Serotonin Metabolism Is Dysregulated in Cholangiocarcinoma, which Has Implications for Tumor Growth

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Abstract
Cholangiocarcinoma is a devastating cancer of biliary origin with limited treatment options. Symptoms are usually evident after blockage of the bile duct by the tumor, and at this late stage, they are relatively resistant to chemotherapy and radiation therapy. Therefore, it is imperative that alternative treatment options are explored. We present novel data indicating that the metabolism of serotonin is dysregulated in cholangiocarcinoma cell lines, compared with normal cholangiocytes, and tissue and bile from cholangiocarcinoma patients. Specifically, there was an increased expression of tryptophan hydroxylase 1 and a suppression of monoamine oxidase A expression (enzymes responsible for the synthesis and degradation of serotonin, respectively) in cholangiocarcinoma. This resulted in an increased secretion of serotonin from cholangiocarcinoma and increased serotonin in the bile from cholangiocarcinoma patients. Increased local serotonin release may have implications on cholangiocarcinoma cell growth. Serotonin administration increased cholangiocarcinoma cell growth in vitro, whereas inhibition of serotonin synthesis decreases tumor cell growth both in vitro and in vivo. The data presented here represent the first evidence that serotonin metabolism is dysregulated in cholangiocarcinoma and that modulation of serotonin synthesis may represent an alternative target for the development of therapeutic strategies. [Cancer Res 2008;68(22):9184–95]

Introduction
Cholangiocarcinomas are devastating cancers of intrahepatic and extrahepatic origin that are increasing in both their worldwide incidence and mortality rates (1, 2). The challenges posed by these often lethal biliary tract cancers are daunting, with conventional treatment options being limited and the only hope for long-term survival being that of complete surgical resection of the tumor (1, 2). Conventional chemotherapy and radiation therapies are not effective in prolonging long-term survival (1); therefore, it is important to understand the intracellular mechanisms of cholangiocarcinoma cell growth, with a view to develop novel chemopreventive strategies.

Serotonin or 5-hydroxytryptamine is a neuromodulator, with both neuroendocrine and neurotransmitter functions, which is synthesized in serotonergic neurons in the central nervous system (3) and enterochromaffin cells throughout the gastrointestinal tract (4). Serotonin is synthesized by the systematic hydroxylation and decarboxylation of the amino acid tryptophan by the enzymes tryptophan hydroxylase (TPH1) and amino acid decarboxylase, respectively (3). There are 16 serotonin receptor subtypes spread over seven receptor families, through which serotonin exerts its multiple effects (5). With the exception of the serotonin 3 receptor, a ligand-gated ion channel, all other serotonin receptors are G protein–coupled, seven-transmembrane receptors that activate intracellular second messenger systems (5). Once serotonin has activated the receptor, it is cleared from the extracellular space by specific reuptake transporters where it undergoes catabolism (6). Degradation of serotonin is carried out primarily by the enzyme monoamine oxidase (MAO), which occurs as two molecular subtypes, called MAO A and MAO B, and have some differences in their tissue and cellular distributions (7). MAO A is more selective for serotonin oxidation by being able to metabolize serotonin with a much lower Km value (and higher affinity for the substrate) than MAO B (8).

Several opposing effects of serotonin on tumor growth have been reported (9). On one hand, serotonin is known as a growth factor for several types of nontumoral cells (10, 11), and it has been proposed to take part in the autocrine loops of growth factors contributing to cell proliferation in aggressive tumors, such as small cell lung carcinoma (12), prostate cancer cells (13), human breast cancer cell lines (14), and bladder cancer (15). In contrast, several studies have also reported that serotonin can inhibit tumor growth, mainly via the specific vasoconstrictive effects of serotonin on the vessels irrigating the tumors (9, 16–18). In addition, the synthesis and secretion of serotonin has previously been shown to be dysregulated in neuroendocrine tumors, with these cells possessing a higher biogenic amine content than normal cells (19–21). Serotonin is involved in the pathogenesis of certain clinical features of cholangiopathies, pruritus, and fatigue, in particular (22, 23). In animal models of chronic cholestasis, this may be due to an enhanced release of serotonin in the central nervous system and
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its interactions with subtype 1 serotonin receptors (23). Cholangiocytes synthesize and secrete serotonin, which is increased in proliferating rat cholangiocytes after bile duct ligation (24). We postulate that this autocrine loop is integral in limiting the growth of the biliary tree as a result of chronic cholestasis. However, to date, nothing is known about the involvement of serotonin in the neoplastic transformation and growth of cholangiocarcinoma.

