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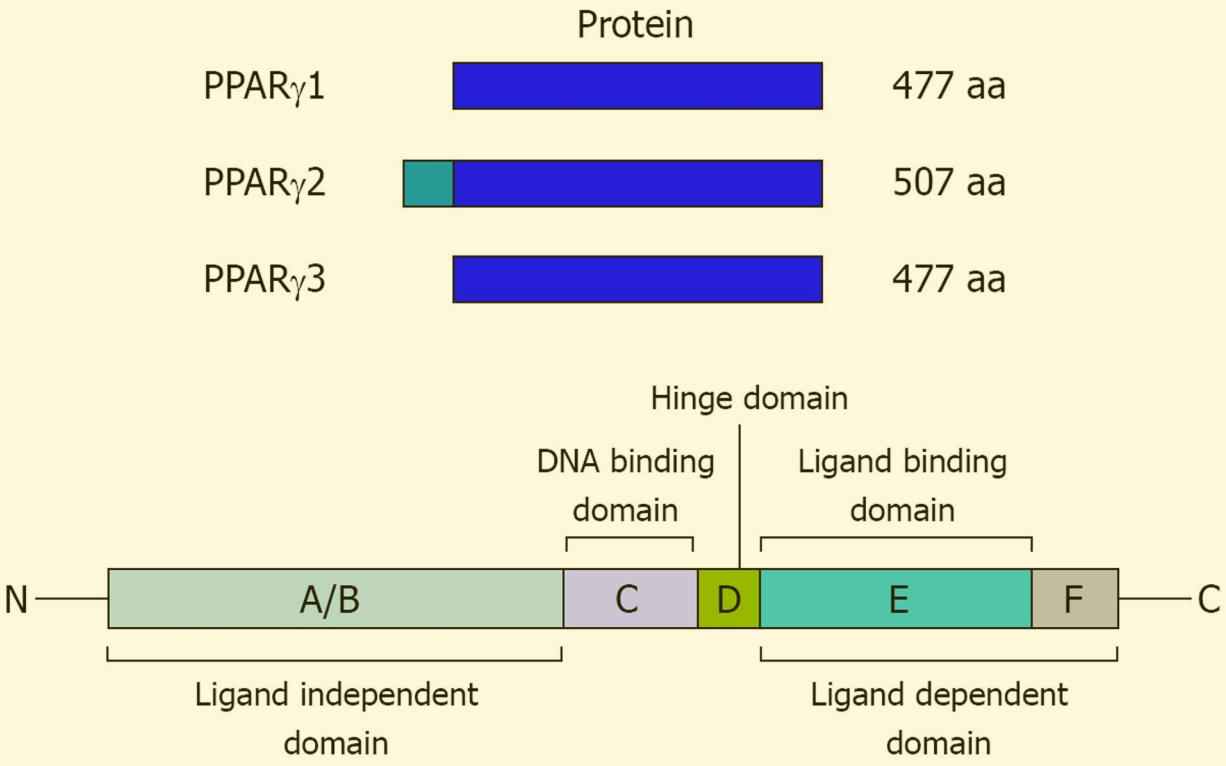

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Contents

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EDITORIAL

Anticancer actions of PPARγ ligands: Current state and future perspectives in human lung cancer

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent nuclear transcription factors and members of the nuclear receptor superfamily. Of the three PPARs identified to date (PPARγ, PPARβ/δ, and PPARα), PPARγ has been studied the most, in part because of the availability of PPARγ agonists (also known as PPARγ ligands) and its significant effects on the management of several human diseases including type 2 diabetes, metabolic syndrome, cardiovascular disease and cancers. PPARγ is expressed in many tumors including lung cancer, and its function has been linked to the process of lung cancer development, progression and metastasis. Studies performed in gynogenic and xenograft models of lung cancer showed decreased tumor growth and metastasis in animals treated with PPARγ ligands. Furthermore, data are emerging from retrospective clinical studies that suggest a protective role for PPARγ ligands on the incidence of lung cancer. This review summarizes the research being conducted in this area and focuses on the mechanisms and potential therapeutic effects of PPARγ ligands as a novel anti-lung cancer treatment strategy.

