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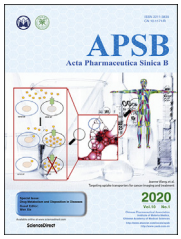

REVIEW

New insights of CYP1A in endogenous metabolism: a focus on single nucleotide polymorphisms and diseases

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Abstract Cytochrome P450 1A (CYP1A), one of the major CYP subfamily in humans, not only metabolizes xenobiotics including clinical drugs and pollutants in the environment, but also mediates the biotransformation of important endogenous substances. In particular, some single nucleotide polymorphisms (SNPs) for *CYP1A* genes may affect the metabolic ability of endogenous substances, leading to some physiological or pathological changes in humans. This review first summarizes the metabolism of endogenous substances by CYP1A, and then introduces the research progress of *CYP1A* SNPs, especially the research related to human diseases. Finally, the relationship between SNPs and diseases is discussed. In addition, potential animal models for *CYP1A* gene editing are summarized. In conclusion, CYP1A plays an important role in maintaining the health in the body.

Abbreviations: CYP, cytochrome P450; EOAs, *cis*-epoxyoctadecenoics; FSH, follicle stimulating hormone; HODEs, hydroxyoctadecdienoic acids; IQ, 2-amino-3-methylimidazo [4,5-*f*] quinoline; KO, knockout; LIF/STAT3, inhibiting leukemia inhibitory factor/signal transducer and activator of transcription 3; PhIP, 2-amino-1-methyl-6-phenylimidazo [4,5-*b*] pyridine; SNPs, single nucleotide polymorphisms; *t*-RA, all-*trans*-retinoic acid; *t*-ROH, all-*trans*-retinol; WT, wild type.

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1. Introduction

The cytochrome P450 (CYP) enzyme is one of the most abundant and diverse superfamilies, which contains hemoprotein[1]. From prokaryotes to eukaryotes, from plants to animals, from non-human primates to humans, thousands of *CYP* genes have been identified and named[2]. They are mainly involved in the biotransformation of many compounds, leading to a luxuriant world of molecules, including antibiotics in bacteria, ergosterols in fungi, petal pigments in plants, and even human drugs[1,3]. For the decomposition of clinical drugs, human CYP enzymes belong to the Phase I drug metabolizing enzymes[4]. Among the human CYP isoforms, CYP1A is an important subfamily involved in the metabolism of drugs, environmental pollutants and physiological substances[4−6].

CYP1A subfamily contains only two functional genes, *CYP1A1* and *CYP1A2*, which are highly conserved among species[7]. In humans, these two *CYP1A* members are located on chromosome 15 q24.1 in a head-to-head manner[8]. Phylogenetic analysis of *CYP1A* gene shows that the *CYP1A2* gene may rise from *CYP1A1* and they have a common 5′-flanking region, which has been proved to contain bidirectional regulators both for *CYP1A1* and *CYP1A2*[9,10]. Although the transcriptional regulation of *CYP1A1* and *1A2* may be simultaneously controlled by bidirectional gene elements, their expression patterns are different. For example, CYP1A2 is constitutively and specifically expressed in the liver, while CYP1A1 is mainly expressed outside the liver[11,12].

CYP1A-catalyzed reactions include hydroxylation and oxidation of aromatic compounds, in which CYP1A1 is mainly involved in the metabolism of aromatic hydrocarbon, while CYP1A2 prefers aromatic amines and heterocyclic compounds[8]. CYP1A as one of most important phase I drug metabolic enzymes participates in the biotransformation of about 9% of clinical drugs such as analgesics, antipyretics, antipsychotics, antidepressants, and anti-inflammatory drugs[8,13]. In addition to drugs, CYP1A is also involved in the biological activation or deactivation of a large number of pollutants in the environment, such as benzopyrene, aristolochic acid I, ellipticine, PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) and IQ (2-amino-3-methylimidazo [4,5-*f*]quinoline)[14−18]. More importantly, CYP1A is an important contributor to the biotransformation of many endogenous substances, including melatonin[19], retinol[20], linoleic acid[21,22], phosphatidylcholine[23], uroporphyrinogen[24], pregnenolone and progesterone[25,26], estradiol and estrone[27,28], dehydroepiandrosterone and testosterone[25,26].

The role of CYP1A in the metabolism of exogenous substances (drugs and pollutants) has been well evaluated[29]. However, little progress has been made in CYP1A-mediated endogenous metabolism in recent years. Therefore, this article reviews the endogenous substance metabolism mediated by CYP1A, especially the relationship between CYP1A and human diseases.

2. Endogenous substrate metabolism mediated by CYP1A

CYP1A mainly metabolizes sex hormones (including progestogens, androgens, and estrogens), retinol, melatonin, linoleic acid, phosphatidylcholine, and uroporphyrinogen in humans (Table 1). The reaction types of CYP1A include hydroxylation, demethylation, epoxidation, oxidation, and quinol formation.

2.1. *Progestogens: pregnenolone and progesterone*

Progestogens are a set of steroid hormones that bind and activate the progesterone receptor[30]. Progestogens are essential for maintaining pregnancy, estrogen, and menstrual cycles. Progestogens metabolized by CYP1A include pregnenolone and progesterone.

2.1.1. *Pregnenolone*

As an endogenous steroid hormone, pregnenolone is the precursor of steroid hormone transformation, including androgen, estrogen, progestogen, mineralocorticoid, and glucocorticoid[31]. Pregnenolone is also a metabolite of cholesterol *in vivo*, which is catalyzed by cholesterol side-chain cleavage enzyme[32,33]. Compared with CYP1A2, CYP1A1 is the main isoform mediating the biotransformation of pregnenolone (Fig. 1). Previous studies have shown that CYP1A1 is the dominating enzyme and catalyzes the β-hydroxylation of pregnenolone at the C-7 site, with the K_m of 3.2−4.1 μmol/L and CL_{int} of 117−135 pmol/min/nmol[34]. Moreover, the CYP1A1, which involves 7-hydroxylated steroids, may contribute to the activation of immune defense[34]. Furthermore, CYP1A1 also hydroxylates pregnenolone to form 16α- and 17α-hydroxylated pregnenolone[26].

