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Review

Polymorphism of CYP450 and cancer susceptibility[1]

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KEY WORDS cytochrome P-450; phenotype; genotype; polymorphism (genetics); disease susceptibility

ABSTRACT

CYP450s form a superfamily involved in the metabolism of many endogenous and exogenous substrates. In this review, the substrates, probe drugs, genetic polymorphisms, and associated cancers of CYP1A1, CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 are summarized.

INTRODUCTION

Cytochrome P450s (CYP450s) which form a superfamily of heme-thiolate proteins are involved in the primary oxidation of numerous lipophilic compounds including endogenous substrates like fatty acids, steroids, and vitamins as well as exogenous substrates like drugs, dietary substrates, and environmental pollutants. More than 200 cDNAs coding for CYP450s have been isolated so far and classified into fourteen families and twenty subfamilies on the basis of primary amino acid sequence similarity[1]. In the recent years, increased attention has been paid to interindividual and ethnic differences in the gene structures and activities of CYP enzymes, which are important not only for drug use in clinic but also for the explanation of the underlying causes of certain cancers. In this overview, we discuss substrates, probe drugs, and polymorphisms of CYP1A1, CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, and their association with susceptibility to various cancers.

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CYP1A1

CYP1A1 plays a more important role in the bioactivation of precarcinogens than in the biotransformation of drugs. Polycyclic aromatic hydrocarbons (PAHs) are the main substrates that are oxidised to phenolic products and epoxides by CYP1A1[2]. Low amount of CYP1A1 transcript is detected in noninduced human pulmonary macrophages where CYP1A1 is mainly expressed. Therefore, it is an inducible enzyme that can be induced by planar PAHs, 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), flavones and indole derivatives. Agonist binding to the aryl hydrocarbon receptor (AhR), leads to the 90 kDa heat shock protein (Hsp90) to dissociate from the AhR. That is followed by the binding of the ligand-AhR complex to the aryl hydrocarbon receptor nuclear translocator (Arnt), which finally binds to xenobiotic responsive elements (XRE) in the 5′-flanking region of *CYP1A1*. And this leads to the transcriptional activation of *CYP1A1*, followed by increased expression of the enzyme[3]. The induced activity of CYP1A1 can be measured *in vitro* by the ethoxyresorufin-*O*-deethylase (EROD) activity in lymphocytes after being induced by benz(a)anthracene [B(a)A]. The low and high induction phenotypes are in proportions of 89 % and 21 % in respective populations[4].

CYP1A1 is located at chromosome 15 in humans. A T250C point mutation in the 3′-flanking region gives rise to an *Msp*I cleavage site in the rare m2 allele. The frequency of m2 allele is 30 % in Caucasians. Another substitution, A→G, in exon 7 yielding an Ile462Val amino acid exchange in the heme binding region is found to be coupled to the m2 allele[5]. The effects of these mutations on CYP1A1 activity are still ambiguous. Some have reported that neither *Msp*I polymorphism nor the exon 7 base change is correlated with CYP1A1 inducibility. On the other hand, some report that significantly higher level of inducible EROD activity exists among the rare variant alleles when compared with the wild

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types.

Several studies suggest that the genetic polymorphisms of the gene may play a role in a predisposition to cancer. The presence of the *Msp*I [odds ratio (OR) 3.15, $P = 0.0196$] or Ile-Val (OR 1.99, $P = 0.0855$) variant allele of *CYP1A1* increases hepatocelluar carcinoma (HCC) risk among smokers, but poses no increased risk among non-smokers. In the absence of the Ile-Val variant allele, the *Msp*I polymorphism is still associated with smoking-related HCC. Thus, Yu *et al* suggest that tobacco-derived PAHs play a role in HCC risk among chronic HBV carriers, and *CYP1A1* polymorphism is an important modulator of the hepatocarcinogenic effect of PAHs. The *Msp*I and Ile-Val polymorphisms of *CYP1A1* may have different mechanisms for increasing susceptibility to smoking-related HCC[6]. There is a significantly higher prevalence of m2 allele in the patients with squamous cell carcinoma or lung cancer[7]. However, at least for Caucasians, this mutation explains only a fraction of the inducible individuals. Either other genetic or non-genetic factors due to, for instance, a common environment contribute to the familiar resemblance in the CYP1A1 induction measured by EROD activity. Polymorphic mutations in the *Arnt* gene or other genes may link with different inducible activities of CYP1A1.

