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REVIEW

Peroxisome proliferator-activated receptor γ and colorectal cancer

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and ligand-activated transcription factors. PPARγ plays an important role in adipocyte differentiation, lipid storage and energy dissipation in adipose tissue, and is involved in the control of inflammatory reactions as well as in glucose metabolism through the improvement of insulin sensitivity. Growing evidence has demonstrated that activation of PPARγ has an antineoplastic effect in tumors, including colorectal cancer. High expression of PPARγ is detected in human colon cancer cell lines and adenocarcinoma. This review describes the molecular mechanisms by which PPARγ regulates tumorigenesis in colorectal cancer, and examines current clinical trials evaluating PPARγ agonists as therapeutic agents for colorectal cancer.

Key words: Colorectal cancer; Peroxisome proliferator-activated receptors; Ligand; Tumor suppression

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INTRODUCTION

On a global scale, colorectal cancer (CRC) is the third most commonly diagnosed cancer and accounts for about 10% of all cancer death[1,2]. CRC is especially common in Western countries. In China, where CRC was previously thought to be less common, there has been a rise in the incidence of this disease[3-5]. Although surgical resection or radiotherapy is potentially curative for localized disease, advanced colon cancer currently has a poor prognosis. Thus, more efficient treatment approaches are badly needed. Over the past decade, the treatment of cancer has focused on identifying gene networks involved in the regulation of cell growth, differentiation, and cell death. This emphasis has led to more selective treatment regimens focusing on molecular targets in the cancer cells.

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. PPARs are ligand-activated transcription factors and have three different isoforms: PPARα, PPARβ/δ and PPARγ. PPARα activates fatty-acid catabolism, stimulates gluconeogenesis and ketone-body synthesis and is involved in the control of lipoprotein assembly[6]. PPARβ/δ controls cell proliferation, differentiation and survival, especially in keratinocytes[6,7]. PPARγ not only plays an important role in adipocyte differentiation, lipid storage and energy dissipation in adipose tissue, but is also involved in the control of inflammatory reactions and in glucose metabolism through the improvement of insulin sensitivity[6].

PPARγ is activated by binding to its ligands. Endogenous ligands for the receptor include some unsaturated fatty acids and the 15-deoxy-Δ 12,14-prostaglandin J2 (15d-PGJ2), which is suggested to be the most potent endogenous ligand for PPARγ[8,9]. In addition to these natural activators, a wide range of synthetic PPARγ ligands have been developed. The most widely used synthetic agents are thiazolidinediones (TZDs) including ciglitazone, troglitazone, pioglitazone, and rosiglitazone, which have been used clinically to treat type 2 diabetes[10]. Furthermore, non-steroidal anti-inflammatory drugs such as indomethacin, ibuprofen, and fenoprofen have activity as PPARγ agonists.

PPARγ has been detected in cancer cells[11,12], and growing evidence has demonstrated that activation of PPARγ has an antineoplastic effect in many different tumor types, including liposarcoma[13], breast cancer[14], prostate cancer[15,16], and lung cancer[17,18]. However the role of PPARγ in the carcinogenesis of CRC remains controversial. This review will describe the molecular mechanisms by which PPARγ regulates tumorigenesis of CRC, and will examine current research evaluating PPARγ agonists as therapeutic agents for CRC.

PPARγ IN CRC

High expression of PPARγ is detected in the mucosa of the colon and rectum, and is comparable with the high expression found in adipose tissue[19,20]. Similarly, PPARγ is also expressed in human colon cancer cell lines and adenocarcinoma[21,22]. At present, the involvement of PPARγ in the development of CRC is still debated. Most of the available data suggest that PPARγ has an antitumor effect in CRC. PPARγ activation is associated with the inhibition of cell growth *in vitro* as well as xenograft tumorigenesis in nude mice[22-24]. Furthermore, in animal studies, mice with heterozygous deletion of PPARγ (PPARγ+/-) have an increased tendency to develop carcinogen-induced colon cancer compared with wild-type mice[25,26]. Similarly, a deficiency in intestinal PPARγ is associated with enhanced tumorigenicity in mouse small intestine and colon[27]. In addition, PPARγ agonists reduce the number of aberrant cryptal foci (precursor lesions for colon carcinoma) in a chemically induced model of inflammatory bowel disease[28]. The protective role of PPARγ is also supported by studies on the genetic status of PPARγ. Eight percent of primary CRC patients have a loss of function point mutation in one allele of the PPARγ gene, and four mutations in PPARγ are unidentified. The mutations impair the function of PPARγ by affecting the ligand-binding domain, which results in an inability to bind ligands and control gene regulation[29]. Polymorphism in the PPARγ gene has also been found in CRC patients[30]. Furthermore, a recent study showed that expression of PPARγ in CRC is associated with a good prognosis[31], suggesting that PPARγ is a tumor suppressor gene in CRC.

