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Advances in Cytochrome P450 in Tumor Therapy

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Abstract

Cytochrome P450 (CYP450) is a family of heme proteins capable of self-oxidation and is a type of monooxygenase. It was first discovered in the microsomes of liver cells and is distributed throughout various tissues and organs in the body, primarily localized on the inner membranes of the endoplasmic reticulum and mitochondria. CYP450 is involved in the metabolism of various endogenous and exogenous carcinogens and plays a significant role in the metabolism of numerous anticancer drugs and the development of tumors such as lung cancer, thyroid cancer, colorectal cancer, and breast cancer. Therefore, the development of CYP450-related anticancer targeted drugs and their expression in tumors have become a hot topic. This review aims to focus on the progress and clinical translation challenges of CYP450 in tumors.

Keywords

Cytochrome P450, Mechanism, Targeted Drugs, Tumor Therapy

1. Introduction

CYP450 is an important enzyme in phase I metabolism, and there are 18 families and 57 functional genes in the human genome, among which the CYP1, CYP2, and CYP3 families are the most prominent and are responsible for different metabolic functions, respectively. They are involved in drug metabolism and the metabolism of endogenous compounds such as lipids, proteins and hormones to maintain physiological homeostasis. CYP450 plays a key role in pharmacokinetics [1]. Since its properties are closely related to the development of diseases such as cancer and the outcome of chemotherapy, understanding its role and the clinical

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effects of genetic polymorphisms is essential to personalize treatment strategies and enhance drug responses in different patient groups [2]. CYP450 is mainly found in the smooth endoplasmic reticulum and small intestinal epithelial cells, and is closely related to the first phase of metabolism of about 80% of commonly used drugs, including anticancer drugs, and is involved in the synthesis of many hormones. CYP450 is involved in the synthesis of many hormones and has an impact on hormone-associated cancers, so its genetic variants play an important role in tumor and therapeutic aspects [3]. CYP450 plays a key role in tumor development by activating proto-oncogenes, leading to the accumulation of mutations [4]. Therefore, the expression of CYP450 in tumors and its application in tumor therapy, especially the research of CYP450-targeted anticancer drugs has been receiving more and more attention in many fields such as pharmacy, medicine and biology, etc. In this paper, we will review the research progress of CYP450 in tumors and anticancer-targeted drugs.

2. Dual Role of CYP450 in Tumor Development

Human CYP450 consists of at least 57 genes and 58 pseudogenes, which are categorized into 18 families and 43 subfamilies in the kidney, small intestine and liver [5] [6]. Of the 57 isoenzymes identified to date, six are responsible for 90% of drug metabolism: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 [7]. Different isoenzymes affect different metabolic profiles and thus play a pro- or anti-tumorigenic role in tumor development.

2.1. The Pro-Cancer Role of CYP450

The ability of the CYP450 family of enzymes to convert a wide range of environmental pro-carcinogens into active final carcinogens is one of the key mechanisms of their pro-carcinogenic effects [8]. CYP450 (especially the CYP1, 2, and 3 families) converts environmental carcinogens into electrophilic reactive intermediates, leading to the formation of DNA adducts and gene mutations. In addition to the direct conversion of procarcinogens, redox products produced by CYP450 enzymes during metabolism may also be carcinogenic. For example, CYP1A1, CYP1A2, and CYP1B1 convert estradiol to catechol estrogens, which subsequently generate semiquinones that are carcinogenic and form toxic proteins and DNA polymers that lead to cancer progression and thus promote breast and ovarian cancer, whereas CYP17A1 and CYP11A1 play key roles in the synthesis of testosterone, which is converted to 5α-Dihydrotestosterone and the continuous activation and mutation of androgen receptor are closely related to the development of metastatic chemoresistant prostate cancer (CRPC) [9]. CYP2W1 catalyzes the synthesis of prostaglandin E2, which is elevated in the tumor microenvironment, and activates the relevant signaling pathways by binding to prostaglandin E receptor, promoting tumor cell cycle progression, inhibiting apoptosis, and exerting a protumor proliferative effect [10].

