“Intestinal-type” of Adenocarcinoma Preferentially Induced in Right/Caudate Liver Lobes of Rats Treated with Furan

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ABSTRACT

Short-term chronic exposures of rats to furan were recently found by us to preferentially induce a unique liver lobe pattern of development of small intestinal metaplasia and subsequent cholangiofibrosis, being essentially localized to the caudate and right liver lobes (L. W. Elmore, and A. E. Sirica, Cancer Res., 51: 5752-5759, 1991). We now demonstrate the preferential development of primary hepatic adenocarcinomas exhibiting small intestine mucosal cell differentiation, which have arisen at 70 to 90% incidences from the right/caudate liver lobes of Fischer 344 adult male rats by 16 months after their receiving furan by gavage at a daily dose of 30 mg/kg of body weight, five times a week, for 9, 12, and 13 weeks, respectively. In contrast, the incidences of primary hepatocellular carcinomas that developed in the furan-treated rats ranged from 0 to 20%, with the two hepatic carcinoma types observed to be originating from the mediodleft liver lobes. Twenty-six of 27 hepatic adenocarcinomas analyzed exhibited glands containing on average 30.2% goblet cells, 2.1% Paneth cells, and 0.5% serotonin-positive neuroendocrine cells. Phenotypically, the glandular epithelial cells of the furan-induced intestinal-type adenocarcinomas were immunohistochemically positive for cytokeratin 19, but exhibited a heterogeneous pattern of immunohistochemical staining for γ-glutamyl transpeptidase and showed no detectable immunostaining for transforming growth factor α. In addition, many of the glandular structures within these primary hepatic adenocarcinomas showed evidence of basement membrane disruption, as demonstrated by both electron microscopy and immunohistochemical staining for basement membrane laminin. While these intestinal-type adenocarcinomas appeared to have spread intrahepatically, none showed evidence of extrabiliary metastases. However, six of eight randomly selected adenocarcinomas grew progressively and retained their intestinal pattern of differentiation following serial transplantation into the fat pads of young adult Fischer 344 recipient rats. In this study, we also observed one primary hepatic cholangiocarcinoma that was characterized by a more native biliary rather than intestinal-type of differentiation. Interestingly, this was the only primary liver cancer observed by us to exhibit extrabiliary metastasis. In conclusion, our current findings clearly indicate that the small intestinal metaplasia and subsequent cholangiofibrosis developing early in the right/caudate liver lobes of furan-treated rats do not simply reflect reactive changes, but strongly correlate with the high incidences of intestinal-type of primary hepatic adenocarcinoma that occurs in the right/caudate liver lobes of rats after long-term exposures to furan.

INTRODUCTION

Recently, we described a distinct lobe pattern of development of metastatic glandular structures and subsequently formed cholangiofibrosis within the livers of young adult F344 male rats that had received furan by gavage at 45 mg/kg of body weight once a day, five times a week over a 2- to 4-week treatment period (1-3). Specifically, we observed these metastatic glands and related cholangiofibrosis to develop preferentially within the right and caudate liver lobes of the furan-treated rats. In contrast, the most prominent pathological change seen to be characterizing the median and left lateral liver lobes of these animals was a biliary cirrhosis (1-3). In addition, we determined the respective liver lobes of the furan-treated rats to contain either no or very low numbers of putative preneoplastic hepatocellular foci (1).

The more mature metastatic glandular structures appearing in rat liver after the short-term chronic exposures to furan were further shown by us to have a cellular composition that very closely resembled that of the crypts of Lieberkühn of normal adult rat small intestine (1-3). Thus, we found after 16 to 32 days of furan treatment that these metastatic structures were comprised of 82-86% columnar enterocyte-like cells with well-developed striated borders, 13-16% goblet cells, 0.7-1.4% Paneth cells, and 0.2-0.4% serotonin-positive neuroendocrine cells (3). Moreover, we demonstrated that these four intestinal cell types developed sequentially within the metastatic glandular structures of the affected liver lobes, with the columnar enterocyte-like cells being seen as early as day 9, the goblet cells by days 9-12, and the Paneth and neuroendocrine cells by days 16-32 of the furan treatment (3). Also, with respect to cell lineage, our previously reported phenotypic and time course data strongly supported a precursor relationship between earlier appearing hyperplastic bile ductular-like structures and the later appearing metastatic glandular structures occurring within the right and caudate liver lobes of the furan-treated rats (1-3).

