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Detection of endogenous receptors for carbohydrate ligands in primary and metastatic human renal cell carcinoma

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Summary. Frozen sections of primary and metastatic human renal cell carcinoma (RCC) were analyzed for the expression of endogeneous binding sites for carbohydrates. Fluorescent neoglycoproteins, carrying chemically linked carbohydrate residues on bovine serum albumin as a carrier protein, were applied to 44 primary tumor specimens. In the majority of specimens, accessible binding sites with specificity for maltose and *N*-acetylgalactosamine were detected. In specimens of normal kidney no specific binding of carbohydrate ligands was observed under these experimental conditions. Specimens of both the primary tumor and a metastasis were available in 10 cases. When the expression of specific binding sites of primary tumors and metastases was compared, the respective patterns were similar with no clear gain or loss of certain lectins in the metastases. We conclude that binding sites with specificity for maltose and *N*-acetylgalactosamine are present on human RCC and their corresponding metastases.

Key words: Carbohydrate-binding proteins – Metastases – Renal cell carcinoma

The ability of malignant cells to invade normal tissue and penetrate into lymphatic blood vessels as well as to spread to distant sites is a characteristic feature of tumor progression. Growth of tumor cells in distant organs represents one of the major problems in clinical oncology. Renal cell carcinoma (RCC) is the most frequent primary tumor of the kidney. Five-year survival rate is approximately 95% for locally growing low-grade RCC [26]. At the time of diagnosis, 25–40% of all patients have distant metastases [3]. Of all RCC metastases, no more than 50% can be diagnosed at the time of initial presentation [3], when the patient would have a good chance of surving more than 5 years. Clearly then, there is a need for early detection of distant metastases in RCC. Renal carcinomas primarily metastasize to the lungs (75%), bones (41%) and lymph nodes (22%) [3]. Knowledge of the factors that influence metastasis or contribute to organ selectivity is limited (for review see [19]). Tumor metastasis is a multistep process that is not random but directed and under positive and/or negative genetic control (for review see [10]). In the process of metastasis, tumor cells interact with a variety of other cells in the primary tumor, in the circulation and in the target organ. Successful completion of all steps of the metastatic cascade is a prerequisite for the development of metastatic disease.

Most tumors preferentially metastasize to typical target organs. In RCC, primary metastases are found in the lungs in almost two thirds of all patients with disseminated disease [4]. PAGET [20] suggested as long ago as 1889 that metastases could develop only if the seed (the metastatic tumor cells) and the soil (the target organ) matched completely. The molecular factors that contribute to the "selectivity" of tumor metastasis are currently being identified.

Metastatic tumor cells share many similarities with white blood cells: they migrate in the blood throughout the body and are equipped to reach the venules, extravasate and invade solid organs. White blood cells leave the blood vessels for migration into lymph nodes, bone marrow or sites of inflammation. The process of "homing" is mediated by molecules present on both the leukocytes and the vascular edothelium of the target organ. Several recognition systems for leukocyte homing have been described (for review see [21]). Some of these, such as binding of lymphocytes to hepatocytes [16] or the homing receptor on mouse lymphocytes [28], involve interactions between carbohydrates and their tissue receptors, the lectins. Recognition systems similar to those described for white blood cells may exist for tumor cells, including selective protein–carbohydrate recognition [6, 17, 22]. Most probably similar principles may be detected in the organ selectivity of metastatic tumor cells. It was therefore the purpose of this study to analyze the presence of carbohydrate-binding molecules in RCC. No data are

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Table 1. Characteristics of patients and tumors

No. of patients	44
Male	32
Female	12
Mean age (years)	58.9
pT stage	
T1	4
T2	21
T3	19
Pathologic grade	
GI	2
GII	24
GIII	18
Histology	
Clear cell	32
Granula cell	12

available on the presence of endogeneous carbohydrate-binding molecules, such as lectins or carbohydrate-specific autoantibodies, in human RCC.

In our study, 44 RCC specimens, 44 samples of corresponding normal renal tissue and 12 metastases were analyzed for the presence of endogeneous lectins with 11 types of chemically prepared probes, termed neoglycoproteins.

