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GUIDELINES FOR BASIC SCIENCE

Interactions of chemical carcinogens and genetic variation in hepatocellular carcinoma

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Abstract

In the etiology of hepatocellular carcinoma (HCC), in addition to hepatitis B virus and hepatitis C virus infections, chemical carcinogens also play important roles. For example, aflatoxin B_1 (AFB_1) epoxide reacts with guanine in DNA and can lead to genetic changes. In HCC, the tumor suppressor gene *p53* codon 249 mutation is associated with AFB_1 exposure and mutations in the *K-ras* oncogene are related to vinyl chloride exposure. Numerous genetic alterations accumulate during the process of hepatocarcinogenesis. Chemical carcinogen DNA-adduct formation is the basis for these genetic changes and also a molecular marker which reflects exposure level and biological effects. Metabolism of chemical carcinogens, including their activation and detoxification, also plays a key role in chemical hepatocarcinogenesis. Cytochrome p450 enzymes, *N*-acetyltransferases and glutathione *S*-transferases are involved in activating and detoxifying chemical carcinogens. These enzymes are polymorphic and genetic variation influences biological response to chemical carcinogens. This genetic variation has been postulated to influence the variability in risk for HCC observed both within and across populations. Ongoing studies seek to fully understand the mechanisms by which genetic variation in response to chemical carcinogens impacts on HCC risk.

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Key words: Hepatocellular carcinoma; Chemical carcinogens; Aflatoxin B_1; Polycyclic aromatic hydrocarbons; 4-aminobiphenyl; Hepatitis B virus; Hepatitis C virus; Glutathione *S*-transferase; Cytochrome p450 enzymes; Genetic variation

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and rapidly fatal malignancies. Worldwide, more than a half million new cases of HCC are reported each year and most patients die within 1 year of diagnosis[1,2]. Although HCC has marked demographic and geographic variations, occurring mainly in East Asia and sub-Saharan Africa[1], it is also increasing in western developed countries such as the United States[3]. Previous studies indicated that hepatocarcinogenesis is a long-term, multistage process with the involvement of multiple risk factors[4]. The major risk factors include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and chemical exposures[5,6]. In specific geographic regions, such as Qidong, China, 40% of HCC can be attributed to exposure to a single chemical carcinogen, aflatoxin B_1 (AFB_1)[7].

This paper focuses on some representative chemical carcinogens that cause HCC and summarizes advances in our understanding of the correlation between chemical carcinogens and genetic alterations in the development of HCC. There are other exposures which have also been reported to be related with HCC occurrence in animals or for which the correlation between exposure and HCC is not clear. These compounds are not included in this paper.

DAMAGE TO DNA AND INDUCTION OF MUTATIONS OR OTHER GENETIC CHANGES

Aflatoxin

Aflatoxins are carcinogenic in several animal species but with variable potency[4]. AFB_1 is a human hepatocarcinogen and is also a liver carcinogen when fed to certain rodent species[8-10]. It is a secondary metabolite produced by *Aspergillus flavus* and *Aspergillus parasiticus* that occurs in tropical and subtropical regions of the world. It contaminates foods such as corn, rice and peanuts that are stored under tropical conditions[11]. Metabolic studies of AFB_1 have shown that its active form, AFB_1-8, 9-epoxide, is highly mutagenic and carcinogenic for the liver in rats and other experimental animals, with mutagenicity correlating with carcinogenicity[12,13]. AFB_1 has also been implicated by epidemiological studies as a causative factor for HCC in humans[14]. The clinical appearance of cancer is the end result of a long chain of cellular and molecular changes and there is substantial evidence that damage to DNA by environmental chemical carcinogens is critical in this process.

AFB_1 covalently binds to guanine and cytosine residues of DNA both *in vivo* and *in vitro*[15,16] and forms AFB_1-DNA adducts; it also forms RNA and protein adducts impairing DNA, RNA and ultimately protein synthesis[17-19]. AFB_1-DNA adducts were detected by an immunohistochemical assay in smeared HCC tissues and HCC sections[20-22]. The presence of AFB_1-DNA adducts can contribute to genetic alterations in loci involved in the development of HCC. In 1977, Lin *et al*[23] reported that adduct formation by metabolically activated reactive intermediates with hepatocyte DNA could lead to mutations in the host genome. The *p53* tumor suppressor gene is the most frequently mutated gene in human cancers. Two groups found at same time, that mutations of the *p53* gene on chromosome 17 are frequent in HCC and a point mutation at the third position of codon 249 resulting in a G:C to T:A transversion was common in HCC tissues which were collected in China and Africa[24,25]. This hotspot mutation in HCC from regions with high levels of dietary aflatoxins links this genetic change to exposure to aflatoxins. Similar results were confirmed in Taiwan HCC samples[22]. Early epidemiologic studies suggested a synergistic effect of AFB_1 and HBV infection on HCC risk[26,27] but in our latest study in a larger sample size than both prior studies, the effect was additive[28]. The highly aberrant patterns of genetic changes detected in different areas are suggestive of the genotoxic effects of aflatoxin. The combined effects of HBV and high aflatoxin exposure could promote HCC development[22,29]. *In vitro* studies exposing human liver cell lines to AFB_1 found the same codon 249 mutational pattern on *p53*[30,31]. In recent years, the *p53* codon 249 mutation has also been detected in plasma or serum DNA of HCC patients[32-34]. This mutated DNA may serve as a biomarker of exposure to AFB_1 and for detection of early HCC[33].

