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

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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, PPARδ and its agonist have been gaining attention in cancer research in recent years. Despite the paucity of research concerning the direct relationship between PPARδ and gastric cancer, there is substantial evidence that PPARδ may play a role in the development of gastric cancer. This review focuses on recent literature describing the role of PPARδ, especially in its association with nuclear factor-κB (NF-κB), interleukin-1ß (IL-1ß), cyclooxygenase-2 (COX-2) and Wnt-ß-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 PPARδ as a therapeutic target in the treatment of gastric cancer deserves further research focus.

Contents

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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 PPARα and PPARγ as therapeutic targets has led to growing interests in PPARδ. In recent years, the role of PPARδ 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, PPARδ demonstrates strong association with multiple pathways leading to gastric cancer. This review details the relationships between PPARδ and nuclear factor-κB (NF-κB), interleukin-1ß (IL-1ß), cyclooxygenase-2 (COX-2) and the Wnt-ß-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).

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

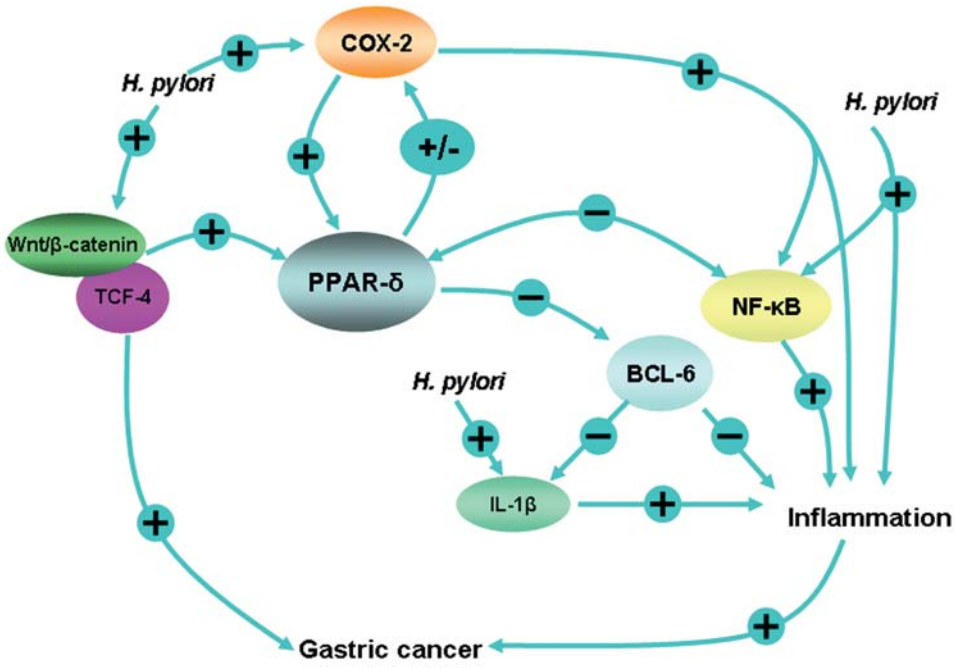

Figure 1. Schematic diagram of how PPARδ may potentially mediate gastric cancer. Gastric cancer can be induced by *H. pylori* through multiple molecular pathways which demonstrate strong associations with PPARδ. PPARδ regulated NF-κB negatively in epithelial and liver cells. It modulates IL-1ß though BCL-6, an inflammation suppressor protein which binds to PPARδ receptor in the absence of ligand and releases from it upon ligand binding. Free BCL-6 suppresses the expression of multiple proinflammatory cytokines. PPARδ activation was found to suppress COX-2 in lung cancer but induce COX-2 liver cancer. PPARδ was also proposed to mediate the tumorigenic role of COX-2, as COX-2-derived PGE2 was able to indirectly activate PPARδ, forming a positive feed back mechanism which up-regulates COX-2. PPARδ was shown to be a downstream target of Wnt-ß-catenin/TCF-4 pathways, and its expression was increased in Apc^{min} mice. However, manipulations of PPARδ 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 proliferator-activated receptor in the early 1990s. Subsequent studies identified PPARγ and PPARδ. Among the three PPARs, PPARα is most highly expressed in muscle and liver, PPARγ is predominately expressed in adipose tissue, and PPARδ 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, PPARα and PPARγ have gained a major focus in the past decade and their physiological functions have been widely studied (6,7). The study of PPARδ has relatively lagged behind and the physiological role of PPARδ is less understood compared with the other two PPAR isoforms.

3. PPARδ and its ligands

PPARδ plays an indispensable role in various physiological processes. Knockout of PPARδ 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). PPARδ can increase high-density lipoprotein (HDL) cholesterol and lower triglyceride level by modulating lipoprotein metabolism. Increased PPARδ activity in the liver has been shown to suppress glucose output and contributes to insulin sensitizing (12). In skeletal muscle, PPARδ regulates the formation of slow-twitch muscle fibers, fatty acid metabolism and transport (13). In cardiac muscle, PPARδ maintains the basal fatty acid oxidation for normal cardiac mechanics (11). PPARδ also modulates inflammation through multiple mechanisms, one of which involves B cell lymphoma-6 (BCL-6), an inflammation suppressor protein which binds to PPARδ 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). PPARδ, but not PPARα and PPARγ, exhibits BCL-6 binding ability (14).