Materials and methods

Patients

Primary tumor specimens from 44 patients with RCC were analyzed for lectin expression. In all patients unilateral nephrectomy was performed. The presence of RCC was confirmed by routine histology in all cases. In all 44 patients an additional specimen was obtained from normal renal tissue at the contralateral edge of the kidney.

In 10 of 44 patients examined, specimens of both the primary tumor and a metastasis were available. A further two metastases were analyzed for lectin expression without the corresponding primary tumor.

The patients comprised 32 men and 12 women with a mean age of 58.9 years. Details of the patients and their histopathological data are summarized in Table 1.

Preparation of neoglycoproteins

Neoglycoproteins were prepared as described previously [6]. Briefly, carbohydrate-free bovine serum albumin (BSA) was chemically glycosylated by conjugation of the diazo-derivatives of *p*-aminophenyl glycosides (in the case of fucose, mannose, sialic acid, *N*-acetylglucosamine and *N*-acetylgalactosamine) or by reductive amination (in the case of lactose, melibiose, cellobiose and maltose), resulting in incorporation of 8–10 and 16–18 sugar moieties per molecule of BSA, respectively. Neoglycoproteins were then labeled with fluorescein isothiocyanate (FITC) [14].

Expression of binding sites for carbohydrate ligands on frozen sections of RCC

Specimens of the tumor and the corresponding normal kidney were snap-frozen in pentane, mounted on cork and stored at −70'C prior to use. For the analysis, 5-μm sections were cut on a cryostat. FITC-labeled neoglycoproteins were added at a concentration of 50 μg/ml in phosphate-buffered saline (PBS) containing 1% BSA and 0.1% sodium azide for 30 min at 4'C. Specimens were washed three times with PBS and fluorescence analyzed using a Leitz fluorescence microscope equipped for FITC fluorescence. Fluorescence was rated positive if fluorescence was distributed either homogeneously over the whole specimen or in spots covering more than one third of the total area.

In the specimens from 19 patients, specificity of staining was analyzed in parallel by addition of a tenfold excess of the respective non-labeled neoglycoprotein plus carbohydrate at 1.25 mM. Labeled but carbohydrate-free BSA was also applied as control to exclude binding by protein–protein interaction.

In order to demonstrate further the localization of endogeneous sugar receptors, the avidin–biotin peroxidase complex (ABC) method, described in detail elsewhere [11], was also applied. Briefly, sections were incubated in 0.3% hydrogen peroxide for 30 min to destroy endogeneous peroxidase acitvity and treated with 1% BSA in PBS (pH 7.2) for 10 min to minimize nonspecific background staining. Excess solution was blotted from the slides. The sections were then incubated with biotin-labeled neoglycoproteins at a concentration between 10 and 200 μg/ml for 30 min, washed for 10 min in PBS, and reincubated with the ABC complex (Dakopatts, Denmark). Sites of localization of peroxidase label were visualized by the addition of the chromogenic substrate diaminobenzidine/hydrogen peroxide, which produces a brown dye that contrasts well with the hematoxylin counterstain. Negative controls were successfully performed by omitting the biotinylated neoglycoproteins from the procedure, by application of biotinylated, nonglycosylated BSA and by blocking the binding of neoglycoproteins with their corresponding sugar at a concentration of 0.1 M plus a tenfold excess of the respecitve non-labeled neoglycoprotein.

Biochemical analysis of sugar receptors

Tumor specimens from 2 patients were trimmed of necrotic and connective tissue, snap-frozen in pentane and stored at −70°C prior to analysis. The frozen tumor was cut into small pieces and homogenized in 5 volumes of 75 mM Na/K-phosphate buffer (pH 7.2) containing 575 mM NaCl, 4 mM β-mercaptoethanol, 2mM EDTA, 100 mM phenylmethanesulfonyl fluoride and 5 μg/ml leupeptin, antipapain and chymostain. To interfere with lectin–ligand interaction, carbohydrates as inhibitors were added, namely 100 mM lactose and xylose, 50 mM fucose, *N*-acetylglucosamine and *N*-acetylgalactosamine and 10 mM *N*-acteylneuraminic acid. Following centrifugation the supernatant was dialyzed for 12 h at 4°C against 2 l of 20 mM TRIS-HCL buffer (pH 7.8) containing 150 mM NaCl, 2 mM β-mercaptoethanol and 2 mM EDTA with six changes, centrifuged to pellet precipitated protein, adjusted to a concentration of 20 mM Ca^{2+} and fractionated by affinity chromatography, as described previously [2]. Further processing and analytic procedures were carried out, as given in detail elswhere [2].

