Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2012, Article ID 656428, 10 pages
doi:10.1155/2012/656428

Review Article

Peroxisome Proliferator-Activated Receptors in Regulation of Cytochromes P450: New Way to Overcome Multidrug Resistance?

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Received 12 June 2012; Revised 16 August 2012; Accepted 17 September 2012

Academic Editor: Soldano Ferrone

Embryonic and tumour cells are able to protect themselves against various harmful compounds. In human pathology, this phenomenon exists in the form of multidrug resistance (MDR) that significantly deteriorates success of anticancer treatment. Cytochromes P450 (CYPs) play one of the key roles in the xenobiotic metabolism. CYP expression could contribute to resistance of cancer cells to chemotherapy. CYP epoxygenases (CYP2C and CYP2J) metabolize about 20% of clinically important drugs. Besides of drug metabolism, CYP epoxygenases and their metabolites play important role in embryos, normal body function, and tumors. They participate in angiogenesis, mitogenesis, and cell signaling. It was found that CYP epoxygenases are affected by peroxisome proliferator-activated receptor α (PPARα). Based on the results of current studies, we assume that PPARs ligands may regulate CYP2C and CYP2J and in some extent they may contribute to overcoming of MDR in patients with different types of tumours.

1. Introduction

Embryonic stem cells are equipped with the multiple mechanisms to protect their integrity against potential mutagenic mechanisms associated with inflammation, infection, and dietary toxins. As well as embryo arise from embryonic stem cells, it is supposed that tumours arise from tumour stem cells [1]. Because of similarities between embryonic and tumour cells, it is well accepted that embryonic cells could be used as powerful tool to study natural mechanisms of cell protection. Thus, understanding of protection mechanisms of the cells may help overcome multidrug resistance (MDR) in different types of tumours.

As we described earlier [2], peroxisome proliferator-activated receptors (PPARs), especially PPARγ, may regulate expression of MDR pumps. It seems that PPARs affect not only the expression of ABC transporters but they also affect certain enzymes of phase I metabolism of xenobiotics.

PPARα and PPARγ ligands have been shown the long history of clinical use as hypolipidemic drugs or for treatment of diabetes [3, 4]. Thus, we suppose that these compounds may contribute to the safe regulation of MDR in cancer treatment.

2. Multidrug Resistance and Cytochromes P450

The resistance of cancer cells to chemotherapy is a serious problem in the treatment of patients with different types of tumours. The multidrug resistance is based on resistance of cancer cells to various substances diverging in structure and function. Resistance mechanisms which are utilized by tumour cell to resist cytotoxic drugs are probably developed in normal cell as protection mechanisms

Table 1: Summary of mechanisms of MDR [5, 6].

Mechanism of MDR	Description
Uptake transport of drug	Decreased expression of uptake transporters (reduced-folate transporters) and alternation in lipid metabolism modifying biophysical properties of the lipid bilayer influence drug uptake
Activation of detoxifying enzymes	Inactivation of drug by phase I and phase II enzymes
Drug sequestration	Drug can be trapped in subcellular organelles such as lysosomes and endosomes and then extruded from the cell
Avoiding to drug induced apoptosis	Occurs mostly via mitochondrial pathway; disruption of balance between pro-/antiapoptotic factors leads to survival of cancer cells
Enhanced DNA reparation	Cells with damaged DNA avoid to senescence, apoptosis, or necrosis
Overexpression of membrane transporters	Enhanced drug efflux by ABC transporters
Alternation in target molecules	DNA metylation, mutation of topoisomerases I and II
Microenvironment	Ph, hypoxia, population of quiescent cells
Altered signaling pathways	Block of apoptosis and expression of genes involved in DNA reparation and efflux pump

against environmental cancerogens [1]. Multidrug resistance includes more mechanisms [5, 6] (see Table 1).

2.1. Metabolism of Xenobiotics. Detoxification pathways metabolise a number of endogenous and exogenous molecules in three phases. Phase I reaction is catalyzed mainly by members of cytochrome P450 (CYP) superfamily that catalyze redox reactions. CYP-drug interaction leads to several results. These reactions result in detoxification (inactivation) in majority of cases. On the other hand, these enzymes can bioactivate several prodrugs to their active form. Unfortunately, the process can also activate certain harmful compounds (such as potential cancerogens) via transformation into electrophilic species. Both reversible and irreversible inhibitions of CYPs cause harmful drug-drug and drug-food interactions. Phase II of xenobiotic metabolism is a conjugation. Products of phase I are conjugated with molecules such as glutathione or glucuronic acid. During phase III, the conjugated molecule is effluxed out of a cell by specific transporters, especially ABC transporters [7, 8].