Key words: Gene expression and regulation; Human lung cancer; Ligands; Peroxisome proliferator-activated receptor γ; Signaling pathways; Therapy

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INTRODUCTION

Lung carcinoma is the most common malignant tumor in the world, and is the leading cause of carcinoma death in the United States[1]. This malignancy causes more deaths than the next three most common cancers combined (colon, breast and prostate). The expected 5-year survival rate for all patients in whom lung cancer is diagnosed is less than 13% compared to 65% for colon, 89% for breast, and 99% for prostate cancer although incremental and significant advances in available systemic treatments have taken place in the last decade to improve survival rates and to provide better palliation for patients with non-small-cell (NSCLC) and small-cell lung carcinoma (SCLC). Cigarette smoking is strongly correlated with the onset of lung cancer and effective tobacco con-

trol efforts have resulted in substantial declines in tobacco use and tobacco-related cancer deaths in the United States[2]. Clinical approaches such as chemo- and radiotherapies have shown only a modest improvement in survival of patients with advanced NSCLC and limited-stage SCLC. However, agents targeting specific kinases and growth factor receptors show promise. For example, Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, and bevacizumab, a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor A are currently used in medical practice and have resulted in improved survival[3]. Unfortunately, targeted therapies which are initially effective in certain small subpopulations of patients, eventually fail to control the tumor. More recently, genomic and proteomic studies have unveiled a means for the molecular profiling of tumor tissue from patients with NSCLC, and could allow tailoring of therapy. Although there are still significant challenges to implementing genomic and proteomic testing in clinical practice, the rapid development of newer technologies provides hope for overcoming these barriers[4]. The limitations in efficacy and safety associated with available treatments for lung cancer especially NSCLC underscore the need for novel agents with improved efficacy and safety profiles. Therefore, understanding and searching for novel molecular mechanisms responsible for lung cancer initiation and proliferation are needed to identify new targets for therapy.

Since their discovery in 1990, peroxisome proliferator-activated receptors (also known as PPARs) have emerged as potential targets for anti-cancer therapies. Although originally cloned in an attempt to identify the molecular mediators of peroxisome proliferation in the liver of rodents, PPARs are now recognized as versatile members of the ligand-activated nuclear hormone receptor superfamily of transcription factors that includes receptors for steroids, thyroid hormone, retinoic acid, and vitamin D, among others[5]. PPARs are considered to play key roles in diverse physiological processes ranging from lipid metabolism to inflammation, and have been implicated in diseases such as cancer, atherosclerosis, and diabetes[5,6]. Although information about the function of PPARs in lung is scarce, data implicating these molecules in key processes in lung biology are rapidly emerging.

Three subtypes of PPARs have been identified and cloned: PPARα, PPARβ/δ, and PPARγ. These subtypes are distinguished by their tissue distribution, and to a lesser degree, by their ligand specificity. PPARα has been implicated in hepatocellular carcinoma in rodents, whereas activation of PAPRβ/δ promotes human lung carcinoma cell proliferation through phosphatidylinositol 3-kinase/Akt activation[7-9]. Of the three PPARs identified to date, PPARγ represents the most promising target in view of the many reports implicating this molecule in lung carcinoma cell growth. As a tumor growth modifier, PPARγ is involved in the regulation of cancer cell apoptosis, proliferation, and differentiation, and through its actions on the tumor cell environment, it affects angiogenesis, inflammation, and immune cell functions[10]. Hence, many studies are underway to test the impact of targeting this receptor for therapeutic purposes. This review focuses on PPARγ, its role in lung carcinogenesis, and the potential therapeutic role of PPARγ agonists in lung cancer.

FUNCTION OF PPARγ

PPARγ was discovered based on its similarity to PPARα. By utilizing three different promoters, a single PPARγ gene encodes three isoforms namely PPARγ1, PPARγ2 and PPARγ3[11]. Analysis of PPARγ1 and γ3 transcripts revealed that they both translate into the same PPARγ1 protein[12]. PPARγ2 protein contains an additional 30 amino acids at its N-terminus compared to PPARγ1 (Figure 1A). Like all nuclear receptors, PPARγ shares a similar structure with functional domains called A/B (ligand-independent domain), C (DNA binding domain), D (hinge domain) and E-F (ligand binding domain) (Figure 1B). PPARγ is highly expressed in adipose tissue and it is a master regulator of adipocyte differentiation[13,14]. In addition to its role in adipogenesis, PPARγ serves as an important transcriptional regulator of glucose and lipid metabolism, and it has been implicated in the regulation of insulin sensitivity, atherosclerosis, and inflammation[15,16]. PPARγ is also expressed in multiple tissues such as breast, colon, lung, ovary, prostate, and thyroid where it was demonstrated to regulate cellular proliferation, differentiation, and apoptosis[17,18]. Several leukocyte populations, including monocytes/macrophages, lymphocytes, and dendritic cells, have also been shown to express PPARγ suggesting a role for this molecule in the regulation of immune responses[19]. In that regard, PPARγ appears to be a negative regulator of macrophage function since its activation suppresses the production of inflammatory cytokines, chemokines, metalloproteases, and nitric oxide[20,21]. These PPARγ-mediated anti-inflammatory effects are not restricted to monocytes, as treatment with PPARγ agonists results in the inhibition of cytokine/chemokine production in several epithelial and stromal cells[22].

