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Review Article

PPAR GAMMA AGONISTS: AN EFFECTIVE STRATEGY FOR CANCER TREATMENT

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ABSTRACT
PPAR-γ regulates cellular differentiation, development and metabolism. They play these essential roles by functioning as transcription factors regulating the expression of genes. The PPARs mainly are of three types α, β and γ. The PPAR-γ expressed in three forms γ1, γ2 and γ3 present in different tissues. When PPAR binds its ligand, transcription of target gene is increased or decreased. Tzds were able to induce cell differentiation and apoptosis or inhibit cell proliferation both *in vitro* and *in vivo*. However, widespread use of thiazolidinediones (TZDs), the clinically used synthetic PPAR gamma agonists, has been limited by adverse effects. So in this review we are suggesting some new molecules other than thiazolidine diones which can act as potential anticancer agents, after explaining the mechanism of action of PPAR-γ agonists as anticancer agents especially thiazolidinediones.
Keywords: PPAR-γ, thiazolidinediones, anticancer effect, other agonists.

INTRODUCTION

Thiazolidinediones (TZDs) are a class of antidiabetic drugs which include pioglitazone, rosiglitazone, ciglitazone and troglitazone, although some of them were removed from the market because of hepatoxicity, weight gain, fluid retention, tumorigenisis of bladder and some other side effects. But many studies have been conducted so far to prove the efficacy of thiazolidinediones as anticancer agents. Thiazolidinediones act through PPARS. PPAR-γ has been reported to act both as a promoter and suppressor of neoplasia, and the role of PPARgamma activating ligands as well as antagonists in therapy remains controversial. Due to ligand binding, PPARs dimerize with retinoid X receptor (RXR). This is required for binding to specific DNA sequences, known as PPAR response elements (PPRE), in the promoter region of target genes. Upon binding to their ligands, PPARs undergo conformational changes allowing release of co-repressors, and recruitment of co activators; followed by the activation of transcription[1]. The role of PPAR-γ in tumor cells has been extensively investigated. Treatment with PPAR-γ agonists exerts biological effects such as control of cell growth, motility, differentiation and apoptosis. Some of the newly invented molecules especially plant derived ones may surpass the side effects shown by glitazones if they develop as new lead molecules for anticancer treatment in future.

PPAR Dependent Anticancer Actions of Thiazolidine Diones

Inhibition of cell growth and differentiation or apoptosis of malignant cells

TZD treatment activates PPAR-γ, stimulating heterodimerization with the retinoid X receptor, recruitment of co activators, and the dissociation of co repressors resulting in[2].

Cell Cycle Arrest

It is due to decreased protein levels of activated cyclins that regulate progress through the cell cycle. These include: cyclin D1 (Cd1), Cyclin E and Cd2. CDK inhibitors block progression of the cell cycle by inactivating the formation of cyclin–CDK complexes, which are crucial for phosphorylation. TZDs increase the cyclin-dependent kinase inhibitors p18, p21 and p27 that can inhibit CDK2/4 and CDK2 respectively, ultimately causing cell cycle arrest. The expression of p21 and p27 increase in the cancer cells exposed to PPARγ ligands, perhaps by inhibition of the ubiquitin-proteosome protein degradation pathway[3].

Apoptosis

Apoptotic action is by decreasing anti-apoptotic proteins such as bcl-2(B-cell leukemia/lymphoma 2)/bcl-x through the activation of capase 3, while increasing the levels of the pro-apoptotic proteins, p53, BAD(Bcl-2-associated death promoter) and phosphatase and tensin homolog (PTEN)[2, 3]. Troglitazone and ciglitazone might inhibit the antiapoptotic function of Bcl-xL/Bcl-2 by blocking BH3 (interacting domain death agonist) domain-mediated heterodimerization with pro-apoptotic Bcl-2 members[4].

