

# TOXIC RESPONSES OF THE LIVER

General Toxicology

4<sup>th</sup> Stage / 2<sup>nd</sup> Semester

University of Mustansiriyah/College of Pharmacy

---

Department of Pharmacology & Toxicology

Lecturer

Nada Sahib Shaker

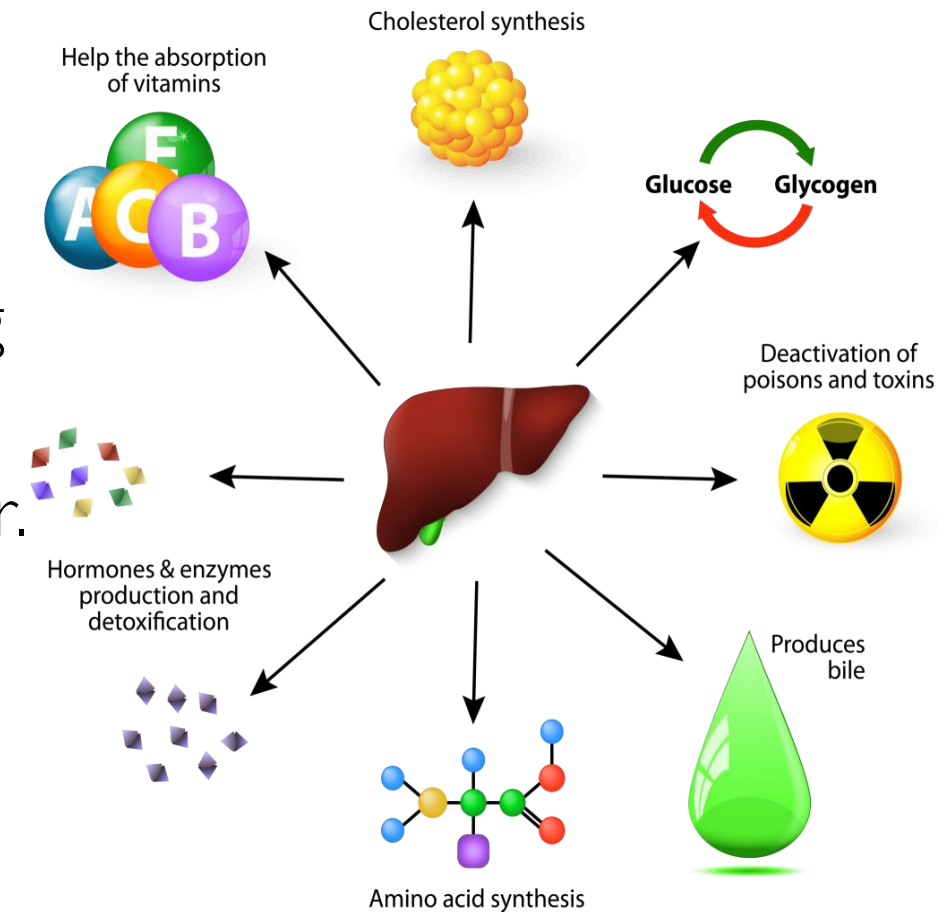
# background

- The liver is the main organ where exogenous chemicals are metabolized and eventually excreted.
- As a consequence, liver cells are exposed to significant concentrations of these chemicals, which can result in liver dysfunction, cell injury, and even organ failure.
- Many industrial chemicals, plant toxins, environmental pollutants, food-borne agents, herbal remedies, and drugs are known to be hepatotoxic.
- In the pharmaceutical industry, adverse effects on the liver are one of the most frequent reasons for discontinuing the development of drug candidates and withdrawal of drugs from the market.

