Cdx2 Protein Expression in Normal and Malignant Human Tissues: An Immunohistochemical Survey Using Tissue Microarrays

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Cdx2 has been identified as a marker of colon cancer in RNA-profiling experiments. We show here that the detection of Cdx2 protein by immunohistochemistry correlates well with RNA transcript levels as detected by oligonucleotide microarrays. Using tissue microarrays containing most normal tissue types and an antibody to the Cdx2 protein, strong diffuse Cdx2 staining was only seen in the nuclei of small and large intestinal epithelium and portions of the pancreatic duct system. In tissue microarrays containing 745 cancers from many anatomic sites, colonic adenocarcinomas showed strong extensive staining in 90% of cases, with adenocarcinomas of the stomach, esophagus, and ovary (endometrioid and mucinous types) showing extensive staining in only 20–30% of cases. Other types of carcinomas showed extensive staining in only ≤1% of cases. Of 30 neuroendocrine tumors examined, carcinoids of the midgut and hindgut had the most cases with extensive staining (73% and 44%, respectively), thus paralleling the distribution of Cdx2 expression in adenocarcinomas. Cdx2 shows a limited range of expression in the spectrum of human tissues and neoplasia and thus may have utility in determining the site of origin of tumors in certain clinical situations.

Cdx2 is a homeobox gene that has been shown to play a role in the development of the small and large intestine in mammals and in the differentiation of intestinal epithelial cells. The *Cdx2* gene is expressed in all but the most distal portions of the intestinal tract during development (1, 2). In a cell culture model, Cdx2 has been shown to decrease cellular replication and induce differentiation to mature intestinal epithelium (3). Cdx2 acts as a transcription factor, increasing the expression of several gene products associated with mature intestinal epithelial cells (3, 4). Perhaps not surprisingly, *Cdx2* has recently been identified as a gene whose expression had a high predictive value for the diagnosis of colonic adenocarcinoma in microarray gene expression analyses (5, 6). The use of Cdx2 as an immunohistochemical marker has been described recently in studies of human gastric and colon cancer, but no comprehensive survey of Cdx2 protein expression has been reported (7–9). To follow up on previous RNA transcript profiling data, we report our findings using immunohistochemistry on tissue microarrays to comprehensively profile the protein expression of Cdx2 in a broad range of human carcinomas and normal tissues.

MATERIALS AND METHODS

Tissue Specimens

Formalin-fixed, paraffin-embedded tissue blocks were obtained from the archives of the Department of Pathology of the University of Virginia Health System with institutional review board approval.

Tissue Microarrays

Targeted tissue areas were marked on H&E-stained sections corresponding to the paraffin blocks. One to three 0.6-mm tissue cores from each case were removed using a manual microarray device (Beecher Instruments, Silver Spring, MD) and inserted into recipient paraffin blocks. The tissue microarrays were sectioned at a 4-μm thickness and placed on charged slides.

Immunohistochemistry

Tissue microarray and standard tissue histologic sections were deparaffinized, rehydrated, and blocked with methanolic 3% hydrogen peroxide. The slides were immersed in 10 mM citrate buffer, pH 6.0 and heated in a 1200W microwave oven at the highest power setting. Evaporated liquid was replenished at 5 minutes, then the slides were heated at high power for an additional 5 minutes. The slides were left in the buffer for an additional 10 minutes before being removed. The antibody used was a mouse monoclonal antibody raised against full-length recombinant Cdx2 protein (AM392—5 M; BioGenex, San Ramon, CA). Immunostaining was performed by hand using the prediluted antibody solution and a 30-minute incubation. After washing, antibody binding was visualized using the avidin-biotin-peroxidase technique (Vectastain Elite ABC kit, Vector Laboratories, Burlington, VT), followed by incubation with 3,3'-diaminobenzidine tetrahydrochloride. The slides were counterstained with hematoxylin.

The immunohistochemical stains were evaluated by two pathologists (HFF and CAM). Only nuclear staining was considered positive, and it was scored on the following basis: 0 (no detectable staining); 1+ (<25% positive cells); 2+ (25–49%); 3+ (50–74%); 4+ (>75%). In general, cases showing 3+ and 4+ staining also had strong intense staining, so intensity was not factored into the scoring.

