

Review Article

The Role of PPAR Ligands in Controlling Growth-Related Gene Expression and their Interaction with Lipoperoxidation Products

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Peroxisome proliferators-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. The three PPAR isoforms (α , γ and β/δ) have been found to play a pleiotropic role in cell fat metabolism. Furthermore, in recent years, evidence has been found regarding the antiproliferative, proapoptotic, and differentiation-promoting activities displayed by PPAR ligands, particularly by PPAR γ ligands. PPAR ligands affect the expression of different growth-related genes through both PPAR-dependent and PPAR-independent mechanisms. Moreover, an interaction between PPAR ligands and other molecules which strengthen the effects of PPAR ligands has been described. Here we review the action of PPAR on the control of gene expression with particular regard to the effect of PPAR ligands on the expression of genes involved in the regulation of cell-cycle, differentiation, and apoptosis. Moreover, the interaction between PPAR ligands and 4-hydroxynonenal (HNE), the major product of the lipid peroxidation, has been reviewed.

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1. THE ROLE OF PPAR IN CONTROLLING GENE TRANSCRIPTION

Peroxisome proliferator-activated receptors (PPARs) are members of the steroid hormone nuclear receptor superfamily which act by altering the transcription of PPAR-regulated genes by means of a recognition sequence known as a peroxisome proliferation responsive element (PPRE) [1].

The term peroxisome proliferator-activated receptor is derived from early observations in rodent livers that certain industrial compounds could cause an increase in size and number of peroxisomes [2, 3]. Subsequently, these compounds, including fibrates, were found to bind to certain recently identified nuclear receptors [4]; hence, the term "PPAR" arose. PPAR agonists are not known to induce peroxisome proliferation in primates or humans, making the term PPARs archaic as well [5]. At least three subtypes of PPARs have been identified: PPAR α , the first

isolated from mice liver in 1990 by Issemann and Green [4] and involved in fatty acid oxidation; PPAR γ , identified by Tontonoz and collaborators as a transcription factor associated with adipocyte determination and differentiation [6]; and PPAR β/δ , ubiquitously expressed and involved in basic cellular functions [7, 8]. Like other steroid hormone nuclear receptors, PPARs contain several modulating domains: a ligand binding domain (LBD) to which the specific PPAR agonist binds; a transactivating domain (activation function 2, AF 2), which undergoes conformational changes, in response to ligand binding, allowing the heterodimerization with RXR and facilitating recruitment of coactivators and release of corepressor; and finally a DNA-binding domain, which interacts with PPRE [3, 9–11].

PPAR coactivator and corepressor are small accessory molecules that are critical determinants of the transcriptional complex. These accessory molecules include coactivator proteins, like PPAR γ coactivator-1 (PGC-1); steroid

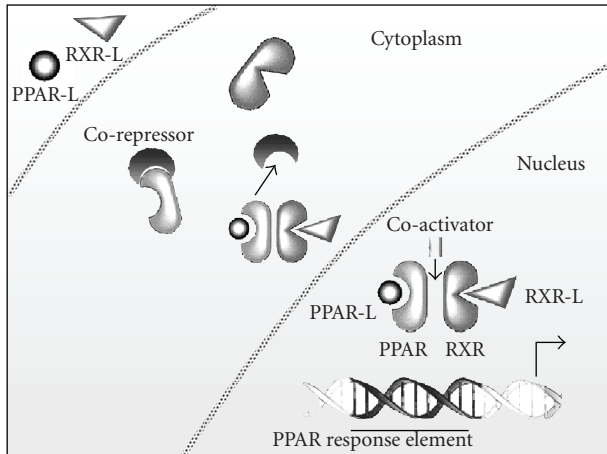


FIGURE 1: Mechanism of PPAR action. PPARs in response to ligand binding in the cytosol, dimerize with RXR, recruit coactivators and release corepressor; in the nucleus a multimolecule complex, formed by PPAR, PPAR ligand, RXR, RXR-ligand, and accessory proteins bind PPRE DNA sequences in the promoters of target genes.

receptor coactivator and CREB (cAMP-response element binding protein)-binding protein, recruited from the activated PPAR; and corepressor proteins, like nuclear receptor corepressor (N-CoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRTs1), released upon PPAR activation [12, 13]. A multimolecule complex formed by PPAR, PPAR ligand, RXR, RXR-ligand (purportedly 9-cis-retinoic acid) and accessory proteins ultimately combine to cause the PPAR response through the binding with PPRE sequences consisting of a direct repeat of the consensus half-site motif (AGGNCA) spaced by a single nucleotide [14] (Figure 1).

