Role of Metabolic Enzymes P450 (CYP) on Activating Procarcinogen and their Polymorphisms on the Risk of Cancers

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Abstract: Cytochrome P450 (CYP450) enzymes are the most important metabolizing enzyme family exists among all organs. Apart from their role in the deactivation of most endogenous compounds and xenobiotics, they also mediate most procarcinogens oxidation to ultimate carcinogens. There are several modes of CYP450s activation of procarcinogens. 1) Formation of epoxide and diol-epoxides intermediates, such as CYP1A1 and CYP1B1 mediates PAHs oxidation to epoxide intermediates; 2) Formation of diazonium ions, such as CYP2A6, CYP2A13 and CYP2E1 mediates activation of most nitrosamines to unstable metabolites, which can rearrange to give diazonium ions. 3) Formation of reactive semiquinones and quinines, such as CYP1A1 and CYP1B1 transformation of estradiol to catechol estrogens, subsequently formation semiquinones; 4) Formation of toxic O-esteriification, such as CYP1A1 and CYP1A2 metabolizes PhIP to N2-acetoxy-PhIP and N2-sulfonyloxy-PhIP, which are carcinogenic metabolites. 5) Formation of free radical, such as CYP2E1 is involved in activation tetrachloromethane to free radicals. While for CYP2B6 and CYP2D6, only a minor role has been found in procarcinogens activation. In addition, as the gene polymorphisms reflected, the polymorphisms of CYP1A1 (-3801T/C and -4889A/G), CYP1A2 (-163C/A and -2467T/delT), CYP1B1 (-48G/C, -119G/T and -432G/C), CYP2E1 (-1293G/C and -1053 C/T) have been associated with an increased risk of lung cancer. The polymorphisms CYP1A1 (-3801T/C and -4889A/G), and CYP2E1 (Psd/Rsa and 9-bp insertion) have an association with higher risk colon cancers, whereas CYP1A2 (-163C/A and -3860G/A) polymorphism is found to be among the protective factors. The polymorphisms CYP1A1 (-3801T/C and -4889A/G), CYP1B1 -432G/C, CYP2B6 (-516G/T and -785A/G) may increase the risk of breast cancer. In conclusion, CYP1A1, CYP1A2, CYP1B1, CYP2A6, and CYP2E1 are responsible for most of the procarcinogens activation, and their gene polymorphisms are associated with the risk of cancers.

Keywords: CYP450, procarcinogens, carcinogens, DNA adduct, gene polymorphisms.

INTRODUCTION

Most of carcinogens chemicals exposure to human are not active by themselves, but they can become bio-active to ultimate carcinogens via cytochrome P450 (CYP450) enzymes [1, 2]. CYP450s are the most important drug metabolizing enzyme family exists among species, and can be found in the liver, intestine, skin, nasal epithelia, lung and kidney etc. [3]. The P450 superfamily is divided into families, such as CYP1, CYP2 and CYP3, and each of the isozyme with its own set of metabolized substrates [3, 4]. Researchers found that CYP1A1, CYP1A2, CYP1B1, CYP2A6, and CYP2E1 are responsible for most of the procarcinogens (eg. polycyclic aromatic hydrocarbons (PAHs), tobacco-related nitrosamines, benzene, styrene, and aflatoxin B1) [5, 6].

The polymorphisms of carcinogen metabolizing enzymes may influence enzymatic activity, and then lead to procarcinogens activation and/or deactivation. Most evidences indicate that both individual genetic susceptibility and cumulative exposure to environmental procarcinogens may result in the development of cancers. Therefore, in the present review, we summarized comprehensive information about 1) the role of different isozyme on the activation of procarcinogens, 2) related mechanism for carcinogens induced structural modifications of cellular macromolecules (such as DNA), 3) the association of CYP450s polymorphisms and risk of cancers development.

1. CYP1A1

This P450 subfamily consists of CYP1A1 and CYP1A2. The expression level of CYP1A1 is very low in the liver, while CYP1A2 is expressed mainly in the liver in humans [3, 7]. CYP1A1 is essentially present in intestine, lung and kidney [3]. Due to their roles in the metabolism of environmental carcinogens (PAHs and heterocyclic amines, which are mainly produced during the combustion process (motor vehicle exhaust, volcanic activity, forest fire, petroleum residues, and tobacco smoke condensate), both of these two enzymes have been studied extensively [3, 8, 9,] [10].