CYP1A2

CYP1A2 is responsible for metabolizing caffeine, acetaminophen, theophylline, imipramine, propranolol, and verapamil. Its activity can be induced with smoking, caffeinated drinks, and omeprazole, and inhibited by cimetidine, quinolones, furafylline, citalopram, fluoxetine, fluvoxamine, paroxetinet, methoxsalen, and moclobemide[8]. The popular probe drug for CYP1A2 activity is caffeine[9]. The distribution of CYP1A2 activity for healthy people appears bimodal in nonsmokers and smokers using the ratio of 1,7-dimethylxanthine/caffeine (17X/137X) in plasma at 6 h after oral administration of 200 mg caffeine. The frequency of PMs is about 5 % in Chinese and 10 % in Caucasians.

CYP1A2 is also located at chromosome 15. Polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP) has been used in the identification of the genetic polymorphisms of *CYP1A2*. Two gene variants are found with functional enzyme activities: one with a G→A point mutation in the 5′-flanking region which gives rise to a *Dde*I cleavage site[10,11] and the other with a C→A mutation in intron 1 resulting in the loss of a *Bsp*120I cleavage site[12]. The mutant frequency is 23 % for the former in Japanese and 44 % for the latter in Caucasians. Similar results are also observed in Chinese population (Tab 1). The former point mutation shifts a high-activity phenotype to a low-activity phenotype in smokers, but not in nonsmokers. And the later point mutant A may either be a direct cause of increased CYP1A2 activity, or be genetically linked to other genetic polymorphisms conferring high inducibility.

Tab 1. Allele frequencies for the 5′-flanking region and intron1 of *CYP1A2* in different population.

Allele	5′-Flanking region		Intron1		Reference
	G	A	A	C	
Chinese	0.75	0.25	0.67	0.33	Unpublished
Japanese	0.77	0.23	–	–	11
German	–	–	0.68	0.32	12

2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)[13] and aflatoxinB1[14] are the main procarcinogens contained in fried foods and environment, and involved in the development of colon cancer, breast cancer and hepatocelluar carcinoma. All of them are mostly bioactivated by CYP1A2 *in vivo*. There are many reports about the relationship between CYP1A2 and the cancers mentioned above. However, the association between the genetic polymorphisms of *CYP1A2* and these cancers is still unknown, partly because the genetic polymorphisms have not yet been intensively explored.

CYP2C19

CYP2C19 participates in metabolizing a lot of clinically used drugs including omeprazole, chloroguanide, citalopram, certain barbiturates, propranolol, diazepam and certain tricyclic antidepressants[15]. Individuals can be divided into two groups, poor metabolizers (PMs) and extensive metabolizers (EMs), depending on the ability of 4′-hydroxylate-*S*-mephenytoin. The PMs and EMs are determined by the mephenytoin *S*/*R* ratio in urine, which has marked ethnic differences[16]. The incidence of PMs is much lower in Caucasian populations (3 % – 5 %) than in Oriental populations (18 % – 23 %).

CYP2C19 is located at chromosome 10. Recent studies have demonstrated two major inactivating mutations in *CYP2C19*: *CYP2C19* × 2 (m1) with a G681A

mutation in exon4 that generates a *SmaI* cleavage site[17] and *CYP2C19* * 3 (m2) with a G636A mutation in exon4 that produces a *Bam*HI cleavage site[18]. Each creates a premature stop codon and a truncated protein. *CYP2C19* * 2 accounts for 75 % – 85 % of the defective alleles in both Caucasian and Oriental PMs. *CYP2C19* * 3 accounts for the remaining defective alleles in Oriental PMs but appears extremely rare in white persons. In our laboratory, the results of genotyping are well in consistence with that of phenotyping and PM can be identified by genotyping analysis with *Sma*I and *Bam*HI, which is more convenient than the phenotyping analysis[19].