2.1.2. *Progesterone*

Progesterone is an important endogenous steroid and progestogen produced in the ovary, placenta, and adrenal gland[35]. It plays an important role in embryogenesis and pregnancy with different mechanisms[36], including maternal immune response regulation[37], inflammation inhibition[38], reduction of uterine contractility[39], improvement of uterine−placental circulation, and luteal phase support[40,41]. In addition, progesterone plays a crucial role in the physiological function of the brain by producing other endogenous steroids, such as neurosteroid[42]. Progesterone deficiency may lead to premenstrual syndrome in 5% of women in the first two weeks of the menstrual cycle[43]. Progesterone therapy can improve symptoms and reduce the damage of progesterone deficiency to brain and electrolyte balance by regulating menstrual hormone levels[43]. However, excessive progesterone treatment affected implantation and decidualization in mice by inhibiting leukemia inhibitory factor/signal transducer and activator of transcription 3 (LIF/STAT3) pathway and endoplasmic reticulum stress[44]. From the above statement, maintaining the homeostasis of progesterone is very meaningful for normal physiological function.

Like other steroid hormones, pregnenolone synthesized from cholesterol is the precursor of progesterone in mammals[45]. Progesterone is mainly metabolized in the liver, accounting for about 2/3 of all metabolic reactions. Glucuronic acid then binds to metabolites to promote kidney excretion[45]. Although progesterone is mainly converted to pregnanediol, direct hydroxylation of progesterone mediated by CYP is also involved[25,26,45]. For example, CYP1A1 shows high hydroxylase activity of progesterone, which results in the formation of 6β-hydroxyl and 16α-

Table 1 Endogenous substrates metabolized by CYP1A.

Category	Substance	Enzyme	Reaction
Sex hormone	Pregnenolone	CYP1A1	16α/17α/7β-Hydroxylation
	Progesterone	CYP1A1	16α/6β-Hydroxylation
		CYP1A2	6β-Hydroxylation
	Estrone	CYP1A1	Quinol formation
		CYP1A2	2/4/16α-Hydroxylation
	Estradiol	CYP1A1	Quinol formation
			2/4/6α/15α-Hydroxylation
		CYP1A2	2/4/16-Hydroxylation
	Estradiol-3-methyl ether	CYP1A1	*O*-Demethylation
		CYP1A2	*O*-Demethylation
			2-Hydroxylation
	Testosterone	CYP1A2	6β-Hydroxylation
Amine hormone	Melatonin	CYP1A1	6-Hydroxylation
		CYP1A2	6-Hydroxylation
			O-Demethylation
Vitamin	*t*-ROH	CYP1A1/2	Oxidation
	t-RAL	CYP1A1/2	Oxidation
Fatty acid	Linoleic acid	CYP1A2	9,10/12,13-Epoxidation
			13-Hydroxylation
Porphyrinogen	Uroporphyrinogen	CYP1A2	Oxidation
Phospholipid	Phosphatidylcholine	CYP1A2	Hydrolysis

/, the different molecular site of metabolic reaction.

hydroxyl progesterone (Fig. 1), with the V_{max} at 16.4 and 7.7 pmol/min/pmol P450, respectively[25]. In contrast, CYP1A2 is more likely to mediate hydroxylation at the C-6 site (Fig. 1), resulting in the formation of 6β-hydroxyl progesterone[26].

2.2. *Estrogens: estrone and estradiol*

Estrogen is the most basic sex hormone for women. It promotes the development of female reproductive system and helps to form secondary sexual characteristics[46]. Estrone, estradiol, and estriol are the three main endogenous estrogens in women, with estrogenic hormone activity[46]. Estrogens metabolized by CYP1A include estrone and estradiol.

2.2.1. *Estrone*

Estrone is a weak female hormone, mainly converted from cholesterol in the gonads[47]. As an estrogen receptors agonist, estrone exhibits less activity than estradiol[48,49]. However, estrone, as a precursor, can be metabolized to estradiol[47]. Sulfotransferases and glucuronidases conjugate estrone into estrogen conjugates,

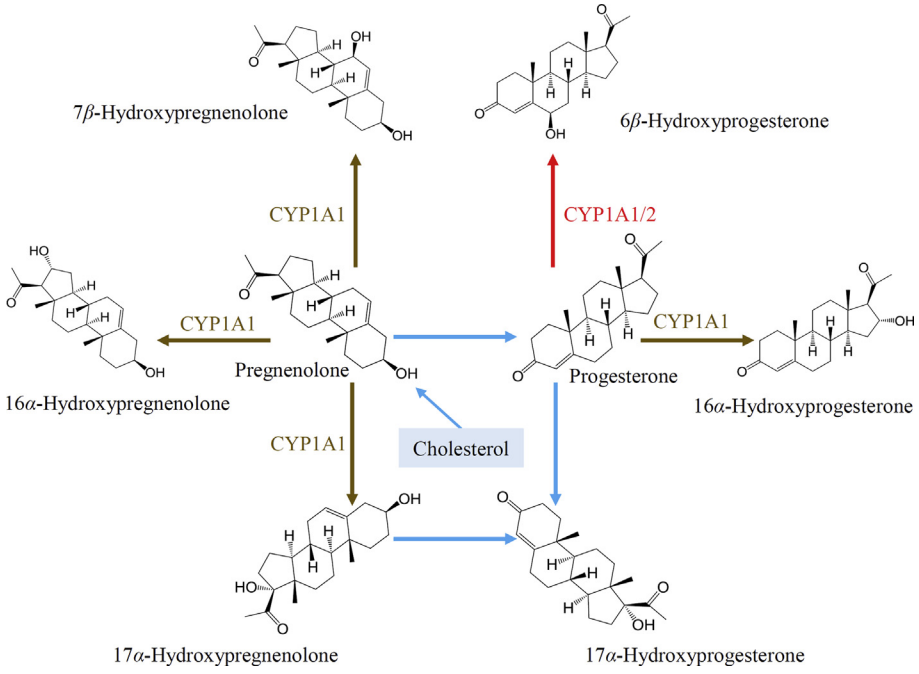

Figure 1 CYP1A-mediated metabolism of progestogens.