1.1. Role of CYP1A1 on Procarcinogens Activation

There is a widely accepted paradigm for CYP1A1 mediated carcinogens activation. CYP1A1 can metabolize PAHs to reactive epoxide intermediates, which could covalently bind to DNA, and result in tumors. The common examples include activation of Benzo[a]pyrene (B[a]P) and 7,12-Dimethyl benzanthracene (7,12-DMA). CYP1A1 firstly oxidizes B[a]P to B[a]P-7,8-oxide, and then the metabolite hydrolyzes to B[a]P-7,8-diol, further oxidized
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1.2. Association of CYP1A1 Polymorphisms and Risk of Cancer

CYP1A1 gene is located on chromosome 15q22–q24, four different polymorphisms of CYP1A1 gene, CYP1A1*2A, *2C, *3 and *4 have been described (http://www.imm.ki.se/CYPalleles/CYP1A1.htm). CYP1A1*2A and CYP1A1*2C polymorphisms are more widely studied due to not only their higher genotype frequency but also due to their possible involvement of an increased risk of several cancers [15, 16].

The CYP1A1*2A allele has a thymine (T) to cytosine (C) transition at an MspI site in 3’-noncoding region (rs4646903, -3801T/C), which has been associated with a higher enzymatic activity [17-19]. An adenine (A) to guanine (G) transition in exon 7 creates the second allelic variant (CYP1A1*2C, rs1048943, -4889A/G), which leads to an increase in enzymatic activity. These two polymorphisms have been found to increase risk of lung cancer, breast cancer, and colon cancer in specific ethnic groups [19-23]. As recently meta-analysis suggests that -3801T/C polymorphism is associated with the increased risk of lung and cervical cancer, in contrast, a higher frequency of lung cancer, leukemia, esophageal carcinoma, and prostate cancer may result from the -4889A/G polymorphism [24].

1.3. Role of CYP1A2 on Procarcinogens Activation

During the cooking of meats and fish, the heterocyclic amine may form and most of them are PhIP [25]. CYP1A2 mainly mediates PhIP activation as follows [26]: PhIP is firstly oxidized into \( \text{N}^2 \)-hydroxy-PhIP, and subsequently activated esters form, which can bind covalently with DNA (Fig. 2) [27]. Except CYP1A2, CYP1A1 also plays an important role in PhIP activation in extrahepatic tissues, e.g., the lung [11].

1.4. Association of CYP1A2 Polymorphisms and Risk of Cancer

CYP1A2 is highly polymorphic, besides CYP1A2*1F (rs762551, -163A/C), CYP1A2*1C (rs2069514, -3860G/A), and CYP1A2*1D (rs3569413, -2467T/delT) are three commonly studied CYP1A2 polymorphisms. Previous studies showed that -163A/C single nucleotide polymorphisms (SNP) could increase the activity of CYP1A2 [28, 29], while -3860G/A has been reported to decrease enzymatic activity [30]. Besides, other researchers found that smokers with -3860G/A, -2467T/delT and -163A/C polymorphism associated with elevated CYP1A2 activity [31-33]. CYP1A2 polymorphisms are found to be associated with the increase of cancer, however, the conclusions are inconsistent.

A significant association between lung cancer and the -2467T/delT has been observed in Tunisian population [34], male European smokers [33]. Besides, many researchers have concerned associations between the -163A/C polymorphism and lung cancer risk in Tunisian smokers [29], Europeans (independent of smoking status) [33], Latinos [35]. Although Deng et al. showed no association between -163A/C polymorphism and risk of lung cancer, the subgroup analysis indicated that -163A/C polymorphism may increase a trend risk for squamous cell carcinoma of lung in Caucasians [36]. Moreover, a recent meta-analysis showed that -163A/C polymorphism contributed to the risk of lung cancer under all four genetic models, and their subgroup analysis based on ethnicity further suggested that -163A/C polymorphism might increase the risk of lung cancer in Caucasians [37]. Taken together, -163A/C polymorphism is probably associated with the risk of lung cancer in special population.

CYP1A2 polymorphisms have also been evaluated if with association of other cancers risks, such as bladder cancer, stomach cancer, breast cancer etc. Altayli et al. observed smokers who carrying CYP1A2 -734CC genotype with a higher risk in development bladder cancer in a Turkish population [38], which in agreement with the finding of Pavanello et al. [39] who reported that -2467T/delT polymorphism may alter heavy cigarette smoking influence on the risk of bladder in Caucasian males. Moreover, genetic polymor-
phism of -163A/C did not influence the association of heterocyclic amine intake with stomach cancer in Japan [40], while genetic polymorphisms of -1545T/C (rs2470890) were associated with gastric cancer [41]. Another meta-analysis suggests that the -163A/C and -3860G/A polymorphism is a protective factor against colorectal cancer among Asians [42], which in consistent with AYARI et al. found that -3860G/A variant may reduce the risk of breast cancer [43]. Many meta-analyses have also been performed to clarify the influence of -163A/C, -2467T/delT and -3860G/A to all cancer risks, and the results were inconsistent. Wang et al. found that -163A/C polymorphism is probably associated with increased risk to cancer in Caucasians, however, this phenomenon has not been found in Asians and the mixed population [44]. In contrast, Li et al. showed that Caucasian population with -2467T/delT while -163A/C or -3860G/A has a higher risk in cancer development [45].

