EXPRESSION OF CYTOCHROME P450 IN TUMOR TISSUES AND ITS ASSOCIATION WITH CANCER DEVELOPMENT

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Role of CYPs in tumor development
   3.1. Metabolic activation of carcinogens by CYPs
   3.2. Single nucleotide polymorphism (SNP) and CYPs
   3.3. Role of CYPs in metabolism of anticancer drugs
4. Expression of CYPs in tumor tissues
   4.1. Breast cancer
   4.2. Colon cancer
   4.3. Lung cancer
   4.4. Esophageal cancer
   4.5. Liver cancer
   4.6. Prostate cancer
   4.7. Brain tumor
   4.8. Others
5. Conclusions
6. References

1. ABSTRACT

CYPs (cytochrome P450s) catalyze the conversion of numerous numbers of xenobiotics including carcinogens and drugs. CYPs can be involved in metabolic pathways of activation of procarcinogens and/or inactivation of carcinogens during the tumorigenic processes. Recently, increasing number of cancer tissues as well as normal tissues have been found to express a variety of CYPs. The local expression of CYPs in tumors appears to be very important for the management of cancers since CYPs expressed in tumors may be involved in activation and/or inactivation of anticancer drugs. The expression of CYPs in tumors may also convert endogenous substrates to metabolites that facilitate cancer development. In this review, we summarize the association of CYP expression in cancer tissues with carcinogenesis and cancer treatment.

2. INTRODUCTION

Cytochrome P450 (CYP) was named from the characteristic absorption peak of its reduced CO-complex at 450nm. CYP is a multi-gene superfamily of constitutive and inducible heme-containing monoxygenases that are involved in metabolisms of a diverse range of xenobiotics and endogenous substrates (1). CYP enzymes (P450s) are localized in mitochondria and endoplasmic reticulum. These enzymes catalyze the monoxygenase reaction using molecular oxygen and equivalent electrons transferred from the NADPH-P450 reductase (a flavoprotein containing both FAD and FMN) in endoplasmic reticulum, or from ferredoxin (an iron-sulfur protein) and ferredoxin-reductase (a flavoprotein containing FAD) in mitochondria. Mitochondrial P450s are mostly involved in endogenous sterol metabolisms including biosyntheses of steroid hormones, vitamin D3, and bile acids.

Microsomal CYPs metabolize both endogenous and exogenous substrates. The conversion of xenobiotics to more hydrophilic forms by the CYP monoxygenase system is particularly important in protecting the body from small molecular weight foreign compounds (2). As schematically illustrated in Figure 1, xenobiotics undergo a variety of cellular metabolic pathways. In the body, xenobiotics are metabolized by the phase I enzymes including the microsomal CYP families and epoxide hydrolases. The metabolites are then modified by the phase II enzymes that include UDP-glucuronosyltransferases (UGTs), sulfotransferases, glutathione S-transferases, and N-acetyltransferases. These reactions generally result in pharmacological inactivation or detoxification. Conjugated metabolites of xenobiotics are further subjected to specific transport machineries, thus facilitating elimination from the body. However, CYPs incidentally convert xenobiotics to more active and/or toxic compounds that may form DNA-adducts resulting in the initiation and promotion of
Expression of cytochrome P450 in tumor

3. ROLE OF CYPS IN TUMOR DEVELOPMENT

3.1. Metabolic activation of carcinogens by CYPs

The CYP enzymes (P450s) are capable of metabolizing a variety of carcinogens, such as polycyclic aromatic hydrocarbons, heterocyclic amines, nitrosamines, azo-dyes, and alkylating agents (3, 4). CYP1A1, CYP2A6, CYP2E1, and CYP3A4/5 are the major P450s that metabolize carcinogens in quality and quantity (3). The metabolism of carcinogens by the CYP enzymes may produce active derivatives that lead to the tumor initiation. As shown in Figure 1, carcinogens exposed to cells are metabolized, and subsequently activated or discharged. Carcinogen-DNA adducts produced in oncogenes or tumor suppressor genes often yield mutations in these genes, which may lead to cell death or cancerization when DNA repair function does not rescue the DNA damage (Figure 1).

