25

DNA Repair Capacity-Related to Genetic Polymorphisms of DNA Repair Genes and Aflatoxin B1-Related Hepatocellular Carcinoma Among Chinese Population

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1. Introduction

Primary liver cancer (PLC) is the sixth most commonly occurring cancer and the third most common cause of cancer deaths in the world (1). This tumor has two main pathological types: hepatocellular carcinoma (HCC) and cholangiocellular carcinoma. HCC, the most common pathological form of PLC, occurs more often in specific regions which include eastern and southeastern Asia, Melanesia, and sub-Saharan Africa (1, 2). Once diagnosed, survival rates for HCC are poor: 75% of patients die within 1 year, and 5-year survival rate is only 3 - 5% (3, 4). Therefore, insight into the tumorigenesis mechanisms of HCC will broaden and deepen implications in understanding and preventing occurrence of the cancer.

It has been known that chronic infection with hepatitis virus [including hepatitis virus B (HBV) and hepatitis virus C (HCV)] is the most common cause of HCC worldwide (3). In sub-Saharan Africa and Southern China, chronic exposure of aflatoxin B1 (AFB1) may present a special environmental hazard, especially in individuals chronically infected with HBV (1, 2, 5-8). However, increasing epidemiological evidence has exhibited that although many people are exposed to these risk factors, only a relatively small proportion of chronic infectors or exposure person develop HCC (3, 9, 10). This indicates an individual susceptibility related to genetic factors such as DNA repair capacity might be associated with HCC carcinogenesis (3, 11). In recent years, evidence has been accumulated to support the hypothesis that common genetic polymorphisms in genes involved in long process of

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carcinogenesis may be of importance in determining individual susceptibility to HCC (3, 9, 12). Therefore, the existence of low penetrate genetic polymorphisms may explain the reason why only a small portion of individuals, even in high-risk areas, develop HCC in their life span. This study reviews recent efforts in identifying genetic variants which may have impact on risk of HCC.

2. Epidemiology of AFB1-related HCC in China

In China, HCC is the third or fourth most common malignant tumors and accounts for about 55% of the world's HCC cases, more than 340,000 each year (1, 13). This tumor occurs more often in eastern and southeastern China, including Jiangsu, Shanghai, Zhejiang, Fujiang, Guangdong, and Guangxi, mainly because of high AFB1 exposure and/or chronic infection of HBV and HCV (13). In the high AFB1-exposure areas such as Guangxi Zhuang Autonomous Region, this tumor is the most common occuring cancer (13, 14). Moreover, the incidence rate gradually increases with age increasing in above-mentioned AFB1-exposure areas (15). Males are always more frequently affected than females but high male to female ratios of > 3 in the high AFB1-exposure areas (15). Although the incidence rates of this tumor in low AFB1-exposure areas in China have markedly decreased (because of the control of hepatitis virus infection), they have changed little in high AFB1-exposure areas (13, 15). For example, during May 2007 to April 2008, incidence rates were 117.8/100,000 and 103.1/100,000 for Xiangzhou and Fusui (two main high AFB1-exposure areas of China), respectively (13, 16). This was similar to the results before ten years (17).

Because of the very poor prognosis, HCC is the second most common cause of death from cancer in China (18). In the past thirty years, total mortality rate of HCC gradually increased from 12.5/100,000 to 26.26/100,000 (Fig 1A), regardless of countryside areas or urban areas (Fig 1B). This trend was more noticeable in male population than female population (Fig 1C), possibly because male individuals featured more high AFB1 exposure. Supporting aforementioned hypothesis, a recent study from high AFB1-exposure areas has demonstrated these having longer exposure years or higher exposure levels of AFB1 would face lower 5-years survival rate (4).

3. AFB1 exposure and DNA damage and repair

AFB1 is an important mycotoxin produced by the moulds Aspergillus parasiticus and Aspergillus flavus (19). This toxic agent has been found as contaminants of human and animal food, particularly ground nuts (peanuts) and core, in tropical areas such as the Southeastern China as a result of fungal contamination during growth and after harvest which under hot and humid conditions (8, 14, 19, 20). Epidemiological evidence has shown dietary ingestion of high levels of AFB1 presents a significant environmental hazard of HCC (16, 17, 21). Experimental animal models have also shown that AFB1 can induce HCC; whereas DNA damage should play an important role during hepatocellular carcinogenesis (19, 22, 23). Therefore, AFB1 has been classified as a category I known human carcinogen by the International Agency for Research on Cancer (24).

