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Invited Review

Gene expression and cell turnover in human renal dysplasia

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Summary. Kidney malformations are common causes of chronic renal failure in children. Dysplastic kidneys represent a unique model of perturbed **epithelial**-mesenchymal interaction which leads to the formation of malformed branching tubules surrounded by **un**-differentiated and metaplastic mesenchymal cells. We have found that human dysplastic epithelia express PAX2 (a transcription factor), BCL2 (a survival factor) and galectin-3 (a cell **adhesion/signaling** molecule). These genes are implicated in oncogenesis and their persistent expression may drive proliferation of dysplastic cysts, hence explaining the massive growth of some multicystic dysplastic kidneys. We have also detected prominent apoptosis in undifferentiated tissues around dysplastic epithelia, and this may provide a potential mechanism for the well-documented regression of dysplastic kidneys. Hence, although these kidneys may not have any excretory function, it is incorrect to consider them as 'end stage organs' because they are highly active in terms of cell turnover and gene expression; furthermore, these processes can be correlated with patterns of tissue growth and involution. Further elucidation of 'molecular lesions' in renal malformations may lead to novel therapies to enhance the differentiation of progenitor cells.

Key words: Apoptosis, **BCL2,** Cyst epithelium, Galectin-3, **PAX2,** Proliferation, **WT1**

Introduction

Kidney malformations are the commonest causes of chronic renal failure in young children (Warady et al., 1997) and these lesions are increasingly diagnosed in the fetal period by ultrasound imaging (Noia et al., 1996). Several histopathological categories of renal malformations are well-recognised in clinical practice (Risdon and Woolf, **1998a):** in 'renal agenesis' the kidney is absent; in 'renal dysplasia' the organ contains poorly differentiated and metaplastic tissue (i.e. cartilage), and may contain massively dilated cysts in multicystic dysplastic kidneys; in 'renal hypoplasia' the organ has fewer nephrons than normal; in 'vesicoureteric reflux' urine passes retrogradely from the urinary bladder into the ureter and into a kidney which may itself be malformed. These congenital anomalies can occur in isolation or as part of a multiorgan syndrome and can be sporadic or inherited (Woolf and **Winyard,** 1998). Many of the malformations are associated with obstruction of the urinary tracts and we have shown that experimental ureteric obstruction in animals reproduces some features of human dysplasia (Attar et al., 1998). In order to attempt to understand the pathogenesis of these developmental disorders, it is necessary to understand not only the anatomy but also the cell biology and genetic control of kidney development, or nephrogenesis.

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Cell turnover and gene expression in normal nephrogenesis

The human metanephros, or precursor of the adult kidney, appears at five weeks of gestation when it consists of nephrogenic mesenchyme which condenses around the ureteric bud epithelium (Fig. **1A)** (Risdon and Woolf, **1998b).** Each tissue induces its neighbour to differentiate so that the mesenchyme forms nephrons and interstitial cells while the ureteric bud forms the branching collecting ducts as well as the urothelium of the renal pelvis and ureter. The first glomeruli form by nine weeks and nephrons continue to be generated until 34 weeks; thereafter, growth continues by modification of pre-existing nephrons. In the human metanephros, these events are not only associated with cell proliferation **(Winyard** et al., **1996a),** an obvious prerequisite for growth, but also with a tightly controlled degree of programmed cell death, or apoptosis (Fig. 2) **(Winyard** et al., **1996b).** This balance between cell proliferation and death has been postulated to regulate the number of cells within nephrons which is essential for normal **morpho**genesis. Although a low level of glomerular filtration

occurs in the fetus before birth, with fetal urine constituting the major part of amniotic fluid in the second half of gestation, kidney excretory function is not critical for fetal survival since the placenta removes circulating waste. After birth, however, infants who have major malformations of the kidneys may require dialysis and subsequent renal transplantation.