In the present study, we show a dysregulation of the cellular machinery responsible for the metabolism of serotonin in cholangiocarcinoma cell lines and human samples, which results

Figure 1. TPH1 expression is increased in cholangiocarcinoma. TPH1 levels were assessed in six cholangiocarcinoma cell lines, as well as a nonmalignant cholangiocyte cell line H69, by real-time PCR (A) and immunoblotting (B). Columns, average (n = 3); bars, SE. Asterisk denotes significance (P < 0.05) compared with TPH1 expression in H69 cells. TPH1 levels were also assessed in biopsy samples from 48 cholangiocarcinoma patients and healthy controls by immunohistochemistry. C, representative photomicrographs of the TPH1 immunoreactivity. Magnification, 40x. D, staining intensity was assessed as described in Materials and Methods. Columns, average of all cholangiocarcinoma patients compared with control samples, as well as a function of tumor grade (degree of differentiation); bars, SE. Asterisk denotes significance (P < 0.05) compared with TPH1 immunoreactivity in control biopsy samples.
in an increased production and secretion of serotonin from cholangiocarcinoma. Furthermore, we show that the increased secretion of serotonin has growth-promoting effects on cholangiocarcinoma cells and that inhibiting serotonin synthesis significantly blocks cholangiocarcinoma cell proliferation in vitro and in vivo.

Materials and Methods

Cell lines. We used six human cholangiocarcinoma cell lines (Mz-ChA-1, HuH-28, HuCCT-T1, CCLP1, SG231, and TFK-1) with different origins. Mz-ChA-1 cells from human gallbladder (25) were a gift from Dr. G. Fitz (University of Texas Southwestern Medical Center). HuH-28 cells from

Figure 2. MAO A expression is decreased in cholangiocarcinoma. MAO A levels were assessed in six cholangiocarcinoma cell lines, as well as a nonmalignant cholangiocyte cell line H69, by real-time PCR (A) and immunoblotting (B). Columns, average (n = 3); bars, SE. Asterisk denotes significance (P < 0.05) compared with MAO A expression in H69 cells. MAO A levels were also assessed in biopsy samples from 48 cholangiocarcinoma patients and healthy controls by immunohistochemistry. C, representative photomicrographs of the MAO A immunoreactivity. Magnification, 40 ×. D, staining intensity was assessed as described in Materials and Methods. Columns, average of all cholangiocarcinoma patients compared with control samples, as well as a function of tumor grade (degree of differentiation); bars, SE. Asterisk denotes significance (P < 0.05) compared with MAO A immunoreactivity in control biopsy samples.
human intrahepatic bile duct (26) and TFK-1 cells from extrahepatic cholangiocarcinoma (27) were acquired from Cancer Cell Repository, Tohoku University. These cells were maintained at standard conditions, as described (28). In addition, CCLP-1 (29), HuCC-T1 (30), and SG231 (31), also from intrahepatic bile ducts, were a kind gift from Dr. A.J. Demetris (University of Pittsburg) and were cultured as described (29–31). The human immortalized, nonmalignant cholangiocyte cell line H69 (from Dr. G.J. Gores, Mayo Clinic) was cultured as described (32).

Real-time PCR. RNA was extracted from all cell lines using the RNeasy Mini kit (Qiagen, Inc.), according to the instructions provided by the vendor, and reverse transcribed using the Ready First Strand cDNA Synthesis kit (SuperArray). These reactions were used as templates for the PCR assays using a SYBR Green PCR Master Mix (SuperArray) in the real-time thermal cycler (ABI Prism 7900HT sequence detection system) using commercially available primers designed against human TPH1, MAO A, and the specific serotonin receptor subtypes (SuperArray). A ΔΔCT analysis was performed using the normal cholangiocytes as the control sample. Data are expressed as relative mRNA levels ± SE (n = 3).

