Cellular adaptations, cell injury, and cell death

Monday Feb 7
Terms

- Etiology
- Pathogenesis
- Morphologic changes
- Functional derangements and clinical manifestations
Hypertrophy

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Hyperplasia

Photos removed for copyright reasons.
Transmissible murine colonic hyperplasia

Photo and diagram removed for copyright reasons.
Photos removed for copyright reasons. 
Source: CD-ROM in [RC].
• Control colon, H&E 200x
• TMCH colon, H&E 200x
• TMCH colon, BrdU 200x
Hepatic regeneration

• In normal adult liver, only 0.5 to 1.0% of cells are undergoing DNA replication
• After partial hepatectomy, the remaining cells proliferate to replace the lost tissue mass
• Hepatocytes begin to divide by 12 hours, and 1 to 2 days later 10% of the cells are synthesizing DNA
• Once liver mass is restored, some 1 to 2 weeks later, the rate of DNA synthesis decreases
Factors driving compensatory hyperplasia

- HGF from nonparenchymal cells acts via c-Met expressed on hepatocytes
- TGF-alpha and EGF are also mitogenic for hepatocytes
- IL-6 and TNF-alpha are produced early in hepatic regeneration, and are necessary for the proliferative response
- A priming event is necessary for hepatocytes to respond to these cytokines and growth factors (degradation of ECM, release of norepinephrine, insulin, glucagon, etc.?)
Resolution of compensatory hyperplasia

- TGF-beta is an important inhibitor, which is also produced by nonparenchymal cells in the liver
- The adult stem cells of the liver do not appear to play an important role in hyperplasia following partial hepatectomy
Pathologic hyperplasia

- Hyperplasia constitutes a fertile soil in which neoplasia may develop.
- Hyperplasia in certain organs is a risk factor for cancer.
- But in tissues with a high turnover rate, hyperplasia may be a beneficial response when mature cells are injured or killed, necessitating compensatory renewal.
Metaplasia

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Source: Figure 1.6 in [RC].
Reversible & irreversible injury

**Normal Cell**

**NORMAL REVERSIBLE CELL INJURY IRREVERSIBLE CELL INJURY**

**Injury**
- Swelling of endoplasmic reticulum & mitochondria
- Clumping of chromatin

**Recovery**

**Death**
- Myelin figures
- Nuclear condensation
- Lysosome rupture
- Membrane blebs
- Swollen mitochondria with amorphous densities

**Necrosis**
- Swelling of endoplasmic reticulum and loss of ribosomes
- Fragmentation of cell membrane & nucleus

Figure by MIT OCW.
Necrosis and apoptosis

Figure by MIT OCW.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Necrosis</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell size</strong></td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
</tr>
<tr>
<td><strong>Nucleus</strong></td>
<td>Pyknosis, karyorrhexis, karyolysis</td>
<td>Fragmentation into nucleosome size fragments</td>
</tr>
<tr>
<td><strong>Plasma membrane</strong></td>
<td>disrupted</td>
<td>Intact, altered structure</td>
</tr>
<tr>
<td><strong>Cellular contents</strong></td>
<td>Enzymatic digestion, leakage</td>
<td>Intact, release in apoptotic bodies</td>
</tr>
<tr>
<td><strong>Adjacent inflammation</strong></td>
<td>Frequent</td>
<td>No</td>
</tr>
<tr>
<td><strong>Physiologic or pathologic role</strong></td>
<td>Always pathologic</td>
<td>Often, but not always, physiologic</td>
</tr>
</tbody>
</table>
Cellular and biochemical sites of damage

- Reactive Oxygen Species
  - $O_2^-$
  - $H_2O_2$
  - $OH^-$
- Intracellular $Ca^{2+}$
- Membrane Damage
- Protein breakdown
- DNA damage
- Plasma membrane
  - Loss of cellular contents
- Lysosome
  - Enzymatic digestion of cellular components
- Mitochondria
  - Cell death
  - Loss of energy-dependent cellular functions
- ATP

Figure by MIT OCW.
Consequences of ATP depletion

Ischemia

Mitochondrion

↓ Oxidative phosphorylation

↓ ATP

↓ Na pump

↑ Influx of Ca^{++}, H_{2}O, and Na^{+}

↑ Efflux of K^{+}

ER swelling

Cellular swelling

Loss of microvilli

Blebs

↑ Anaerobic glycolysis

↓ Glycogen

↓ pH

Clumping of nuclear chromatin

Other effects

Detachment of ribosomes, etc.