and some CYP isoforms also hydroxylate it into catechol estrogens or estriol[47]. Both CYP1A1 and CYP1A2 are involved in the biotransformation of estrone, but they mediate different reaction types (Fig. 2). CYP1A2 is thought to be involved in estrone metabolism by direct hydrolysis of C-2, C-4, and C-16 sites[50,51]. In contrast, CYP1A1 oxidizes estrone to quinol at the C-10 position[28].

2.2.2. *Estradiol*

Estradiol is the main sex hormone in women. It plays an important role in regulating estrous cycle, menstrual cycle, and female secondary sexual features. Estradiol also plays an important role in skin, liver, fat, and bone[52]. Estradiol is converted into the less potent estrogens to be inactivated and hydroxylated into catechol estrogens through CYP enzymes.

CYP1A metabolizes estradiol at multiple sites. CYP1A1 is the main isoform mediating the hydroxylation of estradiol at different sites (Fig. 2A). The hydroxylation of estradiol at C-2 and C-4 is the main metabolic pathway. CYP1A1 mediates the hydroxylation of estradiol at a relatively low K_m of 2.9 and 2.7 μmol/L, respectively[53]. The V_{max} of CYP1A1 at C-2 and C-4 are 14.7 and 0.4 nmol/min/nmol P450, respectively, which indicates the main production of 2-hydroxylation estradiol compared with 4-hydroxylation estradiol[53,54]. Moreover, CYP1A1 also hydroxylates estradiol at C-6 and C-15, and forms α-hydroxylated estradiol at corresponding sites[55]. In addition to participating in the hydroxylation of estradiol, CYP1A1 is also involved in the quinol formation, with the product of 10β,17β-dihydroxy-1,4-estradiene-3-one[28]. Compared with CYP1A1, CYP1A2 contributes to the hydroxylation of estradiol at C-2 and C-4 with a lower V_{max}[50,53,56] (Fig. 2A). CYP1A2 also participates in the hydroxylation of estradiol at C-16, while the C-2 hydroxylation estradiol is a dominant hydroxylated metabolite catalyzed by CYP1A2[51,53] (Fig. 2A).

Estradiol can be converted from estradiol 3-methyl ether. CYP1A1 and CYP1A2 metabolize estradiol 3-methyl ether to estradiol through 3-demethylation reaction with the V_{max} of 0.07 and 0.02 pmol/min/pmol P450, respectively[57] (Fig. 2B). CYP1A2 also hydroxylates estradiol 3-methyl ether at C-2 to increase its hydrophilicity, which may contribute to its excretion from the body[58].

2.3. *Androgens: testosterone*

Testosterone, the main sex hormone in men, regulates the development of male reproductive tissue and contributes to the second sexual characteristics of men[59]. Testosterone is mainly metabolized in the liver. In addition to the conjugation pathway and 17-ketosteroid pathway, hydroxylation and oxidation of hepatic CYP enzymes are additional pathways for testosterone metabolism[60]. CYP1A1 hydroxylates testosterone to produce 6β-hydroxyl testosterone, with the K_m and V_{max} at 10.1 μmol/L and 14.8 pmol/min/pmol P450, respectively[25].

