

Preclinical Development

Cytochrome P450 1B1 Gene Polymorphisms
as Predictors of Anticancer Drug Activity: Studies
with *In vitro* ModelsAudrey Laroche-Clary¹, Valérie Le Morvan¹, Takao Yamori², and Jacques Robert¹

Abstract

Cytochrome P450 1B1 (CYP1B1) is found in tumor tissue and is suspected to play a role in oncogenesis and drug resistance. *CYP1B1* gene polymorphisms have been associated with the risk of developing lung and other cancers. They may be associated with tumor response to anticancer drugs. We have determined 4 frequent nonsynonymous gene polymorphisms of *CYP1B1* in the human tumor cell lines panels of the National Cancer Institute (NCI) and the Japanese Foundation for Cancer Research (JFCR): rs10012 (R48G), rs1056827 (A119S), rs1056836 (L432V), and rs1800440 (N453S). Numerous anticancer drugs have been tested against these panels that offer the opportunity to detect associations between gene polymorphisms and drug sensitivity. CYP1B1 single nucleotide polymorphisms were in marked linkage disequilibrium. The L432V allelic variants were significantly associated with reduced sensitivity to DNA-interacting anticancer agents, alkylators, camptothecins, topoisomerase II inhibitors, and some antimetabolites. For instance, in the NCI panel, cell lines homozygous for the V432 allele were globally 2-fold resistant to alkylating agents ($P = 5 \times 10^{-10}$) and 4.5-fold to camptothecins ($P = 6.6 \times 10^{-9}$) than cell lines homozygous for the L432 allele. Similar features were exhibited by the JFCR panel. Cell lines homozygous for the V432 allele were globally less sensitive to DNA-interfering drugs than cell lines having at least 1 common allele. There was no significant association between mRNA expression of CYP1B1 and CYP1B1 genotype, and no significant association between CYP1B1 mRNA expression and drug cytotoxicity. These observations open the way to clinical studies exploring the role of *CYP1B1* gene polymorphisms for predicting tumor sensitivity to chemotherapy. *Mol Cancer Ther*; 9(12); 3315–21. ©2010 AACR.

Introduction

Cytochrome P450 1B1 (CYP1B1) is an unusual cytochrome whose physiologic functions remain obscure. It is expressed at low levels in normal tissues and was even found exclusively expressed in tumor cells in immunohistochemical studies (1). However, some expression was detected at the level of mRNA transcripts in normal tissues such as kidney, uterus, breast, and prostate (2) but was systematically lower than in tumor tissues, justifying its designation as a universal tumor antigen (3). CYP1B1 substrates have been found among polycyclic aromatic compounds (2) and estradiol (4), which can be converted after 4-hydroxylation into a DNA-binding

quinone with carcinogenic potency. The regulation of *CYP1B1* at the transcriptional level involves its activation by the aryl hydrocarbon receptor AHR, a transcription factor similar to the nuclear receptors. The involvement of other transcriptional regulators remains unknown.

Several studies have shown that *CYP1B1* could be associated with drug response. Transfection of the human *CYP1B1* cDNA in Chinese hamster ovary V79 cells was associated with the induction of resistance to docetaxel (5) using lymphoblastoid cell lines of the CEPH collection. Huang et al. (6) showed an association between *CYP1B1* gene expression and sensitivity to daunorubicin. However, tumor resistance or sensitivity to most drugs did not seem to be associated with *CYP1B1* gene expression (5).

As all cytochromes P450, *CYP1B1* gene undergoes many allelic variations, especially within the coding sequence. At least 4 common, nonsynonymous single nucleotide polymorphisms (SNP) have been identified: R48G (rs10012), A119S (rs1056827), L432V (rs1056836), and N453S (rs1800440), all with allelic frequencies higher than 10% in Caucasian populations. These polymorphisms may first be of interest in molecular epidemiology. The V432 variant has been associated, for instance, with the risk of lung (7), prostate (8), and head and neck (9) cancers. They may also be of interest in pharmacogenetics, because CYP1B1 is involved in the

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biotransformations of xenobiotics, including drugs, and its variations may be associated with changes in the cytotoxic activity of anticancer drugs. To our knowledge, this has never been explored until now.