Several natural and synthetic compounds have been identified as activators of PPARγ. The insulin sensitizing anti-diabetic drugs known as *thiazolidinediones* (TZDs) were the first compounds identified as PPARγ agonists[23]. The TZDs, rosiglitazone and pioglitazone, are currently in clinical use for the treatment of type-II diabetes, while troglitazone was withdrawn from clinical use because it was linked to idiosyncratic liver toxicity[24]. Other non-TZD synthetic ligands include certain non-steroidal anti-inflammatory drugs such as isoxzolidinedione JTT-501[25], tyrosine-based GW7845[26] and DH9, a newly synthesized PPARγ agonist[27]. Naturally occurring compounds that activate PPARγ include long chain polyunsaturated fatty acids which are found in fish oil (e.g. n-3-PUFA, n-6-PUFA), eicosanoids

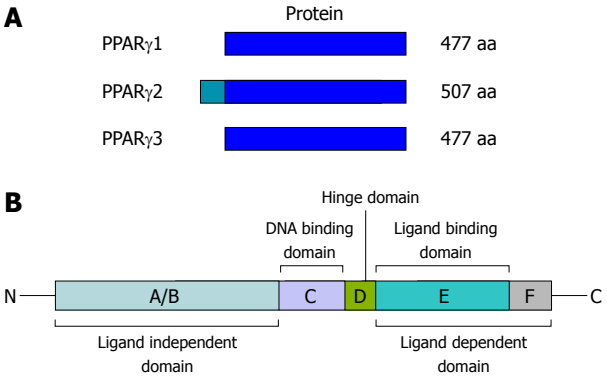

Figure 1 Structure of human peroxisome proliferator-activated receptor (PPAR)γ protein isoforms and domains. A: AR proteins. The three subtypes of mRNAs give rise to two different PPARγ proteins. Transcription of the PPARγ1 and 3 promoters result in the same protein of 477 amino acids (aa). The PPARγ2 protein of 507 amino acids is produced by transcription from the promoter γ2 area; B: main structure of PPARγ. PPARs contain the following functional regions: an N-terminal A/B domain (ligand-independent domain), a C-domain (DNA-binding domain), a D-domain (hinge domain), and a C-terminal domain (E-F ligand-dependent domain).

[e.g. 15-deoxy-$\Delta^{12,14}$ prostaglandin J_2 (15d-PGJ_2)], lipid hydroperoxides [e.g. 9(s)-HODE and 13(s)-HODE], as well as 15d-PGJ_2 and 12/15 lipoxygenase products 15-hydroxyeicosatetraenoic acid (15-HETE) and 13-hydroxyoctadecadienoic acid (13-HETE)[28-30]. Compounds from several medicinal plants such as Saurufuran A from *Saururus chinesis*[31], flavonoids such as chrysin and kampferol[32], phenolic compounds from *Glycyrrhiza uralensis*[33], and curcumin from *Curcumin longa*[34,35] have also been shown to activate PPARγ. Recently, several new compounds such as (S)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-2-yl-propionic acid (17j), a new series of 2-aryloxy-3-phenyl-propanoic acids and *aleglitazar* were identified as potent human PPARα/γ dual agonists with demonstrated oral bioavailability and certain encouraging responses[36-38].

The synthetic ligands described above and some natural ligands have been used to elucidate the role of PPARγ in cellular functions both *in vitro* and *in vivo*. However, several caveats should be taken into consideration when interpreting such studies. First, the natural ligands that regulate PPARs *in vivo* have not been completely elucidated. Second, not all PPARγ ligands exert their effects through PPARγ since there is strong evidence for the activation of PPARγ independent signals, particularly with the natural ligand 15d-PGJ_2, among others[39-41]. Third, high affinity ligands for PPARγ (e.g. the TZDs) may exert partial agonist/antagonist activity[42]. The latter might be due to the fact that individual TZDs induce different PPARγ conformations that influence the recruitment of different coactivator/corepressor molecules. Thus, the activity of the PPARγ transcriptional complex is influenced by the context of a given gene and its promoter, and by the relative availability of pertinent coactivator/corepressor molecules in the cell or tissue of interest.

PPARγ AND PPARγ LIGANDS IN LUNG CANCER

Among the three PPAR subtypes, the role of PPARγ has been investigated the most in lung cancer occurrence, progression and therapy. PPARγ is expressed in many cancers including colon, breast, and prostate, and with few exceptions, PPARγ ligands are antiproliferative in these tumor cells. Similarly, PPARγ is expressed in both SCLC and non-SCLC (NSCLC)[43]. NSCLC accounts for 80% of malignant lung cancer and SCLC constitutes the remainder[44]. Based on the cellular phenotype, NSCLC is further subdivided into squamous cell carcinoma, adenocarcinoma, and large cell carcinomas[45]. SCLC tumors grow rapidly, and are more likely to metastasize earlier than NSCLC. PPARγ ligands induce growth arrest and promote changes associated with differentiation as well as apoptosis in a variety of lung carcinoma cell lines, although most of the knowledge available in this area has been generated in NSCLC[46,47]. One recent animal study demonstrated a reduction of endogenous PPARγ ligands coinciding with increased PPARα before the formation of lung tumors induced by treatment with 4-(methylnitrosamino)-l-(3-pyridyl)-lbutanone (NNK)[48]. These results suggest that increased PPARγ activity by its ligands and inhibition of PPARα could prevent the formation of lung tumors and/or enhance the effectiveness of therapy against lung cancer[48]. This study also suggests the possibility of using endogenous PPARγ ligands such as 13-HETE and 15-HETE as tumor markers for lung cancer.

