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Aberrant Expression of Polycystin-1 in Renal Cell Tumors

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Abstract

Polycystin-1 (PC1) is a cellular transmembrane protein coded by the polycystic kidney disease (*PKD1*) gene, prevalently expressed in developing/mature kidney and in autosomal polycystic kidney disease (ADPKD). Limited data are available concerning the PC1 involvement in renal tumorigenenesis. Polycystin-1 expression was evaluated in 8 clear cell renal cell carcinomas (RCCs), 7 tubulopapillary cell type tumors, 3 solid RCCs developed in patients with von Hippel-Lindau disease (VHLD), one RCC developed in a patient on chronic haemodialysis and one angiomyolipoma in a patient with Tuberous sclerosis (TS). In the normal kidney, consistent level of polycystin-1 was detected in distal tubules, collecting duct, glomerular podocytes and vascular smooth muscle cells. The strongest immunoreactivity against polycystin-1 was observed in epithelial cells lining the cystic components in all ADPKD tissues. Five cases of clear cell type RCCs and two-tubulopapillary cell type RCCs consistently expressed PC1. In the VHL disease associated renal carcinomas, both the neoplastic cells and cystic tissue areas weakly expressed PC1. In TS-associated angiomyolipoma, the vascular component was PC1 positive, while the tumoral cells were scarcely stained. The present report indicates consistent expression of the *PKD1* gene product polycystin-1, in normal kidney, ADPKD tissues, and renal cell carcinomas. The findings suggest that the level of PC1 expression is linked to tumor cell type, being a more frequent event in clear cell RCC.

Introduction

The *PKD1* gene product, polycystin-1 (PC1), is a cellular transmembrane glycoprotein prevalently expressed in epithelial and mesenchymal cells of developing and mature kidney as well as in autosomal dominant polycystic kidney disease (ADPKD) (1-4). Cellular components in other organs such as liver, skin and brain also express PC1 although at lower level (5,6). The precise function (s) of PC1 have not yet been elucidated, but the presence of known cell adhesion domains in the extra cellular portion of the molecule suggests a role in cell-to-matrix and/or cell-to-cell interactions (5-8). In ADPKD, it has been reported that structural alterations of polycystin-1 leads to an increased epithelial cell proliferation and kidney cysts formation (5).

Concerning the role of polycystin-1 in renal tumorigenesis, no correlation between ADPKD and renal cell carcionoma (RCC) has yet been established,

but the occurrence of renal carcinoma in patients with acquired polycystic kidney disease secondary to haemodyalisis is well documented (9). In the same context, bening and malignant renal neoplasms are frequently found in kidneys of patients suffering of either von Hippel-Lindau disease or of tuberous sclerosis complex (10,11). On the other hand, cystic changes involving the entire tumor may be seen in various renal neoplasms, such as cystic renal cell carcinoma, cystic nephroma and partially differentiated cystic nephroblastoma (9). At the cellular level, a number of molecular anomalies were described in both sporadic RCCs and tumors related to various cystic kidney lesions including over-expression, of c-myc, bcl-2, c-met, and c-Ets oncoproteins as well as deregulated expression of growth factors (12-16). In this regard delineation of specific molecular processes that lead to transforming events in acquired polycystic kidney but not in ADPKD or autosomal recessive polycystic kidney disease (ARPKD) may reveal other functions of polycystin-1, such as the tumor suppressor activity (17).

In the present study, the level of expression of polycystin-1 was evaluated in histologically different renal tumors using 3 polyclonal antibodies raised against both synthetic peptides and the fusion protein corresponding to the sequences of intra- and extra cellular domains of the molecule. The intensity of polycystin-1 expression in the neoplastic tissues was assessed by immuno-histochemistry and correlated to that observed in normal kidney and ADPKD cystic parenchyma.