2. CYP1B1

CYP1B1 is constitutively expressed in normal tissues [3, 46], but its protein level is much higher in tumor cells [3, 47, 48]. Except for CYP1A1, CYP1B1 also plays an important role in PAHs activation, and the pro-carcinogens substrate of the two enzymes is found to be very similar [6, 11, 49, 50] e.g CYP1B1 can also help in the bio-activation of carcinogenic PAHs, such as B[a]P in human and rodents species [51, 52]. Moreover, B[a]P has been found to be involved in CYP1B1 induction via the aryl hydrocarbon receptor [51].

Long time and excessive exposure to estrogen is the principle factor for the development of breast cancer in women [53, 54]. The oxidative metabolites of estrogen (mediate by CYP1B1 and CYP1A1), in particular, the catechol estrogens, are mainly responsible for the development of estrogen carcinogenesis [14, 55, 56]. CYP1B1 and CYP1A1 mediate the estradiol (E2) oxidation to 2-hydroxyestradiol and 4-hydroxyestradiol, and then these catechol metabolites undergo one-electron oxidation to form reactive semiquinones intermediates, which could directly bind covalently with DNA (Fig. 3) [14]. Furthermore, molecular oxygen could receive the unpaired electron, which results from semiquinonones, subsequently formation of reactive oxygen species [57-59], results in lipid peroxidation, protein oxidation and DNA damage [60, 61].

2.1. Association of CYP1B1 Polymorphisms and Risk of Cancer

CYP1B1 has more than 179 polymorphism sites (http://ncbi.nlm.nih.gov/dbSNP). There are four commonly studied gene, Arg48Gly (rs10012, -48G/C), Ala119Ser (rs1056827, -119G/T), Leu432Val (rs1056836, -432G/C) and Asn453Ser (rs1800440, -453A/G). Besides, -48G/C, -119G/T and -432G/C have been shown to result in an increased catalytic activity of CYP1B1 [62]. Bandiera et al. [63] further concluded that -Ser453 allele may reduce CYP1B1 catalytic activity on procarcinogens metabolism (e.g. PAHs). Till present, many epidemiology studies from different parts of the world have evaluated the association between CYP1B1 polymorphism and cancer risk. Unfortunately, a reliable conclusion has not been found.

CYP1B1 is implicated in the metabolic activation of estrogen, which plays a key role in women breast cancer development. Economopoulos et al. reported race-specific association between 432G/C polymorphism and breast cancer risk may well exist [64]. The same, Li et al., reported that Chinese women who carrying -432G/C gene may have a higher risk of cervical cancer [65]. Moreover, a meta-analysis suggests that -48G/C, -119G/T and -453A/G polymorphisms have no influence on the risk of breast cancer [66]. -432G/C polymorphism has also been reported without association of endometrial cancer risk [67] and postmenopausal breast cancer risk [68].

During food, especially red meat is cooked at high temperatures, PAHs and heterocyclic amines always form, which could
increase the risk of colorectal cancer [69]. CYP1B1 is involved in this kind of pro-carcinogens activation. Trubicka et al., reported that no association has been found between the -48G/C, -119G/T and -432G/C alone with colorectal cancer risk, while haplotypes of -119G/T and -48G/C or -119G/T and -432G/C showed an association [70]. Hlavata et al. reported that individuals with -Ser453 allele may decrease the risk of development of colorectal cancer [71]. In contrast, Mei et al., showed that -453A/G polymorphism has no association with the risk of colorectal cancer among Caucasians [72].

CYP1B1 plays an important role in hormone metabolism, which associated with endocrine-induced cancers such as prostate cancer. Cui et al., conducted a meta-analysis found that exception for Asians, -432G/C polymorphism has no association with prostate cancer risk [73], while Yang et al., showed that -432G/C allele is significantly associated with an increased prostate cancer risk in Asians [74]. Recently, Zhang et al. addressed the same conclusion that no evidences show that -432G/C had a significant association with prostate cancer in overall population. After subgroup analyses by ethnicity, they found that -432G/C was significantly associated with prostate cancer risk in Asians [75].

