Peroxisome proliferator-activated receptor δ and gastric cancer (Review)

CHUNG W. WU, JUN YU and JOSEPH J.Y. SUNG

Department of Medicine and Therapeutics, Prince of Wales Hospital, Institute of Digestive Disease, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, P.R. China

Received March 4, 2009; Accepted April 3, 2009

DOI: 10.3892/or_00000456

Abstract. Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily which form heterodimers with retinoid X receptors (RXRs) in nucleus and bind to the PPAR response elements (PPREs) of target genes, leading to a wide spectrum of physiological functions. With an improved understanding of its physiological role, PPAR δ and its agonist have been gaining attention in cancer research in recent years. Despite the paucity of research concerning the direct relationship between PPAR⁸ and gastric cancer, there is substantial evidence that PPAR_δ may play a role in the development of gastric cancer. This review focuses on recent literature describing the role of PPAR δ , especially in its association with nuclear factor- κB (NF- κB), interleukin-1 β (IL-1 β), cyclooxygenase-2 (COX-2) and Wnt-B-catenin/TCF-4 pathways on gastric tumorigenesis and highlights critical discrepancies that need to be resolved for a more comprehensive understanding of how this receptor modulates gastric tumorigenesis. The potential role of PPAR δ as a therapeutic target in the treatment of gastric cancer deserves further research focus.

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Correspondence to: Professor Joseph J.Y. Sung, Department of Medicine and Therapeutics, Prince of Wales Hospital, Institute of Digestive Disease, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, P.R. China E-mail: joesung@cuhk.edu.hk

Key words: gastric cancer, PPARδ, NF-κB, IL-1β, COX-2, Wnt pathway

1. Introduction

Gastric cancer is the second leading cause of cancer-related death in the world (1,2) and the progress against it has been slow. Early stage gastric cancer is asymptomic, and at the time when gastric cancer demonstrates specific symptoms, it has usually proceeded to an advanced stage which subsequent therapy may have little impact (3). Screening for gastric cancer is still not commonly practiced in most countries and currently there is no promising adjuvant therapy. The need to explore novel therapeutics and chemopreventive agents is obvious.

The success of PPAR α and PPAR γ as therapeutic targets has led to growing interests in PPAR δ . In recent years, the role of PPAR δ in cancer has attracted considerable research focus, especially in the formation of intestinal polyps and colon cancer. But still its role in gastric cancer has not been described. Nonetheless, PPAR δ demonstrates strong association with multiple pathways leading to gastric cancer. This review details the relationships between PPAR δ and nuclear factor- κ B (NF- κ B), interleukin-1 β (IL-1 β), cyclooxygenase-2 (COX-2) and the Wnt- β -catenin/TCF-4 pathways respectively, which are summarized in Fig. 1.

2. PPARs

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. PPARs form heterodimers with retinoid X receptors (RXRs) in nucleus and bind to the PPAR response elements (PPREs) of target genes. PPREs are DNA sites composed of direct repeats of two core recognition motifs. In the absence of ligands, co-repressors bind to PPARs and induce condensation of chromatin and sequestration of promoter region, inhibiting transcriptional activity. In the presence of PPAR ligands, ligand-binding replaces the co-repressors from PPARs and triggers conformational changes of the heterodimer that facilitates the recruitment of transcriptional co-activators. Natural endogenous ligands of PPARs are mostly lipophilic molecules generated from fat and cellular metabolism with relatively low binding affinity. PPARs respond to them as lipid sensors by regulating gene transcription. However, function of PPARs is not only restricted to fat metabolism but also involved in a variety of physiological processes (4).

PPAR α, γ and δ/β are the three PPAR isotypes in mammals. PPAR α was the first to be identified when it demonstrated