Results

Tumor histology

In all specimens the presence of RCC was confirmed by histopathologic HE sections. Pathologic staging for the tumors was a follows: 4 stage T1 tumor, 21 T2 tumors and

Table 2. Positive staining of frozen sections of human normal kidney, renal cell carcinoma and metastases with FITC-labeled neoglycoproteins

Patient					Normal kidney												Renal cell carcinoma												Metastases											
No.	S	A	TNM	G	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
1	m	76	pT1pN0M0	II																																				
2	f	72	pT1pN0M0	II													+			+			+	+	+															
3	m	58	pT1pN0M0	II																																				
4	m	35	pT1pN0M0	I																			+	+				+												
5	m	52	pT2pN0M0	II									+			+	+		+	+		+	+	+															
6	f	50	pT2pN0M0	III	+						+	+				+	+	+	+			+	+	+				+												
7	m	62	pT2pN0M0	III													+						+	+	+		+													
8	m	66	pT2pN0M0	II	+															+	+		+					+												
9	m	36	pT2pN0M0	I													+	+		+		+	+	+	+		+												
10	f	81	pT2pN0M0	II																			+	+															
11	m	57	pT2pN0M0	II													+					+	+	+	+															
12	m	51	pT2pN0M0	II																					+		+	+												
13	f	62	pT2pN0M0	II																	+		+	+	+														
14	m	48	pT2pN0M0	II													+							+				+												
15	m	67	pT2pN0M0	II																																				
16	f	45	pT2pN0M0	II	+																				+															
17	f	64	pT2pN0M0	II													+	+		+			+	+															
18	m	57	pT2pN0M0	III						+	+	+							+				+	+				+												
19	f	68	pT2pN0M0	III	+	+											+	+	+			+	+	+																
20	m	84	pT2pN0M0	II													+		+		+		+																	
21	m	52	pT2pN0M0	III	+						+	+																												
22	m	56	pT2pN0M0	II									+				+		+				+	+															
23	m	60	pT2pN0M0	II	+	+				+	+	+							+																				
24	f	57	pT2pN1M0	III																			+	+															
25	m	50	pT2pN1M0	III		+						+					+	+	+			+	+	+		+													
26	m	51	pT3pN0M0	III																			+	+															
27	f	50	pT3pN0M0	II																				+				+											
28	m	64	pT3pN0M0	III													+		+	+		+	+	+			+												
29	f	61	pT3pN0M0	II													+	+	+	+		+	+	+	+														
30	m	69	pT3pN0M0	III													+		+			+	+	+															
31	f	63	pT3pN0M0	III													+						+	+				+											
32	m	79	pT3pN0M0	II																				+	+														
33	m	81	pT3pN0M0	II																			+	+															
34	m	53	pT3pN0M1	II	+	+				+	+	+					+				+	+	+	+				+											
35	m	55	pT3pN0M1	II																													+		+					
36	f	69	pT3pN0M1	III													+	+	+	+	+	+	+	+	+	+	+							+	+					
37	m	55	pT3N1M0	II														+					+	+	+			+		+			+		+					
38	m	66	pT3pN1M0	III																				+				+											
39	m	66	pT3pN1M1	III	+		+				+						+	+	+		+	+	+	+	+		+	+					+	+	+			+	+
40	m	62	pT3pN1M1	III													+							+					+				+	+	+				+
41	m	54	pT3pN1M1	II														+				+	+					+	+				+	+	+				
42	m	32	pT3pN2M1	III	+	+						+				+			+				+		+								+	+					
43	m	51	pT3pN2M1	III																		+		+				+	+				+	+					+
44	m	55	pT3pN0M1	III													+	+		+	+	+	+	+		+	+	+	+				+	+	+	+	+	+	+
45	m	59	pT3pN1M1	II																														+		+		+		
46	m	67	pT3pN2M1	III																															+	+		+		