In a recent 2-year carcinogenesis bioassay conducted by the National Toxicology Program, furan was reported to induce high incidences of intrahepatic cholangiocarcinomas in both male and female F344 rats (4). It was further reported by Maronpot et al. (4) that in a separate but concurrent study, young adult male rats gavaged 5 days/week with 30 mg furan/kg of body weight for 13 weeks also exhibited a prominent cholangiocarcinoma within their right and caudate liver lobes and, after several additional months without further treatment, yielded a 100% incidence of intrahepatic cholangiocarcinomas. However, it was not clear from this latter study as to whether these reported biliary cancers were also arising from the right and caudate liver lobes. Also, the published histomorphological features of these tumors were determined only in tissue sections stained with hematoxylin and eosin and no information on the specific parenchymal cell composition of the neoplastic liver lesions was given. Thus, the aim of the current study was to determine if the hepatic tumors induced within rat liver after long-term furan treatment could be correlated both in terms of their cellular composition and their liver lobe site(s) of origin with the small intestinal metaplasia and cholangiofibrosis that occurs early and essentially within the right and caudate liver lobes of rats following short-term chronic exposures to furan. In addition, the hepatic tumors generated by the procedures reported in the present study were evaluated in terms of a number of phenotypic and biological parameters, including their immunohistochemical staining for cytokeratin 19, GGT, basement membrane laminin, TGF-α, their ultrastructural features, their transplantability into young adult syngeneic rats, and for changes in their glandular cell composition following serial transplantation.
**MATERIALS AND METHODS**

**Chemicals.** Furan (99%+) was purchased from Aldrich Chemical Co., Inc., Milwaukee, WI. Hydrogen peroxide, 3,3'-diaminobenzidine, pepsin, protease XXIV, bovine serum albumin, hematosyn solution, carmine (certified) and metanil yellow were purchased from Sigma Chemical Co., St. Louis, MO. Eosin Y was obtained from MC/B, Norwood, OH; Peel-A-Way embedding kit from Vector Laboratories, Inc., Burlingame, CA.

**Animals.** Young adult male F344 rats, 160-190 g, were purchased from Harlan Sprague Dawley, Indianapolis, IN. They were housed, one or two per cage, in filter top plastic cages and were maintained under a 12-h light, 12-h dark illumination cycle at 22°C in an approved biohazard animal facility. AIN-76A diet (Teklad Premier, Madison, WI) and drinking water were administered ad libitum throughout the experimental period. All of the animal experimentation described in this study was approved by our Institutional Animal Care and Use Committee (Animal Protocol 9103-1424).

**Furan Treatments.** Two separate experiments were performed to evaluate the carcinogenicity of furan. In the first experiment, 12 rats were administered furan in corn oil at 30 mg/kg of body weight given by gavage once in the morning, five times a week, for 13 weeks. In the second experiment, three groups of 10 rats each were given at 30 mg/kg of body weight of furan as described above, for 6, 9, or 12 weeks, respectively. In both experiments the rats were sacrificed by lethal injection of sodium pentobarbital (Steris Labs, Inc., Phoenix, AZ) at 16 months after initiation of the furan treatment. A complete postmortem examination was then performed on each rat with particular attention being paid to the liver lobe distribution of the hepatic tumors. Samples of all resulting hepatic and nonhepatic tumors, as well as random nontumorous portions of each liver lobe were obtained for microscopic examinations and in the case of hepatic tumors, for transplantation.

