Cadherin-6, a Cell Adhesion Molecule Specifically Expressed in the Proximal Renal Tubule and Renal Cell Carcinoma


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ABSTRACT

Cadherins are a family of calcium-dependent, cell-cell adhesion molecules that play an important morphoregulatory role in a wide variety of tissues. Alterations in cadherin function have been implicated in tumor progression in a number of adenocarcinomas. Despite the increasing number of new cadherins identified, little is known about cadherins in normal renal tissue and renal carcinomas. A novel cadherin transcript, cadherin-6, was recently described to be present in renal cancer cell lines and fetal kidney, but no data on protein expression nor tissue localization has been reported.

In this study, we demonstrate that the expression of cadherin-6 is restricted to the proximal tubule epithelium. This finding is critical because these cells give rise to the majority of neoplasms of this organ. Furthermore, we demonstrate typical cadherin features of cadherin-6, including cytoplasmic binding to α- and β-catenin. We present data of cadherin-6 expression in a series of 32 primary renal cell cancers. Cadherin-6 expression tended to vary with histology in these samples. Whereas the majority of renal cell cancers with histology-associated poor prognosis (i.e., high grade clear cell carcinomas and sarcomatoid renal tumors) show aberrant expression of cadherin-6, in tumors with a favorable prognosis (i.e., low grade clear cell carcinomas and papillary cancers), normal cadherin-6 expression was predominant. Overall, these findings demonstrate specific expression of cadherin-6 in the proximal renal tubules in normal human kidney and suggest that alterations of cadherin-6 expression are associated with progression of renal cell carcinoma.

INTRODUCTION

Renal cell cancer accounts for approximately 3% of all adult malignancies. Surgical treatment is an effective therapy only in early-stage renal tumors. Advanced stages of renal neoplasms are associated with poor prognoses, because these malignancies are typically refractory to chemo- and radiotherapy. Immunotherapy, both active and passive protocols, demonstrate partial and complete remission in a limited subset of patients (1, 2). Prognostic markers are needed to identify patients who are at risk for recurrence and metastasis of renal cell carcinoma and, thus, would benefit from additional therapeutic modalities. Current prognostic factors like tumor grade, renal vein involvement, and extension to regional lymph nodes are of limited value in this respect (3).

Cadherins, a family of cell-cell adhesion molecules, have demonstrated their utility as prognostic markers in a variety of neoplasms. Dysfunction of cadherins has a major impact in the progression of epithelial tumors (4). Loss or abnormal expression of cadherins in tumors can lead to tumor invasion and disease progression, as demonstrated for E-cadherin expression in prostate (5), stomach (6), bladder (7), breast (8), cervical cancer (9), and other tumors. Similar results have been demonstrated for P-cadherin, for example in breast cancer (8), gingival carcinomas (10), and gastric neoplasms (6).

Studies of the role of abnormal cadherin expression as a marker in renal cell carcinoma progression are less conclusive. Although the proximal tubular cell is thought to be the cellular origin of the majority of renal cell carcinomas, the pattern of cadherin expression in the normal proximal tubule epithelium is not well understood (11–13). Interestingly, for E-cadherin, which has been shown to be expressed in a high proportion of low grade renal carcinomas (14), the expression pattern failed to correlate with disease progression (15, 16). Normally, E-cadherin expression is restricted to the distal renal tubules and collecting ducts (17). N-cadherin, a cell adhesion molecule found in a variety of different tissues, is expressed during fetal development in renal tissue and is found in the adult kidney only in the proximal renal tubule (18). However, N-cadherin expression in renal cell cancer also failed to show a correlation with tumor progression. Tani et al. (16) suggested that another unknown cadherin may be important in these tumors.

Shimazui et al. (19) reported that cadherin-6, a newly identified cadherin molecule, is involved in the development of the kidney. In adult renal tissue, however, only faint or negligible expression of cadherin-6 mRNA could be demonstrated (19, 20). Neither protein expression nor tissue localization of cadherin-6 was examined in these studies. Shimazui et al. (21) reported a complex pattern of cadherin mRNA expression in different renal cancer cell lines. This finding suggested the involvement of several cadherins in renal tumors (21).