# LIVER PHYSIOLOGY

## General Liver Functions:

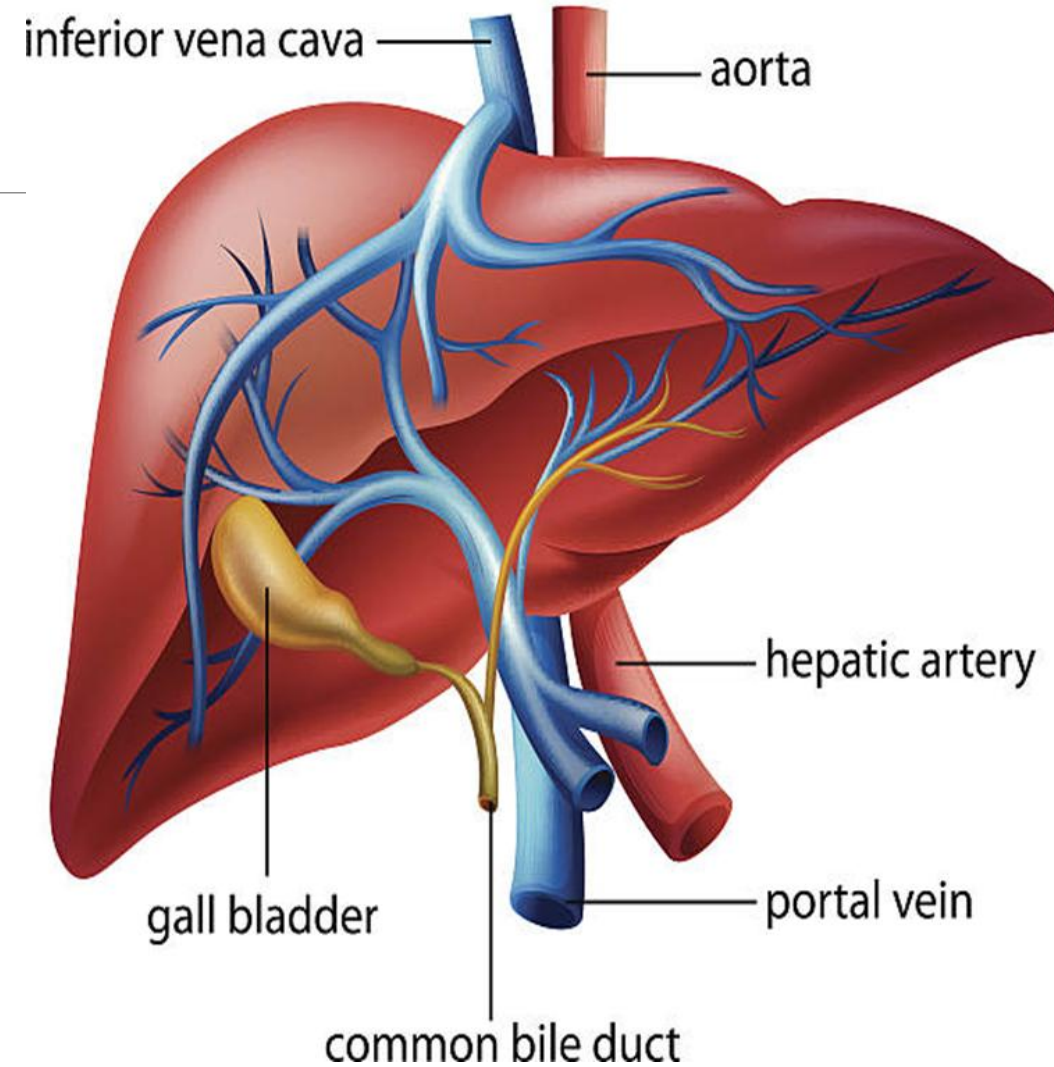
- 1) Processing of foods and other substances absorbed from the intestinal tract.
- 2) Maintenance of glucose and cholesterol levels in the blood.
- 3) Synthesis of proteins such as albumin, and clotting factors.
- 4) Formation and excretion of bile via the gallbladder.
- 5) Biotransformation and detoxification of endogenous, and exogenous agents.
- 6) An integral contributor to both innate and adaptive immunity.



- Hepatic Function:

- The liver is the first organ to encounter ingested nutrients, vitamins, metals, drugs, and environmental toxicants as well as waste products of bacteria that enter portal blood.
- Efficient scavenging or uptake processes extract these absorbed materials from the blood for catabolism, storage, and/or excretion into bile.