Immunoblotting. After trypsinization, all cell lines (1 × 10⁶) were resuspended in lysis buffer (33) and sonicated. ImmunobLOTS to detect TPH, MAO A, and β-actin were performed, as previously described (33), using specific antibodies against each protein (Santa Cruz Biotechnology). Data are expressed as fold change (mean ± SE) of the relative expression after normalization with β-actin.

Cholangiocarcinoma tissue array analysis. Immunoreactivity for serotonin, TPH1, MAO A, the cholangiocyte marker CK-19, and the neuroendocrine markers chromogranin A and neuron-specific enolase (NSE) were assessed in commercially available Accumax tissue arrays.
(Isu Abxis Co., Ltd.) by immunohistochemistry, as described (24), using specific antibodies. These tissue arrays contain 48 well-characterized cholangiocarcinoma biopsy samples from a variety of tumor differentiation grades, as well as four control liver biopsy samples. Semiquantitative analysis was performed by three independent observers, in a blind fashion, using the following variables. Staining intensity was assessed on a scale from 1 to 4 (1, no staining; 4, intense staining), and the abundance of positively stained cells was given a score from 1 to 5 (1, no cells stained; 5, 100% stained). The staining index was then calculated by the staining intensity multiplied by the staining abundance that gave a range from 1 to 20.

Serotonin secretion. All cell lines were trypsinized, and the resulting cell pellet was resuspended in HBS buffer (1 × 10⁷ cells/mL). Cells were then incubated for 6 h at 37°C, and the amount of serotonin released into the medium was assayed using a commercially available serotonin EIA kit (Invitrogen) according to the manufacturer’s instructions.

Hepatic bile was collected aseptically from T-tube drainage during postoperative days 1 to 3 from patients with intrahepatic stones (n = 12) or gallstones in association with common bile duct stones (n = 11) and from cholangiocarcinoma patients (n = 14). Bile samples were immediately frozen at −80°C until analysis.

MTS cell proliferation assays. Cell lines were seeded into 96-well plates (10,000 per well) in a final volume of 200 μL of growth medium and allowed to adhere to the plate overnight. Cells were serum-starved for 24 h before stimulation with serotonin (10⁻⁸ to 10⁻⁶ mol/L) or p-chlorophenylalanine (CPA; a specific TPH1 inhibitor; 0.25–1 mmol/L, IC₅₀ 250 μmol/L; ref. 34) for 48 h. In parallel experiments, cells were pretreated with commercially available specific serotonin receptor antagonists, all at 10 μmol/L (5HTR 1A antagonist, (S)-Way100135 dihydrochloride; 5HTR 1B antagonist, SB216641 hydrochloride; 5HTR 1D antagonist, BRL 15572 hydrochloride; 5HTR 2A antagonist, spiperone hydrochloride, 5HTR 2B, SB204741; 5HTR 2C, (S)-Way100135 dihydrochloride; 5HTR 2D antagonist, SR121417 hydrochloride; 5HTR 2E antagonist, SR121417 hydrochloride; 5HTR 2G antagonist, competition for histopathology or Masson’s trichrome staining for collagen visualization.
Tumor protein, selectively expressed by cholangiocytes, was evaluated after CK-7 immunohistochemical staining (36). Furthermore, the expression of specific neuroendocrine markers chromogranin A and NSE was assessed using immunohistochemistry (36). In each case, sections were counterstained with hematoxylin before analysis.

Light microscopy and immunohistochemistry observation were taken by BX-51 light microscopy (Olympus) with a videocam (Spot Insight, Diagnostic Instrument, Inc.) and processed with an Image Analysis System (Delta Sistemi). Three pathologists independently performed analysis in a blind manner. The degree of inflammation and fibrosis was evaluated in five randomly nonoverlapping fields (magnification, 20×) for each slide using light microscopy of Masson's stained sections, as previously described (37); the necrotic mass was evaluated by quantitative morphometry on LM images, as previously described (38, 39), and expressed as area of necrosis/total area of tumor × 100. For each sample, more than five nonoverlapping fields (magnification, 20×) were studied.