↓ Protein synthesis

Lipid deposition

Figure by MIT OCW.
Mitochondrial dysfunction

Mitochondrial injury or dysfunction (Increased cytosolic Ca\(^{2+}\), oxidative stress, lipid peroxidation)

Mitochondrial membrane

Cytochrome c, other pro-apoptotic proteins

Mitochondrial permeability transition (MPT)

Apoptosis

Figure by MIT OCW.
Ca\textsuperscript{2+} in cell injury

- Extracellular Ca\textsuperscript{2+}
- Injurious agent
- Increased cytosolic Ca\textsuperscript{2+}
- Endoplasmic reticulum
- Mitochondrion
- Ca\textsuperscript{2+}
- Increased cytosolic Ca\textsuperscript{2+}
- Endonuclease
- Protease
- Phospholipase
- ATPase
- Disruption of membrane and cytoskeletal proteins
- Decreased phospholipids
- Decreased ATP
- Membrane damage
- Nucleus chromatin damage

Figure by MIT OCW.
ROS in cell injury

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Source: Figure 1.14 in [RC].
Necrosis

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Source: Figure 1.19 in [RC].
Ischemic cell injury

Reversible Injury

- Ischemia
- Mitochondria
- ↓ Oxidative phosphorylation
- ↓ ATP
- ↓ ATP
  - ↓ Glycolysis
  - ↑ Glycolysis
  - ↑ Influx of Ca\(^{2+}\), H\(_2\)O, and Na\(^+\)
  - Efflux of K\(^+\)
- ↓ Na pump
- ↓ pH
- ↓ Glycogen
- Detachment of ribosomes
- ↓ Protein synthesis
- Lipid deposition

Irreversible Injury (Cell death)

- Membrane injury
- Loss of phospholipids
- Cytoskeletal alterations
- Free radicals
- Lipid breakdown
- Others
- ↑ Leakage of enzymes (CK, LDH)
- ↑ Ca\(^{2+}\) influx
- Intracellular release and activation of lysosomal enzymes
- ↓ Basophilia (↓ RNP)
- Nuclear changes
- Protein digestion

Figure by MIT OCW.
Chemical Injury

- $\text{CCl}_4$
  - SER
- $\text{CCl}_3$
  - Microsomal polyenoic fatty acid
- Lipid Radicals
  - $^+\text{O}_2$
  - LIPID PEROXIDATION
    - Autocatalytic spread along microsomal membrane
  - Release of Products of Lipid Peroxidation
    - Damage to Plasma Membrane
      - ↑ Permeability to $\text{Na}^+$, $\text{H}_2\text{O}$, $\text{Ca}^{2+}$
    - Cell Swelling
    - Massive Influx of $\text{Ca}^{2+}$
    - Inactivation of Mitochondria, Cell Enzymes, and Denaturation of Proteins

- Membrane Damage to RER
  - Polysome Detachment
  - ↓ Apoprotein Synthesis
  - Fatty Liver

Figure by MIT OCW.
Mechanisms of apoptosis

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Source: Figure 1.28 in [RC].
Extrinsic pathway of apoptosis

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Source: Figure 1.29 in [RC].
Intrinsic pathway of apoptosis

Figure removed for copyright reasons.
Source: Figure 1.30 in [RC].
Reticulum cell sarcoma model

B cell lymphoma
Reticulum cell sarcoma (RCS)
MMTV-encoded superantigen

Syngeneic CD4+ Vb16+ T cells
Produce B cell growth factors
“Reverse immune surveillance”

Th1 cytokines
Normal spleen

Figure by MIT OCW.
Photos removed for copyright reasons.
Source: CD-ROM in [RC].
• Normal spleen, H&E 100x
• RcsX spleen, H&E 100x
• Normal spleen, H&E 200x
• RcsX spleen, H&E 200x
• Normal spleen, H&E 400x
• RcsX spleen, H&E 400x
• RcsX spleen, iNOS 400x
• RcsX spleen, activated caspase-3 400x