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Invited Review

The pathogenesis of polycystic kidney disease

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Summary. Polycystic kidney disease (PKD) is a genetic or acquired disorder characterized by progressive distention of multiple tubular segments and manifested by fluid accumulation, growth of non-neoplastic epithelial cells and remodeling of the extracellular matrix resulting ultimately in some degree of renal functional impairment, with the potential for regression following removal of the inductive agent(s). It is due to an aberration of one or more factors regulating tubular morphogenesis. Human PKD can pursue a rapid course with renal failure occurring perinatally (infantile PKD) or an indolent course without renal failure developing during the life of the individual (adult PKD). Human acquired PKD develops in atrophic and scarred end-stage kidneys with non-cystic forms of renal disease. Cell proliferation, fluid secretion, impaired cell-cell and cell-matrix interaction, defective function of the Golgi apparatus, cell undifferentiation, and an abnormal matrix have been implicated in the pathogenesis of PKD based on clinical and experimental studies.

Under normal conditions, the dynamic turnover of tubular epithelia and matrices are tightly regulated to maintain tubular morphology. The basic defect in PKD is tubular dysmorphogenesis. Our finding indicates that the principal phenotypic features of autosomal dominant PKD (ADPKD) are altered structure and function of the Golgi complex, altered structure and composition of the matrix and cell undifferentiation, all of which are probably interrelated. If the gene product of the ADPKD 1 gene results in a defective matrix, the abnormal Golgi function and cell differentiation may be due to faulty matrix-cell communication.

Key words: Polycystic kidney disease, Fluid secretion, Cell proliferation, Cell-Matrix interaction

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Introduction

Polycystic kidney disease (PKD) is a genetic or acquired disorder with progressive distention of multiple tubular segments or glomerular capsules, and is manifested by fluid accumulation, growth of non-neoplastic epithelial cells and remodeling of the extracellular matrix resulting ultimately in some degree of renal functional impairment, with the potential for regression following removal of the inductive agent(s). It is a localized, segmental event due to an aberration of one or more factors regulating tubular or glomerular capsular morphogenesis (Baert, 1978). Human PKD can pursue a rapid course with renal failure occurring perinatally or early in life or an indolent course without renal failure developing during the life of the individual. Human acquired PKD develops in atrophic and scarred end-stage kidneys with non-cystic forms of renal disease. Clinically, this form of PKD regresses in the native kidneys following renal allograft transplantation with correction of the azotemic state (Ishikawa et al., 1983). Such a regressive phenomenon has been elucidated in cystic disease in rats induced by the administration of diphenylthiazole (DPT) or its hydroxylated derivative (phenol-II) (Fig. 1), where the lesions recede following withdrawal of either compound (Kanwar and Carone, 1984; Carone et al., 1992).

Mechanisms involved in cystogenesis

The evolution of epithelial lined cystic spaces may be the result of normal or abnormal developmental processes prevalent during embryonic or adult life. Embryonic cells divide, and form a cellular condensate, and at the morula stage, cell-cell contacts generate a polarized-transporting epithelium, the trophoectoderm, leading ultimately to the formation of a cystic structure, the blastocyst (Rodriguez-Boulan and Nelson, 1989). Conceivably, by an analogous process, simple or multilocular cysts develop frequently and have been described

in essentially all human organs. Many types of normal epithelial cells tend to grow as cystic structures, exemplified by the finding that such cells *in vitro*, particularly in hydrated gels, form cysts consisting of polarized cell monolayers (Grantham et al., 1989).

In certain forms of PKD, cystic changes involve a specific segment of all nephrons, e.g., the collecting tubules in human autosomal recessive or infantile PKD (Fig. 2A). In other forms of PKD, cystic change involves random tubular segments of a very small number of nephrons, e.g., in human autosomal dominant PKD (Fig. 2B) or acquired PKD (Fig. 2C). Usually, the cysts are lined by a simplified cuboidal or flattened epithelium resting on a greatly thickened tubular basement membrane (BM, Fig. 3A).

