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15-Hydroxyprostaglandin Dehydrogenase (15-PGDH) and Lung Cancer

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Abstract

15-Hydroxyprostaglandin dehydrogenase (15-PGDH) catalyzes NAD⁺-linked oxidation of 15 (S)-hydroxyl group of prostaglandins and lipoxins and is the key enzyme responsible for the biological inactivation of these eicosanoids. The enzyme was found to be under-expressed as opposed to cyclooxygenase-2 (COX-2) being over-expressed in lung and other tumors. A549 human lung adenocarcinoma cells were used as a model system to study the role of 15-PGDH in lung tumorigenesis. Up-regulation of COX-2 expression by pro-inflammatory cytokines in A549 cells was accompanied by a down-regulation of 15-PGDH expression. Over-expression of COX-2 but not COX-1 by adenoviral-mediated approach also attenuated 15-PGDH expression. Similarly, over-expression of 15-PGDH by the same strategy inhibited IL-1 β -induced COX-2 expression. It appears that the expression of COX-2 and 15-PGDH is regulated reciprocally. Adenoviral-mediated transient over-expression of 15-PGDH in A549 cells resulted in apoptosis. Xenograft studies in nude mice also showed tumor suppression with cells transiently over-expressing 15-PGDH. However, cells stably over-expressing 15-PGDH generated tumors faster than those control cells. Examination of different clones of A549 cells stably expressing different levels of 15-PGDH indicated that the levels of 15-PGDH expression correlated positively with those of mesenchymal markers, and negatively with those of epithelial markers. It appears that the stable expression of 15-PGDH induces epithelial-mesenchymal transition (EMT) which may account for the tumor promotion in xenograft studies. A number of anti-cancer agents, such as transforming growth factor- β 1 (TGF- β 1), glucocorticoids and some histone deacetylase inhibitors were found to induce 15-PGDH expression. These results suggest that tumor suppressive action of these agents may, in part, be related to their ability to induce 15-PGDH expression.

Keywords

Prostaglandin dehydrogenase; Cyclooxygenase-2; Lung Cancer; Tumor suppressor; Epithelial-mesenchymal transition

INTRODUCTION

Lung cancer is the highest mortality of all cancers among men and women in the U.S. The 5-year survival rate is only 8–14% and has improved marginally in the last 25 years despite

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extensive research efforts (1). New approaches for the management of lung cancer are very much needed. One of the most significant approaches so far is to identify risk factors that are associated with the development of lung cancer and to develop effective measures to curtail or to eliminate the impact of these risk factors. One such potential target is the enzyme called cyclooxygenase (COX) catalyzing the synthesis of prostaglandins (PGs) which appear to be involved in cell proliferation, migration, angiogenesis and tumor metastasis (2).

There are three isoforms of COX reported so far. COX-1 is considered constitutive and is expressed in most cell types (3). COX-2 is regarded inducible and is expressed in response to mitogens, tumor promoters and inflammatory cytokines in some inflammatory cells and cancer cells (3). COX-3 is an alternate splicing variant of COX-1 and is expressed in some neural cells (4). It appears that only COX-2 and its ensuing coupling enzyme responsible for the synthesis of PGE₂, microsomal PGE synthase, were reported to over-express in lung tumors (5,6). Consequently, compounds that may inhibit the activities of these two enzymes are of particular value in the management of lung cancer. A notable example is the extensive evaluation of non-steroidal anti-inflammatory drugs (NSAIDs) which are known to target on COX-2 as anti-cancer therapeutics (7). However, the levels of PGs are controlled not only by the synthetic enzymes but also by the degrading enzyme, a fact that has been overlooked in studying prostaglandins and cancer.

The key enzyme involved in degrading PGE₂ is NAD⁺-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH). This enzyme catalyzes the oxidation of 15(S)-hydroxyl group of PGs and lipoxins. The products, 15-keto-metabolites, exhibit greatly reduced biological activities rendering this enzyme being a key enzyme responsible for the biological inactivation of these eicosanoids (8). Its functional role in cardiovascular and pulmonary systems has been extensively studied. However, its potential role in lung cancer and other cancers remains to be defined. Whether this enzyme is altered in expression in lung tumors much as COX-2 is not clear. Whether its expression is related to COX-2 expression in a specific manner remains to be elucidated. If COX-2 is oncogenic in nature, could its antagonistic enzyme, 15-PGDH, be a tumor suppressor? Could some anti-cancer therapeutics exhibit their action, at least in part, by inducing the expression of tumor suppressive 15-PGDH? These questions have recently been explored by a few interesting and revealing reports.