The relative risk of lung cancer in Japanese smokers compared with nonsmokers is approximately 5 times higher in men and 3 times higher in women, indicating that smoking contributes by far the most to the susceptibility of lung cancer compared with other risk factors (6). Tobacco smoke is well known to contain many carcinogens, such as benzopyrene and nitrosamine. Benzopyrene is a procarcinogen and does not exhibit carcinogenicity. However, it undergoes metabolic activation by the phase I enzyme CYP1A1 into epoxides that are mostly converted to inactive metabolites by the phase II enzyme glutathione S-transferases (GSTs), particularly by the Mu class (GSTM1) of GSTs (7). However, the epoxides transported into the nucleus may bind DNA resulting in the formation of DNA-adducts that exhibit strong carcinogenicity. The DNA-adducts of benzopyrene derivatives produced by CYP1A1 are capable of causing specific mutations in p53 gene, a tumor suppressor gene related to cell repair and apoptosis (8). When the DNA adducts target the p53 gene in particular, genetic alterations in the p53 gene cause errors in DNA repair at an accelerating pace, leading to carcinogenesis (9).

Low molecular weight carcinogens related to tobacco smoke are also metabolically activated by CYP2E1 (10). CYP2E1 was originally found as the major form of ethanol-inducible CYPs. CYP2E1 catalyzes and activates a broad range of carcinogens such as nitrosamines. The CYP2E1 level in the human liver greatly varies among individuals. This is probably due to differing induction levels by environmental factors. However, the inductions of CYP2E1 in extra-hepatic tissues have not been well investigated.

3.2. Single nucleotide polymorphism (SNP) and CYPs

Genetic polymorphism is defined as the occurrence at a gene locus of variants at a frequency of greater than 1% of the same population (11). In particular, a single nucleotide substitution gives rise to SNP (singlenucleotide polymorphism) (12). As appearances and characters differ with the individual, one SNP locus occurs per approximately 1,000 nucleotides in an individual (13). Recently, many SNPs are reported in CYP genes using high-throughput technologies such as DNA microarray (14). A CYP gene with SNP results in individual differences in the transcriptional and translational efficiencies, enzyme properties, and ultimately in enzyme activities (13). Smokers with high CYP1A1 activity and low GST activity are expected to have a high risk of lung cancer, as a study has reported that the polymorphism of CYP1A1 and GST is associated with the risk of lung cancer (15). On the other hand, the enzymes CYP2E1 and CYP2A6 have been reported to be highly expressed in bronchial epithelium (16). We reported that high CYP2E1 activity in smokers might be associated with the development of lung cancer arising from bronchial epithelium (10). Enzyme SNPs as well as the induction of enzyme expression by the increased exposure to carcinogens differ among racial groups (9, 17). Therefore, the susceptibility of individuals to lung cancer may be difficult to diagnose only by a single enzyme SNP (18), suggesting the requirement of systematic studies of a series of genes encoding the phase I and phase II enzymes.

3.3. Role of CYPs in metabolism of anticancer drugs

The most relevant CYP genes to drug metabolism are CYP1, CYP2 and CYP3. Recently, CYPs have been shown to be involved in the metabolism of several essential anticancer agents such as tamoxifen, taxol and vinca
alkaloids. For instance, CYP3A enzymes not only inactivate the major anticancer drugs but also activate some anticancer prodrugs, such as cyclophosphamide and ifosfamide (19). Tamoxifen is the drug of first choice for the treatment of estrogen-receptor-positive breast cancer (20) and also used as a preventative agent in women who are at an increased risk of developing breast cancer (21). Tamoxifen is extensively metabolized in the human liver. The formation of 4-hydroxytamoxifen, a potent anti-estrogen with high affinity for the estrogen receptor, is related to the therapeutic benefit achieved by the tamoxifen treatment. CYP2B6, CYP2C9, CYP2D6, and CYP3A enzymes (CYP3A4, CYP3A5, and CYP3A7) are capable of catalyzing the 4-hydroxylation of tamoxifen. Although CYP3A enzymes are important for the activation of tamoxifen, CYP3A4 also converts tamoxifen to α-hydroxytamoxifen that is associated with an increased risk of endometrial cancer (22). Similarly, other CYP enzymes could be involved in both activation of pro-anticancer drugs and inactivation of anticancer drugs, and incidentally involved in conversion of them to carcinogens. As CYP3A enzymes are expressed in extrahepatic tissues such as digestive tract (23–25), many CYPs are expressed in varieties of extrahepatic tissues including cancer tissues. When the CYP enzymes catalyzing activation and/or inactivation of anticancer drugs are expressed in cancer tissues, the CYP-mediated drug metabolisms in tumors may be a relevant clinical factor in tumor sensitivity to these anticancer drugs.

