Abstract. The treatment options for breast cancer include endocrine therapy, targeted therapy and chemotherapy. However, some patients with triple-negative breast cancer cannot benefit from these methods. Therefore, novel therapeutic targets should be developed. The cytochrome P450 enzyme (CYP) is a crucial metabolic oxidase, which is involved in the metabolism of endogenous and exogenous substances in the human body. Some products undergoing the metabolic pathway of the CYP enzyme, such as hydroxylated polychlorinated biphenyls and 4-chlorobi-phenyl, are toxic to humans and are considered to be potential carcinogens. As a class of multi-gene superfamily enzymes, the subtypes of CYPs are selectively expressed in breast cancer tissues, especially in the basal-like type. In addition, CYPs are essential for the activation or inactivation of anticancer drugs. The association between CYP expression and cancer risk, tumorigenesis, progression, metastasis and prognosis has been widely reported in basic and clinical studies. The present review describes the current findings regarding the importance of exploring metabolic pathways of CYPs and gene polymorphisms for the development of vital therapeutic targets for breast cancer.

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1. Introduction

Breast cancer is a malignant tumor that occurs in the lobule and the ductal epithelium of the breast (1). It ranks first in terms of incidence among malignancies in female patients worldwide (2). In 2005, ~1 million new cases of breast cancer were reported worldwide and cases were growing at a rate of 5-20% per year (3). With the development of medical technology and the increasing awareness of cancer prevention, the mortality rate of breast cancer is decreasing every year. In 2019, ~268,600 new cases of invasive breast cancer and 41,760 deaths associated with breast cancer were reported in USA women (2). Numerous studies have focused on the pathogenesis, progression, prognosis and treatment of breast cancer. Notably, increasing attention has been paid to the role of metabolic oxidase in breast cancer.

Cytochrome P450 (CYP) enzymes are a large family of self-oxidizing heme proteins belonging to the class of mono-oxygenases, and these compounds are involved in the synthesis of hormones, second messengers and other endogenous substances in the body, and in the regulation of detoxification and substance metabolism (4). Under normal conditions, CYPs are widely expressed in multiple human organs and are mainly located in the liver (5). During the course of the disease, such as breast cancer, CYPs are selectively expressed in different types of neoplasms (6). Notably, this phenomenon demonstrates the biological importance of exploring tumor-inherent metabolic pathways. Therefore, the present review focuses on the effects of the CYP metabolic pathway and its gene polymorphism on the occurrence, progression, treatment and prognosis of breast cancer.

2. CYP: Background

In 1958, CYP was first identified in rat liver microsomes (7). It is a B-group cytochrome with iron protoporphyrin as a prosthetic group (7). CYPs are a large superfamily of intact
membrane-conserved proteins found in animals, plants and micro-organisms (8). CYPs are named according to the specific absorption peaks of the complex at a wavelength of 450 nm (9). In the process of naming these compounds, the numbers after CYP stand for different families, the letters after the family indicate their subfamilies and the numbers after the subfamily indicate peptides. For instance, CYP1B1 represents the cytochrome P450 family 1 subfamily B polypeptide 1 (7,10). As terminal oxygenases, CYPs transport electrons through the iron ions of heme in its structure, oxidize heterologous substances, enhance the water solubility of heterologous substances and ease their excretion (11). The human CYP superfamily includes 18 families, 26 subfamilies and >50 subtypes with catalytic functions (11,12). Furthermore, >40% of the CYP amino acid sequences are classified into the same family and represented by Arabic numerals, and those with the same rate of ≥55% within the same family are categorized under the same subfamily (10). CYPs are mainly distributed in the liver and individual forms of CYPs are present in the extrahepatic tissues, such as the small intestine, kidney, lung and ovary (13,14). The CYP1, CYP2 and CYP3 families account for >70% of the total CYP content of the liver and are responsible for the metabolism of most drugs (15). It is the prime superfamily enzyme system involved in phase I drug metabolism and in mediating drug oxidation, reduction or hydrolysis (15). CYPs not only catalyze the phase I metabolic reactions of various endogenous substances (e.g., sex hormones, glucocorticoids and arachidonic acid) and exogenous substances (e.g., drugs, poisons and procarcinogens) (16,17), but are also closely related to the occurrence of disease, the generation of drug resistance and the susceptibility of tumors (18). Considering that gene polymorphisms are widespread among family members, individual differences are present in the distribution of CYPs in tissues and organs, resulting in discrepancies in the susceptibility to certain tumors. Therefore, the association between CYP enzymes and tumorigenesis has received increasing attention, and numerous studies have been conducted to determine the relevance of CYP enzymes in tumorigenesis.

3. Effect of CYP on steroid hormones

Breast cancer is a hormone-dependent tumor (19). The interaction of androgen, estrogen, progesterone and their receptors is involved in the occurrence and development of breast cancer (19). Long-term high levels of estrogen exposure factors (e.g., early menarche, late menopause, non-fertility and late child-birth) is a risk factor for breast cancer, which can directly or indirectly work via the estrogen signaling pathway (20-22). The function of estrogen is achieved by binding to the corresponding receptor. Estrogen receptor-α (ERα) accelerates tumor growth by stimulating abnormal cell proliferation and inhibiting apoptosis (23-25). Furthermore, ERα promotes mitosis by directly upregulating cyclin D1 and Myc expression, and interacts with EGFR and other receptor tyrosine kinases to activate the Ras/MAPK/PI3K/Akt signaling pathway, thereby stimulating tumor cell proliferation, enhancing DNA mutations and contributing to the development of breast cancer (26-28).

