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Immunohistochemical analysis on normal nephrogenesis and Wilms' tumour using monoclonal antibodies reactive with lymphohaemopoietic antigens

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Summary. Adult and fetal human kidneys were investigated for the reactvities of monoclonal antibodies, BA-1, BA-2 and BA-3 against human leukocytes. In developing metanephros, their reactivities changed reflecting the stage of nephrogenesis. Thus BA-1 stained both metanephric blastema and ureteric bud. Glomerular and proximal tubular development was characterized by the disappearance of BA-1 reactive antigen and the appearance of CALLA defined by BA-3. Immuno-electron-microscopically CALLA was solely located on the glomerular epithelial membrane and on the microvilli of the proximal tubules. BA-2 constantly stained ureteric bud-derived tissues. These observations were applied for the analysis of histogenesis of Wilms' tumour. Tumour blastema of the classical type reacted only with BA-1. Epithelial components in the classical as well as the epithelial type reacted both with BA-1 and BA-2. CALLA was only detectable in glomeruloid and the connecting tubular structures, while these were unstained by BA-1. Stromal components in the classical and the sarcomatous type did not express any of these antigens. Staining patterns were identical in surgically removed and xenotransplanted tumours. These studies establish that each component of Wilms' tumour can clearly be interpreted regarding its histogenesis and that epithelial components corresponding to proximal tubules are identified in Wilms' tumour.

Key words: Kidney embryology – Wilms' tumour – Lymphocyte – Tumour antigens – Immunoperoxidase technics

Introduction

Monoclonal antibodies raised against human leukocytes have successfully been used to understand the differentiation pathway of various types of leukocytes. Recent studies have shown that some of these antibodies detect functionally important molecules (Foon and Todd 1986). Precise localization of the antigens in the whole body has been investigated and it has been found that some of the antibodies raised against leukocytes also react with non-haematopoietic cells with remarkable specificities (Hsu and Jaffe 1984; Jones et al. 1982; Metzgar et al. 1981; Platt et al. 1983). BA-1, BA-2, and BA-3 antibodies, for example, which detect different cell surface molecules on human leukocytes (Pirruccello and LeBien 1985; Kersey et al. 1981; Ritz et al. 1980), were applied to investigate the ontogeny of human kidney by the immunofluorescence technique (Platt et al. 1983). These antigens were found to be differently expressed during metanephric development in a well-programmed manner and thus could be used as differentiation antigens for human kidney.

In this study we examine the distributions of these antigens during nephrogenesis by means of immunoperoxidase staining and immunoelectron microscopic technique. By these methods histological localization of antigen-positive cells especially their relationship to adjacent tissues as well as precise localization of the antigens within cells can be fully investigated. We also discuss the histogenesis of Wilms' tumour which has been thought to originate from the metanephric tissue, comparing the expression of these antigens in this tumour with that in human fetal kidney.

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Materials and methods

Source of tissue. Mature human renal tissues were obtained from normal portions of kidneys removed from eight patients with renal tumours. Fetal renal tissue from 6 cases were obtained from gynecosurgical abortions at various gestational stages (two abortuses each of 10, 18, and 23 weeks gestation estimated by crown-to-rump length). Twelve Wilms' tumour tissues were obtained from six surgical specimens at the time

Table 1. Histology of Wilms' tumours examined

I. Surgical specimens

Case	Age/Sex	Histology
1.	2y /F	Nephroblastic, triphasic (glomeruloid structures+)
2.	2y /F	Nephroblastic, triphasic
3.	2y /F	Nephroblastic, triphasic
4.	2y /M	Nephroblastic, triphasic
5.	1y /M	Nephroblastic, triphasic
6.	2m /M	Sarcomatous, clear cell sarcoma

II. Transplanted tumours

Tumor lines	Passage No	Histology
OW1	40	Nephroblastic, triphasic
OW2	30	Nephroblastic, triphasic
SW	45	Nephroblastic, monomorphous epithelial
SA	33	Sarcomatous, clear cell sarcoma
HO[a]	10	Sarcomatous, clear cell sarcoma
DW	31	Sarcomatous, rhabdoid tumor