In this study, we focused upon cadherins that may play a role in the cell-cell adhesion in the proximal renal tubular epithelium and, therefore, possibly may be involved in invasion and progression of renal cell cancer. We demonstrate for the first time that cadherin-6 expression occurs only in proximal renal tubules of the normal kidney. Furthermore, in an evaluation of a series of primary renal cell carcinomas, we find that cadherin-6 expression is frequently altered in tumors with histologies associated with poor prognosis.

MATERIALS AND METHODS

Surgical Specimens. Fresh renal tissue was obtained at the time of surgery at The Johns Hopkins Hospital. The specimens were immediately frozen in liquid nitrogen and stored at −70°C. Frozen sections were cut at a thickness of 6 μm, mounted on poly-L-lysine-coated slides, air dried for 30 min, and used immediately for immunohistochemistry.

Renal Cancer Cell Lines. Human primary renal cancer cell lines from the ATCC3 were used. 786-O and 769-P were cultured in RPMI 1640 supplemented with 10 mm HEPES buffer, 5 mm sodium pyruvate, and 10% FBS. McCoy's 5a medium with 10% FBS was used as medium for Caki-1 and Caki-2. Primary renal cell cancer cell lines were derived from surgical specimens by digestion with collagenase (2 mg/ml in HBSS with calcium and magnesium). RCC74 originated from a papillary renal cell carcinoma, stage II, nuclear grade III–IV. RCC71A was derived from a sarcomatoid renal cancer, stage II, nuclear grade IV. RCC 71A and RCC74 did not show any expression of E- and

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3 The abbreviations used are: ATCC, American Type Culture Collection; FBS, fetal bovine serum.
P-cadherin on immunohistochemistry and only faint expression of N-cadherin. NK-1 is a proximal renal tubule cell strain derived from a normal kidney. Primary renal cell lines were cultured in DMEM, supplemented with 10% FBS, 1-glutamine, penicillin, streptomycin, and transferrin phosphate as described previously (22).

Northern Analysis. For Northern analysis of cadherin-6 mRNA, a random prime-labeled sequence corresponding to nucleotides from position 2108 to 2323, according to the cDNA sequence published by Shimoyama et al. (19) was used as a probe as described previously (23). Multitissue blots (2 μg of poly(A) mRNA each) obtained from Clonetech Laboratories (Palo Alto, CA) were probed using the methodology described previously (24).

Antibodies. A rabbit polyclonal anti-cadherin-6 antibody was generated against a sequence in the intracytoplasmic domain of cadherin-6 as described (25). This 15-mer (NH₂-terminal-RRRTPTARDNTDVRDF-COOH terminal) is unique by search at the National Center for Biotechnology Information using BLAST network service (26) for cadherin-6 in humans and K-cadherin in rats. Anti-E-cadherin clone 36 is a mouse monoclonal antibody (Transduction Laboratories, Lexington, KY) described previously (27). 13A9 and IG5 are mouse monoclonal antibodies against N-cadherin and α-catenin, respectively (28). Anti-β-catenin clone 14 is a mouse monoclonal antibody (Transduction Laboratories), which is described elsewhere (29). F23 (a kind gift from Dr. Neil H. Bander, Memorial Sloan-Kettering Cancer Center, New York, NY) is a mouse monoclonal antibody specific for proximal renal tubules (30). CY-90 is a mouse monoclonal anti-cytokeratin 18 antibody (Sigma Immunochemicals, St. Louis, MO; Ref. 31).