RESULTS AND DISCUSSION

Down regulation of 15-PGDH expression in lung and other tumors

Levels of PGE₂ are known to be significantly elevated in lung and other tumors (9). This has been primarily attributed to the consequence of the over-expression of synthetic enzymes, COX-2 and microsomal PGE synthase. Whether the degrading enzyme, 15-PGDH, plays any role in contributing to the elevated levels of PGE₂ in tumors is not clear. Heighway et al. (10) reported that 15-PGDH was under-represented at least 2-fold in 69% of lung tumor in a cDNA microarray study. Ding et al. (11) also showed that 100% of lung tumor-tissue pairs exhibited a 2-fold decrease in 15-PGDH expression and 61% exhibited a 10-fold decrease using quantitative RT-PCR analysis. Down-regulation of 15-PGDH in tumors was also observed in other cancers. Celis et al (12) first described that the loss of 15-PGDH and three other protein markers was associated with the progression of human bladder transitional cell carcinomas. Similar findings in transitional cell carcinoma were also reported by Gee et al. (13). Yan et al. (14) discovered that the median expression of 15-PGDH in colon tumor samples was at least 17-fold below the median expression in normal colon. Similarly, Backlund et al. (15) found that 15-PGDH is down-regulated in colorectal as well in other cancers using activity and microarray analysis. Very recently, Wolf et al. (16) also described that 15-PGDH is under-expressed in primary breast tumors. It appears that down-regulation of 15-PGDH expression is a common feature as opposed to up-regulation of COX-2 expression in various types of

cancers. The consequence of such a reciprocal regulation results in an amplified elevation of PGE₂ in tumor tissues. However, the mechanism responsible for such a reciprocal regulation remains to be determined.

Reciprocal regulation of the expression of COX-2 and 15-PGDH

A549 human lung adenocarcinoma cells possessing the capacity of expressing both COX-2 and 15-PGDH were used as a model system to explore the mechanism for reciprocal regulation of COX-2 and 15-PGDH (17). Resting cells express little COX-2, but significant level of 15-PGDH. IL-1 β , TNF- α or phorbol ester (PMA) induced the expression of COX-2 as revealed by Western blot analysis. Combination of PMA and IL-1 β or TNF- α induced synergistically the expression of COX-2. Interestingly, cytokines and cytokine plus PMA-induced expression of COX-2 were accompanied by a down-regulation of 15-PGDH in each case (18). This was evident from both Western blot analysis and activity assay of 15-PGDH. It appears that the higher the expression of COX-2 was induced, the lower the expression of 15-PGDH was found. This was further supported by the observation that over-expression of COX-2 but not COX-1 by adenovirus-mediated approach led to a decrease in the expression of 15-PGDH indicating that there is a specificity for COX-2. Furthermore, down-regulation of the IL-1 β -induced expression of COX-2 by siRNA approach resulted in an increase in the expression of 15-PGDH by COX-2-siRNA but not by COX-1-siRNA suggesting that it was indeed the expression of COX-2 attenuating the expression of 15-PGDH. The IL-1 β -induced reduction of the expression of 15-PGDH was shown not to be mediated by COX-2-derived products since the presence of COX-2 inhibitors did not block the attenuation of the expression of 15-PGDH. Exogenous PGE₂ also did not induce the reduction of the expression of 15-PGDH. However, over-expression of 15-PGDH by transfection with recombinant plasmid encoding 15-PGDH or adenovirus-mediated approach attenuated IL-1 β -induced expression of COX-2. On the contrary, down-regulation of 15-PGDH expression by 15-PGDH-siRNA or 15-PGDH-antisense approach resulted in an increase in IL-1 β -induced expression of COX-2 but not that of COX-1. In fact, it was further observed that A549 clones expressing different degrees of 15-PGDH showed also different levels of COX-2 expression after IL-1 β induction. The levels of IL-1 β -induced COX-2 expression appeared to correlate inversely with those of 15-PGDH expression in the cells. These results support the contention that the expression of COX-2 and 15-PGDH is regulated reciprocally in A549 cells. Similar feature of the reciprocal regulation of the expressions of COX-2 and 15-PGDH was also found in other cell types. Backlund et al. (15) demonstrated that epidermal growth factor which stimulated the expression of COX-2 induced a down-regulation of the expression of 15-PGDH in colon cancer cells, HCT-15 and HCA-7. Similarly, Pomini et al. (19) showed that IL-1 β increased COX-2 expression but decreased 15-PGDH expression in villous trophoblasts.

