Repression of Prostaglandin Dehydrogenase by Epidermal Growth Factor and Snail Increases Prostaglandin E_2 and Promotes Cancer Progression

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Abstract

Prostaglandin E_2 (PGE_2), a proinflammatory bioactive lipid, promotes cancer progression by modulating proliferation, apoptosis, and angiogenesis. PGE_2 is a downstream product of cyclooxygenase (COX) and is biochemically inactivated by prostaglandin dehydrogenase (PGDH). In the present study, we investigated the mechanisms by which PGDH is down-regulated in cancer. We show that epidermal growth factor (EGF) represses PGDH expression in colorectal cancer cells. EGF receptor (EGFR) signaling induces Snail, which binds conserved E-box elements in the PGDH promoter to repress transcription. Induction of PGE_2 catabolism through inhibition of EGFR signaling blocks cancer growth *in vivo*. In human colon cancers, elevated Snail expression correlates well with down-regulation of PGDH. These data indicate that PGDH may serve a tumor suppressor function in colorectal cancer and provide a possible COX-2–independent way to target PGE_2 to inhibit cancer progression. (Cancer Res 2006; 66(13): 6649-56)

Introduction

The intestine represents a unique system to study carcinogenesis. Homeostasis of the intestinal epithelium is governed by a host of balanced regulatory mechanisms that are often subverted during the transformation process (1, 2). These include Wnt (3, 4), bone morphogenetic protein/transforming growth factor-β (TGF-β; refs. 5, 6), Notch (7), and Hedgehog (8) signaling pathways. Interestingly, whereas prevention of cancer in the intestine remains an important clinical goal, the only clinically tested chemopreventive agents do not directly regulate any of these pathways. Rather, aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) are known to block production of a bioactive lipid prostaglandin E_2 (PGE_2) at normal doses of drugs.

Prostaglandins, including PGE_2, derive from prostaglandin endoperoxide H_2 synthase-1 and -2 [cyclooxygenase-1 (COX-1) and COX-2] enzymes and regulate many biological functions, including hemostasis, salt balance, female reproduction, and immune responses (9). COX-2 production of PGE_2, the most abundant prostaglandin in gastrointestinal tumors, can promote carcinogenesis by modulating apoptosis, proliferation, and angiogenesis (10, 11). Recent studies suggest that administration of PGE_2 accelerates tumor progression (12), and that PGE_2 may stabilize β-catenin through axin regulation (13). Although NSAIDs confer a protective effect by blocking PGE_2 synthesis, the endogenous mechanism for inactivating PGE_2 through catabolism by prostaglandin dehydrogenase (PGDH) remains poorly understood.

Previously, we observed down-regulation of PGDH in a subset of colorectal carcinomas and found preliminary evidence suggesting that epidermal growth factor (EGF) regulates PGDH expression (14). In the present study, we examine the mechanism of PGDH repression by EGF and conduct meta-analysis of PGDH expression in multiple cancers, including colon, breast, liver, lung, and prostate. Our data suggest that EGF represses PGDH expression. Specifically, EGF can induce Snail to bind the PGDH promoter and repress transcription. We show that disruption of EGFR signaling induces PGDH expression and activity *in vivo*. Finally, analysis of clinical data sets supports the hypothesis that PGDH is repressed in multiple cancers, and that elevated Snail expression correlates with down-regulation of PGDH in colon cancers.

Materials and Methods

Cell lines and reagents. HCT-15, HCA-7, HCT-116, and HT-29 cells were in McCoy's 5A medium containing 10% fetal bovine serum, 100 units/mL penicillin, and 100 μg/mL streptomycin in a 5% CO_2 atmosphere. EGF and actinomycin D were from Sigma (St. Louis, MO), and erlotinib (Tarceva) was obtained from Genentech (South San Francisco, CA).

Quantitative real-time PCR. PCR reaction contained iQ SYBR Green Supermix (Bio-Rad, Hercules, CA), 50 ng of each primer, and 5 μl of 1:1,000 diluted reverse transcriptase template in a 25-μL reaction volume. Amplification specificity was confirmed by melt-curve analysis, and expression values were normalized to *β-actin*. See Table 1 for oligonucleotide sequences.

RNA interference. A short hairpin RNA retroviral expression system, pRetroSuper (15), was employed to knock down Snail expression as previously described (16).

Immunoblotting. Cells were washed with PBS and lysed with radioimmunoprecipitation assay buffer. Proteins were separated on precast SDS-PAGE gels and electrotransferred onto polyvinylidene difluoride membranes. Antibodies: PGDH (200-179; 1:2,000) from Novus Biologicals; E-cadherin (H-108; 1:1,000) from Santa Cruz Biotechnology (Santa Cruz, CA); β-actin (A-5441; 1:2,500) from Sigma.

Transient transfection and reporter gene analysis. Transfection of a 2.4-kb PGDH promoter luciferase construct was carried out with Lipofectamine (Invitrogen, Carlsbad, CA) using 100 ng of reporter plasmid and 5 ng of pRL-SV40. Firefly and *Renilla* luciferase activities were measured and normalized with a dual luciferase assay (Promega, Madison, WI).