Cytochromes P450 (CYPs) are major enzymes in the phase I of the drug metabolism. They metabolise not only various xenobiotics but also a lot of endogenous substrates. Recently, 57 genes have been classified into 18 families and 44 subfamilies according to a degree of homology. Human genome contains also 58 pseudogenes [9]. CYPs are globular hemoproteins consisting of alpha and beta structures. Several of these secondary motifs are roughly coplanar to the prosthetic heme group. CYPs are localized in the mitochondria and the endoplasmic reticulum. Mitochondrial CYPs are involved in the metabolism of endogenous substrates whereas microsomal CYPs metabolise both endogenous and exogenous substrates. The enzymes primary act as monooxygenases. They incorporate one atom of molecular oxygen into the substrate and one into water. These reactions usually change hydrophobic molecule into the polar compound which increases their water solubility. The reaction requires a source of electrons. NADPH cytochrome P450 reductase in the endoplasmic reticulum and ferredoxin in the mitochondria serve as such a source [6, 7].

The presence of active cytochromes P450 in tumours could have negative impact on chemotherapy-mediated cell death because of deactivation of antineoplastic drugs. Cytochromes P450 responsible for the metabolism of xenobiotic are members of CYP1, CYP2, and CYP3 families. The most important group of enzymes are CYP3A, especially CYP3A4 [7]. Also members of CYP2 family have nonnegligible effect on the drug metabolism. CYP2C subfamily metabolizes about 20% of clinically important drugs [10]. Antineoplastic drugs which are substrates of CYP2C involve paclitaxel, bexarotene, cyclophosphamide, ifosfamide, imatinib mesylate, idarubicin, tamoxifen, and tretinoin [11]. CYP2J2 also participates in the drug metabolism [12].

On the other hand, different expression of CYPs between the tumour tissue and surrounding normal tissue has potential to be used for patient-specific therapy. It could be used for the development of prodrugs which are nontoxic to normal cells and are activated to the cytotoxic form only in tumours by specific CYP expressed in tumour cell. The preferential expression of certain CYP in tumour could serve as a target for cancer immunotherapy [13].

3. Cytochrome P450 Epoxygenases

Enzymes belonging to CYP2C and CYP2J subfamilies are epoxygenases. The human CYP2C subfamily is represented by four highly homologous genes: CYP2C8, 2C9, 2C18, and 2C19 located in an approximate 500-kb cluster on chromosome 10q24. The CYP2C subfamily represents about 18% of total adult liver cytochrome P450 content [10]. CYP2C are highly polymorphic. Human CYP2J2 is the only member of CYP2J subfamily. CYP2J2 constitutes about 1-2% of total cytochromes P450 content in liver. CYP2J2 gene is localized on the short arm on chromosome 1 in locus 1p32.1 [9].

Besides of participation in drug metabolism, epoxygenases have important endogenous function. They convert arachidonic acids to epoxyeicosatrienoic acids (EETs), namely