CYP450 enzymes are also able to promote cancer by affecting intracellular sig-

naling pathways. For example, reactive oxygen species (ROS) produced by CYP2E1 when metabolizing ethanol can activate the p38/MAPK and ERK1/2 signaling pathways to promote hepatocellular carcinoma. The genes of CYP450 enzymes are polymorphic, and the genetic polymorphisms of CYP1A1, CYP1A2, CYP1B1, and CYP2E1 lead to inter-individual differences in the enzyme activity, which in turn affects its role in cancer development and progression, increasing the risk of numerous cancers [8]. CYP2E1 is also involved in the metabolic activation of carcinogens and has an important role in the regulation of hepatocellular carcinoma cell proliferation, apoptosis, and chemotherapeutic drug sensitivity [11]. The CYP2S1 gene, also in the CYP2 subfamily, has also been shown to be highly expressed in lung and thyroid cancers, and both animal and cellular experiments have demonstrated that knockdown of CYP2S1 significantly inhibits the proliferation, invasion, and migration abilities of lung and thyroid cancer cells, and suppresses lung and thyroid cancer progression [12] [13].

Some CYP enzymes are able to influence cell proliferation and apoptosis by regulating intracellular signaling, such as CYP2C9, whose expression is increased in breast cancer cells, promotes proliferation and inhibits apoptosis by regulating the expression of cell cycle-related proteins, on the other hand, the EETs produced by CYP450 in the metabolism of fatty acids can induce the proliferation and angiogenesis of tumor cells by altering the cellular microenvironment thereby promoting tumor growth and metastasis [14].

CYP450 enzymes are also capable of interacting with other tumor-associated molecules and participating in tumor progression. For example, CYP1A1 is able to interact with the aromatic hydrocarbon receptor (AhR) to activate downstream signaling pathways and promote tumor cell proliferation and invasion [15]. In conclusion, CYP450 exhibits pro-oncogenic effects in a variety of tumors, and the study of its pro-oncogenic mechanism may provide new ideas for the targeted therapy of certain tumors.

2.2. The Anti-Cancer Effects of CYP450

CYP450 can regulate endogenous oncogenic signals to achieve tumor inhibition. It has been shown that CYP4B1 expression is significantly down-regulated in adrenocortical tumors, and its inhibition is an early event in tumorigenesis [16]. CYP450 monooxygenase system generates reactive oxygen species (ROS) during metabolism, and moderate ROS can regulate cellular signaling pathways, but excessive ROS can lead to cellular oxidative stress damage, and even trigger apoptosis, which can have an inhibitory effect on cancer cells [17]. Inhibition Reactive oxygen species generation is a major mechanism of CYP450 in anticancer, and the accumulation of ROS can inhibit EGF/EGF-R, thus blocking ERK and PI3K/Akt/NF-κB signaling pathways and inhibiting cancer cell proliferation. ROS can also inhibit cell proliferation by decreasing the phosphorylation of JAK1/2 and Src, blocking the phosphorylation of STAT3/STAT5 and down-regulates the expression of cell cycle proteins D1, B1, E, CDK2 and CDK4, leading to cell cycle arrest,

and similarly activates p53 and triggers p21, which inhibits most CDKs, ultimately leading to cell cycle arrest. Accumulation of ROS also induces DNA damage and activates PARP, leading to a decrease in NAD+, which inactivates GAPDH and inhibits glycolysis, ultimately leading to ATP depletion and triggering energetics. This leads to ATP depletion and triggers an energy crisis, thus inhibiting cancer cell proliferation. It is by affecting the intracellular redox state that CYP450 influences the proliferation, differentiation and apoptosis of tumor cells, as well as their invasive and metastatic abilities [18].