Note: R.N. DuBois is the B.F. Byrd Jr. Professor of Molecular Oncology and the recipient of an NIH MERIT award R37-DK47297.

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Table 1. Oligonucleotide sequences

Gene	Region	Forward primer	Reverse primer
Quantitative real-time PCR			
PGDH		5′-TCTGTTCATCCAGTGCGATGT	5′-ATAATGATGCCGCCTTCACCT
Snail		5′-GTGTGCTCGGACCTTCTC	5′-GCAGGTATGGAGAGGAAGAG
E-cadherin		5′-CCGCCATCGCTTACACCATCC	5′-CTCTCTCGGTCCAGCCCAGTG
COX-2		5′-CCCTTGGGTGTCAAAGGTAA	5′-GCCCTCGCTTATGATCTGTC
β-Actin		5′-AGAAAATCTGGCACCACACC	5′-AGAGGCGTACAGGGATAGCA
Electrophoretic mobility shift assay			
PGDH	E-Box 1	5′-CCTAAAGACCAACTGGATAGAAGGAGAGC	5′-GCTCTCCTTCTATCCAGTTGGTCTTTAGG
PGDH	E-Box 2	5′-CTCCGTGATTGGCAGGCAGCTGACAGAAG	5′-CTTCTGTCAGCTGCCTGCCAATCACGGAG
PGDH	E-Box 3	5′-CCACGACTGTGTCACCTGCCCCCTGAGCG	5′-CGCTCAGGGGGCAGGTGACACAGTCGTGG

Electrophoretic mobility shift assays. Electrophoretic mobility shift assay was done as previously described (17). See Table 1 for oligonucleotide sequences.

Laser capture microdissection, tissue collection, and *in situ* hybridization. With Vanderbilt University Institutional Review Board (IRB) approval, human colorectal tumor and matching normal mucosa specimens were obtained from surgical resections. With University of Connecticut IRB approval, hyperplastic crypts were microdissected from fresh-frozen tissue sections following isolation of human aberrant crypt foci (ACF) and matching normal mucosa with an Olympus close-focus magnifying endoscope. ^{35}S-labeled *PGDH* riboprobes were used for *in situ* hybridization as previously described (18).

Immunohistochemistry. Paraffin sections of adult Apc^{Min} intestine were dewaxed, rehydrated, and incubated overnight at 4°C with previously published antibodies against E-cadherin (Santa Cruz Biotechnology H-108; 1:100) and Snail (Santa Cruz Biotechnology E-18; 1:100). Negative controls received no primary antibody. The Vectastain ABC peroxidase system (Vector Laboratories, Burlingame, CA) was used for immunodetection.

***In vivo* PGDH functional assay.** C57Bl/6 and C576Bl/6-Apc^{Min} mice were obtained from The Jackson Laboratory (Bar Harbor, ME). Analysis of PGE_2 urinary metabolites (PGE-M) following catabolism by PGDH was done by liquid chromatography tandem mass spectrometry (LC-MS/MS) of urine collected overnight following daily gavage of erlotinib (50 mg/kg) or vehicle for 1 week. All mice were housed and used in accordance with the NIH and institutional guidelines on the care and use of laboratory animals.

LC-MS/MS. The major urinary metabolite of PGE_2, 11α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid (PGE-M), was measured in urine; 400 μL of urine was derivatized using methoximine HCl (16% w/v) in 1.5 mol/L sodium acetate solution. Samples were purified by extraction using a C18 SepPak, after which 12.4 ng of [$^2H_6$]*O*-methyloxime PGE-M internal standard was added. Samples were dried under nitrogen, resuspended in 50 μL mobile phase A [95:4.9:0.1 (v/v/v) 5 mmol/L ammonium acetate/acetonitrile/acetic acid], and analyzed by LC-MS/MS.

Subcutaneous tumorigenicity assays and gas chromatography/MS. Following xenograft establishment, nude mice (n = 4) were gavaged daily with erlotinib (50 mg/kg) or vehicle for 1 week. Gene expression was