Nephrogenesis is controlled by genes which enhance or inhibit growth by affecting precursor cell survival, proliferation, differentiation and morphogenesis: these genes code for transcription factors, growth/survival factors and adhesion molecules (Woolf and Winyard, 1998). Transcription factors are proteins which bind to DNA and alter the activity of numerous other genes: hence they can be seen as molecules which 'orchestrate' normal development. As examples, at the same time that human renal mesenchymal cells begin to differentiate into nephron tubules they express a transcription factor called WT1 and then aggregate into condensates and undergo a burst of proliferation with increased expression of the PAX2 transcription factor and the BCL2 survival factor (Fig. 3) (Winyard et al., 1996a).

In the collecting duct lineage, PAX2 is detected in the branching tips of the ureteric bud where its expression correlates with markers of cell proliferation (Figs. 2C, 3A) (Winyard et al., 1996a). Additionally, we found that galectin-3, a secreted ß-galactoside binding protein, is a marker for the ureteric bud/collecting duct lineage (Winyard et al., 1997): the protein was immunolocalised in the apical domains of actively proliferating ureteric bud branch tips (Fig. 3G) but, as the lineage matured, galectin-3 was detected in the basal domain of medullary collecting ducts. Later in nephrogenesis, both proliferation and PAX2 expression are downregulated while WT1 expression becomes restricted to glomerular podocyte epithelia and galectin-3 is only expressed in collecting duct intercalated cells, where staining is cytoplasmic or nuclear (Winyard et al., 1996a, 1997).

In mice which have been genetically-engineered to lack either WT1 (Kreidberg et al., 1993) or PAX2 (Torres et al., 1995) proteins, the metanephros fails to form, while ablation of the mouse BCL2 gene leads to fulminant apoptosis and renal hypoplasia (Veis et al., 1994). Madin Darby canine kidney cells, a line derived from the collecting duct, form cysts when grown in collagen I gel, and this process in inhibited by galectin-3 which coats the basal surface of these structures (Bao and Hughes, 1995). These *in vivo* and *in vitro* animal experiments suggest that the expression of these genes may also be critical in human nephrogenesis. In the remainder of this review, we will discuss a number of