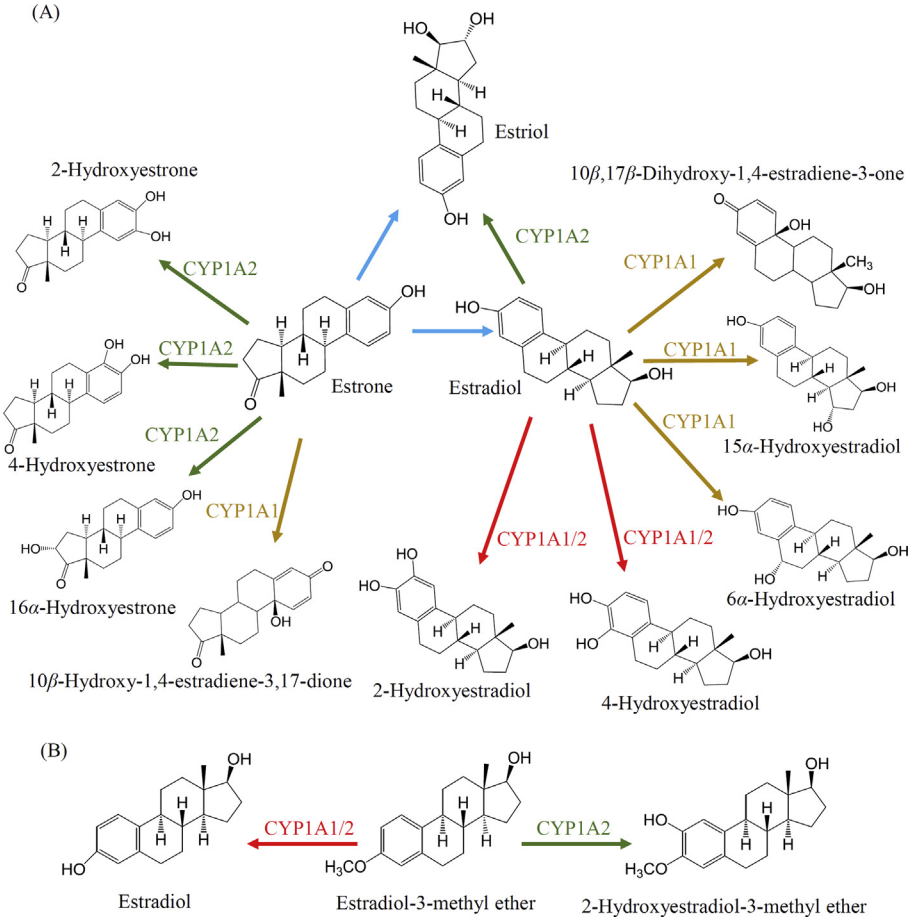

Figure 2 CYP1A-mediated metabolism of estrogens and estradiol 3-methyl ether. (A) CYP1A-mediated metabolism of estrogens. (B) CYP1A-mediated metabolism of estradiol 3-methyl ether.

2.4. *Nonsteroidal substances: melatonin, retinol, linoleic acid, phosphatidylcholine, and uroporphyrinogen*

2.4.1. *Melatonin*

Melatonin is a hormone that is released from pineal gland, and regulates the sleep-wake cycle[61]. It has been used as a supplement for the treatment of insomnia[62]. As a metabolite of tryptophan pathway, melatonin can be further hydroxylated to hydroxymelatonin[19]. CYP1A1 and CYP1A2 both catalyze melatonin to form 6-hydroxymelatonin, and CYP1A2 is the primary isoform, which promotes this biotransformation[19,63] (Fig. 3A). In addition, CYP1A2 catalyzes the *O*-demethylation of melatonin to produce *N*-acetylserotonin[63] (Fig. 3A). In recent ten years, a new metabolite of melatonin has been reported, named melatonin metabolite VII, which is also a metabolite mediated by CYP1A2[64].

2.4.2. *Retinol*

All-*trans*-retinoic acid (*t*-RA), which is a metabolite of all-*trans*-retinol (*t*-ROH), triggers a variety of signaling pathways by binding to the nuclear receptor of retinoic acid. Its activated signal transduction pathway participates in many biological and pharmacological activities of retinoids in human body[20,65,66]. The oxidation of *t*-ROH to *t*-RA is mainly achieved by two dehydrogenation reactions. The first reaction, *t*-ROH to *t*-RAL, is called rate-limiting step[20]. Compared with other CYP isoforms, CYP1A1 and CYP1A2 exhibited retinol dehydrogenase activity with a relative low K_m (8 μmol/L for CYP1A1 and 9 μmol/L for CYP1A2) and high V_{max} (507 pmol/min/nmol CYP for CYP1A1 and 491 pmol/min/nmol CYP for CYP1A2)[20] (Fig. 3B). At the same time, CYP1A1 and CYP1A2 also showed high activity of retinal dehydrogenase, forming the functional metabolite *t*-RA[20] (Fig. 3B). These studies indicate that CYP1A1 and CYP1A2 are two major enzymes for human *t*-ROH to form *t*-RA, compared with other CYP isoforms.

2.4.3. *Linoleic acid*

Linoleic acid is an omega-6 polyunsaturated fatty acid that can only be absorbed from the diet because the human body cannot synthesize it. As linoleic acid is the precursor of arachidonic acid biosynthesis, it contributes to the physiological level of prostaglandins, leukotrienes, and thromboxane (metabolites of arachidonic acid). Linoleic acid is metabolized by a variety of enzymes, including CYP, lipoxygenase, and cyclooxygenase. In particular, CYP1A2 converts linoleic acid into hydroxyoctadecdienoic acids (HODEs) and *cis*-epoxyoctadecenoics (EOAs) (Fig. 3C) with comparable catalytic activity[22].

2.4.4. *Phosphatidylcholines*

Phosphatidylcholines are a group of phospholipids and essential elements of biological membranes. CYP1A2 possesses an unusual catalytic activity similar to phospholipase D-type hydrolysis enzymes. Based on the metabolic activity, CYP1A2 converts phosphatidylcholine to choline and phosphatidic acid[23,67,68] (Fig. 4A). This may imply the important physiological role of CYP1A2, because as a signal transduction messenger, phosphatidic acid plays a key role in regulating cell activity[67].