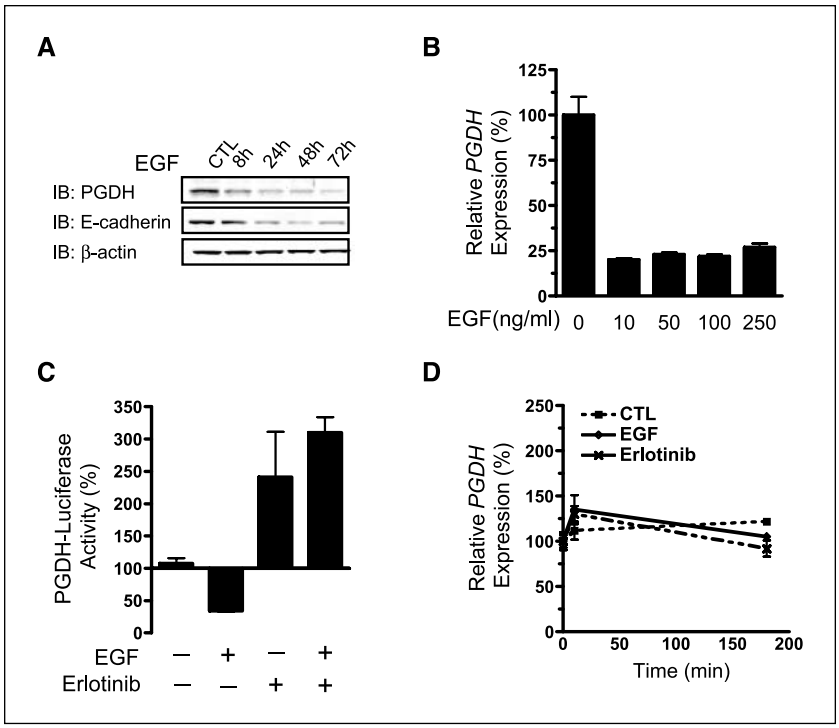

Figure 1. EGF represses transcription of *PGDH*. *A,* immunoblot analysis of PGDH and E-cadherin protein following EGF (100 ng/mL) stimulation of HCT-15 colorectal carcinoma cells. *B,* quantitation of *PGDH* following 48 hours of EGFR activation in HCT-15 cells. *C,* PGDH promoter activity in HCT-15 cells following 48 hours of modulation of EGFR signaling with EGF (100 ng/mL) or erlotinib (5 μg/mL), a small-molecule inhibitor. *D,* quantitation of *PGDH* transcripts in HCT-15 cells following 48 hours of treatment with EGF or erlotinib in the presence of actinomycin D (5 μg/mL). Experiments were replicated in multiple cell lines. *Columns,* mean; *bars,* SE. *IB,* immunoblot.