Several genes that are selectively upregulated by a given PPAR isotype have been identified over the years and a majority of these genes is known to play a central role in energy metabolism. Moreover, microarray technology and genome wide identification of PPRES suggest the existence of many other target genes that were not previously known to be regulated by PPAR. The identified PPRES putative sequences on target genes for PPARs are listed in Table 1.

Recent evidence indicates that the PPAR response can result both in gene activation and repression. As far as it regards gene repression, PPAR γ was shown to be unable to bind to DNA while it is associated with the corepressor complex. In contrast to PPAR γ , the interaction between NCoR/SMRT and PPAR β/δ does not impair its DNA binding [54, 55]. PPAR γ , after ligand binding, dissociates from the corepressor, and binds to DNA via PPRES. The liberated corepressor protein SMRT interacts with the signal transducer and activator of transcription-3 (STAT3), which inhibits STAT-dependent transactivation [56]. Recent data suggest that PPAR γ -mediated transrepression may involve stabilization of corepressor recruitment after posttranslational PPAR modification by sumoylation [57].

In macrophages, PPAR β/δ was shown to function as an activator of the monocyte chemoattractant protein (MCP-1)

gene by sequestering a transcriptional repressor, specifically the transcriptional repressor B-cell lymphoma-6 (BCL-6) [37, 58]. The ligand-induced activation of PPAR β/δ releases the corepressor BCL-6, which is thought to inhibit MCP-1 expression. Hence, PPAR β/δ can function as an intrinsic transcriptional repressor, a mechanism that is also shared by other nuclear receptors such as the thyroid hormone receptor (NR1A1, NR1A2), retinoic acid receptor (NR1B1, NR1B2, NR1B3), Rev-Erb (NR1D1, NR1D2) and COUP-TF (NRT2F3).

The best-documented mechanism by which PPAR α can transrepress non-PPRES containing genes is its ability to physically interact with the p53 subunit of nuclear factor (NF)- κ B, which inhibits NF- κ B-dependent transactivation [59]. However, PPAR α activators do not inhibit all NF- κ B-driven target genes and their effect is promoter context-dependent. Taken together, data obtained about PPAR transcriptional regulation demonstrated that PPARs can also modulate the transcriptional activity of non-PPRES containing genes via transrepression.

2. PPAR LIGANDS

PPAR ligands are a heterogeneous group that includes both endogenous and exogenous ligands [60]. Activating ligands for PPARs are semiselective for the subtype and selectivity depends on ligand concentration and cell type. Endogenous ligands include unsaturated fatty acids that bind all three PPARs, with PPAR α exhibiting the highest activity, while saturated fatty acids are weak PPAR ligands in general [61]. Biological modifications of linoleic acid, linolenic acid, eicosapentaenoic acid (EPA), and arachidonic acid originate PPAR α activators [62–64]. Moreover, the oxidized form of EPA, eicosanoids (15-hydroxy-eicosatetraenoic acid, HETE and HODEs), and leukotriene B4 has also been reported to be PPAR α activators [62–66].

The natural ligands of PPAR γ include several prostanoids such as 15-deoxy-prostaglandin J2 (15d-PG J2) and 15-hydroxy-eicosatetraenoic acid (HETE), which are metabolites of arachidonic acid [67]. 15d-PG J2 (the most widely used natural ligand for PPAR γ) is gamma-selective at low concentrations but also activates alpha at higher levels [68, 69]. Like PPAR α , PPAR β/δ is activated by long chain fatty acids, including several polyunsaturated fatty acids and eicosanoids [3]. Erucic acid has been reported to be more selective for PPAR β/δ than other PPAR subtypes [70].

Synthetic ligands of PPARs have been demonstrated to possess pharmacological activity. The triglyceride-lowering/high-density lipoprotein (HDL)-raising fibrates (gemfibrozil, fenofibrate, clofibrate, ciprofibrate) are PPAR α agonists used clinically to treat dyslipidemia [71, 72]. The insulin-sensitizing thiazolidinedione (TZD) class (troglitazone, pioglitazone and rosiglitazone) is PPAR γ activators that are used to treat diabetes mellitus [73, 74]. Several nonsteroidal anti-inflammatory drugs (NSAIDs), in particular indomethacin and ibuprofen, bind to PPAR γ and are weak PPAR γ agonists at high micromolar concentrations [75, 76].

The first PPAR β/δ -selective agonists (L-165041 and GW501516) were shown to augment HDL-C in diabetic mice as well as in obese rhesus monkeys, in which they decreased elevated levels of triglycerides and insulin [77, 78].