[a] This transplanted tumour was obtained from case no. 6

of operation and from six serially transplanted tumours in nude mice. The histological types are indicated in Table 1, that were typed according to the criteria of the Armed Forces Institute of Pathology (Bennington and Beckwith 1975), Beckwith and Palmer (1978), and Sariola et al. (1985). So called nephroblastic types examined included seven classical triphasic types and one monomorphous epithelial type. Classical triphasic Wilms' tumours consisted of three components, which are blastemal, epithelial, and stromal components. We found no anaplasia in our cases of classical type. The monomorphous epithelial type consisted only of epithelial components. The sarcomatous types found included three clear cell sarcomas and one malignant rhabdoid tumour. The transplanted tumour, HO line, was derived from case 6. Several different parts were obtained from each of these tissues. Some parts of them were embedded in the O.C.T.-compound (Miles scientific, Naperville, USA), and stored at −80° C until use. The other parts were fixed by 4% paraformaldehyde at 4° C for 6 hours followed by differential washing in phosphate buffered saline, pH 7.4 (PBS) containing graded concentration of sucrose. The fixed tissues were frozen and stored.

Monoclonal antibodies. Mouse monoclonal antibodies used in this study were BA-1 (Hybritech, California, USA) against B-cell associated antigen (Abramson et al. 1981), BA-2 (Hybritech) against cell surface polypeptide p24 (Kersey et al. 1981), and BA-3 (Hybritech) against common ALL antigen (CALLA) (Ritz et al. 1980).

Immunoperoxidase staining. Five or more non-fixed frozen specimens of each tissues mentioned above were sectioned (4–6 microns) in a cryostat (Tissue-Tek II, Miles Scientific, Naperville, USA), placed on albumin-coated microscopic glass slides, and air-dryed for 30 min. Sections were fixed in cold 100% acetone for 10 min followed by air-drying. After washing in cold PBS, sections were reacted with appropriately diluted monoclonal antibodies in a moist chamber for 30 min at room temperature. The sections were washed in cold PBS, and were reacted with horse-raddish peroxidase (HRP)-labeled rabbit anti-mouse immunoglobulins (DAKOPATTS, Grostrup, Denmark) for 30 min at room temperature. Finally the sections were washed in cold PBS and color reaction was carried out in Karnovsky solution containing 20 mg/dl 3,3′-diaminobenzidine and 0.005% hydrogen peroxide (H_2O_2) for 2–5 min. Reaction was judged under light microscopy.

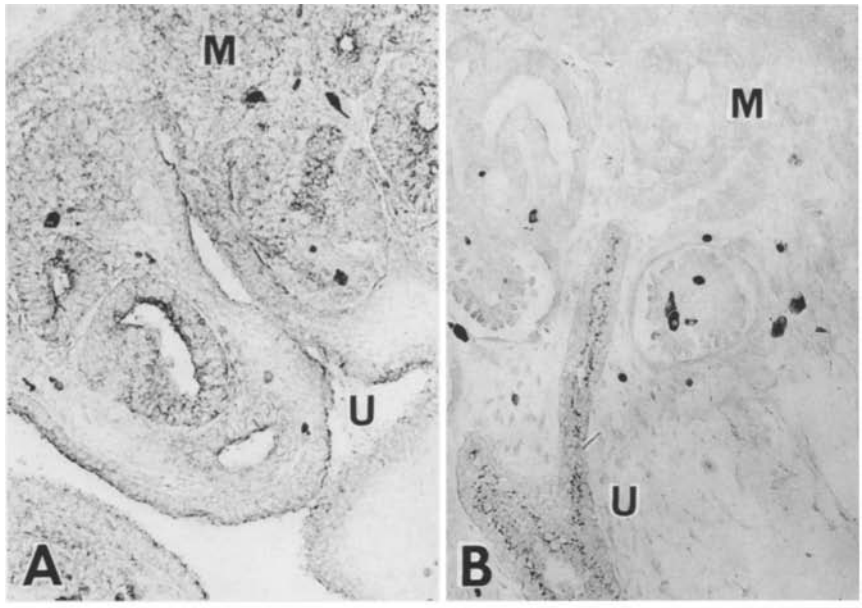
Immuno-electron microscopy. Tissue sections fixed with 4% paraformaldehyde were reacted with monoclonal antibodies and HRP-labeled antibody as mentioned above. After the reaction, sections were washed in PBS, fixed with 1% glutaraldehyde for 20 min, washed in PBS, and preincubated with incomplete Karnovsky solution without H_2O_2. Then they were incubated in Karnovsky solution for 2 min to 5 min, washed in PBS, and post-fixed again with 2% osmium tetraoxide for 30 min. After dehydration with graded ethanol series, the sections were embedded in Quetol 812 (Nissin EM, Tokyo, Japan) by inverted gelatin capsule method. Ultrathin sections were cut by ultramicrotome, and examined by electron microscope (JEM 1200EX, JEOL, Tokyo, Japan). Further details have been reported by Hata et al. (1980).