Immunohistochemistry. Immunohistochemistry was performed at room temperature unless mentioned otherwise using the Histostain-Kit (Zymed Laboratories, Inc., San Francisco, CA). Air dried sections were fixed in 3.7% formaldehyde in TNC buffer (10 mm Tris, 150 mm NaCl, and 2 mm CaCl₂; pH 7.4) for 20 min. Extraction was carried out prior to fixation for 10 min in TNC buffer containing 2% Triton X-100 and the protease inhibitors leupeptin (50 μg/ml) and phenylmethylsulfonfluoride (10 mm) if the sections were to be used for cadherin-6, E- or N-cadherin staining. Between each step, rinsing was carried out using TNC buffer three times for 2 min. Sections were blocked with 10% nonfat dry milk for 1 h before incubating with the primary antibody at a dilution of antisera in 3.75% BSA and TNC buffer: 1:1000 for cadherin-6, 0.5 μg/ml for E-cadherin and β-catenin, 1:50 for N-cadherin, 1:100 for α-catenin, and 1:1000 for F23. After rinsing, sections were incubated with a secondary antibody at different concentrations up to 1 mg/ml. In contrast to the former analysis revealed the presence of a single band of 120 kDa cadherin-6. A unique peptide sequence located in the cytoplasmic domain of cadherin-6, because the analysis of 16 different adult tissues demonstrated detectable mRNA message only for kidney. In this tissue, three transcripts of about 3.6, 4.0, and 8 kb were observed (Fig. 1A). All cadherin transcripts of the renal cancer cell line, we cloned a novel cadherin cDNA using degenerate PCR technology (32). A homology search revealed that the sequence of this cadherin was identical to that of cadherin-6, recently characterized by Shimoyama et al. (19) to be present in some renal carcinoma lines and in fetal kidney tissue. The localization of expression of cadherin-6 in the normal kidney as well as the possible alterations of cadherin-6 expression in renal cell cancer was not determined in this previous study.

By Northern analysis we confirmed the tissue specificity of cadherin-6, because the analysis of 16 different adult tissues demonstrated detectable mRNA message only for kidney. In this tissue, three transcripts of about 3.6, 4.0, and 8 kb were observed (Fig. 1A). All other tissues, including normal adult prostate, were negative.

Characterization of the Cadherin-6 Antibody. To more fully characterize the expression pattern of cadherin-6 in both normal and neoplastic renal tissues, we developed a polyclonal antiseraum against cadherin-6. A unique peptide sequence located in the cytoplasmic domain of cadherin-6 was used as the antigen.

The specificity of this antibody was assessed by immunoblotting and immunofluorescence with and without blocking peptide. The former analysis revealed the presence of a single band of 120 kDa (Fig. 1B), the size of a typical cadherin, in the renal cancer cell line RCC74. Furthermore, the lack of reactivity of this antiseraum with E- or P-cadherin was demonstrated by immunoblot analysis of cell lines known to be positive for these cadherins (data not shown).

Immunofluorescent staining of RCC74 cells with the cadherin-6 antiseraum demonstrated immunoreactivity at the cell-cell border (Fig. 1C), whereas no staining was observed using preimmune rabbit serum. To demonstrate the specificity of our antibody for cadherin-6, the synthetic peptide used as antigen was added to the primary antibody at different concentrations up to 1 mg/ml. In contrast to the
positive staining of normal kidney without the peptide, there was no
staining observed at concentrations as low as 0.01 mg/ml. To exclude
nonspecific effects, the same peptide was added to anti-E-cadherin
antibody, followed by immunohistochemical staining. Under these
conditions, staining was unaffected (data not shown).

Expression of Cadherin-6 in the Proximal Tubule of the Normal
Kidney. We established a cell culture of proximal renal tubular
epithelium (NK-1), which showed positive staining of F23 and cy-
tokeratin 18, indicating its origin from the epithelium of the proximal
renal tubule (data not shown). With cadherin-6 antiserum, NK-1 cells
showed positive immunoreaction at the cell-cell border in typical
cadherin-like pattern at areas of cell-cell borders but not at cell
membranes without cell-cell contact (Fig. 2a).