The exact mechanisms linking modulation of PPARγ to cancer growth inhibition remain unclear, but include effects on transcription factors and gene expression, among others. In addition, current evidence suggests that PPARγ ligands affect the intracellular machinery involved in cell signaling and cell cycle control, the suppression of mitogenic factors and tumor promoters, the induction of tumor suppressors, the prevention of tumor cell recognition of extracellular mitogenic signals, the break down of nicotine and nicotinic acetylcholine receptor-induced cell survival, and the expression of angiogenic factors needed for the development of the vascular networks that supply tumor cells (Figure 2)[49]. These mechanisms are discussed below as they relate to the actions of PPARγ ligands in lung cancer.

PPARγ ligands, cell cycle progression and apoptotic-signaling pathways

Several studies demonstrate that PPARγ ligands affect apoptosis and cell cycle control in lung cancer cells. For example, PPARγ ligands have been found to inhibit the growth of A549 adenocarcinoma cells due to G0/G1 cell cycle arrest through the upregulation of mitogen-activated protein kinases extracellular signal-regulated kinases 1 and 2 (ERK1/2) and the downregulation of G1 cyclins D and E[22]. Troglitazone inhibits NSCLC proliferation in

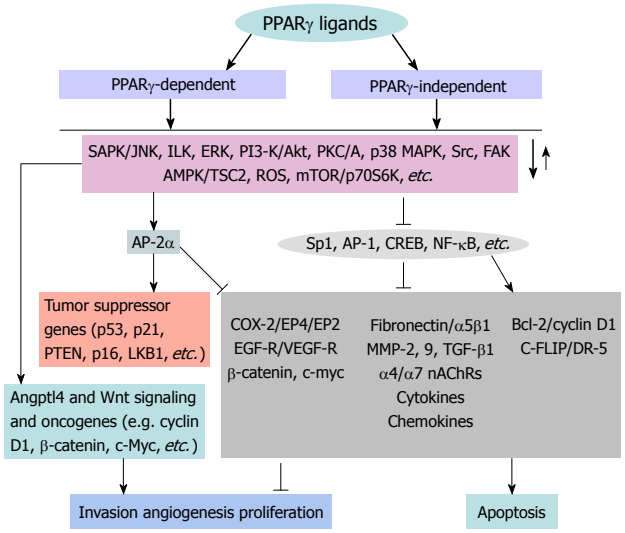

Figure 2 Anti-lung cancer actions of PPARγ ligands. Through PPARγ-dependent and -independent signals, PPARγ ligands activate or inactivate (mostly) kinase signaling pathways [e.g. stress-activated protein kinase/c-Jun NH2-terminal kinase (SAPK/JNK), integrin-linked kinase (ILK), phosphatidylinositol 3-kinase (PI3-K)/Akt/GSK-3β, extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38MAPK, Src, FAK, and AMP-activated protein kinase (AMPK)/tuberous sclerosis complex 2 (TSC2)/mammalian target of rapamycin (mTOR)/p70S6K]. This results in the regulation of multiple depicted downstream effectors including expression of growth factors, tumor promoters, cytokines, chemokines, cell cycle control genes, nicotinic acetylcholine receptors, apoptotic genes, expression of tumor suppressor gene through inhibition or induction of transcription factors [e.g. Sp1, AP-1, AP-2, nuclear factor-κB (NF-κB), CRE, *etc.*]. These effects contribute to the inhibition of cell growth and induction of apoptosis in human lung cancer cells. Note that PPARγ signaling has also been associated with tumor promoter activity in some cancer cells such as colon and breast, and this was linked to increased β-catenin, c-Myc, cyclin D1, vascular endothelial growth factor (VEGF), Angptl4 and Wnt 5 expression. COX: Cyclooxygenase; TGF: Transforming growth factor; DR-5: Death receptor 5; MMP: Matrix metalloproteinase; C-FLIP: Cellular FLICE inhibitory protein.