In contrast to the above finding, data from other groups question the antineoplastic effect of PPARγ in CRC. Two different groups have reported that administration of TZD enhanced colon polyp number in the APC^{min} mouse model of CRC[19,32]. These mice harbor a nonsense mutation in the tumor suppressor gene APC resulting in an increased frequency of small and large intestinal adenocarcinoma[33,34]. PPARγ ligands do not induce polyp formation in wild-type mice, implying the potential need for a predisposed genetic susceptibility in order for PPARγ ligands to induce the protumorigenic effect[25]. Together, these studies indicate that early treatment with PPARγ ligands before the first step of carcinogenesis occurs might prevent tumor formation. Activation of PPARγ after tumor initiation, as in APC^{min} mice, might be inefficient or deleterious[35]. Clearly, further investigation will be required to determine the role of PPARγ in the carcinogenesis and treatment of CRC.

ANTINEOPLASTIC MECHANISMS OF PPARγ LIGANDS IN CRC

The molecular mechanisms for the antitumor effect of PPARγ activation remain incompletely elucidated. DNA microarray studies show that PPARγ ligand treatment is associated with change of gene expression involved in apoptosis, cell proliferation, and angiogenesis in colon cancer cells[36,37]. A large proportion of studies have indicated that both synthetic TZDs and the natural ligand, 15d-PGJ2, inhibit the proliferation of colon cancer cell lines in a dose-dependent manner which is reversed by the specific PPARγ antagonist GW9662[38,39]. In addition to PPARγ dependent actions, several pieces of indirect and direct evidence have suggested that the anticancer activity of PPARγ ligands could occur independently of PPARγ. For example, sensitivity of cancer cells to TZDs induced growth inhibition and did not correlate with the level of PPARγ expression, and several orders of magnitude discrepancy existed between the concentration required to produce antitumor effects and that to modify insulin action[40]. In addition, the *in vitro* antitumor effects appear to be structure-specific irrespective of their potency in PPARγ activation, i.e., troglitazone is active while rosiglitazone is not[41]. Troglitazone-induced apoptosis can not be blocked by GW9662 both *in vitro* and *in vivo*[42]. Moreover, TZD analogs, which although devoid of PPARγ activity, retain the ability to induce apoptosis with a potency equal to that of their parental TZDs in cancer cell lines with varying PPARγ expression status[43]. The following section will provide an overview of recent findings concerning plausible PPARγ-dependent and independent mechanisms underlying the antitumor effect of PPARγ ligands.

INDUCTION OF APOPTOSIS

PPARγ agonists induce apoptosis, which partly explains their antineoplastic effect. In colon cancer cells, treatment with the PPARγ ligands (pioglitazone, troglitazone) up-regulates the proapoptotic protein Bax and downregulates the antiapoptotic protein Bcl-2[44-46]. Alternative expres-

sion of Bax and Bcl-2 causes apoptosis by the release of cytochrome C and subsequent activation of several effector caspases. Cell death and apoptosis after troglitazone treatment are abolished by pan-caspase inhibitors[47]. The antiapoptotic protein XIAP might also be a target for the induction of apoptosis by PPARγ ligand treatment. Our recent study indicates that 15d-PGJ2 and troglitazone mediate XIAP ablation in colon cancer cells by facilitating ubiquitination and proteasomal proteolysis. PCR analysis indicated that the mRNA level of XIAP remains unaltered in drug-treated cells, indicating that repression is mediated at the post-transcriptional level. Moreover, this drug-induced XIAP repression can be rescued by proteasome inhibitors, and is preceded by increased ubiquitination[48]. Our study also shows that treatment of colon cancer cells with rosiglitazone stimulates expression of the tumor suppressor gene PTEN[41], which is consistent with previous studies in pancreatic cancer cells[49,50]. This effect is probably mediated through the binding of PPARγ on the specific PPAR response elements which are present in the promoter of that gene, indicating that PTEN is a direct PPARγ target gene.

