed, the remaining hepatocytes (liver cells) increase in number to preserve the functional capacity of the liver.
- **Pathological hyperplasia:** As hemangioma
- **Atypical (aka Dysplasia)**
What is Dysplasia?

• A derangement of cell growth that leads to tissues with cells of varying size, shape and appearance

What makes dysplasia identifiable?
Dysplasia can be identified only in mature cells (not Stem) **why?**
As immature cells expected to change in Size, shape as they grow and mature

What causes dysplasia?
Chronic inflammation or irritation
- Dysplasia is **not considered reversible** (irreversible)

- Dysplasia in respiratory tract and cervix are usually “pre-cancerous”
• [http://www.cmdrc.com/YoungWomansHealthCare/](http://www.cmdrc.com/YoungWomansHealthCare/)
What is Metaplasia?

- Replacement of one cell type with another
- How does it differ from dysplasia?
  - It is a reversible changes and not precancerous but if sever it can changed to dysplasia

What causes metaplasia?

Chronic irritation or inflammation

E.g. Respiratory tract ciliated columnar epithelium replaced by stratified squamous epithelium as a result of chronic irritation by cigarettes in heavy smokers.
Normal ciliated epithelium

Metaplasia
Chronic injury or irritation

Dysplasia
Persistent severe injury or irritation
General Principles of Cell Injury

The cellular response to injurious stimuli depends on:

- The type of injury, its duration, and its severity

The consequences of cell injury depend on:

- The type and adaptability of the injured cell

The “point of no return” at which cell death has irreversibly occurred is difficult to determine
Possible Biochemical Mechanisms of Cell Injury

1) ATP depletion.

2) Generation of reactive oxygen free radicals.

3) Loss of $\text{ca}^{++}$ homeostasis.

4) Defect in plasma membrane permeability.

5) Mitochondrial damage.
1- ATP depletion

ATP is essential for every cellular process:

- Maintenance of cell osmolarity
- Transport processes
- Protein synthesis

Therefore loss of ATP results in rapid shutdown of most critical homeostatic pathways
**Definition Of Free Radicals**
Extremely unstable, highly reactive chemical species with a single unpaired electron in an outer orbital

**Effects:**
In cells they attack and degrade nucleic acids, proteins, lipids and carbohydrates

They initiate autocalytic reaction, i.e. molecules that react with free radicals are converted into free radicals

**Examples Of Free Radicals**
- Hydroxyl (OH·)
- Hydrogen (H·)
- Superoxide (O₂·⁻)
- Hydrogen peroxide (H₂O₂·)
Free radicals constitutes an important mechanism of cell injury

**It Contributes To:**
- Chemical and radiation injury
- Oxygen and other gaseous toxicity
- Cellular aging
- Microbial killing by phagocytic cells
- Inflammatory damage
- Tumor destruction by macrophages
- Others
3-Increased Cytosolic Calcium:

**Sources**
- Mitochondria
- Endoplasmic reticulum
- External to the cell

**Effects:** (activates enzymes)
- **ATPase**
  - decreased ATP
- **Phospholipase**
  - decreased phospholipids
- **Protease**
  - disruption of membrane and cytoskeletal proteins
- **Endonuclease**
  - nuclear chromatin damage
Increased Cytosolic Calcium, source and consequences

Injurious agent

Mitochondrion

Endoplasmic reticulum

Increased cytosolic Ca++

- ATPase
  - Decreased ATP
- Phospholipase
  - Decreased phospholipids
- Protease
  - Disruption of membrane and cytoskeletal proteins
- Endonuclease
  - Nuclear chromatin damage
4-Defects in Plasma membrane permeability:

**Causes:**

1. Direct damage by toxins (bacterial, viruses, physical or chemical injury)
2. Damage secondary to ATPase loss or from calcium-mediated phospholipase activation

**Effects:**

1. Loss of membrane barriers
2. Breakdown of the concentration gradient of metabolites
Mitochondrial integrity is needed for cell survival

**Causes:**
Increase Cytosolic calcium, free radicals

**Effects:**
No ATP generation
Release of cytochrome c into cytoplasm
Apoptosis
What is Apoptosis?

- It is the programmed cell death (single cell death)
- It is also called regulated cell death

**Types of apoptosis:**

- It may be Physiological or pathological
- **Physiological apoptosis** as during development and Worn out cells
- **Pathological apoptosis** as diseased or tumor in cells
What happens to the cell in Apoptosis

Morphology of Apoptosis

• Nuclear changes
  – Karyolysis
• Nuclear dissolution and chromatin lysis

  – Pyknosis
• Clumping of the nucleus
• has a picnotic nucleus

  – Karyorrhexis
• Fragmentation of the nucleus

• Cytoplasmic changes
• Fragmentation of the cytoplasm and formation of apoptotic bodies
What is necrosis?

Cellular changes to group of cells after local cell death.

- It is a **visible change** because of
  - Autolysis: **Lysosomes** break and dissolve cells
  - Immune response to clean area by **neutrophiles**

- It is called **Messy cell death** because it:
  - Initiates inflammation by lysosomes and neutrophils infiltration
  - May lead to Gangrene – large mass of tissue undergoes necrosis
**DIFFERENCE B/W APOPTOSIS AND NECROSIS**

**APOPTOSIS**
- Chromatin condensation
- Cell shrinkage
- Preservation of organelles and cell membranes
- Rapid engulfment by neighboring cells preventing inflammation
- Biochemical hallmark - DNA fragmentation

**NECROSIS**
- Nuclear swelling
- Cell swelling
- Disruption of organelles
- Rupture of cell and Release of cellular contents
- Inflammatory response
**APOPTOSIS**

- Cell shrinking
- Blebbing
- Nuclear condensation

**NECROSIS**

- Swelling of the cell and organelles
- Rupture of the cellular membrane
- Cell content release

**APOPTOSIS (cont.)**

- Formation of apoptotic bodies
  - Posterior phagocytosis of the apoptotic bodies by macrophages

**NECROSIS (cont.)**

- Cell content release (cont.)
  - Posterior activation of an inflammatory response
Thanks