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Potential role of CYP1B1 in the development and treatment of metabolic diseases

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ABSTRACT

Cytochrome P450 1B1 (CYP1B1), a member of CYP superfamily, is expressed in liver and extrahepatic tissues carries out the metabolism of numerous xenobiotics, including metabolic activation of polycyclic aromatic hydrocarbons. Surprisingly, CYP1B1 was also shown to be important in regulating endogenous metabolic pathways, including the metabolism of steroid hormones, fatty acids, melatonin, and vitamins. CYP1B1 and nuclear receptors including peroxisome proliferator-activated receptors (PPARs), estrogen receptor (ER), and retinoic acid receptors (RAR) contribute to the maintenance of the homeostasis of these endogenous compounds. Many natural flavonoids and synthetic stilbenes show inhibitory activity toward CYP1B1 expression and function, notably isorhamnetin and 2,4,3′,5′-tetramethoxystilbene. Accumulating evidence indicates that modulation of CYP1B1 can decrease adipogenesis and tumorigenesis, and prevent obesity, hypertension, atherosclerosis, and cancer. Therefore, it may be feasible to consider CYP1B1 as a therapeutic target for the treatment of metabolic diseases.
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1. Introduction

Cytochrome P450 1B1 (CYP1B1) is a heme-thiolate monooxygenase involved in NADPH-dependent phase I metabolism of a variety of xenobiotics. In 1991, a novel cytochrome P-450 (P450EF) that is induced by benzo[α]anthracene and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was purified from C3H10T1/2 mouse embryo fibroblasts (Pottenger, Christou, & Jefcoate, 1991). P450EF was subsequently identified as a new member of CYP1B subfamily (Savas, Bhattacharyya, Christou, Alexander, & Jefcoate, 1994). In the same year, the cDNA sequence of

Abbreviations: AA, Arachidonic acid; AHR, aryl hydrocarbon receptor; Ang II, angiotensin II; B[*a*]P, benzo[*a*]pyrene; CYP, Cytochrome P450; DB[*a,l*]P, dibenzo[*a,l*]pyrene; EETs, epoxyeicosatrienoic acids; ER, estrogen receptor; HETE, hydroxyeicosatetraenoic acids; HFD, high-fat diet; IOP, intraocular pressure; LPC, lysophosphatidylcholine; PCG, primary congenital glaucoma; POAG, primary open-angle glaucoma; PPAR, peroxisome proliferator-activated receptor; RAR, retinoic acid receptor; RCC, renal cell cancer; ROS, reactive oxygen species; Scd1, stearoyl CoA desaturase 1; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TMS, 2,4,3′,5′-Tetramethoxystilbene; Tyr, tyrosinase.

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human CYP1B1 was cloned from primary cultures of normal human epidermal keratinocytes (Sutter et al., 1994). In contrast to two other CYP1 family enzymes, CYP1A1 and CYP1A2, CYP1B1 is expressed in a variety of tumor tissues. Oral benzo[a]pyrene (B[*a*]P)-treated *Cyp1a1/1a2/1b1*(−/−) mice showed the same the "rescued" response as that seen in the *Cyp1a1/1b1*(−/−) mouse, whereas *Cyp1a1*(−/−) mice ingesting B[*a*]P died due to severe immunosuppression (Dragin et al., 2008), suggesting that the CYP1B1 is necessary in immune tissues. In this study, it was also observed that the phenotype of oral B[*a*]P-treated *Cyp1a1/1a2/1b1*(−/−) mice was similar to that of the BaP-treated wild-type and the corn oil-treated control mice, whereas there was substantial bone marrow hypocellularity in oral B[*a*]P-treated *Cyp1a1*(−/−) and *Cyp1a1/1a2*(−/−) mice. These studies suggest that inhibition of CYP1B1 expression may contribute to the protection against bone marrow hypocellularity. An early study revealed that CYP1B1 was expressed in 122 of 127 tumor tissues, including brain, breast, and colon tumors (Murray et al., 1997). The higher expression of CYP1B1 in tumor cells than the surrounding normal tissue has led to much interest on the role of CYP1B1 in tumorigenesis and its treatment.

