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Allelic Deletions in Renal Tumors: Histopathological Correlations[1]

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ABSTRACT

Allelic loss on the short arm of chromosome 3 (3p) is considered to be one of the early detectable events in the pathogenesis of renal cell carcinoma (RCC). Conflicting reports, however, suggest that this event may be absent in some renal tumors. The present study attempts to further define subgroups of renal tumors associated with 3p deletions. In addition, we have also attempted to identify late genetic events associated with tumorigenesis and tumor progression.

Eighty-two primary renal tumors (69 RCC and 13 oncocytic tumors) were analyzed by restriction fragment length polymorphism analysis directed at chromosomes 3, 11p, 17p, and 18q. Results were correlated with histopathological information.

Deletions of 3p were seen in nonpapillary RCC of all cell types, but were absent in oncocytic and most papillary tumors. Among the 60 nonpapillary RCC, significant correlations were seen between deletion of 17p and tumor grade ($P = 0.037$), P stage ($P = 0.027$), and nodal metastases ($P = 0.042$).

We therefore conclude that 3p deletions, although not specific to any cell type or histological pattern of RCC, are seen in a majority of clear cell nonpapillary RCC but are absent in oncocytic and most papillary tumors. Additional allelic losses on chromosome 17p are associated with advanced disease and, therefore, may be related to tumor progression. Further studies on larger series of patients with extended follow-up will be necessary to investigate the prognostic value of molecular genetic markers in RCC.

INTRODUCTION

The loss of tumor suppressor genes appears to be involved in the pathogenesis of many solid tumors, including colon (1), breast (2), bladder (3–5), and kidney (6–8). Initially an ordered loss of genetic material was postulated in the development and progression of these tumors, however, more recently the emphasis has shifted toward the net accumulation of genetic events.

Recently, several reports on RCC[4] demonstrated frequent deletions of the short arm of chromosome 3 (3p); whether these deletions occurred in all RCC remains controversial. Some investigators, including ourselves, have suggested that 3p deletions were not present in papillary RCC (9, 10). We, along with others, have previously suggested that within the nonpapillary RCC, 3p deletions may be specific to the clear cell phenotype (8, 11). Oncocytic tumors on the other hand are rare renal tumors which may have a different cell of origin and different biological potential than RCC, and there is some evidence that they also lack 3p deletions (8, 12).

Several other studies have demonstrated additional deletions in RCC which included portions of chromosomes 5, 6, 10, 11, 13, 17, 18, and 19 (6–8, 13). In general, additional deletions were associated with higher grade and stage tumors, which is consistent with the hypothesis that these events may be associated with tumor progression. Individually, these series have been small, which precludes proper statistical analysis. Currently, no therapy is effective in the treatment of metastatic RCC, and thus surgery remains the mainstay of therapy. Survival of patients correlates best with the stage of tumor at nephrectomy (14). Thus, this tumor system is ideal for studying the prognostic significance of genetic events as patients receive uniform treatment.

In the present study, 82 primary renal tumors (60 nonpapillary RCC, 9 papillary RCC, and 13 oncocytic tumors) were analyzed by RFLP analysis directed at chromosomes 3, 11p, 17p, and 18q. Results were correlated with histopathology. The study attempted to determine whether: (*a*) 3p deletions were specific to any subgroup of renal tumors; (*b*) deletions of 3p, 11p, 17p, and 18q were associated with established adverse prognostic factors or tumor progression.

MATERIALS AND METHODS

Tissue and Histopathological Diagnosis. Tumor specimens were obtained from radical nephrectomy specimens from 82 patients admitted at Memorial Sloan-Kettering Cancer Center between 1986 and 1990. Normal kidney tissue from an area away from the tumor or peripheral blood from each patient served as normal controls. Adjacent sections were processed for histopathological evaluation. Diagnostic specimens were formalin fixed and paraffin embedded. Six-μm thick sections were stained with hematoxylin and eosin and reviewed by a single pathologist (V. E. R.) with no prior knowledge of the RFLP results. Each tumor was characterized for cell type, histological growth pattern, pathological grade, using the Fuhrmann System, and pathological stage according to the tumor-node-metastasis classification system (15).

DNA Isolation, Southern Blotting, Hybridizations, and Autoradiography. High molecular weight DNA was isolated from tumor and normal tissue by standard phenol-chloroform methods or by the nonorganic method developed by Oncor (Gaithersburg, MD). Restriction digests of 10-μg aliquots of paired tumor and normal samples were performed in parallel, fractionated on 0.7% agarose gels, and transferred to nylon membranes (Sure blot; Oncor) as previously described (8). Membranes were washed, prehybridized and hybridized with [^{32}P]dCTP labeled probes as previously described (8). Washes were performed under stringent conditions (final wash at 65°C).