Results

Expression of metabolic enzymes for serotonin is dysregulated in cholangiocarcinoma. The de novo synthesis of serotonin is predominantly performed by TPH1 in the gastrointestinal tract (3, 34). The expression of TPH1 mRNA was significantly upregulated (from 2.5-fold to 50-fold) in five of six cholangiocarcinoma cell lines when compared with the nonmalignant H69 cells (Fig. 1A). This trend was confirmed by TPH1 protein expression, as shown by immunoblotting (Fig. 1B). In addition, immunohistochemical analysis of human liver biopsy samples indicated that there is also increased TPH1 immunoreactivity in cholangiocarcinoma samples compared with control, as assessed by three independent observers (Fig. 1C and D and data not shown). Analysis of the TPH1 immunoreactivity as a function of the differentiation grade of the tumor showed a correlation between staining intensity and the degree of differentiation (Fig. 1D). More specifically, whereas there is an increased expression of TPH1 in all cholangiocarcinoma samples compared with normal liver samples, the increase is more evident in tumors with a differentiation grade of 1 (well differentiated) compared with the less-differentiated grade 3 (Fig. 1D).

In contrast to TPH1 expression, the MAO A mRNA levels were significantly decreased in cholangiocarcinoma cell lines compared with H69 cells (Fig. 2A), which was paralleled by the protein...
expression, as shown by immunoblotting (Fig. 2B). Similarly, immunohistochemical analysis showed a suppression of MAO A expression in human biopsy samples, as assessed by three independent observers (Fig. 2C and D and data not shown). However, when MAO A immunoreactivity was expressed as a function of tumor differentiation grade, there was no correlation between the degree of differentiation and the expression of MAO A (Fig. 2D).

Serotonin secretion is increased in cholangiocarcinoma. Taking the changes in the expression of serotonin synthesis and degradation enzymes together, it would be reasonable to expect an overall increase in serotonin production and secretion from cholangiocarcinoma cells. Indeed, the secretion of serotonin was increased in five of six cholangiocarcinoma cell lines (Fig. 3A). Serotonin immunoreactivity was also increased in the human biopsy samples contained on the cholangiocarcinoma tissue array, as assessed by three independent observers (Fig. 3B and C and data not shown). Analysis of serum samples from cholangiocarcinoma patients versus age-matched controls revealed no significant difference in serotonin levels (data not shown), which is not surprising, given that the normal tissue surrounding the tumor presumably has normal degradation machinery (i.e., MAO A expression) and would possibly take up the excess serotonin and metabolize it. We then performed a pilot study with a limited number of bile samples taken from cholangiocarcinoma patients. As controls, we used bile samples collected from patients affected by intrahepatic cholelithiasis (e.g., nonmalignant disease). Analysis of these treatment groups revealed an increase in serotonin levels in cholangiocarcinoma patients compared with controls (Fig. 3D).

Expression of neuroendocrine markers in cholangiocarcinoma samples. Because serotonin production is dramatically increased in a number of neuroendocrine tumors, we assessed the expression of neuroendocrine markers and cholangiocyte markers in the tumor biopsy samples. CK-19 immunoreactivity was observed in a similar intensity in cholangiocarcinoma tissue and nonmalignant liver tissue (Fig. 4). There was no observable expression of the neuroendocrine markers chromagranin A and NSE in nonmalignant livers but was expressed in a number of the cholangiocarcinoma biopsy samples studied (44% and 63% of cholangiocarcinoma samples studied for chromagranin A and NSE, respectively), suggesting the emergence of a neuroendocrine or "carcinoid-like" phenotype.

Increased local serotonin secretion has implications on cholangiocarcinoma cell growth in vitro. The potential implications of the increased local serotonin secretion were explored in vitro using the cholangiocarcinoma cell lines. Treatment of the SV40-transformed human cholangiocyte cell line H69 with various concentrations of serotonin had no significant
effect on cell proliferation (Fig. 5A), whereas treatment of all of the cholangiocarcinoma cell lines with serotonin (10^{-7} \text{ to } 10^{-5} \text{ mol/L}) caused a significant increase in cell proliferation after 48 hours as shown by MTS cell proliferation assays (Fig. 5A and Supplementary Fig. S1). Cholangiocarcinoma cell lines expressed all serotonin receptor subtypes, with the vast majority being up-regulated compared with the H69 cholangiocyte cell line, except for 5HTR 1B, 5HTR 1F, 5HTR 2B, 5HTR 3C, and 5HTR 7 (which are all down-regulated; Supplementary Table S1). Furthermore, specific inhibition of the serotonin receptors 5HTR 1A, 5HTR 2A, 5HTR 2B, 5HTR 4, and 5HTR 6 effectively prevented the growth-promoting effects of serotonin (Supplementary Fig. S2).