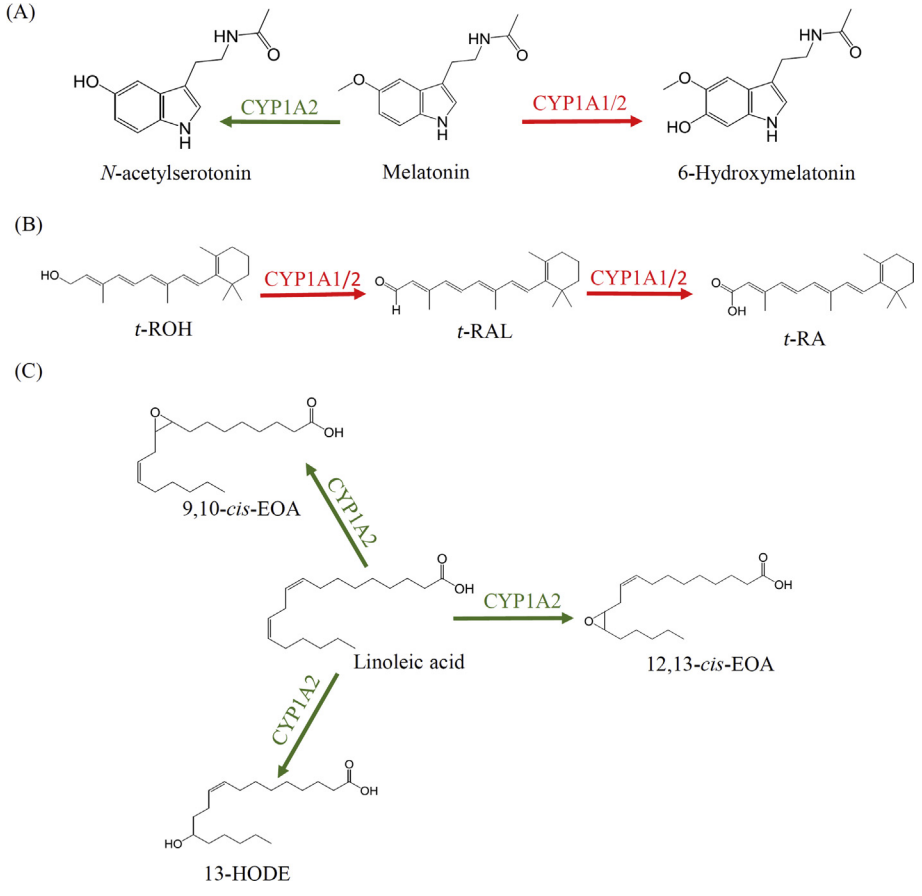

Figure 3 CYP1A-mediated metabolism of melatonin (A), *t*-RAL (B) and linoleic acid (C). *t*-ROH, all-*trans*-retinol; *t*-RAL, all-*trans*-retinal; *t*-RA, all-*trans*-retinoic acid; EOA, *cis*-epoxyoctadecenoic; HODE, hydroxyoctadecdienoic acid.

2.4.5. *Uroporphyrinogen*

Uroporphyrinogen, a macrocyclic compound surrounded by four pyrrole rings, is a metabolite in the synthesis of heme. Previous studies have also found that human CYP1A2 catalyzes the oxidation of uroporphyrinogen[24,69] (Fig. 4B).

2.5. *Summary*

CYP1A metabolizes a series of endogenous substances and determines their metabolic pathway and conversion rate. However, most of these metabolic results come from *in vitro* studies. In order to further understand the physiological function of CYP1A, it is necessary to explore the important role of CYP1A in the metabolism of these endogenous substances *in vivo*. In particular, CYP1A knockout or humanized animal models are helpful to reveal the role of CYP1A in endogenous metabolism *in vivo*.

Although the role of CYP1A in the transformation of endogenous substances has attracted more and more attention, few physiological substrates have been found in recent years. In particular, *CYP1A1* or *CYP1A2* mutations are reported to be associated with many human diseases, suggesting that CYP1A may affect these diseases by regulating the formation or metabolism of some endogenous mediators. Therefore, more mature techniques are needed to find the potential physiological substrates of CYP1A. Metabolomics combined with *Cyp1a* gene editing animal models is a good method to study the metabolism of endogenous substances and their physiological functions of CYP1A.

3. Single nucleotide polymorphisms (SNPs) of CYP1A and diseases

3.1. *General information on CYP1A polymorphisms*

The difference of CYP1A expression among individuals was reported, and the variation of CYP1A activity in drug metabolism was also observed[13,70,71]. These differences may be partly attributed to the genetic diversity of *CYP1A*, which is named single nucleotide polymorphisms (SNPs). SNPs refer to the polymorphism of DNA sequence caused by single nucleotide variation at the genomic level. They account for almost 80% of human genetic variation, and are also the key factor leading to CYP1A variation among individuals[72]. At the Pharmacogene Variation Consortium (https://www.pharmvar.org/), there are 27 and 48 SNPs for human *CYP1A1* and *CYP1A2*, respectively, of which 14 and 40 variants have been identified. Through these changes, the metabolic capacity of CYP1A may change, and ultimately affect the metabolism of many clinical drugs, carcinogens, and endogenous substances.

CYP1A is known for its metabolism of certain substances, especially sex hormones. Changes in CYP1A metabolic capacity may lead to hormone imbalance, thereby altering sensitivity to certain diseases. In this section, we will focus on the relationship between single nucleotide changes in *CYP1A1/2* and human diseases. Literatures in the past ten years (2010−2019) were reviewed and retrieved with "cyp1a1 polymorphism" and "cyp1a2 polymorphism" respectively in "PubMed" (https://www.ncbi.nlm.nih.gov/pubmed/). Table 2 summarizes the evidence of the association between *CYP1A* polymorphism and human diseases over the past decade. Eleven SNPs of *CYP1A1* in human diseases such as chronic obstructive pulmonary disease, male infertility, and various cancers were collected. Among these SNPs, rs4646903 and rs1048943 are two widely studied mutations (Table 2).

*CYP1A1*2A* (SNP ID: rs4646903), also known as *MspI*, has T−C mutation at 3801. *CYP1A1*2A* is reported to be positively correlated with the risk or incidence of a series of cancers, including esophageal, oral, laryngeal, prostate, cervical, bladder, and lung cancers (Table 2). *CYP1A1*2A* is also associated with some hormone-related diseases due to its involvement in the biotransformation of sex hormones. For example, *CYP1A1*2A* increases the risk of prostate cancer, cervical cancer, and recurrent pregnancy loss in humans[78−80,85]. *CYP1A1*2C* (SNP ID: rs1048943) contains an A to G transition at 2455, which results in the modification of the protein from isoleucine to valine. *CYP1A1*2C* is reported to be associated with a variety of cancers and hormone-related diseases, including prostate cancer, breast cancer, and male infertility[93−95,100]. For *CYP1A2*, nine SNPs are found to be associated with human diseases, including hypertension, age-related macular degeneration, and some cancers (Table 2). Among them, rs762551 is one of the most studied

