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اسم المادة باللغة العربية: السموم العامة

اسم المادة باللغة الإنكليزية: **General toxicology**

المرحلة: الرابعة

التدريسي: م.د. محمد مالك عبدالرحمن

عنوان المحاضرة باللغة العربية: الاستجابات السامة للكبد (الجزء الثاني).

عنوان المحاضرة باللغة الإنكليزية: **Toxic Responses of the Liver (PartII)**

Toxic Responses of the Liver (PartII)

Tumors

Chemically induced neoplasia can involve tumors that are derived from hepatocytes, bile duct progenitor cells, the ductular "bipolar" progenitor cells, and the periductular stem cells. Hepatocellular cancer has been linked to chronic abuse of androgens, alcohol, and a high prevalence of aflatoxin-contaminated diets. In addition, viral hepatitis, metabolic diseases such as hemochromatosis and α1-antitrypsin deficiency, and NASH are major risk factors for hepatocellular carcinoma. The synergistic effect of coexposure to aflatoxin and hepatitis virus B is well recognized.

The malignant transformation of hepatocytes occurs as a result of increased cell turnover due to chronic liver injury, persistent inflammation, regeneration, and cirrhosis. Direct DNA binding of carcinogens or their reactive metabolites (eg, aflatoxin metabolites) or indirect DNA modifications by reactive oxygen species generated during inflammation and cell injury can lead to genetic alterations in hepatocytes resulting in impaired DNA repair, the activation of cellular oncogenes, and inactivation of tumor suppressor genes. An overall imbalance between stimulation of proliferation and inhibition of apoptosis in the liver leads to the survival and expansion of these preneoplastic cells. This concept is supported by the observation that 30% of hepatocellular carcinomas show mutations in the tumor suppressor gene p53; the mutation rate is up to 70% in areas with high aflatoxin exposure. The functional inactivation of p53 by mutations prevents the induction of apoptosis.

Critical Factors in Toxicant-Induced Liver Injury

Uptake and Concentration

Hepatic "first pass" uptake of ingested chemicals is facilitated by the location of the liver downstream of the portal blood flow from the gastrointestinal tract. Lipophilic compounds, particularly drugs and environmental pollutants, readily diffuse into hepatocytes because the fenestrated epithelium of the sinusoid enables close contact between circulating molecules and hepatocytes. Thus, the membrane-rich liver concentrates lipophilic compounds. Other toxins are rapidly extracted from blood because they are substrates for transporters located on the sinusoidal membrane of hepatocytes.

Phalloidin and microcystin are illustrative examples of hepatotoxins that target the liver as a consequence of extensive uptake into hepatocytes by sinusoidal transporters. Ingestion of the mushroom *Amanita phalloides* is a common cause of severe, acute hepatotoxicity in continental Europe and North America. Microcystin has produced numerous outbreaks of hepatotoxicity in sheep and cattle that drank pond water containing the blue-green alga *Microcystis aeruginosa.*

Because of its dual blood supply from both the portal vein and the hepatic artery, the liver is presented with appreciable amounts of all toxicants in the systemic circulation. Vitamin

A hepatotoxicity initially affects stellate cells, which actively extract and store this vitamin. Cadmium hepatotoxicity becomes manifest when the cells exceed their capacity to sequester cadmium as a complex with the metal-binding protein, metallothionein (MT). Iron poisoning produces severe liver damage. Hepatocytes contribute to the homeostasis of iron by extracting this essential metal from the sinusoid by a receptor-mediated process and maintaining a reserve of iron within the storage protein ferritin. Acute Fe toxicity is most commonly observed in young children who accidentally ingest iron tablets. The cytotoxicity of free iron is attributed to its function as an electron donor for the Fenton reaction, where hydrogen peroxide is reductively cleaved to the highly reactive hydroxyl radical, an initiator of lipid peroxidation. Accumulation of excess iron beyond the capacity for its safe storage in ferritin is initially evident in the zone 1 hepatocytes, which are closest to the blood entering the sinusoid.