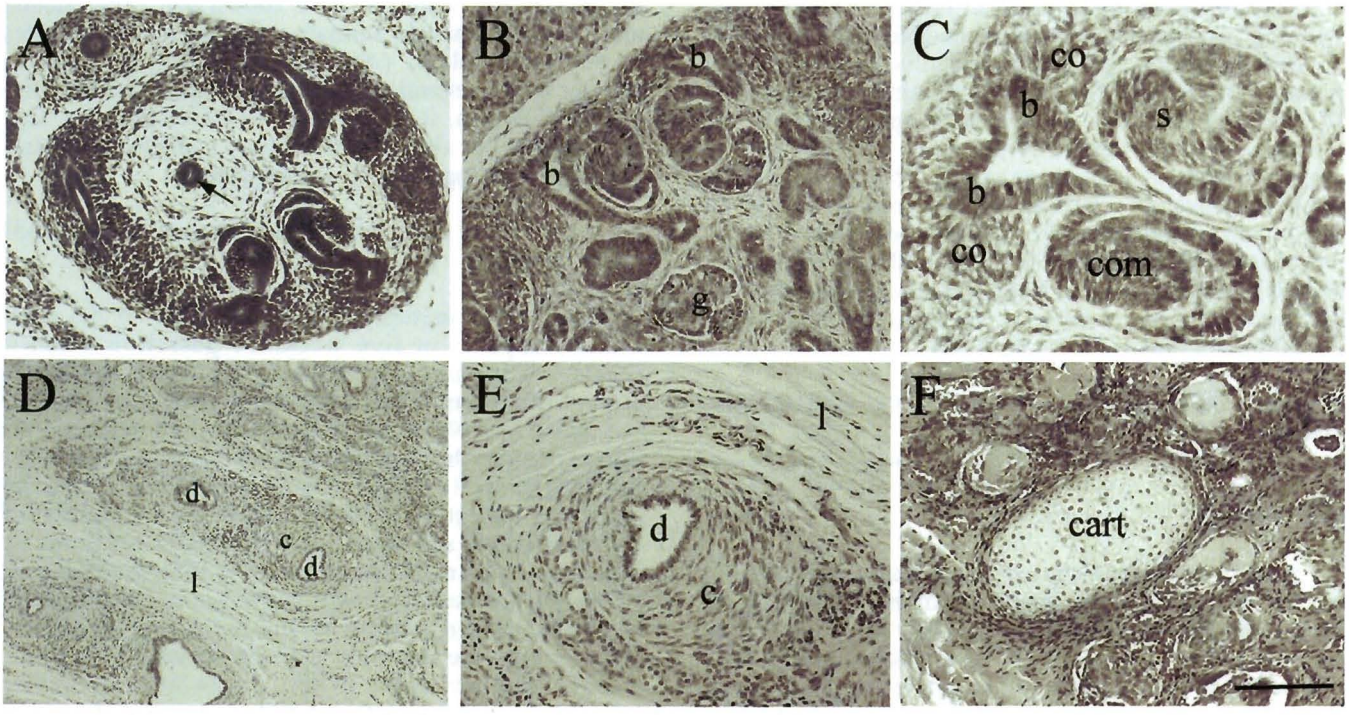

Fig. 1. Histology of normal and dysplastic renal development. Haematoxylin and eosin stained sections of developing human kidneys at 42 days (A) and 77 days (B and C) of gestation, and postnatal dysplastic kidneys (D-E). **A.** Metanephros showing the central ureteric bud (arrowed) with peripheral branches surrounded by condensing mesenchyme. **B and C** show higher power views of ureteric bud branches (b) surrounded by mesenchymal condensates (co). Early nephron precursors including comma (com) and S-shaped bodies (s) and an immature glomerulus (g) are also seen. **D and E** show dysplastic tubules (d) surrounded by closely packed cells in the fibromuscular collarettes (c) and more distant loosely packed cells (l). **F** shows metaplastic cartilage (cart). Bars: A, B, E, F, 200 μm; c, 80 μm; D, 500 μm.

Table 1. Gene expression in human dysplastic renal malformations. A summary of the current literature on sites of mRNA expression and protein distribution of potentially important molecules in human dysplastic kidneys.

Structural proteins		
Vimentin	protein	dysplastic tubules, collars and undifferentiated cells around tubules (Winyard and Woolf, 1998)
Cytokeratin	protein	dysplastic tubules and cyst epithelia (Winyard and Woolf, 1998)
α-smooth muscle actin	protein	collars around dysplastic tubules (Winyard and Woolf, 1998)
Transcription factors		
WT-1	protein	collars and undifferentiated cells around dysplastic tubules (Winyard et al., 1996a)
PAX-2	protein	dysplastic tubules and cyst epithelia (Winyard et al., 1996a)
Survival factors		
BCL-2	protein	dysplastic tubules and cyst epithelia (Winyard et al., 1996a)
Growth factors/growth factor receptors		
HGF	protein	dysplastic tubules, surrounding cells and cyst fluid (Kolatsi-Joannou et al., 1997)
MET (HGF receptor)	protein	dysplastic tubules and cyst epithelia (Kolatsi-Joannou et al., 1997)
IGF-II	mRNA	collars and cells around dysplastic tubules (Matsell et al., 1997)
	protein	cyst epithelia (Matsell et al., 1997)
IGF binding protein-2	mRNA, protein	cyst epithelia (Matsell et al., 1997)
PDGF-A	mRNA, protein	cyst epithelia and surrounding cells (Liapis et al., 1997)
TNF-α	protein	interstitial cells (Cale et al., 1998)
Cell adhesion molecules		
α1 integrin subunit	protein	cyst epithelia (Daikha-Dahmane et al., 1997)
α2 and α6 integrin subunits	protein	dysplastic tubules and cyst epithelia (Daikha-Dahmane et al., 1997)
Galectin-3	protein	apical location in dysplastic tubules and cyst epithelia (Winyard et al., 1997)
Miscellaneous		
PCNA	protein	nuclei of 10 – 50% of dysplastic tubules and cyst epithelial cells (Winyard et al., 1996a)