We wanted to explore in this study the potential interest of *CYP1B1* gene polymorphisms in a preclinical model in order to determine whether genotyping could be of interest in the clinical setting for predicting drug response. We have chosen the National Cancer Institute (NCI) panel of human tumor cell lines as a model, as we have already done in several studies (10–14), because the freely available database of drug sensitivity was of invaluable help in establishing relationships between molecular characteristics and chemosensitivity. In addition, we validated our study by the exploration of the Japanese Foundation for Cancer research (JFCR) panel of human tumor cell lines to show whether the relationships observed could be extrapolated to other ethnic backgrounds.

Materials and Methods

Cell models

In this study, we used 2 independent sets of human tumor cell lines for which *in vitro* sensitivity to a panel of anticancer drugs had been established, the NCI-60 collection (15) and the JFCR-45 collection (16). DNA extracts from 59 of the 60 NCI cell lines of the panel were kindly provided by Dr. S. Holbeck, Cancer Therapeutic Branch, NCI, Bethesda, MD. One cell line, MDA-N, is no longer available in the panel. DNA extracts were prepared from unviable cell pellets of the 42 cell lines of the JFCR-45 collection. The cell lines of both panels were not grown in our laboratory; they had been extensively molecularly characterized by the NCI and the JFCR, respectively, and we rely on the identification made by these 2 organisms.

Polymorphism identification

All 4 nonsynonymous polymorphisms of *CYP1B1* were identified by pyrosequencing in the 2 cell line collections. Direct sequencing of PCR fragments without any further purification was carried out on the Pyrosequencer PyroMark ID system (Qiagen) according to the instructions of the manufacturer. The primers used were as follows: for R48G (rs10012): sense, 5' AGACCACGCTCCTGCTACTCCT 3'; antisense, 5' dR-Biotin-CCGCGTTCCGATCAGTG 3'; pyrosequencing, 5' CAACGGAGGCGGCAG 3'. For A119S (rs1056827): sense, 5' dR-Biotin-CTGCCCCATAGTGGTGCT 3'; antisense, 5' GGACACCACACGGAAGGAG 3'; pyrosequencing, 5' CCACGGAAGGAGGCGA 3'. For L432V (rs1056836): sense, 5' dR-Biotin-CTACCACATTCCC-AAGGACACT 3'; antisense, 5' GCTGGTCAGGTCC-TTGTG 3'; pyrosequencing, 5' CGGGTTAGGCCACTT 3'. For N453S (rs1800440): sense, 5' AACCCGGA-GAAGTTTATCCAG 3'; antisense, 5' dR-Biotin-CCC-ACTGAAAAAATCATCACTCTG 3'; pyrosequencing, 5' AAGGACGGCCTCATC 3'.

Drug cytotoxicity

After identification of the genotypes of each cell line, the 50% growth inhibitory concentrations (GIC_{50}) of 136 core drugs *vis-à-vis* the 59 NCI cell lines, expressed as $-\log_{10}(GIC_{50})$, were extracted from the DTP database (<http://dtp.nci.nih.gov>) and are indicated in Supplementary Table 1. Similarly, GIC_{50} values of 53 agents against the cell lines of the JFCR collection were extracted from the original publication (16). Drugs were grouped into 8 categories according to a function of their known mechanism of action [for details, see (17)]: alkylating or platinating agents acting on the N⁷ of guanine; other alkylating agents acting on N² and O⁶ of guanine; antimetabolites; antifolates; topoisomerase I inhibitors; topoisomerase II inhibitors; and spindle poisons, subdivided into *Vinca* alkaloid-type and taxane-type mechanisms of action. With each cell line collection independently, it was possible both to directly compare the mean GIC_{50} values of each drug in the various genotypes and to use a paired Student's *t* test in order to analyze the data related to drug classes.

Gene expression data

We extracted the gene expression data of the NCI panel from the DTP database; 12 different sets of data generated with U95 and U133 Affymetrix microarrays are available and display highly significant correlations between them. Expression levels are indicated in Supplementary Table 1. For the JFCR panel, we obtained the *CYP1B1* gene expression data generated from Affymetrix microarrays (probe set #202437_s_at) kindly provided by Dr. J. Kanno (18) (Division of Cellular and Molecular Toxicology, National Institute of Health Sciences, Tokyo, Japan).