Bioactivation and Detoxification

One of the vital functions of the liver is to eliminate exogenous chemicals and endogenous intermediates. Therefore, hepatocytes contain high levels of phase I enzymes, which have the capacity to generate reactive electrophilic metabolites. Hepatocytes also have a wide variety of phase II enzymes, which enhance the hydrophilicity by adding polar groups to lipophilic compounds and target these conjugates to certain carriers in the canalicular or plasma membrane for excretion. Generally, phase II reactions yield stable, non-reactive metabolites. Although electrophiles may be effectively conjugated and excreted, if the intermediate is highly reactive, some of these compounds can react with proteins and other target molecules before an interaction with a phase II enzyme is possible. In contrast, if the amount of the reactive metabolite exceeds the capacity of the hepatocyte to detoxify it, covalent binding to cellular macromolecules will occur and potentially result in cell injury. Thus, the balance between phase I reactions, which generate the electrophile, and conjugating phase II reactions determines whether a reactive intermediate is safely detoxified or may cause cell dysfunction or injury.

Regeneration

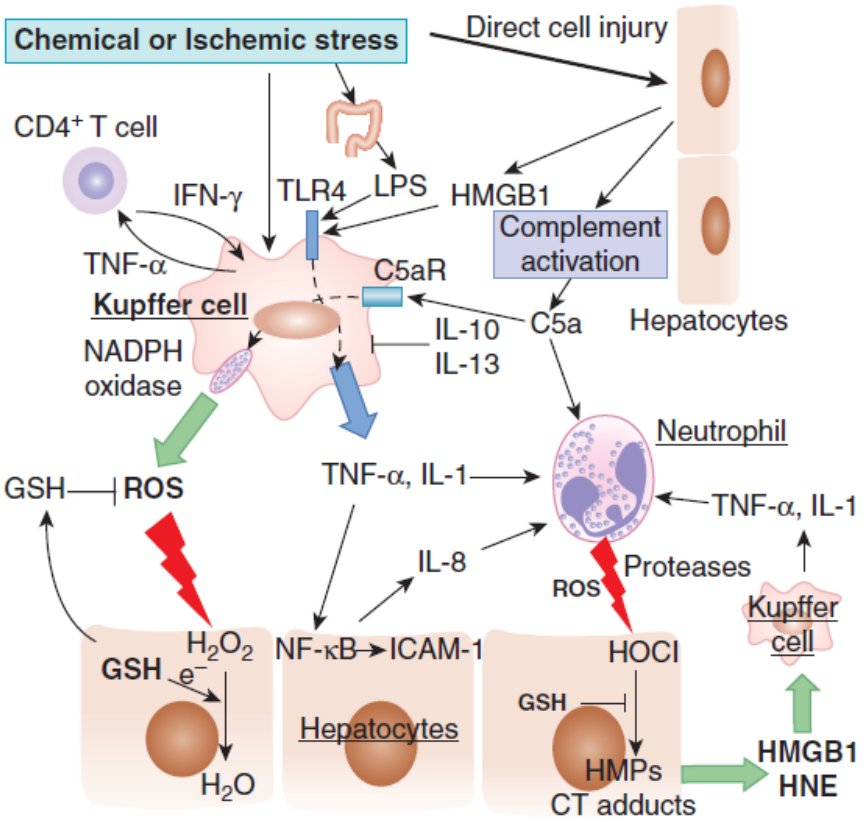
The liver has a high capacity to restore lost tissue and function by regeneration. Loss of hepatocytes due to hepatectomy or cell injury triggers proliferation of all mature liver cells. This process is capable of restoring the original liver mass. Hepatocytes are normally quiescent, that is, they are in G0 phase of the cell cycle. In order to proliferate, they need to enter the cell cycle. The process is initiated by cytokines (TNF-α, IL-6), which prime hepatocytes to respond to essential growth factors such as HGF and TGF-α. Both cytokines and growth factors are involved in the activation of transcription factors and ultimately expression of cell cycle-regulating proteins. 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 (autoprotection) or a different hepatotoxin (heteroprotection). In addition to the dose of the hepatotoxicant, other factors such as age, nutritional status, and disease state may influence tissue repair.

Inflammation

The activation of resident macrophages (Kupffer cells), NK and NKT cells, and the migration of activated neutrophils, lymphocytes, and monocytes into regions of damaged liver is a well-recognized feature of the hepatotoxicity produced by many chemicals. The main reason for an inflammatory response is to remove dead and damaged cells. However, under certain circumstances, these inflammatory cells can aggravate the existing injury by release of directly cytotoxic mediators or by formation of pro and anti- inflammatory mediators (Figure 1).