AFB1 is metabolized by cytochrome P450 enzymes to its reactive form, AFB1-8,9-epoxide (AFB1-epoxide), which covalently binds to DNA and induces DNA damage (19, 25-28). DNA damage induced by AFB1 includes AFB1-DNA adducts, oxidative DNA damage,

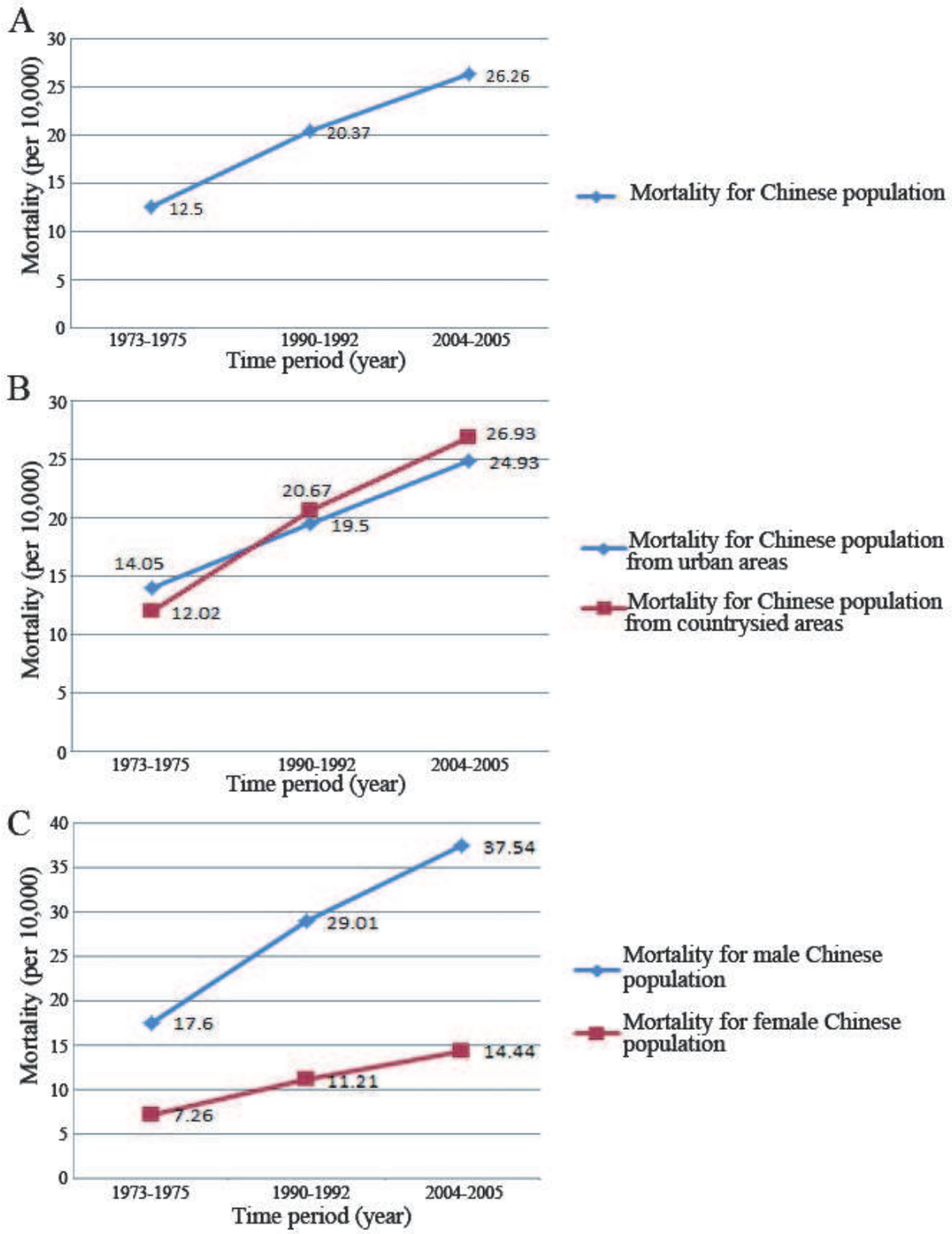

Fig. 1. The mortality rates of HCC in China during 1973 and 2005. Total mortality rates (A), regardless of in urban areas or countryside areas (B), were significantly increasing from during 1973 and 1975 to during 1990 and 1992 or to during 2004 and 2005. This increasing mortality rates were more remarkable among male population (C).

and gene mutation (Fig. 2). Among these AFB1-DNA adducts, 8,9-di-hydro-8-(N^7-guanyl)-9-hydroxy–AFB1 (AFB1-N^7-Gua) adduct is the most common type identified and confirmed in vivo researches (19, 25-27, 29, 30). The formation of this adduct proceeds by a precovalent intercalation complex between double-stranded DNA and the highly electrophilic, unstable AFB1-epoxide isomer (31, 32). After that, the induction of a positive charge on the imidazole portion of the formed AFB1-N^7-Gua adduct gives rise to another important a DNA adduct, a ring-opened formamidopyridine AFB1 (AFB1-FAPy) adduct (33, 34). Accumulation of AFB1-FAPy adduct is characterized by time-dependence, non-enzyme, and may be of biological basis of genes mutation because of its apparent persistence in DNA (19, 33, 34). Furthermore, above adducts are capable of forming subsequent repair-resistant adducts, depurination, or lead to error-prone DNA repair resulting in single-strand breaks (SSBs), double-strand breaks (DSBs), base pair substitution, or frame shift mutations (35, 36). Additionally, AFB1 exposure also induces the formation of such oxidation DNA damage as 8-oxodeoxyguanosine ($8\text{-}_{oxod}G$), a common endogenous DNA adduct (36-38). Although these DNA adducts are mainly produced in liver cells, they are also found in the peripheral blood white cells (39, 40). Recent studies have shown that the levels of AFB1-DNA adduct of the peripheral blood white cells are positively and lineally correlated with that of liver cells, implying analysis of AFB1-DNA adducts in the peripheral blood white cells may substitute for the elucidation of tissular levels of adducts (39, 41).