The list of normal tissues examined is given in Table 1. Focal heterogeneous Cdx2 expression was present in the pancreatic tissue microarray samples, and standard histologic sections of this organ were also examined for confirmation of this finding.

The list of tumors examined is given in Table 2. The following tumors were absent from or not well represented in the arrays, and additional cases were obtained and examined as standard histologic sections: germ cell tumors (12 additional cases), ampullary carcinoma (6 cases), and neuroendocrine carcinomas of the gastrointestinal tract, biliary tract, lung, and pancreas (30 cases).

TABLE 1. Cdx2 Immunohistochemical Staining in Normal Tissues

No staining	
Adipocytes	Peripheral nerve
Adrenal cortex	Pituitary
Adrenal medulla	Placental membranes
Anal squamous epithelium	Placental villi
Astroglia	Prostate
Bartholin gland	Salivary gland, minor
Bile duct epithelium	Salivary gland, parotid
Bladder transitional epithelium	Salivary gland, submandibular
Blood vessels	Seminal vesicle
Bone	Skeletal muscle
Bone marrow	Skin, squamous epithelium
Breast (duct epithelium)	Skin, sweat glands
Breast (lobular epithelium)	Smooth muscle, uterus
Bronchial epithelium	Spinal cord
Brunner glands	Spleen
Cartilage (bronchus)	Stomach, antrum
Endocervical epithelium	Stomach, fundus
Endometrial epithelium, proliferative	Synovium
	Tendon
Endometrial epithelium, secretory	Testis, Leydig cells
Endometrial stroma	Testis, rete
Endometrial stroma, decidualized	Testis, seminiferous tubules
Epidiymis	Thymus
Esophagus, squamous epithelium	Thyroid
Esophagus, submucosal glands	Tonsil
Fallopian tube	Ureter
Gallbladder	Urethra, male
Ganglia, peripheral	Vagina, squamous epithelium
Heart, myocardium	Vas deferens
Kidney, cortex	Vulva, squamous epithelium
Kidney, medulla	Umbilical cord
Lacrimal gland	
Liver, hepatocytes	2+ staining
Liver, portal tracts	Pancreatic ducts, intermediate to large cts
Lung alveoli	
Lymph node	4+ staining
Lymphatics	Appendiceal epithelium
Melanocytes	Colonic epithelium
Mesothelium	Pancreatic centroacinar cells
Neurons (cerebellum)	Pancreatic ducts, interacinar
Neurons (cerebrum)	Rectal epithelium
Ovarian stroma	Small intestinal epithelium
Ovary, corpus luteum	
Ovary, primary follicle and germ cells	
Pancreatic acinar cells	
Pancreatic islets	
Parathyroid	

RNA Gene Expression Profiling

Gene expression profiles of a subset of tumor cases were obtained on U95a GeneChips (Affymetrix, Santa Clara, CA), as reported previously (6).

RESULTS

The degree of Cdx2 protein expression, as determined by immunohistochemistry, was compared with the level of *Cdx2* RNA transcript levels for a subset of tumors. Transcript levels determined by hybridization to GeneChip oligonucleotide arrays (Affymetrix Inc.) were available for 20 breast adenocarcinomas, 19 colon adenocarcinomas, 2 gastric adenocarcinomas, 12 lung adenocarcinomas, 12