Up to now, there is no report about the relationship between CYP2C19 and susceptibility to cancer. But it is one of the best examples of CYP450s whose individual and ethnic differences in response to drugs has been fully examined. Some non-genetic factors that influence the enzyme activity of CYP2C19 have also been identified so far. Rifampicin is a potent inducer[20], and administration of a therapeutic dose of fluvoxamine significantly decreases the *S/R* ratio of mephenytoin[21].

CYP2D6

CYP2D6 takes part in the biotransformation of the antihypertensive drug debrisoquine, neuroleptics, lipophilic β-blocking agents, and tricyclic antidepressants[22]. The urinary ratio of 4-hydroxydebrisoquine and debrisoquine at 8 h intervals following oral administration of the probe drug debrisoquine is used to distinguish the PM and EM phenotypes. The frequency of PM is about 7 % in Caucasians and 1 % in Chinese[23].

CYP2D6 is located at chromosome 22. Three major gene variants have been found with the functional mutations: *CYP2D6* * 3 in which A2367 is deleted causing a frameshift mutation, *CYP2D6* * 4 in which a G1934A mutation causes a splicing defect and *CYP2D6* * 5 where the whole functional gene has been deleted. The *CYP2D6* * 5 allele is evenly distributed among black, Asian, and Caucasian populations. However, *CYP2D6* * 3 and *CYP2D6* * 4 are almost exclusively presented in Caucasian populations, which are consistent with the results of phenotyping analysis in that the incidence of PM is higher in Caucasian populations than in Oriental populations[24]. Thus, antidepressants are prescribed in lower doses for Chinese. In Caucasians, *CYP2D6* * 3, *CYP2D6* * 4, and *CYP2D6* * 5 represent 0 % – 2 %, 75 %, and 5 % – 10 % of PMs, respectively. The remaining 10 % of PMs are due to other rare mutations, some of which have recently been characterized, such as *CYP2D6* * 6, *CYP2D6* * 7, *CYP2D6* * 8, *CYP2D6* * 9, and *CYP2D6* * 16[25].

Tobacco-specific nitrosoamine 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone is the only precarcinogenic compound found to be metabolized by CYP2D6[26]. The PM of CYP2D6 metabolizes nicotine at a slower rate as compared to the EM. Ayesh *et al* showed a link between the phenotypes and lung cancer[27]. But genotyping analysis did not support any association between lung cancer risk and the *CYP2D6* alleles. The incidences of nonfunctional alleles are higher in the people with hepatocellular carcinoma[28], but lower in the people with breast cancer and head and neck squamous cell cancer than in reference patients[29]. The genetic polymorphisms of *CYP2D6* may contribute more to hepatocellular carcinoma than to the lung cancer. However, the substrates mediated by CYP2D6 for those cancers remain to be elucidated.

CYP2E1

Drugs such as chlorzoxazone, acetaminophen, theophylline, dapsone, and some volatile anesthetics are all substrates for CYP2E1. Its inducers include ethanol, imidazole, acetone, and isoniazid, while disulfiram, dihydrocapsaicin, phenethylisothiocyanate, and chlormethiazole are all its inhibitors[30]. Phenotyping for CYP2E1 is carried out by oral administration of the probe drug chlorzoxazone, and the ratio of 6-hydroxychlorzoxazone/chlorzoxazone in plasma is determined[31].

