CLINICALLY RELEVANT OF CYTOCHROME P450 FAMILY ENZYMES FOR DRUG-DRUG INTERACTION IN ANTICANCER THERAPY

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Absract – *In the oncology field, the knowledge of secondary mechanisms for drug metabolism allow physicians to improve the efficacy of cancer therapy. This review provides an overview on the commonly occurring, functionally and/or clinically relevant Cytochrome P450 (CYP) superfamily. Particular highlight were attempt on genetic variations in the CYP2D6 gene and the pharmacokinetics and/or response of drug-based chemotherapy. In addition, current genetic polymorphisms responsible of variability in drug-drug interaction between anticancer drugs and antidepressant are discussed. Further, effective re-evaluation of drug design based on CYP enzymes profile may eventually be personalized and individualized to the patient for maximum efficacy of the therapies.*

KEY WORDS: *Pharmacogenetics profile, Phase I enzyme. Personalized therapy, Drug metabolism.*

INTRODUCTION

Cytochrome P450 (CYP450) isoenzymes are a group of heme-containing enzymes involved in the metabolism of many drugs, steroids and carcinogens[1]. In particular, these isoenzymes are responsible for catalyzing the oxygenation of a broad number and variety of endogenous and xenobiotic substrates. CYP450-catalyzed reactions can be divided into four categories: hydroxylation reactions where a hydroxyl group replaces hydrogen atom; epoxidation reactions where an oxygen is introduced into a carbon-carbon p-bond; heteroatom oxidations where an oxygen is added to a nitrogen, sulfur, or other heteroatom; or reduction reactions which occur under conditions of limited oxygen assuming that an alternate electron acceptor is available[2]. Drugs can interact with CYP450 enzymes as inhibitor, inducer or substrate (Table 1). Drugs that inhibit CYP450 enzymes generally lead to decreased metabolism of other drugs metabolized by the same enzyme, resulting in higher drug levels and increased toxicity. Induction of the CYP450 system results in the increased clearance of concomitant drugs metabolized by the same enzyme. Drugs that induce CYP450 enzymes increase the production of specific enzymes of the CYP450 system by leading to increased metabolism and decreased concentrations of drugs metabolized via the same pathway. Beyond these regulatory mechanisms that involve drugs which induce or inhibit CYP450 enzymes, genetic polymorphisms associated with altered CYP450 expression or catalytic activities have been identified[3].

Table 1. Major human cytochrome P450 (CYP) enzymes involved in drug metabolism.