3. THE ROLE OF PPAR LIGANDS IN AFFECTING CELL PROLIFERATION AND DIFFERENTIATION

Although a direct control of PPAR transcription is limited to a very small number of growth-related genes (see Table 1), the ability of PPAR ligands to inhibit cell growth by inducing cell differentiation or apoptosis has long been demonstrated in several cell lines. In general, the PPAR α and the PPAR γ ligands display an inhibitory effect on cell growth, while PPAR β/δ have different effects, strictly dependent on the cell type. Indeed, in murine colorectal cells, the Apc- β -catenin tumour-suppressor pathway was shown to repress PPAR β/δ expression [79]. More recently it was suggested that ligand activation of PPAR β/δ induces expression of cyclooxygenase-2 (COX2), which could theoretically promote cell growth and inhibit apoptosis through mechanisms that involve the production of prostaglandins and/or inflammation-dependent signalling [80]. However, there are several observations that are inconsistent with the idea that ligands of PPAR β/δ potentiate cell growth. For example, inhibition of cell growth is observed in a variety of different cells and cell lines cultured in the presence of highly specific PPAR β/δ ligands including human colonocytes [81], a human lung adenocarcinoma cell line [82], mouse lung fibroblasts [83], rat cardiomyocytes [84], a human keratinocyte cell line [85], normal human keratinocytes [86], and mouse primary keratinocytes [87]. Some evidence about the effects of PPAR ligands on cell differentiation, cell cycle progression, and apoptosis induction is illustrated as follows.

3.1. Effect of PPAR ligands in differentiation induction

The first demonstration of PPAR γ involvement in adipocyte differentiation was given by Tontonoz et al. (1993) [6]. Subsequently, PPAR γ and PPAR α ligands have been demonstrated to induce differentiation alone or in association with other differentiation inducers. It has been demonstrated that clofibrate, a PPAR α ligand, increases the differentiation of HL-60 cells induced by retinoic acid and all-trans retinol [88]. Other PPAR α activators, including putative endogenous ligands such as fatty acids, induce differentiation and inhibit proliferation in keratinocytes [89]. The PPAR α ligand, ciprofibrate induces differentiation of HL-60 cells and its effect is potentiated by phorbol 12-myristate 13-acetate (TPA) [90]. Benzafibrate induces differentiation of HL-60, U937, and K562 cells [91]. PPAR γ ligands induce terminal differentiation of human liposarcoma cells “in vitro” and in patients suffering from advanced liposarcoma [92], and promote terminal differentiation of malignant breast epithelial cells “in vitro” [93]. Our research group demonstrated that both PPAR α (clofibrate and ciprofibrate) and PPAR γ ligands (troglitazone and 15d-PG J2) inhibit growth of HL-60 human leukemic cells and induced the onset of monocytic like differentiation [94]. In another leukemic cell line, U937

cells, PPAR γ ligands inhibited proliferation but did not induce differentiation (except the higher doses of 15d-PG J2 which induced a poor monocytic differentiation) [94] indicating that the differentiation induction by PPAR ligands is cell-type specific.

Several experimental results indicate that ligand activation of PPAR β/δ induces terminal differentiation of keratinocytes [86, 87, 95, 96] and it has also been shown that differentiation of breast and colon cancer cell lines is associated with increased expression of PPAR β/δ [97]. PPAR β/δ expression also increases following differentiation in human primary macrophages or in monocyte/macrophage cell lines [98]. In addition, activation of PPAR β/δ using a selective agonist promotes oligodendrocyte differentiation in a mouse cell culture [99].

3.2. Effect of PPAR ligands on cell cycle progression

Evidence has been demonstrated that PPAR ligands inhibit cell growth by acting on cell cycle progression. Fibrates, in a dose dependent-manner, significantly alter the cell cycle distribution, mainly leading to G0/G1 phase increase and a G2/M phase reduction in human leukemic cell lines [91]. In HL-60 human leukemic cells, both PPAR α and PPAR γ ligands increase the proportion of G0/G1 cells [100]. PPAR γ , ectopically expressed in nonprecursor fibroblastic cell lines, induces the conversion to adipocytes and induces the expression of p21 and p18, two cyclin/cyclin-dependent kinase (CDK) inhibitors [101]. Troglitazone arrests U937 cells in the G1 phase of the cell cycle [102] and inhibits cyclin D1 expression in MCF7 cells [103]. PPAR γ activation induces cell cycle withdrawal of preadipocytes via suppression of the transcriptional activity of E2F/DP DNA-binding complex [104]. E2F activity is regulated by the tumour suppressor retinoblastoma protein (pRb) that, when hypophosphorylated, binds and inactivates the E2F transcription factor [105]. Interestingly, PPAR γ ligands inhibit pRb phosphorylation in vascular smooth muscle cells [106–108], increasing the amount of hypophosphorylated pRb able to bind E2F. Others found that troglitazone inhibits the growth of six of nine pancreatic cancer cell lines, by inducing G1 phase cell cycle arrest through the up-regulation of the expression of p21 [109].