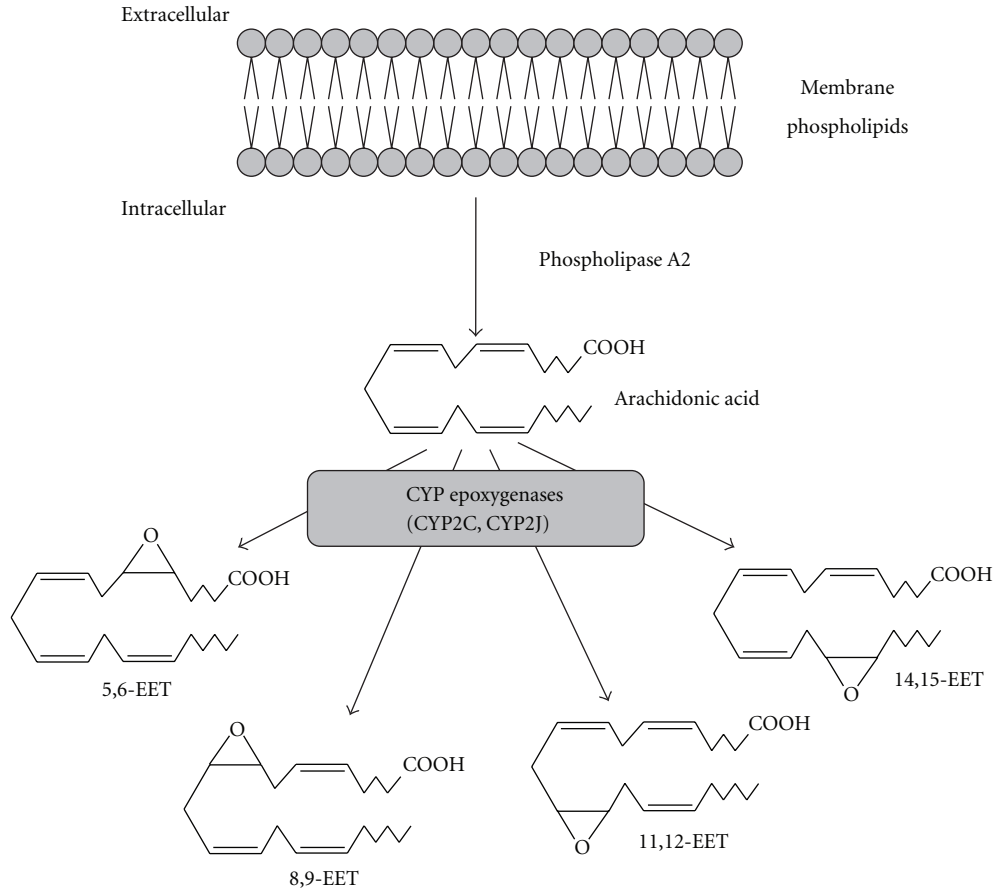

Figure 1: Conversion of arachidonic acid to EETs. Arachidonic acid is released from membrane phospholipids by phospholipase A2. CYP epoxygenases (CYP2C and CYP2J) convert AA into four regioisomeric EETs.

5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET (see Figure 1). These compounds seem to be involved in many biological processes such as inflammation, mitogenesis, cell signaling, regulation of vascular tone, and ion channels. EETs are metabolized mainly by soluble epoxide hydrolase to dihydroxyeicosatrienoic acids (DHETs) which are less active than EETs. Both EETs and DHETs can serve as ligands for peroxisome-proliferator-activated receptors (PPARs) α and γ and stimulate PPAR/RXR heterodimer binding to peroxisome proliferator response element (PPRE). The other EET-producing CYPs are CYP4X1 and CYP2U1 but they have minor contribution [14].

Altered EETs production is important for tumour tissue. CYP epoxygenases and their metabolites are involved in angiogenesis which is essential for growth, survival, and metastatic potential of most solid tumours. EETs produced by epoxygenase pathway by CYP2C and CYP2J2 are involved in angiogenesis but this process is not clearly understood. In endothelial cells, EETs are involved in several signaling pathways, including PI3K/Akt, ERK1/2, and Src/STAT-3. It has been shown that 11,12-EET activates sphingosine kinase 1 and thus it causes activation of Akt kinase and transactivation of epidermal growth factor (EGF) receptor [15]. 11,12-EET as well as CYP2C9 overexpression leads to increasing expression of EphB4, the important factor in the vascular development during embryogenesis [16]. Effect of EETs and VEGF on angiogenesis is closely linked. 14,15-EET induces VEGF expression and angiogenesis via Src-STAT-3 [17]. In turn, VEGF stimulates phosphorylation of AMP-activated protein kinase (AMPK). It leads to the induction of CYP2C expression [18]. CYP2C8 and 2C9 expression is induced also by hypoxia. CYP2J2 also promotes metastasis by the upregulation of matrix metallopeptidase-9 [19]. Beside angiogenesis, EETs also significantly promote tumour growth by increased proliferation activity through PI3K and MAPK pathway and transactivation of EGFR. EETs also inhibits apoptosis in tumour cell lines [20]. The modulation of immunological response could be another way by which the CYP epoxygenases and their metabolites influence tumours. High level of CYP2J2 in human acute monocytic leukemia cell line may explain high degree of immunosuppression [21].

3.1. CYP2C Expression during Human Embryogenesis; Normal Adult and Tumour Tissues. Expression of CYP2C during human embryogenesis has been investigated in several studies. In the earlier study, Treluyer et al. have examined CYP2C mRNA and protein in foetal livers in age ranging from 16 to 40 weeks of intrauterine development (UID). They detected CYP2C8, 2C9, and 2C18 mRNA at level of approximately

Table 2: Summary of CYP2C and CYP2J2 expression in normal adult tissues. Expression levels estimated at protein and mRNA level [23, 25].

Tissue	CYP protein	CYP mRNA
Gastrointestinal system		
Salivary glands	CYP2C8, CYP2C9	CYP2C8, CYP2C18, CYP2C19, CYP2J2
Stomach	CYP2C9	
Liver	CYP2C9, CYP2J2	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Pancreas	CYP2C9, CYP2J2	
Small intestine	CYP2C8, CYP2C9, CYP2J2	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Large intestine	CYP2C8, CYP2C9, CYP2J2	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Urinary system		
Bladder		CYP2C8, CYP2C18, CYP2J2
Kidney	CYP2C8, CYP2C9, CYP2J2	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Endocrine system		
Adrenals	CYP2C8, CYP2C9	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Pituitary gland	CYP2C9, CYP2J2	CYP2C8, CYP2C9, CYP2C18, CYP2J2
Cardiovascular system		
Myocardium	CYP2C9, CYP2J2	CYP2C8, CYP2J2
Lymphoid tissues		
Tonsils	CYP2C8, CYP2C9	
Spleen	CYP2C9	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Lymphatic nodes	CYP2C9	
Thymus		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Respiratory system		
Trachea		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Lung	CYP2C9, CYP2J2	CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Skin		
Epidermis	CYP2C9	
Mammary gland		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Reproductive system		
Endometrium	CYP2C9	
Ovary		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
uterus		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
placenta		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
prostate		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
testes		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2
Musculoskeletal system		
bone marrow		CYP2C8, CYP2C18, CYP2J2
skeleton muscle		CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2J2

10% of adult levels but proteins and protein activities were undetectable which suggests possible posttranscriptional control mechanisms [22].