Figure 1. Schematic diagram of how PPAR δ may potentially mediate gastric cancer. Gastric cancer can be induced by *H. pylori* through multiple molecular pathways which demonstrate strong associations with PPAR δ . PPAR δ regulated NF- κ B negatively in epithelial and liver cells. It modulates IL-1 β though BCL-6, an inflammation suppressor protein which binds to PPAR δ receptor in the absence of ligand and releases from it upon ligand binding. Free BCL-6 suppresses the expression of multiple proinflammatory cytokines. PPAR δ activation was found to suppress COX-2 in lung cancer but induce COX-2 liver cancer. PPAR δ was also proposed to mediate the tumorigenic role of COX-2, as COX-2-derived PGE2 was able to indirectly activate PPAR δ , forming a positive feed back mechanism which up-regulates COX-2. PPAR δ was shown to be a downstream target of Wnt- β -catenin/TCF-4 pathways, and its expression was increased in Apc^{min} mice. However, manipulations of PPAR δ in Apc^{min} mice were shown to lead to different effects on tumorigenesis.

the ability to bind with chemicals that causes peroxisome proliferation, thus coined the term peroxisome proliferatoractivated receptor in the early 1990s. Subsequent studies identified PPAR γ and PPAR δ . Among the three PPARs, PPAR α is most highly expressed in muscle and liver, PPAR γ is predominately expressed in adipose tissue, and PPAR δ is abundantly expressed throughout the body but only at low levels in the liver (5). Being identified as molecular targets of lipid metabolism and tumorigenesis, PPAR α and PPAR γ have gained a major focus in the past decade and their physiological functions have been widely studied (6,7). The study of PPAR δ has relatively lagged behind and the physiological role of PPAR δ is less understood compared with the other two PPAR isoforms.

3. PPAR_ð and its ligands

PPAR[®] plays an indispensable role in various physiological processes. Knockout of PPAR[®] in mice has demonstrated multiple defects such as embryonic lethality, myelination defects, heart failure, decreased fat mass, and impaired skin inflammatory and wound healing response (8-11). PPAR[®] can increase high-density lipoprotein (HDL) cholesterol and lower triglyceride level by modulating lipoprotein metabolism. Increased PPAR[®] activity in the liver has been shown to suppress glucose output and contributes to insulin sensitizing (12). In skeletal muscle, PPAR[®] regulates the formation of slow-twitch muscle fibers, fatty acid metabolism and transport (13). In cardiac muscle, PPAR[®] maintains the basal fatty acid oxidation for normal cardiac mechanics (11).

PPAR δ also modulates inflammation through multiple mechanisms, one of which involves B cell lymphoma-6 (BCL-6), an inflammation suppressor protein which binds to PPAR δ receptor in the absence of ligand and releases from it upon ligand binding (14). Free BCL-6 suppresses the expression of multiple proinflammatory cytokines and chemokines (15,16). PPAR δ , but not PPAR α and PPAR γ , exhibits BCL-6 binding ability (14).

Several naturally occurring eicosanoids such as prostaglandin A1, iolprost, and 15d-J2 are capable of activating PPAR δ (17-20). Fatty acids derived from very low-density lipoprotein enhance the expression of PPAR δ and are suggested to act as endogenous ligands (21). Although currently there is no PPAR δ agonist approved for clinical use, several synthetic agonists developed by combinational chemistry and structure-based drug design were shown to have high affinities for PPAR δ (22). Among them, GW501516 has been the most widely used selective agonist in demonstrating the physiological role of PPAR δ in both *in vitro* and *in vivo* studies.

4. Roles of PPARô in tumorigenesis

PPAR δ is involved in the control of cell proliferation, cell differentiation, and apoptosis, which is why its role in cancer development sparks both interests and debates (Table I). It has been shown that agonist-induced activation of PPAR δ causes growth inhibition in several solid tumor types including skin and lung (23-25), possibly through the inhibition of cell proliferation (26). PPAR δ activation has been shown to potentiate