Statistical analysis

The chi-square test was used for comparing the distribution of the cell lines among genotypes. Pearson coefficients of correlation were computed for comparing continuous variables (drug GIC_{50} and gene expression data). To study the pharmacologic parameters as a function of the genotype, we analyzed the variances of drug GIC_{50} values or *CYP1B1* gene expression for each genotype and calculated the significance of the differences in mean values, using a general linear model taking into account the unbalanced size of the groups. The Bonferroni correction was applied to take into account the number of tests done. The 2 cell line collections were studied independently, the NCI collection as a training set and the JFCR collection as a validation set, to decrease the probability of generating falsely positive observations.

Results

Distribution of allelic variations in the cell panels

The 4 polymorphisms studied were identified in the 101 cell lines of the 2 panels and the detailed genotypes are presented in Supplementary Tables 2 and 3. Allele frequencies and genotype distributions in both panels are presented in Table 1. There was a slight deviation from

Table 1. Allele frequencies of CYP1B1 variants and genotype distribution in the 2 panels studied

	Rare allele frequency, %	No. wild-type	No. heterozygous	No. variant
NCI panel				
R48G	20	42	10	7
A119S	20	42	10	7
L432V	50	20	19	20
N453S	21	40	13	6
JFCR panel				
R48G	23	29	7	6
A119S	23	29	7	6
L432V	73	5	13	24
N453S	7	38	1	3

the Hardy–Weinberg equilibrium, with less heterozygous genotypes than expected. This remained close to the limit of significance ($P = 0.04$ – 0.06) in all cases. The proportions of the variant alleles were different in the 2 populations, reflecting the differences of the ethnic origin of the tumor cell lines.

The 4 SNPs were in highly significant linkage disequilibrium, especially the R48G and the A119S polymorphisms were always identical in the 101 cell lines studied. Concerning the NCI panel, a minimum of 5 haplotypes were necessary to describe the population; we named them A–E (Table 2). In the JFCR panel, haplotype E was absent, but 1 haplotype that we named haplotype V, was required in supplement for a complete description of the population (Table 2). Haplotype distribution was different in 2 populations, haplotype A being the most frequent in the NCI panel and haplotype D in the JFCR panel (near 50% in both cases).

For both panels, it was possible to divide the whole sets in 3 categories, cell lines containing only haplotype A, the most frequent haplotype (A/A), cell lines heterozygous for this haplotype (A/X), and those not containing this haplotype (X/X).

Relationships between gene polymorphisms and chemosensitivity

We explored the associations that could exist between genotypes and cell sensitivity with a series of relevant

antiproliferative drugs and molecules in the NCI and the JFCR panels, using the same statistical approach as the one we already used in previous studies (8–12). The R48G and A119S polymorphisms are studied together because their variations are identical.

The L432V polymorphism was a major determinant of cell sensitivity to many drugs. In the NCI panel, most drugs identified as alkylating (or platinating) agents and topoisomerase I inhibitors were significantly more active against homozygous wild-type (L432) cells than against homozygous variant (V432) cells, the heterozygous cell lines behaving generally close to the homozygous variant lines. This is also the case for several topoisomerase II inhibitors and for some antimetabolites such as gemcitabine, cytarabine, methotrexate, and raltitrexed. Figure 1A gives a series of examples of significant relationships, and Table 3 indicates the IC_{50} ratio and the significance reached for a series of 12 representative drugs. When drug families were considered as a whole, the association between the L432V polymorphism and the cytotoxicity reached 5×10^{-10} for the N^7 alkylators and 2×10^{-7} for the topoisomerase I inhibitors. Because of the small number of L432 cell lines in the JFCR panel, we could do only the statistical analysis between homozygous V432 cells and the sum of heterozygous and homozygous L432 cell lines. There again, significant differences were found for many drugs, such as alkylators, topoisomerase I, and II inhibitors, having in common the property of interacting with DNA (Fig. 1B and Table 4). When these drugs were considered as a whole (i.e., after exclusion of hormones, spindle poisons, and interferons from the database), the significance of the association reached 1.2×10^{-9} .

