Liver regeneration

Feb 9, 2005

The legend of Prometheus
Partial Hepatectomy

- Important model for studying cellular regeneration (Higgins and Anderson 1931)
- Hundreds of studies have now addressed the control and consequences of cellular regeneration
- Simple surgical procedure in which 1 or more hepatic lobes are removed without damage to the remaining lobes
Partial HPx: cellular events

• The residual lobes first grow by hyperplasia, and then by hypertrophy to match the mass of the removed lobes
• All of the existing mature cell types composing the liver regenerate
• Nearly all of the parenchymal cells in the remaining liver lobes participate in 1 or 2 proliferative cycles
• Within 7-10 days, liver mass is restored
Partial HPx: pathogenesis

• Regeneration of the liver is a pathophysiological process
• Essentially a process of compensatory hyperplasia
• The increase in liver volume/mass does not restore original macroanatomy
Partial HPx: rat model

- Most of what is known is based on 2/3 HPx in rats
- Process is divided into:
  - “Priming” phase in which cell acquire an enhanced capacity to proliferate
  - Proliferation phase
  - Termination phase
Partial HPx: still unknown

- Division of mature liver cells or stem cell proliferation?
- Triggered by increase release of growth factors or decrease in concentration of circulating inhibitors?
- Mechanisms responsible for “memory” of liver mass and precise termination of liver regeneration?
Partial HPx: cell cycle entry

- At the time of HPx, virtually all hepatocytes are in $G_0$
- After HPx, all hepatocytes synchronously enter the cell cycle
- Maximal DNA synthesis occurs 24 hours after HPx
Chemical injury

CCl₄
\[ \downarrow \]
SER

CCl₃
\[ \downarrow \]
Microsomal polyenoic fatty acid

Lipid Radicals
\[ \downarrow \]+O₂

LIPID PEROXIDATION
Autocatalytic spread along microsomal membrane

Membrane Damage to RER

Polysome Detachment

\[ \downarrow \]
Apoprotein Synthesis

Fatty Liver

Release of Products of Lipid Peroxidation

Damage to Plasma Membrane

\[ \uparrow \]
Permeability to Na⁺, H₂O, Ca²⁺

Cell Swelling

Massive Influx of Ca²⁺

Inactivation of Mitochondria, Cell Enzymes, and Denaturation of Proteins

Figure by MIT OCW.
Regeneration after liver injury

- Many toxins can cause liver damage (necrosis and inflammation)
- Hepatotoxic models are:
  - Easier to perform
  - More clinically relevant
  - Less reproducible
Carbon tetrachloride ($\text{CCl}_4$)

- Classical hepatotoxin
- Induces liver injury by metabolites arising from $\text{P}_{450}$-dependent breakdown
- First step is formation of reactive trichloromethyl radicals
- Trigger lipid peroxidation
CCl₄ regeneration

• Acute, reversible liver injury following a single oral, intraperitoneal, or subcutaneous dose
• In mice (22-28 g), single i.p. injection (0.1 ml/kg diluted in corn oil)
• Can enhance hepatotoxicity by simultaneous administration of phenobarbital
Acetaminophen

- Frequent cause of acute liver failure
- Normally undergoes biotransformation in the liver by a combination of glucuronidation and sulphation
- After overdose, these pathways are overwhelmed and $P_{450}$-dependent metabolism takes place
- Formation of $N$-acetyl-benzoquinoneimine
Portal Tract
Limiting Plate (6-8 cells)
Periportal (6-8 cells)
Centrilobular (8-10 cells)
GS+ (1-3 cells)

Central Vein

Portal Tracts (triads)

Figure by MIT OCW.
Mechanisms of apoptosis

Figure removed for copyright reasons.
Extrinsic pathway of apoptosis

Figure removed for copyright reasons.
Source: Figure 1.29 in [RC].
Intrinsic pathway of apoptosis

Figure removed for copyright reasons.
Source: Figure 1.30 in [RC].
Ischemic cell injury

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

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

Figure by MIT OCW.