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Review

15-Hydroxyprostaglandin dehydrogenase as a novel molecular target for cancer chemoprevention and therapy

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ABSTRACT

Cyclooxygenase-2 (COX-2), a rate-limiting enzyme in arachidonic acid cascade, plays a key role in the biosynthesis of prostaglandin E_2 (PGE_2) upon inflammatory insults. Overproduction of PGE_2 stimulates proliferation of various cancer cells, confers resistance to apoptosis of cancerous or transformed cells, and accelerates metastasis and angiogenesis. Excess PGE_2 undergoes metabolic inactivation which is catalyzed by NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH). In this context, 15-PGDH has been speculated as a physiological antagonist of COX-2 and a tumor suppressor. Thus, overexpression of 15-PGDH has been known to protect against experimentally induced carcinogenesis and renders the cancerous or transformed cells susceptible to apoptosis by counteracting oncogenic action of PGE_2. In contrast, silence of 15-*PGDH* is observed in some cancer cells, which is associated with epigenetic modification, such as DNA methylation and histone deacetylation, in the promoter region of 15-PGDH. A variety of compounds capable of inducing the expression of 15-PGDH have been reported, which include the histone deacetylase inhibitors, nonsteroidal anti-inflammatory drugs, and peroxisome proliferator-activated receptor-gamma agonists. Therefore, 15-PGDH may be considered as a novel molecular target for cancer chemoprevention and therapy. This review highlights the role of 15-PGDH in carcinogenesis and its regulation.

Contents

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1. Introduction

Prostaglandins are produced by cyclooxygenase (COX) from arachidonic acid, and regulate many biological functions including homeostasis, reproduction, and immune response [1]. Aberrant overexpression of COX-2 has been frequently observed in various cancer tissues and transformed cells [2]. This leads to the accumulation of specific prostaglandins, particularly prostaglandin E_2 (PGE_2). In most malignancies, the oncogenic effects of COX-2 have been attributed to excess accumulation of PGE_2 [3]. PGE_2 is known to play a role in tumorigenesis by stimulating proliferation and migration of transformed cells as well as angiogenesis. It also confers resistance to cancer cell apoptosis [3].

The intracellular accumulation of PGE_2 is controlled not only by synthesis but also by degradation. One of the key enzymes involved in prostaglandins catabolism is nicotinamide adenine dinucleotide (NAD^+)-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH). This enzyme oxidizes the 15(*S*)-hydroxyl group of PGE_2 to generate 15-keto-prostaglandin, which exhibits greatly reduced biological activity (Fig. 1) [4]. Therefore, 15-PGDH plays an essential role in the biological inactivation of PGE_2. The enzyme is widely distributed in various mammalian tissues [5].

Down-regulation of 15-PGDH has been observed in several human cancer specimens together with up-regulation of COX-2 expression [6]. Genetic mutation or deletion of 15-*PGDH* can contribute to carcinogenesis as a consequence of increased accumulation of PGE_2 [7–10]. Although the majority of studies on 15-PGDH support the tumor suppressive function of this enzyme, a high expression level of 15-PGDH as well as COX-2 was observed in a malignant as well as normal ovarian tissue, and expression of 15-PGDH was induced by some cytokines, the tumor promoter phorbol 12-myristate 13-acetate (PMA), and a sex hormone, suggesting possible involvement of this enzyme in the carcinogenic process as well [11,12]. This review highlights the role of 15-PGDH as a putative tumor suppressor and molecular mechanism underlying its regulation.

2. 15-PGDH as a putative tumor suppressor

Multiple lines of evidence from studies with various cell lines and experimental animals provide mechanistic basis for the tumor suppressor function of 15-PGDH. Down-regulation of 15-PGDH at both mRNA and protein levels has been found in various malignancies (Table 1) [9,10,13–19]. The level of 15-PGDH is high in the normal tissue compared to the human cancer tissues, such as breast, colon, stomach, lung, skin, kidney, small intestine, pancreas, and liver [13]. The genetic disruption of *15-Pgdh* completely blocks production of the urinary PGE_2 metabolite [13]. Knocking out the murine 15-*Pgdh* gene markedly sensitizes normally resistant C57BL/6J mice to colon tumor induction by carcinogen azoxymethane (AOM) [15]. In addition, the number of AOM-induced aberrant crypt foci, which are the earliest neoplastic precursor lesions, increased in 15-PGDH null mice compared to those formed in the 15-PGDH wild type mice. Moreover, the loss of 15-PGDH expression was observed in adenomas formed in patients with familial adenomatous polyposis [15]. Based on these findings, it is likely that inactivation of 15-PGDH is closely linked to the earliest steps in the development of colonic dysplasia.

The tumor suppressor function of 15-PGDH was also supported by genetic ablation of 15-*PGDH* in cancer cells. Small interfering RNA (siRNA) knock down of 15-*PGDH* stimulated proliferation of human medullary thyroid carcinoma [17] and breast MCF-7 cells [10], increased the motility of bladder cancer cells [9], and enhanced the cell cycle entry of MCF-7 cells [10]. The anchorage-independent growth of MCF-7 and human medullary thyroid caricinoma cells was also increased by siRNA-mediated suppression of 15-*PGDH* [10,17]. In contrast, optimal expression of 15-PGDH contributes to the inhibition of malignant phenotypes, such as cancer cell proliferation, invasion, and metastasis. When 15-PGDH was overexpressed in cancer cells, including those of breast [10,20], colon [20], lung [21], and glioma [22], the proliferation of these cells was decreased. Moreover, mice bearing cancer cells transfected with 15-*PGDH* gene showed marked retardation of xenograft tumor growth [10,20,21]. 15-PGDH overexpression also led to suppression of angiogenesis