## Human Liver Anatomy



## Hepatic Function:

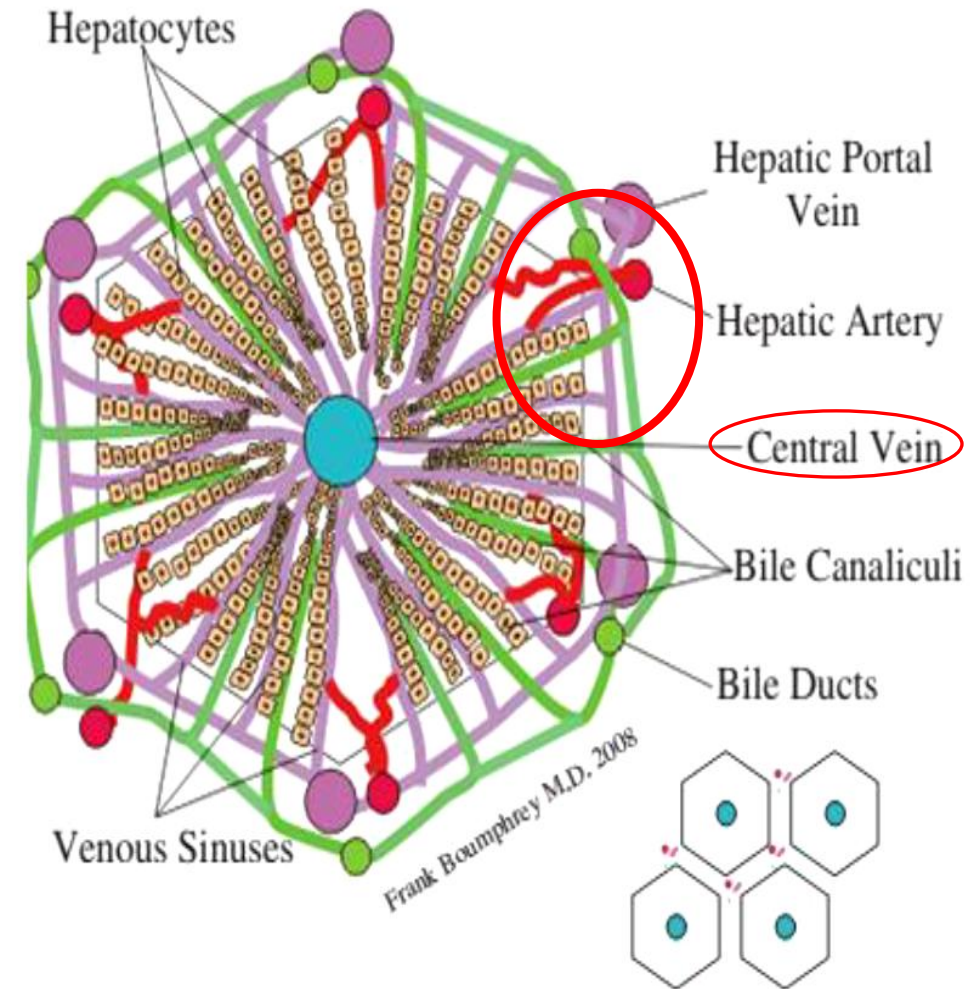
- Chemical-induced liver injury is typically initiated by the formation of a toxic metabolite, which triggers intracellular responses that can progress to dysfunction or death of hepatic cells.
- These intrahepatocellular events can in turn lead to secondary events involving the activation of other cells that magnify or attenuate the initial injury.
- Loss of function also occurs when toxicants kill a considerable number of cells and when chronic insult leads to the replacement of cell mass by non-functional scar tissue.

**TABLE 13–1 Major functions of liver and consequences of impaired hepatic functions.**

Type of Function	Examples	Consequences of Impaired Functions
Nutrient homeostasis	Glucose storage and synthesis Cholesterol uptake	Hypoglycemia, confusion Hypercholesterolemia
Filtration of particulates	Products of intestinal bacteria (e.g., endotoxin)	Endotoxemia
Protein synthesis	Clotting factors Albumin Transport proteins (e.g., very low-density lipoproteins)	Excess bleeding Hypoalbuminemia, ascites Fatty liver
Bioactivation and detoxification	Bilirubin and ammonia Steroid hormones Xenobiotics	Jaundice, hyperammonemia-related coma Loss of secondary male sex characteristics Diminished drug metabolism Inadequate detoxification
Formation of bile and biliary secretion	Bile acid–dependent uptake of dietary lipids and vitamins Bilirubin and cholesterol Metals (e.g., Cu and Mn) Xenobiotics	Fatty diarrhea, malnutrition, vitamin E deficiency Jaundice, gallstones, hypercholesterolemia Mn-induced neurotoxicity Delayed drug clearance