On frozen sections of normal renal tissue, we could demonstrate
staining for cadherin-6 in the renal tubular epithelium at the cell-cell
borders (Fig. 2b). To further characterize this staining in the renal
tubular epithelium, serial sections of normal renal tissue were pre-
pared from surgical specimens and immunohistochemically stained
for cadherin-6, F23, and E-cadherin as shown in Fig. 2, c–e. The
staining of cadherin-6 in the renal cortex (Fig. 2d) shows the same
distribution as the staining for the membranous glycoprotein F23 (Fig.
2e), which is specific for the proximal renal tubules (30). The same

Fig. 1. Northern, Western, and immunofluorescent
analysis of cadherin-6 expression. A, Northern analysis
with a cadherin-6 cDNA probe of multiple tissue blots [2
μg of poly(A) mRNA in each lane] demonstrates tissuespecific expression of cadherin-6 mRNA in renal
mRNA. B, specificity of the polyclonal anti-cadhenn-6
antibody generated against a cytoplasmic peptide se-
quency by Western blotting. SDS gel electrophoresis of
RCC74 protein extract (100 μg of total protein loaded)
blotted with either cadherin-6 (cad-6) antiserum
(1:10,000) or rabbit preimmune (preim.) serum
(1:10,000) shows a specific band at about M, 120,000 for
the cadherin-6 protein. C, immunohistochemistry of pap-
illary renal cancer cell line (RCC74) with cadherin-6
expression at the areas of cell-cell contact.

On higher power, cadherin-6 immunofluorescence (Fig. 3a) ap-
ppears not to be limited to the areas of cell-cell contact but also is
present in the areas of the basal membrane. This finding correlates
with the localization of the coexpressed α-catenin (data not shown)
and β-catenin (Fig. 3b). In contrast, E-cadherin-positive (Fig. 3c)
and N-cadherin-positive (Fig. 3d) tubular cells, which also demonstrate
colocalization with α- and β-catenin (data not shown), do not show an
enhancement of staining at the basal membrane.

Interaction of Cadherin-6 with the Catenins. The classical
cadherins are known to interact with a family of cytoplasmic proteins
termed catenins. Interaction of cadherins with these proteins is a
prerequisite for normal cadherin function (33). To investigate the potential interaction of cadherin-6 with these proteins, we performed immunoprecipitation and immunonconcentration experiments. The autoradiograph of cadherin-6 immunoprecipitates from metabolically labeled RCC74 cells (Fig. 4A) demonstrates coprecipitation of proteins with the apparent molecular weights ($M_c 102,000$ and $M_c 92,000$) corresponding to that of $\alpha$- and $\beta$-catenin. To determine the identity of the coprecipitating species as catenins, we carried out Western blotting of immunoprecipitates obtained with cadherin-6 and $\beta$-catenin antibodies (Fig. 4B). We immunoprecipitated with either cad-

Fig. 2. Immunostaining of cadherin-6 in normal human kidney. a, cadherin-6 immunoreactivity in NK-1 cells, a strain of normal proximal tubular renal cells. The staining of cadherin-6 is located at the cell borders in areas of cell-cell contact; no staining is observed at cell membranes without cell-cell contact. b–e, frozen sections of normal kidney. b, cadherin-6 staining at the cell-cell border of the renal tubular epithelium. Note honeycomb staining pattern. c–e, immunostaining of serial sections of normal renal tissue. In these panels, the two arrowheads indicate the same proximal renal tubules, and the arrows show the identical distal renal tubule in each section surrounding a glomerulus. c, F23 (1:1000), an antibody specific for the proximal renal tubules. d, cadherin-6 antiserum (1:1000) showing positive staining of tubules having an identical distribution to that of F23. e, anti-E-cadherin ($1 \mu g/ml$) expression in the distal renal tubules. a, $\times 1000$; b–e, $\times 400$. 

Fig. 3. Immunofluorescent staining of sections of normal human kidney with fluorescein-conjugated secondary antibody and nuclear counterstaining with 4',6-diamidino-2-phenylindole. a, cadherin-6 immunoreactivity of positive proximal renal tubules at the areas of cell-cell contact and enhanced staining at the basal membrane (arrowheads). b, $\beta$-catenin is localized in the proximal (arrowheads) and distal renal tubules (arrow). Note the observed enhancement of the basal membrane in proximal renal tubules identical to the localization of cadherin-6 expression. c, E-cadherin-positive distal renal tubules (arrow) without enhanced staining at the basal membrane; proximal renal tubules show no staining (arrowheads). d, N-cadherin-positive proximal renal tubules (arrowheads). Note N-cadherin-negative distal renal tubules (arrow). $\times 400$. 