More recently, CYP2C9 protein was detected in foetal liver between 8 to 24 weeks of gestation in lower levels than in adults (about 1-2%). CYP2C9 expression increases with the foetal age and it reaches approximately 30% of mature value in the third trimester. CYP2C19 protein was also detected as early as 8 weeks IUD but protein level is similar in all gestational ages. Measurement of enzyme activities shows similar pattern as protein analysis. Contrary to the adult liver, CYP2C19 protein level is higher than CYP2C9 in the foetal liver [10]. Bieche et al. have also confirmed expression of CYP2C8, CYP2C9, CYP2C18, and CYP2C19 mRNA in foetal liver [25].

CYP2C proteins are expressed also in various adult healthy and tumour tissues. Enayetallah et al. detected human epoxygenases CYP2C8 and 2C9 in different tissues by immunohistochemistry [23]. CYP expression in different human tissues at mRNA level was analyzed by Bieche et al. [25]. Their results are summarized in Table 2. CYP2C enzymes are mainly hepatic proteins [25]. Expression of different CYPs mRNAs in the lung tissue has been studied by Leclerc and coworkers. Moderate expression level of CYP2C9 and 2C18 and low level of CYP2C8 and 2C19 were detected in the bronchial mucosa. Low levels of CYP2C were detected in parenchymal cells [24].

In comparison to the normal tissue, there are differences in CYP2C expression pattern in tumour tissue. Enayetallah et al. proved CYP2C8 and 2C9 protein expression in different human neoplasms by immunohistochemistry. Positive immunostaining for CYP2C9 was detected in cholangiocarcinoma, stomach, and lung adenocarcinomas, breast carcinoma, squamous cell carcinoma of mouth, tongue,

larynx, and pharynx. CYP2C8 and CYP2C9 proteins were detected in prostate adenocarcinoma. CYP2C8 and 2C9 epoxygenases were also detected in endometrial carcinoma. Basal skin cell carcinoma was positive only for CYP2C9 [23]. Expression of CYP2C8 occurs also in the majority of ovarian tumour regardless of histological type, stage, or grade [26]. Lower expression of CYP2C mRNA in comparison to normal tissue was detected in squamous cell carcinoma of lung [24].

3.2. CYP2J2 Expression during Human Embryogenesis: Normal Adult and Tumour Tissues. Expression of CYP2J2 during human embryogenesis has been also investigated. The expression of CYP2J2 has been studied in the liver [25, 27] and extrahepatic tissues. CYP2J2 mRNA has been detected in the foetal liver as early as in 11-week-old foetus. The highest expression of CYP2J2 was detected in foetal liver and heart at comparable levels. CYP2J2 transcripts can be also detected in intestines, lungs, kidneys, adrenals, testes, and brain but in lower levels than in the liver. Only small interindividual variability was observed in mRNA level whereas differences are more obvious at the protein level [27]. CYP2J2 mRNA is also strongly expressed in placenta [25].

Expression of CYP2J2 in various normal adult tissues at protein [23] and mRNA levels [25] is summarized in Table 2. In contrast to CYP2C expression, which is mainly hepatic, CYP2J2 expression was detected predominantly in extrahepatic tissues [25].

Increased CYP2J2 expression was detected in the most of esophageal, pulmonary, breast, stomach, liver, and colon carcinomas in comparison with adjacent normal tissue and also in tumour cell lines [28]; it was also detected in endometrial carcinoma, cholangiocarcinoma, and squamous cell carcinomas of tongue, pharynx, and larynx [29]. Unlike Jiang et al. [28], Enayetallah et al. [29] detected lower level of CYP2J2 expression in liver and kidney carcinomas in comparison with surrounding healthy tissue. Interestingly, CYP2J2 protein was undetectable in prostate and pancreatic adenocarcinomas. CYP2J2 expression was detected only in some squamous cell carcinomas of lungs and small part of lung adenocarcinomas [29]. The discrepancy remains unclear. Leclerc et al. detected increased CYP2J2 expression in lung adenocarcinomas but CYP2J2 mRNA was underexpressed in squamous cell carcinoma of lungs [24]. Increased expression of CYP2J2 was detected also in ovarian tumour [30]. Recently, highly selective expression of CYP2J2 was detected in hematological malignant diseases [31].