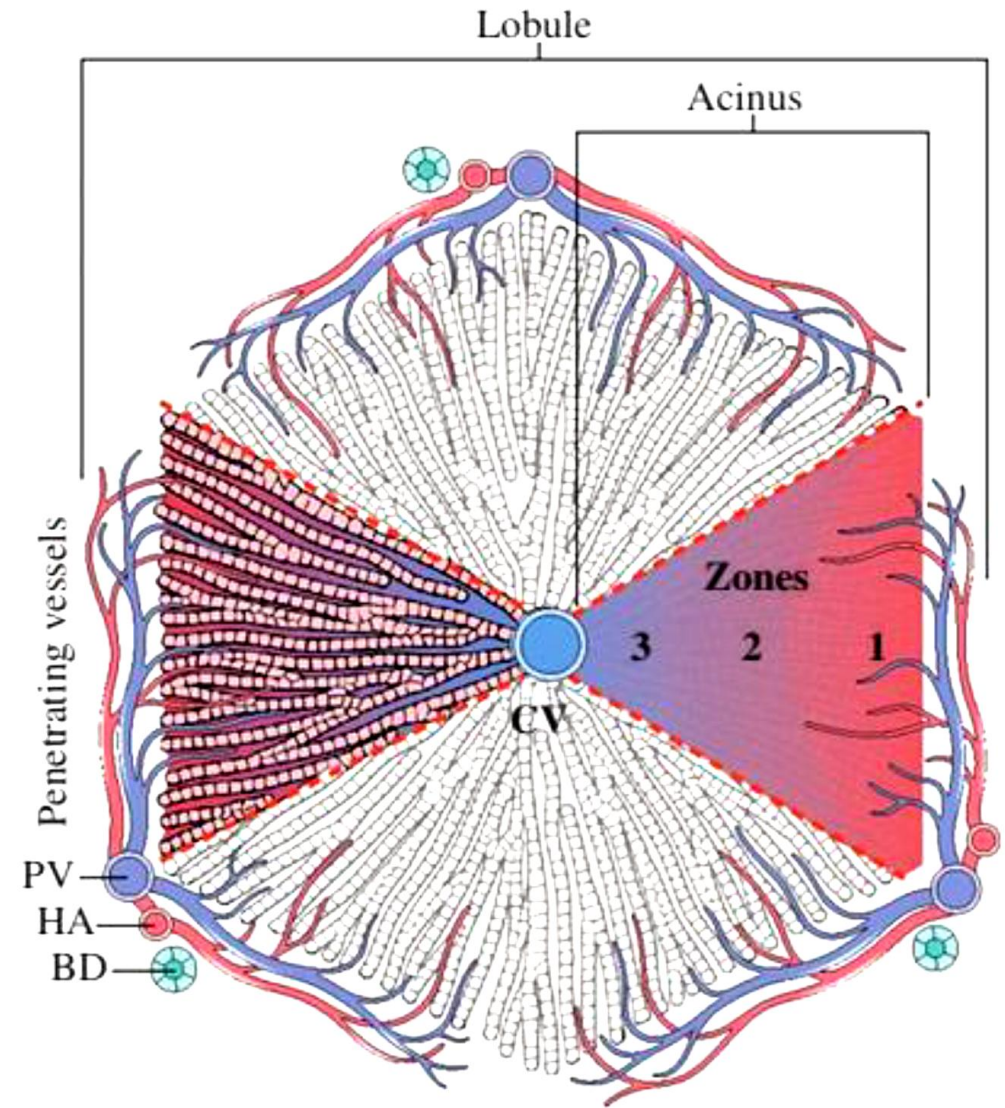
# Structural Organization

- The liver is divided into hexagonal lobules oriented around terminal hepatic venules (**central veins**).
- At the corners of the lobule are the portal triads, containing a branch of the portal vein, a hepatic arteriole, and a bile duct.
- Blood entering from the portal vein and hepatic artery mixes in the penetrating vessels enters the sinusoids, percolates along the cords of parenchymal cells (hepatocytes), flows into terminal hepatic venules, and exits the liver via the hepatic vein.



# Structural Organization

- The lobule is divided into three regions known as periportal (nearest portal triad), centrilobular (surrounding the central vein), and midzonal (between periportal and centrilobular).
- The base of the acinus is formed by the terminal branches of the portal vein and hepatic artery, which extends out from the portal tracts.
- The acinus has three zones: zone 1 is closest to the entry of blood, zone 3 is about the terminal hepatic vein, and zone 2 is intermediate.
- the three zones of the acinus roughly coincide with the three regions of the lobule.



# Structural Organization

- Blood entering the acinus consists of oxygen-depleted blood from the portal vein (60% to 70% of hepatic blood flow) plus oxygenated blood from the hepatic artery (30% to 40%).
- Oxygen rapidly leaves the blood to meet the high metabolic demands of the parenchymal cells. Hepatocytes in Zone 3 are exposed to substantially lower concentrations of oxygen than hepatocytes in Zone 1.
- In comparison to other tissues, zone 3 is hypoxic.
- These anatomical substructures are important because liver lesions caused by chemical exposure usually appear preferentially in one of them.