CYP2E1 is located at chromosome 10. In Caucasians there is complete linkage disequilibrium between the two point mutations, C-1019T and G-1259C, in the 5′-flanking region which results in *Rsa*I and *Pst*I polymorphism, respectively. The genotypes can therefore be divided by the digestion with the two restriction endoenzymes into three types: type A (homozygous "normal" alleles, *Rsa*I + *Pst*I-, c1/c1), type B (heterozygous, c1/c2), and type C (homozygous alleles with the nucleotide exchanges, *Rsa*I- *Pst*I+, c2/c2)[32,33]. In intron 6 another genetic polymorphism is identified by *Dra*I which distinguishes three genotypes: CC, CD, and DD[34]. The c2 rare allele frequency is about 0.05 in Caucasians and 0.23 in Oriental populations. And the frequency of C rare allele is about 0.1 and 0.18 in Caucasians and Oriental populations respectively, which shows an apparent ethnic difference. Patients with the mutated genotype appear less inducible than the wild

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types after ethanol ingestion. Thus we should pay more attention to the PM patients of CYP2E1 especially when we use volatile anesthetics as they are very sensitive to them. Recently two new defective alleles were found: *CYP2E1* * 2 with a G1168A point mutation in exon2 causing an R76H amino acid substitution and *CYP2E1* * 3 with a G10059A base substitution in exon 8 yielding a V3891 amino acid exchange. Their effects on the activity of CYP2E1 are still unclear[35].

CYP2E1 is of critical importance in the metabolic activation of many low-molecular-weight carcinogens including halogenated and nonhalogenated alkenes and alkenes, and *N*-nitrosamines that are ubiquitous in the environment, present in tobacco smoke, and formed endogenously in stomach[36]. Although there has been a considerable controversy in the past about the relationship between cigarette smoking and hepatocelluar carcinoma, most recent studies have implicated cigarette smoking as a major nonviral risk factor for hepatocelluar carcinoma. Homozygote for the c1/c1 genotype significantly increases the risk of developing hepatocelluar carcinoma in cigarette smokers[37]. The same result is observed in patients with esopharyngeal carcinoma[38]. However, the reports about the association between the *Rsa*I and *Pst*I polymorphism and lung cancer are conflicting. One study showed that the c2/c2 allele was less common among patients with lung cancer[39], while a Finish population study did not observe any difference in the allele frequency between cancer patients and controls[40]. This contradiction also exists in the studies of the possible relationship between the genetic polymorphism of *CYP2E1* and alcoholic liver disease. So the mechanistic reason why c1/c1 homozygotes of *CYP2E1* are more susceptible to hepatocelluar carcinoma merits further study. No functional significance of the polymorphism detected by *Dra*I digestion is currently known. This may be explained by its position in intron 6 that does not have any effect on the gene expression.

CYP3A4

CYP3A4 is the most abundant CYP isoenzyme expressed in the liver and intestine of humans. *In vivo*, it participates in the biotransformation of more than sixty percent of drugs including nifedipine, erythromycin, imipramine, cyclosporine A, troleandomycin, quinidine, midazolam, lidocaine, diltiazem, and flutamide. Phenobarbital, dexamethasone, rifampicin, and phenytoin sodium can induce the activity of CYP3A4, while troleandomycin, erythromycin, triacetyloleandomycin, ketoconazole, and gestodene inhibit it[41]. Although erythromycin, midazolam, and dapsone are used as probe drugs in the phenotyping analysis of CYP3A4, they all have limitations and lack correlation with each other, which holds back the research on the substrates and activity distribution of CYP3A4 *in vivo*[42].

CYP3A4 is located at chromosome 7. An adenine (A) to guanine (G) transition is identified in the 5′ promotor region of the *CYP3A4* gene at positiion −292 in a sequence motif known as the nifedipine-specific element. The incidence of the G allele are 3.6 %, 54.6 %, 9.3 %, 0.0 %, and 0.0 % for white Americans, black Americans, Hispanic Americans, Japanese Americans, and Chinese Americans, respectively. However, this promotor region polymorphism does not appear to play a major role in determining the constitutive *CYP3A4* expression[43].