Baert microdissected two cases of autosomal dominant PKD (ADPKD) at an early stage of the disease, and localized cystic dilatations to a few proximal, distal and collecting tubules and loops of Henle, while most nephrons were normal (1). The nephrons that had undergone cystic change were, however, free of obstruction. Thus, the expression of the gene defect in ADPKD results in a localized loss of normal tubular morphogenesis, which requires A: accumulation of tubular fluid, B: tubular epithelial cell growth, and C: perturbations of the macromolecular interactions of glycoproteins and assemblage of the extracellular matrix. The plausible roles of these three

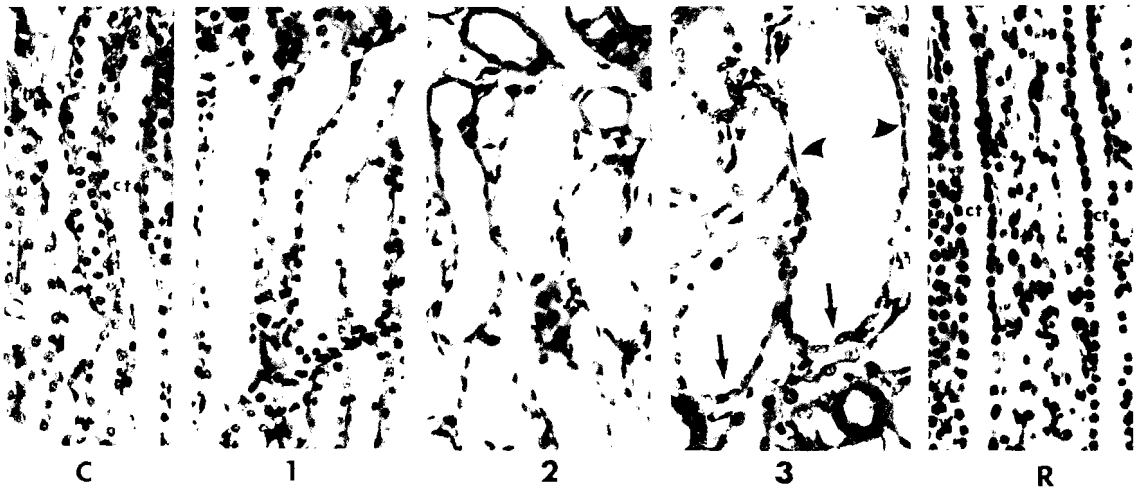

Fig. 1. Control (C); Phenol II-treated for (1), (2), and (3) days and recovery (R) (7 days after withdrawal of Phenol II) rat kidneys. Cystic changes in the outer medulla/inner cortex develop and regress rapidly. x 200