The molecular mechanisms underlying the carcinogenic effects of AFB_1 have also been investigated in rodent models. AFB_1-induced HCC in Fischer 344 rats showed activating mutations in codon 12 of *K-ras*[35], but in human HCC, the incidence of point mutation of *K-ras* and *N-ras* oncogenes was low[36]. In an *in vitro* study, AFB_1 interfered with the molecular mechanisms of cell cycle regulation[37]. AFB_1 also induced mitotic recombination[38], and minisatellite rearrangements[39]. Mitotic recombination and genetic instability may therefore be alternative mechanisms by which aflatoxin contributes to genetic alterations in HCC[40].

Vinyl chloride (VC)

VC is a major industrial chemical, a wide-spread environmental contaminant and a known animal and human carcinogen[41]. VC is a colorless toxic gas extensively used in the plastic industry. It is absorbed after respiratory exposure and is activated primarily in hepatocytes by the enzyme cytochrome P450 (CYP2E1). Its metabolites can react with DNA bases to form DNA adducts[42]. After metabolic activation, VC induces several DNA adducts and various studies have shown that these DNA adducts are responsible for specific mutations[43]. VC is a multipotential carcinogen in animals[9,43].

In humans, a causal relationship has been found between occupational exposure to VC and angiosarcoma of the liver[44,45]. In 1983, Evans *et al*[45] reported two cases of HCC among VC workers. Afterwards, in HCC in workers exposed to VC, a high prevalence of *K-ras*-2 mutation was reported[46,47]. The *p53* mutation pattern in HCC in workers exposed to VC includes point mutations in codons 175, 245, 248, 273 and 282 but it is still unclear whether these genetic changes are directly associated with exposure to VC[48]. However, another study concluded that in humans, A:T base pair mutations in *p53* induced by VC represent a specific mutational "signature"[43].

Polycyclic aromatic hydrocarbons (PAHs) and 4-aminobiphenyl (4-ABP)

Cigarette smoking is associated with a significantly increased HCC risk in several epidemiologic studies in Taiwan[49], China[50] and Japan[51]. Chemical carcinogens in tobacco smoke include polycyclic aromatic hydrocarbons such as benzo(a)pyrene [B(a)P], N-nitrosamines and aromatic amines such as 4-aminobiphenyl. PAHs are

ubiquitous environmental pollutants produced during all types of combustions of organic materials. Thus, they are found not only in cigarette smoke but also in polluted air, smoked and charbroiled foods, as well as contaminating fats and grains[52]. PAHs, especially B(a)P are known animal and human carcinogens[53]. In male infant mice, exposure to either B(a)P or manufactured gas plant residues which contain known carcinogens, including benzene and PAH, induces liver tumors[54]. In a wild brown bullhead catfish population, a decline in liver neoplasms was observed after a reduction in PAH exposure[55].

In humans, PAH-DNA adducts have been detected in HCC tissue samples[56,57]. Associations with HCC were found for PAH-DNA adducts levels in liver tissues and for the combination of PAH-DNA adducts levels with some susceptibility factors including HBV infection, exposure to AFB_1 and other factors[56]. In our study on paraffin tumor tissues and paired plasma samples from HCC patients, we found that the highest PAH-albumin adducts were present in those with the highest mean PAH-DNA adducts in liver, although the results were not statistically significant[57]. A recent study demonstrated that PAH-albumin adducts are associated with increased risk of HCC especially among those with high aflatoxin exposure and that environmental PAH exposure may enhance the hepatic carcinogenic potential of hepatitis B virus infection[56].