TABLE 2. Immunohistochemical Staining of Cancers

Staining Pattern	0	1+	2+	3+	4+
Ampullary carcinoma	2	1	1	1	1
Bladder/ureter transitional cell carcinoma	7	0	0	0	0
Breast adenocarcinoma	70	0	0	0	0
Carcinoid tumors					
Lung	5	2	0	0	0
Common bile duct	1	1	0	0	0
Foregut (stomach)	3	0	0	0	0
Midgut (ileum & appendix)	0	0	1	1	7
Hindgut (rectum)	2	2	1	3	1
Cholangiocarcinoma	8	7	2	0	0
Colorectal adenocarcinoma	0	4	2	5	49
Gallbladder adenocarcinoma	4	2	0	0	0
Gastroesophageal adenocarcinoma	88	23	20	15	18
Germ cell tumors					
Dysgerminoma	3	1	0	0	0
Embryonal Carcinoma	3	0	0	0	0
Seminoma	6	0	0	0	0
Yolk sac tumor	1	1	2	1	0
Hepatocellular carcinoma	12	0	0	0	0
Lung carcinoma					
Adenocarcinoma	33	1	1	0	0
Large cell undifferentiated carcinoma	1	0	0	0	0
Small cell/Neuroendocrine carcinoma	2	0	0	0	0
Squamous cell carcinoma	13	0	0	0	0
Melanoma	1	0	0	0	0
Mesothelioma	28	0	0	0	0
Ovarian tumors					
Clear cell ca	1	1	0	0	0
Endometrioid adenocarcinoma	7	1	0	1	1
Granulosa cell tumor	8	0	0	0	0
Mucinous adenocarcinoma	4	0	0	1	0
Serous papillary carcinoma	39	1	1	0	0
Undifferentiated carcinoma	7	0	0	0	0
Pancreatic tumors					
Ductal (typical) adenocarcinoma	16	8	0	0	0
Mucinous adenocarcinoma	0	0	0	0	1
Acinar cell carcinoma	2	0	0	0	0
Islet cell tumor	10	2	1	0	1
Prostate adenocarcinoma	100	1	0	1	0
Renal cell carcinoma	35	0	0	0	0
Salivary gland tumors					
Acinic cell carcinoma	4	0	0	0	0
Adenoid cystic carcinoma	17	0	0	0	0
Polymorphous low grade adenocarcinoma	3	0	0	0	0
Salivary duct carcinoma	3	0	0	0	0
Sarcomatoid carcinoma (various sites)	14	0	0	0	0
Thyroid tumors					
Follicular carcinoma	9	0	0	0	0
Papillary carcinoma	12	0	0	0	0
Uterus (Endometrioid carcinoma)	18	3	1	1	0

lung squamous carcinomas, 10 renal carcinomas, 8 hepatocellular carcinomas, 14 ovarian carcinomas, and 30 prostate adenocarcinomas. For comparison to the semiquantitative immunohistochemical scoring, the hybridization intensity of *Cdx2* on the GeneChips, which represents the range of RNA transcript levels, was scaled into quartiles. In general, there was good agreement between the average immunohistochemical score and the average transcript score for the subgroups of cancers (Fig. 1).

Table 1 shows the immunohistochemical results for the panel of normal tissues examined. Strong, diffuse Cdx2 staining was seen in intestinal epithelium, including tissue from the duodenum, ileum, appendix, colon, and rectum. The epithelium of major pancreatic ducts showed focal patchy staining, whereas centroacinar cells and the epithelium of pancreatic interacinar ductules and small pancreatic ducts showed strong diffuse staining. Pancreatic acinar epithelium and islet cells did not stain for Cdx2. No other normal tissue types had detectable Cdx2 staining. Figure 2 shows examples of Cdx2 immunohistochemistry in pancreas and other normal tissues.

Table 2 contains the results of Cdx2 immunohistochemical findings for the complete set of tumors examined. Extensive nuclear staining (>50% of cells) for Cdx2 was most commonly seen in colorectal adenocarcinomas (54 of 60, 90%; Figs. 3–4). Other adenocarcinomas with extensive nuclear Cdx2 staining included gastroesophageal adenocarcinomas (33 of 164,
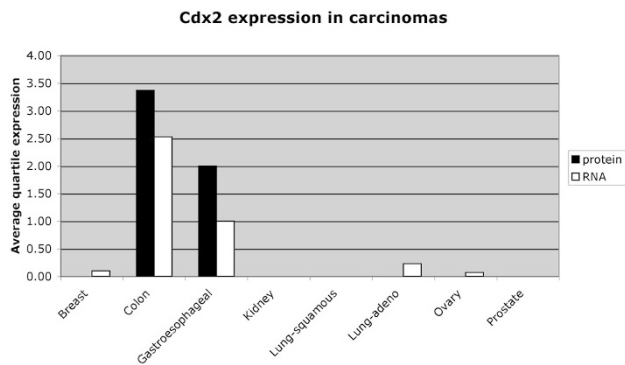
Cdx2 expression in carcinomas

FIGURE 1. Comparison of Cdx2 RNA and protein expression in carcinomas. The scaled hybridization intensity values obtained from oligonucleotide microarray analysis of RNA transcripts present in tumor samples were translated into quartiles and assigned values of 1, 2, 3, or 4 (from lowest to highest fluorescence intensity), with a zero value indicating no fluorescence above background. The staining pattern of Cdx2 immunohistochemistry obtained from histologic sections of the same tumors were also separated into 5 groups (0 through 4, see Materials & Methods section). The mean score for each cancer type is shown, with protein levels represented by **filled bars** and RNA levels represented by **open bars.** There is good correlation between the results of RNA and protein expression detected by these methods, with both methods showing colorectal adenocarcinomas with the highest level of expression, followed by gastroesophageal adenocarcinomas.