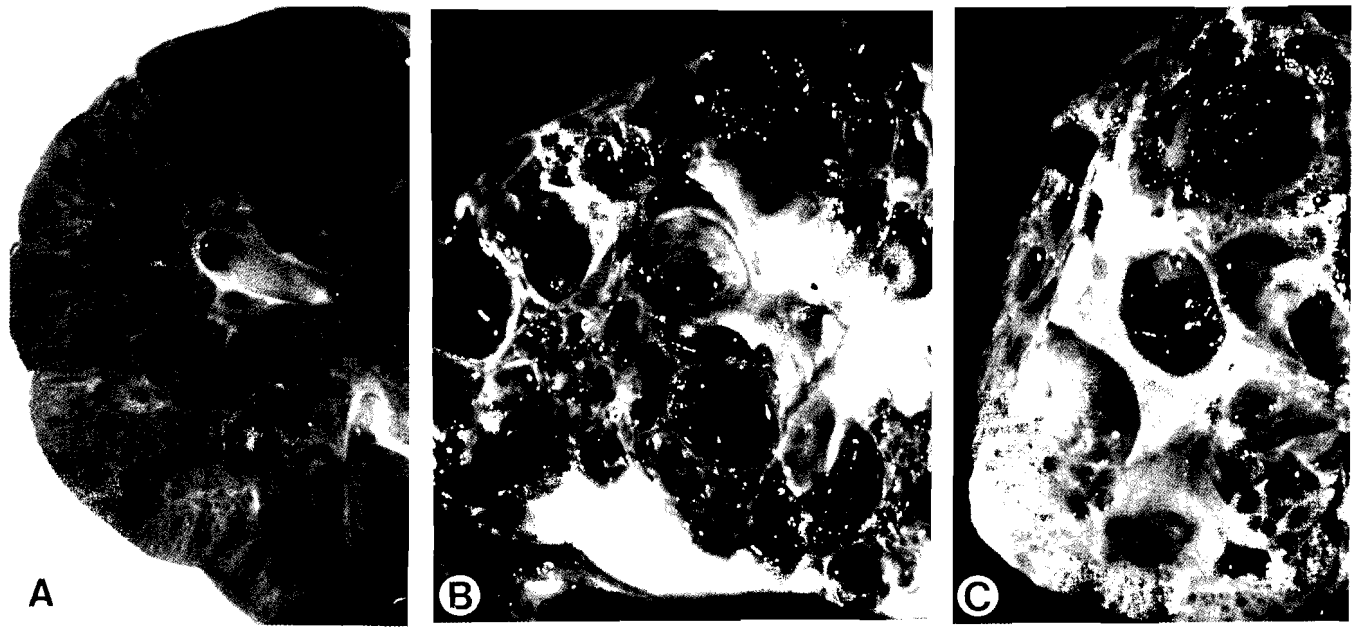

Fig. 2. Examples of human autosomal recessive (panel A), autosomal dominant (panel B) and acquired (panel C) PKD. In autosomal recessive PKD all collecting tubules are involved to about the same extent producing a radial cystic pattern (papilla to cortical surface), while in autosomal dominant and acquired PKD cysts occur in any segment of the nephron, and vary greatly in size and involve only a small percentage of the nephron population.

changes in the pathogenesis of PKD will be discussed in more detail.

Fluid accumulation

It is well established that epithelial cells lining the cysts have the same functional capabilities as that of the tubular segments from which they arose. Analysis of cyst fluid in ADPKD reveals that the sodium concentration of some cysts are close to that of plasma, typical of proximal tubules; while other cysts have a low sodium concentration compared to plasma, typical of distal tubules (Gardner, 1969). Direct evidence for active transport by cysts from ADPKD kidneys was obtained by determining the transport characteristics of cystic epithelium *in vitro* using the Ussing chamber (Perrone, 1985).

More recent studies indicate that the sequestration of fluid in cysts is due to accumulation of glomerular filtrate and/or transepithelial secretion of fluid. Scanning electron microscopic studies of the ADPKD kidneys, at a late stage of the disease, revealed that most cysts (73%) had lost their tubular connections, suggesting that fluid had accumulated primarily by transepithelial secretion (Grantham et al., 1987). Other studies also suggest that transepithelial secretion with fluid accumulation contributes to the evolution and growth of the cysts (Avner et al., 1988; Ye et al., 1992a). In