Ligand activation of PPAR β/δ with GW0742 prevents cell cycle progression from G1 to S phase and attenuates cell proliferation in N/TERT-1 keratinocyte cells [110].

3.3. Effect of PPAR ligands on apoptosis induction

Inhibition of cell proliferation by PPAR ligands is also supported by their effect on apoptosis induction. PPAR γ ligands seem to be more effective than PPAR α in inducing apoptosis, since its proapoptotic activity has been demonstrated in a wide variety of experimental cancer models [111]. PPAR γ ligands have been reported to reduce levels of FLICE-inhibitory protein (FLIP), and apoptosis-suppressing protein that blocks early events in TRAIL/TNF (Tumor necrosis factor-related apoptosis inducing ligand/Tumor necrosis factor) family death receptor signalling [112]. 15d-PG J2 and

TABLE 1

Genes containing PPRE putative sequences	Function of gene	Ref.
<i>Lipid metabolism</i>		
P450 4A6	Omega oxidation of fatty acids	[15]
malic enzyme gene	Fatty acid synthesis	[16]
apoA-I and apoA-II.	Components of HDL	[17]
LPL (lipoprotein lipase)	Hydrolysis of triglycerides	[18]
UCP3 (Uncoupling protein 3)	Fatty acid transport and thermogenesis	[19]
CEH (Cholesteryl ester hydrolase)	Hydrolysis of stored cholesterol esters in macrophage foam cells and release of free cholesterol for high-density lipoprotein-mediated efflux	[20]
Aox/ACO (Acyl-CoA oxidase)	Beta-oxidation in peroxisome	[21]
HD (enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase)	Beta oxidation in perixosome	[21]
ILK (Integrin-linked kinase)	Integrin-mediated signaling	[22]
HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A synthase and reductase)	Cholesterol biosynthesis	[23]
LRP (lipoprotein receptor-related protein)	Lipoprotein metabolism, neurological function, tissue remodelling, protease complex clearance, cell signal transduction	[24]
CPT1beta (human carnitine palmitoyltransferase 1beta)	Fatty acid mitochondrial beta-oxidation	[25]
FABP (fatty acid binding protein)	Lipid transport (solubilization of long-chain fatty acids)	[26]
ADRP (Adipose differentiation-related protein)	Maintenance of lipid stores in non-adipocytes	[27]
FIAP (The fasting-induced adipose factor)	Circulating lipoprotein lipase inhibitor secreted from adipose tissue	[28]
<i>Carbohydrate metabolism</i>		
betaGK (beta-cell-specific glucokinase)	Glucose-sensing apparatus in pancreatic beta-cells	[29]
GPDH (Glycerol 3-phosphate dehydrogenase)	NAD-dependent enzyme that catalyzes the oxidation of sn-glycerol 3-phosphate to dihydroxyacetone phosphate. It restores NAD+.	[30]
UGDH (UDP-glucose dehydrogenase)	Biosynthesis of complex carbohydrates and detoxification of toxic compounds in the liver	[31]
PDK (Pyruvate dehydrogenase kinase)	Modulation of pyruvate dehydrogenase complex activity	[32]
SHP (Small heterodimer partner)	Bile acid-dependent down regulation of gluconeogenic gene expression in liver	[33]
<i>Inflammation</i>		
Prm3 (thromboxane receptor (TP) beta promoter)	Thromboxane receptor (TP) beta transcription	[34]
IL-1ra (Interleukin-1 receptor antagonist)	IL-1 receptor signaling blockage	[35]

TABLE 1: Continued.

