**Necrosis** = when the cell dies because of the irreversible injury or a pathogenic reasons.

**Apoptosis** = Programmed cell death / a genetically determined process of cell self-destruction (physiological or pathological condition) / a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.

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**Types of cell injuries**

- **reversible**
  - Cell can get back to normal
  - No damaged compartments
  - Little function, but still alive.

- **irreversible**
  - Very severe injury
  - Irreversible injury = cell death or necrosis

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**Morphologic changes:**

- dilatation of ER
- **mitochondrial** swelling and densities
- Cytoplasmic **myelin figures** appearance.
- **plasma membrane** blebbing and blunting
- nuclear clumping of **chromatin**.

**- Cell swelling** (hydropic change), k⁺-Na⁺ pumps aren't working >>> swelling of the whole organ

**- Fatty change** (damage of membranes phospholipids so they accumulate in the cytoplasm, forming fatty droplets.)

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**Definitions:**

- Mitochondrial densities & dysfunction.
- Loss of **plasma membrane** and **intracellular membranes** >>> cellular enzymes leak out.
- Loss of DNA and **chromatin** structural integrity.
- Dilatation of ER, mitochondria.
- More **myelin figures**
- Increased cytoplasmic **eosinophilia**

**Nuclear changes:**

*Pyknosis:* shrinkage and increased basophilia
*Karyorrhexis:* fragmentation
*Karyolysis:* basophilia fades

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**Cell damage = enzyme leakage to the blood stream.**

**Activation of enzymes called caspases**
Types of cell death

- **apoptosis**
  - Controlled, regulated by genes & regulatory pathways
  - Can be modified
  - It is the basic mechanism of some chemotherapeutic agents that treat cancer.
  - Causes: sun induced injury & growth factors.
  - The dead cells are removed by macrophages.
  - Peaceful cell death (no inflammation reaction)
  - Form apoptotic bodies (releasing of cellular content without disrupting of the plasma memb.) no leak of enzymes

- **necroapoptosis**
  - Rapid, uncontrollable
  - Leads to severe disturbances.
  - Causes: ischemia, toxins, infections, traumas.
  - Leads to local inflammation.

- **necrosis**
  - Rapid, uncontrollable
  - Leads to severe disturbances.

- **Autophagy**
  - Self-eating (Lysosomal digestion of the cells own components)
  - Survival mechanism in times of nutrient deprivation and starvation, by recycling cells contents to provide nutrients and energy.
  - Involves formation of autophagic vacuoles which are derived from the ER, vacuole fuses with lysosome to form autophagolysosome.
  - May lead to atrophy.

- Failure of adaptation causes apoptosis.

**Mechanism**

- **Mitochondrial pathway**
  - Intrinsic (because the process starts in the mitochondria)
  - Regulated by Bcl-2 protein family which control mitochondrial membrane permeability & it is composed of: Bcl2 & BclX (antiapoptotic - prevent apoptosis) Bax & Bak (proapoptotic - activate apoptosis.) BH3 (sensors in the cytoplasm.)

- **Extrinsic** (because the process starts outside at the surface of the cell)
  - Death receptors includes a family of TNF receptor which have a cytoplasmic domain causes cell death.
  - The prototypes of these receptors:
    1) TNF1 (Type1 tumor necrosis factor) receptors.
    2) Fas receptors.

**Physiologic**

1. During embryogenesis of the uterus.
2. Hormonal deprivation
   - Endometrium (apoptosis due to lack of estrogen) & lactating breast cells.
3. Steady state population (gut, skin)
   - End of function (eg: neutrophils apoptosis in the site of inflammation.)
   - Self-reacting lymphocytes

**Pathologic**

1. DNA damage (Rx, chemoTx, temperature, UV, hypoxia) 
   - activate p53 to repair the damage if it doesn’t repair the damage the cell will die by apoptosis.
2. Accumulation of misfolded proteins
3. Some infections (adenovirus, HIV, hepatitis viruses)

Eg: when ischemia happens, some cells die by necrosis & others by apoptosis.