4. EXPRESSION OF CYPs IN TUMOR TISSUES

CYP expression has been studied in a variety of human tumors as well as normal tissues. Especially, breast cancer, colon cancer, and lung cancer have been intensively investigated. These studies also used a variety methods, such as detection of CYP activity, identification of proteins by immunoblotting or immunohistochemistry, and detection of mRNA by Northern blotting (NB), reverse transcriptional PCR (RT-PCR) and real-time quantitative polymerase chain reaction (RTqPCR). The expression of CYPs in tumor and normal tissues was summarized in Table 1.

4.1. Breast Cancer

Today, estrogens are well known to act as growth factors that promote cancer cell growth. Estrogens interact with estrogen receptors and trigger the signal transduction that promotes cell proliferation. However, there is no consistent evidence of increased serum estrogen level or other systemic estrogen abnormalities in women with breast cancer. Biosynthesis of estrogens from androgens catalyzed by aromatase (CYP19) occurs mostly in gonads and placenta of humans, which regulates serum estrogens. However, recent studies in the expression and regulation of the CYP19 gene have uncovered the important roles of local expression of CYP19 in varieties of tissues that regulates the cellular estrogen levels in paracrine and/or autocrine manners (26). Intratumoral production of estrogens plays an important role in the proliferation of breast cancer cells, especially in post-menopausal women. More than 70% of breast carcinoma specimens are estrogen-dependent, and aromatase expressed in breast cancer cells and surrounding stromal cells is up regulated compared to non-cancerous cells (27). Therefore, the blockade of the estrogen-dependent pathway by tamoxifen and aromatase inhibitors has been a target for prevention and management of breast cancer (28–31).

In addition to metabolisms of carcinogens and anticancer drugs, CYPs are the major enzymes to mediate the estrogen metabolism, and the metabolites also play a role in the initiation and progression of breast cancer (32). CYP1B1 converts 17β-estradiol to the carcinogenic 4-hydroxyestradiol, suggesting that the increased expression of CYP1B1 in breast tissues may be associated with the increased risk of breast cancer. In contrast, CYP1A1 and CYP3A4 catalyze the conversion of estradiol to non-carcinogenic 2-hydroxyestriadiol, which may protect cells against estrogen-induced carcinogenesis. Therefore, the expression of CYPs in breast cancer and surrounding tissues is of great interest for the management of breast cancer.

Several forms of CYPs have been identified in breast cancer. Aryl hydrocarbon hydroxylase (AHH) activity reflecting the expression of CYP1A1 (17) was observed in 153 primary breast cancers, and the high AHH activity was demonstrated to be associated with poor prognosis (33). Several groups have demonstrated the expressions of CYP1A1 and aryl hydrocarbon receptor in breast cancer (34, 35). CYP1A1 was expressed in 40% of breast cancers (36, 37). Goth-Goldstein et al. (34) reported that CYP1A1 expression was higher in breast tumors compared to that of normal breast tissues, while El-Rayes et al. (38) reported that CYP1A1 expression determined by immunohistochemistry was significantly lower in malignant breast tumor tissues as compared with normal tissues. CYP3A4 was detected both in breast tumors and in normal tissues (38). CYP3A was found in 22% of breast cancers determined by immunohistochemistry (36, 37).

CYP1B1 mRNA by RT-PCR (39) and CYP1B1 protein by immunohistochemistry and immunoblotting (40, 41) have been detected in breast cancer. CYP2C was identified in breast cancer by immunoblotting and CYP2C expression level in tumor tissues was similar with that in normal tissues (42). Two of 5 breast tumors expressed CYP2C judged by immunohistochemistry (43). CYP2E1 expression showed to be higher in breast tumors compared in normal breast tissues (38, 44).