4-ABP is a well-studied aromatic amine and a known bladder carcinogen in both experimental animals and humans[58]. It is metabolized by hepatic CYP1A2 to yield *N*-hydroxyABP, a direct-acting mutagen capable of inducing tumors at sites of application[59]. Animal studies have demonstrated that administration of 4-ABP to dogs results in the formation of *N*-(deoxyguanonsin-8-yl)-4-ABP (dG-C8-ABP) as the major DNA adduct (approximately 70 percent of total adducts) in hepatocytes and bladder cells[60,61]. In BALB/c mice, there was a linear relationship between levels of dG-C8-ABP in liver DNA and liver tumor incidence[62]. In human liver tissues, higher levels of 4-ABP-DNA were observed in HCC cases compared with controls[63]. Even though there was a dose (number of cigarettes smoked/day)-related increase in 4-ABP DNA and an association with mutant p53 protein expression in bladder cancers[64], so far there are no reports on *p53* or other specific gene mutations caused by exposure to PAHs or 4-ABP in HCC.

Arsenic (As)

As is a human carcinogen with various target tissues including liver[65]. Ecological, case-control and cohort studies have documented a significant association between HCC and ingested inorganic arsenic through medicinal, environmental and occupational exposures in Taiwan and other countries[66]. A recent study indicated that fetal exposure to inorganic arsenic in mice produces tumors in adulthood in a variety of organs, including liver[67]. Several potential mechanisms for arsenical-induced hepatocarcinogenesis have been proposed including oxidative DNA damage, impaired DNA repair, acquired apoptotic tolerance, hyperproliferation, altered DNA methylation and aberrant estrogen signaling[68]. A marked overexpression of hepatic ER-α at the transcript and protein levels occurred in adult males bearing HCC induced by in utero arsenic exposure[69]. Increases in hepatic *cyclin D1* expression, an ER activated hepatic oncogene, also occurred[70].

Ethanol

Ethanol is a hepatotoxin and the most prevalent cause of cirrhosis, a primary clinical predictor of HCC, in western countries. Additionally, alcohol is an important solvent for chemicals and promotes the absorption of ingested toxins[71]. Ethanol damages the liver through oxidative-stress mechanisms; alcoholic hepatitis shows increased levels of isoprostanes, a marker of oxidative damage[72]. Oxidative stress can also cause the accumulation of oncogenic mutations. For example, increased oxidative stress associated with iron overload has been associated with *p53* mutations in HCC[73]. Oxidative damage may also accelerate telomere shortening which is correlated with the development of liver cirrhosis, chromosomal instability and HCC[74].

METABOLISM OF CHEMICAL CARCINOGENS

Most chemical carcinogens are not intrinsically reactive. They require metabolic conversion into biologically active forms by phase Ⅰ enzymes, including various CYP enzymes. Activated metabolites of chemical carcinogens are subject to metabolic conjugation and other kinds of detoxification by phase Ⅱ enzymes including epoxide hydrolase, arylamine *N*-acetyltransferases (NAT) and glutathione *S*-transferases (GST). Studies have demonstrated gene-environment interactions in which risk of HCC from exposure to environmental agents was modulated by genetic susceptibility related to genetic variations in chemical carcinogen metabolism genes.

AFB_1

The CYP enzymes are a superfamily of hemeproteins that are important in the oxidative, peroxidative and reductive metabolism of endogenous compounds and participate in the chemical carcinogenesis process[75]. Aflatoxin is activated by CYP1A2 and CYP3A4 to AFB_1-8, 9-epoxide, which covalently binds with DNA to form DNA-adducts, primarily AFB_1-N7-guanine[76,77]. CYP2A6 and CYP2B6 likely represent minor forms in the *in vitro* activation of AFB_1[78]. The overall contribution of these enzymes to AFB_1 metabolisms *in vitro* depends on the affinity of the enzyme but *in vivo* it also depends on expression levels in human liver where CYP3A4 is predominant[40]. Expression of CYP1A1/2 and 3A4 in liver tissues of hepatocellular carcinoma cases and controls was detected and their relationship to HBV and AFB_1- and 4-ABP-DNA adducts was also investigated[79].

For CYP3A4, in contrast to control tissues, there was a significant association with AFB_1-DNA adducts in tumor and adjacent non-tumor tissues of HCC cases.

Humans show large interindividual variations in xenobiotic metabolism activities that lead to different susceptibilities to the genotoxic actions of carcinogens[80]. A model using human liver epithelial cell lines stably expressing P450 cDNA revealed that CYP1A2 and CYP3A4 both contribute to the formation of AFB_1-induced *p53* mutation whereas CYP2A6 does not appear to play a significant role[31]. In an *in vitro* study, inhibition of CYP1A2 and CYP3A4 by oltipraz, a drug which has been reported to inhibit AFB_1 activation in human hepatocytes, was shown[81].