CYP450 enzymes may exert anticancer effects by affecting the expression of certain oncogenes. For example, enzymes such as CYP1A1, CYP1B1 and CYP3A4 can, under certain circumstances, affect the expression of the p53 gene, which is an important oncogene capable of inducing cell cycle arrest and apoptosis, thereby inhibiting tumorigenesis [19]-[21]. CYP450 metabolites may interact with certain transcription factors, altering their activities and thus regulating processes related to cell growth CYP450 metabolites (e.g., oxidized lipids) may feedback regulate the activity of Nrf2, forming a metabolic-transcriptional interplay network, which upregulates the expression of detoxification enzymes upon activation of Nrf2 and inhibits oxidative damage and proliferation of tumor cells [22].

It has been found [23] that CYP3A5 specifically inhibits the phosphorylation of the Ser473 site of AKT by blocking mTORC2 kinase activity and can inhibit the AKT signaling pathway and upregulate the expression of the metalloproteinase inhibitors TIMP1 and TIMP2, which directly inhibits the activity of matrix metalloproteinase 2/9 (MMP2/9), a key enzyme in the degradation of the fine MMP2/9 is a key enzyme in the degradation of extracellular matrix, and its reduced activity inhibits tumor cell invasion and metastasis. Jaehyeon Kang *et al.* found [24] that CYP1A1 inhibits tumor proliferation by ω-hydroxylation of polyunsaturated fatty acids, generating lipid signaling molecules (e.g., HETEs), interfering with the formation of the cyclin D-CDK4/6 complex, and ultimately blocking cell cycle progression. In colon cancer, knockdown of CYP2S1 was found to increase the level of endogenous prostaglandin E2 (PGE2), which reduces the phosphorylation of β-catenin and activates β-catenin signaling, and ultimately promotes the proliferation of colon cancer cells, so CYP2S1 may play a role in cancer inhibition in colon cancer [25].

In summary, whether the same CYP450 isoenzyme acts as an "accomplice" or a "traitor" in a specific tissue depends on the combination threshold of tissue type, substrate profile, and reactive oxygen species (ROS) levels: In estrogen-rich tissues such as the breast or ovaries, CYP1A1/1B1 converts estradiol into carcinogenic catechol estrogens and DNA adducts, exhibiting pro-carcinogenic effects. However, when ROS levels are excessively high or the substrate is ω-3 polyunsaturated fatty acids, these enzymes instead catalyze lipid-derived HETEs and activate the p53, Nrf2 pathways, inducing cell cycle arrest or even apoptosis, exhibiting anti-carcinogenic effects. Similarly, CYP2S1 promotes PGE_2 synthesis and proliferation when highly expressed in lung cancer; however, in colorectal cancer, insufficient substrates or elevated ROS levels instead inhibit β-catenin signaling, exerting

anti-carcinogenic effects. In summary, high ROS levels, anti-carcinogenic substrates, or specific tissue microenvironments can reverse the "camp" of CYP450. As such, CYP450 plays a dual role in tumorigenesis and progression. Investigating its mechanisms of promoting or inhibiting tumor progression in specific cancers may provide new directions for treatment strategies.

3. Progress of CYP450 in Tumor Therapy

Tumor chemotherapy is the use of chemical drugs to kill tumor cells in order to achieve therapeutic purposes. The mode of administration is mainly through oral or intravenous injection into the body. However, even in groups of patients with the same treatment regimen, inter-individual drug metabolizing ability and therapeutic response can still show large differences. Therefore, it is important to investigate the pharmacodynamic and pharmacokinetic properties of chemotherapeutic drugs, and CYP450 enzymes play a key role in drug metabolism, both in the activation and in the inactivation of drugs. The current research direction is to investigate the expression level of CYP450 enzyme and the effect of gene polymorphisms on tumor therapy, aiming to provide some new perspectives for individualized antitumor chemotherapeutic drug delivery regimens.