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

4. Roles of PPARδ in tumorigenesis

PPARδ 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 PPARδ causes growth inhibition in several solid tumor types including skin and lung (23-25), possibly through the inhibition of cell proliferation (26). PPARδ activation has been shown to potentiate

A comparison of roles of PPARδ in cancer.

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	(23)
Lung	Cell line	-	L165041 mediated prostaglandin I2-induced cell apoptosis in human lung cancer cell line A549	(24)
Breast	Mouse	+	PPARδ agonist GW7845 accelerated tumor formation and resulted in predominantly squamous cell carcinomas	(27)
	Cell line	+	PPARδ agonist stimulated cell proliferation in human breast cancer cell lines T47D and MCF7	(28)
Prostate	Cell line	+	PPARδ agonist stimulated cell proliferation in human prostate cancer cell lines LNCaP and PNT1A	(28)
Liver	Cell line	+	PPARδ 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 PPARδ null Apc^{min} mice did not exhibit significant difference in number and size of intestinal polyps from Apc^{min} mice	(10)
	Mouse	-	PPARδ null Apc^{min} mice developed significantly larger tumors than Apc^{min} mice regardless of sex	(71)
	Mouse	-	Female PPARδ null Apc^{min} mice developed more intestinal polyps than Apc^{min} mice	(25)
	Mouse	+	PPARδ agonist GW501516 induced both polyp size and growth in Apc^{min} mice	(31)
Colon	Cell line	-	When inoculated as xenografts in nude mouse, PPARδ 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 PPARδ null Apc^{min} mice developed significantly greater number of polyps than Apc^{min} mice	(71)
	Mouse	=	PPARδ agonist GW501516 did not significantly induce polyp growth in Apc^{min} mice	(31)
	Mouse	-	PPARδ 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)

-, PPARδ plays an anti-tumorigenic role; +, PPARδ plays a pro-tumorigenic role; =, no significant roles for PPARδ 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 PPARδ in gastrointestinal cancers. Gupta *et al* reported that exposure of genetically engineered mice predisposed to intestinal polyposis (Apc^{min}) to PPARδ agonist significantly increased the number and size of intestinal polyps (31), whereas down-regulation of PPARδ in colon cancer cells was able to induce apoptosis (32). Disruption of PPARδ 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 PPARδ as a target gene of oncogenic Ras protein, and K-Ras mediated transformation of intestinal epithelial cells had up-regulated PPARδ (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 PPARδ (25). To date, there is no conclusive evidence on whether PPARδ is anti- or pro-tumorigenic. Modulation of it was found to lead to different consequences in different types of cancer. Research on PPARδ 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-κB) activation (40), leading to cell proliferation, excessive angiogenesis, inhibition of apoptosis and formation of gastric tumors. Epidemiologically, pro-inflammatory 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 long-term 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 side-effects remain to be better defined. Peroxisome proliferator-activated 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, PPARδ demonstrates particularly strong association with multiples pathways leading to gastric cancers.

6. Potential effects of PPARδ in gastric cancer

To date, there is only one study in literature trying to demonstrate the relationship between PPARδ and gastric cancer (46). In this particular study, Yu *et al* showed that PPARδ 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 PPARδ expression. In contrast, there was no suppression of PPARδ in the MKN28 gastric cell line, which had lower COX-2 expression. This leads to uncertainty whether PPARδ 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 PPARδ may mediate effects on gastric cancer development. These factors include nuclear factor-κB (NF-κB), interleukin-1ß (IL-1ß), cyclooxygenase-2 (COX-2) and the Wnt-ß-catenin/TCF-4 pathways.

PPARδ and NF-κB. Evidence showed that NF-κB signaling plays a pivotal role in inflammation-associated cancer. Activation of the NF-κB pathway by stimulation such as *H. pylori* infection begins with signal-induced phosphorylation of IκB, an inhibitory protein that binds to NF-κB in the cytoplasm. This releases NF-κB 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-κB, 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 PPARδ agonist inhibited cytokine-induced nuclear translocation of NF-κB in epithelial cells (49). PPARδ null mice showed enhanced NF-κB expression in liver, and were more susceptible to chemically induced hepatoxicity (50). On the other hand, NF-κB activation down-regulated PPARδ activity during cardiac hypertrophy, possibly through protein-protein interaction between PPARδ and subunit p65 of NF-κB (51). Therefore, NF-κB and PPARδ have been shown to be negative regulators of each other. PPARδ activity may suppress NF-κB-mediated inflammation; however, this modulation is yet to be validated in the development of gastric cancer.