CYPs are involved in the biosynthesis and oxidative metabolism of sex hormones. Estradiol is gradually synthesized from cholesterol by the catalytic action of enzymes, such as CYP11, CYP17 and CYP19 family (29). Subsequently, estradiol is converted into various hydroxyl products by enzymatic oxidation, and the hydroxyl products undergo glucuronidation, sulfation, esterification and O-methylation metabolism, leading to the production of carcinogens (30). CYP1B1 is highly expressed in breast carcinoma tissues, and this compound metabolizes estrogen to 4-hydroxyestradiol and simultaneously binds to and activates ER, thereby promoting cell mitosis in breast tissues (29). This excessive growth stimulation may promote breast cancer occurrence (31). In addition, reactive estrogen semiquinone/quinone intermediates are the metabolic redox products of 4-hydroxyestradiol (32), causing DNA destruction, induction of cell transformation and initiation of tumorigenesis (33,34). Bradlow et al (35) demonstrated that the metabolite 16α-hydroxyestradiol of CYP2C9 and CYP3A4 is positively associated with the incidence of breast cancer. Furthermore, based on an epidemiological case-control study (36) and prospective study (37), elevated levels of 16α-hydroxyestradiol are associated with increased risk of breast cancer. Conversely, ERs also regulate CYP expression in breast tumors (38). CYP2B6 expression is markedly increased in ER-positive breast tumors because ERα regulates CYP2B6 gene expression in human breast cancer cells by directly binding to functional estrogen response elements located in the upstream regulatory region of CYP2B6 (38). Notably, Fukasawa et al (39) revealed a novel compound, NK150460, which inhibits 17β-estradiol (E2)-dependent transcription without affecting binding of E2 to ER. Contrary to expectations, NK150460 inhibits the proliferation of not only ER-positive, but also some ER-negative breast cancer cell lines, such as T-47D, MCF-7, and SK-BR-3; however, it never inhibits the proliferation of non-breast cancer cell lines (39). At present, inhibiting the synthesis of estrogen is still an important regimen for the treatment of luminal-type breast cancer. Although estrogen is considered to serve a causal role in breast cancer, as aforementioned, there is increasing evidence that the way estrogen is metabolized is related to the risk of breast cancer. This may explain why the effect of endocrine therapy is not always satisfactory. Therefore, studies clarifying the mechanism of estrogen metabolism in patients with breast cancer are an exciting domain of investigation. This could provide patients with precise endocrine targeted therapy in the future.

4. CYP gene polymorphism: A friend or foe in breast cancer

In addition to participating in estrogen metabolism, the gene polymorphisms of CYPs carry huge implications for the risk and prognosis of breast cancer. CYP3A4 mRNA expression is negatively associated with the morbidity of breast cancer (40). Additionally, Johnson et al (41) reported that the CYP3A polymorphism site rs10235235 is negatively associated with the morbidity of patients with breast carcinoma with late menarche. Johnson et al (42) further revealed that CYP3A4 SNP (rs10273424), a non-coding variant at the CYP3A locus, is associated with reduced risk of breast cancer in younger women below the age of 50 years at the time of diagnosis. However, polymorphisms in the CYP17, CYP19 and CYP1A1 genes are closely associated with breast cancer

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susceptibility (43-45). Women with CYP1A1 T6235C and A4889G genotypes rather than AA and TT are more likely to develop low-grade tumors; 85.9% of tumors in the AA and TT genotype groups are grade III; however, only 76.1% of polymorphism carriers are grade III (46). There was no significant difference in survival related to CYP1A1 gene status (46). Sangrajrang et al (29) performed genetic testing on the breast tissue of 1,067 Thai women and revealed that CYP1A2, CYP2C19 and CYP17 polymorphisms serve a crucial role in estrogen metabolism and affect the individual susceptibility of Thai women to breast cancer. Furthermore, CYP1A2 rs2470890 is prominently associated with the prognosis of patients with breast cancer and might serve as a novel genetic indicator of prognosis of patients with breast carcinoma (47). Raskin et al (48) demonstrated that CYP19 Val (80) polymorphisms and its haplotypes are associated with increased risk of breast cancer in young women with breast cancer susceptibility gene mutations. In addition, the association between six SNPs of CYP8A1 and breast cancer risk has been reported in detail (49,50). Patients with homozygotes of minor alleles of rs5602, rs477627 and rs6125671 exhibit increased risk of breast cancer compared with normal alleles (49). Furthermore, the minor allele homozygotes of rs477627 have a protective effect in Caucasian populations (49). Among Caucasian women with progesterone receptor-positive breast cancer, the cancer risk is associated with the rs6095541 and rs6095543 alleles (50). Notably, genetic polymorphisms in CYPs vary among different ethnicities (49). Justenhoven et al (51) reported that the CYP2C19*17 variant is associated with reduced risk of breast cancer in the German population; however, this variation is common in Europeans but rare in Asians. Additionally, Ruiter et al (52) suggested that CYP2C19*2 polymorphisms are associated with increased survival time in European patients with breast cancer who have been treated with tamoxifen. Among female Chinese Han patients, the carriers of the A allele of CYP2C19*3 are 2.19 times more likely to be attacked by breast cancer than those of the G allele (53). However, this variant of CYP2C19*3 is rare among the European population (53). The relationship between the gene polymorphisms of CYPs and breast cancer has been clarified, thus contributing to the prediction of populations with high-risk tumor and determine individuals susceptible to tumors. However, at present, numerous conflicting results have been reported, and this may be associated with various reasons, such as region, ethnicity and sex. To the best of our knowledge, limited information is available regarding the interaction between the CYP gene and other genes or environmental factors. Therefore, an in-depth study on the association between CYP gene polymorphisms and tumorigenesis is important for early tumor screening, targeted therapy and therapeutic efficacy.