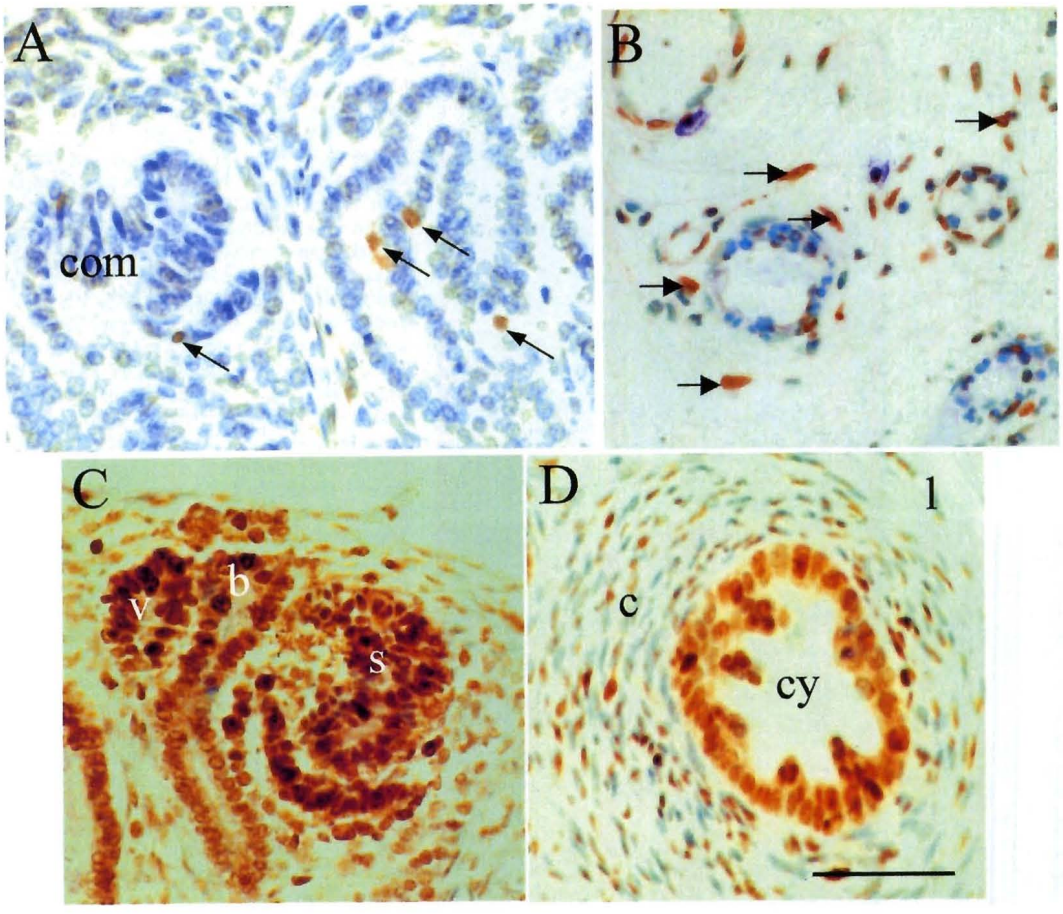

Fig. 2. Apoptosis and proliferation in normal and dysplastic renal development. A and C are sections of the nephrogenic cortex from 10 weeks of gestation, whilst B and D are dysplastic kidney sections. A and B show *in situ* end-labeling. C and D show immunohistochemistry for PCNA, a surrogate marker of proliferation. In **A** apoptosis is seen (arrows) in cells of the early nephron precursors such as comma shaped bodies (com). In **B** a high point prevalence of apoptosis is also seen in undifferentiated cells surrounding dysplastic tubules. **C** shows active proliferation in cells at the tips of the ureteric bud (b), renal vesicles (v) and S-shaped bodies. A high level of proliferation is seen in the dysplastic cyst epithelium in **D**, with a lower level in surrounding cells. Bars: 60 μm.