**Transplantation of Tumors.** Samples of eight randomly selected primary hepatic tumors were analyzed for progressive growth following transplantation into interscapular and inguinal fat pads of groups of 2 to 3 adult F344 recipient rats. For this procedure, the tumor samples were minced into 1- to 2-mm pieces in ice-cold sterile PBS, pH 7.6, and immediately thereafter, individual tumor pieces were inserted with a trochar into surgically exposed fat pads of recipients under ether anesthesia. Each tumor piece was secured in place by a single incision was then closed with a single wound clip. Recipient rats each received a total of 2 to 3 tumor pieces individually transplanted from single tumors to different fat pad sites. When tumor transplants grew to 1-2 to 2-2.5 cm in diameter, the recipients were sacrificed and the neoplasms were either processed as described below or were further propagated into new recipient rats. If after 6 months the recipients showed no evidence of a palpable tumor at any of the sites of transplantation, they were sacrificed without further evaluation.

**Histology, Histochemistry, and Immunohistochemistry.** Tissue samples were fixed in 10% buffered neutral formalin or in 95% ethanol/1% glacial acetic acid, dehydrated in alcohols, and embedded in low-melting-point paraffin, as described previously (1, 3, 5, 6). All staining procedures for light microscopy were performed on 5-μm-thick tissue sections, and routine histological examinations were conducted in all cases on sections stained with hematoxylin and eosin. Immunohistochemistry was performed, as described previously (1-3, 5, 6), with the following antibodies: affinity-purified anti-EHS mouse tumor laminin (1, 2, 5); antiserum prepared against Triton X-100-purified rat renal GGT (1, 2); monoclonal anti-cytokeratin 19 (1, 2, 3, 5, 6); and monoclonal anti-serotonin (3). An antiserum prepared against human lysozyme (DAKO Corp., Carpinteria, CA) was used to immunohistochemically detect Paneth cells. Here, formalin-fixed tissue sections were incubated in 0.06% hydrogen peroxide for 15 min, treated with 0.025% protease XXIV in PBS for 7 min at room temperature, blocked with normal goat serum for 30 min, incubated overnight at 4°C with a 1:600 dilution of the anti-lysozyme antiserum in PBS containing 0.1% bovine serum albumin and then immunostained using an appropriate Vectastain avidin-biotin complex horseradish peroxidase kit, as described previously (1, 2, 3, 5, 6). Between each step the tissue sections were washed at least 15 minutes in PBS. Tissue sections of normal rat small intestine were included as a positive control. TGF-α immunostaining was performed essentially according to the staining conditions which have been previously described (1, 3, 5, 6) by using a monoclonal anti-TGF-α antibody (Oncogene Science, Inc., Manhasset, NY) diluted 1:200 in PBS containing 0.1% bovine serum albumin. The specificity of TGF-α staining was assessed by immunobosorbing the diluted antibody with a 20-fold concentration of either recombinant human TGF-α or murine EGF overnight at 4°C. Mayer’s mucicarmine method was used to stain for the presence of mucin (1, 7).

**RESULTS**

The furan-treated rats in both experiments exhibited very high incidences of hepatic adenocarcinomas at 16 months after initiation of the chemical exposures (Fig. 1A; Tables 1 and 2). In the first experiment, this incidence was 90% (Table 1), and in the second experiment, it was 75% and 71% for rats that received furan for 9 and 12 weeks, respectively (Table 2). As further demonstrated in Table 2, even when furan was administered for only 6 weeks, 44% of the treated rats were found to have a hepatic adenocarcinoma at the end of the 16-month experimental period. In contrast, the incidence of hepatocellular carcinoma in the first experiment was only 20% (Table 1), while in the second experiment, no hepatocellular carcinomas were observed. In the second experiment only, we also detected two rats with large cell leukemia, one rat with a hepatic angiosarcoma, and one rat with a s.c. fibrosarcoma (data not shown). However, we do not know if these latter sporadic neoplasms arose spontaneously or developed as a consequence of the furan exposures. No further analyses were performed on these four rats and tumors, as well as on two other furan-treated rats from the second experiment that died of undetermined causes prior to the end of the 16-month experimental period.

