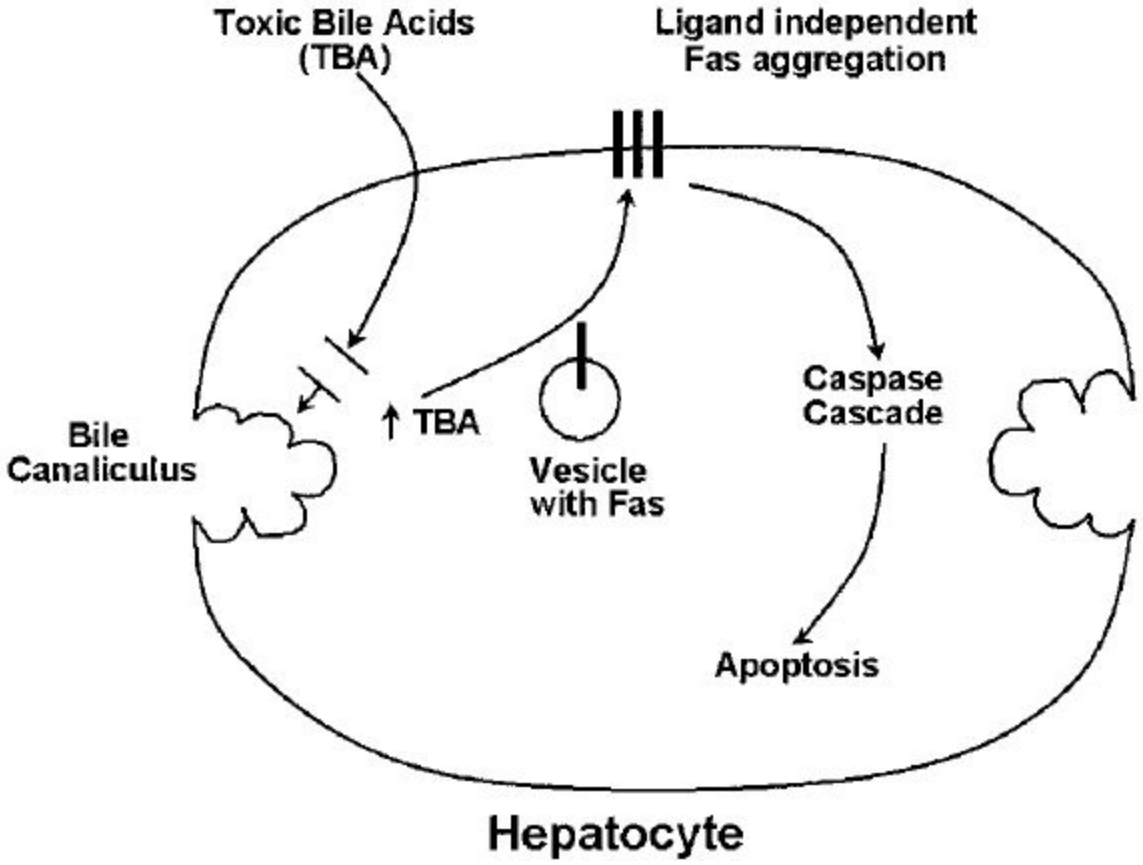
Toxic Response of the hepatobiliary system

- Lobular Model
    - Central vein with triads of portal vein, artery, bile duct at hexagonal perimeter
- Acinar Model
    - Three zone model with Zone 1 closest to penetrating venule near portal triads and zone 3 being farthest (or nearest to terminal hepatic vein)
- Hepatocytes differ in their function and enzyme activity in different areas of the lobules/acini, allowing for different zonal patterns of toxic injury