Table I. A c	comparison	of roles	of PPAR _ð	in cancer.
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Type of cancer	Experiment model	Role in cancer formation	Main phenotypic character	Refs.
Skin	Mouse	-	PPARδ null mice demonstrated earlier onset, enhanced size and growth of tumor compared with wild-type in response to chemically induced skin cancer	
Lung	Cell line	-	L165041 mediated prostaglandin I2-induced cell apoptosis in human lung cancer cell line A549	
Breast	Mouse	+	PPARδ agonist GW7845 accelerated tumor formation and resulted in predominantly squamous cell carcinomas	(27)
	Cell line	+	PPAR δ agonist stimulated cell proliferation in human breast cancer cell lines T47D and MCF7	(28)
Prostate	Cell line	+	PPAR δ agonist stimulated cell proliferation in human prostate cancer cell lines LNCaP and PNT1A	
Liver Cel	Cell line	+	PPAR δ agonist accelerated cell proliferation by a feed forward mechanism through inducing COX-2 expression and COX-2 derived PGE ₂ in human hepatocellular carcinoma cell line HuH7, HepG2 and Hep3B	(29,30)
	Mouse	-	Chemically induced liver toxicity led to increased serum alanine aminotransferase level, bile duct hyperplasia, regenerative hyperplasia observed in PPARδ null mice, but not in wild-type mice	(50)
Small intestine	Mouse	=	Female PPAR ^δ null Apc ^{min} mice did not exhibit significant difference in number and size of intestinal polyps from Apc ^{min} mice	(10)
	Mouse	-	PPARô null Apc ^{min} mice developed significantly larger tumors than Apc ^{min} mice regardless of sex	(71)
	Mouse	-	Female PPAR δ null Apc ^{min} mice developed more intestinal polyps than Apc ^{min} mice	(25)
	Mouse	+	PPARð agonist GW501516 induced both polyp size and growth in Apc ^{min} mice	(31)
Colon	Cell line	-	When inoculated as xenografts in nude mouse, PPAR ^δ null human colon cancer cell HCT116 was less able to form tumor than wild-type HCT116 cells	(33)
	Cell line	-	PPARδ agonist GW501516 suppressed apoptosis in a dose-dependent manner in wild-type HCT116 cells; this effect was not displayed in PPARδ null HCT116 cells	(31)
	Mouse	-	Female PPAR δ null Apc ^{min} mice developed significantly greater number of polyps than Apc ^{min} mice	(71)
	Mouse	=	PPARð agonist GW501516 did not significantly induce polyp growth in Apc ^{min} mice	(31)
	Mouse	-	PPAR δ null Apc ^{min} mice developed 6 times more polyps than did Apc ^{min} mice, regardless of sex	(25)
	Mouse	-	Azoxymethane was able to induce more colon polyps in PPARδ null mice than in wild-type mice	(25)

-, PPAR^δ plays an anti-tumorigenic role; +, PPAR^δ plays a pro-tumorigenic role; =, no significant roles for PPAR^δ demonstrated in tumorigenesis.

the development of breast, prostate and liver cancers (27-30). There are conflicting data regarding the anti- or pro-tumorigenesis effects of PPAR δ in gastrointestinal cancers. Gupta *et al* reported that exposure of genetically engineered mice predisposed to intestinal polyposis (Apc^{min}) to PPAR δ agonist significantly increased the number and size of intestinal polyps (31), whereas down-regulation of PPAR δ in colon cancer cells was able to induce apoptosis (32). Disruption of PPAR δ in human cancer cells was also able to decrease their ability to form tumors when inoculated as xenografts in nude mice

(33). More recently, Shao *et al* reported PPAR δ as a target gene of oncogenic Ras protein, and K-Ras mediated transformation of intestinal epithelial cells had up-regulated PPAR δ (34). Opposite to these findings, in both the Apc^{min} model and chemically induced model, colon polyp formation was found to be greater in size in mice nullizygous for PPAR δ (25). To date, there is no conclusive evidence on whether PPAR δ is anti- or pro-tumorigenic. Modulation of it was found to lead to different consequences in different types of cancer. Research on PPAR δ in gastrointestinal tumorigenesis has so far been mainly focused on small intestine and colon, and findings were rather contradictory.

5. Background of gastric cancer

Gastric cancer is the second leading cause of cancer-related death in the world (1,2). The incidence of gastric cancer has been decreasing in the developed world over the past few decades but is still increasing in the developing world. Global new incidence is expected to reach 960,000 in 2010 and 1.1 million in 2020 with majority of cases occurring in developing countries. Risk factors for gastric cancer include Helicobacter pylori (H. pylori) infection, smoking and dietary factors such as insufficient fresh fruit and vegetable consumption and high salt uptake. A family history of gastric cancer will also increase individual susceptibility to the disease (35). It is now a widely accepted view that H. pylori infection is the primary initiator of the inflammatory and morphologic alterations such as atrophic gastritis and gastrointestinal metaplasia (36,37) mediated by COX-2 overexpression (38), up-regulation of cyclinD1 by the Wnt signaling pathway through interaction of mucin 1 with ß-catenin (39) and transcription factor (e.g., NF-KB) activation (40), leading to cell proliferation, excessive angiogenesis, inhibition of apoptosis and formation of gastric tumors. Epidemiologically, proinflammatory genotypes of the IL-1b and COX-2 gene are associated with an increased risk of gastric cancer and its precursors. The effects are most likely mediated through the induction of hypochlorhydria and severe gastritis with the subsequent development of gastric atrophy (41,42).