Of particular interest is our observation that the primary hepatic adenocarcinomas which developed in the furan-treated rats were preferentially localized to the right/caudate liver lobes. This unique liver lobe pattern of tumor development is exemplified by data derived from our first experiment and shown in Table 1. Although it appeared to us that the majority of primary adenocarcinomas seemed to have arisen in the right liver lobe, it was difficult in some cases to clearly distinguish tumor margins, particularly in relation to the caudate liver lobe. Thus, we categorize the hepatic site of the tumors as being either right/caudate or median/left lobes (Table 1). The distinct right/caudate lobe distribution of the primary adenocarcinomas in liver of the furan-treated rats was confirmed in our second experiment (data not shown). It is also interesting that the two primary hepatocellular carcinomas that developed in the first experiment originated from the median/left lobes. In addition, we did not observe in any of the liver lobes of the furan-treated rats from both experiments the presence of combined hepatocellular-cholangiocellular carcinomas.

The epithelial glandular structures within the furan-induced hepatic adenocarcinomas were characterized by their abundant mucin production (Fig. 2A), and for many glands, by a disruption of their basement membrane, as demonstrated by both immunohistochemical staining for basement membrane laminin (Fig. 1C) and by electron microscopy (Fig. 1D). These glandular structures in these tumors were also
found to exhibit a homogeneous pattern of staining for cytokeratin 19 as well as a heterogeneous pattern of immunostaining for GGT, but none of the biliary adenocarcinoma analyzed in this study had detectable immunostaining for TGF-α (data not shown). In contrast, the two resulting hepatocellular carcinomas displayed positive immunohistochemical reaction for TGF-α, which could be blocked by preabsorption of the antibody with recombinant TGF-α but not with EGF (data not shown).

Perhaps the most notable result of this study is our finding that 26 of the 27 furan-induced hepatic adenocarcinomas examined exhibited evidence of small intestinal differentiation as reflected by the presence of goblet cells, Paneth cells, and serotonin-positive neuroendocrine cells (Fig. 2; Table 3). Even though all of the “intestinal-type” of adenocarcinomas appeared to have spread intrahepatically, none showed evidence of extrahepatic metastases. However, of the eight primary intestinal-type tumors randomly selected for transplantation into the fat pads of young adult syngeneic rats, six demonstrated progressive growth (i.e., Fig. 1B). Moreover, the tumor transplants could be serially passaged, grow rapidly, and retain their intestinal pattern of differentiation, although the percentage of the different small intestinal mucosal cell types were generally less in the transplants than in those of the original primary tumors (Table 3).

Table 1

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<th>Hepatic neoplasm</th>
<th>Tumor incidence in liver lobes b</th>
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<tr>
<td></td>
<td>Right/caudate</td>
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<tr>
<td>Hepatic adenocarcinoma</td>
<td>9/10</td>
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<tr>
<td>Hepatocellular carcinoma</td>
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* Twelve rats were treated daily with a 30-mg/kg of body weight dose of furan 5 times/week for 13 weeks. Sixteen months after initiation of the furan treatment, 10 surviving animals were analyzed for hepatic tumor incidence.

b Number of tumor-bearing animals/total number of surviving animals at the time of sacrifice.

In these 3 rats, a larger hepatic neoplasm was observed in the region of the right/caudate lobes, hence the tumor incidence indicated here may reflect intrahepatic spread rather than separate primary neoplasms.

Table 2

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<th>Hepatic neoplasm</th>
<th>Tumor incidence c after the following treatment period</th>
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<td></td>
<td>6 weeks</td>
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<tr>
<td>Hepatic adenocarcinoma</td>
<td>4/9</td>
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<tr>
<td>Hepatocellular carcinoma</td>
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* Twenty-four of the 30 furan-treated rats were analyzed. Details of the furan treatment are given in “Materials and Methods,” with data on the 6 excluded animals being described in “Results.”

b Number of tumor-bearing animals/total number of animals analyzed in each group.

c Only tumors with histological features compatible with malignancy (4), including piling up of epithelial cells in glandular structures, disruption of basement membranes with microinvasion, nuclear hyperchromasia, cellular hyperbasophilia, and increased nuclear/cytoplasmic ratios were considered in this analysis.