Conversely, blocking serotonin synthesis, CPA, a specific TPH1 inhibitor, markedly inhibited cholangiocarcinoma cell proliferation, particularly at 1 mmol/L (Fig. 5B and Supplementary Fig. S3). Once again, no effect was observed in H69 cells. Taken together, this indicates that the increased serotonin secretion from cholangiocarcinoma cells may have a growth-promoting effect on tumor progression.

The effects of serotonin and CPA on cell cycle progression were assessed by BrdUrd uptake assays in Mz-ChA-1 cells. Consistent with the MTS assays described above, there was an increase in the number of BrdUrd-positive nuclei per field after serotonin treatment (Fig. 5C), whereas treatment with CPA decreased the number of BrdUrd-positive cells (Fig. 5C). This suggests that increased serotonin secretion from cholangiocarcinoma cells may exert its effects by regulating cell cycle progression.

Inhibition of serotonin synthesis inhibits cholangiocarcinoma tumor growth in vivo. By treating an in vivo xenograft model of cholangiocarcinoma tumors with the TPH inhibitor, we significantly suppressed tumor growth (Fig. 6A and B). In addition, the latency of tumor growth (i.e., time taken for tumor volume to increase to 150% of the original size) was increased after CPA treatment compared with vehicle treatment (Fig. 6C). Analysis of liver enzymes in the serum revealed that there was no significant difference in AST (vehicle, 96.0 ± 11.7 versus CPA, 75.6 ± 13.5) and ALT levels (vehicle, 42.3 ± 13.1 versus CPA, 33.0 ± 4.4) between CPA-treated and vehicle-treated animals, both of which fell within the reference range, suggesting that the CPA treatment was well tolerated and did not cause any liver damage. Histologic analysis of liver, heart, and kidney also indicated no significant organ damage caused by the chronic CPA treatment (data not shown).

Histologic analysis of the excised tumors revealed that all cells within tumors from CPA-treated and vehicle-treated animals were CK-7–positive, indicating cholangiocyte phenotype (Supplementary Fig. S4). CPA treatment significantly decreases the area of tumor necrosis (Supplementary Fig. S4), and semiquantitative analysis fibrosis shows that CPA increased fibrosis within the tumor (Supplementary Fig. S4). Furthermore, the xenograft tumors also expressed chromagranin A and NSE, in both vehicle-treated and CPA-treated animals (Supplementary Fig. S5).

Discussion

The major findings of this study relate to the dysregulation of serotonin metabolism in cholangiocarcinoma. We showed that (a) expression of the enzyme responsible for serotonin synthesis in the gastrointestinal tract, TPH1, is up-regulated in cholangiocarcinoma; (b) the enzyme responsible for serotonin degradation, MAO A, is markedly decreased in cholangiocarcinoma samples; and (c) this results in an overall increase in serotonin secretion from cholangiocarcinoma cells and in the bile from cholangiocarcinoma patients. This increase in serotonin production and secretion resulted in an increased cholangiocyte proliferation in vitro, and inhibition of serotonin synthesis by CPA decreased cell proliferation in vitro and in vivo xenograft model of cholangiocarcinoma. These data suggest that the dysregulation of serotonin metabolism may be a key feature associated with the progression of cholangiocarcinoma, and the modulation of this metabolic pathway may result in the development of an effective adjunct therapy to treat this deadly disease.

Consistent with our findings that serotonin metabolism is dysregulated in cholangiocarcinoma, increased serotonin secretion is the defining feature of a number of other neuroendocrine tumors classified as carcinoid tumors (19–21). Within these tumors, serotonin is thought to stimulate cell proliferation (40, 41) and cause symptoms of the carcinoid syndrome, including diarrhea, and damage to the valves of the heart (42). Here, we show that cholangiocarcinoma, while not strictly classified as carcinoid tumor, not only secreted serotonin but displayed features of a neuroendocrine phenotype, such as chromagranin A and NSE expression (43).