Densitometry. Autoradiographs were analyzed with an Ultrascan XL Laser Densitometer (Pharmacia LKB Biotechnology). If normal tissue demonstrated heterozygosity for a particular probe, then the ratio of corresponding tumor and normal alleles was calculated after correcting for the DNA in each lane, using constant bands or the autoradiographic signal of a heterozygous locus of another probe using the same membrane. Since partial allelic loss rather than complete LOH in RCC due to infiltrating lymphocytes has previously been demonstrated (16), a decrease in signal intensity in one allele of at least 25% in tumor tissue was considered LOH. In addition, identical criterion for LOH was successfully used in our previous study which showed excellent correlations between conventional cytogenetics and RFLP analysis (8).

Probes. The following probes with chromosome map position, locus, and restriction enzyme used in this study were obtained from the American Type Culture Collection (Rockville, MD): p627 (3p24-25; cRAF1; *Taq*I), pH3H2 (3p21; DNF15S2; *Hind*III), pHF12-32 (3p14-21; D3S2; *Msp*I), pEFD134.7 (3q26.2-qter; D3S45; *Msp*I), pADJ762 (11p15.5; D11S12; *Taq*I), pbc-N1 (11p15.5; HRAS1; *Taq*I), pEW301 (17p11.1-2; D17S58; *Taq*I), pYNZ22 (17p13.3; D17S5; *Taq*I), and 0S-4 (18q21.3-qter; D18S5; *Taq*I).

Statistical Analysis. Fisher's exact test was used to investigate the relationship between molecular genetic data and pathological parameters (grade, P

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[4] The abbreviations used are: RCC, renal cell carcinoma; RFLP, restriction fragment length polymorphism; LOH, loss of heterozygosity; NI, noninformative.

stage, nodal status, and metastasis status). Only tumors informative at a particular chromosomal arm were included in each analysis.

RESULTS

Histological and RFLP data are presented in Table 1, whereas representative autoradiograms for LOH are shown in Fig. 1. LOH for 3p was reported if any one of the chromosome 3 probes showed LOH. 3p was considered NI only if pH3H2 and p627 were both NI irrespective of whether pHF12–32 or pEFD134.7 was NI or showed no LOH. If either pHF12–32 or pEFD134.7 showed LOH, in all cases pH3H2 or p627 also showed LOH or were NI. In the present study, as well as in previous studies (6, 8, 13), the results of pH3H2 and p627 showed concordance. If deletions were present on chromosome 3, then they were always detected by pH3H2 and p627 as long as these probes were informative. The extensive deletion mapping performed by Anglard *et al.* (6) demonstrate that these two probes reside within the minimally deleted segment of 3p.

In Table 1, LOH for 11p was reported if either pADJ762 or pbc-N1 demonstrated LOH. 11p was considered to show no LOH if at least one probe was informative, while it was considered NI if both probes were NI. Individual probe results did not allow us to delineate the region of interest on chromosome 11p as pADJ762 demonstrated a low rate of heterozygosity and in cases informative for pADJ762, pbc-N1 was either NI or gave the same result as pADJ762.

Thirteen tumors demonstrated LOH for one or both of the 17p probes; 4 demonstrated LOH for both probes, 2 demonstrated LOH for pEW301 and were NI for pYNZ22; 4 demonstrated LOH for pYNZ22 and were NI for pEW301, and 3 demonstrated no LOH for pEW301 yet LOH for pYNZ22. The LOH results on these last 3 tumors suggest that the chromosomal area of interest on 17p resides distal to pEW301. In Table 1, LOH for 17p was reported if either pEW301 or pYNZ22 showed LOH. 17p was considered to show no LOH if pYNZ22 retained heterozygosity, while pEW301 was either NI or showed no LOH. 17p was considered to be NI if pYNZ22 was NI while pEW301 was either NI or retained heterozygosity.

The results for 18q in Table 1 represent the results of the probe OS-4 and thus we can only state that a deletion of some portion of chromosome 18 has occurred, not necessarily confined to the long arm.