CYP Gene	CYP allele*	Substrates	Inhibitors	Inducers
1A2	*1F	Amitriptyline, caffeine, clomipramine cyclobenzaprine, fluvoxamine, estradiol, haloperidol, imipramine, mexiletine, naproxen, ondansetron (in part), phenacetin, propranolol, riluzole ropivacaine, tacrine, theophylline, verapamil, warfarin, zileuton, zolmitript	Amiodarone, cimetidine, fluoroquinolones, fluvoxamine, furafylline, interferon, methoxsalen, mibefradil, ticlopidine	Brussel sprouts, char-grilled meat, insulin, methyl cholanthrene, modafinil, nafcillin, anaphthoflavone, omeprazole, tobacco
2A6		Bilirubin, Cotinine, Coumarin, 1,7dimethylaxanthine, Efavirenz, Letrozole, Nicotine, Pilocarpine, Tegafur	Decursinol angelate menthofuran, 8-methoxypsoralen, Pilocarpine, Selegiline, Tranylcypromine	Artemisinin, Carbamazepine, Dexamethasone, Estrogens, Phenobarbital, Rifampicin
2B6	*6	Bupropion, cyclophosphamide ifosphamide, omeprazole	Thiotepa rifampin	Phenobarbital, phenytoin,
2C19	*2 *3 *17	Amitriptyline, citalopram, clomipramine, cyclophosphamide, Clopidrogel, diazepam, E-3810, hexobarbital, imipramine N-deME, indomethacin, lansoprazole, S-mephenytoin, R-mephobarbital, moclobemide, nelfinavir, nilutamide, pantoprazole, phenytoin, phenobarbitone, primidone, progesterone, proguanil, propranolol, teniposide, R- warfarin	Cimetidine, felbamate, fluoxetine, fluvoxamine, indomethacin, ketoconazole, lansoprazole, modafinil, omeprazole, paroxetine, probenicid, ticlopidine, topiramate	Carbamazepine, norethindrone, prednisone, rifampin
2C9	*2 *3	Amitriptyline, celecoxib, diclofenac. Fluoxetine, fluvastatin. Glipizide, ibuprofen, irbesartan, losartan, naproxen, Phenytoin, piroxicam, rosiglitazone, sulfamethoxazole, suprofen, tamoxifen, torsemide, tolbutamide, S-warfarin	Amiodarone, fluconazol, fluvastatin, fluvoxamine, isoniazid, lovastatin) paroxetine, phenylbutazone, probenicid, sertraline, sulfaphenazole, teniposide, trimethoprim, zafirlukast	Rifampin, secobarbital
2D6	*3 *4 *5 *6 *7 *10 *41 *XN	Alprenolol, amitriptyline, amphetamine, bufuralol, carvedilol, chlorpromazine, clomipraminecodeine, debrisoquine, desipramine, dexfenfluramine, dextromethorphan, encainide, Flecainide, fluoxetine, fluvoxamine, haloperidol, imipramine, lidocaine, metoclopramide, methoxyamphetamine, S-metoprolol, Mexiletine, minaprine, nortriptyline, ondansetron, paroxetine, perhexilin, perphenazine, phenacetin, phenformin propafenone, propanolol, quanoxan, risperidone, sparteine, tamoxifen, thioridazine, timolol, tramadol, venlafaxine	Amiodarone, celecoxib, chlorpheniramine, chlorpromazine, cimetidine, clomipramine, cocaine, doxorubicin, fluoxetine, halofantrine, levomepromazinemethadone, moclobemide, paroxetine, quinidine, ranitidine, reduced haloperidol ritonavir, sertraline, terbinafine	Dexamethasone rifampin
2E1		Acetaminophen, aniline, benzene, chlorzoxazone, enflurane, ethanol, Halothane, isoflurane, methoxyflurane, N,N-dimethylformamide, sevoflurane, theophylline	Diethyl-dithiocarbamate, disulfiram	Ethanol, isoniazid

We performed a review by means of a structured computerized search in the Medline database (1980-2015-may). Keywords were, polymorphism, drug interactions, cytochrome P450 (CYP), anticancer drug, genotyping, and antidepressant drugs. Articles exclusively in English words were selected. References in relevant articles were also retrieved.

Table 1. Major human cytochrome P450 (CYP) enzymes involved in drug metabolism *(Continued)*.

CYP Gene	CYP allele*	Substrates	Inhibitors	Inducers
3A4/ 3A5	*2 *3 *22	Alfentanyl, alprazolam, amlodipine, astemizole, atorvastatin, azithromycin, buspirone, caffeine, cerivastatin, chlorpheniramine, cisapride, clarithromycin, cocaine, codeine, cyclosporine, dapsone, dextromethorphan, diazepam, diltiazem, erythromycin, estradiol, felodipine, fentanyl, finasteride, haloperidol, hydrocortisone, indinavir, lercanidipine, lidocaine, lovastatin, methadone, midazolam, nelfinavir, nifedipine, nisoldipine, nitrendipine, pimozide, progesterone, propranolol, quinidine, quinine, ritonavir, salmeterol, saquinavir, sildenafil, simvastatin, tacrolimus, tamoxifen, taxol, terfenadine, testosterone, trazodone, triazolam, verapamil, vincristine, zaleplon, zolpidem	Amiodarone, azithromycin, cimetidine, ciprofloxacin, clarithromycin, delaviridine, diethyl-dithiocarbamate, diltiazem, erythromycin, fluconazole, fluvoxamine, gestodene, grapefruit, juice, indinavir, interleukin-10, itraconazole, ketoconazole, mibefradil, mifepristone, nefazodone, nelfinavir, norfloxacin, norfluoxetine, ritonavir, saquinavir	Barbiturates, carbamazepine, efavirenz, glucocorticoids, modafiniln, nevirapine, Phenobarbital, phenytoin, pioglitazone, rifampin, St. John's wort, troglitazone