3.1. The Role of CYP450 in Drug Metabolism

The CYP450 enzyme family plays an irreplaceable and critical role in drug metabolism, which makes it extremely important in the field of tumor therapy. Different CYP450 enzymes metabolize different types of drugs, such as CYP3A4, which can metabolize a variety of drugs, including the anticancer drugs doxorubicin and vincristine. Specifically, CYP3A4, which is abundantly expressed in the liver, is one of the most important drug-metabolizing enzymes in the body and is involved in the metabolism of many anticancer drugs. Studies have shown that CYP3A4 can metabolize doxorubicin into active metabolites, which can inhibit DNA synthesis and repair in tumor cells, thus exerting antitumor effects [26]; while for vincristine, CYP3A4 is involved in its oxidative metabolism, which affects the pharmacokinetics of the drug *in vivo*, and then influences the efficacy and toxicity of the drug [27]. The activity of CYP3A4 is not static and is affected by a variety of factors, including genetic factors, environmental factors, and other drugs. When the activity of CYP3A4 changes, it will directly affect the metabolism rate and degree of the above anticancer drugs. If the activity of CYP3A4 is enhanced, it may lead to accelerated metabolism of the drug in the body, making the concentration of the drug in the blood circulation decrease, thus affecting its therapeutic effect [28].

3.2. Correlation between CYP450 Expression Level and Tumor Chemotherapy Resistance

Modern molecular biology research has confirmed that cytochrome P450 (CYP450) plays a key role in the metabolic clearance and biotransformation of most antitumor drugs; at the same time, its overexpression and genetic polymorphism are

also closely related to the formation of resistance to tumor chemotherapy. After antitumor drugs are metabolized by CYP450 enzymes, their prototypes or metabolites can be recognized and bound by transmembrane efflux pumps such as P-glycoprotein (P-gp). This process relies on ATP hydrolysis for energy supply and actively pumps the drug out of the cell, leading to a significant decrease in the intracellular accumulation of active drug, thus weakening the antitumor effect and inducing drug resistance [29] [30]. It has been found that inhibition of CYP1B1 expression can reverse cisplatin resistance in triple-negative breast cancer cells, CYP3A4 as a key metabolizing enzyme dominates the inactivation metabolism of vincristine, and CYP3A5 gene polymorphisms may affect the drug concentration through an indirect pathway, and in osteosarcoma, especially the high expression of CYP3A4/CYP3A5 in metastatic foci leads to local concentration reduction of vincristine by accelerating the inactivation of the drug. decrease in the local concentration of vincristine, which in turn induces therapeutic resistance [31]-[33].

Ulrich M Zanger *et al*. found [34] that CYP450 enzymes can inactivate some anticancer drugs. For example, the high expression of CYP3A4 and CYP2C8 enzymes in breast cancer tissues metabolizes chemotherapeutic drugs, such as paclitaxel, into inactive forms, decreasing the effective concentration of the drug in the cells and leading to increased resistance of tumor cells to paclitaxel. CYP450 enzymes are involved in the activation process of anticancer drugs. Take cyclophosphamide as an example, it needs to be catalyzed by CYP2B6 for 4-hydroxylation to generate the active metabolite 4-hydroxycyclophosphamide (4-OH-CY), which is finally converted into the cytotoxic phosphoramidonium nitrogen mustard to exert antitumor effects. If the expression level of CYP2B6 in tumor tissues is low, the activation of cyclophosphamide is insufficient, which affects the therapeutic effect; while a high expression level may lead to premature inactivation of the drug, which also reduces the therapeutic effect. Meanwhile, CYP2B6 also plays a secondary role in tamoxifen metabolism, and its variation may indirectly lead to therapeutic failure or differences in efficacy by affecting the degree of tamoxifen activation, but the mechanism is not yet fully cleared, and needs to be evaluated in combination with comprehensive assessment of polymorphic enzyme genotypes [35].

CYP2S1, as a newly discovered member of the CYP450 family, also plays an important role in tumor progression and therapy.CYP2S1 (as well as CYP2W1) can efficiently reduce AQ4N（an effective topoisomerase II inhibitor） to the active metabolite AQ4 under hypoxic conditions. When the expression level of CYP2S1 is too high in tumors, the reductive metabolism of AQ4N is significantly advanced, which leads to its depletion or loss of AQ4N in the region of normoxia or close to it. When CYP2S1 is expressed at a high level in tumors, the reduced metabolism of AQ4N will be significantly advanced, which will be consumed or inactivated at the normal oxygen partial pressure or near the normoxic region, resulting in the inability of the drug to reach the hypoxic target area, which will weaken the therapeutic effect and may induce drug resistance [36].

