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

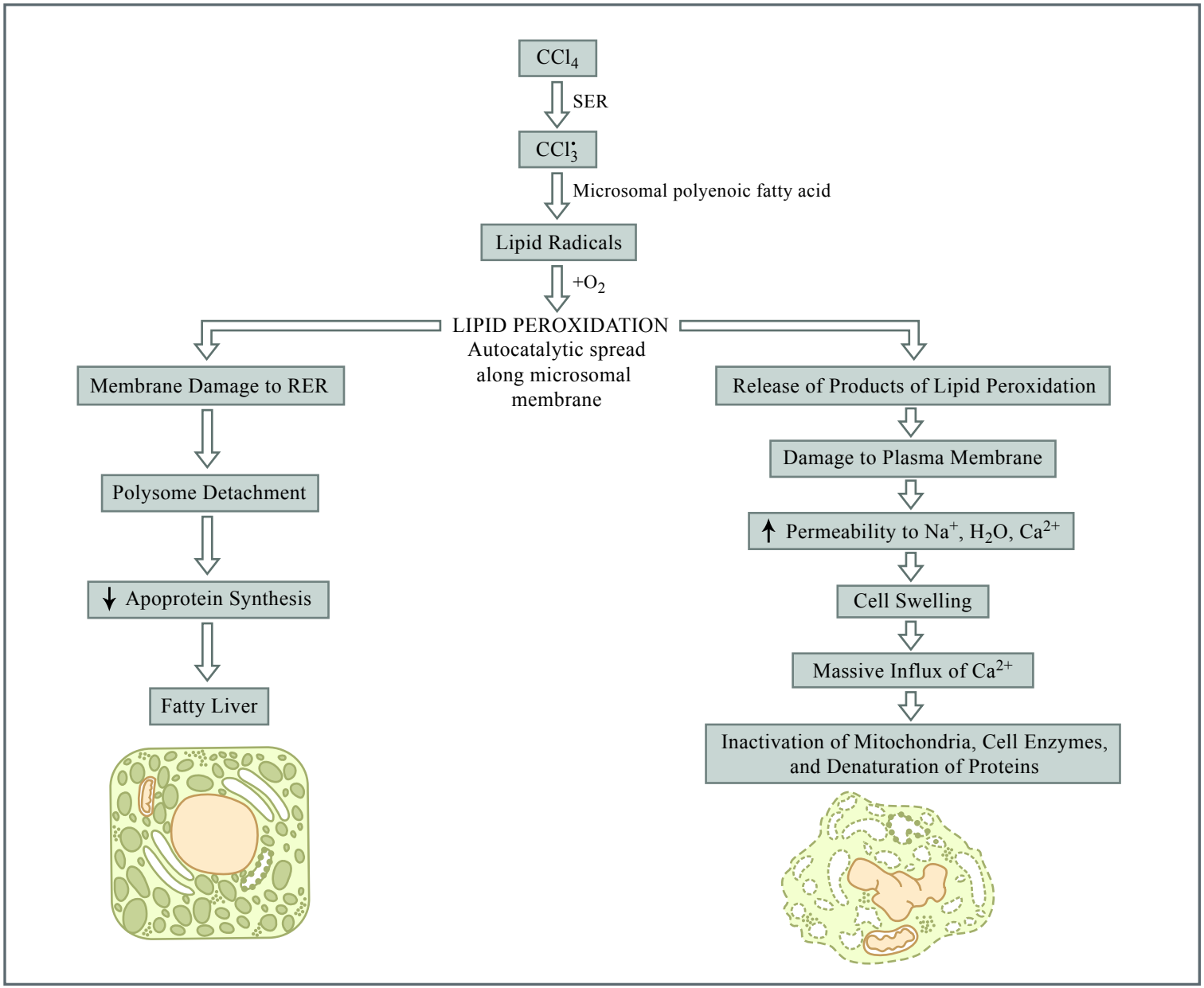


Figure by MIT OCW.