4. Peroxisome Proliferator-Activated Receptors (PPARs)

As we mentioned above, PPARs, especially PPARα, play a role in the regulation of certain enzymes of phase I metabolism of xenobiotics. Therefore, they could contribute to the multidrug resistance of tumours.

The PPARs belong to nuclear receptors superfamily. PPARs are ligand-dependent transcriptional factors as well as steroid, thyroid, and retinoid receptors. PPAR ligands are both endogenous and exogenous compounds [32] (see Table 3). PPARs receptors consist of three members: PPARα, PPARβ/δ, and PPARγ encoded by different genes. PPARγ gene contains three different promoters which give rise to three different mRNA transcripts: PPARγ1, PPARγ2, and PPARγ3. PPARγ1 and PPARγ3 are translated to the identical protein PPARγ1. Moreover, Chen et al. described additional three mRNA transcripts of PPARγ in human THP-1 macrophages: PPARγ4, PPARγ5, and PPARγ7. Only PPARγ4 encodes novel protein isoform; PPARγ4. PPARγ5, and PPARγ7 are translated to protein PPARγ1 [33]. Each of PPARs has different ligand, target genes, and biological role. The expression of PPARs varies widely among tissues. PPARα is highly expressed in cells with active fatty acid oxidation including hepatocytes, cardiomyocytes, enterocytes, and proximal tubuli of kidneys. PPARβ/δ is expressed ubiquitously and often in higher level than PPARα and PPARγ. PPARγ is expressed mainly in adipose tissue (PPARγ2) and immune system (PPARγ1). PPARs are important for various biological processes such as energetic homeostasis, development, differentiation, apoptosis, neoplastic transformation, inflammatory response, and tissue regeneration. They are involved in chronic diseases such as diabetes, obesity, and atherosclerosis [34].

PPARs bind to the peroxisome proliferator response element (PPRE) in the promoter of target genes as heterodimer with retinoid X receptor (RXR). Besides ligands, PPARs interact with a lot of coregulator proteins. Coactivators such as PPAR binding protein (PBP), SRC-1, p300, CBP, PGC-1α) stimulate PPAR target genes expression and corepressors; for example, SMRT and N-CoR inhibit expression of target genes. PPARα and to a lesser extend PPARβ/δ are associated with the heat shock protein complexes [32, 34].

Similar to other nuclear receptors, PPARs are phosphoproteins. Therefore, their transcriptional activity can be also affected by crosstalk between phosphorylation and dephosphorylation. The effect of phosphorylation depends on cellular context, receptor subtype, and residue metabolised. For example, MAPK pathway activates PPARα in hepatocytes, whereas it inhibits PPARγ activity in adipocytes [35].

4.1. PPARs Expression during Prenatal Development. PPARs play an important role in the development of germ cells and embryos. Each of three PPARs isoforms are expressed in somatic and germ cells of testes and ovaries, PPARγ more than others [36]. It has been known that PPARβ/δ and PPARγ are necessary for implantation and survival of the early embryo. PPARγ and PPARβ/δ are highly expressed in mouse placenta but functional redundancies or compensations between them are not fully operative [37]. The homozygous disruption of PPARγ results in the death of 10-day-old embryo. PPARγ null mice embryos have showed abnormal development of the foetal and maternal vascular network in placenta, severe myocardial thinning, and overall growth retardation [38, 39]. Similarly, the most (but not all) PPARβ/δ null mice embryos died at age of 10 days due to placenta failure. PPARβ/δ promotes differentiation of

Table 3: Overview of PPARs endogenous and exogenous ligands according to [32].