Many studies have also been performed to clarify the potential contribution of -119G/T, -48G/C and -432G/C to other cancer risks, including bladder cancer, lung cancer and sporadic renal cell cancer. Results show those individuals with the genotypes -119G/T and -432G/C are at approximately 1.6-fold increased risk for bladder cancer [76]. Meta-analysis suggests that -432G/C, -119G/T and -48G/C polymorphism are low risk factors in lung cancer development [77, 78]. As compared to homozygous subjects with Ser119 or heterozygotes, the homozygous individuals with Ala119 had twice the risk for developing renal cell cancer [79].

3. CYP2A

In human, the CYP2A family consists of CYP2A6, CYP2A7 and CYP2A13. CYP2A6 is predominantly expressed in the liver, while CYP2A13 is mainly expressed in the respiratory tract [3]. CYP2As are important enzymes of tobacco-specific rocarcinogenic nitrosamines \( \alpha \)-hydroxylation [3, 80, 81].

CYP2A6 and CYP2A13 play an important role in tobacco-specific procarcinogenic nitrosamines metabolic activation, such as 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-buta-none (NNK), 4-(methyl-nitrosamino)-1-(3-pyri-dyl)-1-butanol (NNAL), \( N \)-nitrosonornicotine (NNN), \( N \)-Nitrosopyrrolidine (NPyR), and \( N \)-nitrosopiperidine (NPIP), into active lung carcinogens [82-85] (Fig. 4). The activated nitrosamines are the first to be used for hydroxylation, and then these unstable metabolites are rearranged to give diazonium ions that react with DNA, finally they exert their genotoxicity (Fig. 4). Besides, kushida et al., found that the same as CYP2A6, CYP2E1 is also involved in the activation of NYPY, and NNK, except NNN [84]. Their results suggested that CYP2E1 predominantly mediates metabolic activation of relatively short alkyl chain(s) (N-nitrosamines), whereas CYP2A6 is mainly responsible for relatively bulky alkyl chain(s) (N-alkyl nitrosamines) metabolic activation [84]. CYP2A6 and CYP2A13 are further involved in the activation of aflatoxin B1 [85].

3.1. Association of CYP2A6 Polymorphisms and Risk of Cancer

Till date, 31 numbered CYP2A6 allelic variants have been reported, meanwhile, due to a whole gene deletion in CYP2A6*4, Asians carrying this gene are considered to be poor metabolizer [86, 87]. CYP2A6*4 is more prevalent among in Asian (such as Japanese, Koreans and Thais individuals) [88-92]. Besides, the frequency is lower among non-Asian, such as Brazilians, French indi-
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individuals and Canadians [88, 93-95]. Moreover, most studies reported that the CYP2A6*4 is associated with a reduced risk of tobacco related to lung cancer in Asians [88, 96-98].

Studies have also been performed to clarify the potential contribution of CYP2A6*2 and CYP2A6*4 to other cancer risks, including bladder cancer and esophageal cancer. Rossini et al., showed that CYP2A6*2 has no effect on the risk of esophageal cancer in western population [99], which can be explained by the CYP2A6*2 allele result in a non-function enzyme [100]. Song et al., provide the evidence that the CYP2A6*4 gene defect may reduce the risk of bladder cancer in the Central China [101].

3.2. Association of CYP2A13 Polymorphisms and Risk of Cancer

CYP2A13 is mainly involved in several procarcinogens metabolic activation. Till date, researchers have identified a lot of CYP2A13 gene polymorphisms, and three of them, CYP2A13*7 (Arg101Stop, -578C/T), Arg257Cys (-3375C/T) and -7520C/G are known to exhibit functional consequences [102]. Both -7520C/G and -3375C/T may decrease CYP2A13 activity, and -578C/G even results in the formation of non-functional protein [103-105]. It was suggested that the variant -7520C/G, -3375C/T and -578C/G, which could reduce enzymatic activity, may provide protection against procarcinogens toxicity. In fact, there are inconsistent reports on the association of these gene and cancer risk. Wang et al. reported that individuals with -3375C/T allele might decrease the risk of lung cancer, but has no protection effects against lung squamous cell carcinoma [106]. However, Song et al. did not find any significant association between the variant allele -3375C/T and bladder cancer [101]. Timofeeva et al. also found that CYP2A13 polymorphism has no significant association with lung cancer risk in Caucasian patients [107], which in agreement with Tamaki et al. reported that CYP2A13 polymorphism has no association with lung cancer in Japanese [96]. Sharma et al further reported that CYP2A13 haplotype carrying variant alleles of -478T/C/-494T/C while not -7520C/G or -3375C/T, has association with lower risk of head and neck cancer in North Indians [108].