5. Effect of CYPs on tumor angiogenesis

Angiogenesis is one of the major characteristics of malignant tumors, which are rich in blood supply. Angiogenesis is regulated by pro-angiogenic and anti-angiogenic factors via a complicated process. Under normal conditions, the dynamic balance is maintained between pro-angiogenic and anti-angiogenic factors during physiological angiogenesis. When this balance is broken by pathogenic factors, pathological angiogenesis, such as tumor angiogenesis, might occur. Breast cancer cells flourish in the tumor microenvironment. Diverse components of the breast cancer microenvironment, such as pathological neovascular structures, may promote breast cancer progression and metastasis (54). The CYP4 family can hydroxylate arachidonic acid (AA), and the product of this metabolism is a novel lipid mediator, which may be involved in the proliferation of breast cancer cells and tumor angiogenesis (55). 20-Hydroxy-icosatetraenoic acid (20-HETE) is converted from AA by the omega-hydroxylase enzymes from the CYP family 4 and subfamily A (CYP4A) genes (55). 20-HETE is the main pro-inflammatory metabolite that regulates vascular remodeling and neovascularization under ischemic or hypoxic conditions (55-57). Additionally, 20-HETE serves an important role in epidermal growth factor and vascular endothelial growth factor (VEGF) activation, pro-angiogenic effects and the stimulation of endothelial cell proliferation, migration and cell survival (55,58). In tumors, the CYP4A/20-HETE axis promotes endothelial cell migration and neovascularization (59,60). When N-hydroxy-N’-(4-butyl-2-methylphenyl)formamidine (HET0016), a highly selective inhibitor of 20-HETE synthesis, is used alone in tumor-bearing animals, tumor neovascularization is reduced (61,62). When the level of different pro- and anti-angiogenic factors in tumor lysates is detected, prominent changes occur after HET0016 treatment compared with placebo-treated tumors (63,64). When certain indicators, including extravascular cell space (EES), vascular parameters and tumor angiogenesis, are analyzed, HET0016 treatment reduces EES, tumor blood volume, permeability and tumor angiogenesis (63,64). In the field of cancer, triple-negative breast cancer is not sensitive to chemotherapeutics. The inhibition of the synthesis of 20-HETE is expected to be a breakthrough in the treatment of triple-negative breast cancer. Further investigation is required to explore how 20-HETE inhibitors could be more effective in decreasing tumor growth and neovascularization.

In addition, compared with other members of the large CYP family 4, CYP4Z1 is unique and vital in the development of breast cancer. A 52% increase in CYP4Z1 mRNA expression was identified in breast cancer tissues compared with non-cancerous tissues (65). Yu et al (66) demonstrated that CYP4Z1 overexpression activates the PI3K/Akt and ERK1/2 signaling pathways and induces human breast cancer angiogenesis and tumor growth. Additionally, Wang et al (67) demonstrated that CYP4Z1 3'untranslated region may be involved in the regulation of E-cadherin protein, thus affecting the migration of breast cancer cells. In addition, in ER-positive breast cancer cells, the regulation of the CYP4Z1 RNA network may be associated with tamoxifen resistance during breast cancer treatment (68). Further in vivo experiments are required to confirm whether CYP4Z1 could be a therapeutic target in restraining cancer progression.

6. Effect of CYPs on pre-metastatic niche formation and metastasis via the arachidonic acid metabolic pathway

The tumor interstitial microenvironment serves an essential role in the occurrence, development and metastasis of breast cancer. The breast carcinoma microenvironment has numerous components, including suppressive immune cells,
reprogrammed fibroblasts, pathological neovascular structures, altered extracellular matrix and certain soluble factors, which together facilitate a pro-tumorigenic environment (54). Tumor-associated macrophages (TAMs) are the main component of the tumor microenvironment and are among the most abundant inflammatory stromal cells (69). According to different functional characteristics, TAMs are usually divided into the M1 and M2 subtype. The M1 type is equipped with antitumor effects, while M2 activates the generation of tumor growth factors, such as VEGF, and promotes tumor growth, invasion and metastasis (70-72). Furthermore, the role of TAMs that construct a protective niche of tumor cells in distant organs is slowly being recognized (73). Notably, targeting TAMs in part prevents tumor metastasis by inhibiting the production of multiple endogenous factors, including chemokines, inflammatory factors and growth factors (74-76).

CYP4A, a key inducible cytochrome P450 enzyme, catalyzes the synthesis of 20-HETE from AA in human tissues (77), as shown in Fig. 1. 20-HETE is a novel lipid mediator, which promotes tumor growth and angiogenesis (78) and induces the transformation of the tumor stromal microenvironment into the pro-tumorigenic environment (79,80). The expression levels of 20-HETE-producing enzymes of the CYP4A family are upregulated in invasive breast carcinoma tissues (73). CYP4A/20-HETE induces the transformation of macrophage to M2 phenotype via the STAT3 signaling pathway, and CYP4A/20-HETE activation is an important medium for promoting niche formation before tumor cell metastasis, leading to distant colonization of tumor cells (73). Therefore, downregulation of CYP4A/20-HETE expression has therapeutic potential in the tumor microenvironment.