15-PGDH is a tumor suppressor

Down-regulation of the expression of 15-PGDH in lung and other tumors suggest that this enzyme is a tumor suppressor. Ding et al. (11) demonstrated that A549 cells infected with adenovirus encoding 15-PGDH showed retardation of the tumor growth in athymic nude mice model as compared to cells infected with adenovirus encoding inactive mutant 15-PGDH or with adenoviral vector alone. Examining the effects of adenovirus-mediated 15-PGDH expression on cellular changes in A549 cells, we found that over-expression of this enzyme induced apoptosis of A549 cells. This was demonstrated by the observations that fragmentation of DNA and cleavages of pro-caspase 3 and poly(ADP-ribose) polymerase occurred in these 15-PGDH over-expressing cells. Furthermore, these cells also exhibited significantly decreased expression of an anti-apoptotic protein Bcl-2 without altering the expression of apoptotic proteins p53 and BAX indicating that the apoptosis induced by the over-expression of 15-PGDH was independent of the p53 pathway. Bcl-2 is known to prevent the release of apoptosis-inducing factor (20) and cytochrome C from the mitochondria (21), which is

assumed to be a key event during apoptosis. Over-expression of 15-PGDH down-regulates the expression of Bcl-2 protein indicating a role for the 15-PGDH in apoptosis. Cell surface CD44 is the receptor for hyaluronate, a major glycosaminoglycan component of the cellular matrix, and may promote tumor invasion (22). Adhesion to the cellular matrix, a critical step in the metastatic process, has been found to be CD44-dependent in several malignancies (23,24). Expression of 15-PGDH in A549 cells appeared to cause down-regulation of CD44. In fact, stable clones of A549 cells expressing different levels of 15-PGDH exhibited varied expression of CD44. The expression of CD44 was inversely related to the expression of 15-PGDH. Exogenous hyaluronidase which is known to chemosensitize tumor cells to cytotoxic drugs and to induce the expression of an apoptotic oxidoreductase WWOX (25) was also able to induce the expression of 15-PGDH (11). These evidences support the contention that 15-PGDH functions like a tumor suppressor in lung cancer.

Glucocorticoids induce 15-PGDH expression

Glucocorticoids represent one of the most widely used anti-inflammatory drugs (26). Their actions appear to go beyond the anti-inflammatory effects and have been shown to include inhibition of lung cancer cell growth and regulation of cell cycle (27) and chemosensitization of other cytotoxic anti-cancer drugs (28). Considering the inflammatory and proliferative roles of prostaglandins, we examined the effect of glucocorticoids on the induction of 15-PGDH expression in A549 cells. Dexamethasone and other glucocorticoids induced the expression of 15-PGDH in a time- and dose-dependent manner in A549 cells (17). Maximal induction can be achieved at the therapeutic level of low nanomolar concentrations of glucocorticoids in A549 cells as opposed to the induction at the micromolar concentrations in human erythroleukemia (HEL) cells (29). Induction was inhibited by the addition of pro-inflammatory cytokines and phorbol ester. These pro-inflammatory agents were also shown to induce COX-2 expression. PMA was found to be the most effective stimulator of COX-2 expression and the most potent inhibitor of dexamethasone-induced 15-PGDH expression. The characteristic of the reciprocal regulation of the expressions of COX-2 and 15-PGDH is also operative here. The induction of 15-PGDH expression by dexamethasone was blocked by a glucocorticoid receptor antagonist RU486 and by a nuclear translocation inhibitor geldanamycin, indicating that the induction is a genetic mechanism. The fact that glucocorticoids are able to induce the expression of 15-PGDH suggests that the anti-inflammatory and anti-cancer effects of these agents may act, in part, by promoting the degradation of pro-inflammatory and proliferative prostaglandins.