4. CYP2B

In human, the CYP2B family consists of CYP2B6 and CYP2B7. CYP2B6 has found with expression in the liver and in some extrahepatic tissues, whereas recent research has revealed that
CYP2B7 has only mRNA expression in lung tissue [1, 109]. Although CYP2B6 is not a main enzyme in drug metabolism but it is involved in procarcinogens activation such as aflatoxin B1 and dibenzanthracene [110, 111]. However, comparing the relative efficiency of CYP2B6 with other P450s on mutagenic activation, results indicated that CYP2B6 has less contribution in aflatoxin B1 activation [111].

4.1. Association of CYP2B6 Polymorphisms and Risk of Cancer

The human cytochrome CYP2B6 is a highly polymorphic enzyme, to date, 29 alleles have been identified in CYP2B6. Besides, the *6 allele is the most common at a frequency of 15-60% across populations, which consists of two amino acid changes Gln172His (-516G/T, rs3745274) and Lys262Arg (-785A/G, rs2279343). Subsequently, the *6 allele may decrease 50-75% hepatic liver expression [110, 112-114]. As its minor role in the procarcinogens metabolic activation, CYP2B6 polymorphisms associated with cancer susceptibility have not been well studied. However, as CYP2B6 mediate testosterone metabolism, an activity alteration in this enzyme may affect hormone exposure, subsequently influence the risk of breast cancer. Based on above findings, Justenhoven et al. reported that the genetic variants -516G/T and -785A/G were associated with a higher risk of breast cancer [114].

5. CYP2D

The CYP2D family consists of CYP2D6, CYP2D7 and CYP2D8. CYP2D6 is a functional enzyme, while CYP2D7 and CYP2D8 have been found to be non-functional genes [115-118]. CYP2D6 is expressed in various tissues, such as the liver, breast, intestine, lung and kidney [3, 119, 121], and accounting for 30% of drugs biotransformation on the market [120, 121]. However, limited reports have shown that CYP2D6 is involved in the procarcinogens activation. Crespi et al found that NNK exposure to 2D6/Hol cells may produce a decrease in relative survival and increase in mutant rate, this result suggests that CYP2D6 could mediate the metabolic activation of NNK [122].

5.1. Association of CYP2D6 Polymorphisms and Risk of Cancer

CYP2D6, located on chromosome 22, is a polymorphic gene with more than 90 documented alleles [http://www.snpedia.com/index.php/CYP2D6] [117]. The main variant alleles are CYP2D6*2, *3, *4, *5, *6, *9, *10, *17. Meanwhile, CYP2D6*2XN (rs16947, rs1135840) has been shown to increase in CYP2D6 activity, while CYP2D6*9 (rs5030656), *10 (rs1065852), *17 (rs28371706) leads to catalytically less active CYP2D6, and CYP2D6*3 (rs35742686), *4 (rs3892097), *5, *6 (rs5030655) even leads to the formation of no functional protein [http://www.snpedia.com/index.php/CYP2D6]. The allelic variant distribution differs among different ethnic groups. CYP2D6*2, *3, *4, *5, *6, *10 & *41 are more common in Caucasians, *2 and *17 are more frequently observed in Africans and *10 is more prevalent in Asians [123-125]. However, the association between CYP2D6 alleles and cancer development is rather complicated. Surekha et al have confirmed that the CYP2D6*4 polymorphism is associated with breast cancer [126]. Morrow et al. demonstrated that CYP2D6 genotype has no influence on the risk of recurrence in breast cancer [127]. In addition, a recent survey with 123 cases and 129 healthy controls has showed that no association was found between CYP2D6 and gastric cancer risk in Han ethnic population of Hunan Province [128]. Huang et al., found CYP2D6 *10ant has association with lung cancer in the Chinese [129]. And meta-analysis of case-control studies demonstrated that the heterozygote (GC) of rs1135840 may increase the risk of cancer, while the heterozygote (A/del) of rs35742686, G allele and G carrier (AG + GG) of rs16947 and homozygote (CC) of rs1135840 might be protective factors for cancer [130].