Results

The fetal kidney (metanephros) develops from two originally separate cell lineages such as the metanephric blastema and the ureteric bud (Potter 1972). The metanephric blastema cells aggregate and form a cell mass around the terminal portion of the ureteric bud (ampulla). It then becomes a spheroid, forms a vesicle, elongates to an S-shape, and finally differentiates into the nephron after capillary invasion occurs. The ureteric bud forms many branches in metanephros and differentiates into the collecting tubules.

BA-1 stained almost all immature cells derived from both the metanephric blastema and the ureteric bud (Fig. 1 A). In the metanephric tissue, blastema cell masses, spheroids, vesicles, and S-bodies at the stage when the lower limbs have not yet formed double-layered hemisphere were intensely stained by BA-1. After primitive glomeruli were formed accompanying the invasion of capillaries, glomerular epithelial cells became negative as can be seen in Fig. 2 A. With differentiation of proximal and distal tubules as a result of elongation of S-bodies, proximal tubules and Bowmann's capsules gradually lost the reactivity for BA-1 while distal tubules remained positive. As nephron developed further, BA-1 stained Henle's loop more strongly. With regard to the reactivity of BA-1 to ureteric bud, it decreased as the tissue matured into collecting tubules and eventually disappeared as could be seen in adult kidney.

BA-2 reacted only with the ureteric bud and its derivatives in primitive metanephros where capillary invasion and glomerular formation have not yet begun (Fig. 1 B). This reactivity of BA-2 to ure-



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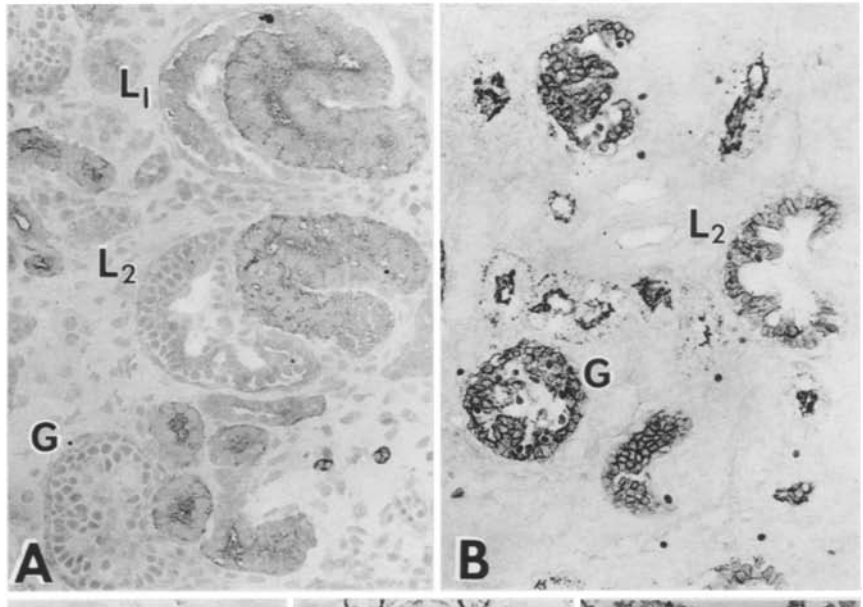

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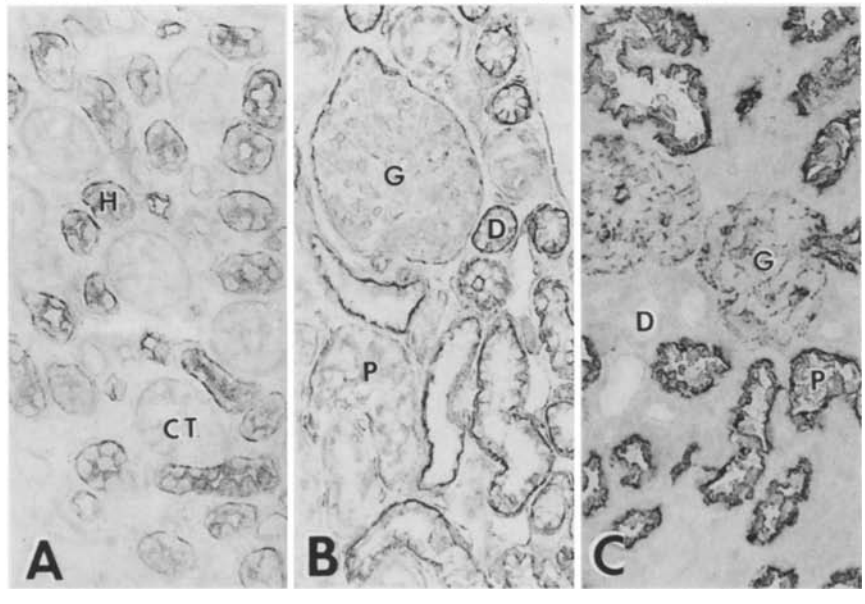