FITC, Fluorescein isothiocyanate; *S*, sex; *m*, male; *f*, female; *A*, age; *TNM*, TNM classification (UICC, 1987); *G*, grade; *1*, mannose; *2*, mannose-6-phosphate; *3*, fucose; *4*, xylose; *5*, sialic acid; *6*, *N*-acetylglucosamine; *7*, *N*-acetylgalactosamine; *8*, maltose; *9*, cellobiose; *10*, melibiose; *11*, lactose (red); *12*, lactose (diaz)

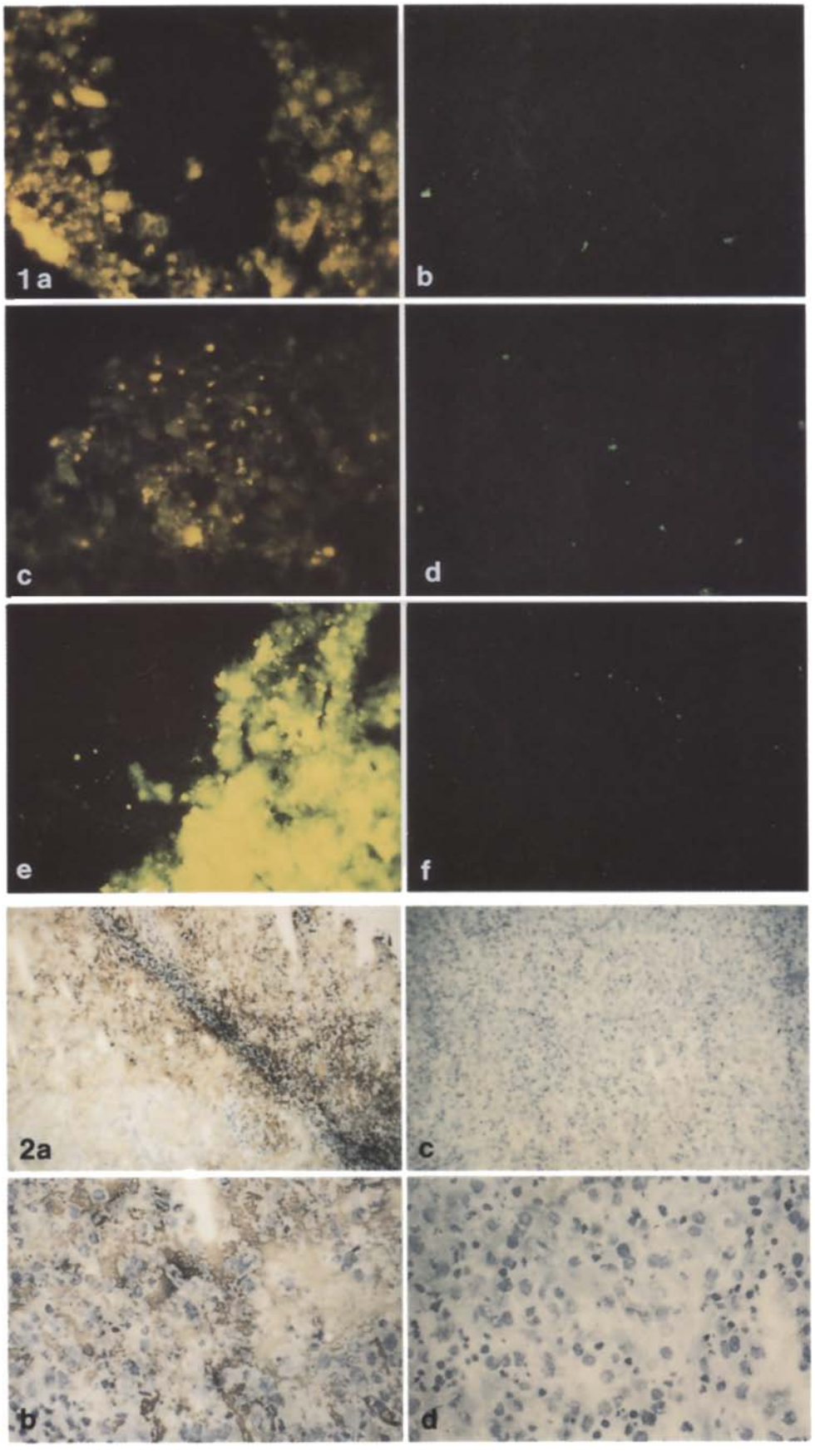

Fig. 1a–f. Staining of human renal cell carcinoma sections by fluorescent neoglycoproteins. **a** Staining of tumor tissue by fluorescein isothiocyanate (FITC)-labeled *N*-acetylgalactosamine-BSA (×400). **c** Staining of tumor tissue by FITC-labeled maltose-BSA (bovine serum albumin) (×400). **e** Staining of tumor tissue (*right*) and adjacent normal kidney tissue (*left*) by FITC-labeled maltose-BSA. **b, d, f** Inhibition of fluorescence of the corresponding tissue by addition of a tenfold excess of the respective non-labeled neoglycoprotein plus carbohydrate at 1.25 mM

Fig. 2a–d. Staining of human renal cell carcinoma by biotinylated neoglycoproteins and avidin-biotin peroxidase complex reagents. **a** Staining of tumor tissue by *N*-acetylgalactosamine (×400). **b** Staining of tumor tissue by maltose (×400). **c, d** Inhibition of staining of the corresponding tissue by addition of a tenfold excess of the respective non-labeled neoglycoprotein plus carbohydrate at 1.25 mM

Table 3. Distribution and intensity of neoglycoprotein staining of renal cell carcinoma

Carbohydrate specificity	Cell membrane	Cytoplasm
Monosaccharides		
Mannose	++	+
Mannose-6-phosphate	+	(+)
Fucose	+	−
Xylose	+	−
Amino sugars		
Sialic acid	(+)	−
N-Acetylglucosamine	+	−
N-Acetylgalactosamine	++	+
Disaccharides		
Maltose	++	(+)
Cellobiose	+	−
Melibiose	(+)	−
Lactose (red)	+	−
Lactose (diaz)	+	−

++, Strong; +, medium; (+), weak but significant; −, negative