4.2. Colon Cancer

Colorectal cancer is one of the most common neoplasms in the world, the incidence rate of which is close to that of lung cancer in Caucasian individuals (45). The major risk factor of colorectal cancer is various polycyclic aromatic hydrocarbons (PAHs) included in food (46, 47). Many studies have been reported that colorectal cancer is related to genotypes of various CYPs, which metabolize varieties of PAHs. However, there are few studies of CYPs expression in colorectal epithelium.
### Expression of cytochrome P450 in tumor

Table 1. The expression of CYPs in various tumors and corresponding normal tissues. Superscript reveals the number of reference. Parentheses indicate % positive rate in the specimens.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>CYP Expression</th>
<th>Tumor tissue</th>
<th>Normal tissue</th>
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<tbody>
<tr>
<td></td>
<td>Protein</td>
<td>RNA</td>
<td>Protein</td>
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<tr>
<td>Breast Cancer</td>
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<tr>
<td>CYP1A</td>
<td>BH (40%)</td>
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<td>IHC (40%)</td>
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<tr>
<td>CYP1A</td>
<td>BH</td>
<td></td>
<td>IHC</td>
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<tr>
<td>CYP1B</td>
<td>BH (33%)</td>
<td></td>
<td>RT-PCR</td>
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<tr>
<td>CYP2C</td>
<td>BH (135%)</td>
<td></td>
<td>IB</td>
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<tr>
<td>CYP2E1</td>
<td>BH</td>
<td></td>
<td>IHC</td>
</tr>
<tr>
<td>CYP3A</td>
<td>BH (22%)</td>
<td></td>
<td>IHC</td>
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<tr>
<td>CYP3A4</td>
<td>BH</td>
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<td>IHC</td>
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<tr>
<td>Colon Cancer</td>
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<tr>
<td>CYP1A</td>
<td>BH</td>
<td></td>
<td>IHC</td>
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<tr>
<td>CYP1A</td>
<td>EAA</td>
<td></td>
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<tr>
<td>CYP1B</td>
<td>BH</td>
<td></td>
<td>IHC</td>
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<tr>
<td>CYP3A</td>
<td>BH (55%)</td>
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<tr>
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<td>IB</td>
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<td>Lung Cancer</td>
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<td>CYP1A</td>
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<td>NH</td>
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<tr>
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<td>EAA</td>
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<td>IB</td>
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<td>IHC</td>
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<td>CYP3A</td>
<td>IB (100%)</td>
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<td>IHC</td>
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<td>IB</td>
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<td>Esophageal Cancer</td>
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<tr>
<td>CYP1A</td>
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<td>IHC</td>
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<td>CYP2A</td>
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<tr>
<td>CYP3A</td>
<td>BH (69%)</td>
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<td>IHC</td>
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<tr>
<td>CYP3A</td>
<td>IB</td>
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<tr>
<td>CYP3C</td>
<td>BH (25%)</td>
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<td>IB</td>
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<td>Liver Cancer</td>
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<td>CYP1A</td>
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<td>CYP1A</td>
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<tr>
<td>CYP3A</td>
<td>BH (100%)</td>
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<td>CYP1B</td>
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<td>IHC</td>
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<td>CYP2E1</td>
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<td>CYP2F2</td>
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<td>Prostate Cancer</td>
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<td>CYP1A</td>
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<td>IHC</td>
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<tr>
<td>CYP3A</td>
<td>BH (100%)</td>
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<td>CYP3A</td>
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<tr>
<td>CYP3A</td>
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<td>Brain Cancer</td>
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<td>CYP1A</td>
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<td>CYP1A</td>
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<td>CYP2C</td>
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<tr>
<td>Bladder Cancer</td>
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<td>IHC</td>
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<td>CYP2E2</td>
<td>BH (29%)</td>
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<tr>
<td>CYP3A</td>
<td>BH</td>
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<td>IHC</td>
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</table>