	endogenous ligands	exogenous ligand
PPARα	Unsaturated fatty acids (oleic, palmitoleic, linoleic, arachidonic acid)	Hypolipidemic drugs (bezafibrate, clofibrate, ciprofibrate, fenofibrate, gemfibrozil, nafenopin, WY-14643)
	Saturated fatty acids (palmitoic and stearic acid)	Phytanic acid
	5, 6-, 8, 9-, 11, 12-, 14, 15-eet	Nsaids (indomethacin)
	Hydroperoxyeicosatetraenoic acids (hetes)	Dehydroxyepiandrosterone (DHEA)
	20, 14, 15-heet	Phtalates
	Prostaglandins (PGD2, PGD1)	Anticonvulsants (valproic acid, phenobarbital)
	Leucotriene B4 (LTB4)	Telmisartan
	Vldl	Phytol
		Perfluorinated alkyl and sulfonyl acid comp. (pfoa, pfna, pfos)
		Oxirane compounds
		Etya
		Epoxyisoprostane
		Drf-2519
		Bm 17.0744
		Benz[a]anthracene
		Di- and trichloroacetic acid
		Mk-886*
PPARβ	Mono-and polyunsaturated fatty acids	Tetradecylthioacetic acid
	Saturated fatty acids	Hypolipidemic drugs (WY-14643, bezafibrate)
	Prostaglandins (PGA1, PGD1, PGD2)	Valproic acid
	13-S-hydroxyoctadecadienoic acid (13-S-HODE)	Benz[a]anthracene
	4-hydroxynonenol (4-HNE)	Treprostinil sodium
	VLDL, oxldl	Gw-501516
		Sulindac sulfide*
PPARγ	Unsaturated fatty acids (linoleic, linolenic, arachidonic, eisosapentateonic acid)	Thiazolidinediones (e.g., ciglitazone, pioglitazone, rosiglitazone, troglitazone)
	9-s-hode, 13-s-hode 15-s-hete, 5-s-hete, 12-s-hete	Nsaids (indomethacin, diclofenac, oxaprozin, zaltoprofen, ibuprofen, nimesulide, sulindac sulfide*) Hypolipidemic drugs (bezafibrate, WY-14643, atorvastin)
	Lysophosphatidic acid	Phtalates (MEHD, DEPH)
	Hexadecylazelaicphosphatidylcholine	Bisphenol A diglicidyl ether
	Prostaglandins (PGD1, PGD2, PGA1)	Natural (plant) phenols (genistein, curcumin, resveratol)
	Nitroalkane derivate of linoleic acid	Telmisartan
	Oxldl	Jtp-426467
		Pemoline
		Phenylacetate
		Dhea
		LY171883
		2-bromopalmitate
		antidiabetic drugs (glimepiride, tolbutamide, chlorpropamide, gliclazide, glibenclamide, SR-202)
		F-L-Leu
		abietic acid
		organotin compounds tributyl- and triphenyltin
		perfluorooctanic acid (PFOA)
		T0070907*
		GW9662*

*Antagonist.

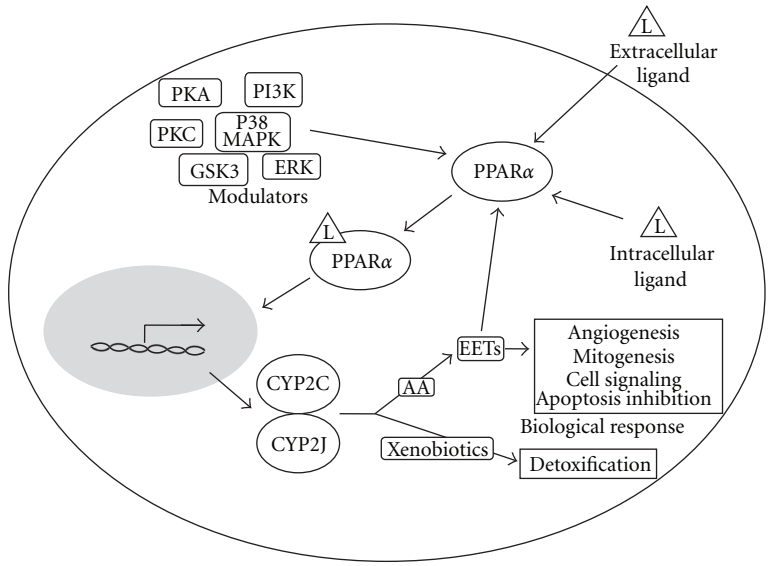

Figure 2: Our proposed model of PPARα effect on CYP2C and CYP2J (simplified): activation of PPARα results in CYP2C and CYP2J expression. CYP2C and CYP2J convert arachidonic acid (AA) to EETs, which have cytoprotective function and also can serve as PPARα ligand, resulting in feedback mechanism. CYP2C and CYP2J also metabolise xenobiotics.

giant cells. Both PPARγ and PPARβ/δ are also required for accumulation of lipid droplets in placenta [37, 38].

Rodent experiments also have showed that PPARα participates on later skin development [40]. PPARβ/δ plays a role in the development of skin, hair follicles [40], muscles [36], and nervous system [41]. Similar to PPARβ/δ, PPARγ also has an influence on developing nervous system [41] and muscles [36]. PPARβ/δ and PPARγ together play a role in adipose tissue differentiation.

There is few information about PPARs expression in human prenatal development. Huin et al. have investigated expression of PPARs in gastrointestinal tract in human foetuses from 7 to 22 weeks of IUD by immunohistochemistry. Every three isoforms of PPARs have been detected as early as in 7-week-old foetus. With the exception of stomach, PPARγ is the predominant isoform in digestive tract [42]. PPARγ is also highly expressed in human placenta, where it is important for differentiation and function of trophoblast [43].