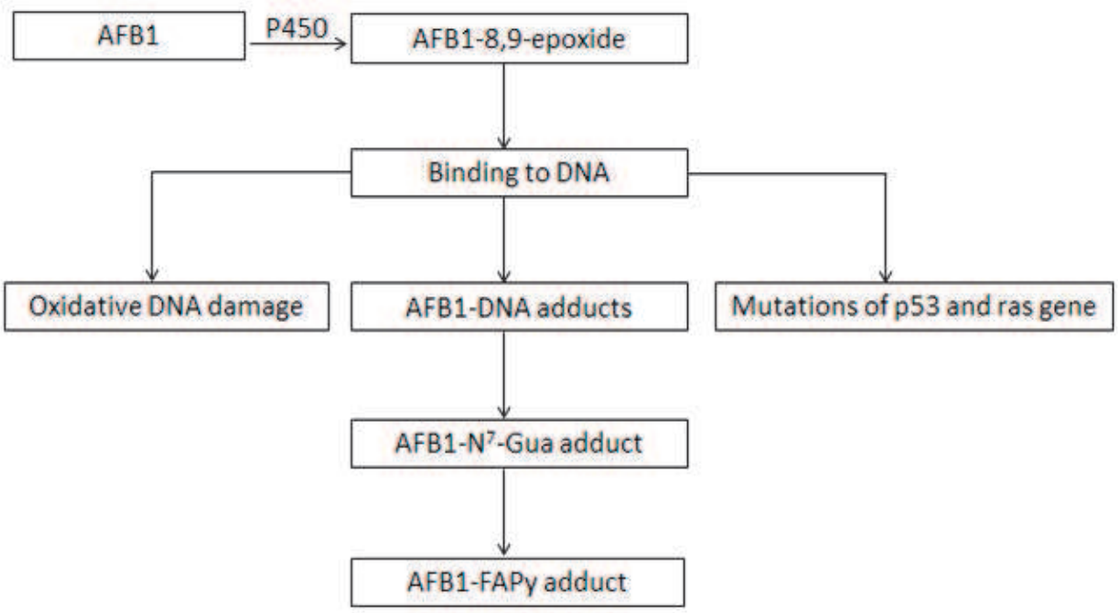

Fig. 2. The DNA damage induced by AFB1.

For genes mutations induced by AFB1 exposure, the experimental and theoretical researches are briefly on the p53 gene (42-49). Reaction with DNA at the N^7 position of guanine preferentially causes a G:C > T:A mutation in codon 249 of this gene, leading to an amino acid substitution of arginine to serine (44-50). In high AFB1-exposure areas, this mutation is present in more than 40% of HCC and can be detected in serum DNA of patients with preneoplastic lesions and HCC (41). While codon 249 transversion mutations are either very

rare or absent in low or no AFB1-exposure areas (49, 51, 52). Using the human p53 gene in an in vitro assay, codon 249 has been exhibited to be a preferential site for formation of AFB1-N^7-Gua adducts, evidence consistent with a role for AFB1 in the mutations observed in HCC (50, 53). Therefore, the codon 249 mutation of p53 gene has been defined as the hot-spot mutation of p53 gene resulting from AFB1 and has become the molecular symbol of HCC induced by AFB1 exposure (54-56).

A wide diversity of DNA damage produced by AFB1 exposure, if not repaired, may cause chromosomal aberrations, micronuclei, sister chromatid exchange, unscheduled DNA synthesis, and chromosomal strand breaks, and can be converted into gene mutations and genomic instability, which in turn results in cellular malignant transformation (19). Nevertheless, human cells have evolved surveillance mechanisms that monitor the integrity of genome to minimize the consequences of detrimental mutations (54). AFB1-induced DNA damage can be repaired through the following pathways: nucleotide excision repair (NER), base excision repair (BER), single-strand break repair (SSBR), and double-strand break repair (DSBR) (12, 28, 57). During the process of damage removed by aforementioned repair pathways, DNA repair genes play a central role, because their function determines DNA repair capacity (12). It has been shown that reduction in DNA repair capacity related to DNA repair genes is associated with increased risk of cancers (4, 39-41, 58-62). Thus, genetic polymorphisms in DNA repair genes which contribute to the variation in DNA repair capacity may be correlated with risk of developing cancers, including AFB1-related HCC.