Several results in Table 1 deserve special comments: (*a*) 3p deletions were found in 17 of 20 informative pure clear cell, nonpapillary tumors; in 2 of 6 informative pure granular, nonpapillary tumors (Tumor 22, 49); in 2 of 2 informative tubulopapillary basophilic tumors (Tumor 61, 69), and in several tumors with mixed cell types; (*b*) 3p deletions were not seen in any oncocytic tumors (10 informative tumors); (*c*) of 34 pure clear cell RCC, 3p deletions occurred in 17 of 20 informative cases and 17p deletions occurred in 2 of 17 informative cases, of note, both tumors with 17p deletions also had 3p deletions; (*d*) of 22 nonpapillary RCC informative at 3p and 17p, 5 tumors had deletions of both 3p and 17p; (*e*) of the two stage P_1 tumors included in the series, one showed a 3p deletion and the other a 17p deletion.

In order to assess prognostic implications of genetic alterations seen in RCC, only nonpapillary tumors ($n = 60$) were included in the analysis to correlate allelic losses with pathological parameters. Significant correlations were found between deletions of 17p and tumor grade, P stage, and nodal metastases (Table 2). Deletions of 17p occurred in 6 of 13 informative high grade and 3 of 22 informative low grade tumors; in 8 of 20 high stage and 1 of 15 low stage tumors and in 3 of 4 node-positive and 6 of 31 node-negative tumors.

DISCUSSION

Numerous reports have confirmed deletions of 3p in RCC by both cytogenetic and molecular genetic analysis. These data suggest that a tumor suppressor gene(s) resides on 3p and, when inactivated, promotes tumorigenesis. Experimental evidence supports this hypothesis as the introduction of 3p into a RCC cell line modulated its growth (17).

Based on our earlier study with the use of cytogenetic and RFLP analysis in 50 renal tumors, we suggested that 3p deletions were an early event in the pathogenesis of RCC, and that allelic loss on chromosomes 17p and 18 and increased dosages of genetic material on chromosomes 5q and 7 may be associated with tumor progression (8).

The present study demonstrates that 3p deletions, although not always associated with clear cell phenotype as had previously been suggested, were absent in many of the papillary tumors. Two of our papillary tumors demonstrated 3p deletions, which had basophilic cell types and may represent variants of RCC (possibly collecting duct tumors) rather than typical RCC which are derived from the proximal tubules. Of the remaining pure tubulopapillary tumors, 0 of 5 informative tumors had deletions of 3p, consistent with previous reports (8–10).

One study has suggested an inverse relationship between allelic deletions at 3p and 17p in RCC (18). In the present study, two pure clear cell acinar RCC had concomitant losses of 3p and 17p (Tumors 13, 40) and 5 nonpapillary RCC informative at both 3p and 17p demonstrated concomitant deletions (Tumors 13, 40, 48, 51, 58). These observations, together with our observation that deletions of 17p correlate with higher grade tumors and tumors with nodal metastases, suggest that deletions of 17p are associated with tumor progression rather than being specific to a particular histopathological subtype.

These observations support the hypothesis that an underlying genetic defect at the submicroscopic level, possibly a mutation, is shared by tumors of a given tissue, whereas subsequent genetic changes associated with tumor progression could be shared by tumors of varying histology.

Deletions of 17p have been described in a variety of solid tumors and may be associated with tumor progression. It appears that in RCC the same is true, as deletions of 17p significantly correlated with tumor grade, stage, and nodal metastases. Although further deletion mapping studies on the tumors included in this study are needed to better define minimally deleted segment and the gene(s) on chromosome 17p, a recent study by Reiter *et al.* (19) is of particular significance. According to this study, 48% of RCC cell lines derived from advanced stage renal tumors showed losses at 17p, 33% of which also sustained *p53* mutations, suggesting that the abnormalities of *p53* gene are common and may be involved in progression of RCC tumors. It is, therefore, not unreasonable to speculate that abnormalities of the same gene locus may be involved in the tumors included in our study.

Two tumors were classified as P_1 (<2.5 cm in diameter) and in some pathological series these would be considered as adenomas. We have demonstrated a 3p deletion in one and a 17p deletion in the other, thus demonstrating similar genetic alterations as RCC.