part by stimulating the expression of the GADD 153 (for *growth arrest and DNA damage inducible gene-153*)[50]. Also, troglitazone was found to induce apoptosis in NCI-H23 cells *via* a mitochondrial pathway through the activation of ERK1/2[51]. Others have shown similar results using CRL-202 cells, and further demonstrated that troglitazone downregulated the expression of the anti-apoptotic molecules Bcl-w and Bcl-2 as well as decreased the activity of stress-activated protein kinase (SAPK)/c-Jun NH2-terminal kinase (JNK)[52]. PPARγ ligands also induce the expression of death receptor 5 (DR5) and increase DR5 distribution at the cell surface in addition to reducing cellular FLICE-like inhibitory protein levels in human lung cancer cells. These agents cooperated with tumor necrosis factor-related apoptosis-inducing ligand to enhance apoptosis in human lung carcinoma cells[53]. One report found that PPARγ ligands 1-[(trans-methylimino-N-oxy)-6-(2-morpholinoethoxy)-3-phenyl-(1H-indene-2-carboxylic acid ethyl ester (KR-62980)] and rosiglitazone induce NSCLC apoptotic cell death mainly through PPARγ-dependent reactive oxygen species formation *via* increased expression of proline oxidase, a redox enzyme expressed in mitochondria[46].

PPARγ ligands and kinase signaling pathways

Reports implicate alterations in the mammalian target of rapamycin (mTOR) signaling pathway in the anti-tumor effects of PPARγ ligands. Rosiglitazone, for example, was reported to reduce the phosphorylation of Akt, an upstream positive modulator of mTOR, and increase phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a negative modulator of mTOR, in NSCLC H1792 and H1838 cells; this resulted in inhibition of cell proliferation[54]. Although the effects of rosiglitazone on Akt and PTEN were blocked by the selective PPARγ antagonist GW9662 and restored by transient overexpression of PPARγ, cell growth was not entirely restored suggesting the involvement of additional PPARγ-independent mechanisms of action. Further work revealed that rosiglitazone increased the phosphorylation of AMP-activated protein kinase α, a target of LKB1, and tuberous sclerosis complex 2 (TSC2), another potential tumor suppressor and upstream downregulator of mTOR. The latter pathway was independent of PPARγ since GW9662 and PPARγ siRNA did not affect it[54,55]; others have shown similar increases in PTEN expression induced by rosiglitazone[56].

One recent study showed that troglitazone may bind directly to EGFR, inhibit its signaling, and stimulate its internalization independent of PPARγ in several cells including lung cancer cells[41]. In that work, inhibition of EGF-induced Akt phosphorylation most likely accounted for the growth arrest of lung cancer cells treated with troglitazone[41].

Tumor suppressor genes are also affected by PPARγ ligands. For example, PGJ_2 and ciglitazone stimulated the expression of p21 mRNA and protein expression in NSCLC, and this coincided with a reduction in cyclin D1 mRNA expression[57]. Of note, p21 antisense oligonucleotides significantly blocked lung carcinoma cell growth inhibition observed with PPARγ ligands thereby establishing an important role for p21 in this process. These findings are consistent with those of others showing that the proliferation of A549 cells injected subcutaneously into nude mice was inhibited significantly by treatment with ciglitazone, and this coincided with increased expression of PPARγ and p21, and with downregulation of cyclin D1[58]. A connection between another tumor suppressor gene, p53, and PPARγ ligands has also been demonstrated by showing that 15-deoxy-PGJ_2, together with docetaxel, stimulates apoptosis in NSCLC through inhibition of Bcl-2 and cyclin D1, and overexpression of caspases and p53[47].

More recently, we reported that rosiglitazone and dietary compounds such as fish oil (which contain certain kinds of fatty acids such as ω3 and ω6 polyunsaturated fatty acids known to work as PPARγ ligands) inhibit integrin-linked kinase (ILK) expression through PPARγ signaling and the recruitment of a PPARγ co-activator, PGC-1α[59]. ILK is a unique intracellular adaptor and kinase that links cell-adhesion receptors, integrins, and growth factors to the actin cytoskeleton and to a range

of signaling pathways that are implicated in the regulation of anchorage-dependent tumor cell growth/survival, cell cycle progression, invasion and migration, and tumor angiogenesis[60]. This effect was associated with activation of p38 MAPK followed by induction of the transcription factor AP-2α and, ultimately, inhibition of NSCLC cell proliferation[59]. Docosahexaenoic acid, a component of ω3 polyunsaturated fatty acid, is reported to inhibit the growth of lung cancer cells mainly through the induction of pro-apoptotic signaling pathways such as ERK1/2 and p38 MAPK suggesting its chemopreventive effect in lung cancer[61].

