Editorial

Environmental toxicants impact on liver physiology and function

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Abbreviations: GI, gastrointestinal; MC-LR, microcystin-leucine arginine, CCl4, carbon tetrachloride; HCC, hepatocellular carcinoma; AFBO, radical AFB1-exo-8,9-epoxide; TNF-α, tumor necrosis factor alpha

Editorial

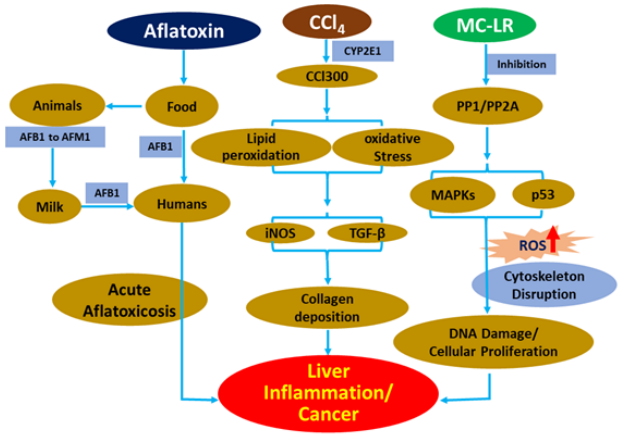
The liver is the primary site of contact for different types of orally consumed therapeutic drugs, biologicals and chemicals, and various other xenobiotics from intestinal absorption, hence making this organ extremely susceptible to injury. The susceptibility of toxic exposure to these chemicals most often results from the absorption through the gastrointestinal (GI) tract once the drugs are ingested orally. Exposure to these environmental toxicants is an inevitable fallout from the fast-growing industrialization all over the world and is particularly higher in developing countries.[1] We present the three critical environmental chemico-biological toxicants that have emerged as serious hepatotoxins.

Microcystins have extensively been evaluated for liver toxicity and it has been reported that microcystins lead to toxicity in the vertebrate liver cells through a highly evident unspecific organic anion transporter (bile acid-carrier transport system). About hundred different isoforms of microcystin have been uncovered so far, and microcystin-leucine arginine (MC-LR) has been revealed to be the most abundant and also the most extreme toxic variant among all microcystins. The MC-LR induced toxicity in the liver has been reported to cause necrosis, cytoskeletal impairment, and also leads to an increase in liver weight, the pooling of blood and also blebbing of the hepatocytes.[2] In mammals, MC-LR toxicity is often due to the microcystins significant binding to the key cellular enzymes-protein phosphatases (PP1 and PP2A) and it has been put forward that they are the prominent tumor promoters both *in-vivo* and *in-vitro*. The primary passage of human contact with liver toxicant, MC-LR is due to the consumption of infested drinking water, which may be because of the combination of acute and chronic exposure to either very low or higher doses.[3] Once an organism or a cell is exposed to MC-LR, it is transported into the hepatocytes through an organic anion transporting polypeptides-OATP1B1 and OATP1B3. In hepatocytes, both the acute as well as chronic exposure can obstruct PP-1 and PP-2A. In case of acute exposure, MC-LR can cause damage to the DNA-viz directly or indirectly via mutagenesis or through ROS generation.[4]. The inhibition of phosphatases-PP-2A and PP-1 hinders the NF-κB and NF-AT factors that can alter the target genes, including the p53 tumor suppressor gene.[2] MC-LR induces formation of ROS and causes the release of $Ca2^{+}$ which activates a number of Caspases followed by cytoskeletal damage resulting in the induction of apoptosis. Inside the membrane of hepatocytes, MC-LR influences ceramide production and causes release of the mitochondrial cytochrome C and results in apoptosis.[5]