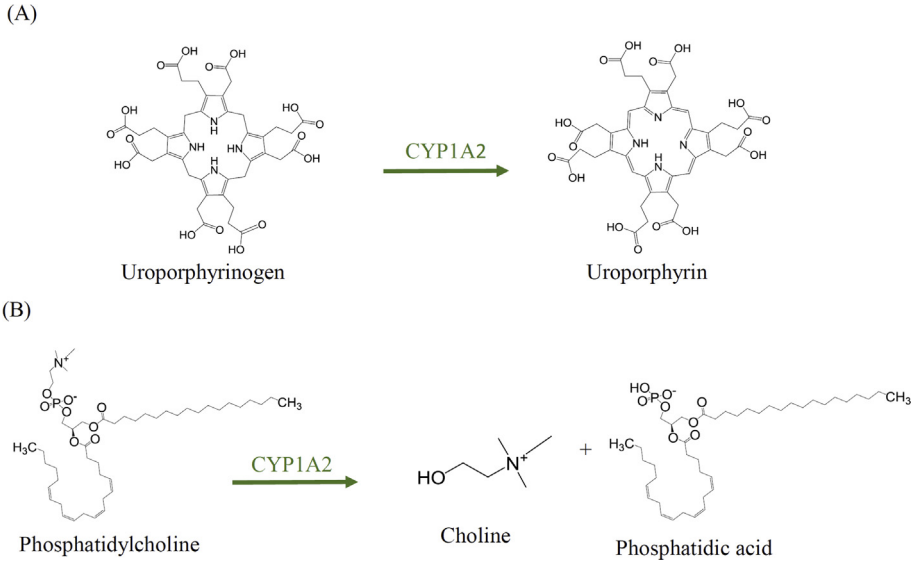

Figure 4 CYP1A-mediated metabolism of uroporphyrinogen (A) and phosphatidylcholine (B).

Table 2 Summary of *CYP1A* SNPs in 2010−2019.

Gene	SNPs	Disease	Cor.	Ref.
CYP1A1	rs4646903 (3801T > C)	Esophageal cancer	P	73
		Oral cancer risk	P	74,75
		Laryngeal cancer risk	P	76
		Colorectal cancer	N	77
		Prostate cancer	P	78
		Cervical cancer	P	79,80
		Bladder cancer	P	81
		Lung cancer	P	82,83
		Chronic obstructive pulmonary disease	P	84
		Recurrent pregnancy loss	P	85
		Coronary artery diseases	No	86
CYP1A1	rs1048943 (2455A > G)	Oral cancer risk	P	74,75
		Laryngeal cancer risk	P	76
		Esophageal cancer risk	P	87−91
		Colorectal cancer	P	92
		Lung cancer	P	82,166,167
		Prostate cancer	P	93,84
		Breast cancer	P	95,96−98
		Endometriosis	P	99
		Bladder cancer	P	81
		Male infertility	P	100
		Renal cancer	P	101
		Bone tumor susceptibility	P	102
		Adult leukemia	P	103
		Essential hypertension	P	104
		Chronic obstructive pulmonary disease	P	84
		Hypertension	P	104
		Coronary artery diseases	No	86
CYP1A1	*CYP1A1**4 (2453C > A)	Endometrial cancer	P	105
		Male infertility	P	100
CYP1A1	rs4646422,Gly45Asp	Gastric cancer	P	106
	4889A > G	Sporadic breast cancer	P	107
	6235T > C	Sporadic breast cancer	P	107
	11599G > C	Bladder cancer	P	81
	113T > C	Bladder cancer	P	81
	264T > C	Breast cancer	P	108
CYP1A1	rs4986883	Coronary artery diseases	No	86
CYP1A1	rs1799814	Coronary artery diseases	No	86
CYP1A2	rs2069514 (−3860G > A)	Colorectal cancer	N	109
		Breast cancer	N	110
		Breast cancer	N	111
		Mental disorders	No	112
CYP1A2	rs762551 (−163C > A)	Breast cancer	P	113
		Breast cancer	N	108
		Ovarian cancer	N	113
		Mammographic density	N	114
		Mammographic density	P	114
		Lung cancer	P	115−118
		Bladder cancer	N	115,119−121
		Bladder cancer risk	P	122
		Age-related macular degeneration	N	123
CYP1A2	rs762551 (−163C > A)	Hypertension	P	124
		Colorectal cancer	N	109
		Cholangiocarcinoma	P	125
		Hypertension	P	104,124
		Mental disorders	No	112
		Super-refractory schizophrenia	P	126
CYP1A2	164C > A	Infant birth size	N	127
	rs3569413	Lung cancer	P	117,128
	rs2470890	Lung cancer	P	129
	rs2472299	Lung cancer	P	129
	rs1378942	Hypertension	P	124
	rs1133323	Hypertension	P	124

Cor, correlation between SNPs and diseases; P, positively related; N, negatively related; No, not correlated; Ref, references.

mutants. *CYP1A2*1F* (SNP ID: rs762551) has a C to A mutation at -163, which may be related to breast cancer, ovarian cancer, mammographic density, and risk of infant birth size, because it is involved in the biological transformation of sex hormones[108,113,114,127].

3.2. Breast cancer

Breast cancer is one of the most common cancers among women worldwide[130]. In many breast cancer cases, hormone receptors, such as estrogen and progesterone receptors, have been diagnosed as overexpression, which is believed to contribute to the growth and proliferation of cancer cells[131,132]. Most breast cancer patients are hormone-dependent at the early stage, and excessive exposure to endogenous estrogen in women's life can promote the occurrence of breast cancer[133–135]. Previous studies have shown that the concentrations of some estrogens, especially 17β-estradiol, in plasma or tumor tissues of breast cancer patients increase, compared with those of normal breast tissue[133,136,137]. All these evidences suggest that hormone receptors and estrogens play an important role in the occurrence and development of breast cancer.

Estrogen has complex effects on breast cancer. One possible mechanism of estrogen carcinogenesis is that estrogen stimulates cell proliferation through estrogen receptors, and ultimately promotes the occurrence and development of cancer[138,139]. Another hypothetical carcinogenic mechanism is estrogen metabolites rather than estrogen activating in estrogen-induced cancer[140–142]. These hypotheses and evidence suggest that estrogen has a double-edged role in breast cancer, suggesting the importance of estrogen balance in women.