Figure 1: Self-perpetuating inflammatory response after chemical or ischemic stress. *C5aR, C5a complement receptor; CT, chlorotyrosine protein adducts; GSH, reduced glutathione; HMGB1, high-mobility group box-1; HMPs, hypochlorous acid modifi ed proteins; HNE, hydroxynonenal; HOCl, hypochlorous acid; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL-1, interleukin-1, LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; TLR4, toll-like receptor-4; TNF, tumor necrosis factor.*

Kupffer cells and neutrophils are potent phagocytes, which have a vital function in host defense and removal of cell debris. Formation of reactive oxygen species by NADPH oxidase is a critical tool for these cells. Upon activation, Kupffer cells generate mainly



hydrogen peroxide, which can diffuse into neighboring liver cells and create an intracellular oxidant stress leading to cellular stress and injury. Kupffer cells can be activated by bacterial products, opsonized particles, and activated complement factors to cause oxidant stress and cell injury.

Recent evidence suggests that not only bacterial products but also intracellular proteins, for example, HMGB-1, which are released during necrotic cell death, can bind to toll-like receptors on Kupffer cells and trigger cytokine and chemokine formation. However, Kupffer cells can also generate anti-inflammatory mediators such as prostaglandin E2 and interleukin-10, which down regulate formation of proinflammatory cytokines and attenuate toxin-induced liver injury. Thus, Kupffer cells can promote or inhibit an injury process and assist in removal of cell debris and apoptotic bodies. Neutrophils are activated and accumulate in the liver vasculature in response to extensive cell injury or bacterial infection (Fig. 1). The main purpose of hepatic neutrophil recruitment is to remove bacteria and cell debris, at least in part through interactions with the resident macrophages. Neutrophils generate the aggressive oxidant and chlorinating species hypochlorous acid through NADPH oxidase and myeloperoxidase. In addition, neutrophils can release a large number of proteolytic enzymes and bacteriocidal proteins.

Immune Responses

In addition to the activation of an inflammatory 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, tienilic acid, 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. However, the mechanisms of these immune-mediated liver injuries are not well understood. The *hapten hypothesis* assumes that a reactive metabolite covalently binds to cellular proteins and the drug-modified protein is taken up by APCs, cleaved to peptide fragments, which are then presented within the major histocompatibility complex (MHC) to T cells. In support of the hapten hypothesis, antibodies against drug-modified proteins were detected in the serum of patients with halothane hepatitis or with liver injury caused by ethanol, tienilic acid, and dihydralazine. *[An antigen-presenting cell (APC) or accessory cell is a cell that displays foreign antigens complexed with major histocompatibility complexes (MHCs) on their surfaces; this process is known as antigen presentation. T-cells may recognize these complexes using their T-cell receptors (TCRs).]*

Idiosyncratic Liver Injury

Idiosyncratic drug hepatoxicity 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. There are no known mechanisms of cell injury specific for idiosyncratic hepatotoxins.

There are no known mechanisms of cell injury specific for idiosyncratic hepatotoxins. A number of drugs including halothane (anesthetic), nitrofurantoin (antibiotic), and phenytoin (anticonvulsant) are thought to cause injury mainly by immune (allergic) mechanisms.

Other drugs like: isoniazid (antituberculosis), disulfiram (alcoholism), valproic acid (anticonvulsant), or troglitazone (antidiabetic), are considered nonimmune (nonallergic) idiosyncratic hepatotoxins. The antidiabetic drug troglitazone (RezulinR) was withdrawn from the market due to idiosyncratic hepatotoxicity. In preclinical studies, troglitazone did not cause any relevant liver toxicity and despite extensive investigations since withdrawal of the drug, the mechanism of toxicity remains unclear. Several studies suggest that very high concentrations of troglitazone can induce mitochondrial dysfunction in vitro.

Examples of Drugs with Known Idiosyncratic Hepatotoxicity

A. *Immune-mediated (allergic) idiosyncratic hepatotoxicity*
- Diclofenac (analgesic)
- Halothane (anesthetic)
- Nitrofurantoin (antibiotic)
- Phenytoin (anticonvulsant)
- Tienilic acid (diuretic)

B. *Nonimmune-mediated (nonallergic) idiosyncratic hepatotoxicity*
- Amiodarone (antiarrhythmic)
- Bromfenac (analgesic)—withdrawn from market
- Diclofenac (analgesic)
- Disulfiram (alcoholism)
- Isoniazid (antituberculosis)
- Ketoconazole (antifungal)
- Rifampicin (antimicrobial)
- Troglitazone (antidiabetes)—withdrawn from market
- Valproate (anticonvulsant)