*Annotation on CYP variants known to be causing poor metabolizing enzyme profile, referred to Phamacogenomics Knowledge Base www.pharmgkb.com

Recent progresses in the knowledge on individual metabolic profile have provided exceptional opportunities to identify predictive markers for efficacy of cancer therapy. The medicine of the 3rd millennium allow genetic identification of the patients who will benefit from therapy, excluding patients at high risk of severe toxicity[4].

CYP families

The nomenclature of a CYP450 enzyme indicates its similarity in structure to other CYPs (www.cyp-alleles.ki.se accessed june 2015). CYPs that have an higher amino acid sequence homology than 40% are grouped into families, and those with greater than 55% homology are grouped into subfamilies.Thus CYP1, CYP2, and CYP3 represent different families. A letter following the family name indicates the particular subfamily. In humans, the enzymes responsible for drug metabolism belong to the CYP families 1-4 and most of CYP450-catalyzed reactions can be attributed to six main enzymes (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4/5). CYP enzymes in families 5 or higher are typically responsible for processing steroids rather than drug metabolism.

CYP1 Family

CYP1 family consists of three members, CYP1A1, CYP1A2 and CYP1B1. In particular, CYP1A1 and CYP1A2 show high amino acid sequence homology but exhibit very different patterns of tissue expression. CYP1A1 is expressed primarily in extrahepatic tissues such as the lungs, lymphocytes and placenta while CYP1A2 is expressed in the liver[5].

On the other hand, CYP1B1 is constitutively expressed in a wide range of tissues such as brain, colon, heart, kidney, leukocytes, liver, lung, ovary, placenta, prostate, skeletal muscle, small intestine, spleen, and thymus[6]. CYP1A1 and CYP1A2 are substrate-inducible CYP450 enzymes responsible for the metabolism of numerous xenobiotic substrates, including polycyclic aromatic hydrocarbons (PAH) such as the carcinogen benzo(a)pyrene. In particular, these CYPs catalyze the N-oxidation of carcinogenic aromatic and heterocyclic amines found in cigarette smoke and in charred foods[7]. Polymorphisms that influence the transcriptional activity of CYP1A genes seem to have a limited effect on drug metabolism but they can be used as markers for predicting cancer predisposition of some individuals[8,9] since the etiology of several cancers is related to the formation of adducts between DNA and the oxidized products obtained from cytochrome P450 catalyzed reactions.

In addition to its role in the bioactivation of carcinogens, CYP1A2 also plays a significant role in the metabolism of numerous drugs, including analgesics and antipyretics (acetaminophen, phenacetin, lidocaine), antipsychotics (olanzapine, clozapine), cardiovascular drugs (propranolol, guanabenz, triamterene), the cholinesterase inhibitor tacrine used for the treatment of Alzheimer's disease, antidepressants (duloxetine), anti-inflammatory drugs (nabumetone), the

muscle relaxant tizanidine, the hypnotic zolpidem used in the short term treatment of insomnia, the drug riluzole used to treat amyotrophic lateral sclerosis, the 5-lipoxygenase inhibitor zileuton[10]. It has also been shown that CYP1A2 oxidize uroporphyrinogen to uroporphyrin in the course of heme metabolism and hydroxylate estrogen. The ability to utilize estrogen as a substrate has important implications for the role of this enzyme in the bioactivation of environmental pro-estrogens. Estrogens have been proposed as a possible substrates also for CYP1B1 since it has been reported that CYP1B1 polymorphisms are associated to altered kinetics for 2- and 4-hydroxylation of 17 β-estradiol. As with the other members of the CYP1 family, CYP1B1 is also involved in the bioactivation of carcinogens[11].