Genes containing PPRE putative sequences	Function of gene	Ref.
CD36 (scavenger receptor)	Scavenger receptor	[36]
sPLA2-IIA (Group IIA secretory phospholipase A2)	Proinflammatory effect	[37]
AhR (Aromatic hydrocarbon receptor)	Proinflammatory effect	[38]
<i>Growth factors and cell cycle regulators</i>		
SSAT (spermidine/spermine N1-acetyltransferase)	Polyamine catabolism	[39]
GOS2 (GO/G1 switch gene 2)	Cell cycle regulation	[40]
VEGF (Vascular endothelial growth factor)	Vasculogenesis	[41]
IGFBP-1 (Insulin-like growth factor-binding protein 1)	Binding protein of insulin-like growth factor (IGF)-I and IGF-II. Biomarker for metabolic and hyperproliferative diseases	[42]
<i>Detoxification and redox enzymes</i>		
CYP1A1 (Cytochrome P450 1A1)	Degradation of endobiotics and the bioactivation of numerous environmental procarcinogens	[43]
GST (glutathione S-transferase gene)	Antioxidant function	[44]
POX (Proline oxidase)	Redox enzyme	[45]
VDUP-1 (Vitamin D-upregulated protein-1)	Inhibition of thioredoxin-1 which plays a role in the regulation of cellular redox balance (Cellular redox balance)	[46]
<i>Others</i>		
BCM (Beta-carotene 15,15'-monooxygenase)	Vitamin A biosynthesis	[47]
I-BABP (Ileal bile acid-binding protein)	Enterohepatic circulation of bile acids	[48]
PCLN-1 (paracellin-1)	Tight-junction protein, exclusively, in the kidney	[49]
BACE1 (Beta-site amyloid precursor protein cleaving enzyme)	Central causal role in Alzheimer's disease	[50]
nephrin promoter	Nephrin synthesis	[51]
CIDEA (Cell death-inducing DNA fragmentation factor alpha-like effector A)	Proapoptotic protein	[52]
TFF2 (Trefoil factor family 2)	Defense and repair of gastric mucosa	[53]

troglitazone suppress DNA synthesis and induce apoptosis in a dose-dependent way in HT-29 colon cancer cells, whereas ligands for PPAR α and β/δ had no significant effect [113]. Troglitazone inhibited growth of liver cancer cells PLC/PRF/5, HepG2 and HuH-7, by inducing apoptosis through caspase-3 activation [114]. In breast cancer cells, both troglitazone and 15d-PG J2 induce apoptosis [115, 116]. Kondo et al. have shown that the 15d-PG J2-induced

accumulation of p53 results in the activation of a death-inducing caspase cascade mediated by Fas and the Fas ligand in neurons [117]. Activation of PPAR γ by troglitazone or 15d-PG J2 inhibits cell growth via apoptosis and blocks cell cycle in human colorectal cancer [118]. However, in some cell models, both PPAR α and PPAR γ displayed proapoptotic activity, as it has been demonstrated in the HL-60 cell line [100] and in the lymphoblastic leukaemia cell line [119]. In

keratinocytes [120], ovarian cancer cells [121] and in human hepatoma cell line SK-HEP-1 [122], PPAR α ligands have been reported to induce apoptosis.

Colon cancer cell lines cultured in the presence of the PPAR β/δ ligand GW501516 exhibit inhibited levels of apoptosis [123, 124]. It has been postulated that apoptosis is inhibited by PPAR β/δ -dependent downregulation of the tumour suppressor phosphatase and tensin homologue deleted on chromosome ten (PTEN) and upregulation of the 3-phosphoinositide-dependent kinase-1 (PDK1) and integrin-linked kinase-1 (ILK1) [22]. The net effect of this change in activity would have increased phosphorylation of protein kinase B (Akt) and inhibition of apoptosis; and these changes were shown in cultured primary keratinocytes [22]. In mouse keratinocytes, PPAR β/δ inhibits proliferation and promotes cell survival and migration [96, 125, 126]. In contrast with these data, prostacyclin (PGI₂) was shown to promote apoptosis in a kidney cell line, most probably through PPAR β/δ activation [127].

4. THE ROLE OF PPAR LIGANDS IN THE CONTROL OF GROWTH-RELATED GENE EXPRESSION

The effect of PPAR ligands in the expression of growth regulatory genes has been in part illustrated in the previous section. Results obtained until now do not allow the identification of a precise signalling pathway and the PPAR target genes that mediate the antiproliferative effects remain elusive, as genomic responses to PPAR γ activation in cancer cells are highly complicated [128]. PPAR γ ligands seem to be more effective than PPAR α ligands in inhibiting cell growth, thus the majority of data about the gene expression following treatment with PPAR ligands is obtained in PPAR γ ligand-treated cells. Recently, some evidence has been found for PPAR β/δ and its ligands in regulating gene expression. However, the number of growth-regulatory genes, affected by specific PPAR β/δ ligands, is limited and comprises growth-inducing genes such as COX2 [80], and Akt, via transcriptional upregulation of integrin linked kinase (ILK) and 3-phosphoinositide-dependent kinase-1 (PDK1) [22] and the decrease in the level of ERK phosphorylation [110].