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Fig. 1 A, B. Fetal kidney (10 w). **A** BA-1 stained almost all immature cells derived from both the metanephric blastema (*M*) and the ureteric bud (*U*). ×150. **B** Different from BA-1 staining, BA-2 was reactive only with the ureteric bud (*U*). ×150

Fig. 2 A, B. Fetal kidney. **A** (23 w) Glomerular development was characterized by the disappearance of BA-1 defined antigen from lower limb of S-body. L_1; Lower limb of S-body, L_2; More differentiated lower limb than L_1, G; Glomeruloid body. ×200. **B** (18 w) Glomerular (*G*) and proximal tubular development was characterized by the appearance of CALLA detected by BA-3 on precursors of them. ×150

Fig. 3 A–C. Adult renal tissue. **A** BA-1 reacted with the Henle's loop (*H*) but not with the collecting tubules (*CT*). ×150. **B** BA-2 reacted with distal tubules (*D*). ×150. **C** CALLA was positive on proximal tubules (*P*) and glomerular epithelium (*G*). ×160

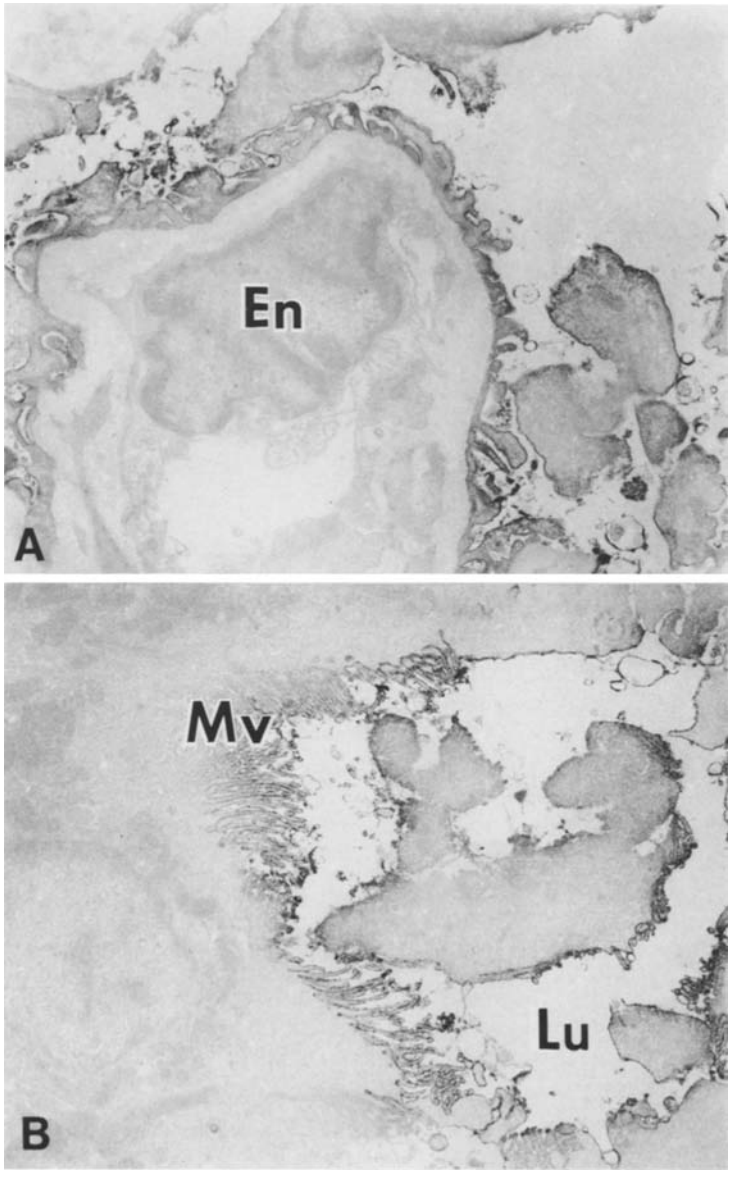


Fig. 4A, B. Adult renal tissue, Immuno-electron microscopy. **A** CALLA was positive only on the cell membrane of glomerular epithelium. En; Endothelial cell ×16000. **B** CALLA was positive on the microvilli (Mv) of proximal tubular epithelium. Lu; Lumen of proximal tubule. ×10000

teric bud-derived components which included collecting tubules, renal pelvis and ureter remained unchanged during metanephric development. BA-2 reactivity to metanephric blastema-derived tissues, however, became evident when primitive glomeruli developed. Thus, all metanephric blastemal components excluding glomerular epithelium began to express reactivity to BA-2. As the nephron developed further, BA-2 reactivity became more prominent in distal tubules than any other part of this cell lineage.

BA-3 did not stain any immature cells before glomeruli developed. As the lower limb of the S-body formed the double layered hemispheres and the capillaries invaded the lower crevice which eventually forms the vascular tuft, glomerular epithelial cells and proximal tubules gradually became positive for BA-3. Other components of fetal kidney tissue were not stained by BA-3 (Fig. 2B).