A low CYP3A4 activity, assessed by dapsone *N*-hydroxylation, is a statistically significant susceptibility risk factor for the development of aggressive bladder cancer[44]. *P53* and *Rb* gene mutations are intermediate biomarkers useful for the predication of neoplastic progression in bladder cancer. Romkes *et al* further confirmed that a low CYP3A4 activity was significantly associated with over expression of *P53* mutation, which indicates that CYP3A4 detoxifies an unknown bladder procarcinogen in the environment that preferentially induces *P53* mutations[45]. People once thought that aflatoxinB1 was activated by CYP3A4 and detoxified by CYP1A2. However, recent studies showed that both CYP1A2 and CYP3A4 took part in the activation and detoxification of aflatoxinB1, and that CYP1A2 was principally responsible for the bioactivation of aflatoxinB1 at low substrate concentrations associated with dietary exposure. Thereby aflatoxinB1 is activated by CYP1A2 and detoxified by CYP3A4 in people with a high CYP1A2 activity[14]. Since CYP3A4 is mainly involved in the activation of aflatoxinB1 in the people with low CYP1A2 activity, the causative role of CYP3A4 in hepatocelluar carcinoma is still dilemmatic and needs to be further studied.

SUMMARY AND FUTURE CONSIDERATION

The substrates, probe drugs, genetic polymorphisms, and associated cancers of the CYP450s mentioned above are all briefly presented in Tab 2 which shows that some CYP450s, such as CYP2E1 and CYP3A4, have not been studied in Chinese population

until now. And there are more than fifty minorities in China that may have large individual and ethnic differences regarding CYP450 activities. However, such differences have not yet been fully explored too. Further extensive studies in individual and ethnic differences of CYP450s should be continued not only for better understanding the genetic or non-genetic factors involved in the polymorphism of CYP450 but also for using drugs correctly.

Effects of non-genetic factors, especially exogenous drugs, on the activities of CYP450 have been paid much more attention recently. A patient usually takes several drugs at the same time. When a drug is an inhibitor of a kind of CYP450, it may increase the plasma concentration of other drug metabolized by the CYP450, which can be dangerous for the patient. Thereby it is meaningful to identify the drugs metabolized or influenced by CYP450s. And this will contribute to the drug interaction studies.

As detailed above, we know that the association between some CYP450s and susceptibility to certain cancers have been confirmed. The genetic polymorphisms of other drug metabolizing enzymes such as glutathione *S*-transferase, *N*-acetyltransferase and epoxide hydrolase are also found to be linked with susceptibility to hepatocelluar carcinoma[46]. But there has not been an effective biomarker of CYP450 for any cancer, and human cancer is a multistage process with the involvement of multiple risk factors, so there is still a long way to go in the identifying the causative role of CYP450 in cancer. Furthermore, since these CYP450s can activate many xenobiotics to highly toxic products, effective inhibitors of them may eventually provide useful tools for the prevention and treatment of the associated diseases.

Tab 2. The substrates, probe drugs, genetic polymorphisms, allele frequencies in Chinese, and associated cancers of some CYP450s.