INHIBITION OF CELLULAR PROLIFERATION

In addition to apoptosis, PPARγ activation inhibits the proliferation of colon cancer cells through the arrest of cell cycle progression. Cyclin D1 is a downstream effector of diverse proliferative and transforming signaling pathways. Activation of cyclin D1 in response to the mitogenic signals leads to G1/S progression and increased proliferation. PPARγ activation in intestinal epithelial cells results in the inhibition of cell cycle and S-phase entry through a decrease in cyclin D1 expression[51,52]. In colon cancer cells, PPARγ ligand treatment not only decreases the protein level of cyclin D1, but also increases the cyclin-dependent kinase (CDK) inhibitors $p21^{CIP1}$ and $p27^{KIP1}$ through both increased transcriptional activity and inhibition of proteasome degradation[53-55]. CDK inhibitors block progression of the cell cycle by inactivating the formation of cyclin/CDK complexes, which are crucial for phosphorylation of the retinoblastoma (Rb) protein when complexed with E2F. By upregulation of CDK inhibitors, PPARγ agonists therefore induce arrest of the cell cycle. In addition, thioglitazone also suppresses the feedback loop containing E2F, cyclin E1, and Rb protein[56]. It is noteworthy that PPARγ ligand-mediated cell cycle arrest is cell specific, and variations in responses exist among different cancer cell lines[43].

INDUCTION OF CELLULAR DIFFERENTIATION

Activation of PPARγ in fibroblasts or preadipocytes leads to full adipocytic cell differentiation with accumulation of lipids, hypersensitivity to hormonal stimulation, and arrest in G1 phase of the cell cycle[57]. Moreover, PPARγ has been demonstrated to induce differentiation in solid tumors both *in vitro* and *in vivo*[58]. In colon cancer cells, TZD treatment inhibits growth and metastasis through differentiation-promoting effects[24]. The ability of PPARγ activation to promote differentiation can be enhanced by the use of an RXR agonist as a combinatorial agent. For instance, the combination of the RXR agonist, bexarotene, with the PPARγ agonist, rosiglitazone, in colon cancer cells causes increased expression of the differentiation marker, CEA, while also decreasing cyclooxygenase-2 expression and prostaglandin E2 synthesis[59]. Thus even though most cells undergo cell death, activation of PPARγ results in the transcription and expression of genes that might cause reversal of differentiated neoplastic cells back into a non-neoplastic, or at least a less malignant state. These reports and others[60,61] suggest a potential role for the combination of RXR and PPARγ agonists in the treatment of CRC.

INHIBITION OF ANGIOGENESIS

Inhibition of angiogenesis is another mechanism by which PPARγ agonists halt the cancer process[62]. Vascular endothelial growth factor (VEGF) is a key regulatory factor of angiogenesis in either physiological or pathological conditions. Previous studies have proved that VEGF is the most powerful angiogenic factor in human cancer, and its overexpression has been associated with the process of metastasis[63]. Removal of VEGF leads to loss of existing tumor vessels and tumor regression[64]. It has been shown that rosiglitazone suppressed primary tumor growth and metastasis by both direct and indirect antiangiogenic actions. Rosiglitazone not only inhibits capillary endothelial cell proliferation and decreases VEGF production by tumor cells *in vitro*, but also suppresses angiogenesis in a variety of primary tumors *in vivo*[65]. In addition to the direct actions on endothelium, PPARγ activation can downregulate angiogenesis-inducing factors such as leptin and tumor necrosis factor α[66], suggesting that PPARγ might be an important molecular target for angiogenesis inhibition.

ADDITIONAL MECHANISMS OF TUMOR SUPPRESSION

The mechanisms of CRC suppression by PPARγ are diverse and complex. To date, an array of targets has been implicated in the antitumor activities of PPARγ ligands, including downregulation of β-catenin[67,68], activation of c-Jun N-terminal protein kinase[69], induction of caveolin-1, caveolin-2[70,71] and proline oxidase[72], upregulation of early growth response-1[73,74] and the tumor suppressor protein p53 and the p53-responsive stress protein GADD45[75]. However, some of these targets appear to be cell type specific due to differences in signaling pathways regulating cell growth and survival in different cell systems.

CLINICAL TRIALS ON THE ANTINEOPLASTIC EFFECTS OF PPARγ LIGANDS

Despite the numerous pre-clinical studies showing the promise of TZDs as anticancer agents in CRC, currently available results of the few clinical trials are neither uniformly positive nor conclusive. A clinical phase II study showed that orally administered troglitazone did not lengthen median progression-free survival or median survival in patients with chemotherapy-resistant metastatic colon cancer[76]. The risk reduction for CRC among diabetic patients taking TZDs do not reach statistical significance[77]. These neutral results emphasize the need to increase the number and length of well-designed clinical studies which will define the role of these promising agents. In addition, PPARγ ligands that are used in cancer treatment might have side effects on lipid and glucose metabolism, and this balance needs to be monitored. Moreover, PPARγ activation in mice has an opposite effect on the development of colon cancer depending on the APC gene background, thus early diagnosis and assessment of genetic predisposition will certainly be pivotal for the success of PPARγ targeted therapy.

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