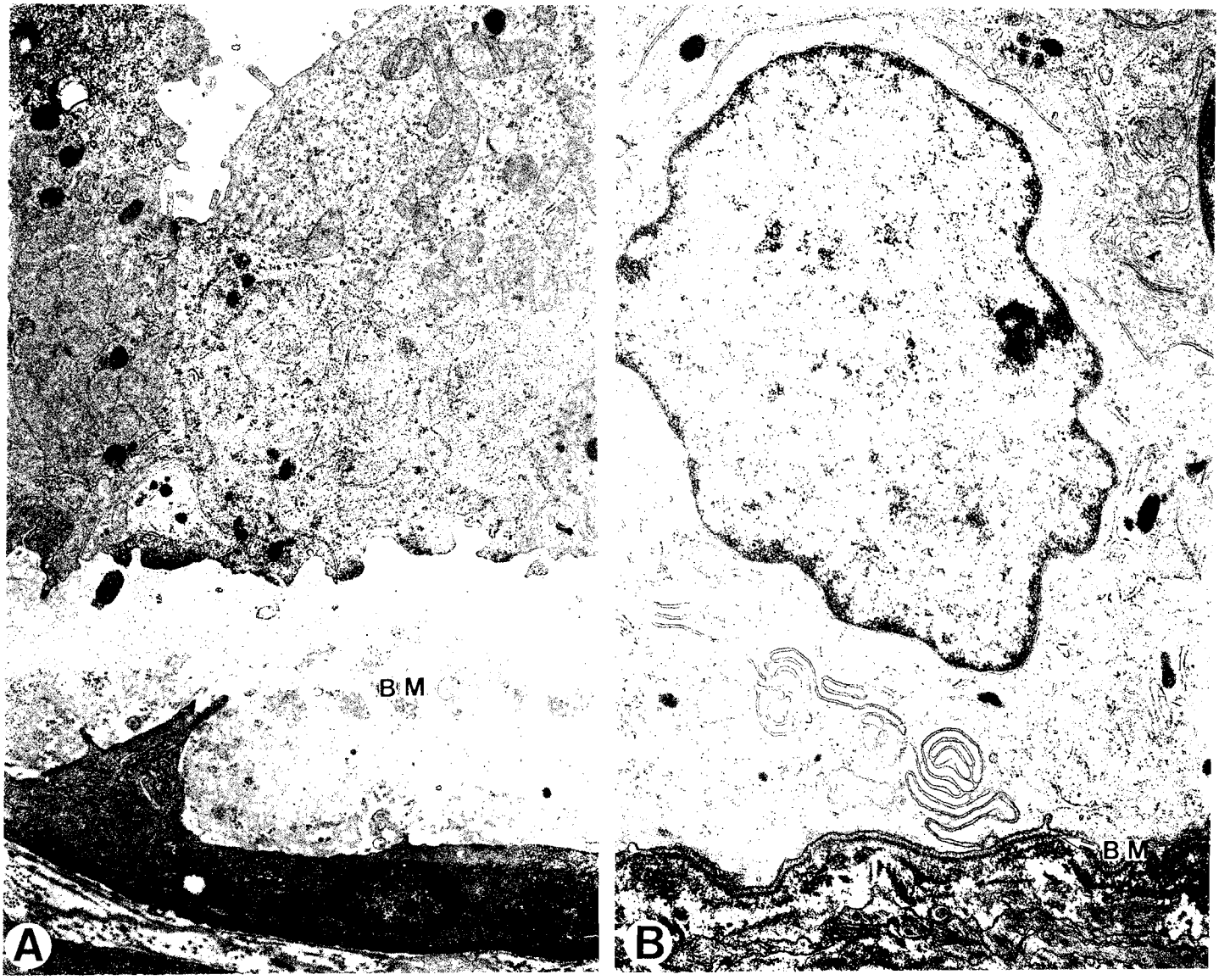

Fig. 3. Human autosomal polycystic kidney: a cyst (panel A) is lined with cuboidal cells and its basement membrane (BM) is extremely thick and reticulated compared to the thin, dense basement membrane (BM) of an adjacent noncystic tubule (panel B). Panel A, x 24,000; Panel B, x 48,000

metanephric organ cultures (Avner et al., 1985), it has been demonstrated that Na-K-ATPase mediates cyst formation in proximal tubules induced by cortisol or triiodothyronine. Fluid transport also was studied in cysts formed *in vitro* by Mardin Darby canine kidney (MDCK) cells grown in hydrated collagen gels (Mangoo-Karim et al., 1989a). Cyst enlargement was accompanied by net fluid secretion, and intracystic pressure exceeded that of the interstitium, indicating that fluid entry was secondary to net solute accumulation. Other studies with this model indicate that epithelial cells proliferation and transepithelial fluid secretion are modulated by the cAMP signal transduction system (Mangoo-Karim et al., 1989b).

The role of various cyst fluid factors in the formation and expansion of the cysts, presumably by raising the cAMP levels, have also been studied in human renal epithelial cells. The findings revealed that the cyst fluid from ADPKD kidneys, by itself, promotes cyst formation by epithelial cells from normal and ADPKD kidneys in *in vitro* collagen gels, and also stimulates the net secretion of fluid into the cysts (Neufield et al., 1992; Ye et al., 1992b).

It is unlikely that fluid secretion *per se* is a primary event in the pathogenesis of PKD, since at onset, cysts are small localized distentions or out-pouchings incorporated in functionally patent nephrons so that fluid accumulation alone could not account for cyst enlargement. When cysts enlarge and apparently separate from their nephrons, net fluid secretion may play an important role in their continued growth.

Cell proliferation

Proliferation is a feature of PKD and an increase in cell number is required for cyst growth. A number of studies indicate that cell proliferation has a role in the development of PKD (Berstein et al., 1987). Foci of tubular cell hyperplasia and micropolyp formation associated with cyst development have been reported in several forms of experimental and human PKD. However, in a study of 87 ADPKD kidneys (Au Gregoire et al., 1987), micropolyps were not seen in 8 cases despite through morphological examination. The high incidence of renal cell adenomas and carcinomas in human acquired PKD would suggest that cell proliferation plays a primary role in the development of renal cysts. However, it has been shown quantitatively that cyst-derived cells from ADPKD kidneys (Carone et al., 1989; Granot et al., 1990) or tubular cells from autosomal recessive cpk/cpk mice (Taub et al., 1990) do not exhibit accelerated growth capacities compared to normal renal epithelial cells and also that they do not possess features of transformed cells *in vitro* (Carone et al., 1989).