# Liver Cells Functions

- Hepatic parenchymal cells (HPCs), also known as hepatocytes, are large epithelial cells that account for about 60% of the cells in the liver.
- HPCs process dietary carbohydrates by converting monosaccharides into energy and synthesis of glycogen for carbohydrate storage.
- HPCs are capable of synthesizing and processing lipids for energy production or export into circulation as lipoproteins.
- HPCs are the source of many circulating proteins, such as albumin, coagulation factors, and complement proteins.

## Hepatic parenchymal cells (HPCs),

- HPCs detoxify circulating substances produced during metabolism. For example, HPCs detoxify ammonia by forming it into urea and then eliminating it by the kidneys.
- HPCs synthesize bile acid which aids in the absorption and processing of dietary lipids.
- HPCs clear the circulation of many endogenous, biologically active substances as well as environmental and dietary toxins.
- HPCs contain large concentrations of both phase I enzymes and phase II enzymes, which facilitates excretion by biliary and renal routes.
- The metabolism of some xenobiotic agents by HPCs can result in toxic metabolites that directly injure these cells.

## Sinusoidal Endothelial Cells:

- Scavenging of lipoproteins via the apolipoprotein E receptor.
- Secrete biologically active molecules such as cytokines, prostanoids, nitric oxide, and endothelins.
- Play a crucial role in maintaining metabolic and immune homeostasis, as well as actively contributing to disease pathophysiology.

## ➤ Kupffer Cells:

- Are the resident macrophages of the liver and constitute approximately 80% of the fixed macrophages in the body.
- A primary function of Kupffer cells is to ingest and degrade particulate matter (e.g., bacteria).
- Kupffer cells are important players in immune responses, they are a major source of cytokines, eicosanoids, and reactive oxygen species (ROS) and can act as antigen-presenting cells.

## Hepatic Stellate Cells:

- Hepatic stellate cells (HSCs) are located between endothelial cells and HPCs.
- Are the major sites for vitamin A storage in the body, these appear to control the local flow of blood in the sinusoids.
- When activated, especially during chronic injury to the liver, stellate cells can assume a myofibroblastic phenotype, synthesizing and secreting collagen and other extracellular matrix proteins and thereby initiating liver fibrosis.

## Other Immune Cells :

- An important role of various immune cells is to initiate a specific response to injury or disease. For example, dendritic cells (DCs) play a key role in antigen processing and in the presentation of antigens to other immune cells along with the production of inflammatory cytokines, such as interferons.
- Natural Killer (NK) Cells and Natural Killer T (NKT) Cells:
- These are subsets of lymphocytes that accumulate in the liver in response to injury and inflammatory challenges; they produce a variety of cytokines that modify the activity of several other cell types in the liver.
- Several studies showed that NK cells have both inflammatory and anti-fibrotic activity.

# Critical factors in toxicant-induced liver injury

Why is the liver the target site or so many chemicals? Why do many hepatotoxicants preferentially damage one type of liver cell?

---

- Location and specialized processes or uptake.
- biliary secretion produce higher exposure levels in the liver than in other tissues.
- the abundant capacity or bioactivation reactions influences the rate of exposure to proximate toxicants.

# Mechanisms and Types of Toxicant-induced Liver Injury

## **CANALICULAR CHOLESTASIS**

- is defined physiologically as a decrease in the volume of bile formed or an impaired secretion of specific solutes into bile.
- Cholestasis is characterized biochemically by elevated serum levels of compounds normally concentrated in bile, particularly bile salts and bilirubin.
- When biliary excretion of the yellowish bilirubin pigment is impaired, this pigment accumulates in skin and eyes, producing jaundice, and spills into urine, which becomes bright yellow or dark brown.
- An increased hepatic uptake, decreased biliary excretion, and increased biliary reabsorption (cholehepatic shunting) of a drug may contribute to its accumulation in the liver.