Although eradication of *H. pylori* appears to be an attractive approach in preventing cancer, the data so far are limited and there is no effective chemopreventive agent available. Therapeutics targeting COX-2 was found to be promising in reducing the risk of gastric cancer; but longterm use of non-steroidal anti-inflammatory drugs (NSAIDs), that inhibit both COX-1 and COX-2, or selective inhibitors for COX-2 could lead to peptic ulcer diseases (43) and increase the risk of cardiovascular disease (44,45). The mechanism behind the beneficial effect of COX-2 inhibition and its sideeffects remain to be better defined. Peroxisome proliferatoractivated receptors (PPARs) appear to be promising targets as chemopreventive agents. Cancer formation is associated with dysregulation of cellular differentiation, proliferation and apoptosis. Modulating these processes through the PPA receptor (PPAR) is a recent approach to cancer chemoprevention and therapy. Despite the paucity of data on the direct relationships between the three PPARs and gastric cancer, PPAR^δ demonstrates particularly strong association with multiples pathways leading to gastric cancers.

6. Potential effects of PPARo in gastric cancer

To date, there is only one study in literature trying to demonstrate the relationship between PPAR δ and gastric cancer (46). In this particular study, Yu et al showed that PPAR8 was highly expressed in both normal gastric and gastric cancer samples. Treating gastric cell line MKN45 that overexpressed COX-2 with the specific COX-2 inhibitor resulted in a time- and dose-dependent suppression of PPAR^δ expression. In contrast, there was no suppression of PPARo in the MKN28 gastric cell line, which had lower COX-2 expression. This leads to uncertainty whether PPAR8 plays a role in the chemopreventive effect of COX-2 inhibitor on gastric cancer. In spite of the paucity of research concerning their direct relationship, various studies have identified factors through which PPAR8 may mediate effects on gastric cancer development. These factors include nuclear factor-κB (NF-κB), interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2) and the Wnt-ß-catenin/TCF-4 pathways.

PPAR δ and *NF*- κ *B*. Evidence showed that NF- κ B signaling plays a pivotal role in inflammation-associated cancer. Activation of the NF-kB pathway by stimulation such as H. pylori infection begins with signal-induced phosphorylation of IkB, an inhibitory protein that binds to NF-kB in the cytoplasm. This releases NF-kB and allows it to translocate into the nucleus where they activate transcription of proinflammatory genes (47,48). Matsumoto *et al* showed that up-regulation of activation-induced cytidine deaminase (AID), a downstream target gene of NF-KB, has led to the accumulation of nucleotide alterations in the TP53 tumor suppressor gene in gastric cells, which mediate the H. pylori infection-induced chronic gastric inflammation (48). Previous studies have demonstrated that PPAR⁸ agonist inhibited cytokine-induced nuclear translocation of NF-κB in epithelial cells (49). PPARδ null mice showed enhanced NF-kB expression in liver, and were more susceptible to chemically induced hepatoxicity (50). On the other hand, NF-KB activation down-regulated PPAR8 activity during cardiac hypertrophy, possibly through protein-protein interaction between PPARδ and subunit p65 of NF-κB (51). Therefore, NF-KB and PPAR8 have been shown to be negative regulators of each other. PPAR& activity may suppress NF- κ B-mediated inflammation; however, this modulation is yet to be validated in the development of gastric cancer.