In adult tissue BA-1 stained Henle's loop intensely (Fig. 3A), but stained Bowmann's capsule, proximal tubules and distal tubules weakly. The glomerular epithelium and collecting tubules were negative. BA-2 reacted mainly with distal tubules and collecting tubules, but reacted weakly with proximal tubules and Bowmann's capsules. Glomerular epithelium and Henle's loop were almost negative (Fig. 3B).

BA-3 stained glomerular epithelium and proximal tubules intensely, and stained Bowmann's capsule faintly (Fig. 3C). The precise localization of this antigen was investigated by immuno-electron

Table 2. Reactivities of monoclonal antibodies on Wilms' tumour

Histology	(Components)	BA-1	BA-2	BA-3
Nephroblastic				
Classical	(B)	+	−	−
triphasic	(Ep)	−	−	+
	(Ed)	+	+	−
	(G)	−	−	+
	(S)	−	−	−
Epithelial monomorphous tubular		+	+	−
Sarcomatous		−	−	−

B: Blastemal component; Ep: Epithelial component showing proximal tubular differentiation; Ed: Epithelial component showing distal tubular differentiation; G: Glomeruloid structure; S: Stromal component

microscopy and it was shown that BA-3 was located on the cell membrane of glomerular epithelium (Fig. 4A) and on the microvilli of proximal tubules (Fig. 4B). Other glomerular components such as mesangial cells and capillary endothelial cells were negative.

Histologically different types of Wilms' tumours were investigated for the expression of BA-1, BA-2 and BA-3 defined antigens and the results are summarized in Table 2.

In surgically resected tumours blastemal tumour components in the classical type (Case 1–5) were found to react with BA-1 only but not with BA-2 and BA-3. Epithelial components in the classical type, however, had a different reactivity from that with blastemal components. Thus, they were reactive both with BA-1 and BA-2 (Fig. 5) but unreactive with BA-3. Of note was the expression of CALLA defined by BA-3 in the classical type of Wilms' tumour (Case 1). As can be seen in Fig. 6 glomeruloid structures and the connecting tubular structures in the classical type were positive for BA-3 while other epithelial components were completely negative for this antibody. In contrast, in the same tissue, BA-1 showed a reciprocal staining pattern. BA-1 did not react with the glomeruloid structures which were positive for BA-3 but did react with blastemal components which were negative for BA-3. Stromal components in the classical type did not express any of these antigens. Similarly none of these antigens were detectable in sarcomatous type (Case 6).