The R48G/A119S polymorphism was in contrast not associated with major changes in cell chemosensitivity. There was a significant difference in cisplatin cytotoxicity in both panels, the cells bearing the variant allele (G48-S119) at the homozygous state being 2-fold less sensitive than the homozygous wild-type cell lines (R48-A119), the heterozygous cell lines ranging in-between. There was also a trend toward a higher relative resistance to the camptothecin derivatives in variant cell lines than in

Table 2. Haplotype distribution of CYP1B1 genotypes distribution in the 2 panels studied

	48-119-432-453	NCI panel	JFCR panel
A	C-C-C-A	47	20
B	C-C-G-G	18	8
C	G-A-G-A	20	17
D	C-C-G-A	12	49
E	C-C-C-G	3	0
V	G-A-C-A	0	6

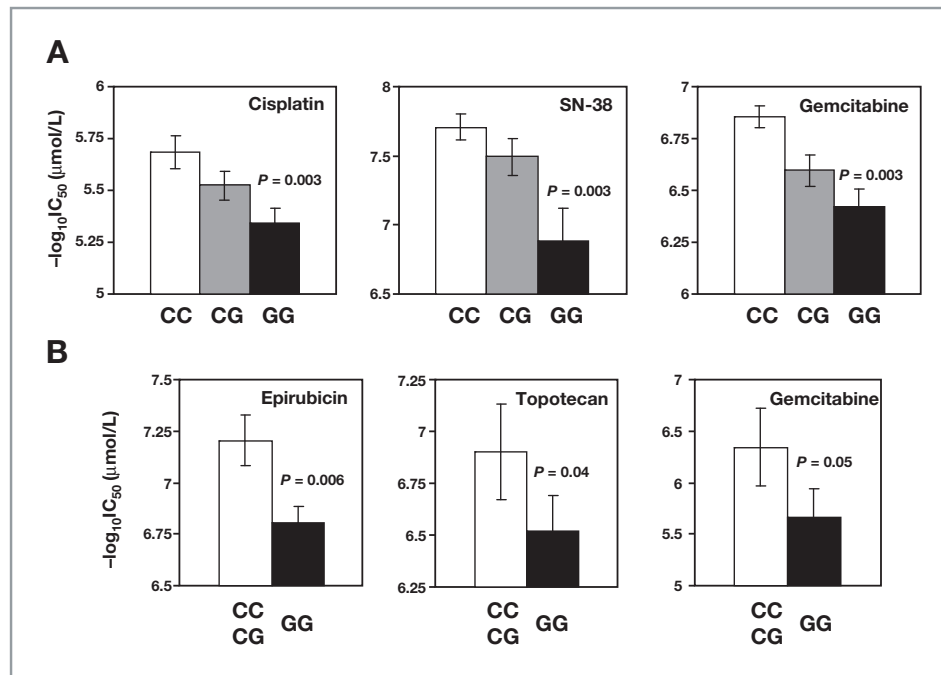


Figure 1. Cytotoxicity of 3 representative drugs against the cell lines of the NCI panel (A) and the JFCR panel (B) according to the CYP1B1 L432V genotype. Cytotoxicity is represented as the opposite of the logarithm of the concentration inhibiting cell growth by 50% ($-\log_{10}IC_{50}$). Data are means \pm SEM. White columns, common homozygous cell lines; gray columns, heterozygous cell lines; and black columns, variant homozygous cell lines. For the JFCR cells, common homozygous cell lines were grouped with heterozygous cell lines. The P value indicates the significance of the difference between common and variant homozygous cell lines.

wild-type cell lines, but this was significant only in the NCI panel when the whole set of camptothecin derivatives was considered together ($P = 4 \times 10^{-5}$).

The N453S polymorphism was associated with cell sensitivity to anticancer drugs. The variant homozygous lines were not large enough for a separate analysis of their association with chemosensitivity, and they were grouped with the heterozygous cell lines. In the NCI panel, the cell lines harboring at least 1 variant allele displayed relative resistance to several alkylators ($P = 5 \times 10^{-10}$) and camptothecin derivatives ($P = 9 \times 10^{-7}$). In the JFCR panel, only 4 cell lines harbor at least 1 S453 allele

and only cisplatin seemed to be significantly less cytotoxic in these cell lines than in the homozygous wild-type cell lines ($P = 0.03$).