CYP2 Family

CYP2 family is the largest family of cytochrome P450s including 13 subfamilies that consist of 16 functional genes (*CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6 CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1*) and 13 confirmed pseudogenes (*CYP2A7PT* (telomeric), *CYP2A7PC* (centromeric), *CYP2A18P, CYP2B7P1, CYP2B7P2, CYP2B7P3, CYP2D7AP, CYP2D8P, CYP2F1P, CYP2G1P, CYP2G2P, CYP2T2P, CYP2T3P*). Most of these CYPs play a significant role in drug metabolism while other members are expressed in a sex-specific manner and support steroid hydroxylation. Three genes, *CYP2A6, CYP2A7*, and *CYP2A13*, comprise the human CYP2A subfamily. In adults, CYP2A6 is primarily expressed in the liver while it is present in extrahepatic tissues at very low levels[12]. CYP2A6 oxidizes numerous compounds including disulfiram, fadrozole, halothane, osigamone, methoxyflurane, pilocarpine, promazine, and valproic acid. Recently bilirubin has been identified as endogenous substrate of CYP2A6[13] in addition to procarcinogens (aminochrysene and aflatoxin B1), and tobacco smoke constituents. CYP2A6 is responsible for the majority of coumarin 7-hydroxylase and nicotine C-oxidase activity in hepatic tissue. It has been identified a CYP2A6 polymorphism present in approximately 0.3% of African-Americans and 1.4% of Caucasians that seems to confer a poor metabolizer phenotype[12], characterized by low or non-existent 7-hydroxylation of coumarin[13]. Moreover, polymorphisms in the *CYP2A6* gene may be related to smoking behavior and lung cancer susceptibility. The CYP2B family in humans consists of a single gene *CYP2B6*. CYP2B6 is involved in the

metabolism of several drugs such as benzphetamine, cinnarizine, bupropion, verapamil and lidocaine and environmental or abused toxicants including nicotine. Numerous *CYP2B6* sequence polymorphisms have been identified; some of these polymorphisms (*e.g.*, C1459T or R487C) are very frequent in human populations (up to 32.6%) and correlate with significantly reduced CYP2B6 protein expression and S-mephenytoin *N*-demethylase activity.

The CYP2C family comprises four genes (*CYP2C8, CYP2C9, CYP2C18*, and *CYP2C19*) encoding products with greater than 80% amino acid homology[14]. Of the four members of the subfamily CYP2C9, and CYP2C19 are the main responsible enzyme for the metabolism of clinically administered drugs as well as several endogenous compounds including arachidonic acid.

CYP2C9 is the most abundantly expressed in hepatic tissue, followed by CYP2C8 and CYP2C19. CYP2C9 shows very strong catalytic activity toward several drugs including the anticoagulant warfarin, the antidiabetic agent tolbutamide, barbiturate sedatives such as hexobarbital, ibuprofen, diclofenac and other nonsteroidal anti-inflammatory drugs, and anticonvulsants such as phenytoin, and trimethadone[13]. The frequency of functional *CYP2C9* polymorphisms is very low at 0.25% in Caucasians and even less in Asians. However, the clinical consequences of these rare, poor metabolizer polymorphism can lead to life-threatening bleeding episodes following administration of warfarin and severe toxicity with phenytoin administration[15] .

On the other hand, CYP2C19 metabolizes primarily the anticonvulsant agent mephenytoin. Moreover, it is responsible for metabolism of proton pump inhibitors such as omeprazole, benzodiazepines such as diazepam, a variety of antidepressants, and the antimalarial drug proguanil.

Among *CYP2C* polymorphisms, the (*S*)-mephenytoin 4'-hydroylase polymorphism of *CYP2C19*, is the most frequently expressed (approximately 3-5% of Caucasians and African-Americans and up to 20% of Asians). This polymorphism confers a poor metabolizer phenotype[16] and is associated to an elevated frequency of adverse effects following mephenytoin administration due to a reduced clearance of mephenytoin. Moreover, it is also related to an increase in the efficacy of proton pump inhibitors (*e.g.*, omeprazole) in the toxicity of some anxiolytic agents as diazepam[17].