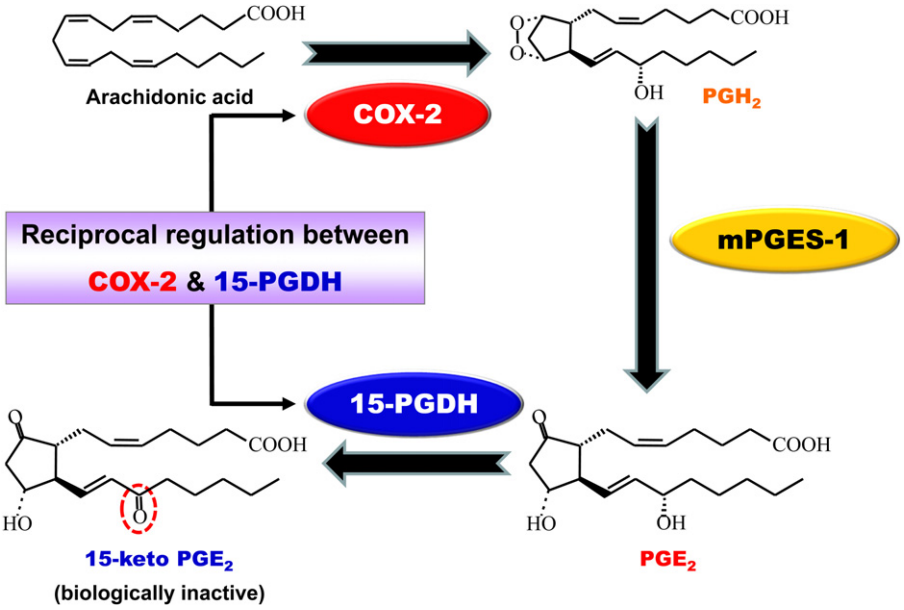

Fig. 1. The biosynthesis and degradation of PGE_2 by COX-2 and 15-PGDH, respectively. The rate-limiting step in the prostaglandin biosynthesis is the conversion of arachidonic acid to PGH_2 which is catalyzed by COX-2. Microsomal prostaglandin E synthase (mPGES)-1 converts PGH_2 to PGE_2. 15-PGDH catalyzes oxidation of the 15-hydroxy group of PGE_2 to 15-keto PGE_2, thereby inactivating oncogenic PGE_2. There is a reciprocal regulation between COX-2 and 15-PGDH expression.

Table 1
Role of 15-PGDH as a tumor suppressor in various cancer models.

Tumor types	Experimental models/tissues	Response	Ref.
Colorectal	15-PGDH knock out mice	Increased tissue level of PGE_2	[15]
	AOM-treated 15-PGDH knockout mice	Increased tumor formation	[15]
	15-PGDH knock out mice crossed $APC^{+/Min}$ mice	7.6-fold increase in colon tumors	[15]
	Specimens from patients with familiar adenomatous polyposis	Loss of 15-PGDH expression	[15]
	Human colorectal carcinoma	Decreased 15-PGDH expression and activity	[13]
	$Apc^{Min+/-}$ mouse adenomas	Decreased 15-PGDH expression	[13]
	Several colorectal carcinoma cell lines	Decreased 15-PGDH expression	[13]
	SW480 cells transfected with 15-PGDH expression vector	Suppression of migration and invasion	[7]
Lung	Athymic nude mice injected with A549 cells expressing wild-type 15-PGDH	Decreased tumor growth	[14]
	Athymic nude mice injected with A549 expressing mutant 15-PGDH (Y151F)	Increased tumor formation	[14]
	Overexpression of 15-PGDH in A549 cells	Enhanced apoptosis	[14]
	Human non-small cell lung carcinoma	Decreased 15-PGDH expression	[14]
Gastric	MKN-28 cells transfected with 15-PGDH siRNA	Increased PGE_2 production and anchorage-independent growth	[19,26]
	Human gastric carcinoma	Decreased expression of 15-PGDH	[26]
Breast	Human breast cancer tissue	Decreased 15-*PGDH* mRNA expression	[10]
	MCF-7 cells transfected with 15-PGDH siRNA	Enhancement of proliferation and colony formation	[10]
	MDA-MB-231 cells with 15-PGDH overexpression	Decreased clonal growth and tumor formation	[10]
Bladder	Human bladder cancer tissues	Complete loss of 15-PGDH expression	[9]
	RT4 cells transfected with 15-PGDH siRNA	Increase of motility and anchorage-independent growth	[9]
Thyroid	Human medullary thyroid cancer TT cells transfected with 15-PGDH siRNA	Increase of proliferation	[17]
Pancreas	Human pancreatic tumor	Decreased 15-*PGDH* mRNA and protein expression	[16]

and invasion by modulating PGE_2 production, vascular endothelial growth factor expression, matrix metalloproteinase-2 synthesis, and CD44 expression in lung [21] and colon cancer cells [7]. The microvessel densities were significantly reduced in xenografts derived from 15-PGDH overexpressing H358 lung cancer cells [21]. In addition, overexpression of 15-PGDH expedites induction of apoptosis via proteolytic cleavage of pro-caspase3 and poly(ADP-ribose) polymerase in lung cancer cells [23]. Furthermore, 15-PGDH plays an important role in regulation of local antitumor immune response [24]. Introduction of *15-PGDH* gene in colon tumor tissue attenuated tumor-induced immune suppression and substantially reduced secretion of immunosuppressive mediators and cytokines, such as PGE_2, interleukin (IL)-10, IL-13, and IL-6 by intratumoral CD11b cells [24].