Fig. 1. Morphological features of furan-induced hepatic intestinal-type adenocarcinomas in F 344 rats. A, light photomicrograph of a representative intestinal-type primary adenocarcinoma replacing a right liver lobe. H & E, ×13.2; B, light photomicrograph of a first passage tumor transplant derived from the primary neoplasm shown in A. H & E, ×13.2; C, immunohistochemical staining of basement membrane laminin limiting a glandular component within a primary intestinal-type adenocarcinoma (thin arrows denote intact laminin-enriched basement membrane, and thick arrows indicate regions of basement membrane disruption). ×13.2; D, electron micrograph of an epithelial cell within a neoplastic gland of an intrahepatic adenocarcinoma exhibiting a fragmented basement membrane (BM denotes intact basement membrane; arrows point to a disrupted region basement membrane). ×26,000.
Lastly, we observed in our study one hepatic cholangiocarcinoma which was characterized by a more native biliary rather than intestinal-type pattern of differentiation (data not shown). This biliary cancer, like the predominant intestinal-type tumors, also exhibited strongly positive immunohistochemical staining for cytokeratin 19, undetectable TGF-α immunostaining, and evidence of basement membrane disruption. However, in contrast to the primary intestinal-type hepatic tumors, this single cholangiocarcinoma showed a uniformly intense immunohistochemical staining for GGT, which was localized to the luminal surface of the malignant epithelial cells, and only a weak histochemical staining for mucin, which could be observed in the lumens of occasional glandular structures within the tumor (data not shown). It is also noteworthy that this was the only primary hepatic biliary cell cancer observed by us to have metastasized to regional lymph nodes.

**DISCUSSION**

In the present study, we have both confirmed and extended the recent findings of Maronpot et al. (4) related to the National Toxicology Program’s carcinogenesis bioassay of furan in F344 male rats. Moreover, we have demonstrated for the first time that 96% of the primary hepatic “cholangiocarcinomas” that developed in our furan-treated rats were characterized by intestinal cell differentiation. In particular, these tumors were found to exhibit the same small intestinal mucosal cell types (i.e., goblet cells, lysozyme-positive Paneth cells, and serotonin-positive neuroendocrine cells) that we previously observed within metaplastic glandular structures of cholangiofibrotic lesions induced in rat liver by 2 to 4 weeks of furan treatment (1-3). Interestingly, the glandular components of the hepatic cholangiocarcinomas analyzed in this study contained on average 30% goblet cells and exhibited abundant mucin production, compared with the 13 to 16% goblet cells and lower amounts of mucin production previously reported by us to be characterizing the metaplastic glandular structures of the very early furan-induced cholangiofibrotic lesions (3). In contrast, the intestinal-like glands of the primary neoplasms and of the very early cholangiofibrotic lesions induced by furan both contained very similar mean percentages of Paneth cells and neuroendocrine cells (Ref. 3; Table 3). Furthermore, the intestinal-like glands of the primary tumors, like those of the very early cholangiofibrotic lesions, were shown in the present study to be characterized by a
strongly positive immunohistochemical staining for cytokeratin 19 and a heterogeneous pattern of immunostaining for GGT, but to also exhibit a disruptive immunostaining pattern for basement membrane laminin, a feature that is consistent with their malignant neoplastic phenotype.

Based on the glandular cell composition of these tumors, it now seems more appropriate to reclassify them as primary hepatic intestinal-type adenocarcinomas (or intestinal-type cholangiocarcinomas) than as just hepatic cholangiocarcinomas, as was previously reported (4). More importantly, it is also now quite evident from our liver lobe analysis of tumor development, that the vast majority of these primary intestinal-type adenocarcinomas appeared to have originated from the right/caudate liver lobes of the furan-treated rats. This finding, in turn, closely correlated with our previously reported data demonstrating that the early development of small intestinal metaplasia and cholangiofibrosis merely reflect a reactive change or whether they are directly related to the subsequent development of primary hepatic intestinal-type adenocarcinomas in the right/caudate liver lobes of this animal model. Less certain, however, is the involvement of adenomas as intermediate lesions in the histogenesis of furan-induced adenocarcinomas. Our limited observation that 44% of the rats that received furan at a 30-mg/kg of body weight dose for 6 weeks later developed some intrahepatic cystic cholangiomas as well as cholangiofibromas, which exhibited variable degrees of dysplasia (data not shown), is at least consistent with an adenoma-dysplasia-carcinoma sequence.