4. Genetic polymorphisms in genes involved in NER pathway and risk of HCC

NER pathway, a major DNA repair pathways in human cells featuring genomic DNA damage, can remove structurally such diverse lesions as pyrimidine dimers, irradiative damage, and bulky chemical adducts, and DNA damage from carcinogens and some chemotherapeutic drugs (63, 64). To date, the mechanism of this pathway is well understood and has been reconstituted in vitro. It consists of several sequential steps: lesion sensing, opening of a denaturation bubble, incision of the damaged strand, displacement of the lesion-containing oligonucleotide, gap filling, and ligation (63, 64). In the fibroblast cells with the deficiency of xeroderma pigmentosum A (XPA) gene, conversion of the initial AFB1-N^7-Gua adduct to the AFB1-FAPy adduct has been found to be more extensive (53). This suggests that NER should be a major mechanism for enzymatic repair of AFB1 adducts (12). It's defects lead to severe diseases related AFB1 exposure, including liver injury and HCC. Accumulating evidence has implied that genetic polymorphisms in NER genes are associated with DNA repair capacity and modulate the risk of cancers (65-69). Molecular epidemiology studies of AFB1-related HCC in China have investigated the associations with several genes involved in NER pathway such as xeroderma pigmentosum C (XPC) and xeroderma pigmentosum D (XPD)(4, 39, 70, 71).

XPC. XPC gene spans 33kb on chromosome 3p25 and contains 16 exons and 15 introns (Genbank accession no. AC090645). This gene encodes a 940-amino acid protein, an important DNA damage recognition molecule which plays an important role in NER pathway (72). It binds tightly with HR23B to form a stable XPC-HR23B complex, the first protein component that recognizes and binds to the DNA damage sites. XPC-HR23B complex can recognize a variety of DNA adducts formed by exogenous carcinogens such as AFB1 and binds to the DNA damage sites (72). Thus, it may play a role in the pathogenesis

of HCC-related AFB1. Some recent studies have showed that defects in XPC have been related to many types of malignant tumors (73-82). Transgenic mice studies also revealed predisposition to many types of tumors in XPC gene knockout mice (83). Furthermore, pathological and cellular researches have exhibited that the abnormal expression of this gene is related to hepatocarcinogenesis (84). These studies suggests the polymorphisms localizing at conserved sites of XPC gene might modify the risk of HCC induced by AFB1 exposure. Recently, four studies from high AFB1-exposure areas of China have approved aforementioned hypothesis (4, 70, 71, 85).

The first study conducted by Cai *et al.*(85) is from Shunde area, Guangdong Province. In this 1-1 case-control study (including 78 HCC cases and 78 age- and sex-matching controls), researchers analyzed between two common polymorphisms—Ala499Val and Lys939Gln—of XPC gene and risk of HCC and found these two polymorphisms modified HCC risk [adjusted odds ratios (ORs) were 3.77 with 95% confidence interval (CI)1.34-12.89 for Ala499Lys and 6.78 with 95% CI 2.03-22.69], especially under HBV and HCV infection condition. Although they evaluated the effects of XPC-hepatitis viruses interaction on HCC risk, they did not elucidate the possible interaction of AFB1 exposure.

The other three studies are from Guangxi Zhuang Autonomous Region (4, 70). Li *et al.*(71), Wu *et al.* (70), and Long *et al.* (4) investigated the modifying effects of genetic polymorphisms XPC on HCC based hospitals. The results showed XPC codon 939 Gln alleles increased about 2-times risk of HCC. Furthermore, Wu, *et al.*(70), and Long, *et al.* (4) quantitatively elucidated AFB1 exposure years and levels and their interactive effects with XPC Lys939Gln polymorphism. They found some evidence of AFB1 exposure-risk genotypes of XPC codon 939 on HCC risk ($22.33 > 1.88 \times 8.69$ for the interaction of AFB1-exposure years and XPC risk genotypes and $18.38 > 1.11 \times 4.62$ for the interaction of AFB1-exposure levels and XPC risk genotypes). Additionally, Gln alleles at codon 939 of XPC gene are observed to be correlated with the decrease of XPC expression levels in cancerous tissues ($r = -0.369$, $P < 0.001$) and with the overall survival of HCC patients (the median survival times are 30, 25, and 19 months for patients with XPC gene codon 939 Lys/Lys, Lys/Gln, and Gln/Gln respectively). This decreasing 5-years survival rates would be noticeable under high AFB1 exposure conditions (the median survival times are 15 months for the joint of XPC gene codon 939 Gln/Gln and long-term AFB1-exposure years and 17 month for the joint of XPC gene codon 939 Gln/Gln and high AFB1-exposure level) (4).