20%), ovarian endometrioid adenocarcinomas (2 of 10, 20%) and mucinous adenocarcinomas (1 of 5, 20%), uterine endometrioid adenocarcinoma (1 of 23, 4.3%), and prostatic adenocarcinoma (1 of 102, 1%). Although no typical ductal pancreatic adenocarcinoma showed Cdx2 staining, the single case of mucinous pancreatic adenocarcinoma showed strong diffuse immunoreactivity.

Neuroendocrine tumors in general exhibited a pattern of Cdx2 staining that mirrored the anatomic distribution of Cdx2 expression in non-neuroendocrine carcinomas. Eight of 9 (89%) midgut and 4 of 9 (44%) hindgut carcinoids showed extensive Cdx2 expression, with carcinoids of the stomach, biliary tract, and lung showing no or only focal Cdx2 expression. The majority of pancreatic islet cell tumors also showed no or little staining for Cdx2, with only 1 of 14 cases (7.1%) showing >50% of cells staining.

DISCUSSION

Cdx2 is a gene essential for normal mammalian development. In adult animals, including humans, it is expressed in intestinal epithelial cells, where it acts as a transcription factor. Genes that are regulated by *Cdx2*, such as sucrase-isomaltase and lactase, are associated with the mature enterocyte phenotype, and the current paradigm is that *Cdx2* is a master "control gene" for intestinal epithelial differentiation. Our data support the use of Cdx2 immunohistochemistry as a marker of intestinal cellular differentiation, even in the malignant state.

The highest frequency of extensive Cdx2 expression was seen in colorectal adenocarcinomas (90%). Ampullary and gastroesophageal adenocarcinomas, which often have histologic and histochemical evidence of intestinal differentiation, also had a substantial percentage of tumors with extensive Cdx2 expression (33 and 20%, respectively). Neuroendocrine tumors arising from various epithelia exhibit Cdx2 expression that mirrors that seen in the native non-neuroendocrine epithelia, with the highest frequency of extensive Cdx2 expression in the midgut (89%) and hindgut (44%). Interestingly, Cdx2 expression has been reported to be lower in the distal colorectum than in the rest of the gastrointestinal tract during development (2), and the hindgut carcinoids in our collection were exclusively from the rectum. It is possible that the lower frequency of rectal carcinoids highly expressing Cdx2, when compared with the frequency of midgut carcinoids, is a reflection of this relative biological difference seen in the cell populations from which these tumors originate. The finding of high Cdx2 levels in neuroendocrine tumors derived from intestinal epithelium suggests that Cdx2 may also be playing a role in normal neuroendocrine cell differentiation, or that Cdx2 expression in gut epithelium does not alone determine differentiation to the absorptive cell phenotype.