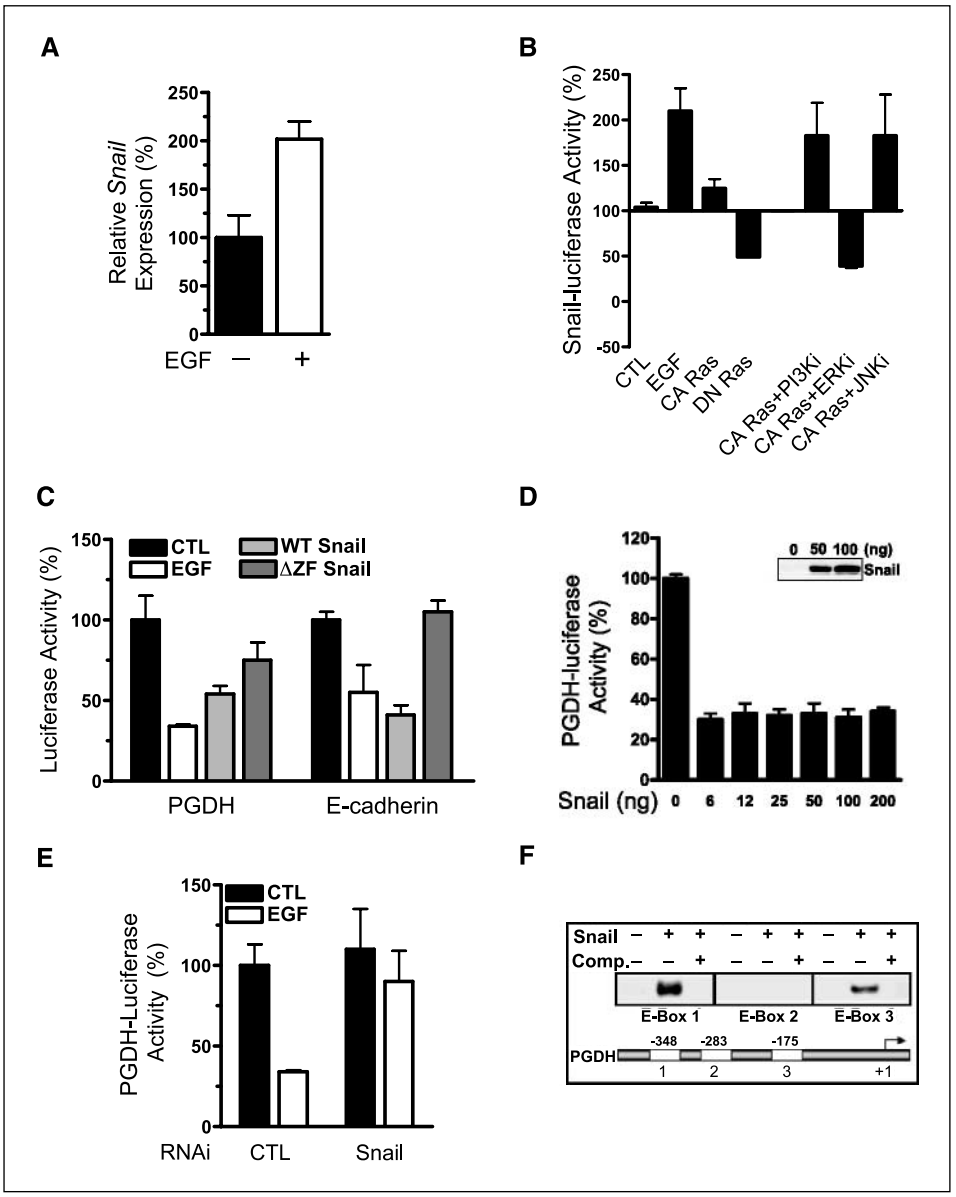

Figure 2. EGF requires Snail to repress PGDH. *A,* quantitation of *Snail* transcripts in HCT-15 cells stimulated with EGF for 24 hours (100 ng/mL). *B,* Snail promoter activity in HCA-7 cells. *CA,* constitutively active; *DN,* dominant negative. *C,* PGDH and E-cadherin promoter activity in HCT-15 cells following addition of EGF (100 ng/mL) or wild-type/mutant Snail for 24 hours. *D,* PGDH promoter activity following transient transfection of Snail in HCT-116 colorectal carcinoma cells. *E,* PGDH promoter activity in HT-29 colorectal carcinoma cells following stimulation with EGF (100 ng/mL) for 24 hours in the presence of short hairpin RNA. *F,* electrophoretic mobility shift assay analysis of Snail binding to *cis* E-box elements in the PGDH promoter; 50× cold oligonucleotide was used for competition of labeled probe. Experiments were replicated in multiple cell lines. *Columns,* mean; *bars,* SE. *RNAi,* RNA interference.

analyzed by quantitative reverse transcription-PCR following isolation of RNA. Upon lipid extraction, PGE_2 levels were assayed by gas chromatography-MS as previously described (19).

Microarray data analysis. Publicly available gene expression data from 117 patients on 24,481 genes (20) was downloaded and analyzed as follows. Estrogen receptor (ER) status was determined by immunohistochemistry-validated microarray analysis, and the association between ER status and relapse-free survival was calculated using the Kaplan-Meier estimator on published outcome data. Pearson correlation coefficients were computed between ER (NM_00012) and PGDH (NM_000860), Snail (NM_00598), COX-2 (NM_000963), and E-cadherin (NM_00436). In addition, meta-analysis of gene expression in human tumor samples was conducted with Oncomine 2.0 (http://www.oncomine.org) on multiple data sets. These data are composed of two general types: two channel ratio data and single channel intensity data. All available data were included in processing and analysis, except for negative single channel intensity values. All data sets were log transformed and median centered per array.

Statistical analyses. Statistical significance was determined as $P < 0.05$ by Student's t test. Spearman's correlation coefficient was computed between Snail and PGDH expression in colorectal carcinoma samples. *In vitro* experiments were replicated in multiple cell lines, and data are expressed as mean ± SE.

Results

EGF represses transcription of PGDH. To increase understanding of the regulation of prostaglandin levels, we examined pathways complementary to COX-2 by which PGE_2 may accumulate and contribute to colorectal carcinogenesis. PGDH (encoded by *HPGD*) catalyzes the rate-limiting step of prostaglandin catabolism, and genetic deletion of *Pgdh* leads to increased tissue levels of PGE_2 (21). To investigate the mechanism for EGF down-regulation of PGDH, we examined several colorectal carcinoma lines, including HCT-15, HCA-7, HT-29, and HCT-116.

We observe that EGF represses PGDH protein by 24 hours and up to 72 hours following treatment (Fig. 1*A*). A similar reduction was observed with E-cadherin expression (Fig. 1*A*). EGF stimulation reduces *PGDH* transcript levels in a dose-dependent manner