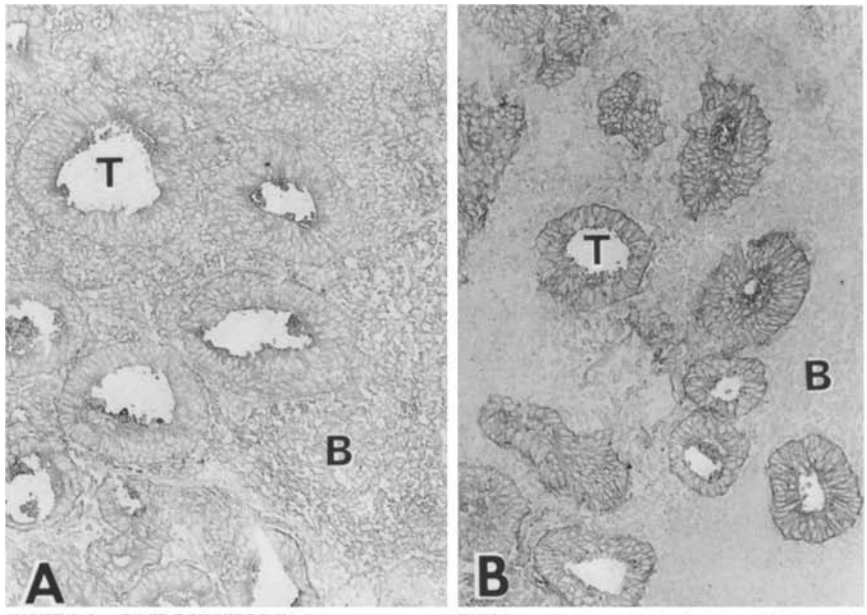
In xenotransplanted tumours identical staining patterns were obtained. Thus in triphasic classical types (OW1 and OW2) tumour blastemas were reacted with BA-1, while epithelial components were reactive both with BA-1 and BA-2. In monomorphous epithelial type (SW) tumour cells were stained by BA-1 and BA-2 showing identical staining patterns to that obtained in epithelial components in OW1 and OW2 as well as in Case 1 through 5. Neither stromal components in classical type nor sarcomatous type (SA, HO, and DW) were reactive to these antibodies.

Discussion

It is well known that antigens expressed on renal tissue components change during nephrogenesis (Ekblom et al. 1981; Platt et al. 1983). This process begins with the interaction of the metanephric blastema and the ureteric bud. In this report we demonstrate that the stage of renal ontogenesis could be shown clearly by immunohistochemical techniques using monoclonal antibodies against lymphohaemopoietic antigens.

From the results we obtained, it became obvious that the components reacting with BA-1, BA-2, and BA-3 changed according to the stage of development of the metanephros. In summary (Fig. 7), BA-1 reacted with both metanephric blastema and ureteric bud derived tissues, though its reactivity changed during differentiation. BA-2 consistently stained ureteric bud derived tissue. CALLA, the antigen recognized by BA-3, however, was expressed only on mature glomerular epithelium and on proximal tubular epithelium. These findings were confirmed by our immuno-electron microscopic procedures. CALLA was located exclusively on cell membrane of glomerular epithelium as well as on the brush border of proximal tubules. No reaction product was observed on basolateral membrane of these cells. Considering these specific localization patterns and also the fact that the antigen became evident after maturation of nephrons, CALLA may play an important role in achievement of normal glomerular and tubular function. Nevertheless, decrease of the BA-1-defined antigen during differention of nephrons may suggest that this molecule is related to early organogenesis. With regard to the molecular nature of BA-1, BA-2, and BA-3 defined antigens in kidney, limited data is available. Metzgar et al. (1981) reported CALLA in kidney defined by J5 to be a protein having molecular weight of 90000 daltons, similar if not identical to that identified in lymphoid cells. Further study for the immunochemical analysis of these antigens is now under investigation. Whatever the function of these antigens, they could clearly interpret renal ontogenesis.