When considering the haplotypes, it seems that the distribution of haplotype A is strongly associated with that of the L432V polymorphism. The distortion concerns only 4 of 59 cell lines in the NCI panel and 4 of 42 cell lines in the JFCR panel. The same association of haplotype A with cell sensitivity to many anticancer drugs was therefore expected (Fig. 2). The statistical significance of the differences observed is somewhat higher when considering the haplotypes than when

Table 3. IC_{50} values of 12 representative drugs against the NCI panel in cells with different L432V genotypes

	IC_{50} values, $\mu\text{mol/L}$			Ratio G/G:C/C	P
	C/C ($n = 20$)	C/G ($n = 19$)	G/G ($n = 20$)		
Cisplatin	2.06	3.00	4.55	2.2	0.003
Oxaliplatin	1.61	1.97	6.61	4.1	0.020
Mitomycin C	0.49	0.41	1.34	2.7	0.017
Carmustine	57.8	69.1	80.2	1.4	0.022
Camptothecin	0.026	0.029	0.088	3.4	0.004
Topotecan	0.034	0.042	0.138	4.1	0.007
SN-38	0.020	0.032	0.129	6.6	0.003
Amsacrine	0.33	0.30	1.01	3.1	0.009
Doxorubicin	0.099	0.117	0.176	1.8	0.18
Etoposide	4.59	4.98	9.50	2.1	0.13
Cytarabine	3.67	7.78	58.2	15.8	0.003
Gemcitabine	0.14	0.25	0.37	2.7	0.003

Table 4. IC₅₀ values of 6 representative drugs against the JFCR panel in cells with different L432V genotypes

	IC ₅₀ values, $\mu\text{mol/L}$		Ratio G/G:C/C + C/G	P
	C/C + C/G (n = 18)	G/G (n = 24)		
Oxaliplatin	2.22	4.61	2.1	0.12
Mitomycin C	0.752	1.98	2.6	0.013
Topotecan	0.146	0.485	3.3	0.04
Doxorubicin	0.074	0.139	1.9	0.04
Amsacrine	0.67	2.41	3.6	0.003
Gemcitabine	0.45	2.19	4.8	0.05

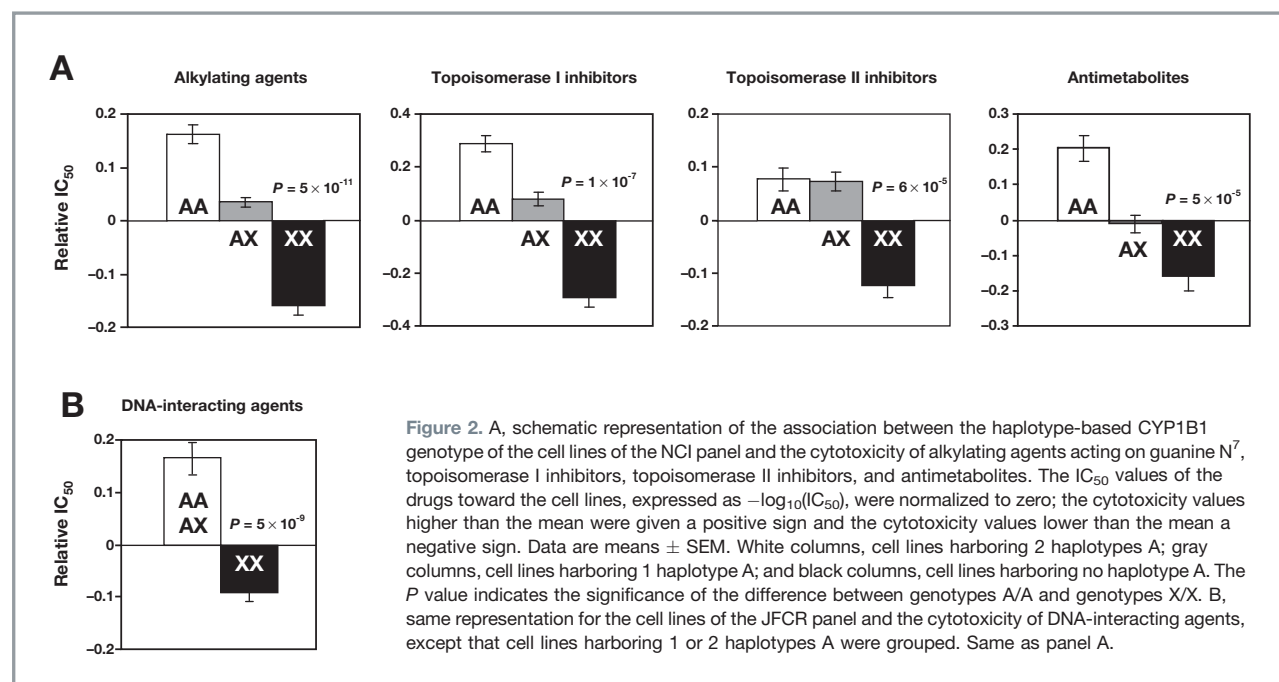
considering the L432V polymorphism alone. In the NCI panel, the significance of the differences between the 2 types of homozygous cell lines reached 5×10^{-11} for the N⁷ alkylators, 2×10^{-9} for the camptothecins, 6×10^{-5} for the topoisomerase II inhibitors, and 8×10^{-8} for the antimetabolites considered as a whole. In the JFCR panel, the homozygous wild-type cell lines were grouped with the heterozygous lines; the association between the presence of haplotype A and cell chemosensitivity to DNA-interfering drugs was 5×10^{-9} .