6. CYP2E1

In human, CYP2E1 is responsible for 2% of the drugs metabolism on the market [3]. Although CYP2E1 plays a minor role in drug metabolism, it mediates most of low molecular weight cancer susceptibility factors for cancer [130]. However, comparing the relative contribution of CYP2E1 to other P450s on mutagenic activation, CYP2B6 polymorphisms associated with cancer susceptibility have not been well studied. However, as CYP2B6 is involved in the procarcinogens activation. Crespi et al found that NNK exposure to 2D6/Hol cells may produce a decrease in relative survival and increase in mutant rate, this result suggests that CYP2D6 could mediate the metabolic activation of NNK [122].

6.1. Association of CYP2E1 Polymorphisms and Risk of Cancer

CYP2E1 gene is located on the 10q24.3-qter [135], Pst I (-1293G/C, rs3813867) and Rsa I (-1053 C/T, rs2031920) polymorphism could alter the enzyme activity and influence related N-nitrosamine-linked carcinogenesis, are thought to be the most common polymorphism in CYP2E1 gene investigated as the potential risk factor of common cancers [136]. Recently, several meta-analyses and case-control studies have indicated that PstI/RsaI polymorphism could increase the risk of gastric cancer [137-140], colorectal cancer [141, 142], oral cancer [143], head and neck cancer [144], bladder cancer [145], esophageal cancer [146, 147], and non-small cell lung cancer [148]. Besides, the interaction between Pst I/Rsa I polymorphism and alcohol consumption could increase the risk of hepatocellular carcinoma [149].

Moreover, there are two another commonly studied polymorphisms, -7632 T/A (rs6413432) with no functional significance of this polymorphism exists, while the variant allele of the 96-bp insertion polymorphism has been shown to express greater enzymatic
activity [150]. Qian et al. performed a meta-analysis demonstrating that 9-bp insertion polymorphism is a risk factor for developing colorectal cancer, while the -7632T/A polymorphism was not associated with colorectal cancer risk under all contrast models [150]. In agreement with Hesham et al. showed that -7632 T/A has no association with colorectal cancer development in the Saudi Population [136].

7. OTHER CYP450 ENZYMES

Yamazaki et al. developed TA1538 cells expressing P450 (expressing of human CYP2C8, CYP2C9, CYP2C19, CYP3A4 or CYP3A5) to investigate their metabolic activation of aflatoxin B1, 2-AAF, PhIP and B[a]P [151]. Results showed that CYP3A4 effectively mediates aflatoxin B1 activation, while CYP2C8 just weakly contributes in its activation. Neither CYP2C8, CYP2C9, CYP2C19, CYP3A4 nor CYP3A5 was proved to be involved in PhIP and 2-AAF activation. B[a]P was activated weakly by CYP3A4, CYP2C19, and CYP2C9, while not activated by CYP2C8 and CYP3A5 [152]. Another study has compared the effectiveness of CYP3A4 and 3A5 activating procarcinogens in reconstituted monooxygenase systems, and it was found that compared to CYP3A5, CYP3A4 had similar or higher activities to 24 tested procarcinogens [152]. Through CYP3A4 and CYP3A5 play limited role of activating procarcinogens, they are involved in the metabolism of most endogenous metabolites and of environmental xenobiotics, and then the reduction enzyme activity may play a role in the risk of developing cancer. CYP3A4 mediates testosterone oxidation to less active hormone (2b, 6b, or 15b hydroxytestosterone), a polymorphism that modifies the enzymatic activity may indirectly increase the conversion of testosterone to dihydrotestosterone, which could mediate prostate cell growth [158]. Meta-analysis showed that the CYP3A4*1B polymorphism has association with a higher risk of prostate cancer among African populations [159], while CYP3A5*3 polymorphism might increase the risk of cancer among Asian and Caucasian populations, but not among African populations [156].

DISCUSSION

Cancer is a leading cause of death worldwide, a report from WHO showed that cancer accounting for 8.2 million deaths in 2012, and the main types of cancer are: lung cancer (1.59 million deaths), oesophageal cancer (400 000 deaths), stomach cancer (723 000 deaths), colorectal cancer (694 000 deaths), breast (521 000...
deaths), liver cancer (745,000 deaths). It is speculated that these figures may rise up to 26.4 million (for new cases) by 2030 [160]. It has been proposed that the complex interplay between environmental factors and genetics plays a critical role in the process of carcinogenesis, including ultraviolet radiation, tobacco smoking, alcoholic beverages, viral infections, bacteria and parasites, dietary factors, and metabolism enzymes polymorphism. Therefore, in the present review, we summarized the role of different isozyme on the activation of procarcinogens, the related mechanism for carcinogens induced structural modifications of cellular macromolecules (such as DNA), and the association between CYP450s polymorphism and cancer risk.