In the study reported by Maronpot et al. (4), only some of the furan-induced primary hepatic cholangiocarcinomas exhibited extrahepatic metastasis after 15 months. Furthermore, transplantation of 21 of the diagnosed primary cholangiocarcinomas into syngeneic rats resulted in growth from four donors and yielded a relatively low number of recipients with metastasis after five to eight passages of the original four transplanted tumor cells lines. In comparison, the only primary cholangiocarcinoma in our study to exhibit extrahepatic metastasis was the one which displayed a more native biliary cell pattern rather than an intestinal cell pattern of differentiation. Interestingly, it has recently been postulated that the prognosis of gallbladder carcinoma in humans may be influenced by whether the neoplasm exhibits intestinal metaplasia or a more native biliary epithelial cell morphology (16, 17). However, a larger number of furan-induced primary hepatic cholangiocarcinomas with the more native biliary cell-type pattern of differentiation need to be analyzed before more definitive conclusions may be drawn as to whether such a histological pattern can be correlated with a more aggressive tumor behavior when compared with that of the intestinal-type of primary hepatic adenocarcinoma. Nevertheless, 75% of eight randomly selected primary liver tumors classified by us intestinal-type adenocarcinomas exhibited progressive growth when transplanted into syngeneic rats, thus providing biological support for the malignant potential of these tumors. It should also be pointed out that, whereas Maronpot et al. (4) stated...
that the microscopic features of the transplanted tumors obtained from their study and analyzed in hematoxylin-eosin-stained tissue sections were essentially identical to those of the furan-induced primary hepatic cholangiocarcinomas, our analysis of cellular composition consistently demonstrated lower mean percentages of various intestinal cell types in the transplanted tumors than those determined for the primary intestinal-type adenocarcinomas.

The fact that we were unable to detect by immunohistochemistry the presence of TGF-α in any of the primary hepatic adenocarcinomas induced by furan is in sharp contrast to positive immunostaining we observed for this growth factor in the two primary hepatocellular carcinomas that developed in this study. This latter finding is in agreement with previously reported data demonstrating the expression of TGF-α by rat hepatocellular carcinoma cells (18). On the other hand, we now have preliminary immunohistochemical data to suggest that the intestinal-like glandular structures of both the cholangiofibrotic lesions and intestinal-type primary adenocarcinomas induced by furan contain cytoplasmic hepatectone growth factor. However, we have not yet determined whether the cells of these intestinal-type glands have mRNA for hepatocyte growth factor or if they express the c-MET oncogene encoding for the hepatocyte growth factor receptor (19).

In summary, we have characterized the cellular composition and some of the phenotypic and biological features of primary adenocarcinomas, which are induced at a very high incidence in the right/caudate liver lobes of furan-treated F344 male rats. These tumors closely resemble in their cellular composition the intestinal type of adenocarcinoma that occurs in human liver and gallbladder (9, 20). In addition, our data strongly implicate small intestinal metaplasia and adenocarcinoma that occurs in human liver and gallbladder (9, 20). In summary, we have characterized the cellular composition and some of the phenotypic and biological features of primary adenocarcinomas, which are induced at a very high incidence in the right/caudate liver lobes of furan-treated F344 male rats. These tumors closely resemble in their cellular composition the intestinal type of adenocarcinoma that occurs in human liver and gallbladder (9, 20). In addition, our data strongly implicate small intestinal metaplasia and related cholangiofibrosis as being early changes relevant to the development of intestinal-type adenocarcinomas that formed in rat liver following longer-term chronic exposures to furan. The predominance of this type of hepatic neoplasm together with the single primary hepatic cholangiocarcinoma with a more native biliary cell morphology seen in this study further suggest that there may be two different cell lineages in the histogenesis of hepatic adenocarcinomas in furan-treated rats, the major one being derived from the metastatic intestinal-like glands within the earlier appearing cholangiofibrotic lesions and the much less common one being derived from the hyperplastic bile ductule-like structures within these same precursor lesions. In human gallbladder cancer, it has also been suggested that there might be two types of adenocarcinoma; one originating from native or non-metastatic gallbladder mucosa and one from metastatic epithelium (17, 21).

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