PPARδ and IL-1ß. Another key factor involved in the inflammatory response to *H. pylori* infection is the pro-inflammatory cytokine IL-1ß. Individuals with specific IL-1ß genotypes that give raise to a higher IL-1ß synthetic level were found to have higher risk of developing gastric cancer upon *H. pylori* infection (52). Zeng *et al* studied IL-1ß gene polymorphisms and their association with gastric cancer in the Chinese population, and found that in low prevalence areas, IL-1ß-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-1ß-511T/T (53). IL-1ß was proposed to be a critical target of PPARδ. Lee *et al* showed that mouse macrophages over-expressing PPARδ had higher IL-1ß expression while PPARδ

t macrophages had reduced IL-1ß expression. Interestingly, treatment with PPARδ agonist (GW501516) reduced IL-1ß expression in wild-type and PPARδ over-expressed macrophages (14). Thus the activation of IL-1ß is PPARδ receptor-dependent while the suppression of IL-1ß is PPARδ ligand-dependent. This could probably be mediated through the inflammation repressor BCL-6 or direct gene targets of PPARδ which have suppressive effects on IL-1ß expression (14,22). However, further study is required to investigate the roles of direct target genes of PPARδ. 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-1ß, through transcriptional repression by promoter binding (16).

PPARδ 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 anti-apoptosis (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 PPARδ and COX-2 in different types of cancers. For example, PPARδ activation induced by agonist L165041 down-regulated COX-2 expression in lung cancer (24). In liver cancer, by contrast, PPARδ activation induced by agonist GW501516 was found to induce COX-2 expression in liver cancer and hepatocellular carcinoma (HCC) cell lines, while inhibition of PPARδ by small interfering RNA suppressed growth of these cell lines (29,30). The induction COX-2 derived prostaglandin E_2 (PGE_2) further activates PPARδ, resulting in a feed forward loop (30). However, Hollingshead *et al* also demonstrated that PPARδ 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 PPARδ in COX-2 tumorigenesis (60). They showed that treatment of COX-2 derived PGE_2 promote intestinal epithelial cell survival and colorectal adenoma growth in Apc^{min} but not PPARδ knockout Apc^{min} mice. Similarly, PGE_2 decreased apoptosis of CRC cells but not cells expressing dominant negative PPARδ protein, suggesting the induction of polyp growth by COX-2 was dependent on PPARδ (60). This idea is consistent with the feed forward mechanism proposed by Xu *et al* (30). Yu *et al* has demonstrated the suppression of PPARδ 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 PPARδ. The modulation of COX-2 by PPARδ was shown to exhibit tissue specificity. Whether PPARδ modulates COX-2 in gastric cancer remains to be elucidated. But there is growing evidence that PPARδ mediates COX-2-initiated tumorigenesis through a feed forward mechanism. It would be interesting to consider interrupting PPARδ as an alternative chemopreventive measure for gastric cancer besides COX-2 inhibitors.

PPARδ and Wnt-ß-catenin/TCF-4 pathway. The Wnt-ß-catenin/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 PPARδ (63-65). The accumulation of ß-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 ß-catenin in gastric cancer (66-69). Treatment of N-methylnitrosourea (MNU) resulted in a more rapid gastric tumor development in Apc^{min} than in wild-type mice (70). The promoter region of PPARδ contains Tcf-4-responsive elements. Thus, increased expression of APC protein could down-regulate PPARδ expression through suppressing the ß-catenin/TCF-4 pathway in colon cancer cell line (63). Gupta *et al* showed that giving PPARδ 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 wild-type human CRC HCT116, but not in PPARδ knockout HCT116 cells, suggesting the antiapoptotic effect is a result of PPARδ activation (31). However, in a study adopting a genetic approach, knockout of PPARδ 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 non-activated PPARδ receptor and ligand-bound activated PPARδ receptor, a scenario described in the case with IL-1ß. Research on PPARδ 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 PPARδ would modulate gastric cancer induced APC mutation.

7. Conclusions

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

deserves further validation. As in IL-1ß signaling and Wnt-ß-catenin/TCF-4 pathways, PPARδ has demonstrated functional difference between its non-activated receptor and ligand-bound activated receptor. It is worthwhile to investigate and distinguish the differences between the effects of PPARδ over-expression by gene delivery and PPARδ activation by ligands, along with attention to similar features occuring in gastric epithelial cells. Regulation of COX-2 by PPARδ remains controversial since PPARδ agonists can lead to different ways of COX-2 modulation in different cancers. PPARδ was also shown to be an important factor in mediating COX-2 tumorigenesis. Clinically, this implies that a higher endogenous PPARδ 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 PPARδ (46,60,63), suggesting modulating PPARδ could be a potential chemo-preventive for reducing risk of gastric cancer. The argument over the tumorigenetic role of PPARδ needs to be clarified. Future studies should try to identify genes that PPARδ 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 PPARδ in different scenarios. The development of gastric cancer employs multiple pathways. Through identifying associations between PPARδ and each of these pathways, this review provides the most updated evidence on how PPARδ may impact on the development of gastric cancer. Unquestionably, the role of PPARδ in gastric tumorigenesis will be better understood if future research effort could focus on demonstrating the direct relationship between them.

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