These results demonstrate that polymorphism at codon 939 of XPC gene is not only a genetic determinant in the development of HCC induced by AFB1 exposure in Chinese population, but also is an independent prognostic factor influencing the survival of HCC, like AFB1 exposure. However, Li *et al.* (71) reported that the proportional distribution of the Val/Val genotype at codon 499 of XPC gene did not differ between cases with HCC and controls in Guangxi Zhuang Autonomous Region, China ($P > 0.05$), dissimilar to the data from another area of China, Guangdong Province (85). Possible explanations for these inconsistent finding may be either due to unknown confounders or due to small sample size.

XPD. XPD gene-encoding protein, a DNA-dependent ATPase/helicase, is associated with the TFIIH transcription-factor complex and plays a role in NER pathway (86, 87). During NER, XPD participates in the opening of the DNA helix to allow the excision of the DNA fragment containing the damaged base. There are two described polymorphisms that induce amino acid changes in the protein: at codons 312 (Asp to Asn) and 751 (Lys to Gln) (87-89). To date, these two polymorphisms have been extensively studied (87, 88, 90-95).

Several groups have done genotype-phenotype analyses with these two polymorphisms and have shown that the variant allele genotypes are associated with low DNA repair ability (96, 97). Recent studies have showed the polymorphisms at codon 312 and 751 of XPD are correlated with DNA-adducts levels, p53 gene mutation, and cancers risk (88, 94, 98-100).

In a hospital-based case-control study in Guangxi (39), we found that the variant XPD codon 751 genotypes (namely Lys/Gln and Gln/Gln) detected by TaqMan-MGB PCR was significantly different between controls (26.3% and 8.6% for Lys/Gln and Gln/Gln, respectively) and HCC cases (35.9% and 20.1% for Lys/Gln and Gln/Gln, respectively, $P < 0.001$). Individuals with variant alleles had about 1.5- to 2.5-fold risk of developing the cancer (adjusted OR 1.75 and 95% CI 1.30-2.37 for Lys/Gln; adjusted OR 2.47 and 95% CI 1.62-3.76 for Gln/Gln). Based on relative sample size (including 618 HCC cases and 712 controls), we stratified genotypes of XPD codon 751 according to matching factors and observed some evidence of interaction between XPD codon 751 Gln alleles and sex. These female having Gln alleles, compared to those without these alleles, featured increased HCC risk. Furthermore, the interactive effects of between variant genotypes of XPD gene codon 751 environment variant AFB1 or another NER gene XPC on HCC risk were also found, with interactive value 0.85, 1.04, and 1.71 for AFB1-exposure years, AFB1-exposure levels, and XPC gene codon 939 risk genotypes ($P_{interaction} < 0.05$). Therefore, the XPD gene codon 751 polymorphism may have potential effect on AFB1-related HCC susceptibility among Chinese population. However, the study from AFB1-exposure areas don't exhibit polymorphism at codon 312 of XPD gene significantly associates with the risk of HCC induced by AFB1.

5. Genetic polymorphisms in genes involved in SSBR pathway and risk of HCC

SSB is a common type of DNA damage produced by AFB1 exposure (36). If not repaired, it can disrupt transcription and replication and can be converted into potentially clastogenic and/or lethal DSBs. This DNA damage is repaired via SSBR pathway (101, 102). SSBR pathway includes four basic steps: *a.* SSB detection and signaling, through poly (ADP-ribose) polymerase (PARP); *b.* DNA break end processing, through the role of polynucleotide kinase (PNK), AP endonuclease-1 (APE1), DNA polymerase β (Pol β), tyrosyl phosphodiesterase 1 (TDP1), and flap endonuclease-1 (FEN-1); *c.* gap filling, involving in multiple DNA polymerases; *d.* DNA ligation, involving in multiple DNA ligases. Of the later three steps of SSBR pathway, x-ray repair cross complementary 1 (XRCC1) is indispensible, because it not only acts as the scaffolding protein of SSBR, but also stimulates the activity of PNK (103).

XRCC1 gene encoding protein (633 amino acids), consists of three functional domains — N-terminal domain (NTD), central breast cancer susceptibility protein-1 homology C-terminal (BRCT I), and C-terminal breast cancer susceptibility protein-1 homology C-terminal (BRCT II) (103-106). This protein is directly associated with Pol β, DNA ligase III, and PARP, via their three functional domains and is implicated in the core processes in SSBR and BER pathway (103). Mutant hamster ovary cell lines that lack XRCC1 genes are hypersensitive to DNA damage agents such as ionizing radiation, hydrogen peroxide, and alkylating agents (103). Furthermore, this kind of cells usually face increasing frequency of spontaneous

chromosome aberrations and deletions. Three single nucleotide polymorphisms in the coding region of XRCC1 gene that lead to amino acid substitution have been described and investigated (12). Of these polymorphisms, the codon 399 polymorphism is of special concern, because this polymorphism resides in functionally significant regions (BECT II) and may be related to decreasing DNA repair capacity, increasing genes mutation, and running-up risk of cancers (12, 107-114).