CYP450s are the most important phase I metabolism enzyme to mediate drugs and other xenobiotics metabolism. Moreover, they are also responsible for most of the procarcinogens such as PAHs, heterocyclic amines, tobacco-related nitrosamines, benzene, styrene, and aflatoxin B1, leading to the formation of ultimate carcinogens [5-6]. Several modes of CYP450s activation of procarcinogens have been summarized in the present review (Fig. 6). 1) Formation of epoxide and diol-epoxides intermediates: CYP1A1 and CYP1B1 mainly mediate most PAHs activation to epoxide intermediates; CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2E1, and CYP3A4 are responsible for the activation of AFB1 to AFB1-2,3-oxide [161]; CYP2E1 is involved in benzene activation to benzene oxide. 2) Formation of diazonium ions: CYP2A6, CYP2A13 and CYP2E1 are responsible for the activation of most nitrosamines to unstable metabolites, which can rearrange to give diazonium ions. 3) Formation of reactive semiquinones and quinines: CYP1A1 and CYP1B1 are responsible for the activation of estradiol to catechol estrogens, subsequently formation of semiquinones; CYP2E1 is responsible for the activation of benzene to semiquinones and quinines. 4) Formation of toxic homoesterification: CYP1A1 and CYP1A2 are responsible for the metabolic activation of PhIP to N2-acetoxy-PhIP and N2-sulfonyloxy-PhIP, which is the carcinogenic metabolite. 5) Formation of free radical: CYP2E1 is responsible for the activation of tetrachloromethane to CCl3 1,1,1-chloro free radicals.

As the review reflected, more or less, the risk of most cancers development is associated with CYP450s polymorphism, which may result in increase/decrease in metabolic activity. Besides, depending on the expression level, each isozyme plays a different role in the development organ cancers development:

Lung is a target organ for the toxicity of inhaled compounds (i.e. PAHs or N-nitrosamines). Lung metabolizing enzymes, such as CYP1A1, 1B1, 2A6, 2A13 and 3A5 often play an important role in the disposition of these compounds [162]. Meanwhile, CYP1A1, 1B1, 2A6 and 2A13 are mainly involved in the procarcinogens bioactivation, leading to target tissue toxicity [162]. Based on above facts, the polymorphisms of these phase I xenobiotic-metabolizing enzyme may associate with increased/decreased risk of lung cancer.

Fig. (6). Main Modes of CYP450s activation of procarcinogens. 1) Formation of epoxide and diol-epoxides intermediates. 2) Formation of diazonium ions. 3) Formation of reactive semiquinones and quinines. 4) Formation of toxic y O-esterification. 5) Formation of free radical.
The polymorphisms -3801T/C and -4889A/G of CYP1A1 [17-19], -163A/C and -2467T/delT of CYP1A2 [28, 29], -48G/C, -119G/T and -32G/C of CYP1B1 [62], and -1293G/C and -1053 C/T of CYP2E1 [153] have been associated with elevated enzymatic activity, which results in an increased risk of lung cancer. Meanwhile, due to a whole gene deletion in CYP2A6*4, Asians carrying this gene are considered to be poor metabolizer [86, 87], and then it might decrease the risk of tobacco related lung cancer in Asians [88, 96-98]. However, there are some inconsistent results existing in some genes. For example, Wang et al. found that individuals carrying CYP2A13 -3375C/T allele have lower the risk of lung adenocarcinoma [106], while others found CYP2A13 polymorphism has no significant association with lung cancer risk in Caucasian and Japanese [107, 96].

The alimentary tract is the first line of defense against orally ingested procarcinogens. Mercurio et al. detected the mRNA level of CYP1A1, 1A2, 3A3 of colon and rectum from five healthy subjects [163]. Similar results were also reported by McKinnon et al. [164] for CYP3A4 and CYP3A5. Recently, the protein expression of CYP3A4, CYP2E1, CYP2C8 and CYP3A5 was determined in human colon mucosa [165, 166]. The polymorphisms -3801T/C and -4889A/G of CYP1A1 [23], PstI/Rsa and 9-bp insertion of CYP2E1 [141, 142, 150] have been reported to have an association with higher risk colon cancers. CYP1A2 -163A/C and -3860G/A polymorphisms have been found to be protective factors against colorectal cancer [42]. While for CYP1B1 -453A/G, some inconsistent results have been observed. Hlavata et al. reported that individuals with -Ser453 allele might decrease the risk of development of colorectal cancer [71]. In contrast, Mei et al. showed that the CYP1B1-453A/G polymorphism was not associated with the risk of colorectal cancer among Caucasians [72].