More recently, expression of PPARs isoforms in the foetal development has been investigated by Abott et al. [44]. They focused on mRNA and protein levels of PPARs in foetuses from days 54 to 125 in different foetal tissues by qPCR and western blotting. They investigate mRNA and protein levels in foetal heart, lung, stomach, liver, intestine, adrenal, kidneys, spleen, and thymus. Their results were consistent with Huin for intestine, but discrepancies were detected in stomach [44].

5. Relationship between CYPs and PPARs

Although PPARs have been considered biological sensors of lipid metabolism, it has been shown that PPARα regulates also various genes involved in the biotransformation. PPARα directs transcription of CYP4 which is important for metabolism of biologically important compounds such as fatty acids. In human hepatocytes, PPARα activates members of CYP1A, CYP2A, CYP2B, CYP2C, CYP2E, CYP2J, and CYP3A subfamilies and some conjugating enzymes (e.g., EPHX2, GSTA, and UGT1A9) [45]. Our proposed model of influence of PPARα on CYP2C and CYP2J is shown in Figure 2. PPARα participates with other nuclear receptors in the regulation of other xenobiotic metabolizing enzymes, such as PXR, CAR, and FXR [8].

5.1. In Vivo and In Vitro Animal Studies. Even if animal models are very useful tool for *in vitro* and *in vivo* studies, differences between rodent and human xenobiotic metabolism are known. PPARα ligand affects CYP2C in both human and rodent but in quite different ways.

In murine liver, PPARα causes downregulation of some genes involved in phase I of biotransformation, including CYP2C11, CYP2C12, and CYP2C29 [45].

EMD 392949 is a ligand for both, PPARα and PPARγ. The oral treatment of male cynomolgus monkey for 4 weeks leads to the increase CYP2C9 expression and stronger induction was observed after longer term exposition. Changes in gene expression were reversed after recovery period. *In vitro*, EMD 392949 suppresses CYP2C expression in rat hepatocytes, as well as fenofibrate treatment [46].

Another PPARα agonist is clofibric acid. Male Wistar rats were treated for 3 days orally by clofibric acid. It led to downregulation of CYP2C11. Liver CYP2C11 expression is regulated by the growth hormone via Janus kinase/signal transducer and activators of transcription proteins (JAK/STAT5b). PPARα downregulates STAT5b transcriptional activity [47].

PPARα agonist fenofibrate causes downregulation of CYP2C11 mRNA and protein in liver of male Wistar rats and male hypertriglyceridemic rats after 20 days of fenofibrate-containing diet. CYP2C6 mRNA and protein was downregulated too, but in lesser extend [48]. Fenofibrate also

affects CYP2C23 expression in kidneys of Zucker diabetic fatty rats. 26-week-old male ZDF rats were fed by fenofibrate for 6 weeks. The treatment results in the significant increase of CYP2C23 protein production in both renal microvessels and kidney cortex [49].

Rodent epoxygenases (as well as human enzymes) and their metabolites have proangiogenic function. Experiments with CYP2C44 knockout mice prove that murine CYP2C44 (catalytic homolog of human CYP2C8 and 2C9) is a target gene for PPARα. WY-14643, PPARα ligand, reduces EETs synthesis by downregulation of CYP2C44 and leads to marked reduction of tumour mass, volume, and vascularization of xenograft tumours. This process is PPARα dependent. The same results were obtained from mouse with human PPARα gene [3, 50].

While in human CYP2J2 is only one member of CYP2J family, in the mouse up to 8 putative homologues (CYP2J5–CYP2J13) exist. This investigation of the role of endogenous epoxygenases in the mouse is difficult. It is possible to use fasting as a model of PPARα activation. *In vivo*, in cardiac-specific CYP2J2 transgenic mice, fasting selectively augments the expression of pyruvate dehydrogenase kinase 4 (PDK4), a target PPARα gene which is selectively induced by PPARα ligand in the cardiac tissue [51].

5.2. In Vitro Studies with Human Cells. EETs produced from arachidonic acid by CYP2C and 2J2 are able to activate PPARα in human HepG2 cell line. In turn, PPARα regulates expression of enzymes responsible for EETs formation resulting in the feedback mechanism [52]. Activation of PPARs, particularly PPARα, by CYP2J2 products was also confirmed in HEK293 cell line by Wray et al. [51]. Their results have shown that 8,9-EET and 11,12-EET, but not 14,15-EET, activated PPARα. CYP2J2 and CYP2C8 epoxygenases products play the important role also in the immunological response. The epoxygenases regulate monocyte/macrophage activation depending on the underlying activation state. Products of epoxygenases in monocyte/macrophage act as the anti-inflammatory tool, at least in part by producing PPARα ligands [21].