15-PGDH expression status also influences the sensitivity to chemotherapeutic agents. Wakimoto et al. demonstrated that inhibition of 15-PGDH expression attenuated the antiproliferative activity of the nonsteroidal anti-inflammatory drugs (NSAIDs) [22]. Adenoviral vector-mediated overexpression of 15-PGDH significantly inhibited growth of human breast and colon xenografts in athymic nude mice [20]. Moreover, the antitumor effect of 15-*PGDH* gene therapy was augmented by coadministration of avastin, an angiogenesis inhibitor [20]. In addition, the chemotherapeutic activity elicited by celecoxib requires the concomitant presence of 15-*Pgdh*, and loss of 15-PGDH imparts resistance to the anti-tumor effects of this selective COX-2 inhibitor [25]. In FVB mice, celecoxib prevents 85% of AOM-induced tumors, but is essentially inactive in suppressing tumor induction in 15-*Pgdh*-null animals. In parallel with the loss of tumor suppressive activity, the reduction of colonic PGE_2 levels by celecoxib administration was also markedly attenuated in 15-*Pgdh* knock out mice [25]. Notably, this phenomenon was also observed in a colon adenoma prevention trial; individuals who further developed adenomas while receiving celecoxib treatment were found to have relatively low levels of colonic 15-PGDH [25]. Based on these findings, the delivery of 15-*PGDH* gene into tumors is likely to confer susceptibility to chemotherapeutic agents by decreasing excess accumulation of oncogenic PGE_2 and may hence be considered as a novel anticancer strategy.

3. Reciprocal regulation of COX-2 and 15-PGDH

Increased expression of COX-2 appears to be inversely related to the expression of 15-PGDH and *vice versa*. 15-PGDH has been known as an endogenous COX-2 antagonist [23]. Down-regulation of 15-PGDH was also observed in various cancer tissues with concomitant overexpression of COX-2 [9,10,13–15,18,19]. In gastric cancer specimens, there was a decreased expression of 15-PGDH and an elevated expression of COX-2 simultaneously [26]. Thus, 15-PGDH expression was found to be inversely correlated with the COX-2 level and lymph node metastasis of gastric cancer [26]. Moreover, IL-1β, tumor necrosis factor-α (TNF-α) and phorbol ester, which are well known inducers of COX-2 expression, significantly down-regulated the expression of 15-PGDH in human lung adenocarcinoma cells [8]. Conversely, the anti-inflammatory cytokines, IL-10, up-regulated the expression of 15-PGDH by antagonizing the 15-PGDH down-regulation induced by pro-inflammatory cytokines, IL-1β and TNF-α, in villous and chorionic trophoblasts [27]. It appears that there is an interplay between COX-2 and 15-PGDH. It was speculated that COX-2-derived products might mediate the inhibition of 15-PGDH expression. However, down-regulation of 15-PGDH expression by IL-β was affected by neither COX-2-derived products and its mimetic compound, such as PGE_2 and a thromboxane A2 analog, nor any of the COX-2 inhibitors in lung adenocarcinoma cells [8]. It appears that the amount of COX-2 expression determines the extent of attenuation of 15-PGDH expression. Liu et al. found that the expression of 15-PGDH was upregulated (128.57%) when COX-2 expression was blocked by siRNA knock down, but down-regulated (51.72%) as a consequence of *COX-2* cDNA transfection in gastric cancer cells [26]. Consistently, when IL-1β-induced COX-2 expression was abrogated by *COX-2* siRNA, 15-PGDH was significantly upregulated [8]. On the contrary, when the level of 15-PGDH expression was increased by transfection with pcDNA3 or adenovirus harboring *15-PGDH*, the level of COX-2 expression induced by IL-1β was decreased in a manner dependent on the level of 15-PGDH expression [8]. This was further supported by the finding that suppression of 15-PGDH expression by 15-*PGDH*-siRNA led to a further increase in the IL-1β-induced expression of

COX-2 but not that of COX-1 [8]. It seems that increased expression of 15-PGDH may impede the expression of COX-2 induced by IL-1β. In another experiment, siRNA knock down of 15-PGDH resulted in a substantial increase of PGE_2 production in gastric cancer (MKN-28) cells and enhanced the anchorage-independent growth of these cells by 31% [19]. The expression of COX-2 protein, not the activity, is responsible for attenuation of 15-PGDH expression. This is reminiscent of the situation in which it is the expression of 15-PGDH protein that inhibits COX-2 expression [8]. Therefore, the expression of COX-2 itself may be responsible for the attenuation of 15-PGDH expression.

Overexpression of COX-2 and repression of 15-PGDH may coordinately increase levels of PGE_2 in the tumor microenvironment, and exacerbate the carcinogenic process. The molecular mechanism underlying reciprocal relationship between COX-2 expression and 15-PGDH remains to be determined.

4. Oncogenic effects of 15-PGDH

Although the role of 15-PGDH as a tumor suppressor has been observed in various malignances, it has recently been reported that 15-PGDH is induced by some cytokines and tumor promoters and overexpressed in certain cancer tissues. Androgens are known to play a critical role in the promotion and progression of prostate carcinogenesis by modulating specific gene expression [28]. Androgens induce the expression of 15-PGDH in hormone responsive human prostate cancer LNCaP cells but not in hormone refractory PC-3 cells [29]. The expression of IL-6 and its receptor has been consistently demonstrated not only in human prostate carcinoma but also in benign prostate hyperplasia. Furthermore, serum levels of IL-6 have been shown to be elevated in patients with metastatic prostatic carcinoma [30]. In prostate cancer cells, androgen-induced expression of 15-PGDH was synergistically enhanced by IL-6 and forskolin [12]. IL-6 was shown to induce expression as well as activity of the androgen receptor through activation of mitogen-activated protein (MAP) kinases, such as extracellular-regulated protein kinase (ERK), and signal transducers and activators of transcription (STAT) 3 [12]. The inhibitors of MAP kinase and Janus kinase (JAK) and casodex, an antagonist of the classical androgen receptor, suppressed the IL-6-induced 15-PGDH activity [12]. It has been known that STAT3 mediates IL-6-induced activation of the androgen receptor as a coactivator of the receptor [31]. The molecular mechanisms responsible for the synergistic stimulation of 15-PGDH expression by IL-6 plus androgen and by forskolin together with androgen are not clear. Increased androgen receptor expression and STAT3 activation may in part account for the synergism in 15-PGDH expression. The oncogenic effects of 15-PGDH was suggested for other cancer types. Thill et al. demonstrated that the protein levels of both 15-PGDH and COX-2 were even more significantly higher in the malignant ovarian tissue specimens compared to the normal tissue [11]. According to the above study, 15-PGDH is highly expressed in breast cancer tissue as well. In addition, 15-PGDH activity was found to be induced by PMA in human lymphoma U937 cells, and this was inhibited by the concurrent addition of dexamethasone [32]. In another study, stable overexpression of 15-PGDH in A549 lung cancer cells appeared to induce epithelial-mesenchymal transition as evidenced by the increased expression of mesenchymal markers, morphological changes, and the xenograft tumor growth in mice [18]. However, the transient overexpression of 15-PGDH in A549 lung cells attenuated cytokines-induced expression of COX-2 and induced apoptosis.