In human tissues, CYP4A11 and CYP4A22 are the most important isozyme types of CYP4A for catalyzing the synthesis of 20-HETE (80). Alexanian et al (81) revealed that the expression levels of CYP4A11 and CYP4A22 in triple negative breast cancer tissues are higher than those in normal breast tissues, indicating an increase in CYP4A/20-HETE activity after the malignant transformation of breast ductal epithelium. The downregulation of cyclooxygenase-2 and CYP4A signaling in human breast carcinoma cells inhibits cancer metastasis by preventing anoikis resistance, migration and invasion (82). The inhibition of 20-HETE synthesis with chemical inhibitor HET0016 reduces proangiogenic factors and inhibits breast cancer growth (62). Borin et al (61) demonstrated that targeting the AA signaling pathway by inhibiting the synthesis of 20-HETE reduces the migration and invasion of metastatic breast cancer cells. Furthermore, an animal study indicated that the incidence of lung metastases in breast cancer can be reduced by inhibiting CYP4A/20-HETE activity (61). Notably, CYP8A1 also is involved in the metabolism of AA. CYP8A1, also known as prostacyclin I2 synthase, is an isomerase, which converts prostaglandin H2 into prostacyclin (PGI2) (83). PGI2 is a type of prostanoid, which exerts a crucial role in cancer-associated inflammation, tumor progression and metastasis (84,85). Notably, CYP8A1 is expressed in breast carcinoma and adjacent tissues and is involved in the inflammation mechanism of breast cancer cells through the aforementioned eicosanoid metabolites (83). In addition, CYP8A1 affects tumor cell survival signaling via AA metabolism pathways, including cell proliferation and apoptosis, tumor cell invasion, metastasis, and angiogenesis (83). Similarly, CYP2C19 is a key enzyme for the synthesis of epoxy-eicosatrienoic acids (EETs) in the AA metabolic pathway (86). The exogenous supplementation of EETs promotes the proliferation of cancer cells in vitro and in vivo (86). In a number of tumor cell lines, such as breast cancer cell lines, EETs stimulate the activation of the MAPK and PI3K/Akt signaling pathways, promote phosphorylation of EGFR (86), alter the tumor microenvironment, and induce immunosuppression in an autocrine and paracrine manner (80). Additionally, EET inhibits cancer cell apoptosis by upregulating the anti-apoptotic proteins Bcl-2 and Bcl-xl and downregulating the pro-apoptotic protein

Figure 1. Schematic representation of arachidonic acid metabolic pathway via the major CYP enzymes. Metabolites (20-HETE, EETs and PGI2) possess tumor-promoting effects on breast cancer. 20-HETE, 20-hydroxy-eicosatetraenoic acids; CYP, cytochrome P450; EETs, epoxy-eicosatrienoic acids; HET0016, N-hydroxy-N0-(4-butyl-2 methyl phenyl) formamidine; PGH2, prostaglandin H2; PGI2, prostacyclin.
Bax (86). Therefore, CYP2C19 serves a vital role in promoting the malignant manifestation of tumors and in the pathogenesis of breast cancer via the EET anabolic pathway. In humans, CYP2C8, 2C9 and 2J2 subfamily members are also involved in the synthesis of EETs. CYP2C8, 2C9 and 2J2 are highly expressed in breast cancer tissues, thus indirectly promoting cancer cell proliferation, migration, angiogenesis and invasion (87). CYP3A4, an activated AA epoxygenase, accelerates STAT3-mediated cell proliferation of breast cancer via EET biosynthesis (88). Furthermore, EETs induce tumor cell proliferation and survival via multiple signaling pathways and molecular mechanisms, including EGFR/P13K/Akt, EGFR/MAPK, TNF-α and prometastatic matrix metalloproteinases (86,89,90). Therefore, novel therapeutics that target the AA metabolic pathway should be the focus for cancer chemoprevention and treatments.

7. Effect of CYP on clinicopathological factors

CYPs are selectively expressed in breast cancer tissues, and their expression levels affect clinicopathological factors and patient prognosis (91). Based on the analysis of the expression levels of CYPs in 393 patients with breast cancer, Haas et al (92) revealed that the expression levels of CYP3A4/5 are markedly associated with lymph node metastasis rate, and high expression levels of CYP1B1 are associated with poor tumor differentiation. Murray et al (91) demonstrated that CYP2S1, CYP3A4, CYP4V2 and CYP26A1 are associated with survival in patients with breast cancer, indicating that CYP can be used as a marker of prognosis for patients with breast cancer. CYP4Z1 is a novel member of the CYP4 family that is upregulated in human breast cancer, and CYP4Z1 expression is positively associated with high-grade malignancy tumors and poor prognosis (66). Patients with breast cancer with high CYP4A22 expression often experience shortened relapse-free survival, which is a negative prognostic factor (73). The down-regulation of CYP4A1 signal transduction may inhibit tumor cell migration and invasion, thereby inhibiting breast cancer metastasis (82). However, the expression of several CYPs may imply favorable clinical outcomes (93,94). CYP2E1 expression is elevated in breast cancer tissues and negatively associated with tumor size (93). High CYP2E1 expression contributes to the production of reactive oxygen species and the occurrence of the oxidative stress reaction in breast cancer cells, resulting in damaged mitochondria and DNA modification, leading to accelerated death of necrotic cancer cells, which may be beneficial to patients with breast cancer to a certain extent (93,94). CYP2E1 could inhibit breast cancer cell metastasis by regulating tumor cell autophagy and stimulating endoplasmic reticulum stress (95). Other mechanisms involved in the adverse prognostic factors mediated by CYPs in patients with breast carcinoma need to be explored further. However, the present review suggests that the inhibition of CYPs may be a novel therapeutic target for improving the prognosis of patients with breast cancer.

