Cell Injury

Hamad Ali Yaseen, Ph.D.
MLS dept, FAHS, HSC
Hamad.ali@hsc.edu.kw
Outline

• Cellular Stress
• Adaptation
• Cell injury
• Cell death
Overview of Cellular Responses to Stimuli

• Cells operate in a very narrow range of physiologic parameters – they maintain homeostasis.

• Homeostasis – equilibrium of the microenvironment of the cell.
  – Chemical – electrolytes, glucose, pH, etc.
  – Physical – temperature, etc.
Stages in cellular response to stress and injurious stimuli

**FIGURE 1-1**  Stages of the cellular response to stress and injurious stimuli.
Overview of Cellular Responses to Stimuli

- **Adaptation**: Reversible functional and structural responses to severe physiologic stresses and some pathogenic stimuli, during which new but altered steady states are achieved. Allowing cells to survive and continue to function.

In another word, it is adjusting to a new situation to preserve viability and function

- **Stress** - any demand on the cell requiring it to adapt
Cellular Adaptations to Stress

- Adaptations are reversible changes in the number, size, metabolic activity, and functions of cells in response to changes in their environment.
- Structural and functional responses.
If the adaptive capability of the cell is exceeded or the stress inherently harmful, cell injury occurs:

- **Reversible** – return to baseline
- **Irreversible** - Cell death, which can be a normal and essential process.
Reversible vs. Irreversible injury

![Graph showing reversible and irreversible injury]

**FIGURE 1-1** Stages of the cellular response to stress and injurious stimuli.
Reversible injury

- Reversible injury is characterized by generalized swelling of the cell and its organelles; blebbing of the plasma membrane; detachment of ribosomes from the ER; and clumping of nuclear chromatin. These morphologic changes are associated with decreased generation of ATP, loss of cell membrane integrity, defects in protein synthesis, cytoskeletal damage, and DNA damage. Within limits, the cell can repair these derangements and, if the injurious stimulus abates, will return to normalcy.
Reversible injury

FIGURE 1-9 Morphologic changes in reversible cell injury and necrosis. A, Normal kidney tubules with viable epithelial cells. B, Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. C, Necrosis (irreversible injury) of epithelial cells, with loss of nuclei, fragmentation of cells, and leakage of contents. The ultrastructural features of these stages of cell injury are shown in.
Irreversible injury

• Persistent or excessive injury, however, causes cells to pass the rather nebulous “point of no return” into irreversible injury and *cell death*. Different injurious stimuli may induce death by necrosis or apoptosis.
**FIGURE 1-1** Stages of the cellular response to stress and injurious stimuli.
Causes of Cell Injury

- **Oxygen Deprivation**
  - Hypoxia – oxygen deficiency
    - Ischemia – decreased blood supply
    - Inadequate oxygenation of blood - pneumonia
    - Reduction in oxygen-carrying capacity of blood
      - anemia, CO poisoning
Causes of Cell Injury

– **Chemical agents**
  - Alter membrane permeability, osmotic homeostasis, enzyme damage
  - Examples – glucose, salt, oxygen

– **Infectious agents**
  - Viruses, bacteria, fungi, protozoans, etc.
Causes of Cell Injury

- **Immunologic reactions**
  - Defend against pathologic organisms
  - Autoimmune reactions against one’s own tissues
  - Allergic reactions

- **Genetic defects**
  - Can cause cell injury by inborn errors of metabolism
  - Accumulation of damaged DNA
Causes of Cell Injury

- **Nutritional imbalances**
  - Protein-calorie insufficiency
  - Vitamin deficiencies
  - Excesses in nutrition
    - Obesity – diabetes mellitus, atherosclerosis
Causes of Cell Injury

– **Physical agents**
  - Trauma
  - Extremes of temperature
  - Radiation
  - Electrical energy
  - Changes in atmospheric pressure
Causes of Cell Injury

- **Aging**
  - Alterations in replication and repair abilities
  - Long term accumulation of toxins, radiation, injuries, etc.?
Mechanisms of cell injury
Mechanism of Cell Injury

• Cellular response to injurious stimuli depends on the type of injury, its duration, and its severity
  – Example: Toxins dose

• Consequences of the injurious stimulus depends on the type, status, adaptability, and the genetic make-up of the injured cell
  – Example: Striated muscle (better regeneration) versus cardiac muscle
Mechanism of Cell Injury

- Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components
  - Mitochondria
  - Cell membranes
  - Protein synthesis
  - Cytoskeletal
  - Genetic apparatus
Cell Injury

- Biochemical mechanisms mediating cell injury and necrosis can be one or many of the following;
  - ATP depletion and decreased ATP synthesis (common in ischemic and toxic injury)
  - Production of reactive oxygen species and free radicals
  - Loss of calcium homeostasis
  - Defects in membrane permeability
  - Irreversible mitochondrial damage
Depletion of ATP

• Adenosine-5'-triphosphate is the fuel molecule in the cells.
• ATP depletion is associated with both hypoxic and chemical injuries.
Depletion of ATP

- Most common types of injury in clinical medicine. Ischemia (inadequate blood supply) injures faster than Hypoxia.
Sodium will accumulate inside the cells due to reduction in Sodium potassium ATPase. Leading to net gain of solute and therefore isosmotic gain of water.
Mitochondrial Damage

- Mitochondria is ATP factory !!!
- They can be damaged by increased cytosolic Calcium, reactive oxygen species, and oxygen deprivation.
- The damage results in formation of high-conductance channel.

**Figure 1-18** Consequences of mitochondrial dysfunction, culminating in cell death by necrosis or apoptosis.
Irreversible injury

• **Necrosis** – Enzymes leak out of lysosomes (organelles that contain acid hydrolase enzymes that break down waste) and cell is digested. Leakage through cell membrane elicits inflammation. Due to ischemia, toxins, infections, trauma

• **Apoptosis** – cell kills itself, no membrane leakage
Necrosis vs. apoptosis

• Necrosis is a form of cell injury that results in the premature death of cells in living tissue. In contrast, apoptosis is a naturally occurring programmed and targeted cause of cellular death. While apoptosis often provides beneficial effects to the organism, necrosis is almost always detrimental and can be fatal.
Necrosis vs. Apoptosis

NORMAL

Enzymatic digestion and leakage of cellular contents

Necrosis

Apoptotic body

Phagocyte

Phagocytosis of apoptotic cells and fragments

Apoptosis
Necrosis

**Features:**

- Degradative action of enzymes on lethally injured cells.
- Membrane integrity is lost and contents leak out causing inflammation.
- Enzymes come from cellular lysosomes or from the lysosomes from recruited leucocytes.
- Enzymes given off from a particular organ can indicate damage to that organ
  - Heart – CPK, troponin
  - Liver – alkaline phosphatase, transaminases (ALT, AST)
Necrosis

Protein factories !!!

FIGURE 1-18 Consequences of mitochondrial dysfunction, culminating in cell death by necrosis or apoptosis.
Necrosis

• Necrotic cells are unable to maintain membrane integrity.
• Their contents often leaks outside the cells causing inflammation in the surrounding tissue.
• Note that cells going through necrosis can loss its function before they die. e.g. myocardial cells.
Necrosis vs. Apoptosis

NORMAL

Enzymatic digestion and leakage of cellular contents

Necrosis

Apoptotic body

Phagocyte

Phagocytosis of apoptotic cells and fragments

Apoptosis
Apoptosis

- Apoptosis is basically cells committing suicide !!!
- Programmed cell death.
- Cell destroys its own nuclear DNA and nuclear and cytoplasmic proteins.
Apoptosis

• Apoptosis has two types:
  – Physiologic
  – Pathologic
Apoptosis

• Physiologic
  – Apoptosis occurs normally during development and throughout adulthood (it is a normal process).
  • Death of specific cell types (unwanted, aged) at defined times during development of the organism
Apoptosis

- **Physiologic examples:**
  - **Involution of hormone-dependent tissue upon hormone withdrawal.** Such as endometrial cell breakdown during menstrual cycle.
  - **Cell loss in proliferating cell populations.** Such as immature lymphocytes in the bone marrow.
  - **Death of host cells that have served their useful purpose.** Such as neutrophils in inflammatory response. (you will learn about this later).
Apoptosis

• Pathologic:
  
  – **DNA damage**
    • Exposure to radiation or chemotherapeutic agents and when repair mechanisms cannot cope with the injury, cells trigger apoptosis program. (why this is important?)