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Cadherin-6 expression in renal cell carcinoma. We have established two primary renal cancer cell lines from tumors of different histological type. RCC74 is from a papillary renal carcinoma and shows intense expression of cadherin-6, whereas RCC71A showed no immunoreactivity (Fig. 6A). No protein signal could be detected for Caki-1 and only very faint expression for Caki-2 and 769-P. Of the ATCC cell lines, only 786-O showed abundant cadherin-6 expression; besides the band at Mr, 120,000, several smaller proteins were detected, presumably due to degradation or abnormal products (Fig. 6A). Attempts to minimize protein degradation by direct solubilization of cultured cells in SDS sample buffer resulted in no change in the pattern of immunoreactive bands. Similar findings have been reported for Ksp-cadherin in the rabbit kidney (35), although the origin of these smaller polypeptides remains unclear.

Three matched pairs of normal renal tissue and renal cell cancer (Fig. 6B) were analyzed demonstrating either up-regulation (sample 140), equal expression (sample 246), or no expression (sample 273) of cadherin-6 in renal tumors compared to normal. On histological examination of these tumors, the two cadherin-6-positive tumors revealed clear cell features, whereas the cadherin-6-negative tumor was an oncocytoma.

DISCUSSION

In this study, we demonstrate that cadherin-6 is specifically expressed in the proximal renal tubule in human kidney. Cadherin-6 shows two features typical of classical cadherins: (a) staining at the cell-cell border at the areas of cell-cell contact; and (b) interaction with the cytoplasmic proteins α- and β-catenin. Furthermore, we examined a series of primary renal cell cancers, finding that loss of cadherin-6 expression is more common in high-grade tumors or tumors with worse prognosis. These observations implicate a possible role of cadherin-6 as an important factor in renal tumor progression.

To understand the development and progression of a given cancer...
type, it is necessary to investigate the normal architecture and function of the cells that are destined to be transformed. One important aspect of carcinogenesis involves cell adhesion molecules as possible factors in tumor invasion, tumor cell circulation, and metastatic implantation. Cadherins are transmembrane glycoproteins that interact in a calcium-dependent, homotypic fashion. Besides the well known classical cadherins epithelial (E-), neural (N-), and placental (P-) cadherin, more than 30 additional cadherins have been described. Cadherins play an important role in tissue compaction and cell differentiation, maintenance of tissue, cell migration, and cell regulation (36). Cadherins are also involved in tumor aggressiveness and tumor invasion (37). In a variety of epithelial neoplasms, loss of cadherin expression correlates with tumor progression. Cadherins are thought to act as tumor invasion suppressor genes, as demonstrated by E-cadherin in gastric and colorectal carcinomas (4), breast cancer (8), skin neoplasm (38), transitional cell carcinoma of the bladder (7), and prostate cancer (24, 39). However, in renal cell cancer, no cadherin molecule correlating with either prognosis or invasion has been identified (15, 16).

Terpe et al. (14) demonstrated that E-cadherin expression can be found in about 30% of all renal tumors and is restricted to low-grade cancers; they suggested that E-cadherin expression may be connected to a dedifferentiation process. Katagiri et al. (15) also investigated E-cadherin expression in renal tumors. They found that none of the metastasis expressed E-cadherin, but about 20% of the primary lesions showed positive immunoreactivity. The authors conclude that E-cadherin may be a prognostic marker in renal cell cancer, but because of the low rate of expression, other cell adhesion molecules may play a more important role. N-cadherin, also called A-CAM, which is known to be expressed during the renal development and in the proximal renal tubules of the adult kidney (40), has also been investigated. Tani et al. (16) reported that E- and N-cadherin expression in renal cell cancer does not correlate with tumor grade. They concluded that aberrations in another pathway must be responsible for the deficient capacity to form polarized tubular structures in kidney cancer. A novel cadherin molecule, cadherin-6, was isolated by Shimoyama et al. (19) from a hepatocellular carcinoma lacking E- and P-cadherin expression. This cadherin showed 97% homology with the cDNA of K-cadherin, which was cloned by Xiang et al. (20) from a rat renal cancer cell line. K-cadherin could not be detected in adult rat kidneys, but RNA transcripts of human cadherin-6 were found by Northern analysis of adult human kidneys and renal cancer cell lines (19). These first reports suggested that cadherin-6 is involved in the development of the kidney and possibly renal cell cancer.