8. Effect of CYPs on carcinogen metabolism

Inter-individual genetic variation in the metabolism of carcinogens is a determinant factor of susceptibility to various types of cancer (96). CYPs serve a profound role in the metabolism of carcinogens (97). The difference in the enzyme activity of CYPs determines the susceptibility to chemical carcinogens (96). Numerous CYPs are involved in catalyzing the metabolism of potential breast cancer-related carcinogens (96). Polycyclic aromatic hydrocarbons (PAHs) are common environmental carcinogens that induce tumorigenesis when they are activated by CYPs (98). They accumulate in breast tissues (99), and are metabolized and activated by CYP1A1 to produce electrophilic epoxy compounds with strong carcinogenic activity, which change the base pairing of DNA, cause codon changes, introduce mutations and eventually lead to cancer (100). Therefore, the activity of CYP1A1 isoenzyme in breast tissues is the key to determine the carcinogenicity of PAHs. The aryl hydrocarbon receptor (AhR) is a transcriptional regulator of CYP1A1, thereby regulating its protein expression (101). To the best of our knowledge, Al-Dhfyan et al (101) were the first to report that the AhR/CYP1A1 signaling pathway regulates the proliferation, development, self-renewal and chemoresistance of breast cancer stem cells by inhibiting phosphatase and tensin homolog and activating β-catenin and Akt signaling pathways. AhR may be a potential drug target for treatment of ER-negative breast cancer in the future. In addition, CYP1B1 can convert the heterocyclic amine 2-amin o-1-methyl-6-phenylimidazole[4,5-b] pyridine in food into N2-hydroxylated derivatives with DNA mutagenicity, which has been linked to the incidence of colon cancer and breast cancer (102). Additionally, CYP2W1 expression is upregulated in breast cancer tissues and is involved in the biological activation of PAH carcinogens (83). CYPs have hallmark effects in the metabolic activation and elimination of numerous carcinogens. A number of chemical carcinogens are mostly indirect carcinogens, which need to be activated by metabolic activation in vivo to interact with cellular biomolecules to cause cancer. The genetic polymorphism of CYPs determines the discrepancy in the metabolism of carcinogens and the susceptibility of tumors in patients (96). In future research, attention should be paid to the metabolic function and genotypes of CYPs in patients to carry out individualized administration for patients with tumors and optimize the clinical therapeutic schedule.

9. Effect of gene polymorphism of CYPs on chemotherapy drug metabolism

The genetic polymorphisms of CYP enzymes in breast tumors have an effect on the drug treatment outcomes of patients with breast cancer. They lead to changes in the response to drugs ranging from adverse reactions to lack of efficacy. The discovery of genetic markers for susceptibility to breast carcinoma has led to a growing body of epidemiological research examining relatively common genetic polymorphisms. Among the 57 identified CYP isoenzymes that catalyze drug metabolism, >20 CYP genes, including CYP1B1, CYP2B6, CYP2C9, CYP2C19 and CYP2D6, have functional polymorphisms. CYP1B1 is a metabolic enzyme for numerous anticancer drugs, including cyclophosphamide, paclitaxel, doxorubicin, docetaxel, cisplatin and 5-fluorouracil (103). Furthermore, the CYP1B1 4326G allele is associated with a decreased response rate, reduced progression-free survival and shorter overall survival in patients with breast cancer.
treated with taxanes (104). CYP2B6 serves a pivotal role in the efficacy of doxorubicin and cyclophosphamide (105). Compared with that in patients with wild-type alleles, the efficacy of neoadjuvant chemotherapy is reduced in patients with breast cancer with CYP2C9*2 heterozygotes (106). Furthermore, the genotypes of CYP2C19 and CYP2D6 influence the therapeutic actions of tamoxifen in patients with breast cancer (107). Similarly, the majority of CYP genes are associated with the clinical efficacy of chemotherapy drugs in patients with breast cancer; these genes include CYP1A2, CYP2A6, CYP2B, CYP2C8, CYP2C9, CYP2E1, CYP2S1, CYP2W1, CYP3A4 and CYP3A5 (97,106,108-110). Furthermore, the genetic polymorphisms of CYPs are closely associated with the hematological adverse reactions caused by chemotherapy drugs in patients with breast cancer (105). Bray et al (105) revealed that CYP2B6*2 and CYP2B6*5 mutant genes are closely associated with a high incidence of drug dose delay and adverse hematological reactions. Nakajima et al (111) demonstrated that leukopenia is associated with CYP2B6 gene polymorphism g.-2320T>C, g.-750T>C, g. 18492T>C. Therefore, this may explain the unsatisfactory therapeutic effect in some patients with breast cancer. Whole genome sequencing of CYPs in patients with breast cancer is important to provide the necessary guarantee to patients to implement precise treatment. Although next-generation sequencing technology is relatively mature now, its high cost limits the actions of patients. In the future, more patients are expected to benefit from it.