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 (CCl_4)

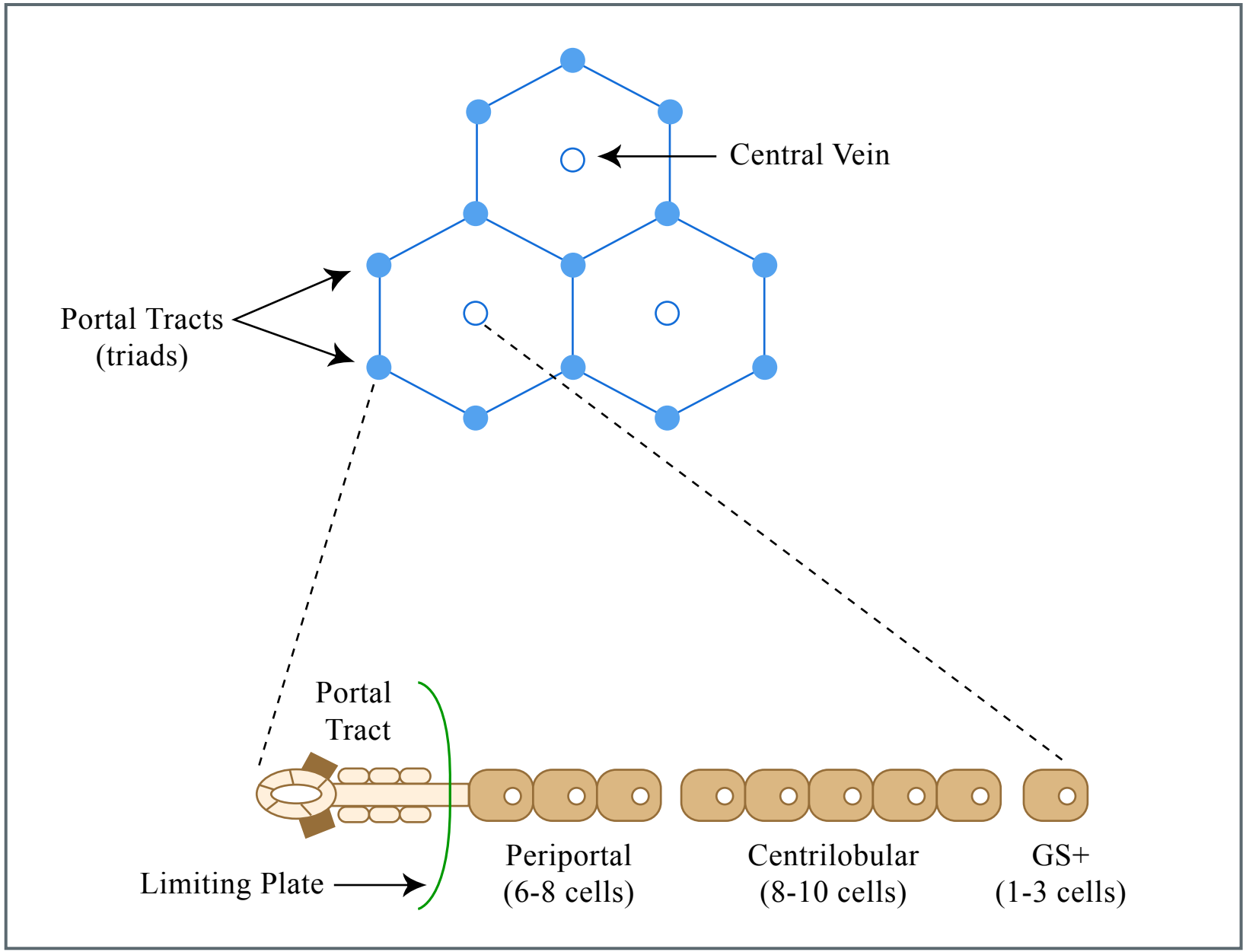
- Classical hepatotoxin
- Induces liver injury by metabolites arising from P_{450}-dependent breakdown
- First step is formation of reactive trichloromethyl radicals
- Trigger lipid peroxidation

CCl_4 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



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Mechanisms of apoptosis

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Source: Figure 1.28 in [RC] Kumar, V., A. K. Abbas, and N. Fausto. *Robbins and Cotran Pathologic Basis of Disease*. Philadelphia PA: Elsevier, 2005. ISBN: 0721601871.