In AFB1-exposure areas from China, a total of six molecular epidemiological studies were found in PubMed database, Wangfang Database, and Weipu database (61, 62, 115-118). However, associations between XRCC1 gene codon 399 polymorphism and individual susceptibility to HCC have been reported in these case-control studies with the results being contradictory. We analyzed the possible causes of contradictory using meta-analysis method (Comprehensive Meta Analysis Version 2, http://www.meta-analysis.com/). Fig. 3 showed the meta-analysis results of the modifying effects of XRCC1 gene codon 399 polymorphism on HCC risk. We found these subjects with Gln alleles had increasing risk of HCC (total crude adjusted OR = 1.34, $P < 0.01$), moreover, there were larger relative weight to assign to those studies with OR-value more than 1. Actually, although Yang *et al.* (116) and Ren *et al.* (118) did not observed significantly risk of XRCC1 gene codon 399 polymorphism in crude logistic regression, they found Gln alleles would increase HCC risk in stratified analysis with susceptive environment variants. A individually matching case-controls demonstrated that subjects having Gln alleles might feature remarkably increasing risk of HCC under longer-term AFB1-exposure years or higher AFB1-exposure levels conditions (adjusted OR > 10) (61). This suggests that the genotypes with codon 399 Gln alleles of XRCC1 should be a risk biomarker of Chinese HCC related to AFB1 exposure.

6. Genetic polymorphisms in genes involved in BER pathway and risk of HCC

Of the oxidative DNA damage resulting from AFB1 exposure, the formation of 8-$_{oxod}$G is thought to be important due to being abundant and highly mutagenic and hepatocarcinogenesis (21, 36-38). The 8-$_{oxod}$G lesions are repaired primarily through the BER pathway (119). The BER pathway facilitates DNA repair through two general pathways: *a.* the short-patch BER pathway, leading to a repair tract of a single nucleotide; *b.* the long-patch BER pathway, producing a repair tract of at least two nucleotides (120). In these two repair sub-pathways, DNA glycosylases play a central role because they can recognize and catalyze the removal of damaged bases (120). This suggests that the defect of DNA glycosylases should be related to the decreasing capacity of the BER pathway and might increase the risk of such cancers as HCC.

Human oxoguanine glycosylase 1(hOGG1) is a specific DNA glycosylase that catalyzes the release of 8-$_{oxod}$G and the cleavage of DNA at the AP site (121, 122). Genetic structure study has revealed the presence of several polymorphisms within hOGG1 locus (123). Among them, the polymorphism at position 1245 in exon 7 causes an amino acid substitution (Ser to Cys) at codon 326, suggesting this polymorphism may glycosylase function (123). A functional complementation activity assay showed that hOGG1 protein encoded by the 326 Cys allele had substantially lower DNA repair activity than that encoded by the 326 Ser allele (124). Similar results were observed in human cells in vivo (122, 125). Therefore, low capacity of 8-$_{oxod}$G repair resulting from hOGG1 326Cys polymorphism might contribute to