Prueksaritanont et al. have investigated effect of clofibric and fenofibric acids and gemfibrozil (PPARα ligands) on human hepatocytes. All three fibrates elevate CYP2C8 mRNA level. Clofibric and fenofibric acids also increase CYP2C8 activity. On the other hand, treatment by gemfibrozil leads to the reduction of CYP2C8 activity [53]. In contrast to rat hepatocytes, treatment of human hepatocytes by EMD 392949 causes strong induction of CYP2C8 [46].

Human CYP2C enzymes are affected also by thiazolidinediones, PPARγ agonists. Troglitazone causes inhibition of CYP2C8, 2C9, and 2C19. Pioglitazone has also potential to inhibit CYP2C8 [4].

6. Discussion

Despite of the huge progress in cancer diagnosis and treatment, development of multidrug resistance in patients with tumour remains the serious problem. Normal cells have different mechanisms to protect themselves against external noxious substances or toxic products of their metabolism. Cancer cells utilize these mechanisms in the protection of anticancer drugs.

CYP epoxygenases, CYP2C, and CYP2J play nonnegligible role in tumors. These enzymes metabolise about 20% of clinically used drugs [10]; moreover, they play a role in angiogenesis [15–18], cell migration, metastasis [19], and immunological response [51]. According to *in vitro* and *in vivo* studies mentioned above, we hypothesize that PPARα ligands affect CYP2C and CYP2J. Moreover, products of CYP2C and CYP2J metabolism of arachidonic acid, EETs, are able to act as PPARα ligands. It results in feedback mechanism [51, 52]. Cytoprotective EETs increase proliferation and cell migration and also inhibit apoptosis [20].

PPARα ligands are used in the treatment of lipid disorders and plasma dyslipidemia. These drugs have the long history of clinical use. They seem to be well tolerated to have low toxicity and have limited side effects [50]. Regulation of CYP2C and/or CYP2J expression in tumour overexpressing these proteins could increase efficacy of anticancer drugs (which are inactivated by CYP2C and CYP2J). Moreover, the angiogenesis could be reduced. Regulation of CYP epoxygenases in monocyte/macrophage could force immunological response. Moreover, the decreased expression of CYP2C and CYP2J in monocytes may lead to the stronger immunological response. Finally, regulation of cytoprotective EETs production may result in reduced proliferation and migration and enhanced apoptosis of tumour cells. All these mechanisms may contribute to better cancer treatment and reduction of multidrug resistance.

7. Conclusion

In conclusion, we assume that detailed investigation of regulation of CYP2C and CYP2J by PPARα provides valuable information which could be useful to overcome multidrug resistance in patients with different types of tumours.

Abbreviations

MDR:	Multidrug resistance
PPAR:	Peroxisome proliferator-activated receptor
ABC transporter:	ATP binding cassette transporter
CYP:	Cytochrome P450
NADPH:	Nicotinamide adenine dinucleotide phosphate
EET:	Epoxyeicosatrienoic acid
DHET:	Dihydroxyeicosatrienoic acid
RXR:	Retinoid X receptor
PPRE:	Peroxisome proliferator response element
IUD:	Intrauterine development
PI3K:	Phosphoinositide 3-kinase
ERK:	Extracellular signal-regulated kinase
STAT:	Signal Transducers and Activators of Transcription

EGF: Epidermal growth factor
EphB4: Ephrin type-B receptor 4
VEFG: Vascular endothelial growth factor
MAPK: Mitogen-activated protein kinase
EGFR: Epidermal growth factor receptor
PBP: PPAR binding protein
CBP: CREB-binding protein
PGC-1α: PPARγ coactivator 1α
SRC-1: Steroid receptor coactivator 1
SMRT: Silencing mediator for retinoid and thyroid hormone receptor
N-CoR: Nuclear receptor corepressor
EPHX2: Epoxide hydrolase 2
GSTA: Glutathione s transferase A
UGT1A9: UDP-glucuronosyltransferase 1A9
PXR: Pregnane X receptor
CAR: Constitutive androstane receptor
FXR: Farnesoid X receptor
JAK: Janus kinase
PDK4: Pyruvate dehydrogenase kinase 4
HETE: Hydroperoxyeicosatetraenoic acid
HEET: Hydroepoxyeicosatrienoic acid
PGD1(D2, A1): Prostaglandin D1 (D2, A1)
HODE: Hydroxyoctadecadienoic acid
VLDL: Very low-density lipoprotein
OxLDL: Oxidized low-density lipoprotein
NSAID: Nonsteroidal anti-inflammatory drug
DHEA: Dehydroeepiandrosteron
PFOA: Perfluorooctanoic acid
PFNA: Perfluorononanoic acid
PFOS: Perfluorooctane sulfonate
ETYA: Eicosatetraynoic acid
MEHP: Mono-2-ethylhexyl phtalate
DEHP: Di-2-ethylhexyl phtalate.

Acknowledgments

This study was supported by LF_2011_009 and CZ.1.05/2.1.00/01.0030.

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