PPARγ ligands and cyclooxygenase-2-related pathways

PPARγ ligands also exert anti-tumor effects by blocking access to mitogenic agents such as prostaglandin E2 (PGE_2), a major cyclooxygenase (COX) metabolite that plays important roles in tumor biology. The functions of PGE_2 are mediated through one or more of its receptors EP1, EP2, EP3, and EP4[62]. Human NSCLC cell lines express EP2 receptors, among other EP receptors, and the inhibition of cell growth by PPARγ ligands like GW1929, PGJ_2, ciglitazone, troglitazone, and rosiglitazone, is associated with a significant decrease in EP2 mRNA and protein expression. Notably, the inhibitory effects of rosiglitazone and ciglitazone, but not PGJ_2, were reversed by a specific PPARγ antagonist GW9662, suggesting the involvement of PPARγ-dependent and -independent mechanisms[62]. Also, ciglitazone suppressed COX-2 mRNA expression and COX-2 promoter activity, while upregulating peroxisome proliferator response element promoter activity in NSCLC cells further suggesting a negative modulator role for PPARγ ligands on the COX-2/PGE_2 pathway in NSCLC[63]. Of note, *in vitro* studies and xenograft models have demonstrated that elevated COX-2 expression is critical for promoting lung tumorigenesis, and that the anti-tumorigenic effects of PPARγ ligands are mediated through suppression of COX-2 *via* increased activity of PTEN, decreased levels of phospho-Akt, and inhibition of nuclear factor-κB (NF-κB) activity[64].

PPARγ and tobacco-related cancer progression

Tobacco is the most common etiologic agent in lung cancer worldwide. Recently, attention has been focused on the role of nicotine and its derivatives in lung cancer and how PPARγ affects this. For example, a recent case-control study of 500 incident lung cancer cases and 517 age- and sex frequency-matched cancer-free controls suggested that PPARγ polymorphisms in Chinese smokers may contribute to the etiology of lung cancer[65]. Also, monocytes and monocyte-derived macrophages from healthy smokers showed increased PPARγ expression as compared to those from healthy non-smokers, which was reproduced by nicotine *in vitro*[66]. Interestingly, concomitant administration of PPARγ agonists can effectively attenuate the effects of nicotine on alveolar type Ⅱ cells[67]. Among the carcinogenic chemicals of cigarette smoking, tobacco-specific nitrosamine 4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) is the most potent. One recent report showed that troglitazone blocked NNK-induced up-regulation of Heme oxygenase-1, Bcl-2, and cellular inhibitor of apoptosis protein 2; and restored Bad activity which was suppressed by NNK through activation of PPARγ[68]. These findings reveal a novel molecular pathway of PPARγ activation against cigarette smoking-related lung cancer. Evidence to date suggests that these effects of nicotine and its derivatives are mediated by nicotinic acetylcholine receptors expressed on the surface of tumor cells, thereby contributing to tumor progression[69-71]. We recently found that rosiglitazone reduced nicotine-induced NSCLC cell growth through downregulation of α4 nAChR-dependent signals including ERK and p38 MAPK; this effect appeared to be PPARγ-independent[72]. We also found that nicotine increases PPARβ/δ gene expression through α7 nAChR-mediated activation of PI3K/mTOR signals. This is important since activation of PPARβ/δ is associated with enhanced cancer progression. These studies unveil a novel mechanism by which nicotine promotes human lung carcinoma cell growth and the impact of PPARs[73].

PPARγ and tumor cell-stromal interaction

Several studies suggest that PPARγ ligands might prevent the interaction of tumor cells with their surrounding stroma, thereby interfering with host-derived and tumor-derived factors with mitogenic and pro-survival effects. An example of this is fibronectin, a matrix glycoprotein residing in the lung stroma that is increased in most, if not all, chronic forms of lung disease[74]. This is true for tobacco-related lung disorders and fibrotic disorders, all associated with increased incidence of lung cancer[75]. Several studies suggest that fibronectin serves as a mitogen and survival factor for NSCLC[76], and fibronectin was recently shown to stimulate tumor cell expression of matrix metalloproteinases, proteases implicated in metastatic disease[77]. These observations support the idea that tumor cell interactions with fibronectin through surface integrin receptors are advantageous for tumors since they stimulate proliferation, survival, and metastases[76]. This idea was suggested by work showing reduced proliferative and metastatic capacity in tumor cells not expressing a fibronectin receptor α5β1 integrin[78]. Interestingly, PPARγ ligands were shown to inhibit fibronectin expression in NSCLC cells by inhibiting transcription factors involved in the regulation of fibronectin gene expression[79]. PPARγ ligands (rosiglitazone and GW1929, but not PGJ_2) were also recently reported to inhibit the expression of the gene encoding for the α5 integrin subunit resulting in reduced expression of the integrin α5β1[80]. Thus, by inhibiting the expression of fibronectin and its integrin α5β1, PPARγ ligands might reduce tumor cell recognition of fibronectin with consequent changes in cell proliferation and apoptosis.