Reported causal mechanisms for PPAR γ growth inhibitory effects include attenuated expression of protein phosphatase 2A and subsequent inhibition of E2F/DP DNA binding [129], the inhibition of cyclins D1 and E, inflammatory cytokines and transcription factors expression [130] and increased expression of an array of gene products linked to growth regulation and cell maturation [128]. Moreover, our and other research groups have demonstrated that the reduction of cell growth by PPAR ligands is accompanied by the downregulation of the c-myc gene in myeloid leukaemia cells [131] and in colon cancer cells [132, 133]. In the HL-60 cell line, both PPAR α (ciprofibrate and clofibrate) and PPAR γ (troglitazone and 15d-PG J2) ligands inhibit c-myc and cyclin D2 expressions [100]. In prostate cancer cells PPAR γ ligands omega-6 fatty acids and ciglitazone down-regulated (1-2-fold) beta-catenin and c-myc expression and the selective PPAR γ antagonist GW9662 abolished the effect of those ligands, demonstrating

a PPAR-dependent mechanism. 15-d PG J2 inhibits N-myc expression in neuroblastoma cells [134] while it does not decrease c-myc expression in vascular smooth muscle cells [135].

The major part of the genes of which expression is modulated by PPAR γ ligands does not contain PPRE putative sequences in their promoter regions. Besides downregulation of c-myc, c-mycb, and cyclin D2 genes, previously reported, an array of non-PPAR γ targets has been implicated in the antitumor activities of troglitazone and/or ciglitazone in several cell systems. These targets include intracellular Ca²⁺ stores [136], phosphorylating activation of extracellular signal-regulated kinases [137, 138], c-JunN-terminal protein kinase, and p38 [139], upregulation of early growth response-1 [140], the CDK inhibitors p27 [141] and p21 [142], the tumor suppressor protein p53 and the p53-responsive stress protein Gadd45 [135], and altered expression of B-cell leukemia/lymphoma 2 (Bcl-2) family members [139]. However, some of these targets appear to be cell-type specific due to differences in signalling pathways regulating cell growth and survival in different cell systems.

Recent findings demonstrate that part of the above mentioned growth-regulatory genes are affected by PPAR ligands, mostly by PPAR γ through a PPAR-independent mechanism. The most important evidence of PPAR-independent effects displayed by PPAR ligands is illustrated in Table 2.

5. THE PRODUCTS OF LIPID PEROXIDATION IN THE CONTROL OF GROWTH-RELATED GENE EXPRESSION

Reactive intermediates produced during oxidative stressful conditions cause the oxidation of polyunsaturated fatty acids such as arachidonic, linolenic, and linoleic acids of membrane lipid bilayers or low-density lipoprotein [156] leading eventually to the formation of several aldehydes. Among the products of oxidative breakdown of polyunsaturated fatty acid, 4-hydroxy-2,3-trans-alkenals have been proposed as ultimate messengers of lipid peroxidation-induced injury, because they can diffuse from the site where they are produced and can reach different intracellular and extracellular targets [157–159]. 4-hydroxynonenal (HNE), the aldehyde most represented in the 4-hydroxy-2,3-trans-alkenal class, has long been investigated, since, at concentrations near to those “physiologically” found in normal cells and plasma, it modulates cellular functions, gene expression and biochemical pathways, without cytotoxic effects [160]. For this reason, HNE has been proposed by several authors as an intracellular signalling mediator, rather than a toxic product of lipid peroxidation [159, 161]. Previous results demonstrated the antiproliferative and differentiative effects of HNE in leukemic cells [162, 163] and the antiproliferative and proapoptotic effects in a number of different cell models [164, 165]. Deeper investigations into HL-60 cells showed that the proliferation block occurred at the level of the G0/G1 stage of the cell cycle [163]. Further experiments showed that the HNE effects depend on the inhibition of the cyclin expression, and especially of cyclins D2, D1, and A [166]. The reduction of cyclin expression can result in a reduced

TABLE 2: PPAR-independent effects on tumor-related genes.