It is intriguing that 15-PGDH metabolizes and inactivates anti-inflammatory lipoxins as well as pro-inflammatory PGE_2. The lipoxins are lipid mediators that are generated and act locally at the sites of inflammation, where they down-regulate polymorphonuclear leukocyte function and promote resolution [1]. 15-PGDH has been known to catalyze the conversion of lipoxin A_4 (LXA_4) to 15-oxo-LXA_4, 13,14-dihydro-15-oxo-LXA_4, and 13,14-dihydro-LXA_4 in a series of reactions. 15-PGDH has been known to be involved in inactivation of lipoxins and 15-epi-lipoxins because these lipoxins are excellent substrates of 15-PGDH [33,34]. The facilitated catabolism of these anti-proliferative eicosanoids may enhance tumorigenesis. Therefore, 15-PGDH expression by IL-6 or other growth factors, and cytokines may contribute to the promotion and growth of some types of cancer through stimulating the catabolism of anti-proliferative eicosanoids.

5. Transcriptional Regulation of 15-PGDH expression

The 15-PGDH gene spans about 31 kb on chromosome 4 and contains 7 exons. There are two regions for clustered putative transcription factor binding sites within 2.4 kb of the 5′-flanking sequence [35]. The distal promoter element of 15-*PGDH* (positions-2152/-1944) contains binding sites for Ets and activating protein-1 (AP-1) flanked by two cAMP-responsive element-binding proteins (CREB1 and CREB2), whereas the proximal element of 15-*PGDH* (−235/−153) contains Ets and AP-1 binding sequences [35] (Fig. 2). The 5′-untranslated region of 15-*PGDH* promoter contains several E-boxes, which are bound by the Snail, Slug, and ZEB1 transcriptional repressors (Fig. 3). Regulation of 15-PGDH expression at the translational and post-transcriptional levels remains poorly understood.

5.1. Epidermal growth factor (EGF) signaling

COX-2 has been identified as an epidermal growth factor (EGF)/transforming growth factor (TGF)-α target gene in intestinal epithelial cells, with robust enhancement of prostaglandin production following EGF receptor (EGFR) activation [36]. PGE_2 induced migration and invasion via rapid transactivation and phosphorylation of the EGFR [37]. Simultaneous blockade of prostaglandin and EGFR signaling by sulindac and the EGFR kinase inhibitor EKI-569 abates tumor formation in Apc^{Min} mice [38]. It is noticeable that the expression of EGFR is inversely associated with survival of patients with colorectal cancer [39].

Increased expression of Snail, Slug, and ZEB1 transcription repressors has been shown in breast, ovarian, colon, skin and

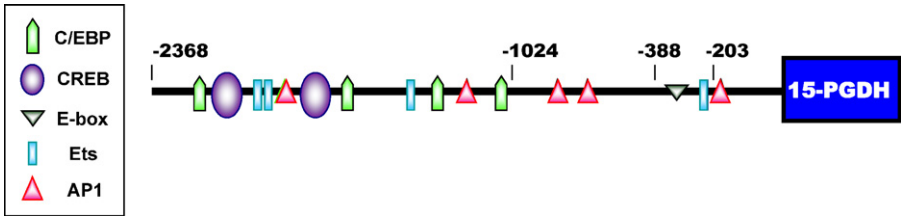

Fig. 2. Schematic representation of the human 15-*PGDH* promoter. The promoter region of human 15-*PGDH* contains binding sites for several transcription factors, including C/EBP, CREB, Ets, and AP-1.