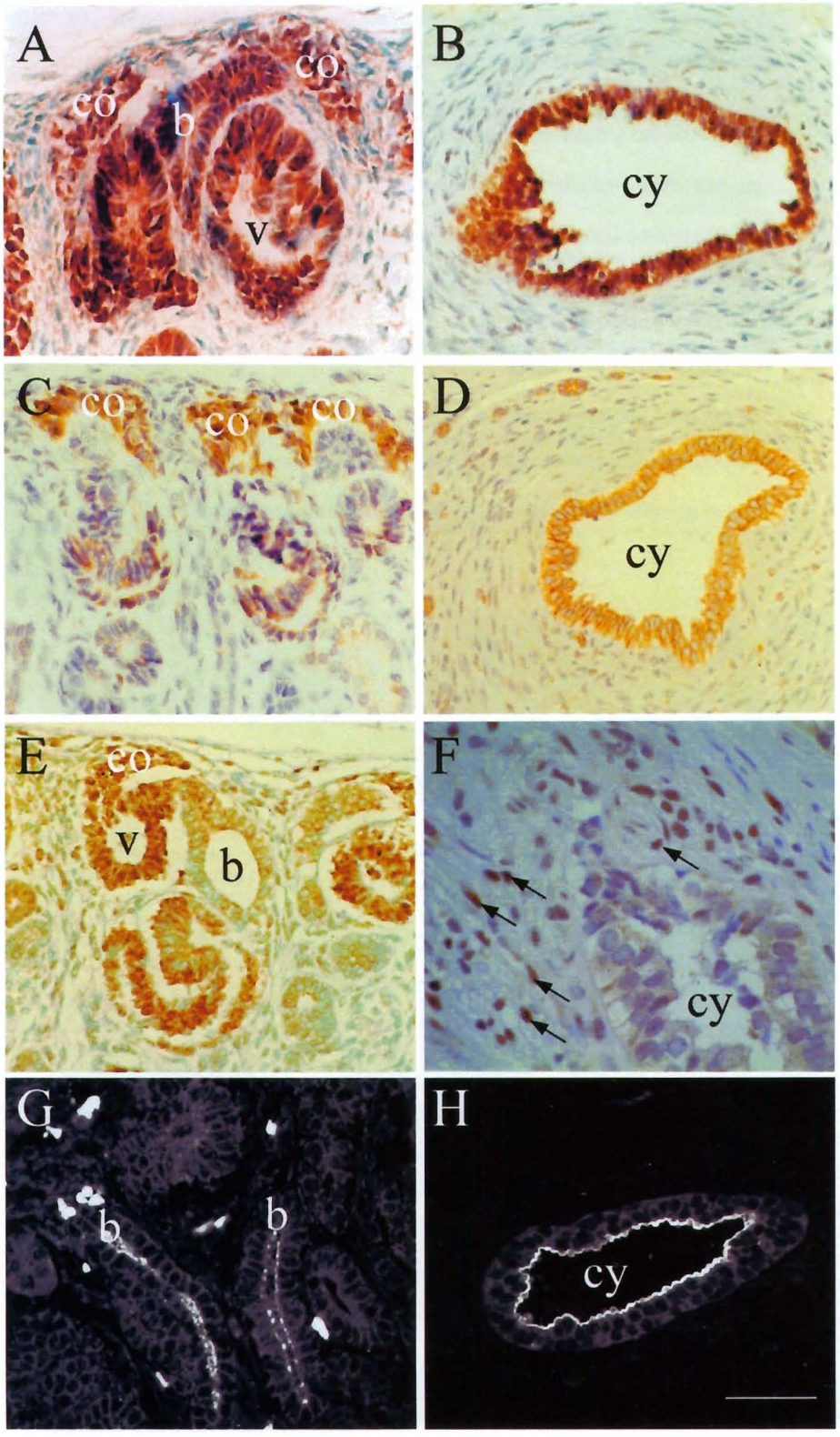

Fig. 3. Protein distribution in normal and dysplastic renal development. A, C, E and G show sections through the nephrogenic cortex of midgestation kidneys whilst B, D, F, and H show cysts in dysplastic kidneys. A and B show immunohistochemistry for PAX2, C and D for BCL2, E and F for WT1 and G and H for galectin-3. A to F are light photomicrographs counterstained with methyl green whilst G and H are confocal images. In **A** PAX2 protein is strongly expressed in the tips of the ureteric bud (b) and in mesenchymal condensates (co) and vesicles; it is not detected in the uninduced mesenchyme. Intense PAX2 expression is also seen, in **B**, in the epithelia of dysplastic cysts (cy), but surrounding undifferentiated cells are negative. **C** shows BCL-2 in the condensed mesenchyme. This is rapidly downregulated by the S-shaped body stage of nephron formation, and BCL2 is not detected in the ureteric bud. In contrast, in **D**, BCL2 is strongly expressed in the cyst epithelia, which are thought to be derived from the ureteric bud, but not in the surrounding mesenchyme-derived cells. Weak WT1 expression is seen in the condensates and renal vesicles in **E**. Increased WT1 expression is seen in glomerular podocytes (not shown; see Winyard et al., 1996a) and this protein is also detected, in **F**, in the cells surrounding dysplastic cysts. In **G and H** galectin-3 protein is seen in an apical pattern in both the developing ureteric bud and cyst epithelia. Bars A, 30 μm; B-E, G, H 50 μm; F, 20 μm.

studies which have addressed the expression of these, and other, molecules in human renal dysplasia. These findings are summarised in Table 1.

Structure of human multicystic dysplastic kidneys

