PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARs) IN HEALTH AND DISEASE

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Received: September 10, 2002

Key words: Orphan receptors / PPARs / Inflammation / Atherosclerosis / Cancer

Peroxisome proliferator-activated receptors (PPARs) belong to the superfamily of steroid-thyroid-retinoid nuclear receptors. PPARs are transcription factors activated by specific ligands and play an important role during cell signalling. Intensive study of PPARs during recent years has revealed their importance in both normal physiology and in the pathology of various tissues. They participate in the regulation of lipid metabolism, inflammation and the development of atherosclerosis or diabetes. They also play a role in the regulation of growth and differentiation of cancer. It has been suggested that PPAR ligands may have potent anticancer effects and therefore may serve as potential anticancer drugs. In this review we focus on a role of PPARs in breast cancer and in glial tumors of the brain.

Nuclear receptors are transcription factors activated by specific ligands which play an important role during cell signalling. They belong to the steroid-thyroid-retinoid receptor superfamily; these include receptors for steroids, thyroid hormone, vitamin A and D derived hormones and some fatty acids. Structurally, they share common features: highly conserved central DNA binding domain (binds receptor to specific DNA sequences – Hormone Response Elements, HRE), ligand binding domain in the COOH-terminal region and variable N-terminal domain. Recently, the three-dimensional structure of DNA binding domains of various nuclear receptors have been described¹. However, in some nuclear receptors the natural ligand (hormone) has not been identified and therefore the term “orphan” receptors (OR) was suggested a decade ago. Searching for such ligands (hormones) has introduced the concept of “reverse endocrinology”². A typical example of this approach is the discovery of 9-cis retinoic acid (a metabolite of vitamin A) as a high-affinity ligand for three variants of retinoid X receptors (RXR). This in turn has led to better understanding of the processes regulated by retinoids³.

Currently, five families of OR are distinguished: 1. liver X receptor – LXR, 2. pregnane X receptor – PXR, 3. constitutive androstane receptor – CAR, 4. farnesoid X receptor – FXR and 5. peroxisome proliferator-activated receptors – PPARs. LXR is an oxysterol receptor and regulates the catabolism of excess dietary cholesterol. PXR is activated by many compounds and by binding to a xenobiotic response element in the

CYP3A4 gene promoter serves as a xenobiotic sensor. The physiological role of CAR is not clear, however, although it is suggested that like PXR it may play a role in the regulation of steroid homeostasis. FXR is a nuclear bile acid receptor^{2,4}.

Peroxisome Proliferator-Activated Receptors (PPARs) were first cloned from mouse liver in 1990 as the nuclear receptor mediating the effects of many synthetic (industrial and pharmaceutical) compounds called peroxisome proliferators (PPs)⁵. PPs influence both the size and number of peroxisomes, which perform various metabolic functions (peroxide derived respiration, beta oxidation of fatty acids, cholesterol metabolism, etc.) within the cell. It has been found that three PPAR isoforms exist: PPAR alpha, PPAR delta (also known as NUC1 or PPAR beta) and PPAR gamma. These are encoded by separated genes, perform separate functions and exhibit different tissue localization (Table 1). Like other nuclear receptors, after activation by ligand, PPARs bind a specific element in the promoter region of target genes. The dimerization of PPAR with RXR and the presence of coactivators are necessary for the transcriptional activity of PPAR responsive element (PPRE) in DNA (Table 2). It is interesting, that not all PPRE in responsive genes mediate increase in transcription. For instance transthyretin, transferrin and/or some apolipoprotein genes are regulated negatively^{6,7,8,9}. There is a wide spectrum of both exogenous and endogenous ligands of PPARs (Table 3) and it has been noted that their interaction with PPARs leads to various functions. PPARs play an important role during rodent

Table 1. Example of different tissue distribution of PPARs

Isoform	Liver	Intestine	Spleen	Fat
α	++++	++++	+	—
β	++	+++	++	—
γ	—	++	+++	++++

Table 2. PPAR-interactive proteins

Protein			
Nuclear receptors	Coactivators	Corepressors	Others
RXR	SRC-1/TIF2	N-Cor/RIP 13	c-Jun
LXR alpha	P300/CBP	SMRT/TRAC	dUTPase
SHP	PBP	RIP 140	
	PGC-1		
	PGC-2		
	ARA 70		
	TSC 2		

Table 3. PPAR ligands

Exogenous PPAR ligands		Endogenous PPAR ligands	
PPAR α	PPAR γ	PPAR α	PPAR γ
WY-14.643	Indomethacin	Palmitic acid	Arachidonic acid
Clofibrate	Ibuprofen	Stearic acid	Eicosapentaenoic acid
Gemfibrozil	Piroxicam	Palmitoleic acid	PGJ2
Nafenopin	Pioglitazon	Oleic acid	15 deoxy PG J12
Bezafibrate	Ciglitazon	Linoleic acid	
	Englitazon	Arachidonic acid	
	BRL-49653	Eicosapentaenoic acid	

hepatocarcinogenesis, during inflammation, atherosclerosis development, lipid metabolism, diabetes, and they also have an important role in cancer^{10–15}.

Rodent hepatocarcinogenesis

It has been found that increase in oxidative stress and proliferation (by decreasing the rate of apoptosis) due to activation of PPs by ligand binding to PPAR alpha leads to hepatocellular adenoma and carcinoma

in rodents^{6, 10, 11}. However, there is no evidence that humans are at increased risk of liver cancer after chronic activation of PPs by PPAR alpha. Epidemiological studies have not revealed any risk of liver cancer development either in patients chronically exposed to the widely used hypolipidemic agents gemfibrozil and clofibrate (synthetic ligands of PPARs)¹⁶.