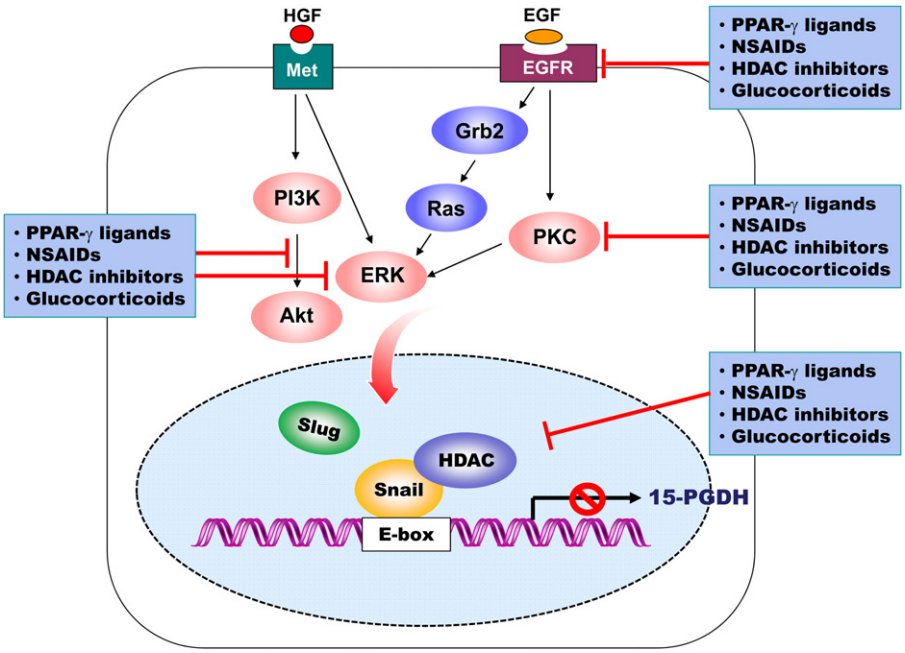

Fig. 3. Possible molecular mechanisms underlying 15-PGDH regulation. Snail and Slug transcriptional repressors may suppress the expression of 15-PGDH by recruiting HDAC to E-box element in 15-PGDH promoter region. EGFR and Met signaling activate the expression of transcription repressors Snail and Slug through activation of their upstream target molecules, such as ERK1/2, Akt, and PKC. The transcriptional repressors recruit the HDAC to the promoter of 15-PGDH and bind to the E-box, thereby suppressing the expression of 15-PGDH. The chemotherapeutic and chemopreventive agents, such as PPAR-γ ligands, HDAC inhibitors, glucocorticoids, and NSAIDs, may suppress the activity of PKC, ERK1/2, and Akt or expression of transcriptional repressor, involved in expression of 15-PGDH.

squamous cell carcinomas, which is correlated with poor prognosis [40,41]. Mann et al. reported that EGF and Snail repress 15-PGDH expression, increase PGE_2 and subsequently induce cancer progression [42]. Elevated Snail expression correlates well with down-regulation of 15-PGDH in human colon and breast cancer tissues [42]. In addition, the adenomas formed in the intestine of *Apc*^{Min} mouse showed a relatively high level of Snail expression, whereas expression of 15-PGDH was almost completely absent [42]. Snail and Slug induced by EGF receptor signaling recruit histone deacetylases (HDACs) which bind to conserved E-box elements present in the promoter of 15-PGDH and repress transcription of this gene [42,43] as illustrated in Fig. 3.

EGF requires Snail to repress 15-PGDH in colon cancer [42]. The cells transfected with wild type Snail construct showed suppression of 15-PGDH transcription in a manner similar to stimulation with EGF, while the cells harboring mutant Snail could not effectively repress transcription of 15-*PGDH*. In addition, erlotinib, an EGFR kinase inhibitor, induced the expression of 15-PGDH while it reduced the expression of Snail, Slug, and COX-2 in colon and lung cancer [42,43].

Phosphatidylinositol-3 kinase (PI3K)/protein kinase B and the Ras/MAP kinase signaling cascades which are the downstream signaling pathways of EGFR play prominent roles in cell survival and cell proliferation. Suppression of ERK activity by inhibiting the upstream MEK kinase blocked the down-regulation of 15-PGDH induced by EGF signaling [43]. Moreover, an MEK kinase inhibitor also suppressed the expression of Slug and ZEB1.

5.2. *Transforming growth factor (TGF)-β signaling*

The anti-inflammatory cytokine TGF-β is well known to mediate potent tumor suppressive effects in some cancers. The TGF-β signaling is initiated by type II receptor, which recruits and phosphorylates a type I receptor. The type I receptor then phosphorylates receptor-regulated Smad, which subsequently translocates into the nucleus where it interacts with DNA binding partners to regulate gene expression (Fig. 4). TGF-β has been shown to antagonize the proinflammatory cytokine-mediated activation of NF-κB [44]. TGF-β signaling is commonly inactivated in colon cancers via mutations of type II receptor or down-stream Smad signaling element [45,46]. TGF-β has been known to induce the expression of 15-PGDH in colon cancer cells [6] and lung adenocarcinoma cells [47]. Treatment of nontransformed Vaco-330

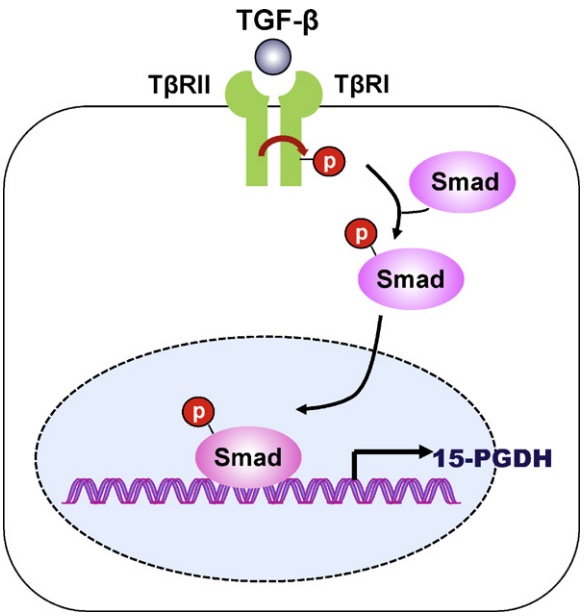

Fig. 4. Involvement of TGF-β signaling in the expression of 15-PGDH. The TGF-β signaling is initiated by type II receptor (TβR II), which recruits and phosphorylates a type I receptor (TβR I). The activated type I receptor then phosphorylates receptor-regulated Smad, which subsequently translocates into the nucleus where it interacts with DNA binding partners to regulate the target gene expression.

colon epithelial cells with TGF-β showed >12-fold induction of 15-PGDH expression as determined by expression microarrays [6]. TGF-β strongly induced expression of 15-PGDH in a colon cancer cell line transfected with a wild type receptor II gene [6]. TGF-β1 increased the luciferase activity of 388 bp-15-PGDH promoter construct in a concentration dependent manner [47]. The type I receptor kinase inhibitor SB431542 attenuated the 15-PGDH activity induced by TGF-β1, suggesting that expression of 15-PGDH by TGF-β appears to be mediated by TGF-β type I and II receptors [47]. Cycloheximide fails to block the TGF-β-induced 15-*PGDH* transcript, suggesting that 15-PGDH transcript is induced as a direct target of the TGF-β signaling pathway without the need for intermediate protein synthesis [6]. In addition, treatment of lung cancer A549 cells with TGF-β and a HDAC inhibitor scriptaid together showed an additive effect in inducing 15-PGDH expression [47].