Breast cancer is the most common cause of cancer related deaths in women, and CYP450s are essential for the estrogen metabolism and formation of mutagenic and/or carcinogenic metabolites, which are important for the development of breast cancer. Several studies have evaluated CYP expression profiles in the breast. Iscan et al. showed that both in tumour and normal tissues, CYP1A1 mRNA level was very low, besides, CYP1B1, CYP2B6, CYP2C, CYP2D6 and CYP2E1 are all expressed in control and tumours tissues, whereas CYP2A6, CYP2A7, CYP2A13, CYP3A4 and CYP3A5 mRNAs have no expression in control or tumours tissue [156]. The polymorphisms of CYP1A1 -3801T/C and -4889A/G [24], CYP1B1-432G/C [64, 65], CYP2B6-516G/T and -785A/G [114], have an association with higher risk of breast cancer. AYARI et al. found that the CYP1A2 -3860G/A variant may reduce the risk of breast cancer [43]. While for CYP2D6*4, some inconsistent results are observed. Surekha et al confirmed that that the CYP2D6*4 polymorphism is associated with breast cancer etiology [126]. In a case-control study, Morrow et al. have demonstrated that CYP2D6 genotype has no significant effect on the risk of recurrence in breast cancer [127].

The same for other organ cancer, not only one CYP450s polymorphism contributes to cancer risks. A significant association has been reported between the CYP1A2 -734CC (Turkish population), -2467T/delT (Caucasian males), CYP1B1 -119G/T, CYP2E1 PstI/Rsa genotype and bladder cancer risk [38, 39, 76]. Song et al. provide the evidence that the CYP2A6*4 gene defect may reduce the risk of bladder cancer in Central China, while not for the variant allele CYP2A13 -3375C/T [101], CYP2E1 PstI/Rsa [142-145] and CYP1A2 -1545T/C [41] polymorphism might increase the risk of gastric cancer, while CYP1A2 -3375C/T did not influence the association of heterocyclic amine intake with stomach cancer in Japan [40]. However, limited reports are associated with the expression of CYP450s in these organs, therefore, a relationship between them and organ cancer risk has not been found through the present review.

It is known that (1) primary prevention; (2) secondary prevention; (3) tertiary prevention [167, 168] are the three main important cancer intervention methods. Moreover, the goal of primary prevention is to prevent cancer occurrence [167, 168], and several mechanisms associated with primary prevention via interference of metabolic enzymes are listed earlier [167, 168].

- Inhibition of activation of promutagens by phase I enzymes.

Since human CYPs catalyze the metabolic activation of procarcinogens, the use of special chemicals that could suppress the expression of CYP and/or inhibit the catalytic activity of these enzymes is an effective strategy for chemoprevention. For example, natural products and their synthetic derivatives were major sources for screening of specific CYP1 inhibitors, according to their structural features; these identified chemicals are divided into the following categories: flavonoids, trans-stilbenes, coumarins, terpenoids, alkaloids, quinones, isothiocyanates and synthetic aromatics [169, 170]. And one of their most important characteristics, responsible for above compounds cancer preventive properties, is their ability to decrease CYP1 enzymes activity.

- Induction of phase II enzymes, which acceleration of capture of reactive metabolites.

However, these mechanisms are just hypothetical. All the CYP450 enzymes discussed in the present review are also involved in the metabolism of therapeutic drugs, and the inhibition or induction of their activity may cause undesired drug-drug interaction.

In addition, reduced glutathione (GSH) represents the most important cell protecting biomolecule against reactive metabolites induced cytotoxicity. For instance, a study found that DNA adduct levels were strikingly enhanced in GSTM1 null patients [171]. Therefore, in our opinion, the best protective effect is achieved by supplying GSH or augmenting glucuronidation capacity to stimulate detoxification. Moreover, further related studies are needed to verify these findings.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES
[21] He and Feng
Role of Metabolic Enzymes P450 (CYP)

Current Drug Metabolism, 2015, Vol. 16, No. 9


Role of Metabolic Enzymes P450 (CYP)

Current Drug Metabolism, 2015, Vol. 16, No. 9 13


[128] Luo, Y.P.; Chen, H.C.; Khan, M.A.; Chen, F.Z.; Wan, X.X.; Tan, B.; Ou-Yang, F.D.; Zhang, D.Z. Genetic polymorphisms of metabo-


Qian, J.; Song, Z.; Lv, Y.; Huang, X. CYP2E1 T7632A and 9-bp insertion polymorphisms and colorectal cancer risk: a meta-analysis based on 4,592 cases and 5,918 controls. *Tumor Biol.*, 2013, 34, 2225-231.