PPARδ and *IL-1β*. Another key factor involved in the inflammatory response to *H. pylori* infection is the proinflammatory cytokine IL-1β. Individuals with specific IL-1β genotypes that give raise to a higher IL-1β synthetic level were found to have higher risk of developing gastric cancer upon *H. pylori* infection (52). Zeng *et al* studied IL-1β gene polymorphisms and their association with gastric cancer in the Chinese population, and found that in low prevalence areas, IL-1β-511T/T genotype is more common in gastric cancer patients than in normal subject. In high-prevalence areas, both control subjects and gastric cancer patients had high prevalence of proinflammatory genotype of IL-1β-511T/T (53). IL-1β was proposed to be a critical target of PPARδ. Lee *et al* showed that mouse macrophages over-expressing PPARδ had higher IL-1β expression while PPARδ knockout macrophages had reduced IL-1ß expression. Interestingly, treatment with PPAR δ agonist (GW501516) reduced IL-1ß expression in wild-type and PPAR δ overexpressed macrophages (14). Thus the activation of IL-1ß is PPAR δ receptor-dependent while the suppression of IL-1ß is PPAR δ ligand-dependent. This could probably be mediated through the inflammation repressor BCL-6 or direct gene targets of PPAR δ which have suppressive effects on IL-1ß expression (14,22). However, further study is required to investigate the roles of direct target genes of PPAR δ . In addition, BCL-6 was found to suppress the expression of

group IIA secretory phospholipase A2 (sPLA2-IIA), an

enzyme that mediates the inflammatory response of IL-1B,

through transcriptional repression by promoter binding (16).

PPARo and COX-2. COX-2, a key enzyme in arachidonic acid biosynthesis, has been reported to be up-regulated in gastrointestinal cancers; and its overexpression is generally regarded to facilitate tumor development. Long-term use of COX-2 inhibitors has already been applied in the prevention of colorectal polyps in patients with familial adenomatous polyposis (FAP), an autosomal dominant disease caused by inactivation of adenomatous polyposis coli (APC) gene, and was shown to result in reduced risk for colorectal cancer (CRC) by 50% (54). In gastric cancer, COX-2 has been implicated in multiple tumorigenic processes including antiapoptosis (55), angiogenesis (56) and invasiveness (57). A population-based study showed that genetic polymorphism of COX-2 gene promoter region -1195A resulting in increased COX-2 expression was associated with 2-fold elevated risk of gastric cancer (42). COX-2 inhibitors were shown to suppress the development of gastric cancer (46,58). Various studies have demonstrated the relationship between PPAR δ and COX-2 in different types of cancers. For example, PPAR8 activation induced by agonist L165041 down-regulated COX-2 expression in lung cancer (24). In liver cancer, by contrast, PPAR_ð activation induced by agonist GW501516 was found to induce COX-2 expression in liver cancer and hepatocellular carcinoma (HCC) cell lines, while inhibition of PPARo by small interfering RNA suppressed growth of these cell lines (29,30). The induction COX-2 derived prostaglandin E_2 (PGE₂) further activates PPAR δ , resulting in a feed forward loop (30). However, Hollingshead et al also demonstrated that PPAR_ð agonists GW0742 and GW501516 were unable to modulate COX-2 in human colon and liver cell lines (59). Wang et al proposed a mediating role of PPARo in COX-2 tumorigenesis (60). They showed that treatment of COX-2 derived PGE₂ promote intestinal epithelial cell survival and colorectal adenoma growth in Apcmin but not PPARδ knockout Apc^{min} mice. Similarly, PGE₂ decreased apoptosis of CRC cells but not cells expressing dominant negative PPAR δ protein, suggesting the induction of polyp growth by COX-2 was dependent on PPAR_δ (60). This idea is consistent with the feed forward mechanism proposed by Xu et al (30). Yu et al has demonstrated the suppression of PPAR8 by COX-2 inhibitor in high COX-2 expressing gastric cancer cell line (46); however, it is not known whether the ameliorating effect of COX-2 inhibitor on the development of gastric cancer is mediated via PPAR\delta. The modulation of COX-2 by PPARδ was shown to exhibit tissue specificity. Whether PPAR δ modulates COX-2 in gastric cancer remains to be elucidated. But there is growing evidence that PPAR δ mediates COX-2-initiated tumorigenesis through a feed forward mechanism. It would be interesting to consider interrupting PPAR δ as an alternative chemopreventive measure for gastric cancer besides COX-2 inhibitors.