E.g: when ischemia happens, some cells die by necrosis & others by apoptosis.
This page is about the important details of **apoptotic mechanisms** (that we can’t ignore)

**Mitochondrial pathway**

**In normal situations:**
The cell is receiving survival signals, growth factors and no hypoxia, ischemia and DNA damage, these signals will improve the production of the anti-apoptotic proteins (Bcl-2 & Bcl-X).
- The mitochondria stores a substance called “cytochrome C”.
- Bcl-2 & Bcl-X guard the membrane to keep the cytochrome C inside the mitochondria in normal conditions and prevent its leakage to the cytoplasm, leads to cell survival and prevention of apoptosis.

**Mitochondrial pathway**

**In abnormal situations:**
When the cells expose to radiation which can lead to
- DNA damage,
- lack of survival signals and growth factors stimulations
- accumulation of misfolded proteins
BH3 sensors are activated, Bax and Bak are activated too and they will antagonize the action of Bcl-2 and Bcl-X, then bax and bak will dimerize in the wall of mitochondria forming a channel, allowing the leakage of cytochrome C and other pro-apoptotic proteins to the cytoplasm, then cytochrome C activates caspase-9 which will start a sequence of events that will lead to cell death.

**Death receptor pathway**

When T lymphocytes is activated, Fas ligand binds with the cells that express Fas receptors (the cells that are going to die by apoptosis), the death domain in the cytoplasm is activated, then it will activate caspase-8 which activate subsequent caspases that lead to destruction of cellular proteins and enzymes and forming of apoptotic bodies.
**Coagulative necrosis**

**Causes:** ischemia all solid organs except in the brain

**Shape:** wood shape, pale area

**Others:**
- Protein & enzymes denaturation.
- The inflammatory cells clean the eosinophilic dead cells.
- preserved for many hours or days

**gangrenous necrosis**

**Causes:** ischemia, coagulation necrosis at diff. planes of the organ.

**Others:**
- It is a clinical term.
- Can be dry or wet.

**Liquefactive necrosis**

**Causes:** bacteria or fungal infections, ischemia or CNS infraction

**shape:** viscous fluid, creamy-yellowish pus

**places:** brain, lungs

**Caseous necrosis**

**Shape:** Cheese-like acellular center surrounded by macrophages & inflammatory cells (granulomatus inflammatory borders)=granuloma

**Others:**
- isn't preserved

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**Fat necrosis**

**Causes:** Lipase enzyme released to the peritoneum and destruct fats, & Ca²⁺ binding.

**Shape:** whitish foci, chalky-like (saponification)

- under the microscope: fatty acid shadows without nuclei.

**Others:** associated with acute pancreatitis

**fibrinoid necrosis**

**Causes:** Fibrin deposition due to antigen-antibody reaction in the walls of blood vessels

**Shape:** pink accumulations (due to the pinkish material in the fibrin.

**Others:**
- This disease is associated with vasculitis.
- can only be seen under the microscope.
## Important pics & tables

<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 content</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</td>
<td>often physiologic and may be pathologic</td>
</tr>
</tbody>
</table>

### Condition | Mechanism of Apoptosis
---|---
**Physiologic**
During embryogenesis | Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus) | Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium) | Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses | Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes | Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways

### Pathologic
- DNA damage: Activation of proapoptotic proteins by BH3-only sensors
- Accumulation of misfolded proteins: Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
- Infections, especially certain viral infections: Activation of the mitochondrial pathway by viral proteins
  - Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

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**MITOCHONDRIAL (INTRINSIC) PATHWAY**
- Cell injury
  - Growth factor withdrawal
  - DNA damage (by radiation, toxins, free radicals)
  - Protein misfolding (ETR stress)

**DEATH RECEPTOR (EXTRINSIC) PATHWAY**
- Receptor-ligand interactions: Fas, TNF receptor
  - Adapter proteins: Bcl-2 family effectors (Bax, Bak)
  - Initiator caspases
  - Executioner caspases

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