4. Pharmacogenetics of CYP450

The CYP450 gene is highly polymorphic, and its variations play an important role in tumor risk and treatment. Differences in CYP450 genotypes in different individuals may lead to different rates of drug metabolism, which in turn affects drug efficacy and adverse effects.

Polymorphisms in the CYP2D6 gene affect its metabolism of a variety of anticancer drugs, such as Tamoxifen. Patients with CYP2D6 hypermetabolic genes have accelerated metabolism of Tamoxifen, resulting in decreased production of active metabolites, which reduces the efficacy of the drug; whereas patients with intermediate or slow metabolism are metabolized slower, and the active metabolite stays in the body for a longer period of time, which may increase the risk of adverse reactions [37]. The latest guidelines recommend a dosage of 20 mg/day for CYP2D6 normal metabolizers (NM), intermediate metabolizers (IM) may consider increasing the dose to 30 mg/day or switching to an aromatase inhibitor (AI), poor metabolizers (PM) should avoid Tamoxifen and instead use AI or other treatment options, and ultra-rapid metabolizers (UM) are recommended to use the standard dose of 20 mg/day, but should be vigilant for insufficient efficacy [38]. It has been found that breast cancer patients with the CYP1B1*3 (L432V) allele tend to produce relatively fewer allergic reactions when treated with paclitaxel-based drugs, which may be brought about by the metabolism of paclitaxel to 4-hydroxyestradiol paclitaxel by CYP1B1*3, which inhibits the toxicity of paclitaxel-based drugs [39]. CYP2C9 gene polymorphisms are associated with head and neck cancer susceptibility and therapeutic outcome, its 3 allele functions poorly, and patients carrying this gene have slower metabolism of cyclophosphamide during chemotherapy, which may affect therapeutic efficacy [40]. CYP2C19 gene polymorphism affects the clearance of cyclophosphamide and tumor response to chemotherapy, and individuals carrying CYP2C192 and CYP2B6*5 have a significantly lower clearance of cyclophosphamide, and therapeutic efficacy is and poorer efficacy [41]. It has been found that CYP2A6 mutation alters the activity of CYP2A6, a heparanase, in which 5-fluorouracil blood concentration is lower in mutant gastric cancer patients compared with wild-type gastric cancer patients, which ultimately leads to a decrease in the efficacy of their chemotherapy as well [42]. It has also been found that the TT genotype has significantly increased both transcriptional and enzymatic activities compared to the CYP2E1 AA and AT genotypes [43].

Currently, by taking the expression level of CYP450 and the impact of polymorphisms of the gene in tumor chemotherapy as a research direction, understanding the CYP450 genotype of patients can help to predict their metabolism rate and therapeutic response to specific chemotherapeutic drugs, so as to realize personalized drug administration, improve the effect of chemotherapy, and reduce the adverse effects.