Therefore, 15-PGDH expression is directly controlled and strongly induced by activation of the TGF-β tumor suppressor pathway. However, the molecular mechanism by which TGF-β regulates 15-PGDH expression remains poorly understood.

5.3. Hepatocyte growth factor (HGF) signaling

HGF signaling via the Met receptor up-regulates COX-2 expression in different cell types [48,49]. In many solid tumors, Met is frequently overexpressed as a result of deregulation in growth factor or oncogenic signaling or stimulation by tumor microenvironmental factors such as hypoxia [50,51]. Met expression is evident in a large proportion of colorectal tumors and associated with a poor prognosis [52,53]. Thus, there is growing interest in targeting HGF/Met signaling therapeutically. Moore et al. have demonstrated that HGF/Met signaling plays an important role in colon carcinogenesis via COX-2 up-regulation and 15-PGDH down-regulation [52]. Notably, inhibition of Met with the small molecule inhibitor SU11274 reduced COX-2 expression and increased 15-PGDH expression in high Met-expressing cells. Both ERK and Akt are required for COX-2 protein up-regulation and 15-PGDH down-regulation as downstream molecules of Met (Fig. 3).

5.4. Ras/MAP kinase signaling

Other signaling enzymes that are likely to be implicated in 15-PGDH expression are protein kinase (PKC) and Ras/MAP kinase. PMA has been known to promote carcinogenesis through activation of PKC signaling [54]. PMA down-regulates the expression of 15-PGDH in human chorion trophoblast cells, which is attenuated by inhibition of PKC [55]. However, contrary to the above findings, Tong et al. reported that PMA induced 15-PGDH activity in human lymphoma U937 cells, which was blocked by the PKC inhibitor staurosporine or GF109203X [32]. The role of PKC in regulation of 15-PGDH expression is controversial depending on the cell type.

Constitutive activation of Ras signaling is thought to promote overexpression of COX-2. COX-2-derived PGE_2 constitutively activates Ras/MAP kinase signaling via EP receptors in a positive autocrine feedback loop [56]. Three distinct groups of well characterized major MAP kinase subfamily members include ERK, c-Jun NH_2-terminal kinase/stress-activated protein kinase and p38 MAP kinase which are serine/threonine protein kinases. The activation of MAP kinases is involved in expression of many inflammation- and oncogenic genes including COX-2. Bile acids, an inducer of colorectal carcinogenesis, has been shown to inhibit the transcription of 15-PGDH via PKC/ERK1/2 activation in the colonocytes [57]. Suppression of bile acid-mediated activation of ERK1/2 and PKC blocked the down-regulation of 15-PGDH [57]. Bile acids induced early growth response factor-1 (Egr-1) and Snail that binds to the 15-PGDH promoter. Silencing Egr-1 or Snail blocked chenodeoxycholate-mediated down-regulation of 15-PGDH. Taken together, these data indicate that bile acids suppress 15-PGDH transcription via activation of PKC/ERK1/2/Egr-1/Snail signaling pathways.

Oncogenic Ras mutations are early genetic events in colorectal cancer that induce COX-2 expression and PGE_2 biosynthesis. The cell harboring K-*Ras* gene exhibited increased phosphorylation of MAP kinases and CREB, proliferation rates, expression of COX-2 and mPGES-1 and PGE_2 and PGI_2 levels. Introduction of 15-*Pgdh* gene into the cells harboring K-*Ras* gene increased the 15-PGDH activity with decreased PGE_2 production and COX-2 expression via suppression of ERK or CREB [58]. When these cells were inoculated onto athymic *nu/nu* mice, they delayed tumor formation and induced apoptosis [58].

Several potential binding sites for CREB, Ets, and AP-1 transcription factors are present within the 2368 bp of the 5′-flanking region of 15-*PGDH* (Fig. 2). It has been reported that the human 15-PGDH promoter is controlled by AP-1 transcription factor in Jurkat leukemic T cells treated with phorbol ester [59]. Induction of 15-PGDH was reversed by coexpression of A-Fos, a dominant negative to AP-1. The Ets family members Ets-1, Ets-2, and PEA3 potently stimulated transcriptional activity of the 15-PGDH promoter in primary cultures of myometrial smooth muscle cells (SMC). PEA3-mediated transcriptional activation was partially repressed by A-Fos, indicative of an involvement of AP-1 proteins. The forkhead transcription factor hepatocyte nuclear factor 3beta (HNF3β) is known as a candidate tumor suppressor in the lung, and the expression of HNF3β leads to growth arrest and apoptosis in lung cancer cells [21]. In a transcriptional profiling study, 15-*PGDH* was identified as one of the major genes induced by HNF3β in lung cancer [21]. HNF3β increases 15-PGDH gene transcriptional activity by directly binding to two regions of the 15-PGDH promoter (−3793 to −3778 bp and −446 to −430 bp). Twenty-four percent of the HNF3β-negative tumors and 50% of the HNF3β-positive tumors were 15-PGDH positive. Therefore, 15-PGDH is considered as a direct down-stream effecter of HNF3β.