Bile Acid-Induced Hepatocyte Apoptosis

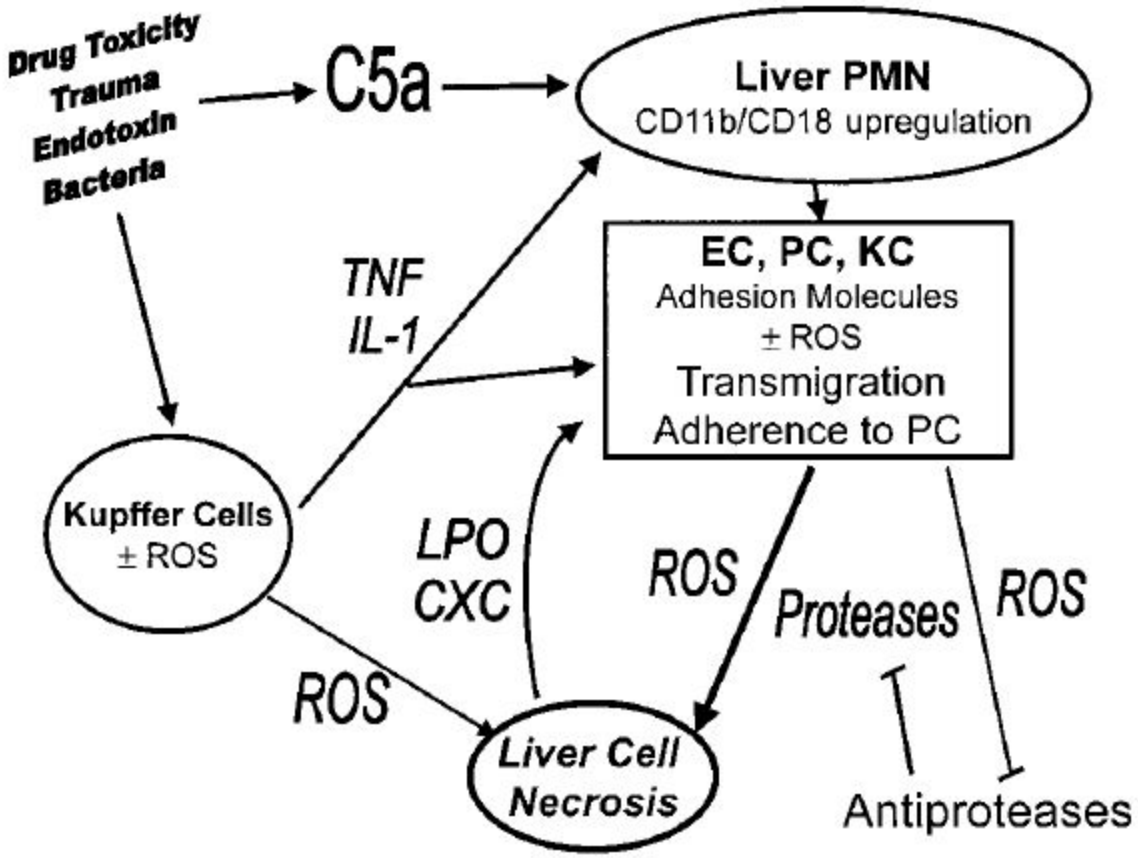
- Retention of bile constituents within hepatocytes is associated with hepatocyte apoptosis
    - Hydrophobic bile acid Glycochenodeoxycholate (GCDC)
    - Stimulate transport of intracellular death receptors to the plasma membrane



Adhesion Molecules and Oxidant Stress in Inflammatory Liver injury

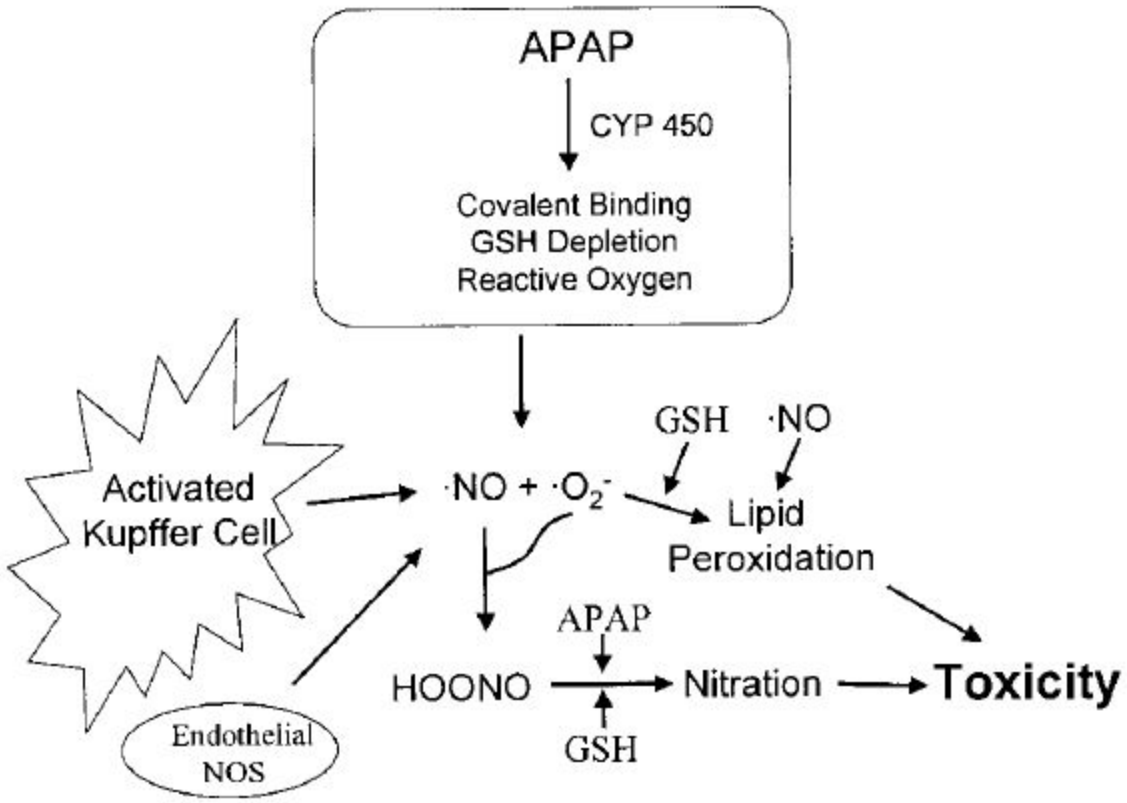
- Phagocytic cells are recruited to hepatic vasculature by local injury and inflammatory mediators such as TNF-alpha, IL-1, compliment, platelet activating factor, other chemokines
- Neutrophils accumulate in sinusoids (great place for neutrophils to hand out)