GST are a family of conjugation enzymes involved in the metabolism of exogenous and endogenous lipophilic compounds for their excretion and detoxification. For AFB_1, the detoxification pathway is *via* GST-mediated conjugation with reduced glutathione (GSH) to form AFB_1 exo- and endo-epoxide GSH conjugates[76,82,83]. Members of the GST family, such as GST-μ (*GSTM1*) and GST-θ (*GSTT1*), are important candidates for involvement in susceptibility to AFB-associated HCC because they may regulate an individual's ability to metabolize the ultimate carcinogen of aflatoxin, the exo-epoxide[83]. Epidemiological studies have suggested that genetic polymorphisms in AFB_1 metabolizing enzymes are factors in individual susceptibility to aflatoxin-related HCC[84,85]. *GSTM1* genotype can be categorized into two classes: the homozygous deletion genotype (*GSTM1* null genotype) and genotypes with one or two alleles present (*GSTM1* non-null genotype); *GSTT1* can also be deleted[86,87]. Carriers of *GSTM1* and *GSTT1* homozygous null genotypes lack the corresponding enzyme activities[86]. Chen *et al*[85] documented a biological gradient between serum AFB_1-albumin adduct levels and HCC risk among chronic HBsAg carriers who had null *GSTM1* and *GSTT1* genotypes but not among those who had non-null genotypes in a Taiwan population. Wild *et al*[88] reported in a Gambian population an association between the *GSTM1* null genotype and AFB_1-albumin adducts, although the association was restricted to people who were not infected with HBV. The effect of aflatoxin exposure on HCC risk was also more pronounced among chronic HBsAg carriers with the *GSTT1* null genotype than those who were non-null[89]. Based on the above studies conducted in different places and others not reviewed, whether or not there are interactions among AFB_1, HBV infection and GSTs genotypes in the development of HCC is still controversial.

VC

Vinyl chloride is primarily metabolized in the liver by the CYP2E1 to form the electrophilic metabolites chloroethylene oxide and chloroacetaldehyde[90]. These metabolites are thought to be the reactive intermediates involved in the formation of VC-DNA adducts. The promutagenic properties of these adducts have been characterized extensively *in vivo* and *in vitro* and involve mainly base pair substitution mutations[91]. Metabolism of the reactive intermediates is thought to involve several pathways that rely on CYP2E1, aldehyde dehydrogenase 2, GSTs, microsomal epoxide hydrolase and other enzymes, presumably to generate less reactive metabolites for excretion[92]. All of those enzymes are known to have polymorphic variants with altered activities that could produce variable VC metabolism[93]. Such variable metabolism could account for differing susceptibilities to the carcinogenic effects of VC in exposed individuals. The GST family is known to be involved in the metabolism of environmental chemical carcinogens including vinyl chloride monomer; it plays critical roles in protection against products of oxidative stress and electrophilic compounds[94,95]. So far, no direct evidence has shown that genetic polymorphisms of metabolizing enzymes are correlated with HCC development caused by VC exposure.

PAH and 4-ABP

CYP1A1 metabolically activates PAH into carcinogenic metabolites (diol epoxides), which covalently bind to DNA to form DNA-adducts[96], while CYP1A2 metabolically activates arylamine carcinogens such as 4-ABP and heterocyclic amines derived from cooked meats[90]. CYP1A1 was generally considered to be involved in extra hepatic carcinogenesis because early studies showed that the expression of CYP1A1 was low in human liver[90]. A later study using more sensitive techniques for the detection of CYP1A1 messenger RNA demonstrated that CYP1A1 is expressed in a high proportion of human liver tissues[97]. A study of the role of CYP1A1 genetic polymorphism in susceptibility to HCC has suggested that CYP1A1 variants are important modulators of the hepatocarcinogenic effect of PAHs. The Msp1 and lle-Val polymorphisms of *CYP1A1* may have different mechanisms for increasing susceptibility to smoking-related HCC[98]. Recently, a second study obtained similar result but in non-smoking HCC patients[99]. These inconsistent findings justify the need for additional studies of larger sample sizes to further evaluate the role of the *CYP1A1* variants in HCC development. Chen *et al*[100] reported genetic polymorphism of *CYP1A2* is associated with HCC risk. Polymorphisms of *CYP2E1* may also play an important role in cigarette smoking-related hepatocarcinogenesis[101].