Carbon tetrachloride (CCl_4) is another environmental hepatotoxin that is culpable for various pathophysiological alterations in the liver. CCl_4 is readily absorbed from the GI tract and the lungs. CCl_4 is significantly metabolized in the microsomal membranes of cells to a profoundly toxic trichloromethyl radical (CCl_3) and free radicals.[6] This initiates lipid peroxidation which binds as well as impairs the cellular enzymes- cytochrome P450, proteins and lipids in multiple cell membranes, particularly the hepatic endoplasmic reticulum.[7] The hepatic damage, in this case, is prominently illustrated by extension and tenderness as well as an increased level of the circulating hepatic enzymes most significantly the serum glutamic oxaloacetic transaminase which may cause death even within a few days to a few weeks after the ingestion. CCl_4 also catabolizes the radical induced lipid peroxidation which may damage the membrane of the liver cells as well as organelles and lead to the swelling and necrosis of the hepatocytes.[8] An acute intake of CCl_4 may lead to centrizonal necrosis, and steatosis-on the other hand, the continuous administration of CCl_4 may ultimately lead to liver fibrosis, cirrhosis, or even hepatocellular carcinoma (HCC). Humans are exposed to CCl_4 preferably through intake of water and other fluids and by inhalation or through ingestion of different foodstuffs contaminated with CCl_4.[9] Administration of CCl_4 induces expression of the pro-inflammatory cytokines viz tumor necrosis factor alpha (TNF-α) and the interleukin-1 beta (IL-1β), which significantly arbitrates apoptosis, inflammation, and fibrosis. Moreover, CCl_4 also leads to the activation of the transforming growth factors (TGF-α and TGF-β) and iNOS which ultimately lead to liver fibrosis.[10]

Amongst other environmental toxicant aflatoxins are the group of mycotoxins produced by the fungus *Aspergillus,* which are considered to be the potent hepatotoxins of the liver. Aflatoxins are mostly found in foodstuffs that are adulterated with the aflatoxin-producing fungus *Aspergillus* or found in dairy products, especially from animals that are fed with the contaminated feed. The most commonly found aflatoxin is the aflatoxin B1 and its major metabolite i.e., aflatoxin M1 was first discovered in milk. AFB1 can induce mutations in genomic DNA, and it can lead to neoplastic transformations through the deregulation of epigenetic conditions.[11] The toxic effects of AFB1 on the liver are closely associated with its metabolic activation to the free radical AFB1-exo-8,9-epoxide (AFBO) through the involvement of the cytochrome P-450 enzymes.[12] It is further associated with the

formation of ROS, especially the hydroxyl radical (HO.), the per hydroxyl radical (HOO^-), and also the superoxide anion.[13] This whole process can further cause oxidative stress due to the contrast between minimal antioxidant defence and the generation of uncontrolled ROS. This process results in harmful effects on biological macromolecules. Exposure of aflatoxins to humans result in acute toxicity called as aflatoxicosis, which is rarely found in developed nations and is more prominent in African and Asian countries. The most common and key symptoms of aflatoxicosis comprise hemorrhagic necrosis of the liver, lethargy, and edema.[14] Furthermore, ingestion of higher quantities of aflatoxin is linked to aflatoxicosis and therefore increased incidence of liver cirrhosis. In addition, sublethal chronic exposure of aflatoxin results in altered immune function as well as compromised nutritional absorption. However, both acute and the chronic exposure of aflatoxin



is significantly associated with the development of HCC (Figure 1).[15]

Figure 1 A comprehensive summary of the impact of Microcystin, Carbon tetrachloride and Aflatoxin on liver diseases and cancer.

Conclusion

In conclusion, environmental toxicants microcystins, CCl_4 and aflatoxins are growing problems that have increased alarmingly and pose a threat all over the globe. In the past decade or so, multiple studies have evaluated the effects of these potential environmental chemicals, and pollutants on liver health and significantly explored their functional aspects in relation to the occurrence and progression of hepatocellular carcinoma. The constant exposure to these environmental toxicants may acts as a potential modifier of the HCC progression as well as in development of several pathological complications in the liver. Further expanded and comprehensive studies on these environmental agents and their associated mechanisms of operation are needed to be explored for an improved understanding of their functions in liver pathology. This will ultimately help in developing new profound intervention strategies to limit their exposure effects on the liver.

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Conflicts of interest

We declare there are no conflicts of interest.

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