Differentiation

The combination of the RXR agonist, bexarotene, with the PPAR-γ agonist, rosiglitazone, in colon cancer cells caused increased expression of the differentiation marker, CEA (carcinoembryonic antigen), while also decreasing cyclooxygenase-2 (COX-2) expression and prostaglandin-E_2 (PGE_2) synthesis. In HT-29 colorectal cancer cells, TZD treatment inhibited growth and metastasis through differentiation-promoting effects.[4,5]

By Reducing IR (Insulin Receptor Gene) Transcription

Various studies have shown that IRs (insulin receptors) is increased in most human breast cancers. Over expression of functional IRs has also been involved in thyroid carcinogenesis. The IR can exert its oncogenic potential in malignant cells via abnormal stimulation of multiple cellular signalling cascades, enhancing growth factor-dependent proliferation. IR gene transcription and receptor protein content were reduced in cells with forced PPARγ over expression, or TZD-induced PPARγ activation. In this regard,

the IR may be considered a new target gene that accounts for the anti-mitogenic response to PPARγ and its agonists. By binding to sequence-specific sites located in the C2 regulatory region of the IR gene, the architectural factor high-mobility group A1 (HMGA1), the ubiquitously expressed transcription factor (Sp1), and the CCAAT enhancer-binding protein (C/EBPβ) exert a positive control over the rates of transcription. The PPARγ can displace Sp1 and C/EBPβ from their binding sites, decreasing the rate of transcription.[5,6]

PPAR Gamma Independent Effect

Inhibition of CDK and Activation of P27 and P21

Ablation of cyclin D1 in breast cancer cells by TZDs was a PPAR gamma independent effect and was mediated by a proteasome-mediated proteolysis. The effect of ciglitazone on the gene transcription of p27 was independent of PPARγ and probably mediated by the specificity protein 1-binding element in the p27 promoter. In pancreatic cancer cells where troglitazone induced the activation of the p21 promoter by GC-rich sites in the proximal region of the p21promoter.[7]

Suppressing Telomerase Activity Independently

Troglitazone reduced the mRNA expression of hTERT (human telomerase reverse transcriptase) and telomerase activity in the MDA-MB-231 breast cancer cell line even in the absence of PPARγ. It was found that there is no correlation between PPARgamma and hTERT mRNA transcript levels in breast cancer patients.[8]

Inhibition of Cell Metastasis

Thiazolidinediones have an inhibitory effect on adhesion to extracellular matrix and invasiveness of cancer cells. TZDs affect gelatinolitic and fibrinolitic activity with a mechanism independent of PPAR gamma activation and there by inhibit pancreatic cancer cell invasiveness. They cause a significant inhibition of MMP-2(matrix metallopeptidase 2) gene expression, down regulation of MMP-9 expression and inhibit the production of MMP-7 in both PPAR gamma expressing and nonexpressing cell cultures[7]. Inhibition of fibrinolsis is due to a PPAR gamma independent up regulation of plasminogen activator inhibitor-1 (PAI-1).

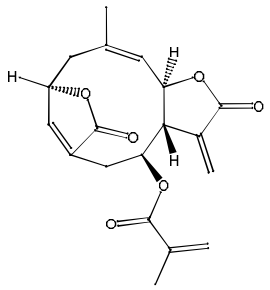
Decreasing Prostaglandin E2

Lung cancer cells elaborate prostaglandin E2 (PGE2). PGE2 is well-known to play an important role in tumorigenesis because of its immunosuppressive and antiapoptotic mediator activity. TZDs inhibited PGE2 production in NSCLC (non–small-cell lung cancer cells) via a COX-2 independent pathway. Thiazolidinediones induces 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme that produces biologically inactive 15-ketoprostaglandins from active PGE2. Thiazolidinediones here enhances catabolism rather than inhibiting the synthesis via PPAR gamma independent effect.[9]

Other Mechanisms

Thiazolidinediones mediate suppression of angiogenesis through VEGF (vascular endothelial growth factor) via VEGF promoter regulation. They scavenge toxic reactive oxygen species (ROS) independently of PPAR-γ mechanisms. Thiozolidinediones causes induction of cellular acidosis through inhibition of the Na^+/H^+ exchanger and release apoptotic factors from the mitochondria. They degrade FLIP (FADD-like IL-l-converting enzyme (FLICE)-inhibitory protein). FLIP inhibits apoptosis induced by tumor necrosis factor (TNF) family death receptor by blocking caspase 8 activation. TZDs mediate the effects on proteasome-mediated degradation of FLIP and down-regulation of PSA (prostate specific antigen) expression.[2,4]