19 T3 tumors. Pathologic grade was grade I in 2 cases, grad II in 24 cases and grade III in 18 cases. Thirty-two tumors were clear cell carcinomas and 12 were granular-type carcinomas (Table 1).

Expression of binding sites for carbohydrate ligands in frozen sections of RCC

The majority of specimens specifically bound the neoglycoproteins carrying *N*-acetylgalactosamine or maltose residues (Table 2). Binding of both carbohydrates was specific, because addition of unlabeled neoglycoprotein at a tenfold excess plus free carbohydrate totally abolished fluorescence (Figs. 1, 2). Inherent differences in the extend of staining between neoglycoproteins obtained by the same synthetic procedure but differing in limited structural properties, namely the structure of the carbohydrate ligand, served as an additional control. For example, 32 of 44 (73%) of the specimens stained positive for maltose, whereas only 13 of 44 (30%) specimens were positive for the β-glucoside cellobiose. Similar findings were made for *N*-acetylglucosamine versus *N*-acetylgalactosamine, the 4′ OH-epimers. Analyzing the expression of binding sites for carbohydrates, the results of immunofluorescence were comparabel to those of the ABC method.

Less than 30% of the specimens tested showed positive staining specifically for monosaccharides (mannose, mannose-6-phosphate, fucose, xylose and sialic acid) under the conditions applied. Specific staining was determined by inhibition of FITC-labeled neoglycoprotein binding after the additon of unlabeled neoglycoprotein and carbohydrate. Probes containing mannose, *N*-acetylglucosamine and fucose exhibited a notable proportion of the non-inhibitable staining under these conditions. When specimens contained tumor with adjacent normal renal tissue, the tumor could clearly be discriminated from normal kidney by bright fluorescence (Fig. 1E).