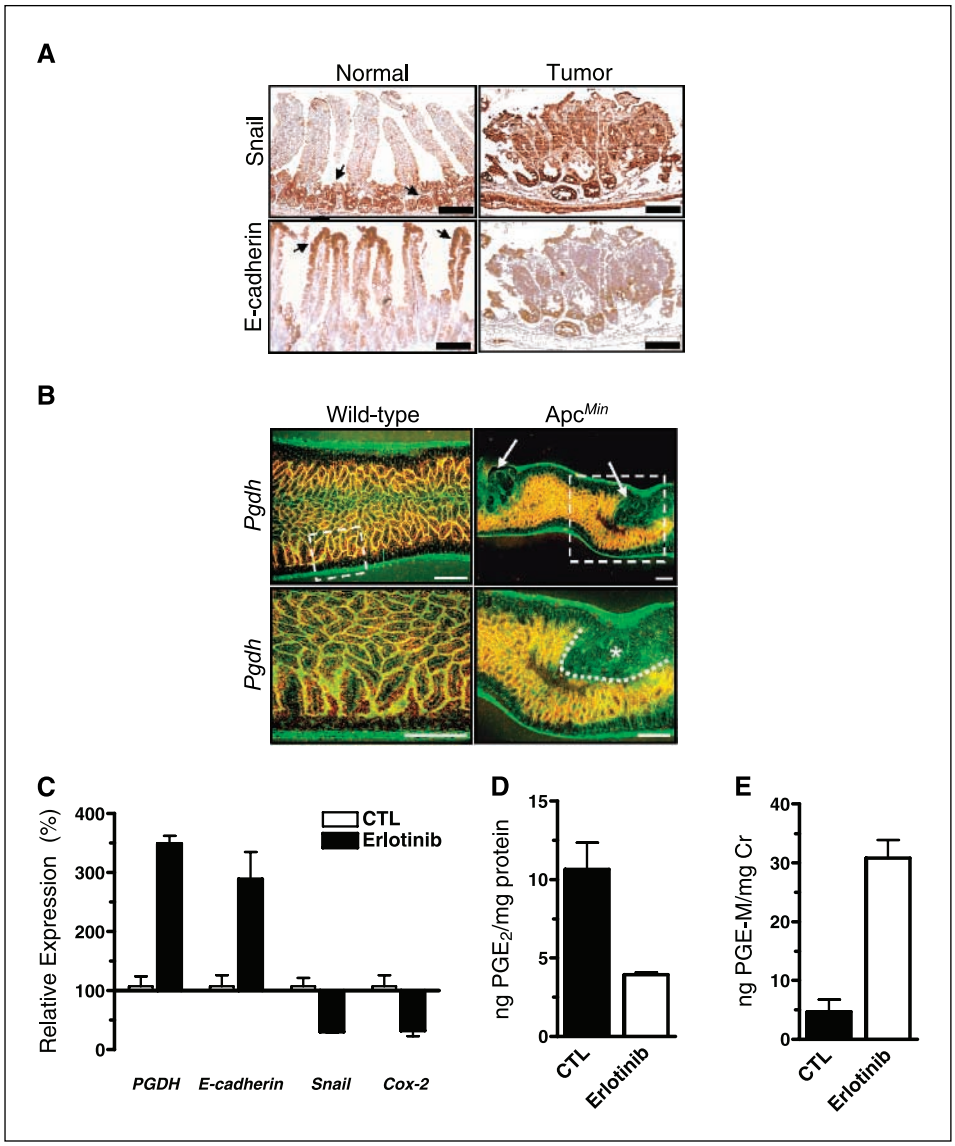

Figure 3. Modulation of EGFR regulates PGDH expression and activity *in vivo*, *A,* immunohistochemistry for Snail and E-cadherin in Apc^{Min} mouse intestine. Bar, 100 μm. *B, in situ* hybridization for *Pgdh* expression in wild-type and Apc^{Min} mouse intestine. *Arrows* and **,* adenoma. Bar, 100 μm. *C,* following establishment of HCA-7 xenografts, age- and sex-matched nude mice (n = 4) were gavaged daily with erlotinib (50 mg/kg) or vehicle for 1 week. Quantitative PCR was done following isolation of RNA. *D,* xenograft PGE_2 levels were measured by gas chromatography-MS following lipid extraction from flash-frozen tissue. *E,* the PGDH enzymatic product (PGE-M) was measured by LC-MS/MS in pooled urine from Apc^{Min} mice following 1-week daily gavage of erlotinib (50 mg/kg) or vehicle control.

(Fig. 1*B*). As EGF causes a similar decrease in steady-state protein and RNA levels, we examined transcriptional activation and stability to determine the specific level of regulation. PGDH promoter activity is decreased by EGF treatment and induced by erlotinib (Tarceva), a small-molecule kinase inhibitor specific for EGFR (Fig. 1*C*). However, pretreatment with erlotinib blocks EGF repression of PGDH-luciferase activity (Fig. 1*C*). In contrast, *PGDH* transcript stability following actinomycin D treatment is not altered by stimulation or inhibition of EGFR activity (Fig. 1*D*). These data suggest that EGF signaling represses transcription of *PGDH*.

EGF requires snail to repress PGDH. Lu et al. report that EGF-dependent repression of E-cadherin requires induction of a transcriptional repressor, Snail (encoded by *Snai1*; ref. 16). Snail and related family members mediate repression of E-cadherin through zinc-finger binding of conserved E-box elements (CANNTG) in the proximal promoter. Inspection of the PGDH promoter revealed a similar arrangement of consensus E-box elements (Fig. 2*F*); thus, we examined the ability of Snail to modulate PGDH expression.

EGF treatment of colon cancer cell lines induces *Snail* in a Ras and extracellular signal-regulated kinase–dependent manner (Fig. 2*A* and *B*). In contrast, we did not observe induction of *Slug* by EGF (data not shown). Addition of wild-type Snail expression construct, even 6 ng, represses *PGDH* transcription in a similar manner to stimulation with EGF (Fig. 2*C* and *D*). Repression of E-cadherin promoter activity is also observed with EGF and wild-type Snail (Fig. 2*C*). However, zinc-finger mutant Snail does not effectively repress transcription of *PGDH* or *E-cadherin* (Fig. 2*C*).

We next employed RNA interference to complement gain-of-function studies of Snail-dependent repression of PGDH. Using HT-29 cells, which express elevated levels of Snail relative to HCT-15 cells, we reasoned that knock down of Snail would induce *PGDH* transcription. Introduction of short hairpin RNA targeted to Snail disrupts EGF repression of *PGDH* transcription (Fig. 2*E*). In gel shift experiments, Snail specifically binds conserved E-box elements in the PGDH promoter (Fig. 2*F*). Shifts were observed with E-boxes 1 and 3 and could be competed away with 50-fold excess of unlabeled oligonucleotide (Fig. 2*F*). Taken together, we

find that Snail can mediate EGF-dependent repression of *PGDH* transcription.