Recent studies suggest a role for transforming genes or oncogenes in the pathogenesis of PKD. Elevated levels of *c-fos*, *c-myc* and *c-K-ras* mRNAs have been reported in cystic kidneys of cpk mice (Cowley et al., 1991). Similarly, *C-erb B2*, a receptor protein that shares homology with epidermal growth factor-receptor (EGF-R) is amplified in certain forms of renal cystic disease (Herrera, 1991). The relationship of these findings to the pathogenesis of PKD requires further clarification.

Renal cystic changes have been reported in transgenic mice, induced by SV40, a gene active in the control of cell proliferation (McKay et al., 1987; Kelley et al., 1991; Trudel et al., 1991). These kidneys develop proliferative tubular lesions, resembling adenomas and some renal cells are transformed and grow as a continuous cell line *in vitro* (Kelley et al., 1991). Thus, the apparent cysts formed may represent a neoplastic process rather than PKD *per se*. In many forms of human and experimental PKD, progression of cysts is slow and cell proliferation is not apparent. In fact, rats treated for 30 weeks with DPT develop progressive, severe PKD with renal failure, however, there was no detectable increase in the growth rate of epithelial cells lining cysts as determined by *in vivo* thymidine labeling (Carone et al., 1987a,b). During the rapid induction of PKD in rats treated with phenol-II, tubular cell proliferation determined by thymidine labeling did not correlate with the development of PKD. Significant tubular cell proliferation was seen after the onset of cystic changes, however, the cell proliferation decreased with time, whereas, the cyst formation progressed (Carone et al., 1992). Collectively, these observations do not provide sufficient evidence to support the hypothesis that cell division is a primary event in the pathogenesis of PKD.

Extracellular matrix (ECM) alterations

Several studies on human and experimental forms of PKD suggest that an abnormal matrix plays a key role in the development of tubular cysts. In cell-matrix interactions, there is a reciprocal dependency between the cell and its ECM. The tubular epithelial cells may be primarily responsible for the synthesis/degradation of ECM components, and the composition of the ECM, in turn, plays a regulatory role in cell mobiility, shape, differentiation, growth and specific gene expression (Hay, 1984; Frjita et al., 1986).

Altered cell-BM interactions may be central to the pathogenesis in some forms of PKD. In DPT-induced PKD in rats, the BMs lining cystic tubules are thickened, and have a loss of staining with ruthenium red, a cationic dye characteristically binding to the proteoglycans (Kanwar and Carone, 1984). Analysis of isolated, purified tubular basement membrane (TBM), revealed an increased content of low molecular weight glycoproteins, fibronectin and type-I collagen, but a normal content of laminin, entactin and type-IV collagen (Butkowski et al., 1985; Carone et al., 1987a,b). By immunohistochemistry, compared to controls, ECM of cysts showed uneven staining for type-IV collagen and laminin, weak or absent staining for heparan sulfate-proteoglycans (HS-PG) and intense staining for

fibronectin (Carone et al., 1988). DPT induced a marked reduction in the *de novo* synthesis of PGs, an increase in chondroitin sulfate-PGs compared to HS-PGs and an apparent reduction in their sulfation in the Golgi saccules (Lelongt et al., 1988).

In an autosomal recessive murine (cpk/cpk) model of PKD, mRNA expression of BM components was found to be altered (Ebihara et al., 1988). At an early stage, expression was reduced, while at a later stage, the messages were abnormally high, which may be related to the compensatory synthesis of BM components due to rapid cyst enlargement. These alterations, presumably, were related to the changes in the mRNA expression of the interstitial cells, as elucidated by *in situ* hybridization studies with cRNA probes generated from the nucleotide sequences of alpha-1 chain of type-IV collagen. Similar altered BM protein biosynthesis was found in the primary cultures of cpk/cpk mouse kidney, suggesting that there is an intrinsic cellular defect which is not related to systemic factors (Taub et al., 1990). Also, the findings of reduced mRNA levels of specific cell adhesion molecules in this model (Rocco et al., 1992), reinforces the concept that the aberrant cell-cell and cell-matrix interactions may ultimately be responsible for cytogenesis of the tubules.