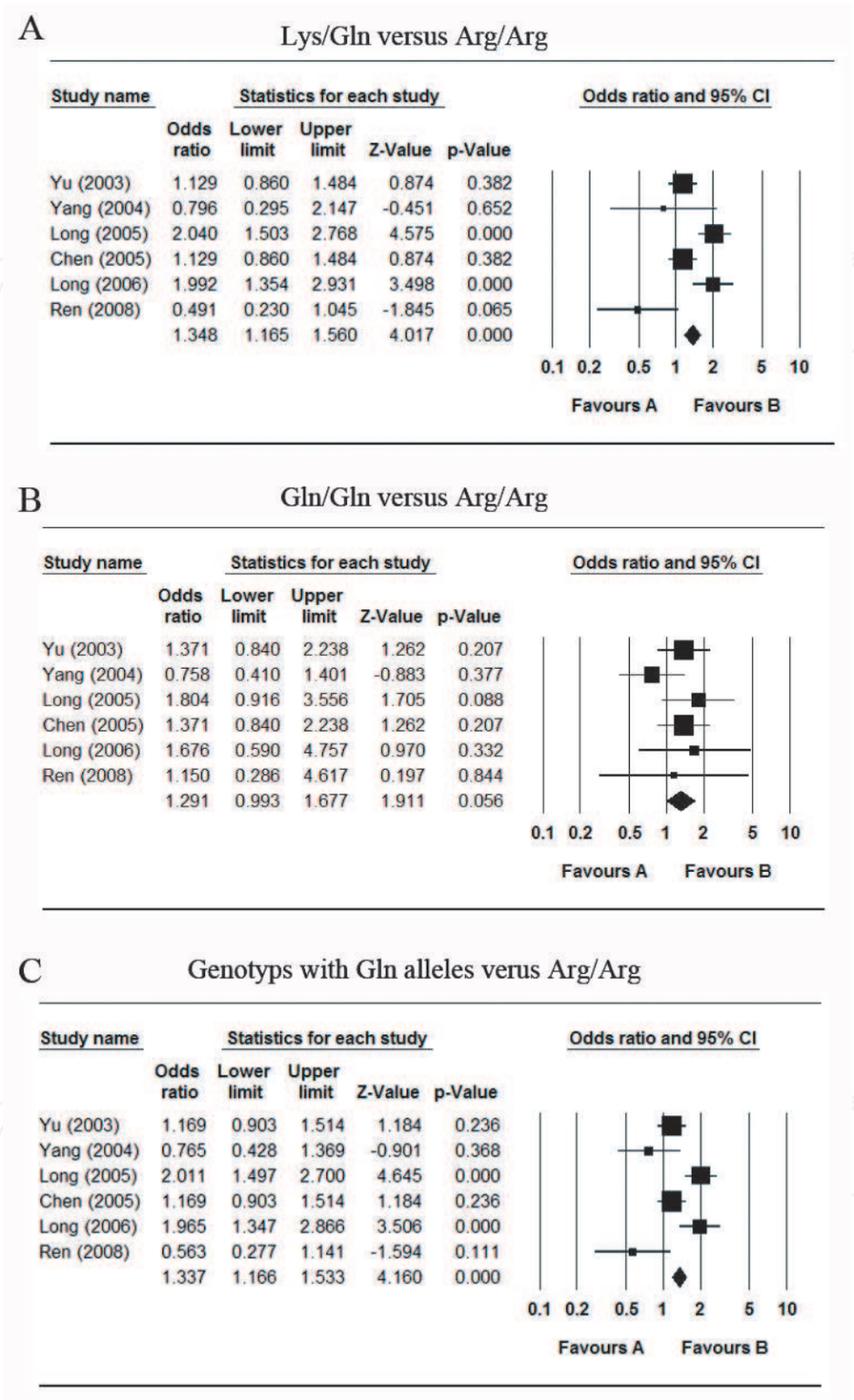

Fig. 3. The meta-analysis of the relationship between XRCC1 codon Lys399Gln polymorphism and HCC risk among China population. Compared with Arg/Arg genotype, Arg/Gln (A) and Gln/Gln (B) genotypes increased HCC risk. This risk effect was also observed in the binding of Arg/Gln and Gln/Gln genotypes (C).

the persistence of 8-$_{oxod}$G in genomic DNA in vivo, which, in turn, could be associated with increased cancer risk (125, 126).

In 2003, Peng *et al.* (126) investigated the correlation among 8-$_{oxod}$G levels, hOGG1 expression, and hOGG1 Cys326Ser polymorphism in Guangxi Autonomous Region. They found that individuals with genotypes with hOGG1 codon 326 Cys alleles faced lower level of hOGG1 expression and higher 8-$_{oxod}$G levels. Supporting their results, Cheng *et al.* (21) reported that hOGG1 expression was significantly linear correlated with HCC. Recently, using the molecular epidemiological methods, Zhang *et al.*(127) found that the distribution of Cys alleles at codon 326 of hOGG1 in HCC cases (43.0%) significantly differed from in controls (33.1%). Logistic regression analysis showed that the genotypes with Cys alleles, compared to without this alleles, increased HCC risk of Chinese population, with adjusted OR-value (95% CI) 1.5 (0.79-2.93) for Cys/Ser and 1.9 (0.83-4.55) for Cys/Cys. These findings suggested pathogenic role of hOGG1 Cys326Ser polymorphism in the hepatocarcinogenesis.

7. Genetic polymorphisms in genes involved in DSBR pathway and risk of HCC

DSBs, although only make up a very small proportion of AFB1-induced DNA damage, are critical lesions that can result in cell death or a wide variety of genetic alterations including large- or small-scale deletions, loss of heterozygosity, translocations, and chromosome loss (19, 128, 129). This type damage is repaired DSBR consisting of non-homologous end-joining (NHEJ) and homologous recombination (HR) (130-133). There are several decades DNA repair genes involves in DSBR pathway and the defects in these genes cause genome instability and promote tumorigenesis (128, 134, 135). In published molecular epidemiological studies, only XRCC3 gene codon Thr241Met polymorphism effects the risk of AFB1-related HCC risk among Chinese population (58, 60).

The product of the XRCC3 gene is one of identified paralogs of the strand-exchange protein RAD51 in human beings (136). This protein correlates directly with DNA breaks and facilitates of the formation of the RAD51 nucleoprotein filament, which is crucial both for homologous recombination and HRR (136-138). Previous studies have shown that a common polymorphism at codon 241 of XRCC3 gene (Thr to Met) modifies the function of this gene ad increases cancers risk (139-143). Two reports from high AFB1-exposure areas of China supported above-mentioned conclusions (58, 60).

