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Mechanisms of alcohol-induced hepatocellular carcinoma

Sreetha Sidharthan · Shyam Kottilil

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Abstract Chronic alcohol abuse is a major risk factor for hepatocellular carcinoma (HCC), the third leading cause of cancer deaths worldwide. Alcohol can also function synergistically with other risk factors to cause HCC. Hence, alcohol consumption is a major factor affecting hepatic carcinogenesis in millions and the cause of a substantial public health burden. Chronic alcohol consumption interferes with several host anti-tumor mechanisms, thereby facilitating hepatocyte proliferation and tumorigenesis. This review summarizes the major mechanisms of alcohol-induced HCC. These include pathways of ethanol metabolism, alcohol-induced oxidative stress and hypomethylation of DNA, and interplay of alcohol with iron elevation, retinoid metabolism, the immune system, inflammatory pathways, and neoangiogenesis. The relevance of each pathway in affecting HCC transformation is a topic of intense investigation. Ongoing research will enhance our insight into the alcohol-induced occurrence of HCC and offer hope in developing better therapeutics.

Keywords Alcohol · HCC · Carcinogenesis

S. Sidharthan
Critical Care Medicine Department, Department of Health and Human Services, Clinical Center, National Institutes of Health, Bethesda, MD, USA

S. Kottilil (✉)
Laboratory of Immunoregulation, Department of Health and Human Services, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bldg10, Rm.11N204, Bethesda, MD 20892, USA
e-mail: skottilil@niaid.nih.gov

Introduction

Primary liver cancer is the fifth most common cancer worldwide and the third leading cause of cancer mortality [1]. More than 80 % of primary liver tumors are hepatocellular carcinomas (HCC) [2]. There are several established risk factors for HCC with distinct geographical patterns of incidence (Table 1) [3–5]. Interestingly, the highest attributable risk for HCC in the US and Europe is heavy alcohol intake [6, 7]. Alcohol consumption is common in the western world and rising in Asia, suggesting it will continue to be a prevalent cause of HCC [8]. In fact, epidemiological studies reveal that consumption of >80 g of alcohol/day for 10 years is an independent risk factor [9]. Data also suggest that alcohol can function synergistically with viral hepatitis and other risk factors to induce HCC [10, 11].This review focuses on nine molecular mechanisms associated with alcohol-induced carcinogenesis (Table 2; Fig. 1).

Acetaldehyde-mediated pathways

In hepatocytes, ethanol is metabolized to acetaldehyde by both alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1). Acetaldehyde is a toxic compound with direct mutagenic and carcinogenic effects in vivo and in vitro [12–14]. During moderate alcohol intake, acetaldehyde is metabolized to acetate by aldehyde dehydrogenase (ALDH). However, chronic alcohol abuse leads to induction of CYP2E1 and high levels of acetaldehyde production [15].

Acetaldehyde can form DNA adducts, for example N^2-ethyl-2′-deoxyguanosine (N^2-Et-dG) and N^2-propano-2′-deoxyguanosine (PdG) which alter the integrity of hepatocyte DNA [16]. PdG, in particular, is capable of initiating

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Table 1 Risk factors associated with HCC

Demographics	Age >50, male gender, Asian ethnicity
Infections	Hepatitis B and C viruses
Underlying diseases	Cirrhosis, obesity, type II diabetes mellitus, hemochromatosis
Toxins	Aflatoxins
Habits	Tobacco use, alcohol use
Drugs	Oral contraceptive use

Table 2 Mechanisms of alcohol-induced HCC

Mechanisms	Mediators
Acetaldehyde formation	↑N^2-propano-2′-deoxyguanosine, ↑N^2-ethyl-2′-deoxyguanosine, ↑O^6-methylguanosyl transferase adduct
Cytochrome P4502E1 induction	↑Reactive oxygen species
Reduced antioxidants	↓Glutathione
Hypomethylation	↓S-adenosylmethionine
Iron overload	↑Iron uptake, ↑reactive oxygen species
Reduced retinoic acid	↑Activated protein 1 (c-jun, c-phos)
Immune surveillance	↓Natural killer cells, toll-like receptor 4, Nanog
Neoangiogenesis	↑Vasoconstriction, portal pressure
Inflammation	↑Lipopolysaccharides, ↑transforming growth factor-β, ↑interleukin 6, ↑tumor necrosis factor-α

replication errors [17]. Acetaldehyde can also form stable adducts with proteins, thereby altering protein structure and function. For example, adducts formed with O^6-methylguanosyl transferase impair DNA repair mechanisms and could mediate carcinogenesis [18]. In addition, acetaldehyde damages mitochondria, resulting in inhibition of fatty acid oxidation [19]. Acetaldehyde stimulates collagen synthesis in hepatic stellate cells, an important step toward cirrhosis [20] and the eventual development of HCC.