# Mechanisms and Types of Toxicant-induced Liver Injury

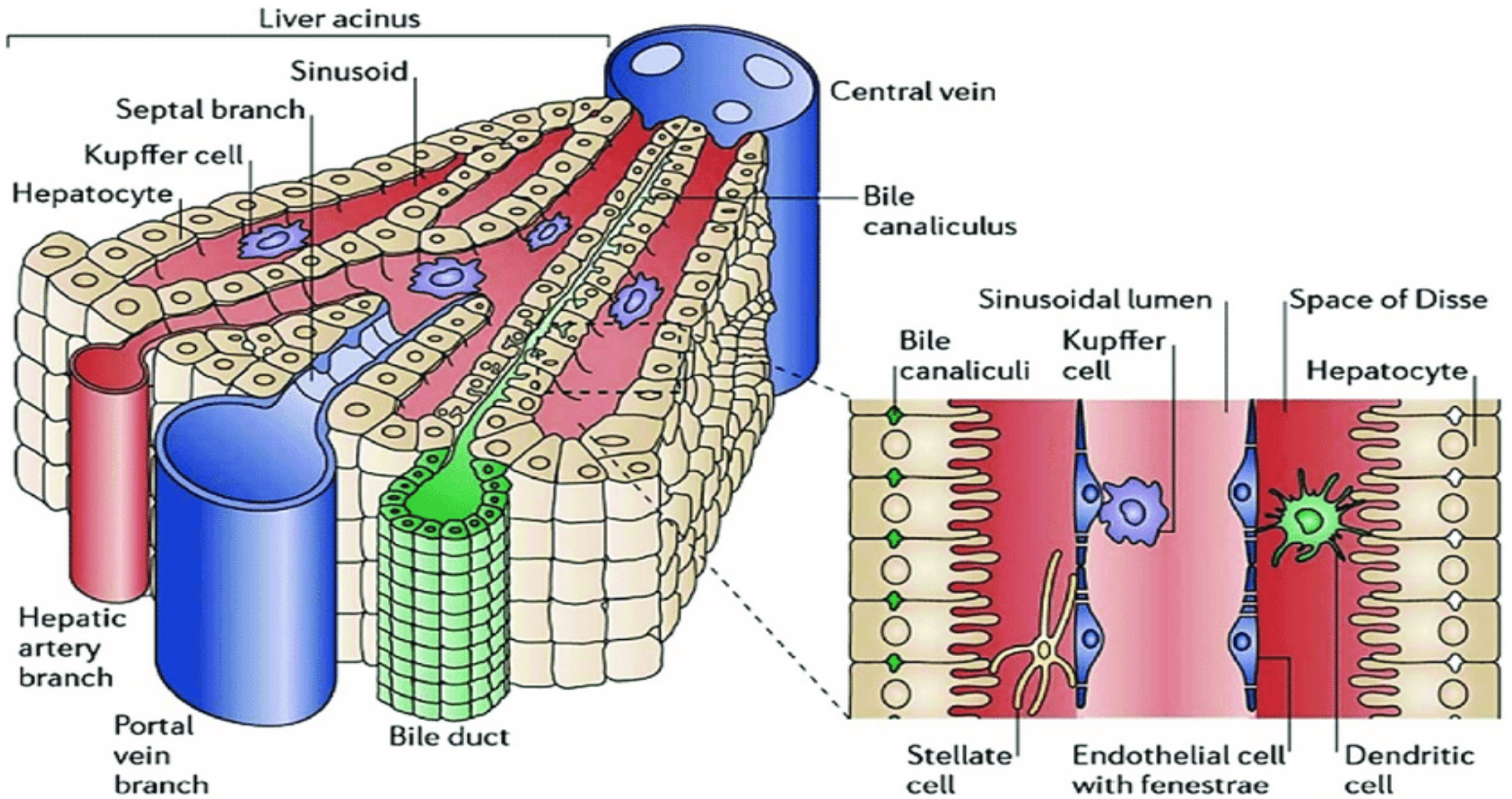
## **SINUSOIDAL DAMAGE**

Hepatic sinusoids are the channels between cords of hepatocytes where blood percolates on its way to the terminal hepatic vein.

The three major types of cells in the sinusoids are endothelial cells, Kupffer cells, and stellate cells.

Sinusoids are lined by thin, discontinuous endothelial cells with numerous fenestrae (or pores) that allow molecules smaller than 250 kDa to cross the interstitial space (known as the space of Disse) between the endothelium and hepatocytes.

The numerous fenestrae and the lack of basement membrane facilitate exchanges of fluids and molecules.



# Mechanisms and Types of Toxicant-induced Liver Injury

## **SINUSOIDAL DAMAGE**

---

The functional integrity of the sinusoid can be compromised by:

- Dilation of the lumen.
- Blockage of the lumen.
- Progressive destruction of its endothelial cell wall.

Dilation of the sinusoid will occur whenever efflux of hepatic blood is impeded.