As mentioned earlier, CYP1A1 and CYP1A2 are involved in the biotransformation of multiple estrogens, and thus are important for maintaining the balance of estrogens (Fig. 2). CYP1A metabolizes a variety of estrogens, such as estrone, estradiol 3-methyl ether, estradiol, pregnenolone, and progesterone, through the hydroxylation of estrogens at different sites. Therefore, polymorphisms in *CYP1A* may affect the metabolic capacity of CYP1A and eventually destroy the balance of estrogen. In fact, some epidemiologic studies have reported the correlation between *CYP1A* SNPs and increased risk of breast cancer[95–98,108–111,113]. However, the metabolic network of sex hormone is complex. The effects of *CYP1A* SNPs on sex hormone metabolism and breast cancer need further study.

3.3. Prostate cancer

Prostate cancer is the most common cancer in men, especially in industrialized countries[143]. The association between prostate cancer and androgen was discovered long before androgen receptors were identified[144]. Prostate studies have found that testosterone therapy promotes prostate growth in experimental animals. In addition, prostate cancer can be eliminated by castration, which greatly reduces testosterone levels in men[145]. In androgen-dependent prostate cancer, androgen affects prostate cancer cells in a dose-dependent manner. Androgen promotes prostate cancer cells at low concentrations and inhibits prostate cancer cells at high levels[144]. Epidemiologic studies also discussed the relationship between *CYP1A1* polymorphisms and prostate cancer risk[146,147]. It was reported that *CYP1A1* SNPs (rs4646903 and rs1048943) were positively correlated with prostate cancer[78,93,94]. CYP1A1 hydroxylates testosterone at the C-6 site, which produces hydrophilic metabolites and promotes the excretion of testosterone[25]. Therefore, *CYP1A1* mutants may interfere with the normal physiological concentration of testosterone, and eventually lead to the occurrence and development of prostate cancer.

Interestingly, although prostate cancer is an androgen-related cancer, estrogen may also play an important role in its carcinogenicity[148–150]. This fact has attracted the attention of researchers because the increased risk of prostate cancer with age does not match the decrease in free testosterone levels in older men. In particular, an increased ratio of estradiol to testosterone was detected with age[148,151–154]. Estrogen receptor is usually detected in the prostate and decreases when canceration occurs, but it is usually retained, and the recurrence rate of prostate cancer is relatively high[149,155,156]. Moreover, animal experimental results show that excessive and inappropriate estrogen exposure can promote the occurrence of prostate diseases and tumors[157]. All these evidences suggest that estrogen receptors and estrogens are also essential for maintaining the biological function of the prostate, as well as for the occurrence and development of prostate cancer. In conclusion, androgen and estrogen play an important role in prostate cancer. CYP1A not only mediates the transformation network of androgen and estrogen, but also plays an important role in maintaining the balance between them. Therefore, *CYP1A* SNPs are associated with human prostate cancer[78,93,94].

3.4. Other sex hormone-related cancers

CYP1A SNPs are associated with other estrogen-related cancers, such as cervical cancer, endometrial cancer, and ovarian cancer[79,80,105,113]. Estrogen has been reported to stimulate the proliferation of cervical epithelial cells, thereby promoting the occurrence of tumors[158]. There is also evidence that the risk of endometrial cancer is positively correlated with estrogen levels in women[159]. In addition, estrogen, especially 17β-estradiol, promotes the growth and development of endometrial and ovarian cancer[160,161]. Therefore, CYP1A-mediated estrogen metabolism may affect the concentration of these hormones and their related metabolites in plasma or specific tissues, and these hormones and metabolites are further involved in the tumorigenesis of such human cancers.

3.5. Male infertility

Androgen is one of the important factors for male infertility. In particular, testosterone is the key hormone of spermatogenesis, which can inhibit the apoptosis of germ cells[162,163]. In addition, androgen deficiency affects the function of epididymis and ultimately inhibits sperm maturation[164]. Estrogen may be also a key substance in human male infertility. Not only the prostate, but also the testis is affected by estrogen. In fetal or neonatal period, excessive estrogen exposure can promote cryptorchidism, sperm malformation, and fertility impairment in male rodents[165]. In fact, *CYP1A1*4* (2453C > A) and rs1048943 (2455A > G) may interfere with the metabolism of testosterone and estrogen, and are reported to be positively correlated with male infertility[100]. A detailed summary of the past decade is also contained in Table 2.

3.6. Recurrent pregnancy loss

The proportion of women with increased follicle stimulating hormone (FSH) and 17β-estradiol in recurrent loss of pregnancy group is significantly higher than that in normal group[168]. Recent studies have shown that CYP1A1 may affect the biological function of placenta, which may be due to its estrogen metabolism[85,169]. In fact, it is reported that the *CYP1A1* SNP rs4646903 (3801T > C) is positively correlated with the risk of recurrent pregnancy loss in humans (Table 2). CYP1A affects both male and female reproductive system. Therefore, CYP1A-mediated metabolic disorders may lead to lower birth or survival rates.

3.7. Mental disorder

Melatonin is a hormone synthesized from the pineal gland in the brain[170]. It is involved in the regulation of circadian rhythm and the management of sleep cycle[171]. Melatonin is a key metabolite in the metabolic pathway of tryptophan[172]. Therefore, melatonin metabolic disorder may affect human emotional disorders or mental disorders[173,174]. However, the metabolic activity of *CYP1A2* SNP (rs2069514) was lower than that of wild type (WT). There was no significant correlation between *CYP1A2* SNP and mental disorders[112]. Similarly, another *CYP1A2* SNP (rs762551) showed no significant dependence on mental disorders with the increase of inducibility[112]. However, for super-refractory schizophrenia, the frequency of *CYP1A2* SNP (rs762551) in super-refractory group (87%) was significantly higher than that in refractory group (53.7%)[126]. Therefore, the role of *CYP1A2* SNP in mental disorders should be studied in more detail.