Expression of cytochrome P450 in tumor

CYP1A and CYP3A were detected by immunohistochemistry (48) and CYP3A4 was identified by immunoblotting (49) in colon cancer. Sterling et al. (50) reported an induced activity of CYP1A1 in human colon cancer. The expression of CYP3A4 was found in normal colon tissues (43, 51), and the presence of CYP3A and CYP3A4 transcripts in human colorectal epithelium and cultured colorectal cell lines have been also reported (52, 53). Five of 9 colon tumors revealed CYP3A expression determined by immunohistochemistry (43). CYP3A catalyzes not only activation of anticancer drugs such as cyclophosphamide and ifosfamide, but also inactivation of two widely used taxanes, paclitaxel and docetaxel, and vinca alkaloids. Therefore, the presence of CYP3A4 enzyme activity in colorectal cancer cells may influence tumor sensitivity to some drugs against colon cancer (25). CYP1B1 was detected by immunohistochemistry in colon cancer (40). Three of 9 colon tumors as well as normal colon tissues expressed CYP2C determined by immunohistochemistry (43).

4.3. Lung Cancer

Lung cancer is the most frequent cancer in the world today, and the epidemic of the disease is still ongoing. The lung constitutes the primary site of entry into the body for a wide variety of inhaled chemicals, such as PAHs. It is important to elucidate the roles of xenobiotic metabolizing enzymes including CYPs for better understanding of the mechanisms of lung carcinogenesis. Nevertheless, there is great controversy due to the low levels of enzymes present in the lung. AHH activity was studied in 105 lung cancers although this study did not show the histological difference of AHH activity level (54).

CYP1A1 is the most intensively studied CYP enzyme in the human lung because CYP1A1 is the major enzyme involved in PAH metabolism and may play a role in the development of lung cancer. Significantly higher levels of CYP1A1 expression and aromatic/hydrophobic DNA adducts were observed in lungs from female smokers compared with normal lung tissues in male smokers (55), suggesting an association with the risk of lung cancer (56). By Northern blotting analysis, CYP1A1 mRNA was found in 23% (10/43) of lung cancers (57). The authors suggested a presence of specific 10 kb mRNA species of CYP1A1 in lung cancer (57) although this tumor specific 10 kb CYP1A1 mRNA has not been followed up in any other studies. CYP1A1 enzyme was also identified by immunoblotting in the study of 12 lung cancer patients (58).

There has been a growing interest towards CYP2A6, which plays the major role in the nicotine metabolism both in vitro and in vivo (59). Miyamoto et al. showed that CYP2A6 gene deletion, which is one of CYP2A6 polymorphism, has the protective effect against lung cancer (60), although the mechanisms of CYP2A6 regulation are not well understood (61). Recently, Su et al. (62) has reported a high expression level of CYP2A13 in the respiratory tract that catalyzes monoxygenation reactions in the nicotine metabolism more efficiently than CYP2A6. CYP3A expression was demonstrated in both tumor and normal tissues by immunohistochemistry (63). CYP3A5 catalyzes the activation of the anticancer prodrugs cyclophosphamide and ifosfamide. CYP3A5 mRNA was found in all of eight lung cancers, and CYP3A4 mRNA in one of eight lung cancers. Both CYP3A5 and CYP3A4 mRNA were also identified in normal lung tissue (64). PAH-DNA adduct levels was reported to have a positive correlation with the amount of CYP3A5 in alveolar macrophages of smokers (65).

CYP1B1 metabolizes both tobacco carcinogens and 17β-estradiol. Spivack et al. (66) reported using real-time quantitative polymerase chain reaction and Western blot that CYP1B1 is commonly expressed in normal lung tissues and lung cancers. CYP2B7 and CYP4B1 mRNA were also identified in normal lung and cancer tissues by RNase protection assay (67).

CYP2E1 metabolizes some tobacco-specific nitrosamines (68). Activated carcinogens by CYP2E1 make oxygen radicals and cause tissue injury (69). Raunio et al. demonstrated the expression of CYP2E1 mRNA in normal lung tissues (70). In addition, normal lung tissues were also found to express CYP1A1, CYP3A5, CYP2B7, CYP4B1 and CYP2F1 mRNA determined by RT-PCR (70). CYP3A4 and CYP3A5 expression were also detected in normal lung tissues by immunohistochemistry (70, 71). CYP2C expression was detected by immunohistochemistry in normal bronchial gland (43).