Induction of CYP2E1 and reactive oxygen species generation

Chronic consumption of alcohol results in a 10–20 fold induction of CYP2E1. This cytochrome is involved in the activation of a variety of procarcinogens, for example aflatoxins, nitrosamines, and polycyclic hydrocarbons, to carcinogens. Induction of CYP2E1 by ethanol is also associated with the generation of hydroxyethyl radicals (HER), which bind to carcinogens, forming neoantigens [21] and leading to lipid peroxidation [22]. Studies report lower levels of oxidized DNA products in the blood of CYP2E1 knock-out mice compared with wild-type mice [23], and profound hepatic injury has been observed in CYP2E1 transgenic mice [24]. In humans, induction of CYP2E1 after ethanol ingestion results in increased levels of reactive oxygen species (ROS), lipid peroxidation, malondialdehyde (MDA), and 4-hydroxynonenol (4-HNE) [25]. Of these, 4-HNE has been shown to result in mutations at codon 249 of p53 tumor suppressor gene, blocking apoptosis of cells and affording them proliferative advantage [26]. Together, these products lead to the formation of DNA adducts with mutagenic potential that promote hepatic carcinogenesis.

Effects on antioxidant defense mechanisms

The augmented generation of ROS as a by-product of alcohol metabolism results in an increased requirement for antioxidants glutathione and α-tocopherol. In this regard, alcohol consumption has been shown to reduce hepatic glutathione concentrations [27], resulting in significant mitochondrial dysfunction and lipid peroxidation [27]. Alcohol also results in a reduction of α-tocopherol levels [28], and superoxide dismutase, catalase, and glutathione reductase activity [29], leading to enhanced lipid peroxidation and hepatic injury [30]. Together, these changes over time result in impaired DNA repair mechanisms and hepatic carcinogenesis [18].

Hypomethylation and DNA stability

DNA methylation is an important epigenetic factor controlling gene expression, in which hypomethylation is associated with increased gene expression. In alcohol-induced cirrhosis, reduced levels of the methyl group donor *S*-adenosylmethionine (SAMe) and increased levels of *S*-adenosylhomocysteine (SAH) result in a decrease in the SAMe/SAH ratio by a factor of 2.5 [31]. In rats, diet-induced SAMe deficiency leads to hypomethylation of oncogenes and DNA strand breaks, factors promoting carcinogenesis [32]. Further research is necessary to elucidate the effects of altered DNA methylation on HCC in humans.

Effects of iron overload

Lauret et al. [33] showed that HCC patients with alcohol-induced cirrhosis had a greater frequency (20.9 %) of heterozygosity for the hemochromatosis gene (C282Y allele) than did patients with alcohol-induced cirrhosis without