- Adhesion occurs via expression of cellular adhesion molecules (CAMS; especially ICAM-1) inducible on all liver cell types
- Adhesion can lead to release of proteases and prolonged reactive oxygen formation This enhances activation of NF-kappa B which increases cytokine, chemokine and adhesion molecule production



Peroxynitrite in Drug-Induced Hepatotoxicity

- Cytochrome P450 metabolism is often a central step
    - In acetaminophen toxicosis, P450 metabolism to N-acetyl-p-benzoquinone imine (NAPQI) depletes up to 90% of hepatic glutathione
- Kupffer cells are important in formation in NO and superoxide, which are potent oxidizers via peroxynitrite formation
    - Peroxynitrite is detoxified by glutathione
- iNOS is also stimulated in acetaminophen toxicity



Hepatotoxicity due to mitochondrial dysfunction

- Many drugs/toxins affect the mitochondria and lead to accumulation of nonesterified fatty acids (NEFAs) in the cytoplasm (microvesicular steatosis)
- Drugs can inhibit b-oxidation in liver leading to microvesicular steatosis
- Drugs can also cause opening of permeability transition pores (PTs) in mitochondrial inner membrane
    - This can lead to decreased cellular ATP production and apoptosis or necrosis
- PT opening can be direct or via increased intracellular calcium (depending on drug)

Summary: Toxicosis -> decreased cellular ATP or direct cellular apoptosis or ROS generation and cellular damage -> accumulation of bile acids and inflammatory activation -> further cellular injury and death

TABLE 11-1 **Poisons that Affect the Hepatobiliary System**

Source	Toxicant	Species
Plants	Alsike clover	Horse
	Cycad (sago) palms	Dogs most commonly exposed
	Forages that induce photosensitization	Livestock
	Pyrrolizidine alkaloids	Livestock
	Quinones	Livestock
	Red clover	Horse
	Steroidal saponins	Primarily ruminants
	Tetradymia spp. and *Artemisia* spp.	Primarily sheep
	Xanthium	Primarily swine; also ruminants and horses
Mycotoxins	Aflatoxins	All
	Fumonisin	All
	Phomopsins	Sheep and cattle
	Sporidesmin	Sheep
Pharmaceuticals	Acetaminophen	Dogs primarily; cats at high doses
	Arsenical antihelminthics	Dogs
	Ketoconazole	Primarily cats
	Nonsteroidal antiinflammatory drugs	All
Toxins	Amatoxins (mushrooms)	All
	Microcystin (blue-green algae)	All
	Nodularin (blue-green algae)	All
Metal	Copper	Primarily in sheep and susceptible breeds of dogs
	Iron	All

Questions:

1. When purposed bred knockout mice with absence of kupffer cells are given liver intoxicants, they exhibit reduced liver damage compared with wild-type mice. Explain why this is, being specific with regards to cellular mechanisms.

2. True/False, cholestasis alone can produce liver injury and increase in hepatocellular enzyme activity?

3. In times of hepatic inflammation, neutrophils will begin to accumulate within the vascular _____ of the liver prior to adhesion. Adhesion will then occur if cells within the liver begin to express _____, under the influence of _____.

Options: Tumor necrosis factor, IL-2, NF-Kappa B, subendothelial spaces, interstitium, sinusoids, reactive oxygen species, compliment, platelet activating factor, ICAM-1

Answers:

4. When purposed bred knockout mice with absence of kupffer cells are given liver intoxicants, they exhibit reduced liver damage compared with wild-type mice. Explain why this is, being specific with regards to cellular mechanisms.
   Kupffer cells produce reactive oxygen species, as well as cytokines and chemokines (such as IL-1 and TNF-alpha), recruiting other inflammatory cells to the liver and increasing the inflammatory damage.

5. **True**/False, cholestasis alone can produce liver injury and increase in hepatocellular enzyme activity? Via bile acid (Glycochenodeoxycholate) induced death receptor activation

6. In times of hepatic inflammation, neutrophils will begin to accumulate within the vascular Sinusoids of the liver prior to adhesion. Adhesion will then occur if cells within the liver begin to express ICAM-1, under the influence of NF-Kappa B.

Options: Tumor necrosis factor, IL-2, NF-Kappa B, subendothelial spaces, interstitium, sinusoids, reactive oxygen species, compliment, platelet activating factor, ICAM-1