In PKD induced by methylprednisone in the rabbit, there was a definitive correlation between the BM alterations and the development and regression of tubular cysts (Ojeda, 1990). Recently, such basement membrane alterations have been reported in a hereditary model of slowly progressive PKD in mice resembling ADPKD (Crowley et al., 1993).

In human ADPKD, BMs lining cysts are greatly thickened and laminated ultrastructurally (Cuppage et al., 1980) and immunohistochemical studies reveal a loss of reactivity to anti-HS-PG in the basal lamina, and a markedly enhanced interstitial reactivity to anti-fibronectin (Carone et al., 1988). Furthermore, ^{35}S-labeling studies revealed decreased synthesis and altered processing of sulfated-glycoproteins by the Golgi complex by ADPKD cells (Liu et al., 1992; Carone et al., 1993). Taken together, the above observations suggest that the alterations in the cell-matrix interactions may contribute to the development of PKD. In support of evidence for the concept that PKD is a primary ECM disorder of extracellular matrix is the findings of common connective tissue anomalies affecting heart valves, cerebral arteries and other organs, such as liver.

Cell undifferentiation and polarity

Several studies suggest that PKD is associated with a developmental arrest or undifferentiation of tubular cells. Polarity is essential for the structural and functional integrity in renal tubular epithelial cells (Rodriguez-Boulan and Nelson, 1989; Molitoris and Nelson, 1990). In differentiated renal epithelia, Na-K-ATPase, the membrane protein vital for tubular reabsorption of sodium, is located in the basal and lateral (B/L) membranes. During development of the renal tubular epithelium, Na-K-ATPase is initially restricted to the apical and lateral membranes, later to the lateral membranes and finally with further differentiation, to the B/L membranes (Minuth et al., 1987; Avner et al., 1992). In human and experimental PKD, Na-K-ATPase has been localized to apical or apical/lateral cell membranes, and it has been postulated that net basal to apical transport of fluid across the epithelium of cystic tubules has an important role in the development and progression of PKD (Wilson and Hreniuk, 1987; Avner et al., 1992). In murine congenital PKD, Na-K-ATPase was localized only to B/L membranes both in non-cystic and cystic proximal tubules (Avner et al., 1992). On the other hand, in cystic collecting tubules, Na-K-ATPase was localized to apical and lateral cell membranes of some, but not all cysts, and its immunoreactivity with the apical domains decreased appreciably with successive developmental stages. In a drug-induced model of PKD, we found that altered localization of Na-K-ATPase in cells lining cysts was detected after the cystic transformation of collecting tubules and rarely was localized to apical cell membranes (Carone et al., 1992). Thus, in these two experimental models of PKD, abnormal localization of Na-K-ATPase does not correlate precisely with the formation and maintenance of all cystic tubules. Moreover, in human autosomal dominant and acquired PKD, the cells lining the cysts seem to retain the ultrastructural features of polarized epithelium (Carone et al., 1994). By immunohistology, Na-K-ATPase, fodrin and ankiryn were localized primarily to basolateral membranes, and E-cadherin was assembled in the lateral membrane domains. In about 25% of the cells of the cysts, however, Na-K-ATPase was localized to the apical as well as to the basolateral membranes. Taken together, these findings suggest that the altered localization of Na-K-ATPase does not have a primary role in the pathogenesis of PKD, and that apical localization of Na-K-ATPase reflects some degree of undifferentiation in PKD cells, a feature characteristic of the early stage of nephrogenesis.

During nephrogenesis, a number of growth factors have been shown to influence the various differentiation events and biosynthesis of sulfated proteoglycans (Liu et al., 1990) in the development of the kidney. In cpk/cpk mouse there is a marked reduction in expression of epidermal growth factor (EGF) in the kidney (Gattone et al., 1990; Horikoshi et al., 1991). There is some ancillary evidence that EGF has a regulatory role in the differentiation of renal cells, so that the loss of EGF expression may contribute to an arrest in the differentiation of cells lining the cystic collecting ducts. Compatible with this, are studies on the gene expression of the sulfated glycoprotein-2 (SGP-2) in mice. The SGP-2 is expressed early in the course of nephrogenesis, and is down-regulated in normal collecting ducts but is persistently expressed at all stages in the epithelium lining cyst in cpk/cpk mice (Harding et al., 1991). These findings suggest a developmental defect and a failure of

cell differentiation in PKD.