	Substrates	Probe drug	Gene location/ chromosome	Genetic polymorphism	Allele frequency in Chinese	Associated cancer	Reference
CYP1A1	PAHs	–	15	T+250→C (3′-flanking region) A462→G (exon7)	–	squamous cell carcinoma lung cancer hepatocelluar carcinoma	2,5,6,7
CYP1A2	caffeine, acetaminophen, theophylline, imipramine, propranolol, verapamil, PhIP, MeIQx, aflatoxinB1	caffeine	15	G-2964→A (5′-flanking region) C734→A (intron1)	0.25 0.67	colon cancer, breast cancer, hepatocelluar carcinoma	9, 11, 12, 13,14
CYP2C19	omeprazole, chloroguanide, citalopram, certain barbiturates, propranolol, diazepam, certain tricyclic antidepressants	mephenytoin	10	G681→A (exon4) G636→A (exon4)	0.366 0.074	–	15, 16, 17, 18
CYP2D6	debrisoquine, neuroleptics, lipophilic β-blocking agents, tricyclic antidepressants, nicotine	debrisoquine	22	A2367 deleted G1934→A Gene deletion	0 0.004 0.057	hepatocelluar carcinoma, breast cancer, head and neck squamous cell carcinoma	22, 24, 25, 27,28,29
CYP2E1	chlorzoxazone, acetaminophen, theophylline, dapsone, some volatile anesthetics, *N*-nitrosamines, halogenated and nonhalogenated alkanes and alkenes	chlorzoxazone	10	C-1019→T (5′-flanking region) G-1259→C (5′-flanking region) T7668→A (intron6) G1168→A (exon2) G10059→A (exon8)	–	hepatocelluar carcinoma	30, 31, 32, 33, 34, 35, 36, 38, 39, 40
CYP3A4	nifedipine, erythromycin, imipramine, cyclosporine A, troleandomycin, quinidine, midazolam, lidocaine, diltiazem, flutamide, dapsone, aflatoxinB1	dapsone	7	A-292→G (5′-flanking region)	–	bladder cancer, hepatocelluar carcinoma	41, 42, 43, 44

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REFERENCES

1 Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ, *et al*. P450 superfamily: update on new sequence, gene mapping, accession numbers and nomenclature. Pharmacogenetics 1996; 6: 1 – 42.

2 Omiecinski CJ, Redlich CA, Costa P. Induction and developmental expression of cytochrome P4501A1 messenger RNA in rat and human tissues: detection by the polymerase chain reaction. Cancer Res 1990; 50: 4315 – 21.

3 James P, Whitlock J. Induction of cytochrome P4501A1. Annu Rev Pharmacol Toxicol 1999; 39: 103 – 25.

4 Catteau A, Douriez E, Beaune P, Poisson N, Bonaiti-Pellie C, Laurent P. Genetic polymorphism of induction of CYP1A1 (EROD) activity. Pharmacogenetics 1995; 5: 110 – 9.

5 Kawajiri K, Nakachi K, Imai K, Yoshii A, Shinoda N, Watanabe J. Identification of genetically high risk individuals to lung cancer by DNA polymorphism of the cytochrome P4501A1 gene. FEBS Lett 1990; 263: 131 – 3.

6 Yu MW, Chiu YH, Yang SY, Santella RM, Chern HD, Liaw YF. Cytochrome P450 1A1 genetic polymorphisms and risk of hepatocellular carcinoma among chronic hepatitis B carriers. Br J Cancer 1999; 80: 598 – 603R.

7 Kawajiri K Chapter 15. CYP1A1. IARC Sci Publ 1999; 148: 159 – 72.

8 Xu ZH, Zhou HH. Cytochrome P4501A2 in drug metabolism. Chin J Clin Pharmacol 1996; 12: 115 – 21.

9 Ou-Yang DS, Huang SL, Wang W, Xie HG, Xu ZH, Zhou HH. Phenotypic polymorphism and gender-related differences of CYP1A2 activity in a Chinese population. Br J Clin Pharmacol 2000; 49: 145 – 51.

10 Chida M, Yoko T, Fukui T, Kinoshita M, Yokota J, Kamataki T. Detection of three genetic polymorphisms in the 5′-flanking region and intron 1 of human *CYP1A2* in the Japanese population. Jpn J Cancer Res 1999; 90: 899 – 902.

11 Nakajima M, Yokoi T, Mizutani M. Genetic polymorphism in the 5′-flanking region of human CYP1A2 gene: Effect on the CYP1A2 inducibility in humans. J Biochem 1999; 125: 803 – 8.

12 Sachse C, Brockmoller J, Bauer S. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 *CYP1A2* gene tested with caffeine. Br J Clin Pharmacol 1999; 47: 445 – 9.

13 Boobis AR, Lynch AM, Murray S. CYP1A2-catalyzed conversion of dietary heterocyclic amines to their proximate carcinogens is their major route of metabolism in humans. Cancer Res 1994; 54: 89 – 94.