Blockage will occur when the fenestrae enlarge to such an extent that red blood cells become caught in them

# Mechanisms and Types of Toxicant-induced Liver Injury

## **FATTY LIVER:**

- Fatty liver (steatosis) is defined biochemically as an appreciable increase in the hepatic lipid (mainly triglyceride) content, which is < 5% by weight in normal human liver.
- The most common cause of hepatic steatosis is insulin resistance due to central obesity.
- Acute exposure to many hepatotoxins, e.g., CCL4, and drugs can induce steatosis.
- Although steatosis alone may be benign, it can develop into steatohepatitis (alcoholic or nonalcoholic), which is associated with significant liver injury.
- Steatohepatitis can progress to fibrosis and even hepatocellular carcinoma.

# FIBROSIS & CIRRHOSIS

- **Hepatic fibrosis (scarring)** is characterized by the accumulation of extensive amounts of collagen fibers, in response to direct injury or inflammation.

---

- With repeated chemical insults:
  - destroyed hepatic cells are replaced by fibrotic scars.
  - Continued collagen deposition, the architecture of the liver is disrupted by interconnecting fibrous scars
- **Fibrosis can progress to cirrhosis** and the liver then has limited residual capacity to perform its essential functions
- The primary cause of hepatic fibrosis/cirrhosis in humans **worldwide is viral hepatitis.**
- In addition, **fibrosis can be induced by chronic exposure to drugs and chemicals especially ethanol and heavy metals.**
- Cirrhosis is not reversible, has a poor prognosis or survival, and is usually the result of repeated exposure to chemical toxicants.

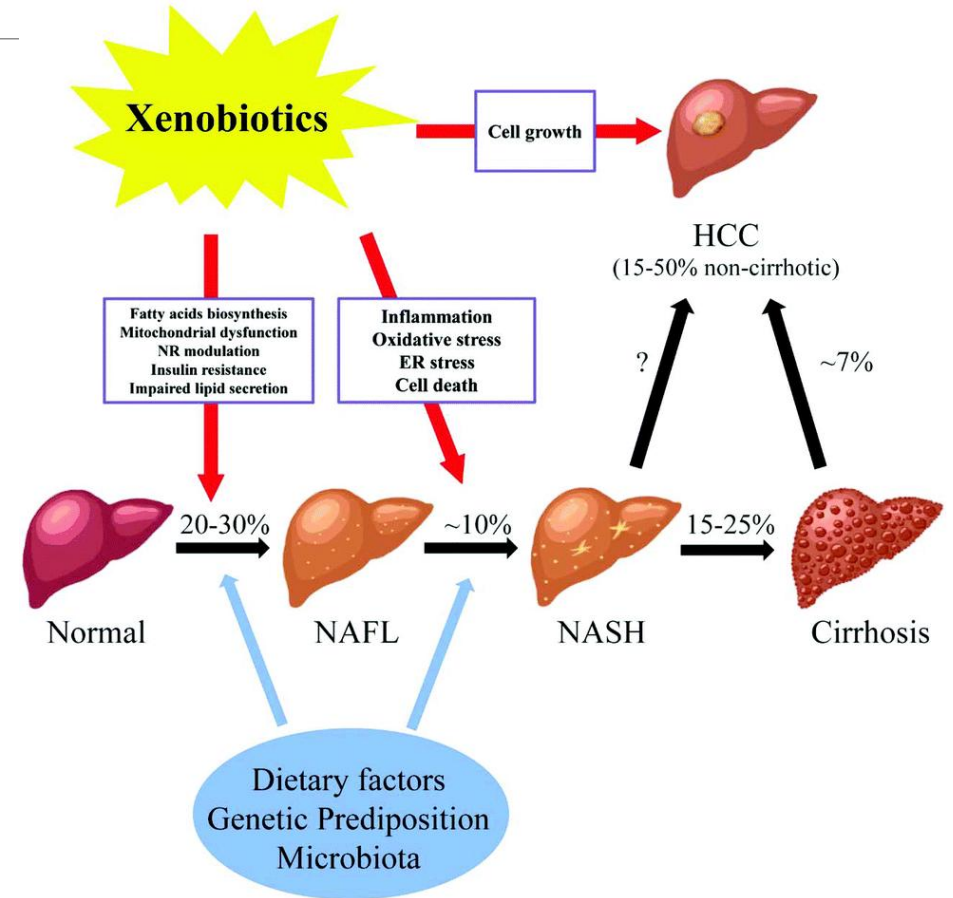
# Mechanisms and Types of Toxicant-induced Liver Injury

## **TUMORS:**

- Chemically induced neoplasia can involve tumors that are derived from:
  - Hepatocytes >> hepatocellular carcinoma (84%)
  - Bile duct cells >> gallbladder cancer and cholangiocarcinoma
  - Sinusoidal lining cells >> angiosarcoma
- Risk factors of liver cancer (mostly hepatocellular carcinoma):
  - chronic abuse of androgens, alcohol, and a high prevalence of aflatoxin-contaminated diets.
  - In addition, viral hepatitis, metabolic diseases, and nonalcoholic steatohepatitis are major risk factors.
- The malignant transformation of hepatocytes occurs as a result of increased cell turnover due to chronic liver injury, persistent inflammation, regeneration, and cirrhosis.