Although a defect in protein sorting has been proposed as one of the pathogenetic mechanisms involved in ADPKD, it is possible that these alterations may be secondary to an arrest in the normal cellular differentiation. As cited above, recent work has shown that sulfated glycoproteins had a greatly delayed processing in the Golgi saccules in ADPKD cells as compared to normal kidney cells (Carone et al., 1993). However, the vesicular trafficking period between the trans Golgi network and the plasmalemma was normal for the secretion of sulfated glycoproteins to the exterior of the cell. The trans Golgi network (TGN) has been proposed as the site of protein sorting in renal epithelial cells (Griffiths and Simons, 1986). Taken together, the kinetic delay in sulfated glycoprotein processing within the TGN supports the hypothesis that a defect in protein sorting may contribute to the pathogenesis of ADPKD.

In a recent report, bcl-2-deficient mice demonstrated fulminant lymphoid apoptosis and PKD with renal failure (Veis et al., 1993). Bcl-2 is a unique oncogene due to its death suppressor activity and intracellular localization. Apoptosis is an energy dependent and actively regulated process of programmed cell death with characteristic fragmentation of genomic DNA into a large number of nucleosome length DNA fragments (DNA laddering). In another recent report, characteristic DNA laddering was seen in genomic DNA prepared from human and animal forms of PKD (Woo, 1993). It was concluded that apoptosis and related reduction of tubular mass leads to renal failure in PKD. These findings raise the possibility that increased oncogene expression and cell proliferation may be due to apoptosis. These findings suggest that one aspect of the phenotype of PKD may be defective expression of bcl-2.

Acquired PKD

Acquired PKD occurs in about 80% of patient with failure of non-cystic kidneys for more than 3 years (Grantham and Levine, 1985; Matson and Cohen, 1990). It is associated with all types of underlying renal disease in patients who have undergone hemodialysis/peritoneal dialysis. However, acquired PKD has been reported in patients with renal failure who did not receive dialysis treatment, suggesting that dialysis is not a prerequisite for the development of this form of PKD. Cysts develop in proximal and distal segments of the nephron, and microdissection studies usually revealed continuity between the cysts and renal tubules. With rapid cyst growth, acquired PKD anatomically resembles ADPKD, however, the cysts have not been detected in other organs or tissues. Toxic factor(s) associated with uremia may be central to the induction of acquired PKD. The duration of uremia seems to best correlate with the prevalence of this disorder, and the cystic disease regresses following renal transplantation and correction of the uremic state (Ishikawa et al., 1983). In addition, there is an extremely high incidence of neoplasms in acquired PKD; about 50% develop multiple adenomas and about 5% develop renal carcinomas. These neoplasms do not regress after renal transplantation and, moreover, their occurrence have been reported in renal transplant recipients. These findings suggest the induction of two separate tubular abnormalities in end stage noncystic kidneys, namely reversible cyst formation and irreversible neoplasia, which are, very likely, cuased by independent pathogenetic mechanisms.

Molecular biology

In 1985, it was reported that an ADPKD gene (PKD1) was linked to the alpha globin gene locus on the short arm of chromosome 16 which is the site of about 95% of disease mutation (Reeders et al., 1985). Recent linkage studies, indicate that ADPKD can be caused by mutations is a second gene (PKD2) which is not linked to the alpha globin gene cluster (Kimberling et al., 1988; Romero et al., 1988). The disease in families carrying PKD2 apparently has a relatively more benign course (Gabow, 1990). The locus of PKD2 is unknown - it is not linked to the alpha-globin complex on chromosome 16. These findings suggest that the defective gene may be translocated to another chromosomal site or that more than one gene defect can induce ADPKD. In view of this apparent genetic heterogeneity, linkage testing in patients at risk for PKD must be utilized with great caution. Efforts are underway to isolate, clone and sequence the PKD1 gene. Hopefully, cloning and sequencing of the PKD gene will offer some insights into the nature of the disorder.

Unfortunately, the reverse genetic analysis does not offer any clue as to the nature of the gene defect and pathogenesis of PKD. For example, none of the ECM proteins map to chromosome 16. This suggests, that the described alterations in the ECM are not directly related to a mutation in a gene coding for the currently known ECM components. Further characterization of the ADPKD phenotype may aid in the exploration to identify the gene or gene products and ultimately in assigning the defined functions to that particular gene.