Histone deacetylase (HDAC) inhibitors induce 15-PGDH expression

HDAC inhibitors have been actively evaluated as potential anti-cancer therapeutics. We suspect that HDAC inhibitors may function, in part, by inducing the expression of 15-PGDH. HDAC inhibitors such as sodium butyrate, scriptaid, apicidin and oxamflatin were found to induce the expression of 15-PGDH, a potential COX-2 antagonist and tumor suppressor, in a time and concentration dependent manner in A549 and H1435 lung adenocarcinoma cells (30). Detailed analysis indicated that HDAC inhibitors activated the 15-PGDH promoter-luciferase reporter construct in transfected A 549 cells. A representative HDAC inhibitor, scriptaid, and its negative structural analog control, nullscript, were further evaluated at the chromatin level. Scriptaid but not nullscript induced a significant accumulation of acetylated histones H3 and H4 which were associated with the 15-PGDH promoter as determined by chromatin immunoprecipitation assay. Transforming growth factor- β 1 (TGF- β 1) also induced the expression of 15-PGDH in a time and concentration dependent manner in A549 and H1435 cells. Induction of 15-PGDH expression by TGF- β 1 was synergistically stimulated by the addition of Wnt3A which was inactive by itself. However, combination of TGF- β and a HDAC inhibitor, scriptaid, only resulted in an additive effect. Together, our results indicate that 15-PGDH is one of the target genes that HDAC inhibitors and TGF- β may induce to exhibit tumor

suppressive effects. In addition to lung cancer cells, TGF- β was also found to induce the expression of 15-PGDH in some colon cancer cells (14). One of the non-responsive colon cancer cell lines became responsive to TGF- β after expressing a TGF- β type II receptor indicating a defective receptor of TGF- β may obstruct the signaling leading to the expression of 15-PGDH.

Is 15-PGDH involved in epithelial-mesenchymal transition (EMT)?

While we were studying the over-expression of 15-PGDH and attempting to stabilize the expression of 15-PGDH in A549 cells, we discovered that A549 cells over-expressing 15-PGDH after becoming stable clones began to show changes in morphology from epithelial-like to mesenchymal-like. Detection of marker changes by Western blot also indicated that the expression of 15-PGDH was positively related to that of mesenchymal markers such as N-cadherin and fibronectin, but was inversely related to that of epithelial markers such as E-cadherin and β -catenin. In other words, the disappearance of epithelial markers and the appearance of mesenchymal markers are going in parallel with the expression of 15-PGDH. This was further supported by the fact that the expression of phospho-ERK, Bcl-2, pro-caspase 3, and MMP-2 was positively related to the expression of 15-PGDH and the mesenchymal nature of the cells. The EMT was also examined in xenograft model in mice. A549 cells stably over-expressing 15-PGDH were also found to generate tumors in a much rapid manner compared to cells stably expressing low level of 15-PGDH. In fact, cells stably expressing anti-sense 15-PGDH showed little production of tumors. These studies support the hypothesis that 15-PGDH is somehow involved in EMT. The hypothesis is strengthened by the fact that TGF- β is known to induce EMT/MET (31) and that TGF- β induces the expression of 15-PGDH when A549 cells express low levels of 15-PGDH but attenuates the expression of the enzyme when cells express high levels of the enzyme. Further studies on the role of 15-PGDH in EMT/MET are warranted.

In summary, 15-PGDH functions antagonistically to COX-2 by degrading the synthesized PGs. The expression of 15-PGDH is down-regulated in lung as well as in other tumors as opposed to the expression of COX-2 being up-regulated. The reciprocal regulation of the expression of COX-2 and 15-PGDH can be also demonstrated in an A549 cellular model in which cytokines- or cytokines plus PMA-induced expression of COX-2 was accompanied by a down-regulation of 15-PGDH. Over-expression of 15-PGDH in A549 cells by adenovirus-mediated approach attenuated cytokines-induced expression of COX-2 and induced apoptosis as evidenced by increased fragmentation of DNA, cleavages of pro-caspase 3 and PARP, and down regulation of Bcl-2 expression. Accordingly, anti-cancer therapeutics such as TGF- β 1, glucocorticoids and histone deacetylase inhibitors were examined for their ability to induce the expression of tumor suppressive 15-PGDH. It was found that these agents were capable of inducing the expression of 15-PGDH in A549 cells as well as in other cell types. However, stable over-expression of 15-PGDH in A549 cells appeared to induce EMT as evidenced by the increased expression of mesenchymal markers and morphological changes, and the increased tumor growth as shown by xenograft studies in mice. The role of 15-PGDH in tumorigenesis is somewhat reminiscent of that of TGF- β in which the growth factor functions as a tumor suppressor in early stages of tumor growth but changes to a tumor promoter at the later stages of tumorigenesis. It is interesting to note that TGF- β also regulates the expression of 15-PGDH in A549 and other cancer cells. Studies on the role of 15-PGDH in tumorigenesis are well warranted.

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