The CYP2D subfamily consists of a single functional member, *CYP2D6*, and four pseudogenes[17]. CYP2D6 is highly expressed in the liver

but also in duodenum and brain . The CYP2D6 enzyme is responsible for the oxidation of more than 70 different pharmaceuticals, including b-adrenergic blocking agents (*e.g.*, labetalol, timolol, propanolol, pindolol, metoprolol), antidepressants (*e.g.*, amitriptyline, paroxetine, venlafaxine, fluoxetine, prozac, trazadone), antiarrhythmics (*e.g.*, flecainide, mexiletine, propafenone), antipsychotics (*e.g.*, clorpromazine, haloperidol, thoridazine), and narcotic analgesics (*e.g.*, codeine, fentanyl, meperidine, oxycodone, propoxyphene). A well known polymorphism in CYP2D6 gene displays a bimodal distribution between poor and extensive metabolizers. The CYP2D6 poor metabolizer phenotype is identified in about 6% of Caucasians[18] and is less common in Asian and African populations[19]. This PM phenotype significantly influence the *in vivo* metabolism of several common drugs including tricyclic antidepressants, haloperidol, metoprolol, propranolol, codeine and dextromethorphan[20]. In most clinical situations, administration of a standard dose of a given CYP2D6 substrate results in elevated blood levels in poor metabolizers and high toxicity. Individuals that possess multiple (up to 13) copies of the *CYP2D6* gene have identified as ultra-rapid metabolizers. Ultra-rapid metabolizers exhibit markedly elevated CYP2D6 levels, increased metabolism and decreased drug efficacy for CYP2D6 substrates, such as tricyclic antidepressants. The ultra-rapid phenotype is dectected in about 4% of Caucasians and up to 29% and 21% of Ethiopian and Saudi Arabian populations, respectively[21].

It has been reported an association between CYP2D6 polymorphisms and altered susceptibility to different diseases, such as Parkinson's disease and lung cancer. In this respect poor metabolizer phenotype seems to confer protection from lung cancer probably because CYP2D6 can modulate smoking behavior through involvement in the dopaminergic signal transduction pathway[22] (Table 2). Moreover, it appears to contribute to the bioactivation of procarcinogenic tobacco-derived nitrosamine NNK[23].

CYP2E1 is the only member of the CYP2E subfamily in humans. This cytochrome P450 isoform is expressed in the liver and in a small number of extrahepatic tissues including lungs and brain[24]. CYP2E1 metabolizes a broad range of substrates, the majority of which are relatively small hydrophobic compounds that act as procarcinogens[25]. In particular, CYP2E1 is responsible for the metabolism of several tobacco-specific *N*-nitrosamines[26] associated with nasopharyngeal cancers but it does not contribute to the bioactivation of the highly carcinogenic tobacco-derived

nitrosamine NNK[27]. Moreover, CYP2E1 is also involved in the metabolism of some clinically significant drugs such as paracetamol, enflurane and general anesthetics such as sevoflurane and halothane[28]. In rare cases, CYP2E1 may convert halothane to a reactive metabolite that forms adducts with hepatic proteins leading to fatal hepatotoxicity[28].

Many CYP2E1 substrates, including acetone, pyridine, pyrazole, and isoniazid, act as CYP2E1 inducers. Genetic polymorphisms at the *CYP2E1* locus are more frequent in some Asian populations (28%)[28] than in Caucasian populations (7%) and have also been associated with differential susceptibility to different chemical-induced cancers.

CYP3 Family

The CYP3 family in humans consists of a single subfamily (CYP3A) comprising four functional genes (*CYP3A4, CYP3A5, CYP3A7, CYP3A43*) and two pseudogenes (*3A5P1, 3A5P2*). CYP3A4 is mainly expressed in the liver and at low levels in the small intestines. CYP3A5 is found sporadically in the liver and is frequently expressed in extrahepatic tissues including the lungs, the colon, the kidney, the esophagus, and anterior pituitary. CYP3A5 and CYP3A4 metabolize the same substrates although usually at different turnover rates.