Relationships between gene polymorphisms and CYP1B1 expression

We first tried to identify correlations between cell sensitivity to anticancer drugs and CYP1B1 expression. There seemed a significant correlation between CYP1B1

gene expression and the resistance to only 2 of the 136 related core drugs of the NCI collection, oxaliplatin ($P = 0.0005$) and tetraplatin ($P = 0.0001$; ref. Fig. 3). However, this was not the case in the JFCR collection, for which no correlation could be evidenced between CYP1B1 expression and the cytotoxicity of any of the 53 drugs of the database, including oxaliplatin ($P = 0.4$).

We then tried to identify relationships between CYP1B1 gene expression and the presence of a given polymorphism or haplotype in the NCI cell panel as well as in the JFCR panel. No significant association between these parameters was detected. None of the polymorphism was involved in the mRNA concentration of CYP1B1 gene, as evaluated with Affymetrix microarrays technology.



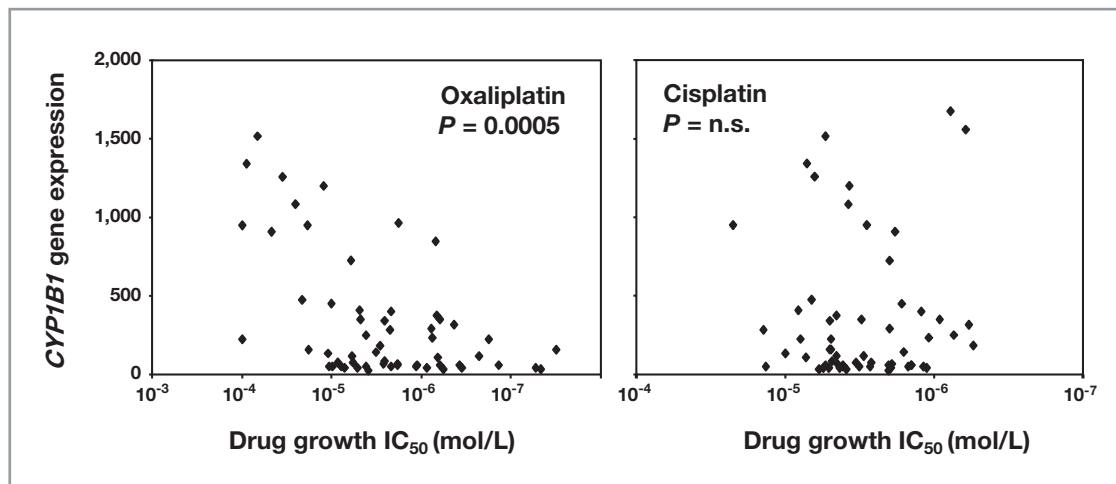


Figure 3. Relationships between *CYP1B1* gene expression and the cytotoxicity of oxaliplatin and cisplatin in the cell lines of the NCI panel. Gene expression and cytotoxicity values were extracted from the DTP database (<http://dtp.nci.nih.gov>).

Discussion

The association that we found between *CYP1B1* genotypes and chemosensitivity seemed very strong and is reinforced by the fact that 2 independent cell line collections behave quite similarly despite differences in genetic background. It remains to be explored whether this important determinant of *in vitro* response to cytotoxic drugs also operates in the clinical setting, that is, whether *CYP1B1* genotyping may help predict treatment response of patients undergoing chemotherapy. The answer could come only from clinical studies, either specifically designed to explore this association or being ancillary to clinical trials implemented with other objectives. DNA collections were not systematically made in former clinical trials, but the development of the concept of individualized chemotherapy prompted a number of investigators to prospectively collect blood samples with this objective. We are in the process of identifying such clinical collections to validate our *in vitro* studies at the clinical level.