  – **Accumulation of misfolded proteins. For example neurodegenerative diseases (AD and PD).**

  – **Cell death in certain infections. Viral!!**
Biochemical features of Apoptosis

• Activation of Caspases.
  – A family of cystein proteases that has more than 10 different members.
  – They can be functionally divided into:
    • Initiator
    • Executioner
Biochemical features of Apoptosis

• DNA and Protein breakdown
  – DNA is broken into 50 to 300 kilo-base pieces by endonucleases.

• Membrane Alterations and recognition by Phagocytes.
  – Apoptotic cells membrane changes in ways that promote recognition of dead cells by phagocytes. (e.g. Movement of phospholipids).
Mechanisms of Apoptosis

• The Mitochondrial pathway of apoptosis (Intrinsic).
• The death receptor- initiation pathway (Extrinsic).
Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of "executioner" caspases. The induction of apoptosis by the mitochondrial pathway involves the action of sensors and effectors of the Bcl-2 family, which induce leakage of mitochondrial proteins. Also shown are some of the anti-apoptotic proteins ("regulators") that inhibit mitochondrial leakiness and cytochrome c-dependent caspase activation in the mitochondrial pathway. In the death receptor pathway engagement of death receptors leads directly to caspase activation. The regulators of death receptor-mediated caspase activation are not shown. ER, endoplasmic reticulum; TNF, tumor necrosis factor.
Necrosis vs Apoptosis

Reversible injury → Recovery

Progressive injury → Necrosis

Myelin figure

Swelling of endoplasmic reticulum and mitochondria

Membrane blebs

Myelin figures

Breakdown of plasma membrane, organelles and nucleus, leakage of contents

Amorphous densities in mitochondria

Inflammation

CONDENSATION OF CHROMATIN

Membrane blebs

CELLULAR FRAGMENTATION

Apoptotic body

Phagocyte

Phagocytosis of apoptotic cells and fragments

FIGURE 1-8 Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.
# Necrosis vs Apoptosis

## TABLE 1-2 Features of Necrosis and Apoptosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Necrosis</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Pyknosis → karyorrhexis → karyolysis</td>
<td>Fragmentation into nucleosome-size fragments</td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact; altered structure, especially orientation of lipids</td>
</tr>
<tr>
<td>Cellular contents</td>
<td>Enzymatic digestion; may leak out of cell</td>
<td>Intact; may be released in apoptotic bodies</td>
</tr>
<tr>
<td>Adjacent inflammation</td>
<td>Frequent</td>
<td>No?</td>
</tr>
<tr>
<td>Physiologic or pathologic role</td>
<td>Invariably pathologic (culmination of irreversible cell injury)</td>
<td>Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage</td>
</tr>
</tbody>
</table>
# Necrosis vs Apoptosis

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<thead>
<tr>
<th></th>
<th>Apoptosis</th>
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<tbody>
<tr>
<td>Natural:</td>
<td>Yes</td>
<td>caused by factors external to the cell or tissue, such as infection, toxins, or trauma</td>
</tr>
<tr>
<td>Effects:</td>
<td>Beneficial</td>
<td>Negative</td>
</tr>
<tr>
<td>Introduction:</td>
<td>Apoptosis programmed cell death (PCD) in humans &amp; multicellular organisms. PCD involves a series of biochemical events leading to a cell destruction and death.</td>
<td>Necrosis is the premature death of cells and living tissue. Necrosis is caused by external factors, such as infection, toxins or trauma. This is in contrast to apoptosis, which is a naturally occurring cause of cellular death.</td>
</tr>
<tr>
<td>result:</td>
<td>Can prevent tumor formation (homeostatis between cell death rate and mitosis rate)</td>
<td>Necrosis results in inflammation, which could become chronic.</td>
</tr>
<tr>
<td>definition:</td>
<td>programmed cell death</td>
<td>the cell or tissue damage due to external factors.</td>
</tr>
<tr>
<td>process:</td>
<td>membrane blebbing, shrinkage of cell, nuclear collapse (nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation), apoptotic body formation. Then, engulf by white blood cells</td>
<td>membrane disruption, respiratory poisons and hypoxia which cause ATP depletion, metabolic collapse, cell swelling and rupture leading to inflammation</td>
</tr>
</tbody>
</table>
FIGURE 1-1  Stages of the cellular response to stress and injurious stimuli.