5. CYP450 Targeting Therapy

Because of the effect of CYP450 expression on tumors, the development of small

molecule inhibitors of CYP450 against tumors has gradually entered people's vision. For example, Q11-1-(4-methyl-5-thiazolyl)vinyl ketone inhibits the expression of CYP2E1, thus reducing the generation of ROS, blocking the activation of IL-6/STAT3 and MAPK pathway, down-regulating pro-inflammatory factors, such as TGF-β, IL-10 and other pro-inflammatory factors, and ultimately to achieve the effect of inhibiting the growth of tumors [44]. A recent study showed [45] that double-stranded RNA adenosine deaminase acting on the activation of RNA 1 (ADAR1) can cause the editing of adenosine (A) to inosine (I) at position 4885 of the CYP1A1 gene, resulting in the mutation of amino acid at position 462 in the coding region from isoleucine (I) to valine (V) (I462V), activation of the PI3K/Akt pathway, induction of heme oxygenase-1 (HO-1) high expression, which resists oxidative stress, and also directly inhibits the natural immune response, leading to progression and drug resistance in non-small cell lung cancer (NSCLC). Inhibition of ADAR1 activity by small molecule inhibitors, siRNA or protein hydrolysis-targeted chimeric (PROTAC) degraders can block the above processes, resulting in tumor suppression and providing a new paradigm for precision treatment of lung cancer. In addition, in hepatocellular carcinoma, the use of targeted siRNA can degrade CYP2E1 mRNA, selectively inhibit the expression of pro-carcinogenic phenotypes, and block its mediated ROS-dependent apoptosis resistance pathway, thereby inhibiting the progression of hepatocellular carcinoma [46].

A study using metabolomics found [47] that epoxy fatty acid (EpFA)-like arachidonic acid metabolites produced by cytochrome P450 monooxygenase were increased in plasma and colon of azomethine* alkane (AOM)/dextran sodium sulfate-induced colon cancer mice and that CYP monooxygenase was overexpressed in colon tumor tissues and colon cancer cells, and furthermore, the production of epoxy fatty acid (EpFA)-like arachidonic acid metabolites by cytochrome P450 monooxygenase from In addition, treatment with 12,13-epoxyoctadecadienoic acid (EpOME) produced from linoleic acid by CYP monooxygenase increased cytokine production and JNK phosphorylation in vitro and exacerbated AOM/DSS-induced colon tumorigenesis *in vivo*. Therefore, the inhibition of AOM/DSS-induced colon tumorigenesis in mice by pharmacological inhibition or genetic knockdown of CYP monooxygenase is expected to be a new target for the prevention or treatment of colon cancer. CYP4A expression is up-regulated in tumor-associated macrophages (TAMs) such as the present one, and it is strongly associated with metastasis, premetastasis formation, and poor prognosis in breast cancer patients. 20-HETE (20-hydroxyeicosatetraenoic acid) catalyzed by CYP4A regulates the expression of M2-type macrophage-derived factors (e.g., TGF-β, VEGF, and SDF-1), which may initiate the microenvironment at future metastatic sites. initiating the microenvironment of future metastatic sites and promoting metastasis. In contrast, HET0016, a CYP4A inhibitor, inhibited pre-metastatic foci formation by decreasing the recruitment and cluster formation of VEGFR1+ myeloid cells and was able to inhibit the expression of metastasis-promoting pro-

teins, such as MMP-9, S100A8 and fibronectin, in the pre-metastatic lungs. Meanwhile, CYP4A/20-HETE-STAT3 signaling plays a crucial role in TAMs for lung pre-metastatic foci formation and metastasis, and when CYP4A is inhibited, p-STAT3 levels are also reduced, which in turn reduces M2 marker expression and VEGFR1+ myeloid cell migration [48].

In ovarian cancer, pro-carcinogenic CYP enzymes (e.g., CYP1B1, CYP4Z1, CYP2J2) drive tumor progression through activation of carcinogens (e.g., polycyclic aromatic hydrocarbons (Polycyclic Aromatic Hydrocarbons，PAHs), metabolism of estrogens, and production of pro-angiogenic factors (e.g., vascular endothelial growth factor，VEGF) or pro-proliferative lipid mediators (e.g., epoxyeicosatrienoic acids, EETs), and have been associated with chemoresistance and poor prognosis. And its targeting strategies are mainly divided into two categories: first, direct inhibition of enzyme activity through small molecule inhibitors (e.g., DMU135 targeting CYP1B1, Tanshinone IIA targeting CYP2J2) to block tumor growth signals; meanwhile, inhibition of CYP4Z1 reduces angiogenesis and metastasis, and second, the use of tumors with high expression of CYP enzymes (e.g., CYP1A1/1B1, CYP4B1) to activate non-toxic prodrugs (e.g., ICT2700, AQ4N, 4-IPO) to release DNA damaging agents or topoisomerase inhibitors in cancer cells to achieve precision killing. In addition, targeting CYP-mediated resistance mechanisms (e.g., CYP3A4/5 causing paclitaxel resistance) can be reversed by combining with enzyme inhibitors (e.g., ketoconazole) or genetic polymorphism-guided dose adjustments. These strategies provide new avenues for tumor-selective intervention in ovarian cancer by targeting inhibition of pro-oncogenic metabolism, activation of selective cytotoxicity, and overcoming drug resistance [49]. Murray *et al.* found that letrozole, a synthetic benzyltriazole derivative, has significantly more inhibitory activity against CYP19 compared to the first-generation inhibitor amiloride. Its key advantage is its high specificity: it does not affect the synthesized levels of glucocorticoids, salocorticoids or thyroid function in the body, even when applied for a long period of time. In addition, letrozole does not inhibit adrenal corticosteroid secretion at high doses. Therefore, letrozole exhibits a high therapeutic index and is undoubtedly a successful case of targeting CYP450 to develop antitumor drugs [50].