Material and methods

Renal cell carcinomas (RCCs). Selected tissue samples from patients undergoing resection for primary renal carcinoma including one patient on chronic haemodyalisis were obtained after nephrectomy (n=16). Both the RCC samples and fragments from the adjacent normal renal tissue were fixed in formalin and embedded in paraffin. Renal tumors were classified according to Thoenes et al. 1986 (18) on the basis of the following parameters: the cytological aspect of the tumor cells, the tumor growth pattern (compact, tubulopapillary, cystic) and nuclear grade of malignancy. This classification yielded 8 clear cell type RCC, six of them were of grade 2 and two of grade 3, seven tubulopapillary carcinomas with chromophilic cells, five of grade 1 and two of grade 2. The tumor in the hemodyalized patient was classified as a clear cell type carcinoma of grade 2.

von Hippel-Lindau disease (VHLD): Two nephrectomies and one tumorectomy were performed in three patients at age of 28, 34 and 43 years because of renal tumors. Clinically, the patients suffering VHLD carried a spectrum of bilateral and multifocal renal lesions including benign cysts and solid renal cell carcinomas. The neoplasms contained numerous cystic formations as well as areas with increased percentage of inflammatory cells.

Tuberous Sclerosis (TS). Bilateral nephrectomy was performed in a 23-year-old patient because of retroperitoneal hemorrhage due to the presence of large angiomyolipoma. The two enlarged kidneys (630 and 1350 gr) contained numerous cystic formations with a diameter ranging between 2 to 5cm and several nodular angiomyolipomas with diameters between 2 to 3 cm. The interstitial stroma showed increased vascularity composed of cellular, hemangiopericytic and collagenous vessel forms.

Autosomal dominant polycystic kidney disease (ADPKD). Renal tissue samples were obtained from three female patients whose disease has not been yet assigned to either PKD1 or PKD2. The kidneys were removed before transplantation in two cases and because of abdominal pain in the third patient.

Immunohistochemistry: The three polyclonal antibodies against PC1 used in the present work have been produced and generously provided by Dr D. Peters from the Department of Human Genetics at the University Medical Center, Leiden, the Netherlands. The antibodies were raised in rabbits against 2 synthetic peptides, the pepPBP1 and pepPBP3, and against a fusion protein fpAH4 corresponding to the predicted amino acid sequence of PC1(19). These three antibodies have been shown to give identical tissue immunostaining. The imunolabeling was performed on 4 μm thick formalin-fixed paraffin-embedded tissue sections according to standard procedures. For antigen retrieval, the slides were immerged in citrate buffer (pH=6) followed by treatment in microwave oven 3 times during 4 min. The appropriate dilution (1/200 to 1/600) of primary antibodies was then applied on slides for 1 hour. Immunoreactivity was revealed using the avidin-biotin complex method (LSAB2 System HRP, Dako Glostrup, Denamrk) with 3-amino-9-ethyl carbazol as chromogene substrate followed by counterstaining. Negative controls consisted of replacement of the primary antibody with non-immune mouse serum or buffer alone. The extent and the intensity of the staining were determined by the objective observer study. The percentage of immunostained cells was obtained by

counting the number of positive cells (over the total number of cells) at x 400.

Results

Polycystin-1 expression in the normal kidney and ADPKD tissues. In the normal renal tissues, an intense and widespread PC1 immunostaining was observed by separate use of all three specific antibodies. The distal tubules and the collecting ducts showed strong PC1 immunoreactivity with a finely granular cytoplasmic staining. Both, the apical and basolateral membranes of the collecting duct cells were clearly labeled, especially in the medullar part. The cytoplasm of the proximal tubular cells was either weakly positive or remained negative. In some areas containing distal tubular structures, all the epithelial cells were positive without intercellular heterogeneity. Within the glomeruli, podocytes were PC1 positive with an obvious cytoplasmic pattern of staining surrounding the nucleus, while parietal epithelial cells were very faintly and scantly positive. Mesangial and endothelial glomerular cells were not stained. Endothelial cells of peritubular capillaries were PC1 negative, as was the interstitial tissue (Fig. 1A). Vascular smooth muscle cells were PC1 positive as were some endothelial cells lining the larger vessels (not shown).