PPARs ligand	PPAR-independent effect	Experimental strategies	Ref.
<i>PPARγ ligands</i>			
Troglitazone in LNCaP prostate cancer cells	Androgen receptor (AR) suppression by facilitating the ubiquitin-dependent proteasomal degradation of the transcriptional factor Sp-1	STG28, a PPAR γ -inactive analogue of troglitazone.	[143]
Troglitazone in mice	Rapidly AMP-activated protein kinase (AMPK) activation through a yet undefined PPAR- γ -independent mechanism, leading to the suppression of insulin-like growth factor-I tumor-promoting activity (IGF-1)	Expression of a dominant-negative AMPK	[144]
Troglitazone and ciglitazone in MCF-7 breast cancer	Repression of cyclin D1 expression, though a post transcriptional mechanism, via proteasome-facilitated proteolysis	Proteasome inhibitors	[145]
Ciglitazone in HT1080 human fibrosarcoma	Increase of MMP-2 expression through ROS production and ERK activation	PPAR γ antagonist GW9662	[146]
Troglitazone and 15-deoxy-prostaglandin J2 (15dPGJ2) in prostate and bladder cancer cells	Troglitazone induces G0/G1 growth arrest and PGJ2 induces apoptosis	PPAR γ antagonist GW9662	[147]
Troglitazone in B cell acute lymphoblastic leukemia cell lines	Apoptosis and cell growth inhibition associated with G1 cell cycle arrest	PPAR antagonists	[148]
Thiazolidinediones (TZD) in human breast cancer	Inhibition of Cyclin D3 expression by decreasing cyclin mRNA levels and by inducing its proteasomal degradation	A dominant negative mutant of PPAR γ	[149]
Troglitazone in mouse skin keratinocytes	Inhibition of cyclin D1 expression	PPAR γ antagonist GW9662 and dominant negative PPAR γ .	[150]
Thiazolidinediones (TGZ) in human colon cancer cells HTC-116	Egr-1 promoter activity increase	Different PPAR γ ligands	[140]
15-deoxy-prostaglandin J2 (15dPGJ2) in colon carcinoma cells	COX2 and VEGF inhibition via AP-1 activity repression	Dominant negative form of PPAR γ and a PPAR γ antagonist	[151]
15-deoxy-prostaglandin J2 (15dPGJ2) induces apoptosis in human B lymphocytes	Apoptosis through the induction of ROS and depletion of glutathione	Dominant negative form of PPAR γ and a PPAR γ antagonist	[152]
15-deoxy-prostaglandin J2 (15dPGJ2) in Jurkat human leukemic cells and PC3 human prostate cancer cells	Apoptosis by increasing the mRNA stability of death Receptor 5 (DR5), a specific receptor for tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL)	PPAR γ antagonist GW9662	[153]
<i>PPARα ligands</i>			
DEHP in mice	Induction of hepatic tumorigenesis	Wild-type and PPAR α -null mice in comparison	[154]
WY14,643 in activated splenocytes isolated from C57BL/6 mice	Apoptosis	Wild-type and PPAR α -null mice in comparison	[155]
<i>PPARβ/δ ligands</i>			
GW0742 in PPAR β -null mouse model	Induction of keratinocyte terminal differentiation and inhibition of keratinocyte proliferation	PPAR δ -null mice	[86]

activity of cyclin/CDK complexes which principally regulate the phosphorylation of the pRb. In highly proliferating tumour cells, pRb is constantly in the hyperphosphorylated status. When hyperphosphorylated, pRb cannot bind to E2F transcription factors that can promote the G1/S cell cycle phase passage. After HNE treatment, pRb remains hypophosphorylated, and E2F remains bound to pRb [167]. HNE not only reduces the phosphorylation of pRb, but also decreases the amount of “free” E2F bound to the P2 c-myc promoter. These effects can explain the blocking of c-myc expression demonstrated in HNE-treated cells.

The hypophosphorylation of pRb proteins may depend on the inhibition of cyclin expression, however, this effect may also be related to the increase of the expression of p21, an inhibitor of the cyclin/CDK complexes, induced by HNE treatment [167]. Another effect of HNE, also important for cell multiplication, is that displayed on telomerase activity and hTERT expression. The activity of telomerase and the expression of its catalytic subunit hTERT, were inhibited by HNE in three different human leukemic cell lines, HL-60, U937 and ML-1 [168]. The binding studies of E-box in the hTERT promoter demonstrated that in HNE-treated HL-60 cells there is a decrease in Myc binding complexes and an increase in Mad-1 binding complexes which could contribute to the switch from c-Myc/Max to Mad1/Max with repressor activity of the transcription.

HNE is able to induce p53 expression in ML-1 cells, according to previous results demonstrating the induction of p53 expression by HNE in the SK-N-BE human neuroblastoma cell line [165]. Moreover, in SK-N-BE cells apoptosis was substantially increased even with 1 μ M HNE. At the same time, the expression of the p53 family members, p63 and p73, was strongly increased as well as the expression of the cyclin/CDK inhibitor p21 and the proapoptotic bax gene. Since p21 and bax are the two main targets for the transcription factor p53, these results indicate that HNE, by acting on p53 gene expression, can regulate the p53 target genes.