Thus, we have demonstrated that within the RCC, deletions of 17p correlate with pathological parameters of poor outcome. To determine whether any genetic marker added additional prognostic information over conventional histopathological criteria, patients must first be stratified into good and poor risk groups by pathological data, and then substratified on the basis of RFLP results. The limited follow-up and size of each of the groups in our series did not provide adequate statistical power to answer this important question, but it is hoped that

Table 1 *Histopathological and RFLP data*

Tumor no.	Cell type[a]	Histological pattern[b]	Grade	Stage[c]	Chromosomal arm[d]			
					3p	11p	17p	18q
1	Cl	Acin	1	2	–	–	NI	NI
2	Cl	Acin	1	2	–	+	+	+
3	Cl	Acin	1	2	–	NI	+	NI
4	Cl	Acin	1	2	–	NI	NI	NI
5	Cl	Acin	1	2	–	+	NI	NI
6	Cl	Acin	1	2	–	+	NI	NI
7	Cl	Acin	1	2	–	+	+	NI
8	Cl	Acin	1	3a	NI	NI	+	NI
9	Cl	Acin	1	3a	NI	+	NI	+
10	Cl	Acin	1	3a	+	NI	+	NA
11	Cl	Acin	1	3b	–	+	+	NI
12	Cl	Acin	2	2	NI	+	NI	+
13	Cl	Acin	2	2	–	–	–	–
14	Cl	Acin	2	2	–	+	+	+
15	Cl	Acin	2	2	NI	+	+	+
16	Cl	Acin	2	2	–	NI	NI	+
17	Cl	Acin	2	2	NI	NI	NI	NI
18	Cl	Acin	2	2	–	+	NI	NI
19	Cl	Acin	2	2	NI	NI	+	NI
20	Cl	Acin	2	2	+	+	+	NI
21	Cl	Acin/pap	2	2	+	+	NI	+
22	Gran	Acin	2	2	–	NA	NA	NA
23	Gran	Acin	2	2	+	+	+	+
24	Gran	Acin	2	2	+	+	+	NI
25	Gran	Acin	2	2	NI	–	+	NI
26	Gran	Tub/acin	2	2	+	NI	+	NI
27	Gran/cl	Acin/pap	2	2	–	+	+	NI
28	Cl	Acin	2	2M1	NI	+	+	NI
29	Cl/spin	Acin/sarc	2	2M1	–	NI	+	+
30	Cl	Acin	2	3a	NI	NI	NI	+
31	Cl/gran	Acin	2	3a	+	NI	–	+
32	Cl/gran	Acin	2	3a	–	NI	NI	NI
33	Gran	Acin	2	3a	+	NI	NI	NI
34	Cl	Pap/acin	2	3a N1	NI	–	NI	NI
35	Cl	Acin	2	3b	NI	NI	+	+
36	Cl	Acin	2	3b	–	+	NI	+
37	Gran/cl	Acin	2	3b	NI	+	–	+
38	Cl	Pap/acin	2	3b N1	–	+	NI	–
39	Cl	Acin	2	4a	–	–	+	+
40	Cl	Acin	3	3a	–	+	–	+
41	Cl	Acin	3	3a	NI	–	NI	NI
42	Cl/gran	Acin	3	3a	–	NI	+	NI
43	Gran/cl	Acin	3	3a	+	–	–	NI
44	Gran/cl	Acin	3	3a	NI	+	+	+
45	Cl	Acin	3	3a M1	NI	+	+	NI
46	Cl/gran	Acin	3	3a N1	–	–	NI	+
47	Cl	Acin/pap	3	3b	–	+	NI	NI
48	Cl/gran	Acin	3	3b	–	NI	–	NI
49	Gran	Acin	3	3b M1	–	NI	+	–
50	Cl	Acin/pap	3	3b N1	NI	NI	+	NI
51	Cl/gran	Acin	3	3c N3	–	+	–	NI
52	Cl/gran	Acin	4	3a	–	NI	NI	+
53	Spin/cl	Sarc/acin	4	3a	NI	NI	NI	NI
54	Cl/spin	Acin/sarc	4	3a M1	NI	+	+	NI
55	Spin/cl/gran	Sarc/sol/acin	4	3a M1	+	NI	+	NI
56	Cl/gran	Acin	4	3a N1	NI	–	–	+
57	Cl/gran/spin	Acin/sarc	4	3a N1	–	NA	NA	NA
58	Spin/cl	Sarc/acin	4	3a N1	–	NI	–	NI
59	Cl/gran/spin	Acin/sarc	4	3c	–	NI	NI	NI
60	Cl	Sarc/acin	4	4a	NI	NI	NI	NI
61	Baso	Tub/pap	1	1	–	NI	NI	NI
62	Baso	Tub/pap	1	1	NI	+	–	NI
63	Gran	Tub/pap	1	2M1	+	NI	NI	NI
64	Cl	Tub/pap	2	2	+	NI	+	NI
65	Cl/gran	Pap/tub	2	2	+	NI	–	+
66	Cl/gran	Pap	2	2	+	+	NI	NI
67	Gran/cl	Tub	2	2	+	+	+	NI
68	Gran/cl	Pap/tub	3	2	NI	+	–	NI
69	Baso	Tub/pap	3	2 N1M1	–	–	–	N1
70	Oncocytic	Oncocytic	1	2	+	NI	+	NI
71	Oncocytic	Oncocytic	2	2	+	+	+	NI
72	Oncocytic	Oncocytic	2	2	NI	+	+	+
73	Oncocytic	Oncocytic	2	2	+	NI	NI	+
74	Oncocytic	Oncocytic	2	2	+	NI	+	+
75	Oncocytic	Oncocytic	2	2	NI	+	+	+
76	Oncocytic	Oncocytic	2	2	+	NI	NI	NI
77	Oncocytic	Oncocytic	2	2	+	NI	+	+
78	Oncocytic	Oncocytic	2	2	+	NI	+	+
79	Oncocytic	Oncocytic	2	2	+	+	+	+
80	Oncocytic	Oncocytic	2	2	+	NI	NI	NI
81	Oncocytic	Oncocytic	2	2	+	NI	+	NI
82	Oncocytic	Oncocytic	2	2	NI	–	+	+