In the ADPKD tissue, PC1 expression was similar to that in the normal kidney, but appeared more intense in all cell components. The most abundant PC1 labeling was detected in the cytoplasm of cyst-lining cells, but as a rule some cysts remained entirely PC1 negative. Overall, the number of PC1 positive cysts ranged from 28% to 60%; approximately 50% all types of renal cells being labeled. Comparatively, nearly 80% of the non-cystic tubules expressed PC1 in all cases. In the fibrous interstitial stroma, numerous cells, mainly myofibroblasts or macrophages were positive (Fig. 1B). Control tissue sections of both normal kidney and ADPKD tissues incubated with the pre-immune serum were entirely negative.

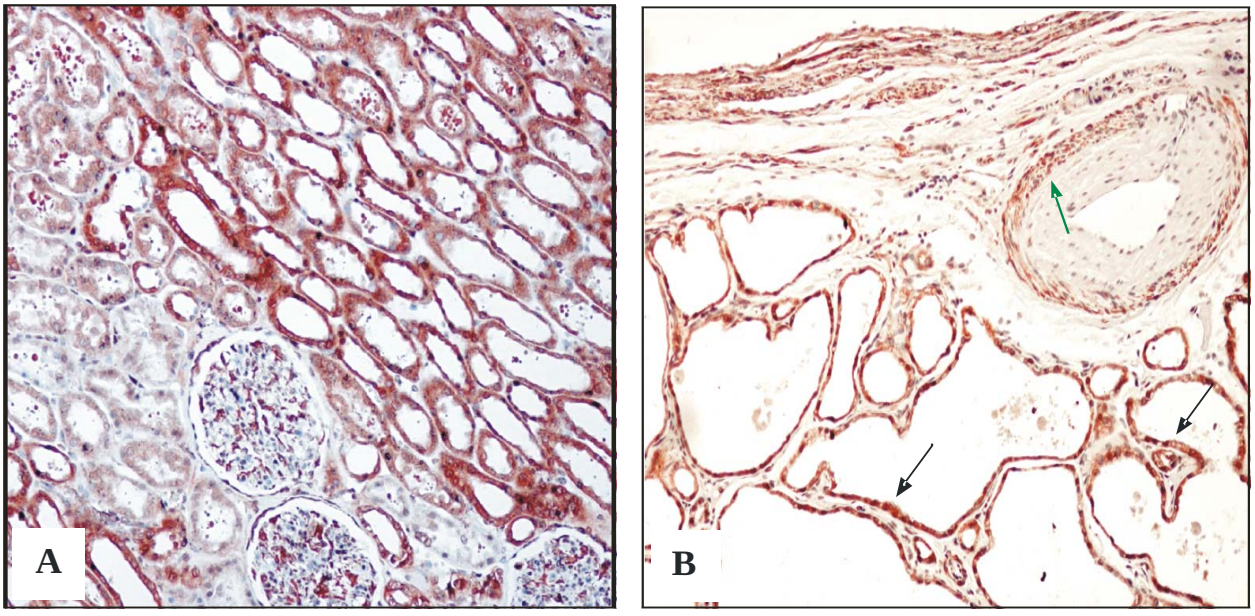

Figure 1: Immuno-peroxydase staining with pepPBP1 anti PC1 antibody of normal human kidney tissue localizing to cortical tubules and glomeruli. Note consistent expression of PC1 protein in renal tubules and glomerular podocytes (A). Immunostaining for polycystin-1 in ADPKD tissue with pepPBP3 antibody showing consistent staining of cyst lining cuboidal epithelium (black arrow) and lower protein level of vascular smooth muscle cells (green arrow) (B).

Renal cell carcinomas (RCCs): The intensity of staining and the percentage of tumor cells expressing PC1 protein varied according to the tumor cell type (Table 1). Five cases classified as clear cell RCC showed tissue areas with consistent cytoplasmic PC1 staining (Figure 2A). Isolated dysplastic tubular nod-

Table 1: Percentage of tumor cells expressing PC1 protein in different types of renal cell tumors.

		PC1 -positive tumor cells			
Tumor cell type	n	< 10%	< 30%	< 50%	> 50 %
Clear cell type RCC	8	1	4	3	0
Tubulopapillary RCC	7	5	1	1	0
von Hippel-Lindau RCC	3	2	1	0	0
TS/angiomyolpoma	1	0	1	0	0

n = number of cases.