10. Conclusion

CYPs serve a multi-faceted role in contributing to carcinogenesis, tumor growth, invasion and metastasis. Additionally, they catalyze phase 1 metabolism of xenobiotics, such as drugs and carcinogens. These CYP gene polymorphisms are associated with drug responses and susceptibility to breast cancer. Notably, the CYP4A/20-HETE axis serves a key role in promoting tumor growth, neovascularization, migration and invasion, and may be a potential target for prevention and therapy of metastasis. Evidence that glioma and breast tumor growth and metastasis can be successfully controlled by HET0016 has been provided by some research groups. Therefore, novel therapeutics targeting the CYP4A/20-HETE metabolic pathway should serve more attention in translational medicine, either as monotherapy or in combination with first-line chemotherapy drugs and radiotherapeutic approaches. An increased understanding of CYPs will provide novel therapeutic targets for clinical precision treatment of patients with breast cancer.

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Authors’ contributions

JY designed and supervised the study. BL drafted the manuscript and prepared the figures. HY performed the literature analysis. DY revised the manuscript. Data authentication is not applicable. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Lakhani SR, Ellis IO, Schnitt SJ, Pan PH and van de Vijver MJ (eds.): WHO Classification of Tumours of the Breast. In: WHO Classification of Tumours. 4th edition. Vol. 4. IARC Press, Lyon, pp 82-134, 2012.
2. Desamitis CE, Ma J, Gandet MM, Newman LA, Miller KD, Goding SA, Jamal A and Siegel RL: Breast cancer statistics, 2019. CA Cancer J Clin 69: 438-451, 2019.
3. Dumitrescu RG and Cotarla I: Understanding breast cancer risk-where do we stand in 2005? J Cell Mol Med 9: 208-221, 2005.
4. Gonzalez FJ and Gelboin HV: Role of human cytochromes P450 in the metabolic activation of chemical carcinogens and toxins. Drug Metab Rev 26: 165-183, 1994.
5. Ding X and Kaminsky LS: Human extrahepatic cytochromes P450: Function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. Annu Rev Pharmacol Toxicol 43: 149-173, 2003.
6. Murray GI: The role of cytochrome P450 in tumour development and progression and its potential in therapy. J Pathol 192: 419-426, 2000.
7. Gajjar K, Martin-Hirsch PL and Martin FL: CYP1B1 and hormone-induced cancer. Cancer Lett 324: 13-32, 2010.
8. Nebert DW and Russell DW: Clinical importance of the cytochromes P450. Lancet 360: 1155-1162, 2002.
9. Luthra A, Denisov IG and Sligar SG: Spectroscopic features of cytochrome P450 reaction intermediates. Arch Biochem Biophys 507: 26-35, 2011.
10. Nelson DR: Cytochrome P450 nomenclature, 2004. Methods Mol Biol 320: 1-10, 2006.
11. Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J and Raunio H: Inhibition and induction of human cytochrome P450 enzymes: Current status. Arch Toxicol 82: 667-715, 2008.
12. Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM and Nebert DW: Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenomics 14: 1-18, 2004.
13. Thelen K and Dressman JB: Cytochrome P450-mediated metabolism in the human gut wall. J Pharm Pharmacol 61: 541-558, 2009.
14. Renaud HJ, Cui JY, Khan M and Klaassen CD: Tissue distribution and gender-divergent expression of 78 cytochrome P450 mRNAs in mice. Toxicol Sci 124: 261-277, 2011.
15. Guengerich FP: Mechanisms of cytochrome P450 substrate oxidation: MiniReview. J Biochem Mol Toxicol 21: 163-168, 2007.
Molecular origin of cancer: Catechol

Meilahn EN, De Stavola B, Allen DS, Fentiman I, Bradlow HL, Epidemiol Biomarkers Prev 6: 505-509, 1997.

metabolites and breast cancer: A case-control study. Cancer

Gooden JK, Cavalieri EL, Stack DE, Devanesan PD, Todorovic R, Yager JD and Liehr JG: Molecular mechanisms of estrogen cancer. Cancer Lett 356: 231-243, 2015.

Levin ER: Bidirectional signaling between the estrogen receptor and human epidermal growth factor receptor 2 signaling pathways in breast cancer: Molecular basis and clinical implications. Breast Care (Basel) 8: 256-262, 2013.

Leigh JR: 4-hydroxylation of oestrogens as a marker for tumour malignancy. Biochem Soc Trans 27: 318-323, 1999.

Leigh JR, Ulubelen AA and Strobel HW: Cytochrome P-450-mediated redox cycling of estrogens. J Biol Chem 261: 16685-16680, 1986.

Yager JD and Leigh JR: Molecular mechanisms of estrogen carcinogenesis. Annu Rev Pharmacol Toxicol 36: 203-232, 1996.

Dwivedy I, Higginbotham S, Johansson SL, Patil KD, Gross ML, Goeden JK, et al: Molecular origin of cancer: Catechol estrogen-3,4-quinones as endogenous tumor initiators. Proc Natl Acad Sci USA 94: 10937-10942, 1997.

Bradlow HL, Hershcopf RJ, Martucci CP and Fishman J: Estrogen receptor-dependent regulation of CYP2B6 in human breast cancer cells. Biochim Biophys Acta 1799: 469-479, 2010.
56. Garcia V, Joseph G, Shkolnik B, Ding Y, Zhang FF, Gotlinger K, Falck JR, Dakarapu R, Capdevila JH, Bernstein KE and Schwartzman ML: Angiotensin II receptor blockade or deletion of vascular endothelial ACE does not prevent vascular dysfunction and remodeling in 20-HETE–dependent hypertension. Am J Physiol Regul Integr Comp Physiol 309: R71–R78, 2015.