3.8. Retinol-related diseases

Retinol, also known as vitamin A, has many biological functions such as immunity, skin nutrition, reproductive ability, embryonic development and optesthesia[175]. Although neonatal survival is associated with CYP1A2 in *Cyp1a2* knockout (KO) mice, the relationship between retinol and reproductive diseases remains unclear[176].

3.9. Hypertension

Linoleic acid is an important precursor of a variety of n-6 polyunsaturated fatty acids. It has many functions according to its concentration in tissues. Linoleic acid metabolism is reported to be directly or indirectly associated with inflammation, atherosclerosis and other metabolic diseases[177,178]. Epidemiological analysis showed that genetic polymorphisms of the *CYP1A1* (rs4646903, rs1048943, rs4986883, and rs1799814) were not associated with the high risk of coronary artery disease[86]. However, *CYP1A1* SNP (rs1048943) and *CYP1A2* SNPs (rs762551, rs1133323, and rs1378942) are positively correlated with hypertension susceptibility[104,124]. This correlation may be due to the disorder of polyunsaturated fatty acid concentration in the population with these *CYP1A* SNPs.

3.10. Energy metabolism-related diseases

Phosphatidylcholine is one of the most abundant phospholipids in mammalian cell membranes. Although the important role of phospholipids in energy metabolism in humans and animals has been confirmed, there are no epidemiological studies on the relationship between CYP1A mononucleotides and energy metabolism-related diseases such as fatty liver[179].

3.11. Porphyria cutanea tarda

CYP1A2 is mainly responsible for the transformation of uroporphyrinogen to uroporphyrin. The accumulation of uroporphyrin in the liver may be a characteristic of human disease, called porphyria cutanea tarda[180]. Nonetheless, the association between *CYP1A2* SNPs and porphyria cutanea tarda remains uncertain.

3.12. Gene editing models for the relationship between CYP1A SNPs and diseases

With the development of genetic engineering technology, gene editing models have become an important tool for studying gene function. The understanding of CYP1A also benefits from this technology and gene editing animals. For example, as early as in 1995, Gonzalez and colleagues reported that neonatal deaths were observed in the *Cyp1a2* global KO mouse model, possibly due to respiratory distress caused by *Cyp1a2* deficiency[176]. *Cyp1a2* KO mice liver cDNA microarray analysis showed that *Cyp1a2* deficiency affected insulin function, lipogenesis, fatty acid biosynthesis and cholesterol biosynthesis[181]. Western diet and benzo[*a*]pyrene can induce fatty liver in *Cyp1a1* deficiency mice, but not in WT mice[182].

Although *Cyp1a* KO and humanized mouse models have been generated and applied to the functional study of CYP1A, new gene editing animal models still need to be developed. First, a tissue-specific KO animal model can be established. CYP1A is involved in the biotransformation of a large number of essential endogenous substances, which may affect biological functions of different tissues such as liver, lung and reproductive system. Therefore, the lack of CYP1A in specific tissues may help to illustrate its role in specific tissues or diseases. Second, time-specific KO animal models could be generated. CYP1A catalyzes the metabolism of different sex hormones, which may affect the biological function of the productive system, leading to abnormal embryonic development and postembryonic growth process. Therefore, *Cyp1a* deficiency may be helpful to reveal its role in the development of life at specific stages of embryonic development or individual growth. Third, *CYP1A* with specific SNPs can be introduced into animal models to explore the global effects of this mutation. Effects of SNPs on CYP1A activity can be detected through overexpression in cell lines. However, the global impact of SNPs on the whole body can only be tested through humanization of this mutant gene. Human *CYP1A* genes, with specific mutations, can be constructed *in vitro* and transferred into embryo to generate the humanized animal model with precise SNPs.

3.13. Summary

With the development of pharmacogenomics, more and more *CYP1A* SNPs have been discovered. *CYP1A* SNPs have attracted more attention in the application of human diseases, especially cancer. In this part, the SNPs of *CYP1A* (11 for *CYP1A1* and 9 for *CYP1A2*) studied most in recent 10 years are reviewed for the first time, and the relationship between

CYP1A SNPs and human diseases is summarized. Although many studies have reported the relationship between CYP1A and human diseases, the pathogenesis of CYP1A-mediated diseases remains unclear. In addition, the direct relationship between the disease and *CYP1A* mutation remains to be further explored. As mentioned above, emerging technologies such as metabonomics and gene editing may help to explain these scientific issues in detail.

4. Conclusions

CYP1A contributes significantly to the biotransformation of many endogenous substances, including melatonin, retinol, linoleic acid, phosphatidylcholine, uroporphyrinogen, pregnenolone and progesterone, estradiol and estrone, dehydroepiandrosterone and testosterone. *CYP1A* SNPs have been widely reported. Some of these SNPs may affect the metabolic ability of endogenous substances, especially some important sex hormones, such as progesterone, androgen and estrogen. Moreover, *CYP1A* mutations are associated with many diseases, including hormone-related cancers and reproductive diseases. In recent years, the gene editing technology, especially CRISPR/Cas9 system, has become a powerful tool for studying the biological function of a certain gene. The development and application of new *Cyp1a* edited animal models will benefit the understanding of CYP1A biological role and regulation function on the homeostasis, especially for the diagnosis and treatment of some diseases.

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Author contributions

Xin Wang was responsible for the conception and design of the review. Jian Lu, Xuyang Shang, Yuan Xu and Rong Shi collected literatures. Jian Lu, Xuyang Shang, Weiguo Zhong and Xin Wang analyzed literatures and summarized results. Jian Lu and Xuyang Shang drafted the manuscript. Xin Wang and Weiguo Zhong revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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