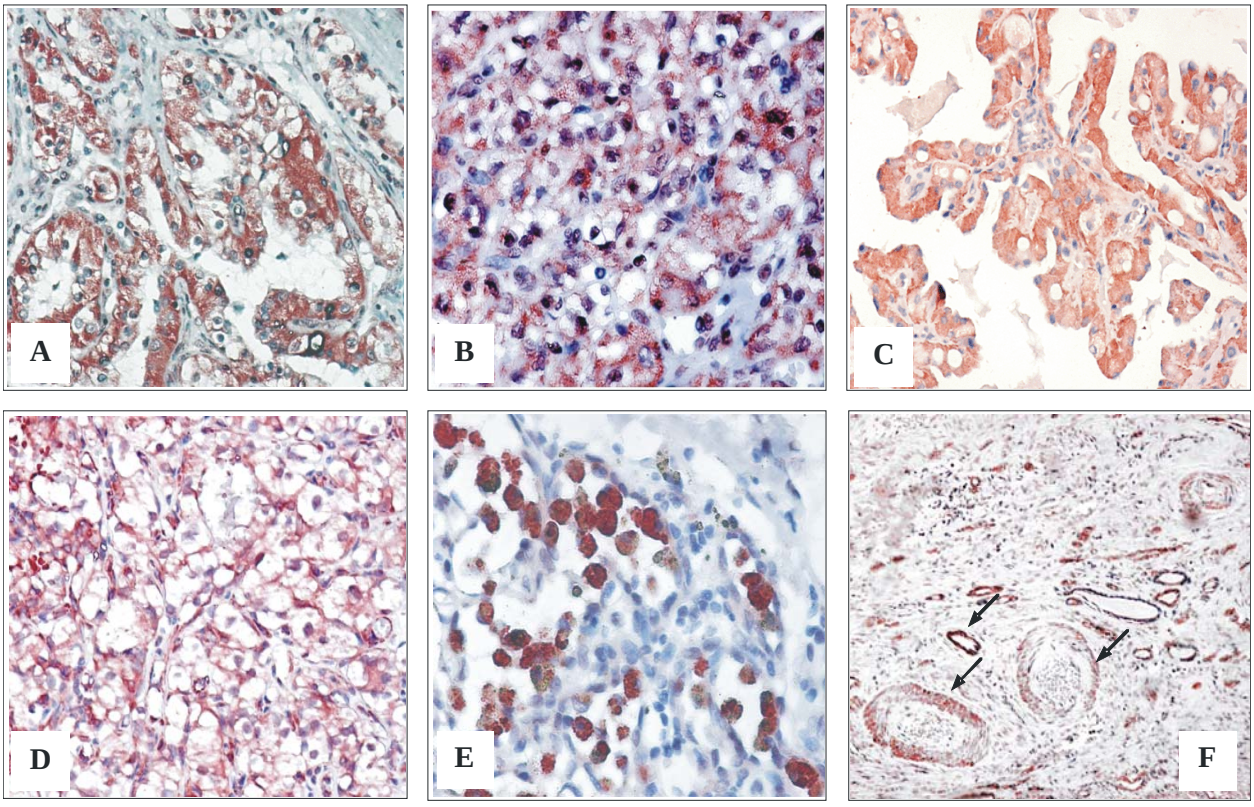

Figure 2: Immuno-histochemical detection of PC1 expression (fpAH4 antibody) in sporadic clear cell type RCC x 400 (A); RCC of clear cell type from patient on chronic hemodyalisis x400 (B); tubulopapillary cell type carcinoma x400 (C); clear cell type RCC in VHLD, x400 (D); Expression of PC1 in an epitheliod tissue area of the angiomyolipoma in TS x400 (E); PC1 immuno-staining od the vascular components of the angiomyolipoma in TS x160 (F).

ules displayed heterogeneous and less consistent but still positive cytoplasmic PC1 labeling, while the tubular elements of the adjacent normal kidney exhibited strong immunoreactivity. The clear cell type RCC developed in the dialyzed patient showed moderate expression of PC1 (Fig. 2B).