57. Seki T, Wang MH, Miyata N and Lanniado-Schwartzman M: Cytochrome P450 4A isoform inhibitory profile of N-hydroxy-N-(4-butyl-2-methylphenyl)-formamidine (HET0016), a selective inhibitor of 20-HETE synthesis. Biol Pharm Bull 28: 1651–1654, 2005.

58. Garcia V, Shkolnik B, Milhau L, Falck JR and Schwartzman ML: 20-HETE activates the transcription of angiotensin-converting enzyme via nuclear Factor-κB translocation and promoter binding. J Pharmacol Exp Ther 336: 525–532, 2010.

59. Chen L, Ackerman R, Saleh M, Gotlinger KH, Kessler M, Mendelowitz LG, Falck JR, Arbab AS, Scicli AG, Schwartzman ML, et al: 20-HETE regulates the angiogenic functions of human endothelial progenitor cells and contributes to angiogenesis in vivo. J Pharmacol Exp Ther 348: 442–451, 2014.

60. Guo AM, Jancic B, Sheng J, Falck JR, Roman RJ, Edwards PA, Arbab AS and Scicli AG: The cytochrome P450 4A/F-20-hydroxyeicosatetraenoic acid system: A regulator of endothelial precursor cells derived from human umbilical cord blood. J Pharmacol Exp Ther 338: 265–274, 2011.

61. Borin TF, Shankar A, Angara K, Rashid MH, Jain M, Iskander AS, Varma NR, Anbari K, Chen CL, Card JW, Yang S, Chen JX, Fu XN, Xie X, Zheng H, Wang C, Wang X, Deng RX, Zou Y, et al: Intravenous formulation of HET0016 decreased human glioma. Onco Targets Ther 9: 1205–1219, 2016.

62. Tariq M, Zhang J, Liang G, Ding L, He Q and Yang B: Macrophage in breast cancer. J Cell Biochem 118: 2484–2501, 2013.

63. Liu Y and Xi T: Competing endogenous RNA networks of CYP4Z1 3'UTR represses migration of human breast cancer cells. Biochem Biophys Res Commun 478: 900–907, 2016.

64. Zheng L, Li X, Meng X, Chou J, Hu J, Zhang F, Zhang Z, Xing Y, Dong J, Sun J, Wu Y, et al: Elevated 14,15-epoxyeicosatrienoic acid by increasing of cytochrome P450 2C8, 2C9 and 2J2 and decreasing of soluble epoxide hydrolase activity. J Cancer Prev 13: 2647–2653, 2008.

65. Wei X, Zhang D, Dou X, Niu N, Huang W, Bai J and Zhang G: Elevated 14,15-epoxyeicosatrienoic acid by increasing of cytochrome P450 2C8, 2C9 and 2J2 and decreasing of soluble epoxide hydrolase associated with aggressiveness of human breast cancer. BMC Cancer 14: 841, 2014.

66. Lu H, Zhang L, Cai H, Chen G, Meng X and Xi T: CYP4Z1 3'UTR represses migration of human breast cancer cells. Biochem Biophys Res Comm 478: 900–907, 2016.

67. Zheng L, Li X, Meng X, Cai H, Hu J, Zhang F, Zhang Z, Xing Y, Liu Y and Xi T: Competing endogenous RNA networks of CYP4Z1 and pseudogene CYP4Z2P confer tamoxifen resistance in breast cancer. Mol Cell Endocrinol 427: 133–142, 2016.

68. Chen L and Zhang J: Role of macrophage polarization in tumor angiogenesis and vessel normalization: Implications for new anticancer therapies. Int Rev Cell Mol Biol 301: 1–15, 2013.

69. Tariq M, Zhang J, Liang G, Ding L, He Q and Yang B: Macrophage polarization: Anti-cancer strategies to target tumor-associated macrophage in breast cancer. J Cell Biochem 118: 2484–2501, 2017.

70. Lao L, Fan S and Song E: Tumor associated macrophages as therapeutic targets for breast cancer. Adv Exp Med Biol 1026: 331–370, 2020.

71. Choi J, Gyamji I, Jang H and Koo JS: The role of tumor-associated macrophage in breast cancer biology. Histol Histopathol 33: 133–145, 2018.

72. Chen XY, Wu TJ, Zhang J, Li Y, Chen HL, Yang GF, Yu W, Liu YZ, Zhang XN, Han CF, et al: CYP4Z1 in tumor-associated macrophages promotes pre-metastatic niche formation and metastasis. Oncogene 36: 5045–5057, 2017.

73. Jia X, Yu F, Wang J, Iwanowycz S, Saaoud F, Wang Y, Hu J, Wang Q and Fan D: Emodin suppresses pulmonary metastasis of breast cancer accompanied with decreased macrophage migration and M2 polarization in the lungs. Breast Cancer Res Treat 148: 291–302, 2014.

74. Ding L, Liang G, Yao Z, Zhang J, Liu R, Chen H, Zhou Y, Wu H, Yang B and He Q: Metformin prevents cancer metastasis by inhibiting M2-like polarization of tumor associated macrophages, Oncotarget 6: 36436–36455, 2015.

75. Davis CE and Pollard JW: Distinct role of macrophages in different tumor microenvironments. Cancer Res 66: 605–612, 2006.