4.4. Esophageal cancer

Proteins and/or mRNA of CYP1A, CYP2A, CYP3A, CYP4A, CYP4B, and CYP2E1 were detected in normal esophageal epithelium (72). CYP1A and CYP3A were identified in tumor esophageal tissues (73, 74). CYP1B1 was detected in squamous cell carcinoma of esophagus by immunohistochemistry (40).

4.5. Liver cancer

Most CYPs associated with drug metabolism were also expressed in hepatocellular carcinomas (43, 75-77). CYP2A4 protein was revealed in 11 of 16 (69%) normal liver tissues by immunohistochemistry although CYP3A4 protein in 2 of 14 (14%) hepatocellular carcinoma cases (78). Kirby et al. showed that the expression levels of CYP1A1, CYP2A1, CYP3A1 and CYP4A1 in tumor tissues decreased in comparison with those in normal tissues (77). Guengerich et al. showed that expression levels of CYP1A2, CYP3A and CYP2E1 in cirrhotic liver tissues decreased in comparison with those of normal liver tissues while the expression level of CYP2C was increased in metastatic liver tissues (79). CYP2E1 is known to have a strong free radical-producing ability, which may cause the cellular injury and DNA damages associated with hepatocellular carcinogenesis. Hirose et al. showed that the level of CYP2E1 expression in hepatocellular carcinoma cells tends to decrease when tumor cells are less differentiated (80).

4.6. Prostate cancer

CYP1A2, CYP3A5, CYP1B1, CYP4B1, CYP2C19 and CYP2D6 mRNA were detected in normal
Expression of cytochrome P450 in tumor

and tumor prostatic tissues by RT-PCR in a study with 28 prostatic samples while CYP3A4 and CYP3A7 mRNA were detected only in normal prostatic tissues (81). In 51 prostatic tumors, expression rates of CYP1A, CYP3A and CYP2C were 63, 61 and 25 percent as determined by immunohistochemistry; respectively (82). CYP2C was also detected in normal and tumor prostatic tissues by immunohistochemistry (43).

4.7. Brain tumor

CYP 1A, CYP2C9, CYP2E1 and CYP3A were identified in normal brain tissues and CYP1A, CYP2B1, CYP2A6, CYP2C, CYP2E1 and CYP3A were found in astrocytoma by immunohistochemistry (83). CYP1B1 was identified in astrocytoma although CYP1B1 expression was not detected in normal brain tissues by immunohistochemistry (40). CYP3A5 and CYP2C9 mRNA were detected by RT-PCR analysis in various brain tumors (84).

4.8. Others

Murray et al. showed that CYP1A, CYP2C and CYP3A were found in 68%, 29%, and 68% of tumors of urinary bladder, respectively, and suggested that the expression levels of CYP1A correlated with bladder tumor grade by immunohistochemistry (85). However, Yokose et al. reported that they did not detect both CYP2C and CYP3A in normal and cancer tissues of urinary bladder (43). CYP1A and CYP3A were present in 51 and 28% of stomach cancer whereas CYP1A and CYP3A were not identified in normal stomach tissues (86). In normal and tumor kidney tissues, CYP3A was identified by immunohistochemistry, and CYP3A4 mRNA was detected by RT-PCR in 65% of renal cell carcinoma and 90% of normal kidney tissues (87).

5. CONCLUSIONS

Various tumors express a variety of CYPs. Studying CYP expression in tumors should be useful and essential to: 1) better understanding of the mechanisms of carcinogenesis, 2) application of a specific CYP expression in tumors as a tumor marker, 3) application of CYP-dependent metabolisms for tumor targeting therapy, 4) utilities of the knowledge in specific metabolisms by CYPs expressed in tumors for selection of anti-cancer drugs. Studies of the local expression of CYPs in tumors will provide insights into mechanisms of carcinogenesis and intratumoral metabolisms of anticancer drugs, which may enable us to develop the present order-made therapy to the tailor-made therapy.

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Expression of cytochrome P450 in tumor


**Abbreviations:** CYP, cytochrome P450, NADPH, nicotinamide adenine dinucleotide phosphate, FAD, flavin adenine dinucleotide, FMN, flavin mononucleotide, AHH, Aryl hydrocarbon hydroxylase, PAH, polycyclic aromatic hydrocarbons

**Key Words:** Cytochrome P450, Tumor, Extrahepatic expression, Drug metabolism, Carcinogenesis, Review

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