14 Gallagher EP, Kunze KL, Stapleton PL. The kinetics of aflatoxin B1 oxidation by human cDNA-expressed and human liver microsomal cytochromes P450 1A2 and 3A4. Toxicol Appl Pharmacol 1996; 141: 595 – 606.

15 Goldstein JA, de Morais SM. Biochemistry and molecular biology of human CYP1A2 subfamily. Pharmacogenetics 1994; 4: 285 – 99.

16 Xie HG, Huang SL, Zhou HH. High performance liquid chromatography determination of urinary 4′-hydroxymephenytoin: a metabolic marker for the hepatic enzyme CYP2C19 in humans. J Chromatogr B Biomed Appl 1995; 668: 125 – 31.

17 de Morais SM, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem 1994; 269: 15419 – 22.

18 de Morais SM, Wilkinson GR, Blaisdell J, Meyer UA, Nakamura K, Goldstein JA. Identification of a new genetic defect responsible for the polymorphism of S-mephenytoin metabolism in Japanese. Mol Pharmacol 1994; 46: 594 – 8.

19 Shu Y, Zhou HH. Individual and ethnic differences in CYP2C19 activity in Chinese populations. Acta Pharmacol Sin 2000; 21: 193 – 9.

20 Feng HJ, Huang SL, Wang W, Zhou HH. The induction effect of rifampicin on activity of mephenytoin 4′-hydroxylase related to ml mutation of *CYP2C19* and gene dose. Br J Clin Pharmacol 1998; 45: 27 – 9.

21 Xu ZH, Xie HG, Zhou HH. *In vivo* inhibition of CYP2C19 but not CYP2D6 by fluvoxamine. Br J Clin Pharmacol 1996; 42: 518 – 21.

22 Meyer CF, Zanger UM, Grant D, Blume M. Genetic polymorphism of drug metabolism. Adv Drug Res 1990; 19: 198.

23 Mahgoub A, Dring LG, Idle IR, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. Lancet 1977; 2: 584.

24 Jorge LF, Eichelbaum M, Griese EU, Inaba T, Arias TD. Comparative evolutionary pharmacogenetics of CYP2D6 in Ngawbe and Embera Amerindians of Panama and Colombia: role of selection versus drift in world populations. Pharmacogenetics 1999; 9: 217 – 28.

25 Marsh JC, Chowdry J, Parry-Jones N, Ellis SW, Muir KR, Gordon-Smith EC. Study of the association between cytochromes P450 2D6 and 2E1 genotypes and the risk of drug and chemical induced idiosyncratic aplastic anaemia. Br J Haematol 1999; 104: 266 – 70.

26 Crespi CL, Penman BW, Gelboin HV. A tobacco smoke derived nitrosamine 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone is activated by multiple human cytochrome P450s including the polymorphic human cytochrome P4502D6. Carcinogenesis 1991; 12: 1197 – 202.

27 Ayesh R, Idle JR, Ritchie JC. Metabolic oxidation phenotypes as markers for susceptibility to lung cancer. Nature 1984; 312: 169 – 70.

28 Agundez JA, Ledesma MC, Benitez PJ. *CYP2D6* gene and risk of liver cancer. Lancet 1995; 345: 830 – 1.

29 Topic E, Stefanovic M, Nikolic V, Zoricic I, Ivanisevic AM, Zuntar I. Detection of CYP2D6 * 3 and 2D6 * 4 allelic variants by PCR-restriction fragment length polymorphism. Clin Chem Lab Med 1998; 36: 655 – 8.