Inflammation

Even if recent opinion on the role PPARs during inflammation is controversial, it is generally accepted that PPARs can inhibit inflammatory responses and therefore they may be candidates for therapeutic intervention in some inflammatory diseases^{15, 17}. Moreover, it has been found that activity of PPARs have effects on endothelial cells and therefore influence vascular response to various factors¹⁸.

Atherosclerosis

The effect of PPARs agonists on vascular smooth muscle cells, macrophages and vascular walls can modulate not only inflammatory but also atherosclerotic processes^{17, 19, 20}. PPAR may affect foam cell formation and modulate plaque stability. PPAR alpha decreases levels of pro-atherosclerotic proteins as fibrinogen and C-reactive protein and PPAR gamma may reduce expression of some metalloproteinases, implicated in plaque destabilization. On the other hand PPAR gamma are also able to stimulate uptake of oxidized LDL, which has pro-atherosclerotic effects^{12, 13}.

Lipid metabolism and diabetes

PPARs play a role in lipoprotein metabolism. Fibrates lower plasmatic levels of cholesterol and triacylglycerols and increase HDL by modulating the reverse cholesterol transport pathway. In consequence there is a decreased risk of coronary heart disease⁹. For this reason synthetic agonists of PPAR alpha (fibrates) are used in the treatment of hyperlipidemia. Agonists of PPAR gamma (thiazolidinediones and their derivatives rosiglitazone, troglitazone, pioglitazone, etc.) can improve insulin sensitivity and therefore have been used as efficient antidiabetics¹⁵. However, many of these antidiabetic compounds were withdrawn from the market due to liver toxicity and less toxic drugs have to be developed for successful and harmless clinical use²¹.

PPARs and cancer

There is evidence that some PPARs can suppress the growth of different types of human cancer by distinct mechanisms including growth arrest, apoptosis and induction of differentiation^{6, 13}. Mutations of PPAR gamma in colon carcinoma lead to loss of ligand binding and suppression of cell growth. This may indicate that functional PPAR gamma is required for the normal growth properties of human colon cells²². However, the detailed signalling pathways leading to growth arrest

and differentiation have not yet been completely elucidated. One possible mechanism is upregulation of tumor suppressor PTEN by PPAR gamma agonists²³. Overall, despite incomplete knowledge it is evident that PPAR ligands (agonists) may have potent anticancer potential and may serve as a rational basis in the therapy of some tumors or in their chemoprevention^{24–27}. This is supported by *in vitro* studies: liposarcoma²⁸, ovarian carcinoma²⁹, breast carcinoma^{30–33}, prostate carcinoma^{34–37}, urinary bladder carcinoma³⁸, some types of B lymphoma³⁹, erythroleukemia⁴⁰, non small cell lung cancer⁴¹, gastric⁴² and colon carcinomas²².

PPARs and breast cancer

It has been found that PPAR gamma, activated by various ligands (thiazolidinedione, gamma linoleic acid, omega-6 fatty acids) stimulates the terminal differentiation of breast cancer cell *in vitro*. Moreover, it seems that dietary fat may influence development of breast cancer and also that sensitivity to estrogen in breast cancer may be diminished by parallel expression of both ER and PPARs^{30–33}. Taken together, the data indicate that PPAR gamma may play an important role in the regulation of growth and differentiation of the mammary gland and may be potentially used in therapy or chemoprevention of breast cancer.

PPARs and glial tumors of the brain

Since the changes of PPARs expression has been demonstrated in various types of cancers it is also interesting to explore the role of PPARs in glial tumors of the brain. It has been found that in contrast to normal astrocytes, the cell lines of malignant astrocytomas express higher levels of PPAR gamma⁴³. Moreover, incubation of malignant astrocytoma cell lines with PPAR gamma agonists ciglitazone and 15-deoxy-Delta (12,14) prostaglandin J(2) [15-deoxy PGJ(2)] reduced cell viability and increased apoptotic rate. This may suggest the role of PPAR in regulation of the apoptotic process in astroglial cells⁴⁴. However, on the contrary, it has been reported that in cerebellar granule cells the PPAR gamma ligands troglitazone, ibuprofen and 15-deoxy PGJ(2) reduced inducible forms of nitric oxide synthase (iNOS) and reduced cell death^{45,46}. We may hypothesize that the effect of PPARs on apoptosis and its signaling in the CNS depends on type of cell. Zhou X.P. et al. studied somatic mutations of the PPAR gamma gene in sporadic cases of glioblastoma multiforme⁴⁷. They found over-represented polymorphic alleles at codons 12 and 449 among patients with glioblastoma compared to controls. Even if the precise consequence of this change is unknown, it raises the possibility of different effects of mutated and non-mutated forms of PPARs in glial tumors. It also seems that as with other tumors the potential of PPARs ligands in glial tumors may have therapeutic value.

CONCLUSION

Intensive study of PPARs during recent years has revealed that these nuclear receptors play an important role both in normal physiology and the pathology of various tissues. They participate in the regulation of lipid metabolism, they play an important role during rodent hepatocarcinogenesis, inflammation and development of atherosclerosis and/or diabetes, and they also have an important role in the regulation of growth and differentiation of cancer cells. It has been suggested that PPAR ligands with agonistic effects may have potent anticancer potential and may serve as a rational basis for therapy of some tumors or their chemoprevention. We can expect many promising results in this field in the near future.

ACKNOWLEDGMENTS

The work was supported in part by grants NC 6726-3/2001, FRVS 1471/2001 and MSM 151100001.

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