Table 1 PPARγ-dependent signals mediate the effects of PPARγ ligands in lung cancer cells

PPARγ ligands inhibit cancer cell growth and induce apoptosis *via*:
↓PGE_2 receptors (e.g. EP2 and EP4)
↑Tumor suppressors (e.g. PTEN, p21, AP-2α, p53)
↓Inflammatory factors (e.g. NF-κB, MCP-1, COX-2)
↓Angiogenic factor (e.g. VEGF)
↓Survival factors (e.g. SAPK/JNK, ILK, Src, FAK, PI3-K/Akt, mTOR)
↑↓Other kinase signals (e.g. ERK, p38 MAPK)
↓Growth factor receptors (e.g. EGF-R, PDGF-R)
↓Extracellular matrices (e.g. Fibronectin, MMP-2, MMP-9)
↓Integrin receptors (e.g. α5β1)
↑↓Others [e.g. cytokines (e.g. IL-13, IL-21, TGF-β1) and chemokines (e.g. MIP-1β)]
↓Bcl-1, c-IAP2, *etc.*
PPARγ ligands stimulate cancer cell growth and reduce apoptosis *via*:
↑Wnt signaling and oncogenes (e.g. cyclin D1, β-catenin, c-Myc)
↑Angiogenic signaling (e.g. VEGF, Angptl4)

PPAR: Peroxisome proliferator-activated receptor; SAPK/JNK: Stress-activated protein kinase/c-Jun NH2-terminal kinase; ILK: Integrin-linked kinase; PI3-K: Phosphatidylinositol 3-kinase; ERK: Extracellular signal-regulated kinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor-κB; VEGF: Vascular endothelial growth factor; IL: Interleukin; TGF: Transforming growth factor; COX: Cyclooxygenase; MCP-1: Monocyte chemotactic protein-1.

PPARγ and angiogenesis

PPARγ might also regulate the generation of the complex vascular network that supplies tumor cells. This idea is supported by studies showing a reduction in blood vessel density in lung tumors generated by the injection of A549 cells into the flanks of SCID mice treated with PPARγ ligands[81]. *In vitro* studies showed that the treatment of A549 cells with troglitazone or their transient transfection with a constitutively active PPARγ construct blocked the production of angiogenic molecules such as ELR + CXC chemokines IL-8 (CXC-8), ENA-78 (CXCL5), and Gro-alpha (CXCL1)[81]. Furthermore, PPARγ activation inhibited NF-κB, a transcription factor known to regulate the expression of many of the pro-angiogenic factors mentioned above. Similarly, rosiglitazone was shown to inhibit mouse lung tumor cell growth and metastasis *in vivo* through direct and indirect anti-angiogenic effects[82].

Although the above studies reveal important anti-cancer effects for PPARγ ligands, it is important to note that PPARγ signaling has also been associated with tumor promoter activity in some cancer cells such as colon and breast, and that this effect was linked to increased β-catenin, c-Myc, Angptl4 and Wnt 5 expression[83-85] (Table 1). PPARγ ligands enhanced 7,12-dimethylbenz(*a*)anthracene-induced rat mammary adenocarcinoma[86] and promoted colonic tumor growth in Apc^{Min} mice fed a high-fat diet[87]. Targeted expression of activated PPARγ in the mammary gland also enhanced tumorigenesis induced by polyoma middle T antigen[84]. These findings need to be confirmed and tested in other tumors. However, these data suggest that activation of specific PPARγ-related pathways may differ depending upon the cells and tumors examined. Internal genetic variations and other factors may be responsible for the outcomes, and these need to be explored further followed by confirmation using relevant *in vivo* models of cancer.

IMPLICATIONS FOR THERAPY AND OTHER CONSIDERATIONS

The studies mentioned above suggest that PPARs are involved in lung cancer cell biology. However, their roles remain uncertain and much needs to be learned before they are targeted for therapeutic intervention, especially when considering PPARγ. Nevertheless, activation of PPARγ is strongly associated with decreased lung carcinoma cell proliferation both *in vitro* and *in vivo*. Furthermore, in primary NSCLC, the expression of PPARγ has been correlated with tumor histological type and grade, and decreased PPARγ expression was correlated with poor prognosis[88]. Because of this, and the fact that synthetic agonists of PPARγ with good safety profiles are currently in use in the clinical arena, PPARγ has emerged as a reasonable target for the development of novel anti-lung cancer therapies. Synthetic and natural PPARγ activators might be useful as well. For example, arachidonic acid inhibits the growth of A549 cells, and this effect is blocked by the synthetic PPARγ inhibitor GW9662[89]. MK886, a 5-lipoxygenase activating protein-directed inhibitor, stimulates apoptosis and reduces the growth of A549 cells through activation of PPARγ[90]. These and related drugs can be used alone or in combination with other drugs for synergistic effects. This was observed when using low doses of MK886 in combination with ciglitazone and 13-cis-retinoic acid on A549 and H1299 cells[90]. Also, dramatic synergistic anticancer effects have been reported for lovastatin (an HMG-CoA reductase inhibitor) and the PPARγ ligand troglitazone in several cell lines including lung cancer cells[91]. An enhancement of the anti-tumor effects of gefitinib by rosiglitazone on A549 cell growth was recently noted suggesting that combination strategies using selective nuclear receptor activators in conjunction with EGFR inhibitors might be effective[92]. More recently, one report showed that the combination of clinically achievable concentrations of troglitazone and nonselective COX inhibitor, aspirin, can produce a strong synergistic effect on the inhibition of lung cancer cell growth and induction of apoptosis[93].