The incidence of human renal dysplasia is at least 1 in 5000 and these organs constitute an interesting model of perturbed epithelial-mesenchymal interaction. These organs contain malformed branching tubules surrounded by undifferentiated and metaplastic mesenchymal cells (Fig. 1D-F). These observations are consistent with the hypothesis that dysplastic tubules represent malformed collecting ducts while the surrounding tissues represent renal mesenchyme which has failed to differentiate into nephrons (Potter, 1972; Woolf and Winyard, 1998). Furthermore, the dysplastic tubules often terminate in cysts which can be massive, especially in multicystic dysplastic kidneys, and distend the abdomen of the affected individual. Other cysts in dysplastic kidneys may arise from glomeruli, based on finding of glomerular tufts attached to cyst walls (Bernstein, 1993), and proximal nephron segments (Matsell et al., 1997).

Structural proteins in human dysplastic kidneys

The epithelia of dysplastic tubules express both cytokeratin and vimentin intermediate filaments (Fig. 4A,B) (Woolf and Winyard, 1998) whereas cystic epithelia only express cytokeratin (Fig. 4D,E), perhaps reflecting the relatively undifferentiated state of the malformed tubules. The compact collections of cells which comprise the 'collars' immediately surrounding dysplastic tubules express both vimentin and α-smooth muscle actin (Fig. 4B,C,F) (Woolf and Winyard, 1998), an observation which would be consistent with transdifferentiation of renal mesenchymal cells towards a smooth muscle phenotype. Further from the tubules and collars, there exist looser collections of undifferentiated stromal type cells, and undifferentiated