6. INTERACTION BETWEEN PPAR LIGANDS AND LIPOPEROXIDATION PRODUCTS

The relationship between oxidative stress-related molecules and PPAR activation has not yet been elucidated. Based upon their capacity to elicit cellular responses to a variety of stimuli, PPARs may represent a class of molecules which allow the biochemical adaptation to a diverse range of internal and external signals. These include oxidised LDL [169] and inflammatory agents as well as 15d-PG J2 [170] and leukotriene B4 [65]. However, other molecules generated during inflammation may be involved. In the cultured mesangial cells, PPAR γ is activated by various oxidative stress-related molecules such as TPA, TNF alpha, and H₂O₂ [171]. The physiological ligand of PPAR γ , 15d-PG J2, is a potential inducer of intracellular oxidative stress that mediates the cytotoxic effects in human neuroblastoma cells [172]. On the other hand, the activation of PPAR α leads to increased oxidative stress in liver cells [173]. On the basis of this link between oxidative stress and PPAR activation and

between oxidative stress and lipoperoxidation induction, our research group investigated, for the first time, the interaction between the major lipoperoxidation product, HNE, and PPAR activation in HL-60 and U937 human leukemic cells [94]. We demonstrated that HNE increases the monocytic differentiation induced by the PPAR α ligand ciprofibrate, and PPAR γ ligands, troglitazone and 15d-PG J2, in HL-60 cells. Whereas, neither PPAR α nor PPAR γ ligands induce U937 differentiation. Moreover, in this cell line, only PPAR γ ligands reduce cell growth. HNE also significantly inhibits cell growth when given alone, and strengthens the growth inhibitory effect of a low dose of PPAR γ ligands. HNE promotes at the same time a great increase in the expression of PPAR γ in both HL-60 and U937 cells, without any modification of the PPAR α expression. These results suggest a synergistic effect of HNE and PPAR γ ligands in blocking cell growth and in promoting the differentiation in HL-60 cells.

More recently, we analysed the effects of PPAR γ ligands (rosiglitazone and 15d-PG J2) and HNE, alone or in association, on proliferation, apoptosis, differentiation, and growth-related and apoptosis-related gene expressions in CaCo-2, colon cancer cells. Results obtained indicate that, in this cell line, PPAR γ ligands and HNE inhibited cell growth and induced differentiation or apoptosis by different signalling pathways. The common feature consisted of the inhibition of c-myc expression, whereas the apoptosis was induced by 15d-PG J2 and HNE and, to a minor extent, by rosiglitazone and the differentiation was induced by rosiglitazone and by 15d-PG J2, but not by HNE. Moreover, HNE induced p21 expression, while PPAR γ ligands did not. Bax expression was increased by HNE and 15d-PG J2, but not by rosiglitazone. HNE did not induce an increase of PPAR γ expression and did not display synergism or antagonism towards PPAR γ ligands.

These various results, obtained in different cell models, strongly demonstrate that the gene expression control exerted by PPAR ligands is dependent on the cell type examined.

An interaction between HNE and PPAR γ has also been demonstrated by Muzio et al. (2006) [174]. These authors found that arachidonic acid induces suppression of human lung tumor A549 cell growth, increases lipid peroxidation and decreases aldehyde dehydrogenase 3A1 ALDH3A1, which may determine an accumulation of endogenous HNE. These phenomena are associated with the increased expression of PPAR γ , suggesting a relationship between endogenous HNE levels and PPAR γ expression. Moreover, it has been postulated that HNE can represent an endogenous modulator of PPAR β/δ activity, since HNE is an endogenous ligand for PPAR β/δ and activates PPAR β/δ target genes [175]. This datum suggest that the binding between HNE and PPAR β/δ can modulate PPAR β/δ activity in all cell types, since PPAR β/δ is ubiquitously expressed.

The different interactions between HNE and PPAR are summarized in Figure 2.

These findings represent an intriguing suggestion about the role played by the lipoperoxidation products in controlling cellular PPAR-dependent responses, not only regarding cell proliferation control but also in the regulation of

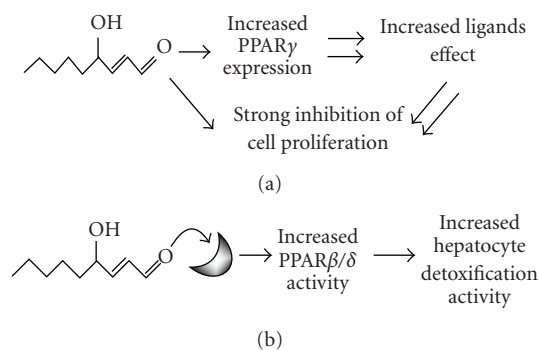


FIGURE 2: Different interactions between HNE and PPAR. (a) HNE increases PPAR γ expression in leukemic cell lines; (b) HNE binds and activates PPAR β/δ .

different metabolic pathways, and indicate that the interaction between oxidative stress products and PPAR activity represents a new research field in expansion.

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