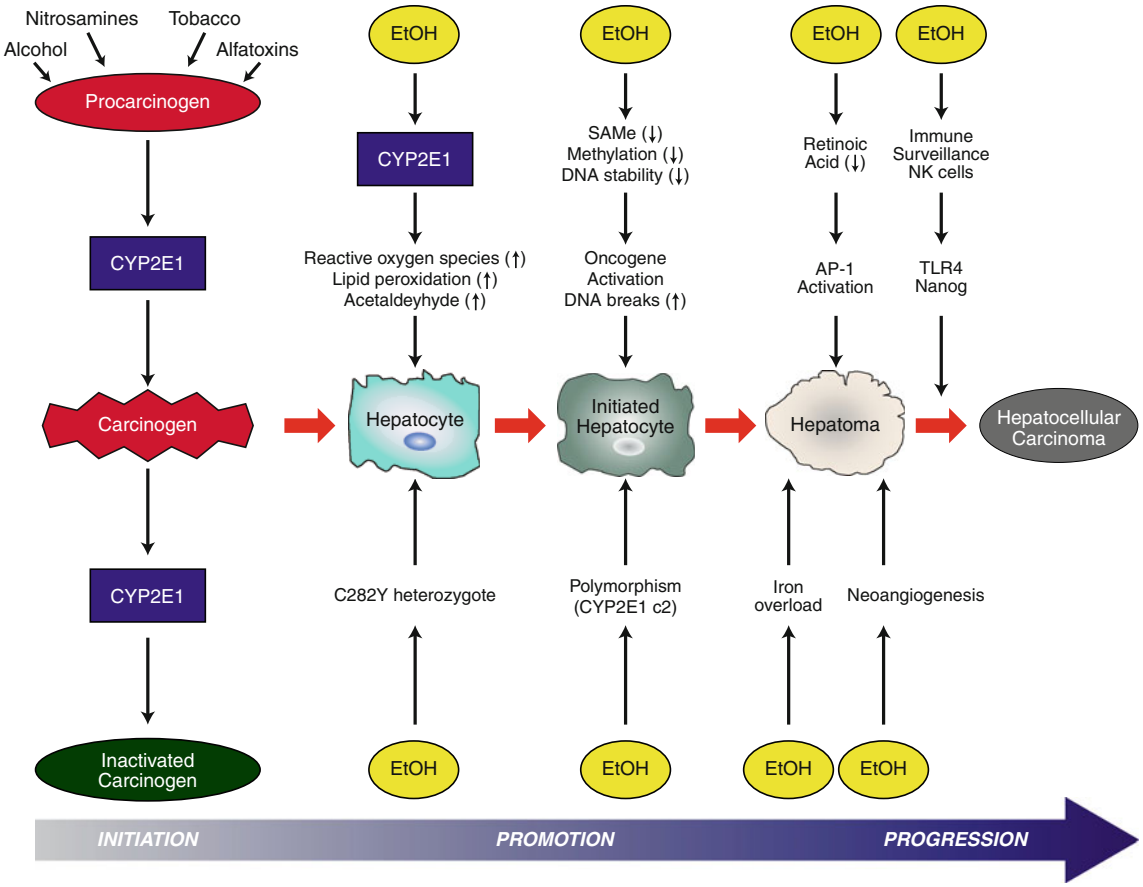

Fig. 1 Interactions between alcohol-induced mechanisms leading to hepatic carcinogenesis. Alcohol mediates several mechanisms of hepatocyte proliferation and carcinogenesis. These include pathways of ethanol metabolism, which generate acetaldehyde and induction of CYP2E1, both of which promote generation of reactive oxygen species, lipid peroxidation, and DNA strand breaks. Alcohol leads to hypomethylation of DNA and also harms the retinoic acid pathway; both of these promote oncogene activation and induce carcinogenesis. Several host factors, for example gene polymorphisms (C282Y heterozygosity and CYP2E1 c2) lead to enhanced incidence of carcinogenesis. Iron overload and neoangiogenesis are both associated with alcoholic liver disease and HCC. Finally, the immune system is of major importance, with NK cells having a protective effect and TLR4/Nanog promoting the alcohol-induced occurrence of HCC

HCC (4.4 %). Heterozygosity for C282Y leads to slightly higher iron levels, which may be important during heavy alcohol consumption. Notably, chronic alcohol abuse increases intestinal iron absorption and hepatic iron stores The higher risk of HCC associated with increased iron stores can possibly be attributed to the generation of ROS from free iron, which can occur directly through the Fenton reaction or indirectly through induction of lipid peroxidation [34]. Increased iron stores can cause DNA strand breaks, p53 mutation, and DNA adducts, factors that promote HCC [35]. Thus, this overload of iron deposition due to alcohol consumption is a likely factor in the development of HCC.