Staining of the tumor cells was observed mainly on the cell membrane. The strongest fluorescence was seen when probes with maltose, *N*-acetylgalactosamine or mannose were used. Intracytoplasmic fluorescence occurred only in some cases and was weak or medium (Table 3).

Expresison of binding sites for carbohydrate ligands on normal renal tissue

For each patient a specimen of normal kidney (obtained from the contralateral edge of the tumor-bearing kidney) was analyzed for binding sites for carbohydrate ligands. Positive staining was observed in only some cases, especially when mannose-BSA (9×), maltose-BSA (7×) and *N*-acetylgalactosamine-BSA (6×) were used. In 19 specimens specificity of the neoglycoprotein binding was analyzed by addition of a tenfold excess of nonlabeled neoglycoprotein plus the respective carbohydrate at 1.25 mM. Non-inhibitable binding could be detected in all of the 19 specimens examined under these conditions.

Expression of binding sites for carbohydrate ligands in frozen section sof RCC metastases

Twelve RCC metastases were available for detection of lectins. In 10 of these the metastasis and primary tumor were analyzed. Sources of metastasis were lymph node (5/12), vena cava (4/12), adrenal gland (1/12) bone (1/12) and skin (1/12). Sugar receptor expression on the primary tumor of patients with metastatic disease was similar to that in patients in whom no metasases were present at time of surgery (Table 2). Patterns of lectin expression on tumor metastases were similar to those of the primary tumors. No overall modifications, e.g. gain or loss of specific lectins in metastases, could be detected. Of 10 pairs of primary tumor and metastases, there were 6 specimens of metastases in which more sugar receptors were expressed than in the primary tumor. Binding sites with specificity for *N*-acetylgalactosamine were detectable in all (5/5) lymph node metastases.

Biochemical analysis of sugar receptors on RCC

Tumor Specimens of 2 patients were biochemically analyzed for carbohydrate-binding proteins by affinity chromatography on immobilized carbohydrates (Fig. 3). It is noteworthy that differences were seen with *N*-acetygalactosamine and maltose as affinity ligands, whereas no significant difference was observed in the cases of lactose, mannose, fucose, *N*-acetylglucosamine and sialic acid.

Discussion

In RCC little information is availabe on the biology of metastasis and the factors that contribute to tumor metastasis have not been precisely defined. However, because of the relative inefficiency of current therapeutic