When the *Cdx2* gene is eliminated by one copy in mice, the animals develop hamartomatous polyps, in which it has been shown that the wild-type *Cdx2* allele is not expressed. This observation has led to the screening of patients with intestinal hamartomatous polyposis syndromes for germline inactivating mutations of *Cdx2*; however, no such mutations have been identified (10). In cell culture experiments, induced expression of *Cdx2* has been shown to arrest proliferation in undifferentiated intestinal cells (3). This observation, along with the heterozygous mouse model, suggests that *Cdx2* may act as a tumor suppressor. However, in surveys of human colon carcinoma, except for a few rare tumors that also expressed high microsatellite instability (MI), gene mutation has not been found (10–12). Because *Cdx 2* is neither mutated, nor is its gene expression lost in most cases of colorectal adenocarcinomas, it seems highly unlikely that it plays a role as a significant tumor suppressor. A subset of colon cancers described as "large cell minimally differentiated carcinomas" has been reported as lacking expression of *Cdx2* (8). These tumors also had a high incidence of MI, suggesting that both MI and Cdx2 loss are molecular alterations in colon cancer manifested by this large cell morphology. Because Cdx2 mutations occur in areas of repetitive DNA sequence within the gene (11), it is likely that Cdx2 is not selected as a tumor suppressor gene when it is mutated in these can-
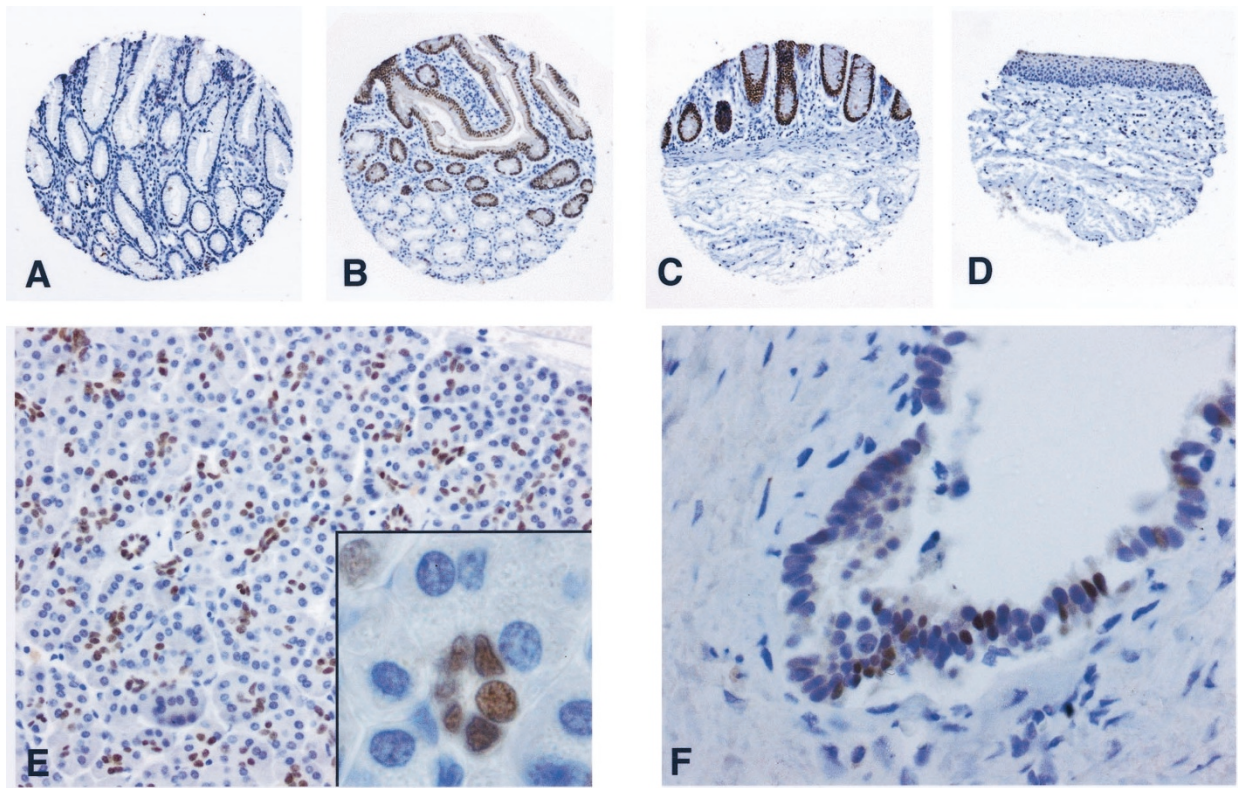
FIGURE 2. Examples of Cdx2 immunohistochemistry in non-neoplastic tissue. **A,** gastric antrum sample in tissue microarray showing no nuclear staining (original magnification, 100×). **B,** duodenum sample in tissue microarray showing staining exclusively in enterocytes. Note that Brunner gland epithelium exhibits no staining (original magnification, 100×). **C,** colon sample in tissue microarray showing staining exclusively in colonocytes (original magnification, 100×). **D,** anus sample in tissue microarray showing no nuclear staining (original magnification, 200×). **E,** standard section of pancreas showing staining of centroacinar cells and small ducts (original magnification, 200×). The *inset* shows a higher power of an acinus (original magnification, 1000×). **F,** large pancreatic duct showing spotty epithelial staining (original magnification, 400×).
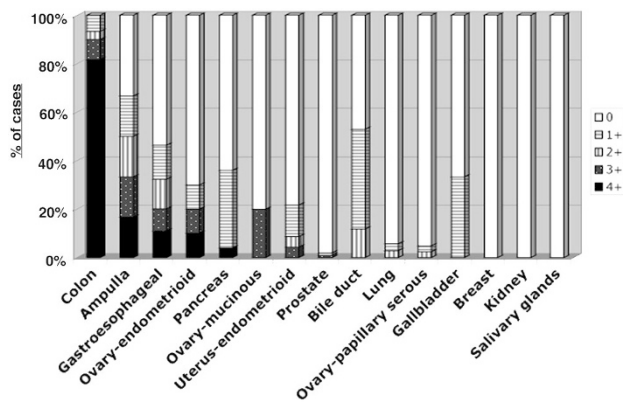