One study demonstrated that combining the PPARγ ligand rosiglitazone with carboplatin dramatically reduced lung tumor growth *in vivo*[94]. Another study showed that the combination of PPARγ ligand with platinum-based drugs exerted beneficial effects in the treatment of lung cancers including those tumors resistant to chemotherapy or acquired resistance to targeted therapy[95]. More recently, one study using selenium (antioxidant), rosiglitazone, sodium phenylbutyrate or valproic acid (histone deacetylase inhibitors) and hydralazine (cytosine-demethylating agent) to prevent the progression of lung cancer in A/J mice treated with NNK demonstrated that chronic administration of rosiglitazone significantly blocked the progression of lung cancer in

Table 2 PPARγ-independent signals triggered by PPARγ ligands in lung cancer cells

↑Tumor suppressors (e.g. LKB1, AMPK, TSC2)
↑ROS production and ERK, SAPK/JNK, p38 MAPK activation (note that this also occurs in PPARγ-dependent pathways)
↓Effects on transcription factors (e.g. AP-1, NF-κB, Smads, Sp1, CRE)
↓Nicotine receptor signaling (e.g. α4 and α7 nAChRs)
↓Apoptosis-related signals (e.g. Bcl-2, cyclin D1, c-FLIP, DR-5)
↑Apoptosis-related signals (e.g. casease 3/7, cyclin D1, p53)

AMPK: AMP-activated protein kinase (AMPK); TSC2: Tuberous sclerosis complex 2.

the A/J mouse model[96]. More tantalizing data were derived from a retrospective analysis demonstrating that thiazolidinedione use was associated with reduced risk of lung cancer. This study revealed a 33% reduction in lung cancer risk among thiazolidinedione users as compared to nonusers after adjusting other variables[97]. Interestingly, a similar risk reduction was not observed for colorectal and prostate cancers[97]. Clearly, as described previously, TZDs have many effects other than PPARγ activation; the elucidation of such mechanisms holds the promise of unveiling new targets for the development of new anti-cancer therapies.

Despite the above findings, enthusiasm for the use of PPARγ ligands as anti-cancer agents should be tempered by the fact that PPARγ ligands stimulated PPARγ transactivation in lung adenocarcinoma cell lines, while little to no effects were noted in squamous cell or large cell carcinomas[98]. Also, it is important that we better define PPARγ-independent pathways triggered by PPARγ ligands to avoid unforeseen effects and to identify new targets for intervention[92,98] (Table 2).

Furthermore, a novel splice variant of human PPARγ1, which is expressed strongly in tumor tissues of primary human lung SCC, was recently identified. This splice variant exhibits dominant-negative properties in human lung tumor cells, and its overexpression renders transfected cells more resistant to chemotherapeutic drug- and chemical-induced cell death[99]. This suggests that the decreased drug sensitivity of PPARγ1-expressing cells may be associated with increased tumor aggressiveness and poor clinical prognosis in patients. Thus, a better understanding of the mechanisms of action of activated PPARs in tumors (and host cells) is required since the dissection of these pathways might unveil better targets for therapy. Nevertheless, the data available to date regarding PPARγ are promising and justify engaging in carefully designed clinical studies to determine the true role of PPARγ ligands in lung cancer, while further work should be performed to identify more selective and effective strategies.

CONCLUSION

Although the exact role of PPARγ in controlling lung tumor growth and apoptosis remains incompletely defined, PPARγ has been implicated both as a tumor suppressor (in most cases) and tumor promoter (in rare cases). Hence, targeting this receptor for therapeutic purposes while minimizing side effects represents a great challenge. Nevertheless, it is clear that selective PPARγ modulation of desired gene sets can be achieved by targeting co-repressor interactions, separating transactivation from transrepression, and favoring specific subsets of co-activators. PPARγ activation results in inhibition of lung tumor growth (particularly NSCLC) both *in vitro* and *in vivo*. Although the exact mechanisms mediating this effect remain incompletely elucidated, data available to date regarding this member of the PPAR family is promising and justify engaging in prospective, randomized clinical studies to determine the true role of PPARγ ligands in lung cancer biology. Further epidemiologic studies are required in patients treated with PPARγ ligands for possible effects on tumor development.

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February 14-16
Lorne, Australia
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Manchester, United Kingdom
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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