Activated metabolites of B(a)P are subject in part to metabolic detoxification by *GSTM1*[102]; *GSTT1* can detoxify smaller reactive hydrocarbons[103]. Diol epoxides are substrates for phase II detoxifying enzymes including *GSTP1*[104]. Alterations in the expression of GSTs have been found in HCC tissues compared to liver tissues from healthy subjects[105]. These alterations may influence the association between exposure and PAH-DNA adduct formation among HCC cases. Chen *et al*[56] reported a significant combinatory effect of PAH-DNA adduct levels and *GSTP1* genotype on HCC risk but in the

same study there were no associations between HCC and *GSTM1* or *GSTP1* genotype. Subjects with high compared to low PAH-DNA adduct levels had a 2-fold higher HCC risk after adjustment either for age, sex and HBsAg or for age, sex, HBsAg, 4-ABP- and AFB_1-DNA adduct levels. Evidence of a possible interaction between GST polymorphisms and smoking was reported in two studies[106,107], with a non significant excess risk reported among light smokers with the *GSTT1* null genotype in one study[107] and a significant excess risk among smokers with a *GSTM1* and *GSTT1* null genotypes and low levels of plasma beta-carotene reported in the other[106].

NAT plays a role in the activation and detoxification of certain carcinogens in tobacco smoke[108]. Two isoforms of NAT1 and NAT2 participate in the metabolic activation and detoxification (*O*- and *N*-acetylation respectively) of aromatic amines (including arylamines and heterocyclic amines)[108], which are found in tobacco smoke. Exposure to 4-ABP, which is primarily a result of cigarette smoking, plays a role in human hepatocarcinogenesis[63]. Wang *et al*[63] found greater levels of 4-ABP-DNA in liver tissues from HCC patients than controls. NAT1 and especially NAT2 are characterized by several allelic variants, which cause variations in acetylation capacity. Agundez *et al*[109] investigated the effect of *NAT2* polymorphisms on HCC and found they are relevant to HCC risk. Results of a study in Taiwan suggested that NAT2 activity may be particularly critical in smoking-related hepatocarcinogenesis among chronic HBV carriers[110]. Farker *et al*[111] reported a significant association between *NAT2* polymorphism and HCC among chronic HBV carriers who were smokers but not among those who were non-smokers. It was postulated that genetic polymorphisms in biotransformation enzymes could be important with regards to individual susceptibility to cigarette smoking-related HCC[109,112].

As

Inorganic arsenic (iAs) is metabolized by reduction of pentavalent iAs to trivalent, followed by oxidative methylation to monomethylated arsenic (MMA), further reduction from pentavalent MMA to trivalent, and finally methylation to dimethyl arsenic[113]. One study indicated that polymorphisms in GST omega 1, which encodes an enzyme that can reduce pentavalent arsenic species, might be related to enzyme activity and patterns of methylated arsenic metabolites[114,115]. Because glutathione plays an important role in arsenic metabolism, its regulation *via* GST polymorphisms may modulate metabolism and, as a consequence, alter urinary excretion profiles. Thus, as low GST activity may decrease the detoxification function of glutathione, it has been hypothesized that humans with null genotypes for *GSTM1* and *GSTT1* may have arsenic methylation capabilities and body retention differences compared to those with non-null genotypes. In addition, humans with null genotypes for *GSTM1* and *GSTT1*, as well as the val/val genotype for *GSTP1*, may be at high risk of cancer due to their glutathione deficiencies[116].

Ethanol

Alcohol consumption also induces the expression of a number of xenobiotic metabolism enzymes that activate procarcinogens[4]. CYP2E1, one of the important members of the CYP super family, catalyses the conversion of ethanol to acetaldehyde and acetate but also metabolizes many exogenous drugs and procarcinogens[116]. As CYP-2E1 is an ethanol inducible enzyme, its functional characterization has been focused on alcoholic liver diseases[117]. Decreased expression of CYP2E1 is associated with poor prognosis of hepatocellular carcinoma[118].

CONCLUSION

Exposure to chemical carcinogens including AFB_1, B(a)P, 4-ABP, arsenic, alcohol and others may act either independently or interact with HBV and HCV to cause DNA damage, induce liver cirrhosis and contribute to the development of HCC. During this process, genetic variation will impact on risk. Various types of genotoxic endpoints including DNA-adducts, point mutations of tumor suppressor genes and other cancer-related genes, small deletions (loss of heterozygosity) and chromosomal aberrations are dominant characteristics of HCC.

Metabolism of chemical carcinogens involves multiple pathways of transformation of certain chemicals. Thus, the regulation of genes coding for many of these metabolic enzymes is important in hepatocarcinogenesis and has lead to studies of inter-individual genetic variation.

Understanding the interaction of viral infection, genetic variation and exposure to environmental chemical carcinogens will help to elucidate mechanisms of human hepatocarcinogenesis and develop more effective strategies for HCC prevention.

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