CYP3A4 is the most important drug-metabolizing cytochrome P450 enzyme in humans and the most abundantly expressed in the liver. It has been reported that CYP3A4 metabolizes more than 120 different drugs and about 60% of the currently administered drugs[29]. In particular, CYP3A4 shows catalytic activity toward macrolide antibiotics such as erythromycin; benzodiazepine sedatives including diazepam and midazolam; immune system modulators like cyclosporine; anti-arrhythmics like quinidine; HIV-directed antiviral agents such as ritonavir and saquinavir; the prokinetic agent cisapride; antihistamines such as astemizole and terfenidine; an array of calcium channel blockers including nifedipine and verapamil; HMG CoA reductase inhibitors like lovastatin; stimulants like caffeine and non-benzodiazepine hypnotics like zolpidem. CYP3A4 enzyme is the major responsible for metabolism of several anticancer drugs such as taxol, etc. Moreover, it is implicated in the etiology of different types of cancers including prostate cancer and leukemia through activation of procarcinogens, such aflatoxin B1, PAHs, NNK[30], and 6-aminochrysene. In addition to its important role in xenobiotic metabolism, CYP3A4 metabolizes

endogenous steroids such as testosterone, progesterone, and androstenedione[31]. Since CYP3A4 metabolizes several clinically used drugs, it is implicated in a wide number of drug interactions[32].

The metabolic activity of CYP3A4 enzymes is highly variable in human populations. Such variability can influence the efficacy and safety of drugs that are metabolized by these enzymes. Although the mechanisms responsible for this are poorly understood, transcriptional induction plays an important role. About 20 variant *C Y P 3 A 4* alleles, that show either higher or lower rates of catalytic activity compared with wildtype CYP3A4, have been identified[33].

CYP4 Family

The CYP4 family in humans consists of five sub-families including 12 functional genes (*CYP4A11, CYP4A20, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1*) and nine pseudogenes (*CYP4A21P, CYP4F9P, CYP4F10P, CYP4F23P, CYP4F24P, CYP4F25P, CYP4F26P, CYP4F27P, CYP4F28P*).

Members of the CYP4A family are expressed primarily in the kidney and to a lesser degree in the liver. CYP4A enzymes is mainly responsible for the hydroxylation of fatty acids and prostaglandins. In details, CYP4A isoforms metabolize medium and long chain length fatty acids at their w-carbon. CYP4A subfamily does not seem to play a direct role in xenobiotic metabolism[34].

In contrast to these four families that are involved in drug or xenobiotic metabolism, the remaining fourteen cytochrome P450 families mainly metabolize steroids or steroids precursors.

CONCLUSIONS

Continued investigation and adaptation of drug dosage with respect to malignancy should likely provide improved risk versus benefit ratios with respect to therapeutic efficacy versus side-effect profiles. This approach could allow the use of new natural remedial either to prevent or minimize toxicity[35]. Further, effective re-evaluation of drug design toward the generation of novel and specific therapies focused on enzyme pertaining to malignancy may eventually be personalized and individualized to the patient for maximum efficacy.

Recently, the knowledge of pharmacogenomics modulators has increased so that individualized preventive therapy adjusted to the patient's genetic profile could get closer to reality[36]. Furthermore, the American Food and Drug Administration and European Medicines agencies (FDA and EMA) have recognized the clinical value of genetic variants in metabolic pathways and have developed guidelines for industry concerning pharmacogenetic data submission with new drugs. They now recommend updating drug labels when compelling data are present according to patient's genetic profile in the field of oncology, neurology and cardiovascular medicine. Furthermore, a detailed knowledge of pharmacology is a prerequisite for application in clinical practice, and physicians might find it difficult to interpret the clinical value of pharmacogenetic test results[37]. Hypnotizing the emerging of new healthy professions[38].

Over the next few years, the emergence of drug-drug interactions in the new therapies as results of genomic alteration (i.e. anti-HIV concomitant with Antivancer), will drives diagnostics company to develop new test able to produce results indicative for tailoring patient's treatment[39]. Promise, the pharmaceutical and biotechnology companies should join each other, in order to develop a commercial test suitable for routine diagnostics to genotyping and phenotyping the individual metabolic profile.

AUTHOR DISCLOSURE
The authors report no conflicts of interest in this work

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