CYP2J2 promotes cell cycle progression by metabolizing arachidonic acid to generate EETs and activating multiple pro-cancer pathways, such as PI3K/Akt, JNK, AMPK, and EGFR phosphorylation, or inhibits caspase-3 activity and reduces apoptosis, whereas C26 blocks pathways such as PI3K/Akt and EGFR by inhibiting the generation of EETs, and at the same time, up-regulates pro-apoptotic C26 plays a therapeutic role by inhibiting the generation of EETs, blocking the PI3K/Akt pathway and EGFR, and upregulating pro-apoptotic proteins (such as Bax/Bcl-2 ratio) to induce caspase-3 activation. C26 specifically inhibits CYP2J2 enzyme activity and has no significant effect on other CYP450 isoforms, reducing the risk of off-target toxicity. In animal experiments, C26 can significantly inhibit tumor growth when administered orally, which has a good basis for drug success

[51]. All these suggest the potential advantages of CYP450 as an anti-tumor targeted therapy.

6. Challenges and Prospects for Clinical Translation of Targeted CYPs

6.1. Challenges

Targeted CYP inhibitors have shown preliminary efficacy in clinical settings. For example, non-steroidal triazole-based aromatase inhibitors such as letrozole are used in the treatment of hormone-sensitive breast cancer, while CYP17 inhibitors like abiraterone have demonstrated promising results in Phase II clinical trials for prostate cancer. siRNA therapy for age-related macular degeneration (AMD) and diabetic macular edema (DME) have all received positive feedback in clinical trials. However, these therapies also face numerous challenges [52] [53]. As mentioned earlier, the same CYP isoform plays a dual role of cancer-promoting or cancer-suppressing in different tumors, e.g., CYP1A1 plays a cancer-promoting role in non-small-cell lung cancer, but in breast cancer, it induces cell-cycle blockade and pro-apoptotic factor expression and inhibits tumor growth. Its metabolites may be oncogenic or chemoprotective due to differences in the tissue microenvironment, leading to opposite efficacy of a single inhibitor in different tumors. Therefore, the contradiction of its dual function makes it necessary for clinicians to be more careful in treatment selection.

Meanwhile, the composition of gut microbes and dietary structure also have an impact on CYP activity due to individualized differences. The metabolism of dietary components (e.g., soybean saponins) by the flora can generate bioactive substances (e.g., soybean saponin B), activate the pregnane X receptor (PXR), induce hepatic CYP3A expression, and significantly alter the efficiency of drug metabolism [54]. One mouse experiment confirmed [55] that different strains of intestinal flora (e.g., Clostridium sensu stricto 1) were strongly positively correlated with CYP3A activity, with individual CYP activity differences up to 10-fold or more. Dietary aspects of CYP expression can also be affected by eating foods that inhibit CYP or foods that induce CYP in people with different dietary habits. For example, ethanol induces CYP2A5 expression through the CYP2E1-ROS-Nrf2 signaling axis, confirming that CYP2E1 is a key source of reactive oxygen species (ROS) generation in alcohol metabolism, and heavy coffee intake induces CYP1A2 activity, and the effect is significantly correlated with genetic polymorphisms, with a stronger induction effect in those carrying the A allele [56] [57].