Interference with retinoid metabolism

Retinoic acid (RA), which is synthesized from retinol, has many effects on cell growth and differentiation [36]. Chronic alcohol consumption is associated with reduced serum and hepatic vitamin A levels [37] and with increased mobilization of retinol from the liver to other tissues [38]. Ethanol is a competitive inhibitor of hepatic retinol oxidation, reducing RA production [39]. Furthermore, ethanol-induced enhancement of CYP2E1 results in an increase in RA catabolism and a subsequent decline in RA levels in the liver [40]. Finally, ethanol exposure results in functional down-regulation of RA receptors and a subsequent increase in activator protein-1 or AP-1 (c-fos and c-jun) transcriptional complex [39]. Together, these changes favor hepatic proliferation and carcinogenesis [40].

Immunological mechanism of alcohol-induced carcinogenesis

Several studies have revealed the pivotal importance of natural killer (NK) cells in immune surveillance of tumors

[41] in animal models. NK cell number and lytic function are substantially reduced in cirrhotics [42], particularly those with a history of alcohol use [43]. Consequently, diminished NK cell function is likely to be important in the development of progressive liver fibrosis and HCC.

Increased incidence of HCC has been observed among HCV core transgenic mice fed with ethanol [44]. A recent study showed that NS5A transgenic mice fed with ethanol developed alcoholic steatohepatitis [45]. However, the same effect was not observed for NS5A Tg mice deficient in TLR4, suggesting the involvement of TLR4 in mediating the effects of alcohol and NS5A [45]. NS5A Tg mice fed an alcohol diet developed HCC, in contrast with wild-type or NS5A TLR4 −/− mice [45]. Interestingly, these NS5A Tg mice fed ethanol expressed increasing amounts of Nanog, a stem cell marker. No induction of Nanog was observed in mice of TLR4 −/− background. Collectively, these results suggest the crucial involvement of Nanog in induction of HCC mediated by alcohol, dependent on TLR4 signaling. Finally, transplantation of p53-deficient hepatic stem cells transfected with either Nanog or TLR4 resulted in HCC, which was abrogated by simultaneous expression of short hairpin RNA against Nanog. These results, also, suggest crucial involvement of Nanog in mediating tumorigenesis.

Neoangiogenesis

Hepatic foci are monoclonal lesions in the liver characterized by high rates of proliferation, changes in cell morphology, and reduced hepatocyte function. Neoangiogenesis seems to be necessary for progression of hepatic foci to HCC, a highly vascular tumor [46]. Although little is known about the direct affects of alcohol on neoangiogenesis, animal models show that ethanol leads to impaired endothelin and nitric oxide signaling, resulting in increased vasoconstriction and hepatic portal pressure [47, 48]. These alcohol-induced changes in microcirculation around transformed cells may be involved in initiation or maintenance of neoangiogenesis in hepatic foci. However, the involvement of ethanol in neoangiogenesis in HCC occurrence and/or progression warrants more detailed evaluation.

Inflammation

Ethanol consumption has systemic and intrahepatic effects that may affect HCC development. Heavy alcohol intake increases gut permeability to lipopolysaccharides (LPS) [49] increasing intrahepatic LPS levels. LPS binds to the CD14/TLR4 complex of Kupffer cells (KC), leading to release of pro-inflammatory cytokines, particularly tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) [50]. Intestinal sterilization of Gram-negative bacteria with antibiotics prevented ethanol-induced liver injury [51]. CD14/TLR4 knockout mice are also resistant to alcohol toxicity, indicating the importance of KCs to the pathogenesis of ethanol-related hepatic injury [52].

Interleukin 6 (IL-6) secreted by KCs is elevated in alcoholic patients with liver disease [53]. IL-6 promotes carcinogenesis by inhibiting hOGG1, a repair enzyme for 8-oxoguanosine adducts [54], and interfering with DNA repair. IL-6 upregulates mcl-1, an anti-apoptotic gene [55]. Further research is necessary to elucidate the extent of its importance to HCC development.

Conclusions

Chronic alcohol consumption is an important risk factor for HCC and hence a major public health burden. The mechanisms involved in alcohol-induced hepatic carcinogenesis are multifold and complex (Fig. 1). Alcohol use can directly induce hepatic carcinogenesis and enhance the possibility of occurrence of HCC in those with viral hepatitis. Further research on understanding the involvement of ethanol metabolism in carcinogenesis and identifying susceptible individuals is vital to reducing the morbidity and mortality associated with chronic liver disease and HCC.

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Conflict of interest Sreetha Sidharthan and Shyam Kottilil have no conflicts of interest to report.

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