A central mechanism for cytogenesis

Based on the considerations of the data cited above it appears that matrix changes and dedifferentiation of epithelial cells are required for the cyst formation. Recent studies, in a wide variety of culture systems, have shown that the terminally differentiated cells can undergo a change in their phenotype depending upon the *in vitro* growth conditions and experimental manipulations (Klinken et al., 1988; Zuk et al., 1989; Reichmann et al., 1992). Taken together, these data suggests that the alterations in growth factor and receptor expression, oncogene activity and ECM: integrin interactions can modulate the differentiated phenotype of renal epithelial cells. Common to all forms of PKD, one can propose that cell-

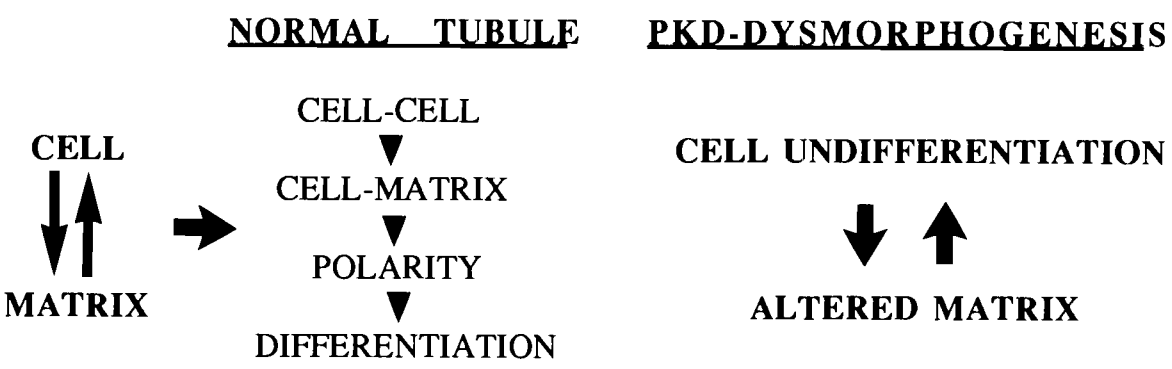

Fig. 4. Cell-matrix interactions in normal and cystic tubules: see text for details.

matrix interactions and epithelial undifferentiation are a prerequisite for cyst formation (Fig. 4). Cell-matrix interactions are reciprocal: the cell has a major role in matrix synthesis and degradation while matrix composition and signaling affect cell division, motility, shape, differentiation and gene expression. Normal cell-cell and cell-matrix interaction(s); along with cell polarity and concomitant vectorial structure and function (cell differentiation) are required to establish and maintain normal tubular morphology. The following cell and matrix alterations have been described in the various types or PKD: impaired cell differentiation; oncogene expression; biosynthesis and post-translational modification of glycoproteins; Golgi processing of glycoproteins; localization of cell membrane proteins; secretion of water and solutes; expression of cell adhesion molecules; chemical and structural composition of the matrix and impaired tubulogenesis. The primary event(s) causing PKD is unknown and the principal phenotypic features in the various forms of PKD remain to be determined. Under normal conditions, the dynamic turnover of tubular epithelia and matrices are tightly regulated to maintain tubular morphology (Fig. 4). The basic defect in PKD is tubular dysmorphogenesis which may be primarily due to a cellular process or matrix alteration with secondary cellular effects including un-differentiation. Thus, it is likely that scientific investigation of the pathogenesis of PKD will yield fundamental insights into the nature of epithelial and matrix biogenesis.

It has recently been shown that the PKD1 gene which accounts for about 85% of ADPKD encodes a 14 kb transcript (Harris et al., 1994). Partial sequence analysis of this transcript reveals that it encodes a novel protein whose function is unknown at present. The large size of the transcript indicates that it encodes a high molecular weight protein of circa 500,000. The large size of the APKD 1 gene product and the occurrence of structural defects in tissues not lined by epithelia (heart valve, cerebral artery, etc.) suggests a defect in a matrix protein. If this proves to be the case, then ADPKD could be due to altered synthesis, assembly or degradation of one or more matrix components. Altered Golgi function and impaired cell differentiation could be due to faulty matrix-cell interaction.

Conclusion

PKD is the result of disturbances in the factor(s) that regulate and maintain the normal morphological features of the renal tubules. Future research into the pathogenesis of PKD would provide basic knowledge and further enhance our understanding of the various pathogenetic mechanisms related to the renal epithelium: matrix biology.

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