Comparatively, the immuhistochemical analysis of tubulopapillary cell type RCC showed lower level of PC1 expression with either no expression or PC1 in 3 cases, or presence of isolated strongly positive neoplastic cells estimated as fewer then 10% with a cytoplasmic pattern of staining in 2 cases (Table 1). A low percentage of the tumor cells were positive in one case with grade 1 of malignancy, while in one case of grade 3, nearly 30 % of the neoplastic cells were positive with a membranous pattern of staining (Fig. 2C). Overall, no clear relationship was found between the nuclear grade of malignancy and the level of PC1 expression in both the clear cell type and tubulopapillary RCCs (Table 2).

von Hippel-Lindau disease. In the three cases studied, the epithelial renal cyst lining cells from the areas of cystic parenchyma did not express PC1. The neoplastic cells of two VHLD-associated solid clear cell type renal carcinomas moderately expressed polycystin-1 (Fig. 2D) while one sample was negative. In contrast, the isolated non-cystically altered normal renal tissue areas exhibited strong expression of polycystin-1 (not shown).

Tuberous sclerosis. The most intense polycystin-1 staining was revealed in the areas of non-tumoral renal cystic parenchyma with similar intensity to that observed in ADPKD samples. In the angiomyolipoma, the vast majority of cystic tubules were moderately PC1 positive, especially the large hypertrophic proximal tubules. Some islets of non-cystic tubules lined by dysplastic epithelium consistently expressed PC1. A strong immunoreacticvity with the PC1 antibody was observed on vascular smooth muscle cells and the epithelioid cell components of the tumor, while the adipose cells were not immunoreactive (Fig. 2E). The highest level of PC1 expression was observed in vascular components of the hyper-cellular type (Fig. 2F).

Table 2: Percentage of cells expressing PC1 protein in various renal cell carcinomas according to nuclear grade of malignancy.

Tumor cell grade	n	PC1 - positive tumor cells			
		< 10%	< 30%	< 50%	> 50 %
Clear cell type RCC	9 *				
Grade 1	6	3	2	1	0
Grade 2	2	1	1	0	0
Grade 3	1	0	0	1	0
Tubulopapillary RCC	7				
Grade 1	3	2	1	0	0
Grade 2	2	1	1	0	0
Grade 3	2	1	1	0	0
von Hippel-Lindau RCC	3				
Grade 1	2	1	1	0	0
Grade 2	1	1	0	0	0
Grade 3	0	0	0	0	0

n = number of cases.
* 8 sporadic RCCs + 1 renal cell carcinoma in a patient under chronic haemodialysis.

Discussion

The level of expression of polycystin-1 protein was examined in various types of renal tumors in comparison with normal kidney and ADPKD tissue. For the normal renal tissues, the presented data are in agreement with previous reports and confirm abundant and granular cytoplasmic PC1 staining of distal tubular cells and collecting ducts whereas proximal tubular cells are essentially negative (6,20,21). In the renal glomeruli, PC1 protein was predominantly found in podocytes with peri-nuclear cytoplasmic pattern of staining, while parietal epithelial cells were scarcely labeled. Comparatively, the highest PC1 immunoreacivity was observed in ADPKD tissues, even though a structural alteration of the *PKD1* gene is common in this disease (6,20,21). Since it is believed that structurally normal polycystin-1 is required to prevent cysts formation, the detection of high level of the molecule in ADPKD tissues may be explained by the synthesis of a truncated large size molecule that is not functional but is still immunoreactive (5,6,20).

Among the renal cell tumors studied, specific but heterogeneous PC1 immunoractivity was revealed, the highest level of expression being present in clear cell type RCC. In most of the tumoral samples analyzed, the PC1 immuno-staining was cytopalsmic but a membranous accentuation was also found. With regard to the clear cell type RCC pathogenesis, it is widely accepted that these tumors share phenotypic characteristics with the proximal tubular cells where polycystin-1 is not expressed (22). Thus, our findings strongly suggest a consistent de novo expression of PC1 at least in neoplastic cells of some clear cell type RCC. In tubulopapillary cell type RCC, a lower level of polycystin-1 was observed, although a consistent level of the protein were found in isolated areas with papillary architecture. The adjacent non-tumoral renal tissue in all RCC cell types with or without cystic structures showed as a rule an elevated level of PC1.