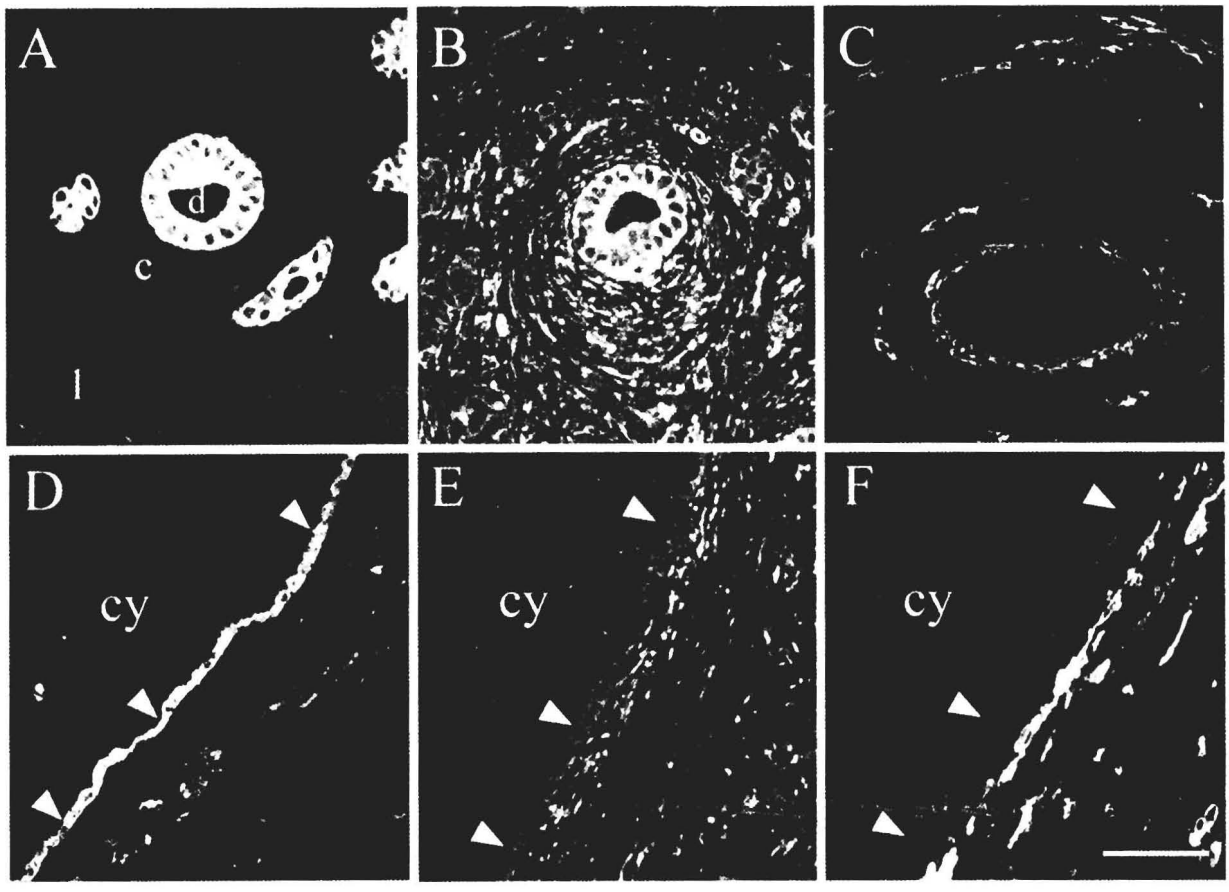

Fig. 4. Intermediate filament and alpha-smooth muscle actin staining of dysplastic tubules and cysts. Confocal laser scanning photomicrographs of fluorescently labeled sections of postnatal dysplastic kidneys. In **A to C** dysplastic tubules (d) surrounded by collarettes of closely packed cells (c) and more loosely arranged cells (l) are seen in each section, whilst the epithelia of dysplastic cysts (cy) are arrowed in **D to F** . Antibodies were directed against: A and D pan-cytokeratin, B and E vimentin and C and F α-smooth muscle actin. In **A-C** tubule epithelia are positive for cytokeratin and vimentin, whilst surrounding collarettes are positive for vimentin and α-smooth muscle actin. In **D-F** cyst epithelia are positive for cytokeratin but negative for vimentin whereas cells adjacent to the cysts are positive for vimentin and α-smooth muscle actin. Bars: 50 μm.

cells around dysplastic tubules reportedly express high levels of collagens I and III (Liapis et al.,1997).

Deregulation of cell proliferation and cell death in dysplastic kidneys

Using human fetal dysplastic kidneys which had been harvested from terminations of pregnancy, we found that dysplastic tubules and cyst epithelia expressed PAX2 protein (Fig. 3B) (Winyard et al., 1996a). Furthermore, the same epithelia displayed high rates of proliferation, as assessed by immunostaining for proliferating cell nuclear antigen (Fig. 2C), a surrogate marker of proliferation (Bravo et al., 1987). Strikingly, dysplastic kidney malformations harvested postnatally had persistent patterns of fetal gene expression (Winyard et al., 1996a,b). Since transgenic PAX2 expression causes renal cysts (Dressler et al., 1993), persistent expression in human renal epithelia may drive proliferation. Other studies confirm the association of PAX2 with pathological growth: Wilms' tumours (Eccles et al., 1992) and renal carcinomas express the gene (Gnarra and Dressler, 1995) and PAX2 transforms murine cells (Maulbecker and Gruss, 1993) and also inhibits the promoter of p53 (Stuart et al., 1995), a tumour suppresser. It is notable, however, that Wilms' tumours and carcinomas have rarely been documented to arise in human dysplastic kidneys (for review see Homsy et al., 1997). The majority of human renal dysplastic cyst epithelia showed positive immunostaining for galectin-3, with an apical localisation of protein (Fig. 3F) (Winyard et al., 1997). This observation is consistent with a ureteric bud origin for these epithelia and with the contention that they are highly undifferentiated.