PPAR Gamma Agonists Other Than Thiazolidinediones



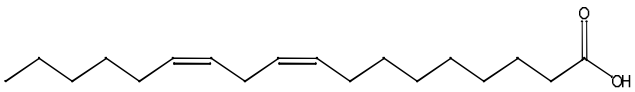
(3S,4R,8R,9Z,12R)-10-methyl-5-methylidene-6,14-dioxo-7,13-dioxatricyclo[10.2.1.0{4,8}]pentadeca-1(15),9-dien-3-yl 2-methylprop-2-enoate

Deoxyelephantopin (ESD)

Deoxyelephantopin (ESD) is a sesquiterpene lactone isolated from *Elephantopus carolinianus* wild plant. This molecule was proved as an anticancer agent due to its actions such as potentiating apoptosis, inhibition of invasion and abolition of osteoclastogenesis.

ESD was proved to be a partial agonist of PPAR-γ by methods such as SPR (surface plasma resonance), transactivation assays, Molecular docking studies and Site directed mutagenesis.[10]

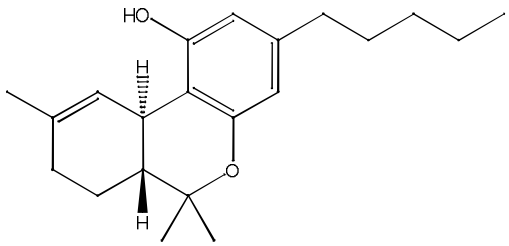
Conjugated Linoleic Acid



linoleic acid

Conjugated linoleic acid (CLA) refers to a group of positional and geometric isomers of the omega-6 essential fatty acid linoleic acid (cis-9, cis-12, octadecadienoic acid). CLA-induces lipid peroxidation and apoptosis *in vitro*.[11] It can activate PPAR gamma in rat adipocytes explaining CLA's anti diabetic effects in Zucker fatty rats. It is thus reasonable to suspect that a portion of CLA's broad spectrum anticarcinogenic activity is mediated by PPAR gamma activation in susceptible tumors.[12]

Cannabinoids

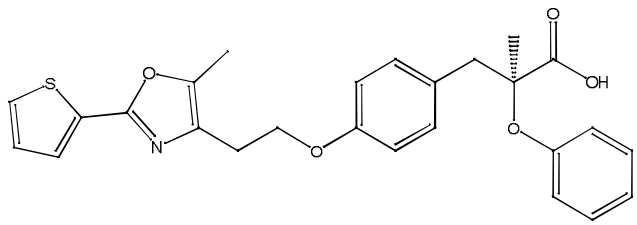


(-)-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol

Cannabinoids are a group of terpenophenolic compounds present in Cannabis (*Cannabis sativa*). Cannabinoids increased the activity and intracellular level of

PPARγ mRNA and protein in an indirect way. Cannabinoids cause endoplasmic reticulum stress and increase of the pseudokinase protein TRIB3 (tribbles homolog 3), which links ER stress to autophagy in its' anti tumoral action. When TRIB3 is genetically inhibited, it dramatically decreases the expression of both PPARγ mRNA and protein. Pharmacological inhibition of PPARγ decreased the cannabinoid-induced cell death and apoptosis. Cannabinoids induces autophagy in cancer cell lines. When PPARγ is absent, autophagy is blocked.[13]

Alpha-Aryloxy-Alpha-Methyl hydrocinnamic acid Derivatives



(s)-2-methyl-3-{4-(2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl) ethoxy)phenyl}-2-phenoxypropionic acid

The above compound is a dual peroxisome proliferators'-activated receptor alpha/gamma agonists. They inhibited cell viability, induces cell cycle arrest and apoptosis.[14]

CONCLUSION

To date, a number of important signaling mechanisms have been identified to underlie TZD-mediated antitumor activities. They are inhibition of Bcl-2/Bcl-xL function and repression of the expression of cyclin D1and FLIP. So thiazolidinediones can act as anticancer agents, but their use has been limited due to their side effects. Even balaglitazone the new chemical entity from the glitazone family is almost dead. But the wide variety of actions of PPARγ as anticancer targets should be exploited to develop new chemical entities. So that new compounds which can act only through the blissful aspect of this target should be developed in future.

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