The human CYP1B1 gene spanning 12 kb in length and located on chromosome region 2p21–22, consists of 3 exons and 2 introns (Tang et al., 1996). Human CYP1B1 shows approximately 40% homology with CYP1A1 and CYP1A2, but its gene structure is simpler. The mRNA is 4.2 kb and its open reading frame begins at the second intron of 5′ end, coding a 543 amino acids residues protein (Murray, Melvin, Greenlee, & Burke, 2001). Several positive and negative regulators exist in the promoter region of the human CYP1B1 gene, but it is structurally different from the genes encoding CYP1A1 and CYP1A2 (Murray et al., 2001; Wo, Stewart, & Greenlee, 1997). CYP1B1 is involved in the metabolism of a wide variety of xenobiotics, such as ethoxyresorufin, theophylline and caffeine, and shows some overlapping metabolic activities with CYP1A1 and CYP1A2. Unlike most CYPs, CYP1B1 expression is not detected in human liver, but CYP1B1 is expressed in many extrahepatic tissues, including lung, colon, eye and kidney. CYP1B1 shows activity toward activation of environmental carcinogens via the hydroxylation of procacinogens, including 27 polycyclic aromatic hydrocarbons and their derivatives, 17 heterocyclic and aryl amine and aminoazo dyes, 3 mycotoxins, 2 nitroaromatic hydrocarbons (Shimada et al., 1996). Consistent with its role in carcinogen activation, carcinogenesis is reduced in *Cyp1b1*-null mice (Buters et al., 1999), suggesting that CYP1B1 plays an important role in metabolic activation of environmental carcinogens.

The expression of CYP1B1 can be induced by xenobiotics such as TCDD, through the aryl hydrocarbon receptor (AHR) (Hankinson, 2016). In addition to the oxidation of xenobiotics, CYP1B1 is involved in the metabolism of many important physiological compounds, including estrogen, arachidonic acid, melatonin and retinoids. A recent study revealed that *Cyp1b1* disruption altered the expression of 560 liver genes, including suppression of peroxisome proliferator-activated receptor γ (PPARγ) and many genes regulated by PPARα (Larsen et al., 2015). PPARs are a group of nuclear receptor that regulates the expression of many down-stream genes, and plays a key role in the homeostasis of lipids and glucose, closely related to metabolic diseases. Metabolic diseases are associated with the disorder of endogenous metabolism, ranging from obesity and atherosclerosis to hypertension and cancer. In terms of obesity, its incidence has been dramatically increased worldwide in recent years. It is estimated that >1/3 of adults and nearly 17% of children in the United States are obese. In 2008, the cost for obesity-related medical diseases was an estimated $147 billion. Some studies have shown that *Cyp1b1* disruption can protect against obesity induced by high-fat diet (HFD) (Larsen et al., 2015; Li et al., 2014). Previous reviews have discussed the role of CYP1B1 in glaucoma (Vasiliou & Gonzalez, 2008). In this review, recent findings are summarized on the impact of CYP1B1 in the regulation of metabolic pathways and the development of metabolic diseases, and the potential therapy for the treatment of metabolic diseases using CYP1B1 modulators are discussed.