FIGURE 3. Results of Cdx2 immunohistochemistry in adenocarcinomas. Immunohistochemical staining was graded 0–4+ based on the percent of cells showing nuclear staining for Cdx2. Colorectal adenocarcinomas had the greatest percentage of cases showing strong diffuse Cdx2 staining (3–4+), followed distantly by ovarian, ampullary, and gastroesophageal adenocarcinomas.

cers but may be mutated as an "innocent by-stander" as a consequence of the DNA mutator phenotype associated with MI. Once inactivated, however, it is also likely that the undifferentiated large cell phenotype is a consequence of *Cdx2* mutation. This hypothesis is supported by studies with the IEC-6 cell line, a human colon cancer cell line

that grows as undifferentiated tumors in nude mice. When Cdx2 expression is induced in these cells, the cells form tumors with glandular and villous structure, and ultrastructural features of both enterocytes and goblet cells are found (3).

The data presented in this study show that strong, extensive nuclear Cdx2 immunohistochemical staining is very common in colorectal adenocarcinomas, with smaller numbers of adenocarcinomas of the stomach, esophagus, pancreas, ovary, and uterus showing this pattern. Of particular note is the differential expression of Cdx2 protein in mucinous tumors of the ovary as compared with adenocarcinomas arising in the colorectum. There often exists some uncertainty as to the primary site of origin of carcinomas in the ovary that show glandular or mucinous differentiation. The ovarian tumors used in this series were carefully screened to include only those cases with an adequate clinical examination to exclude a gastrointestinal primary tumor. Although not completely specific, the relatively low numbers of mucinous ovarian tumors showing extensive Cdx2 expression may make this a useful marker, perhaps as part of a panel of immunohistochemical stains, in separating metastatic gastrointestinal tumors from primary mucinous
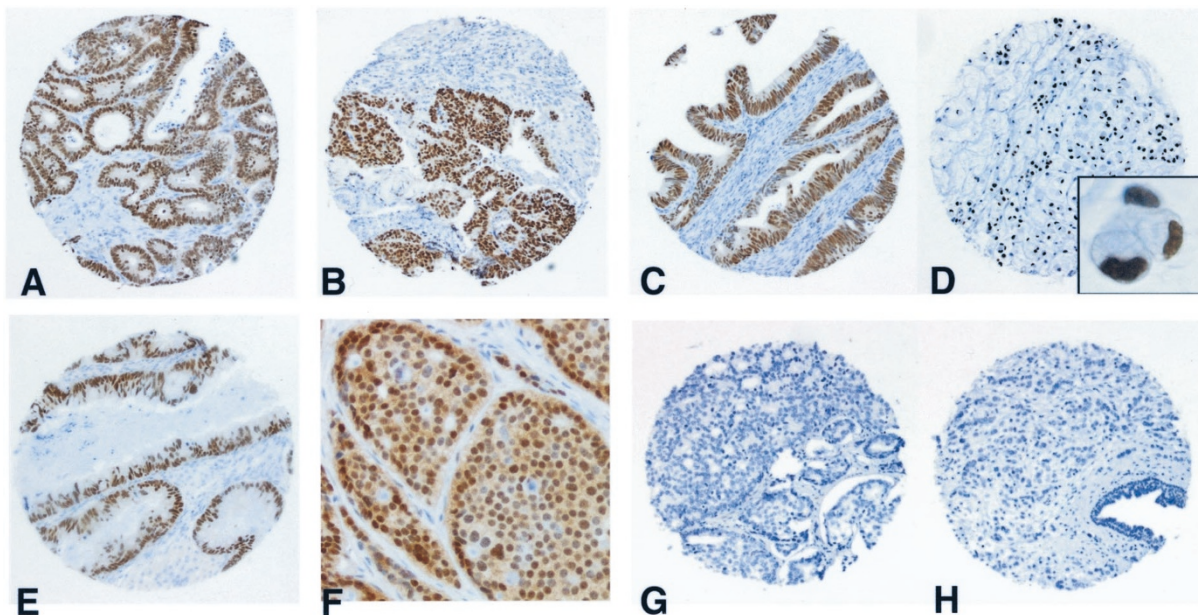
FIGURE 4. Examples of Cdx2 immunohistochemistry in cancers. **A,** colon adenocarcinoma, well differentiated, showing diffuse nuclear staining. **B,** colon adenocarcinoma, poorly differentiated, showing diffuse nuclear staining. **C,** gastric adenocarcinoma, intestinal type, well differentiated, showing diffuse nuclear staining. **D,** gastric adenocarcinoma, signet ring cell type, showing diffuse nuclear staining. **E,** ovarian carcinoma, mucinous subtype, showing diffuse nuclear staining. **F,** carcinoid tumor of ileum, showing diffuse nuclear staining. **G,** prostate adenocarcinoma, negative for staining. **H,** breast adenocarcinoma, negative for staining. **Panels A–E, G,** and **H** are of samples from tissue microarrays (original magnification, 100×; **inset** in **Panel D** is 1000× original magnification), and **Panel F** is from a standard histologic section (200× original magnification).