Extrinsic pathway of apoptosis

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Source: Figure 1.29 in [RC].

Intrinsic pathway of apoptosis

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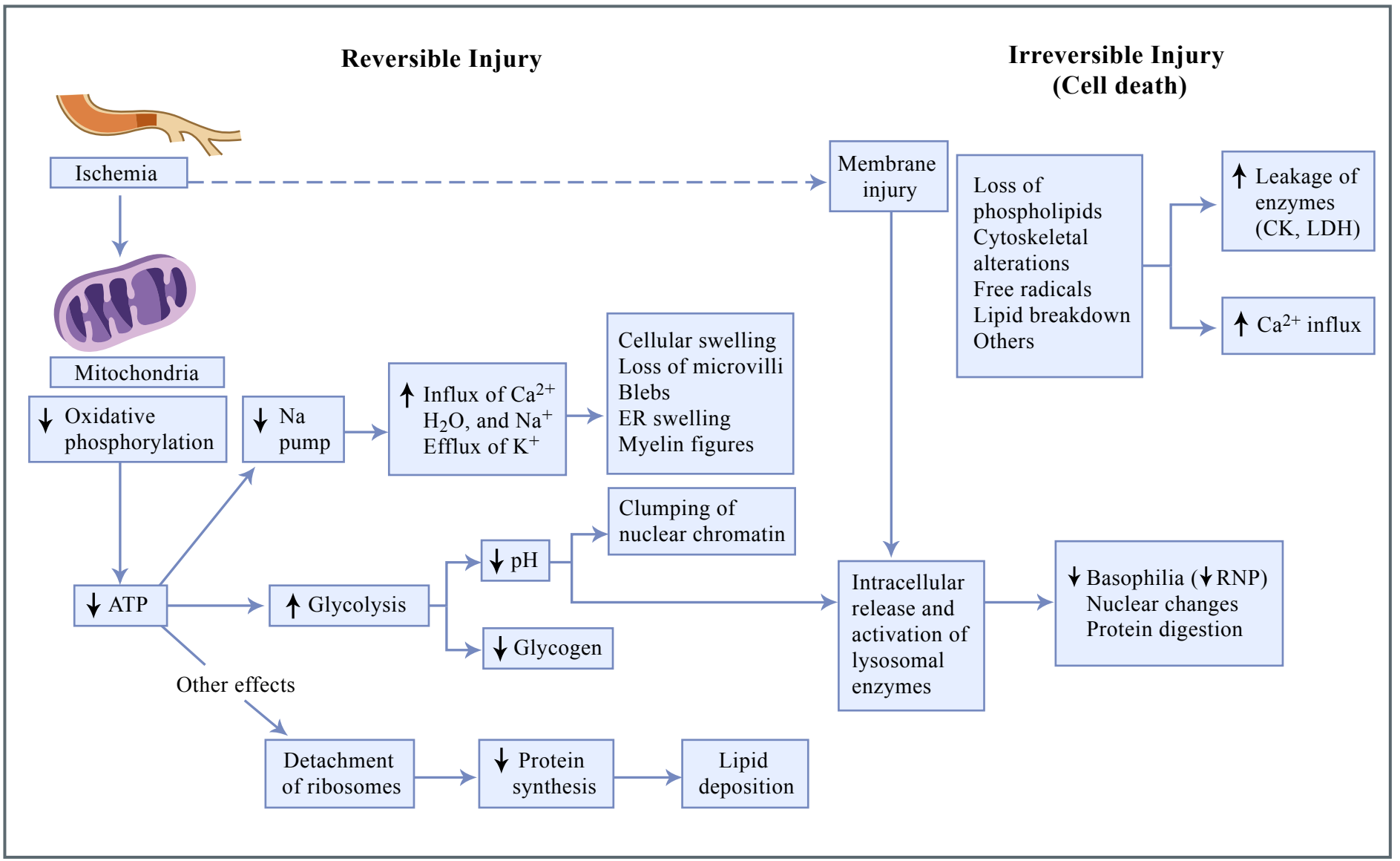
Source: Figure 1.30 in [RC].

Ischemic cell injury



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