Modulation of EGFR regulates PGDH expression and activity *in vivo*. Apc^{Min} mice harbor a nonsense *APC* mutation and spontaneously develop preinvasive adenomas that recapitulate many aspects of the human syndrome, familial adenomatous polyposis coli. Previous reports suggest that EGFR activity is elevated in Apc^{Min} adenoma tissue (22), and introduction of hypomorphic *Egfr* reduces Apc^{Min} tumor burden by 10-fold (22, 23). Moreover, progression of these tumors requires PGE_2 (24, 25). To examine EGF regulation of *Pgdh in vivo*, we evaluated expression patterns of Snail, E-cadherin, and *Pgdh* in Apc^{Min} mouse intestine. In normal mucosa, Snail localizes to the proliferative crypt compartment, whereas *Pgdh* and E-cadherin are restricted to well-differentiated villi (Fig. 3*A* and *B*). Interestingly, examination of adenomas revealed high expression of Snail, whereas *Pgdh* is almost completely absent (Fig. 3*A* and *B*).

Based on our findings that erlotinib, a small-molecule EGFR inhibitor, can induce PGDH *in vitro*, we hypothesized that disruption of EGFR would restore prostaglandin catabolism *in vivo*. Following establishment of PGE_2-dependent HCA-7 xenografts, nude mice (n = 4) were gavaged daily with erlotinib (50 mg/kg) or vehicle for 1 week. Erlotinib treatment nearly eliminated tumor growth (data not shown). In addition, disruption of EGFR signaling induces both *PGDH* and *E-cadherin* while reducing *Snail* and *COX-2* (Fig. 3*C*). As expected, restoration of PGDH reduces intratumoral PGE_2 levels (Fig. 3*D*).

To further examine PGDH repression by EGF *in vivo*, we assessed whole-body prostaglandin catabolism following disruption of EGFR signaling in Apc^{Min} mice. We used LC-MS/MS to assay PGDH catabolic products in urine and hypothesized that EGFR blockade would induce PGDH activity. Accordingly, PGE-M levels increased 6-fold in Apc^{Min} urine following daily gavage with erlotinib (50 mg/kg) for 1 week (Fig. 3*E*). These data suggest that EGFR can regulate PGDH expression and activity *in vivo*.

PGDH expression is repressed in multiple human cancers. Published reports suggest down-regulation of PGDH in a subset of colorectal carcinomas (14, 26). To more thoroughly evaluate the role of PGDH in human tumorigenesis, we conducted meta-analysis to test our hypothesis that PGDH is repressed in multiple cancer data sets generated by outside investigators. Examination of microarray expression data from eight published reports indicates that *PGDH* expression is reduced in multiple human cancers relative to matched normal mucosa (n = 1,114; Fig. 4*A*; data not shown). Moreover, *PGDH* is further diminished upon cancer progression (Fig. 4*A*). Specifically, *PGDH* decreases from normal tissue (n = 222) to primary tumors (n = 571; P = 0.0098) and is further reduced from well-differentiated (n = 99) to poorly differentiated (n = 34) primary tumors (P = 0.0221). Finally, *PGDH* expression is further reduced from primary tumors (n = 107) to metastatic tumors (n = 29; P = 0.0177; Fig. 4*A*; data not shown).

To corroborate these findings, we analyzed a well-annotated set of 117 breast cancers with detailed data on metastatic outcomes (20). Following confirmation that ER status strongly predicts