ovarian carcinomas. More definitive proof of the usefulness of this marker for this purpose will require a more focused study, with a larger number of cases.

Other potential uses of this marker include the workup of metastatic tumors at other sites. The marker may aid in the differential diagnosis of well-differentiated neuroendocrine tumors first detected in the liver. Extensive positive Cdx2 staining predicts a metastasis from a gastrointestinal carcinoid of midgut or hindgut origin. Negative or focal Cdx2 staining predicts a source from the lung, stomach, biliary tract, or pancreas. As has been reported in abstract form by another group (13), our results suggest that Cdx2 immunohistochemistry is also useful in distinguishing primary lung adenocarcinomas from gastrointestinal metastases.

In conclusion, our immunohistochemical survey of Cdx2 protein expression is in excellent agreement with the results of global gene expression studies in which oligonucleotide microarrays were used. It is expected that the "mining" of such global gene expression surveys of human cancers will yield other candidate protein markers that can be assayed by immunohistochemistry to provide useful clinicopathologic information.

Note added in proof: During the review period of this manuscript, two studies were published (Barbareschi M *et al. Am J Surg Pathol* 2003;27:141–9; Werling RW *et al. Am J Surg Pathol* 2003;27:303–10) that similarly examined the range of Cdx2 expres-

sion in normal human tissues and cancers. The portions of these studies that overlap with our data are in good agreement with the distribution of Cdx2 expression we report here.

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Book Review

MacLennan GT, Resnick, MI, Bostwick DG: Pathology for Urologists, 207 pp, Philadelphia, WB Saunders, 2002 ($160.00).

In this book prepared for urologists, Drs. MacLennan, Resnick, and Bostwick have systematically reviewed the major organ systems and the major pathological conditions that affect those organ systems. The chapters are organized by the organ system and include kidney, bladder (urethra, renal pelvis, and ureter), prostate, testis, spermatic cord, penis and scrotum, and adrenal. Each chapter reviews the normal histology (a feature often lacking from general urologic textbooks) followed by pathological conditions. Each entity is briefly described from a clinical standpoint and then correlated with the gross and histological findings. These are then accompanied by several photographs or photomicrographs of the condition with captions pointing out salient features. In addition, congenital disorders of the organ systems are covered where appropriate.

The advantage of this textbook is that it is geared toward urologists rather than pathologists. In particular, this textbook would be an excellent study tool for resident physicians in urology preparing to take their board examinations. Many of the salient features pointed out in the photographs are "classic" board examination questions. This book is also a valuable tool for the practicing urologist, as its organization by organ system makes it a quick and easy reference. As the authors mention in their preface, some very rare entities may be missing from the textbook, but the vast majority of uropathologic conditions are covered in this beautifully illustrated, well-organized textbook.

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