[a] Cell types listed in order of most prevalent to least prevalent in tumor. cl, clear; gran, granular; spin, spindle; baso, basophilic.
[b] Histological patterns listed in order of most prevalent to least prevalent in tumor. acin, acinar; pap, papillary; tub, tubular; sarc, sarcomatoid; sol, solid.
[c] N and M categories were zero unless otherwise specified.
[d] –, loss of heterozygosity; +, no loss of heterozygosity; NA, not available.

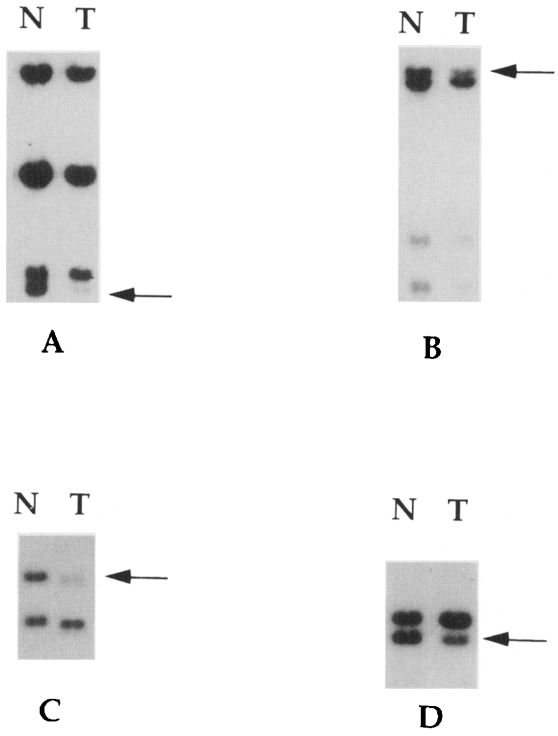

Fig. 1. Representative blots, with *arrow* demonstrating deleted allele. (*A*) Tumor 27 showing LOH for pH3H2. (*B*) Tumor 14 showing LOH for p627. (*C*) Tumor 56 showing LOH for pYNZ22. (*D*) Tumor 43 showing LOH for pYNZ22.

Table 2 *Molecular genetic correlation with pathological parameters for nonpapillary renal cell carcinomas (n = 60) Fisher exact test (P values)*

Parameter	Chromosomal arm deletion			
	3p	11p	17p	18q
Grade[a]	0.204	0.170	0.037	0.461
P stage[b]	0.279	0.160	0.027	0.462
Nodal status[c]	0.217	0.091	0.042	0.322
Metastasis status[d]	0.440	0.384	0.142	0.237

[a] 1, 2 *versus* 3, 4.
[b] P1, P2 *versus* P3, P4.
[c] + *versus* −.
[d] + *versus* −.

as our study population becomes more mature and the numbers are increased, this goal could be successfully achieved.

Although the number of chromosomal arms studied are few, our data suggest that deletions of chromosome 17p are associated with tumor progression. Whether the deletions result in the more aggressive phenotype (higher grade and stage) or the more aggressive phenotype results in genetic instability and subsequent deletions however, remains to be seen.

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