5.5. Epigenetic modulation

Expression of 15-PGDH has been shown to be repressed by an epigenetic mechanism involving histone deacetylation and methylation. Histone deacetylation was associated with 15-PGDH silencing in lung and breast cancer [10,47]. HDAC2 expression is inversely associated with 15-PGDH expression in adenomas in $Apc^{Min/+}$ mice and colorectal cancer [60]. 15-PGDH and HDAC2 are reciprocally coexpressed within both normal and tumor colon tissues and adenomas in $Apc^{Min/+}$ mice [60]. The transcriptional suppressors, such as Snail, Slug, and ZEB1, can interact with HDACs (e.g., HDAC1 and HDAC2), thereby repressing the transcription of target genes, such as *BRCA2* and *E-cadherin* [61,62]. Backlund et al. have reported that Snail can interact with HDAC2 and the resulting HDAC2-Snail complex may suppress the 15-PGDH expression [60].

In many cases, silencing of gene expression by methylation of CpG island in the target gene promoter contributes to carcinogenesis. The silence of the 15-*PGDH* gene has been associated with methylation in the CpG island of the 15-PGDH promoter in the colon, breast, prostate, and gastric cancers [10,19,60,63]. It has been reported that the 15-PGDH promoter is methylated in breast cancer MDA-MB-231 cells and about 30% of primary breast tumors [10]. Treatment with the demethylating agent 5-Aza-2′-deoxycytidine restored expression of 15-PGDH in breast, colorectal, and gastric cancer cells [10,19,60]. Therefore, DNA methylation as well as histone deacetylation is also considered as one of factors involved in 15-PGDH suppression.

6. 15-PGDH as a potential molecular target of chemopreventive agents

Inflammation has been implicated in the development and progression of many cancers [64]. NSAIDs targeting COX-2 have been reported to reduce the levels and biological activity of PGE_2, and consequently suppress the carcinogenesis. Likewise, a wide variety of chemopreventive agents with anti-inflammatory properties suppress the COX-2 expression, PGE_2 production, and HDAC activity by targeting corresponding signaling pathways [65]. Expression of 15-PGDH has been known to be negatively regulated by COX-2 expression and HDAC activity. 15-PGDH is considered as one of the target molecules of HDAC inhibitors and COX-2 inhibitors. HDAC inhibitors, such as sodium butyrate, scriptaid, apicidin and oxamflatin, have been shown to induce the expression of 15-PGDH in lung adenocarcinoma cells [47]. Therefore, chemopreventive agents with COX-2 and HDAC inhibitory activity are expected to exert their chemopreventive activity through induction of 15-PGDH expression. Some substances currently identified to induce 15-PGDH as part of their chemopreventive/chemoprotective activities are listed below.

6.1. NSAIDs

NSAIDs such as indomethacin, sulindac, and celecoxib primarily target COX-2 activity, and also have been known to block, delay and even reverse the carcinogenic processes [66]. Epidemiological studies have shown that individuals taking NSAIDs exhibit a significant reduction in colorectal cancer compared to those individuals who do not intake these agents [66]. A non-COX inhibitor sulindac sulfone has been shown to increase 15-PGDH activity and decrease the PGE_2 levels, which is associated with inhibition of proliferation of human medullary thyroid carcinoma cells [17]. However, other studies revealed that chemotherapeutic and chemopreventive activities of some NSAIDs are mediated through COX-2-independent mechanisms. Diclofenac sodium and meloxicam inhibited the growth of glioblastoma mutiforme cells through induction of 15-PGDH and p21 expression, without suppression of the COX-2 expression [22]. Overexpression of 15-PGDH suppressed cell growth which was associated with increased expression of p21, but the expression level of p21 was not affected in COX-2 siRNA transfected cells. In addition, growth inhibition by NSAIDs was partially reversed by knock down of either *15-PGDH* or *p21*, but not by COX-2 knock down [22]. These results suggest that up-regulation of 15-PGDH and subsequently p21 induced by some NSAIDs may contribute to the suppression of growth of some cancerous cells and these effects are independent of COX-2 inhibition.

6.2. HDAC inhibitors

Several HDAC inhibitors have elicited anti-neoplastic activity in preclinical studies [67]. Some of these inhibitors are currently in phase I clinical trials. Histone deacetylation was observed in the promoter region of 15-PGDH in several cancer tissues [10]. HDAC inhibitors, such as sodium butyrate, scriptaid, and valproic acid, have been reported to induce the expression of 15-PGDH in lung adenocarcinoma and colon cancer cells [47,60]. Pretreatment of colorectal carcinomas cells with sodium butyrate and valproic acid blocked EGF-mediated or Snail-mediated transcriptional repression of 15-PGDH [60]. Snail interacts with HDACs that bind to the 15-PGDH promoter, thereby repressing the 15-PGDH expression [60]. Upregulation of 15-PGDH by HDAC inhibitors is likely to be mediated by blocking the EGF- or Snail-induced HDAC recruitment to the Ets site [60]. Chromatin immunoprecipitation assays examining the 15-PGDH promoter in colon cancer cells showed loss of HDAC2 binding after treatment with an HDAC inhibitor [60]. Sodium butyrate and scriptaid induced significant accumulation of acetylated histones H3 and H4, which were associated with the 15-PGDH promoter [47,60]. In addition, scriptaid stimulated synergistically TGF-β1-induced 15-PGDH expression in lung adenocarcinoma cells [47]. HDAC inhibitors may enhance the 15-PGDH expression by reducing the binding of HDAC to the promoter of 15-PGDH.