30 Wu ZL, Xie HG, Zhou HH. Recent advance of cytochrome P4502E1. Chin J Clin Pharmacol 1997; 13: 57 – 62.

31 Powell H, Kitteringham NR, Pirmohamed M. Expression of cytochrome P4502E1 in human liver: assessment by mRNA, genotype and phenotype. Pharmacogenetics 1998; 8: 411 –

21.
32 Watanabe J, Hayashi SI, Kawajiri K. Different regulation and expression of the human *CYP2E1* gene due to the *Rsa* I polymorphism in the 5′-flanking region. J Biochem 1994; 116: 321 – 6.
33 Watanabe J, Hayashi SI, Nakachi K. *Pst* I and *Rsa* I RFLPs in complete linkage disequilibrium at the *CYP2E1* gene. Nucleic Acids Res 1990; 18: 7194.
34 Uematsu F, Kikuchi H, Moyomiya M. Association between restriction fragment length polymorphism of human cytochrome P4502E1 gene and susceptibility to lung cancer. Jpn J Cancer Res 1991; 82: 254 – 6.
35 Hu Y, Oscarson M, Johansson I, Yue Qy, Dahl ML, Tabone M, *et al*. Genetic polymorphism of human *CYP2E1*: characterization of two variant alleles. Mol Pharmacol 1997; 51: 370 – 6.
36 Guengerich FP, Kim DH, Lwasaki M. Role of human cytochrome P4502E1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 1991; 4: 168 – 79.
37 Yu MW, Yarborough AG, Chiamprasert S. Cytochrome P4502E1 and glutathione S-transferase M: polymorphisms and susceptibility to hepato cellular carcinoma. Gastroenterology 1995; 109: 1266 – 73.
38 Hildesheim A, Anderson LM, Chen CJ. *CYP2E1* genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 1997; 89: 1207 – 12.
39 Persson I, Johansson I, Bergling H. Genetic polymorhism of *CYP2E1* in a Swedish population. Relationship to the occurrence of lung cancer. FEBS Lett 1993; 319: 207-11.
40 Hirvonen A, Husgafvel-Pursiainen K, Anttila S. The human *CYP2E1* gene and lung cancer: DraI and *Rsa*I restriction fragment length polymorphisms in a Finnish study population. Carcinogenesis 1992; 14: 85 – 8.
41 Wang JS, Xu ZH, Zhou HH. Cytochrome P4503A4 and drug metabolism. Chin J Clin Pharmacol 1996; 12: 231 – 5.
42 Kinirons MT, Oshea D, Kim RB, Groopman JD, Thummek KE, Wood AJ, *et al*. Failure of erythromycin breath test to correlate with midazolam clearance as a probe for cytochrome P4503A. Clin Pharmacol Ther 1999; 66: 224 – 31.
43 Ball SE, Scatina J, Kao J, Ferron GM, Fruncillo R, Mayer P, *et al*. Population distribution and effects on drug metabolism of a genetic variant in the 5′ promotor region of *CYP3A4*. Clin Pharmacol Ther 1999; 66: 288 – 94.
44 Fleming CM, Persad R, Kaisary A. Low activity of dapsone hydroxylation is a susceptibility risk factor in aggressive bladder cancer. Pharmacogenetics 1994; 4: 199 – 207.
45 Romkes M, Chern HD, Lesnick TG, Becich MJ, Persad R, Smith P, *et al*. Association of low CYP3A activity with p53 mutation and CYP2D6 activity with *Rb* mutation in human bladder cancer. Carcinogenesis 1996; 17: 1057 – 62.
46 Liu CZ, Bian JC. Genetic polymorphism of toxin metabolizing enzymes and susceptibility to hepatocelluar carcinoma. Chin J Med Genet 1998; 15: 376 – 7.

CYP450 多态性与癌症易感性[1]

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关键词 细胞色素 P-450；表型；基因型；多态现象（遗传学）；疾病易感性

CYP450 是一个超家族，参与了许多内源性和外源性物质的代谢．本文综述了 CYP1A1、CYP1A2、CYP2C19、CYP2D6、CYP2E1 和 CYP3A4 参与代谢的药物和前致癌物，以及诱导和抑制它们的物质；阐述了它们的表型多态性和基因多态性；并简要地概括了近年来引起人们关注的基因多态性与癌症易感性的关系．

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