In targeted therapy, there are also problems such as drug delivery barriers. First, naked siRNAs have a short half-life in serum and are rapidly degraded by A-type nucleases that are widely present in plasma, making them less stable [58]. Second, only a few siRNAs escape lysosomal degradation and are poorly permeable to tumor tissues (impeded by high interstitial pressure), so their targeting efficiency is low [59]. Third, although CYP450 plays a key role in metabolizing xenobiotics and anticancer drugs, facing off-target effects limits its benefits [60].

6.2. Solution Strategies and Prospects

The above problems can be complemented by combination therapies, such as the combination of CYP inhibitors plus immune checkpoint inhibitors.PD-1 antibodies (e.g., nabulizumab) in combination with chemotherapy significantly prolonged the median survival in NSCLC with a reduction in treatment-related adverse effects [61]. Or as mentioned previously, CYP inhibitors (e.g., Q11) can reverse the tumor immunosuppressive microenvironment and enhance PD-1 antibody efficacy. Inhibitors targeting CYP1A1 (e.g., *α*-naphthoflavone) combined with immunotherapy inhibited tumor growth in animal models.

Individualized differences allow for individualized dosing. Fecal mushroom transplantation (FMT) restores immunotherapeutic efficacy by transplanting colonies from PD-1 antibody responders to non-responders, and Akkermansia muciniphila in particular plays a key role through the IL-12-dependent pathway [62]. The CYP1A1*2A/*2C polymorphisms increase the risk of lung cancer (particularly pronounced in smokers), and carriers are advised to limit red meat/ barbecue intake (to reduce PAH exposure) or adjust tamoxifen dose based on CYP2D6 metabolic phenotype (fast/slow metabolizer) for CYP gene polymorphisms plus dietary intervention to address individualized differences [63] [64].

Novel delivery systems, technological breakthroughs in nanocarriers have provided new ideas for the problem of delivery barriers. For example, the use of lipid nanoparticles (LNP) for siRNA drug delivery has significantly improved stability [65]. The metal-organic framework (MOF) ZIF-8 nanoparticles dissociated in acidic tumor microenvironment and promoted lysosomal escape through the "proton sponge effect" to reduce the degradation of siRNA [66]. Although the technology of CYP-targeted therapy is still not fully mature, many studies have demonstrated its significance as a therapeutic target, suggesting the potential advantages of CYP450 as an anti-tumor target therapy.

In conclusion, the central position of CYP450 as a "metabolic switch" in tumor therapy is beyond doubt, and in the future, bifunctional CYP modulators can be further developed to solve the contradiction of its dual regulation in tumors. In the future, bifunctional CYP modulators can be further developed to solve the contradiction of its dual regulation in tumor. It can also be combined with microbiome, metabolome and CYP gene profile to construct personalized drug model.

7. Conclusion

CYP450, as an extremely important enzyme in phase I metabolism, is involved in the biotransformation of various drugs and exogenous carcinogens, and its function is closely related to tumor development and treatment strategies. The expression level and genetic polymorphism of CYP450 gene can significantly affect the enzyme activity, which will lead to the individual differences in the response to chemotherapy. Because of its characteristics, CYP450 has become a new target for precision therapy, however, tissue-specific expression, genetic polymorphisms and differences in intestinal flora lead to heterogeneity in therapeutic efficacy.

Nano-delivery and combined immunotherapy are expected to break through the bottleneck, and in the future, integration of gene-metabolism-microecology data to achieve individualized CYP450 regulation will promote its development from the laboratory to the clinical practice of precision oncology.

Authors' Contributions

Junhua-Ming: Writing-original draft, Visualization. Qing Zhang edited the manuscript. All authors reviewed the manuscript.

Conflicts of Interest

The authors declare no competing interests.

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