Our results confirm the tissue specificity of cadherin-6 and establish for the first time that cadherin-6 is expressed in the proximal tubular epithelium. The distribution of cadherin-6 shows typical staining at the cell borders in areas of cell-cell contact in vitro. In vivo we observed that cadherin-6 is also localized at the basal membrane, along with β-catenin. We speculate that cadherin-6, which is specifically expressed in the proximal tubule, may contribute to the physiological function of these epithelial cells. Interestingly, Thomson et al. (35) describe a similar observation for Ksp-cadherin, which, like

### Table 1 Expression of E-cadherin and cadherin-6 of primary renal cell carcinoma by immunohistochemistry

Renal cell carcinomas were stratified by histological type and tumor grade. Immunoreactivity was scored as positive (pos.), heterogeneous (±), or negative (neg.).

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<th>Tumor</th>
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cadherin-6 in humans, is a kidney-specific cell adhesion molecule in rabbits. In their report, immunofluorescence studies demonstrated that Ksp-cadherin is not limited to the lateral regions of cell-cell contact but showed a much broader basolateral distribution. Originally, their goal was to isolate a Na+/HCO₃⁻ cotransporter at the basolateral membrane, but the sequence of the transcript they identified showed homology to the cadherin family. It has recently been shown that E-cadherin and plakoglobin are involved in the formation of tight junctions (41). Xiang et al. (20) emphasize the possibility that cadherin function may vary from their well-established roles as cell adhesion molecules. Further studies will be necessary to clarify the function of basolaterally localized cadherin-6.

Because the majority of renal cell carcinomas are thought to arise from the proximal renal tubular epithelium (12, 42), a proximal tubular cadherin molecule could play an important role in renal cell tumorigenesis. Some studies demonstrate markers of both proximal and distal renal tubules to be present in renal cell carcinomas (43, 44), suggesting an origin from a metanephric cell rather than from a differentiated tubular renal cell. Our results demonstrate that the cadherin-6 protein is retained in some but not all renal tumors. We established two renal cancer cell lines from primary tumors of different histological types, a papillary renal cell carcinoma that retained cadherin-6 expression and a cadherin-6-negative sarcomatoid renal cancer. By immunohistochemistry, we demonstrated in 32 primary renal cell cancers that high-grade clear cell carcinomas are more likely to show heterogeneity or loss of cadherin-6 expression. Disease outcome varies for renal tumors of different histological type. Sarcomatoid tumors have a poor prognosis (43, 45), and these tumors demonstrated more heterogeneous cadherin-6 reactivity in our study. Papillary renal carcinomas demonstrated uniform positive staining. These tumors, which tend to have a more favorable prognosis (13), have been suggested to originate from the collecting duct (46), although studies are contradictory regarding both these issues (47). Homogeneous staining for cadherin-6, however, is more consistent with the origin of these tumors from the proximal renal tubule and may explain the unusual papillary structure of polarized cells in contrast to solid clear cell carcinomas. However, the use of cell-specific markers to determine cell type of origin can be problematic, and it is certainly possible that acquisition of cadherin-6 expression accompanies cellular transformation in this tumor type. The renal tumor with the most favorable prognosis (48), the oncocytoma, is cadherin-6 negative, but this tumor has been shown to arise most likely from the collecting duct (34), and thus, cadherin-6 expression would not be expected.

In conclusion, we demonstrate that cadherin-6 is specifically expressed in the proximal renal tubules in humans. Cadherin-6 is retained in some but not all renal cell carcinomas. The observation of differential expression of cadherin-6 in renal cancers of different histological type and tumor grade and down-regulation of expression in a significant subset of renal cell carcinomas is consistent with an involvement of this cell adhesion molecule in the progression of renal cell cancer. Additional, direct studies of cadherin-6 dysfunction in renal cell carcinoma will be necessary to expand these findings and to fully elucidate the role of this process in renal cell cancer progression.

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