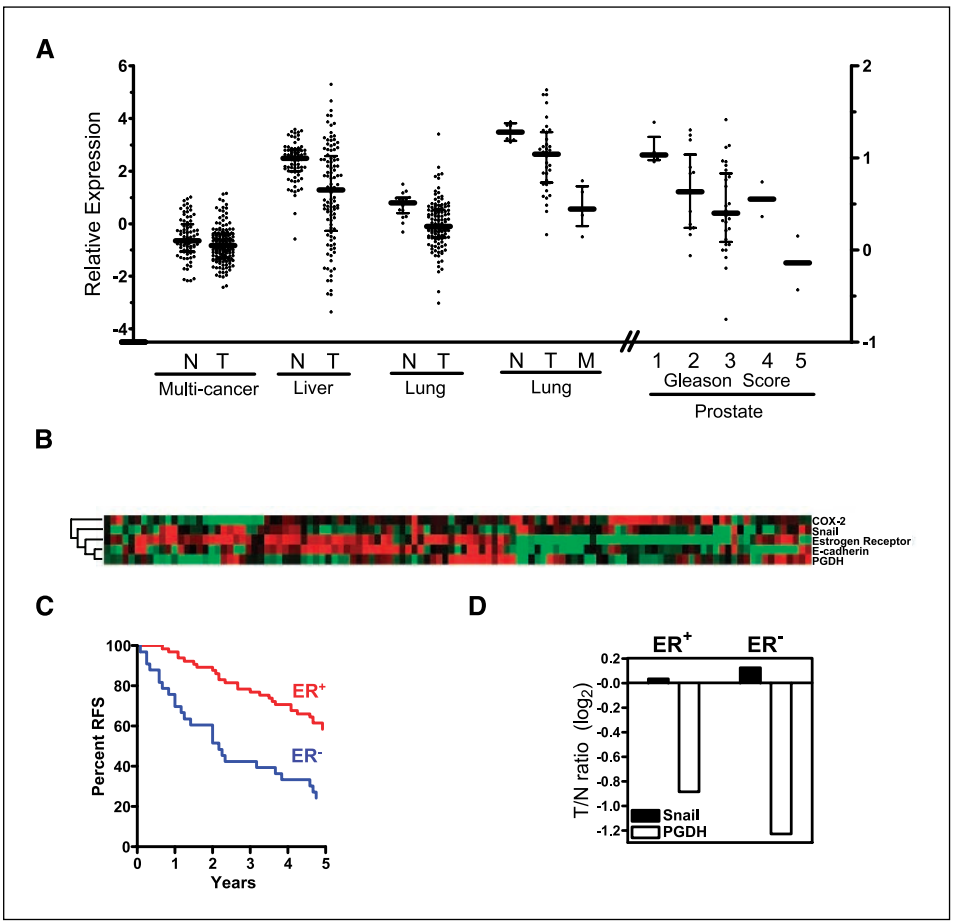

Figure 4. *PGDH* Expression is repressed in multiple human cancers. *A,* meta-analysis of *PGDH* expression data from five published microarray data sets comprising a broad range of epithelial tumors: n = 720 (37); N = 90, T = 190, P = 0.023 (38); N = 76, T = 104, P = 1.5e−08; (39); N = 17, T = 139, P = 5.5e−06 (40); N = 6, T = 40, P = 0.003; T = 40, M = 6, P = 0.002 (41). Gleason: 1 = 4, 2 = 15, 3 = 29, 4 = 2, 5 = 2; P = 0.001. N, normal; T, tumor; M, metastasis. *B* to *D,* analysis of primary data for 117 breast carcinoma patients from (20), specifically distinguishing well-differentiated, ER$^+$ tumors versus poorly differentiated, ER$^-$ tumors. *B,* unsupervised hierarchical clustering for COX-2, Snail, ER-α, E-cadherin, and PGDH. *C,* Kaplan-Meier analysis comparing relapse-free survival (*RFS*) versus ER status. Log-rank test was conducted to determine statistical significance. P < 0.0001. *D,* comparison of Snail and PGDH expression in ER$^+$ vs. ER$^-$ tumors.

Table 2. Analysis of gene expression in human breast cancers

Gene	*N/T* ratio (log 2)	ER correlation coefficient	*P*	Significance
COX-2	0.31	−0.46	<0.0001	*
Snail	−0.07	−0.07	0.443	NS
ER	1.40	—	—	—
E-cadherin	0.31	+0.21	0.020	†
PGDH	1.02	+0.24	0.009	‡

Abbreviation: NS, not significant.
*$P < 0.001$.
†$P < 0.05$.
‡$P < 0.01$.

metastasis-free survival at 5 years (Fig. 4*C*), we compared *Snail, PGDH, COX-2,* and *E-cadherin* to *ER* expression. *PGDH* paired with *E-cadherin* and *ER* in unsupervised hierarchical clustering analysis (Fig. 4*B*; Table 2). Moreover, *PGDH* was repressed and *Snail* expression elevated during cancer progression (Fig. 4*D*).

PGDH inversely correlates with Snail in colorectal cancers. Finally, we examined the expression pattern of *PGDH* in normal intestine and matched dysplasia ranging from ACF (early hyperplastic lesions) to high-grade colorectal carcinomas. *PGDH* seemed to be reduced in both microdissected ACF and colorectal carcinomas, suggesting that PGDH may play a role in prevention of tumor progression (Fig. 5*A*). We quantified *PGDH* and *Snail* transcript levels in 15 pairs of colorectal carcinomas and matched normal mucosa. *PGDH* is significantly reduced in carcinoma tissue and inversely correlates with *Snail* expression, which increases 7-fold on average (Fig. 5*B*). Notably, pairwise comparison shows that expression of *PGDH* and *Snail* seem to be mutually exclusive ($r_s = -0.57$, $P = 0.0005$; Fig. 5*C*).

Discussion

Induction of COX-2 and repression of PGDH provide complementary pathways to increase PGE_2 levels. By inactivating endogenous PGE_2, PGDH provides an important, natural way to reduce this procarcinogenic lipid mediator. These data support a novel pathway that increases PGE_2 *in vivo*: activation of EGFR, known to be involved in colorectal cancer, represses PGDH through Snail.