PPARδ and Wnt-β-catenin/TCF-4 pathway. The Wnt-βcatenin/TCF-4 pathway has been widely implicated in gastric cancer. The role of Wnt-ß-catenin/TCF-4 pathway was first discovered in the developmental process and was later found to be involved in tumorigenesis including the development of various gastrointestinal cancers. The association was identified in FAP, in which the inherited mutated APC was found to cause the development of adenomatous polyps in colon (61,62). Subsequent studies found that APC contributes to the degradation of ß-catenin, a protein which was able to bind with the transcription factor T cell factor 4 (TCF-4) and significantly enhanced transcription of its target genes including oncogenic c-myc, cyclin D1 and transcription factor PPAR δ (63-65). The accumulation of β -catenin in nucleus has been observed in 17-54% of gastric adenocarcinomas. FAP patients were found to have increased risk of gastric cancer (66-69). We and others have found functionally null mutations in APC and functionally activating mutations in β-catenin in gastric cancer (66-69). Treatment of N-methylnitrosourea (MNU) resulted in a more rapid gastric tumor development in Apcmin than in wild-type mice (70). The promoter region of PPAR8 contains Tcf-4responsive elements. Thus, increased expression of APC protein could down-regulate PPARδ expression through suppressing the β-catenin/TCF-4 pathway in colon cancer cell line (63). Gupta et al showed that giving PPAR8 agonist GW501516 to Apc^{min} mice caused development of larger polyps in the intestine compared to that of untreated mice. Pretreatment with GW501516 suppressed apoptosis in wildtype human CRC HCT116, but not in PPARδ knockout HCT116 cells, suggesting the antiapoptotic effect is a result of PPAR_δ activation (31). However, in a study adopting a genetic approach, knockout of PPAR8 was shown to increase the predisposition of Apc^{min} mice to colon and intestinal tumorigenesis (25,71). Such conflicting findings could possibly be a result of the functional difference between nonactivated PPAR8 receptor and ligand-bound activated PPAR8 receptor, a scenario described in the case with IL-1ß. Research on PPAR8 in APC mutant induced colon cancer has sparked as much debate as interest, although this pathway has also been found to increase susceptibility to gastric cancer, little is known about how PPAR8 would modulate gastric cancer induced APC mutation.

7. Conclusions

Although the direct relationship between PPAR δ and gastric cancer is less described, evidence suggests they are linked by pathways including NF- κ B, IL-1 β , COX-2 and Wnt- β -catenin/TCF-4, the relationship is desribed in Fig. 1. PPAR δ was shown to regulate NF- κ B negatively; whether its activation can suppress NF- κ B mediated gastric inflammation

deserves further validation. As in IL-1ß signaling and Wnt-ßcatenin/TCF-4 pathways, PPAR⁸ has demonstrated functional difference between its non-activated receptor and ligandbound activated receptor. It is worthwhile to investigate and distinguish the differences between the effects of PPARo overexpression by gene delivery and PPARδ activation by ligands, along with attention to similar features occuring in gastric epithelial cells. Regulation of COX-2 by PPAR8 remains controversial since PPAR_ð agonists can lead to different ways of COX-2 modulation in different cancers. PPAR8 was also shown to be an important factor in mediating COX-2 tumorigenesis. Clinically, this implies that a higher endogenous PPAR δ receptor level may lead to greater susceptibility to COX-2 mediated gastric cancer. There is also evidence demonstrating that the effect of NSAID or COX-2 inhibitor were at least partially mediated through inhibiting PPAR_(46,60,63), suggesting modulating PPAR8 could be a potential chemopreventive for reducing risk of gastric cancer. The argument over the tumorigenetic role of PPAR⁸ needs to be clarified. Future studies should try to identify genes that PPAR^δ regulates in leading to particular anti- or pro-tumorigenetic effect. Distinguishing tissue specificity and the functional difference between non-activated receptor and activated receptor will help to understand the role of PPAR δ in different scenarios. The development of gastric cancer employs multiple pathways. Through identifying associations between PPAR δ and each of these pathways, this review provides the most updated evidence on how PPAR8 may impact on the development of gastric cancer. Unquestionably, the role of PPAR δ in gastric tumorigenesis will be better understood if future research effort could focus on demonstrating the direct relationship between them.

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