6.3. Calcitriol

Calcitriol (1,25-dihydroxyvitamin D_3), an active metabolite of vitamin D, has been well known as a major regulator of calcium homeostasis and bone mineralization [68]. Calcitriol is an FDA-approved drug and it is currently being evaluated in clinical trials as an anti-cancer agent in prostate cancer patients. Calcitriol has been reported to inhibit invasion, metastasis and tumor angiogenesis and to induce apoptosis in breast [69] and prostate cancer cells [70]. Calcitriol suppresses COX-2 expression while upregulates 15-PGDH, thereby reducing the levels and biological activity of oncogenic prostaglandins, such as PGE_2 [70–72]. The anti-proliferative effects of calcitriol are mediated via the vitamin D receptor (VDR) [69]. It was reported that the VDR protein levels were inversely correlated to the 15-PGDH protein levels in benign and malignant breast cell lines, suggesting a possible link between VDR-associated target genes and prostaglandin metabolism [69]. Calcitriol induces the expression of MAP kinase phosphatase 5 (MKP5), a member of a family of phosphatases that are negative regulators of MAP kinases, causing inactivation of the stress-activated protein kinase p38 [73]. IL-6, a p38-regulated pleiotropic cytokine, is known to be implicated in prostate cancer progression, and suppression of p38 activity by calcitriol may be coupled with induction of 15-PGDH and concurrent suppression of PGE_2. These effects may account for chemopreventive and therapeutic activity of calcitriol.

6.4. Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) ligands

PPAR-γ is a member of the nuclear receptor superfamily of ligand-activated transcription factors. PPAR-γ activators of the thiazolidinedione class (TZDs), such as rosiglitazone and troglitazone, have been shown to suppress the tumor growth, induce apoptosis of cancerous cells, and exert anti-inflammatory and anti-metastatic effects. The anti-proliferative as well as anti-inflammatory effect of PPAR-γ ligands is mediated, in part, through suppression of COX-2 [74]. Some PPAR-γ ligands induce the expression of 15-PGDH and suppress PGE_2 production in non-small-cell lung cancer cells [75]. The Snail family of transcription factors, which includes Snail, Slug, and ZEB1, is an important regulator of epithelial-mesenchymal transition, as well as cell survival. Rosiglitazone, a prototypic member of the TZD family of PPAR-γ activators, specifically decreased expression of Snail which is involved in 15-PGDH suppression, but had no significant effect on expression of either Slug or ZEB1 [76]. siRNA silencing of Snail mimicked the anti-tumorigenic effects of PPAR-γ activation by rosiglitazone. This was associated with the increased expression of E-cadherin and decreased expression of COX-2 and MMPs. Therefore, suppression of Snail expression and consequent 15-PGDH upregulation may contribute to the antitumorigenic effects of PPAR-γ activators.

6.5. Glucocorticoids

Glucocorticoids represent the most widely used anti-inflammatory drugs [77]. Dexamethasone is a potent synthetic member of the glucocorticoid class of steroid drugs. Dexamethasone has been known to elicit hematoprotective effects in cancer patients receiving chemotherapy. Dexamethasone and other glucocorticoids modulate

the expression of several genes involved in inflammatory responses. One of the target genes of glucocorticoid is COX-2 which is suppressed through both transcriptional and post-translational mechanisms [78]. Tong and Tai reported that dexamethasone, prednisolone, triamcinolone, and other glucocorticoids induced the expression and activity of 15-PGDH in lung adenocarcinoma cells [79]. The expression of 15-PGDH induced by dexamethasone was inhibited by pro-inflammatory cytokines and phorbol ester via a PKC-mediated mechanism [79]. In human etythroleukemia (HEL) cells, anti-inflammatory steroids including dexamethasone also increased 15-PGDH activity, which correlated with their glucocorticoid activity [80]. Induction of 15-PGDH expression appeared to be mediated by the glucocorticoid receptor and a nuclear mediated event since the induction was blocked by the receptor antagonist RU486 and by the nuclear translocation inhibitor geldanamycin [79].

7. Conclusion

15-PGDH is a crucial enzyme responsible for the biological inactivation of PGE_2 which has oncogenic potential as evidenced by inducing cell proliferation, migration, angiogenesis and tumor metastasis. Down-regulation of 15-PGDH was observed in several malignancies, such as colorectal [15], lung [14], gastric [26], bladder [9], and pancreas [16] cancers. Therefore, up-regulation of 15-PGDH expression is anticipated to suppress carcinogenic processes and enhance the sensitivity against chemotherapeutic agents. Anticancer therapeutics, such as TGF-β1, glucocorticoids and HDAC inhibitors, have been shown to exert their anti-carcinogenic activity through induction of 15-PGDH. 15-PGDH is considered as an endogenous antagonist of COX-2, and suppression of signal transduction associated with COX-2/PGE_2 pathways may lead to induction of 15-PGDH expression. Therefore, there apparently exists reciprocal regulation between two enzymes. The COX-2-PGE_2 pathway influences most, if not all, of the hallmarks of cancer [81]. These effects are thought to result, at least in part, from PGE_2-dependent activation of signal transduction pathways, such as PI3K/Akt, Ras/MAP kinase, Wnt/β-catenin and EGFR signaling. Several chemopreventive and anticancer agents have anti-inflammatory activities targeting COX-2 and PGE_2. In addition, some anticarcinogenic agents function as DNA methyltransferase inhibitors capable of reversing methylation-induced silencing and restoring the expression of various tumor suppressor genes. Besides ability to induce changes in DNA methylation, some chemopreventive and chemotherapeutic compounds can also regulate gene expression through modulation of histone modifications. Many of these molecules have potential to induce the expression of 15-PGDH, which may contribute to their anticarcinogenic activity. As 15-PGDH can represent a novel molecular target for cancer chemoprevention and therapy, additional studies should follow to search for substances capable of optimally upregulating this tumor suppressing enzyme as well as to elucidate the molecular mechanisms underlying its regulation.

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