The mechanism by which the L432V polymorphism of *CYP1B1* is associated with such an important change in chemosensitivity remains unknown. Clearly, the mRNA expression of *CYP1B1* cannot explain the phenotype because it is associated neither with the genotype nor with the phenotype. This cannot be attributed to a lack of statistical power because no trend emerged from any of the 12 different gene expression data sets that seem homogenous. It can be hypothesized that there is a distortion between mRNA and protein expression and that posttranscriptional regulations may explain a difference in protein levels, explaining, in turn, a difference in cell sensitivity to anticancer agents. However, *CYP1B1* protein expression by itself does not seem as an important determinant of drug resistance. McFadyen et al. (5), using Chinese hamster ovary cells transfected with *CYP1B1* and expressing high protein levels, found a difference in cell

sensitivity to docetaxel only, with a significance of 0.03, whereas no significant difference in cytotoxicity was observed between control and *CYP1B1*-transfected cells after exposure to doxorubicin, 5-FU, carboplatin, or cisplatin. Similarly, Huang et al. (6) observed a significant association between *CYP1B1* mRNA expression and the cytotoxicity of daunorubicin in a collection of human lymphoblastoid cell lines, but no protein expression data are available for comparison.

Another potential explanation for the differences observed between the 2 polymorphic variants lies in the difference of catalytic activity between the 2 forms of the protein. The epidemiologic association between the risk of cancer and the V432 allele has been attributed in lung cancer to a higher bioactivation of environmental procarcinogens (polycyclic aromatic hydrocarbons) to ultimate carcinogens and in breast cancer to higher conversion of estradiol to 4-hydroxyestradiol and the corresponding 3,4-quinone, which are known carcinogens. However, to our knowledge, this has never been proved; the 2 forms of the protein have never been studied separately for their catalytic capacities.

The mechanism of the involvement of *CYP1B1* in drug cytotoxicity remains elusive. The substrate spectrum of *CYP1B1* involves many organic compounds (4), but no anticancer drug metabolites have ever been identified as products of *CYP1B1* activity. In a study on the interactions of anticancer drugs with the conversion of a *CYP1B1* substrate, ethoxyresorufin, which is specifically *O*-deethylated, it was found that estradiol, testosterone, mitoxantrone, and the taxanes exerted a competitive inhibition on this biotransformation, which suggests that these drugs might be substrates for *CYP1B1* (19). However, the set of drugs whose cytotoxicity seem to be highly dependent on *CYP1B1* genotype in our study is quite different; it includes drugs, such as cisplatin or mechlorethamine (nitrogen mustard), clearly not suspected from cytochrome

biotransformation and does not include the taxanes, which are the best candidates for cytochrome bioconversion.

Indeed, the drugs that seemed to be concerned by the CYP1B1 genotype in our study have in common their mechanism of action and not their propensity to be cytochrome substrates. All the drugs involved are known to interact with DNA; this is the case for all alkylating and platinating agents such as mitomycin C, nitrosoureas, nitrogen mustards; for all the camptothecins; for several topoisomerase II inhibitors; and for those antimetabolites that have been shown to induce double-strand DNA breaks after fraudulent incorporation such as cytarabine, gemcitabine but not the thiopurines or the fluoropyrimidines. This strong dependence upon the drug mechanism of action allows to hypothesize that the intervention of CYP1B1 must be found at the level of DNA damage and/or repair. Interactions of CYP1B1 with DNA processing have never been described until now but are strongly suggested by our results.

Finally, the possibility of interactions of other genes with CYP1B1 cannot be excluded. The SNPs we genotyped may reveal only the existence of a specific haplotype while the true functional polymorphism, responsible for the phenotypic differences observed in chemosensitivity, would be located on a distinct gene. However, no known gene involved in DNA repair or

drug resistance could be identified at a reasonable distance from the chromosome 2 locus of CYP1B1 for *cis* interactions. It remains possible that *trans* interactions between CYP1B1 and such a gene might explain our observations. They would proceed, however, without modifications of CYP1B1 mRNA expression. In any case, the intervention of posttranscriptional or posttranslational regulations seems more likely to occur.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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