2. Discovery of CYP1B1 inhibitors

CYP1B1 is highly expressed in a wide of variety of cancers, such as prostate, uterus, and colon cancer. CYP1B1 is involved in the metabolic activation of many environmental procarcinogens. Mutant *CYP1B1* alleles were detected in cancer and glaucoma patients. These findings suggest that the regulation of CYP1B1 expression could act as a therapeutic strategy, especially for cancer treatment. To date, >50 natural products and synthetic compounds have been developed or identified as CYP1B1 inhibitors (Table 1). Stilbene, flavonoids, coumarin, and anthraquinone are the four major types of compounds that inhibit CYP1B1 activity (Fig. 1). 2,4,3′,5′-Tetramethoxystilbene (TMS), a methoxy derivative resveratrol, is a highly potent and selective inhibitor of CYP1B1. Its inhibitory ability for CYP1B1 (IC_{50} = 6 nM) is over 50-fold greater than against CYP1A1 (IC_{50} = 300 nM) and 500-fold higher than for CYP1A2 (IC_{50} = 3000 nM) (Chun, Kim, et al., 2001). It was reported that TMS can protect against chemically-induced and genetic hypertension. Natural flavonoids are an important source of CYP1B1 inhibitors. Methoxy types of flavones and flavonols were shown to selectively inhibit CYP1B1 activity, such as chrysoeriol and isorhamnetin. The synthetic α-naphthoflavone is a strong inhibitor of CYP1B1 (IC_{50} = 5 nM) and CYP1A2 (IC_{50} = 6 nM), compared to CYP1A1 (IC_{50} = 60 nM) (Shimada et al., 1998). More recently, a potent inhibitor of CYP1B1 (IC_{50} = 0.043 nM) was synthesized from α-naphthoflavone, and its water-soluble derivative can eliminate the resistance of docetaxel in MCF-7/1B1 cells (Cui et al., 2015). Several flavonoids from St. John's wort also show inhibitory activity on CYP1B1, including quercetin, rutin, apigenin, and amentoflavone (Chaudhary & Willett, 2006). Some CYP1B1 inhibitors, such as kaempferol and isorhamnetin, can also antagonize the expression of AHR (Rajaraman, Yang, Chen, & Chang, 2009), which lead to inhibition of the expression of CYP1B1. Thus, the inhibitory activity of CYP1B1 in mouse studies is difficult to interpret for both CYP1B1 inhibitors and AHR antagonists. Interestingly, some anticancer agents widely used in clinic are competitive inhibitors of CYP1B1, such as flutamide (IC_{50} = 1.0 μM), paclitaxel (IC_{50} = 31.6 μM), mitoxantrone (IC_{50} = 11.6 μM), and docetaxel (IC_{50} = 28.0 μM) (Rochat, Morsman, Murray, Figg, & McLeod, 2001). CYP1B1 inhibitors can be used to dissect CYP1B1 function and might be considered as therapeutic agents for the treatment of certain diseases as noted below.

3. Transgenic mouse models to determine the biological functions of CYP1B1

In 1999, a *Cyp1b1* knockout mouse line was generated to determine the role of CYP1B1 in the metabolic activation of 7,12-dimethylbenz[*a*]anthracene (DMBA) (Buters et al., 1999). It was noted that 70% of wild-type mice developed highly malignant lymphomas after administration with DMBA, whereas only 7.5% of *Cyp1b1*-null mice had lymphomas. *Cyp1b1* disruption also reduced the tumorigenesis-induced by other procarcinogens, including benzo[*a*]pyrene (B[*a*]P) (Uno et al., 2006) and dibenzo[*a*,*l*]pyrene (DB[*a*,*l*]P) (Buters et al., 2002). These studies demonstrated that CYP1B1 plays a key role in the metabolic activation of environmental procarcinogens. The role of CYP1B1 in primary congenital glaucoma (PCG) was also determined using *Cyp1b1*-null mice on a mixed 129 × 1/SvJ × C57BL/6 J background. The results showed that CYP1B1 deficiency damaged the ocular drainage structure and increased intraocular pressure (IOP), similar to the injury in human PCG patients (Libby et al., 2003). Recently, *Cyp1b1*-null mice on a pure C57BL/6 J background were used to determine the effects of CYP1B1 on hypertension and obesity. To better understand the biological functions of CYP1B1, *CYP1B1*-humanized mice were created through the insertion of the complete native human CYP1B1 gene into the *Cyp1b1*-null mice genome. When fed with a high-fat diet (HFD), the weight gain in *CYP1B1*-humanized mice was similar to wild-type mice, which were higher than *Cyp1b1*-null mice (Li et al., 2014). *CYP1B1*-humanized showed a similar response to the HFD as the wild-type mouse.