The expression of TPH1 has been shown to be strongly expressed in midgut carcinoid tissue (44). The authors postulate that the expression of TPH and other specific proteins on the cell surface can be recognized by CD8+ T cells and constitute an immune recognition of the tumors, which may be of great interest when pursuing an immunotherapeutic treatment strategy (44). The data presented here supports the idea that the expression of TPH1 may be involved in the process of tumor progression and cell proliferation.

In support of our findings that MAO A expression is suppressed in cholangiocarcinoma, many other neuroendocrine tumors that have a dysregulated serotonin synthesis and secretion often have a concomitant decrease in the expression of MAO A (45). In a normal cell, these amine oxidases exert an antiproliferative effect more than likely because the products of amine oxidation, aldehydes, hydrogen peroxide, and other reactive oxygen species are somewhat cytotoxic (45–47). Because in certain tumor cells, the expression of such amine oxidases (including MAO A) are suppressed, in addition to the mitogenic effects of the accumulating serotonin, the potential cytotoxic, antiproliferative effects of amine oxidation are bypassed (45, 46). The mechanism of this decrease in MAO A expression is unclear. However, researchers have shown that the promoter region of MAO A can be hypermethylated under certain conditions (48). Because hypermethylation and subsequent silencing of genes, such as tumor suppressor genes, are a common event in the malignant transformation of cholangiocarcinoma (49), it is therefore conceivable that hypermethylation of the MAO A promoter contributes to the suppression of expression. Indeed, treatment of cholangiocarcinoma cell lines with a DNA methyltransferase inhibitor restores the expression of MAO A.11 This is a topic of ongoing research in our laboratory.

As mentioned previously, the consequences of increased serotonin production on tumor growth depend upon the tumor type in question and, perhaps, the predominant serotonin receptor subtype present (9). On one hand, serotonin is known as a growth

11 S. DeMorrow et al., unpublished observation.
factor for several types of nontumoral cells (10, 11), and it has been proposed to take part in the autocrine loops of growth factors contributing to cell proliferation in aggressive tumors, such as small cell lung carcinoma (12), choriocarcinoma (50), and bladder cancer (15). Depending on the tumor type, either serotonin type 2 or serotonin type 1 receptor antagonists have been found to inhibit the serotonin-induced increase in tumor growth (13–15, 50). In contrast, several studies have also reported that serotonin and a serotonin type 2 receptor agonist can inhibit tumor growth (18). This effect may be related with the specific vasoconstrictive effect of serotonin and a serotonin type 2 receptor agonist on the vessels irrigating the tumor (16–18). Here, we show a proliferative effect of serotonin on cholangiocarcinoma growth, and the inhibition of serotonin production effectively inhibits tumor growth. Further- more, we could show that inhibition of the serotonin receptors 5HTR 1A, 5HTR 2A, 5HTR 2B, 5HTR 4, and 5HTR 6 effectively blocked the growth-promoting effects of serotonin. The effects of increased serotonin accumulation on other aspects of cholangio- carcinoma tumorgenesis, such as malignant transformation, metastatic activity, and angiogenesis, are also being studied in our laboratory.

In conclusion, the data presented here indicate a dysregulated serotonin metabolic pathway in cholangiocarcinoma compared with nonmalignant cholangiocytes. Specifically, there is an increase in the expression of TPH1, the enzyme responsible for serotonin metabolism of serotonin may be useful therapeutic tools for the treatment of this devastating cancer.

Disclosure of Potential Conflicts of Interest

The authors of this article have no financial arrangements to disclose.

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References


10. Mang E,amazon E, aminobutyric acid inhibits cholangiocarcinoma growth through increased suppression of tumor growth in a xenograft model of cholangiocarcinoma patients. Specific inhibition of serotonin production leads to a decreased expression of MAO A, the enzyme responsible for serotonin degradation. This leads to an increased accumulation and secretion of serotonin from cholangiocarcinoma and an increase in serotonin in the bile from cholangiocarcinoma patients. Specific inhibition of serotonin production leads to a suppression of tumor growth in a xenograft model of cholangiocarcinoma, which suggests that agents that modulate the metabolism of serotonin may be useful therapeutic tools for the treatment of this devastating cancer.

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