At present, the reasons for the aberrant PC1 expression in the series of RCC studied remain unknown. One of the possibilities could be related to the cytogenetic anomalies inherent to the tumor cells altering the 16p chromosomal region, the location of the *PKD1* gene. However gain or loss of DNA sequences at the 16p arm have been occasionally described in the renal cell neoplasms (23,24,25). Another explanation could be proposed on the basis of the clonality of both tumoral and cyst wall lining cells that can exhibit different degrees of maturation or differentiation as well as differences in the proliferative activity (26-28). Along this line it has been shown that PC1 is more expressed in fetal than in mature kidney tissues (19,29,30). Remarkably, PC1 which is not clearly detected in mature proximal tubular cells, appears consistently expressed by regenerating proximal cells after tubular injury (21,31).

The two genetic disorders including the von Hippel-Lindau disease and the tuberous sclerosis complex are known to be associated with both benign and malignant renal tumors together with cystic changes of the non-neoplastic kidney (10,11). The dysplastic cyst-lining cells as well as the solid areas in the two studied VHL-associated RCC, did not clearly expressed polycystin-1. In the third VHL-associated renal tumor approximately 45% of cells exhibited cytoplasmic and/or cell membrane PC1 immunoreactivity. Low percentage of cells showing both nuclear and membranous PC1 staining was also observed in neoplasm. This is in accordance with previous studies that demonstrated multiple sub-cellular localizations of PC1 including the outer nuclear membrane particularly in ADPKD tissue (19-21). Similarly, PC1 membranous staining pattern was detected in epithelial cells from the ureteric bud, while the more mature tubular structures were labeled through he cytoplasm during the fetal development (29).

In the tuberous sclerosis kidney, approximately half of the cystic epithelium expressed PC1, but within a given positive cyst, some cells were PC1 negative. The majority of the noncystic tubules were PC1 positive, in particular the epithelial cells in large hypertrophic proximal tubules. In the angiomyolipoma, the highest PC1 expression was revealed in the vascular smooth muscle cells while the adipose cells were not

immuno-stained. However, as shown in Fig. 2E, the epithelioid like cell components in an isolated large angio-myolipomatous nodule consistently expressed PC1. The lower amount of polycystin-1 expression observed in TS could be a consequence of the frequent molecular genetic alterations described within the *TSC2* locus located in the vicinity of the *PKD1* gene at the 16p13 chromosomal region. In this regard, it has been suggested that loss of DNA sequences within the TSC2 gene may alter the level of expression of polycystin-1 in most angiomyolipomas, rhabdomyomas and astrocytomas observed in patients with TS (11,32-34).

To date, no firm correlation between ADPKD and RCC development has been established. Development of renal carcinoma in ADPKD is a rare phenomenon in comparison to the higher incidence of RCC in patients with acquired polycystic kidney disease (9). The difference between these two cystogenic processes remains an intriguing issue, and the definition of specific mechanisms that lead to transforming events in acquired polycystic kidney but not in ADPKD or ARPKD may indeed reveal new functions of PC1 (17). In this context, it has been shown that stable expression of full length *PKD1* cDNA in cultured MDCK cells induces a decrease of the growth rate and protects the cells from apoptosis (35). Conversely, abrogation of the PC1 expression in the MDCK model inhibits tubulogenesis and induces formation of cysts when the cells are grown in three dimensional culture system (17).

In conclusion, the present report indicates consistent expression of the PKD1 gene product polycystin-1, in normal kidney, ADPKD tissues, and renal cell carcinomas. The findings suggest that the level of PC1 expression is linked to tumor cell type, being a more frequent event in clear cell RCC. No significant correlation was revealed between the nuclear grade, and the level of PC1 expression in the different renal cell carcinomas types studied. Further investigations are needed to define whether PC1 expression delineates a particular pattern of tumor cell growth and survival specifically related to the renal carcinoma cell type.

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