76. Hoopes SL, Garcia V, Eden ML, Schwartzman ML and Zelldn DC: Vascular actions of 20-HETE. Prostaglandins Other Lipid Mediat 85: 517–536, 2015.

77. Alexanian A and Sorokin A: Targeting 20-HETE producing enzymes in cancer-rational, pharmacology, and clinical potential. Onco Targets Ther 6: 245–255, 2013.
94. Vaclavikova R, Hubackova M, Stribrna-Sarmanova J, Kodet R, Mrhalova M, Novotny J, Gut I and Soucek P: RNA expression of cytochrome P450 in breast cancer patients. Anticancer Res 27: 4443-4450, 2007.

95. Leung T, Rajendran R, Singh S, Garva R, Krstic-Demonacos M and Demonacos C: Cytochrome P450 2E1 (CYP2E1) regulates the response to oxidative stress and migration of breast cancer cells. Breast Cancer Res 15: R107, 2013.

96. Cardenas-Rodriguez N, Lara-Padilla E, Bandala C, Lopez-Cruz J, Uscanga-Carmona C, Lucio-Monter PF and Florian-Monter E: CYP2W1, CYP4F11 and CYP3A1 polymorphisms and interaction of CYP2W1 genotypes with risk factors in Mexican women with breast cancer. Asian Pac J Cancer Prev 13: 837-846, 2012.

97. Tan BS, Tiong KH, Muruhadas A, Randhawa N, Choo HL, Bradshaw TD, Stevens MF and Leong CO: CYP2S1 and CYP2W1 mediate 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW-610, NSC 721648) sensitivity in breast and colorectal cancer cells. Mol Cancer Ther 10: 1982-1992, 2011.

98. Moorthy B, Chu C and Carlin DJ: Polycyclic aromatic hydrocarbons: From metabolism to lung cancer. Toxicol Sci 145: 5-15, 2015.

99. Goth-Goldstein R, Stampfer MR, Erdmann CA and Russell M: Interindividual variation in CYP1A1 expression in breast tissue and the role of genetic polymorphism. Carcinogenesis 21: 2119-2122, 2000.

100. Nilsson R, Antic R, Berni A, Dallner G, Dettbarn G, Gromadzinska J, Joksic G, Lundin C, Palitti F, Prochazka G, et al: Exposure to polycyclic aromatic hydrocarbons in women from Poland, Serbia and Italy-relation between PAH metabolite excretion, DNA damage, diet and genotype (the EU DIEPHY project). Biomarkers 18: 165-173, 2013.

101. Al-Dhifyan A, Alhosani A and Korashy HM: Aryl hydrocarbon receptor/cytochrome P450 1A1 pathway mediates breast cancer stem cells expansion through PTEN inhibition and beta-Catenin and Akt activation. Mol Cancer 16: 14, 2017.

102. Hsu MH, Baer BR, Rettie AE and Johnson EF: The crystal structure of cytochrome P450 4B1 (CYP4B1) monooxygenase complexed with octane discloses several structural adaptations for omega-Hydroxylation. J Biol Chem 292: 5610-5621, 2017.

103. Mcfadyen MC, Meleod HL, Jackson FC, Melvin WT, Doehmer J and Murray GI: Cytochrome P450 CYP1B1 protein expression: A novel mechanism of anticancer drug resistance. Biochem Pharmacol 62: 207-212, 2001.

104. Marsh S, Somlo G, Li X, Frankel P, King CR, Shannon WD, Meleod HL and Synold TW: Pharmacogenetic analysis of paclitaxel transport and metabolism genes in breast cancer. Pharmacogenomics J 7: 362-365, 2007.

105. Bray J, Sludden J, Griffin MJ, Cole M, Verrill M, Jamieson D and Boddy AV: Influence of pharmacogenetics on response and toxicity in breast cancer patients treated with doxorubicin and cyclophosphamide. Br J Cancer 102: 1003-1009, 2010.

106. Seredina TA, Goreva OB, Talaban VO, Grishanova AY and Lyakhovich YV: Association of cytochrome P450 genetic polymorphisms with neoadjuvant chemotherapy efficacy in breast cancer patients. BMC Med Genet 13: 45, 2012.

107. Schroth W, Antoniadou L, Fritz P, Schwab M, Muerdter T, Zanger UM, Simon W, Eichelbaum M and Brauch H: Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol 25: 3187-3193, 2007.

108. Daraei B, Aghvami M, Pourahmad J and Dinarvand R: A comparison of hepatocyte cytotoxic mechanisms for docetaxel and PLGA-docetaxel Nanoparticles. Iran J Pharm Res 16: 249-265, 2017.

109. Jenkins P, Scaife J and Freeman S: Validation of a predictive model that identifies patients at high risk of developing febrile neutropaenia following chemotherapy for breast cancer. Ann Oncol 23: 1766-1771, 2012.

110. Hlavac V, Brynychova V, Vaclavikova R, Ehrlichova M, Vrana D, Pecha V, Trnkova M, Kodet R, Mrhalova M, Kubackova K, et al: The role of cytochromes p450 and aldo-keto reductases in prognosis of breast carcinoma patients. Medicine (Baltimore) 93: e255, 2014.

111. Nakajima M, Komagata S, Fujiki Y, Kanada Y, Ebi H, Itah K, Mukai H, Yoki T and Minami H: Genetic polymorphisms of CYP2B6 affect the pharmacokinetics/pharmacodynamics of cyclophosphamide in Japanese cancer patients. Pharmacogenet Genomics 17: 431-445, 2007.

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