Deregulation of cell death in dysplastic kidneys

In further studies, we observed that stromal cells around dysplastic kidney tubules have a high point prevalence of apoptosis (Fig. 2B) (Winyard et al., 1996b), as assessed by the presence of pyknotic nuclei stained with propidium iodide (Coles et al., 1993) and *in situ* end-labeling to detect DNA breaks (Gavrelli et al., 1992). This phenomenon was observed in pre- and postnatal specimens and may partly explaining the tendency for some of these organs to regress (Mesrobian et al., 1993; Woolf, 1995). Similar findings on cell death were made by Granata et al. (1997) in postnatal human dysplastic tissues. Other reports have indicated that these cells express the WT1 transcription factor (Winyard et al., 1996a), hence they appear to have been programmed to differentiate, but fail to express BCL2 (Winyard et al., 1996a; Granata et al., 1997), perhaps explaining their tendency to undergo apoptosis rather than differentiate into nephrons.

Growth factors expressed in dysplastic kidneys

Growth factors and their receptors play major roles in mesenchymal-epithelial inductive differentiation in the embryonic kidney (Woolf and Cale, 1997) and investigators have begun to study the expression of these genes in human renal dysplastic tissues. During normal nephrogenesis, hepatocyte growth factor (HGF) is secreted by renal mesenchymal cells and causes ureteric bud growth after signaling through the MET receptor tyrosine kinase (Woolf et al., 1995). Kolatsi-Joannou et al. (1997) found that dysplastic tubule and cyst epithelia expressed MET while immunoreactivity for the ligand was detected in surrounding undifferentiated cells and in cyst lumens. Insulin-like growth factors I and II (IGF I and II) are produced by the normal metanephros and appear to be important for growth of the organ in vitro (Rogers et al., 1991). Matsell et al. (1997), using in situ hybridisation, detected high expression of IGF II in collarettes in pre- and postnatal samples, while IGF binding protein 2 mRNA was localised to cyst epithelia. Liapis et al. (1997) reported that both cyst dysplastic epithelia and surrounding undifferentiated tissues express transcripts for the fibrogenic molecule, platelet derived growth factor A. Tumour necrosis factor-α (TNF-α) is expressed by the normal murine metanephros and addition of the factor to organ culture inhibits the mesenchyme to epithelial transition necessary for nephron formation, as well as increasing apoptosis of precursor cells (Cale et al., 1998). Recently, it has been reported that immunoreactive TNF-α can be detected in the interstitial cells in human dysplastic kidneys and in fetal urine sampled from obstructed urinary tracts (Cale et al., 1999). Furthermore, macrophage infiltrates are prominent in fetal dysplastic kidneys, suggesting a potential source for this cytokine (Cale et al., 1999).

Conclusions

Collectively, these histopathological studies have illuminated the biology of human dysplastic kidneys. Multicystic dysplastic organs are not 'end stage', inactive structures but instead contain cells which are undergoing active proliferation and programmed cell death, albeit in a deregulated manner. In addition, these patterns of cell turnover can be correlated with the expression patterns of transcription factors and secreted growth factor signaling molecules. Cell proliferation, death and transcription factor gene expression are also deregulated in experimental fetal sheep kidney obstruction (Attar et al., 1998), whilst the same manoeuvre upregulates the expression of fibrogenic growth factor in fetal opossum kidneys (Liapis et al., 1994). In future, it is likely that animal models such as these will be very useful in functional studies aimed at determining the importance of these perturbations of cell biology in the genesis of human renal dysplasia.

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