In the first frequent case-control study in Guangxiese (58), we observed that the genotypes with XRCC3 codon 241 Met alleles (namely Thr/Met and Met/Met) was significantly different between controls (33.01%) and HCC cases (61.48%, $P < 0.001$). Met alleles increases about 2- to 10-fold risk of HCC and this running-up risk is modulated by the number of Met alleles (adjusted OR 2.48 and 10.06 for one and two this alleles). Considering small sample size in this study, we recruited, in another independent frequent case-control study (60), a relatively larger sample size to compare the results. Subjects included in this study, 491 HCC cases and 862 age-, sex, race, hepatitis virus infection information-matching controls, were permanent residents of Guangxi areas. Similar to the results of the first report, the distribution of XRCC3 codon 241 Met allele frequency was found to be significantly different between cases (59.7%) and controls (32.1%). Individuals having the Thr/Met or Met/Met were at a 2.22-fold or 7.19 fold increased risk of developing HCC cancer. Above two studies showed this allele multiplicatively interacted with AFB1 exposure in the process

of hepato-tumorigenesis. These results exhibits that the polymorphism at codon 241 of XRCC3 gene is a genetic determinant in the development of HCC induced by AFB1 exposure among Chinese population.

8. Summary

Like most other human malignant tumors, HCC is a complex disease attributed to environment variation and genetic susceptive factors. In high incidence areas of HCC in China, AFB1 is an important environment variation as well as chronic HBV and HCV infection. This toxic variation is characterized by: *a.* the attraction of specific organs, especially liver; *b.* genotoxicity, mainly inducing the formation of AFB1-DNA adducts and the hot-spot mutation of p53 gene; and *c.* carcinogenicity, primarily causing HCC. In the process of AFB1 hepatocarcinogenesis, AFB1-DNA adducts play a central role because of their genotoxicity and interactions with genetic susceptive factors. Numerous studies reviewed in this paper have demonstrated that the hereditary variations in DNA repair genes are associated with susceptibility to AFB1-related HCC among Chinese population. These molecular epidemiological studies have significantly contributed to our knowledge of the importance of genetic polymorphisms in DNA repair genes in the etiology of HCC related to AFB1 exposure. It would be expected that genetic susceptibility factors involved in DNA repair genes for HCC could serve as useful biomarkers for identifying at-risk individuals and, therefore, targeting prevention of this malignant tumor.

However, there are several issues to be noted. Firstly, the conclusions should be drawn carefully, because of conflicting data existing in the same ethnic population in view of between some genotypes of DNA repair genes and the risk of HCC. Secondly, caution should be taken particularly in extrapolating these data to other ethnic populations, because of the difference of population frequencies corresponding to genetic polymorphisms that depends on ethnicity. Thirdly, when risk of a specific polymorphism is considered, AFB1 exposure should be stressed because AFB1 exposure may differ from areas to areas and from individuals to individuals. Lastly, because of the fact that AFB1-related hepatocarcinogenesis is polygenic, no single genetic marker may sufficiently predict HCC risk. Therefore, a panel of susceptive biomarkers is warranted to define individuals at high-risk for this cancer.

9. Acknowledgments

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10. Abbreviations

AFB1, Aflatoxin B1; AFB1-epoxide, AFB1-8,9-epoxide; AFB1-N^7-Gua, 8,9-di-hydro-8-(N^7-guanyl)-9-hydroxy–AFB1; AFB1-FAPy, ring-opened formamidopyridine AFB1; APE1, AP endonuclease-1; BER, base excision repair; CI, confidence interval; DSB, double-strand break; DSBR, double-strand break repair; HBV, hepatitis virus B; HCV, hepatitis virus C; HCC, hepatocellular carcinoma; hOGG1, Human oxoguanine glycosylase 1; NER,

nucleotide excision repair; OR, odds ratio; 8-$_{oxod}$G, 8-oxodeoxyguanosine; PARP, poly (ADP-ribose) polymerase; PLC, Primary liver cancer; PNK, polynucleotide kinase; Pol β, DNA polymerase β; SSB, single-strand break; SSBR, single-strand break repair; XPA, xeroderma pigmentosum A; XPC, xeroderma pigmentosum C; XPD, xeroderma pigmentosum D; XRCC1, x-ray repair cross complementary 1; XRCC3, x-ray repair cross complementary 3; XRCC4, x-ray repair cross complementary 4.

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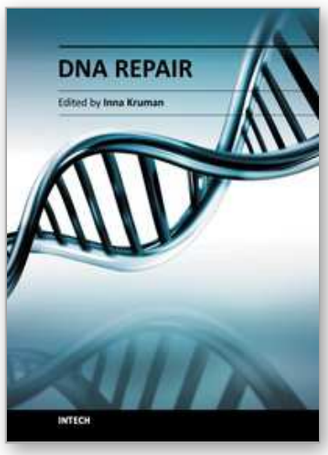

DNA Repair

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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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