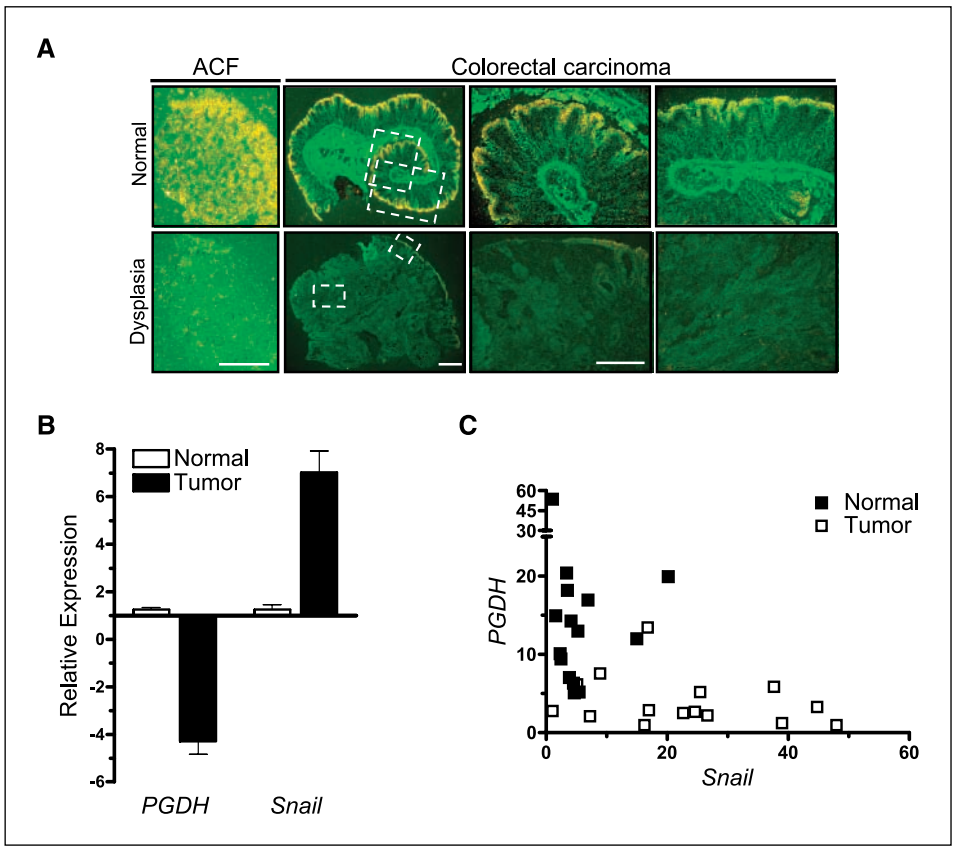

Figure 5. PGDH negatively correlates with Snail in colorectal cancers. *A,* localization of *PGDH* expression by *in situ* analysis of hyperplastic ACF and high-grade colorectal carcinoma. Bar, 100 μm. *B,* summary of quantitative real-time PCR analysis for *PGDH* and *Snail* expression in 15 pairs of human colorectal carcinomas and matched normal tissue. *C,* independent comparison of *PGDH* versus *Snail* for 15 normal and 15 tumor samples. The Spearman coefficient was calculated to determine statistical correlation ($r_s = -0.57$, $P = 0.0005$).

We originally identified COX-2 as an EGF/TGF-α target gene in intestinal epithelial cells, with robust enhancement of prostaglandin production following EGFR activation (27). Other reports from our group indicate COX-2–derived PGE_2 can transactivate the EGFR (28). We now show that EGFR can repress PGDH, allowing PGE_2 to accumulate and activate the pathway repeatedly in a feed-forward cycle.

These findings raise some intriguing questions. What cofactors are necessary for Snail-dependent repression of PGDH? Palmer et al. report a similar mechanism for repression of vitamin D receptor, another gene with tumor-suppressor activity in the colon (29). Does EGF signaling mediate repression in early ACF? Is this linked to repression of PGDH observed in patients with inflammatory bowel disease (30) who are predisposed to develop cancer?

These data also corroborate emerging evidence from gene expression profiles indicating that clinical outcome, including risk of metastasis, is specified relatively early in the transformation process (31). Early identification of high-risk lesions may allow more aggressive monitoring and treatment of specific patients.

By integrating prostaglandins with growth factor signaling, the current findings present important clinical implications. Expression of EGFR is known to be associated with poor survival in patients with colorectal cancer (32), and previous studies indicate poorer prognosis for carcinomas bearing increased COX-2–dependent production of prostaglandins (33, 34). Moreover, simultaneous blockade of prostaglandin and EGFR signaling ablates tumor formation in Apc^{Min} mice (35).

Although EGF and PGE_2 have been targeted individually in human patients, dose-limiting toxicity and selection for resistant clones indicate that administration of these agents in combination may achieve improved clinical outcomes. Moreover, understanding the mechanistic basis of PGDH repression could lead to improved approaches to chemoprevention of cancer. Because PGDH does not degrade anti-thrombotic PGI_2, these data raise the possibility of selectively targeting PGE_2 through PGDH and avoiding some of the cardiovascular side effects attendant with COX-2 inhibition. Thus, EGFR inhibitors may serve a role in cancer treatment or prevention by restoring PGDH expression. Measurement of PGE_2 urinary metabolites provides a possible noninvasive and cost-effective method of monitoring therapeutic response (36).

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