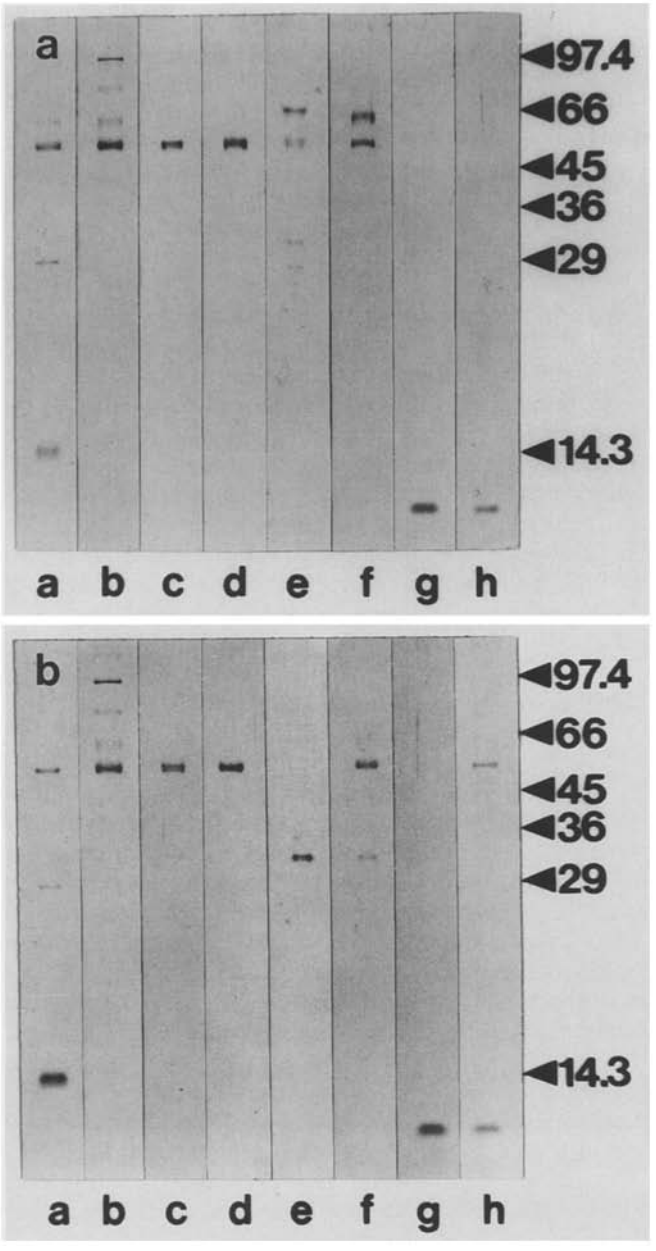

Fig. 3a, b. Visualization of sugar receptors by polyacrylamide gel electrophoresis in the presence of 0.1% sodium dodecyl sulfate and silver staining from two different specimens of human renal cell carcinoma. The total yields in micrograms per 16.2 g of tumor **a** (114 mg in extract) and in micrograms per 6.6 g of tumor **b** (405 mg in extract) are given. **a** Elution from immobilized lactose (*a*, 103 µg), from immobilized mannose (*b*, 150 µg), from immobilized fucose (*c*, 69 µg), from immobiliced *N*-acetylglucosamine (*d*, 186 µg), from immobilized *N*-acetylgalactosamine (*e*, 61 µg), from immobilized maltose (*f*, 137 µg), from immobilized sialic acid moieties of fetuin glycopeptides (*g*, 106 µg) and of bovine submaxillary mucin (*h*, 206 µg). **b** Elution from immobilized lactose (*a*, 93 µg), from immobilized mannose (*b*, 78 µg), from immobilized fucose (*c*, 24 µg), from immobilized *N*-acetylglucosamine (*d*, 78 µg), from immobilized *N*-acetylgalactosamine (*e*, 66 µg), from immobilized maltose (*f*, 63 µg), form immobilized sialic acid moieties of fetuin glycopeptides (*g*, 78 µg) and of bovine submaxillary mucin (*h*, 72 µg). *Arrowheads* designate the position of M_r markers for molecular weight designation

strategies for disseminated disease (for review see [12]) it is of key interest to acquire information on the molecules involved in RCC metastasis. Carbohydrate receptors are known to serve as recognition structures on the cell surface in a variety of physiologic and pathologic events [5, 17, 18, 23].

In a first series of experiments in this field we analyzed frozen sections of human RCC for the presence of sugar receptors. The majority of the specimens examined expressed sugar receptors with specificity for maltose and *N*-acetylgalactosamine. Comparable binding sites were not-detectable in frozen sections of corresponding normal human kidney under the conditions applied. It is of interest to note the importance of such receptors in cell adhesion in murine model system [8, 15].

With respect to maltose binding, it should also be borne in mind that the proximal renal tubules have been shown to be the predominant site for cleavage of maltose in man [1, 24] and other species. It is suggested that human RCC originates from the proximal renal tubules [25]. It should, however, be made clear that the function of the binding sites detected in RCC is as yet unknown.

In 10 patients, pairs of primary tumors and metastases were examined for lectin expression. Patterns of lectin expression did not reveal a clear-cut correlation with metastasis formation, as similarly describes for *N*-acetylgalactosamine-specific receptors in colon cancer [7]. In primary tumors, clones with the propensity to metastasize may rapidly gain a growth advantage over non-metastatic cells [13]. With respect to lectin expression, subpopulations can well exhibit differences, as have been detected for Lewis lung carcinomas grown at different sites [9, 27]. The tumors examined were removed shortly after clinical detection. We have no information as to whether or not in the tumors under study metastatic clones had already gained a growth advantage. The clinical observation that the majority of RCCs have visible or occult metastases at the time of initial presentation suggest that the metastatic clones may have growth advantage in the tumor that we studied. If this had been the case, it would not be surprising that lectin patterns differed little between primary tumor and metastasis.

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