# Critical factors in toxicant-induced liver injury

1. Uptake and concentration
2. Bioactivation and detoxification
3. Regeneration
4. Inflammation & immune response
5. Idiosyncratic reaction



# 1- uptake & concentration

- Lipophilic drugs readily diffuse into hepatocytes because the fenestrated epithelium of the sinusoid enables close contact between circulating molecules and hepatocytes.
- Other toxicants are rapidly extracted from blood because they are substrates for sinusoidal transporters.
- Examples:
  - *Phalloidin and microcystin* are illustrative examples of toxicants that target the liver as a consequence of extensive uptake into hepatocytes by sinusoidal transporters.
  - *Hepatic iron homeostasis:*
    - ✓ The cytotoxicity of free iron is attributed to its function as an electron donor or the formation of reactive oxygen species, which initiate destructive oxidative stress reactions.
    - ✓ Accumulation of excess iron beyond the capacity or its safe storage in ferritin leads to liver damage.

## 2- bioactivation & detoxification

- Hepatocytes have very high constitutive activity of the phase I enzymes that often convert xenobiotics to reactive electrophilic metabolites.
- hepatocytes have a rich collection of phase II enzymes that add a polar group to a molecule and thereby enhance its removal from the body
- The balance between phase I and phase II reactions determines whether a reactive metabolite will initiate liver cell injury or be safely detoxified.
- the susceptibility to potential hepatotoxicants can vary markedly between individuals because the expression of phase I and II enzymes and of the hepatic transporters can be influenced by:
  - ✓ genetics (e.g., polymorphism of drug-metabolizing enzymes)
  - ✓ lifestyle (e.g., diet, consumption of other drugs and alcohol)

### 3-REGENERATION:

- The liver has a high capacity to restore lost tissue and function by regeneration.
- Loss of hepatocytes due to hepatectomy or cell injury triggers the proliferation of all mature liver cells.
- Tissue repair is dose-responsive up to a threshold, after which the injury is too severe and cell proliferation is inhibited.
- Stimulation of repair by exposure to a moderate dose of a hepatotoxicant strongly attenuates tissue damage of a subsequent high dose of the same chemical.
- Inhibition of mitosis with colchicine prevented tissue repair and aggravated liver injury after hepatotoxicant.

## 4-inflammation & Immune Response

- The activation of resident macrophages (Kupffer cells), NK cells, and the migration of activated neutrophils, lymphocytes, and monocytes into regions of damaged liver is a well-recognized feature of hepatotoxicity produced by many chemicals.
- The main reason for an inflammatory response:
  - Remove dead and damaged cells.
  - Under certain circumstances, can aggravate the existing injury by release of directly cytotoxic mediators or formation of inflammatory mediators.

## 4-inflammation & Immune Response

Immune-mediated reactions may also lead to severe liver injury.

---

Drugs and chemicals that have been suggested to cause immune-mediated injury mechanisms in the liver include halothane, and dihydralazine.

A delay in onset of the injury or the requirement for repeated exposure to the drug and the formation of antibodies against drug-modified hepatic proteins are characteristic features of immune reactions.

## 5- Idiosyncratic Liver Injury:

- Idiosyncratic drug hepatotoxicity is a rare but potentially serious adverse event, which is not clearly dose-dependent, is at this point unpredictable, and affects only very few of the patients exposed to a drug or other chemicals.
- idiosyncratic toxicity is a leading cause of failure of drugs in clinical testing and it is the most frequent reason for posting warnings, restricting use, or even withdrawing the drug from the market.
- idiosyncratic hepatotoxicity is observed after consumption of herbal remedies and food supplements.
- Because idiosyncratic hepatotoxicity is a rare event for most drugs, it is likely that a combination of gene defects and adverse events need to be present simultaneously in an individual to trigger the severe liver injury.

---

To be continued in the next lecture

**THANK YOU**