These basic observations in normal human



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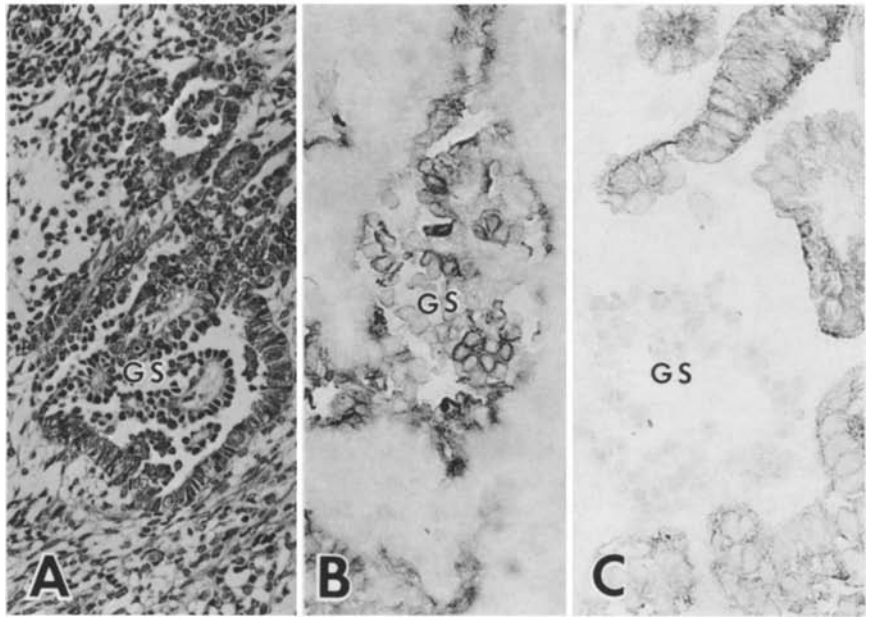

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Fig. 5A, B. Classical type of Wilms' tumour. **A** BA-1 reacted both with the blastemal component (*B*) and the tubular structures (*T*). ×120. **B** BA-2 reacted only with the tubular structures (*T*). ×120

Fig. 6A–C. Glomeruloid structure in the classical type of Wilms' tumour. **A** Hematoxylin-Eosin stain (*HE*) GS; Glomeruloid structure. ×240. **B** CALLA was positive only on the glomeruloid structure (*GS*). ×300. **C** BA-1 defined antigen was positive on tubular structures but negative on the glomeruloid structure (*GS*). ×300

nephrogenesis were applied for the analysis of classical Wilms' tumour (Table 1). This tumour has been thought to be derived from the metanephric tissue because the histology resembles that of developing metanephric tissue (Gonzalez-Crussi and Franklin 1984). Our results demonstrate that tumour blastema was stained only by BA-1, most of epithelial components by both BA-1 and -2, glomeruloid structures and connecting tubular structures by BA-3, and stromal components by none of these. The staining patterns of these antibodies on tumours were identical in tumours resected from the patients and prepared from the xenografts. These specific reactivities of BA-1, BA-2, and BA-3 in Wilms' tumour tissues clearly reflect their normal counterparts found in fetal kidney. There have been only a few reports on the histogenesis of Wilms' tumour examined by monoclonal antibodies. Borowitz et al. (1986) studied the distribution of CALLA and p24 antigen in Wilms' tumour using J5 and DU-ALL-1 antibodies, which detect the same antigens as defined by BA-3 and BA-2, respectively, and found that this tumour was positive for p24 but not for CALLA. From this result they suggested that Wilms' tumour arises from the primitive renal cells which have not yet expressed CALLA because p24 appears earlier then CALLA in normal renal ontogenesis (Platt

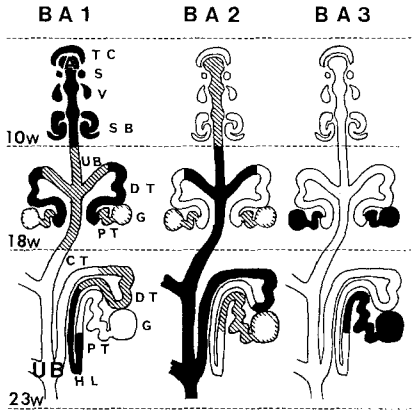

Fig. 7. Schematic reactivities of BA-1, BA-2, and BA-3 with fetal kidney. Expression of BA-1, BA-2, and BA-3 reactive antigens on different gestational stage of nephrogenesis were illustrated. Metanephric tissue: *TC*, Tissue cap; *S*, Spheroid; *V*, Vesicle; *SB*, S-body; *G*, Glomerulus; *PT*, Proximal tubules; *DT*, Distal tubules; *HL*, Henle's loop. Ureteric bud (*UB*): *A*, Ampulla; *CT*, Collecting tubules. Intensity: ■ = strong, ▨ = weak; □ = negative

et al. 1983). Yeger et al. (1985) also reported the absence of CALLA in Wilms' tumor using J5. Furthermore epithelial components were also reported to lack the characteristics of proximal tubules because the monoclonal antibody against brush border of proximal tubules failed to stain these components (Oosterwijk et al. 1986). These reports and the hypothesis that CALLA is closely related to the formation of microvilli (Metzgar et al. 1981; Platt et al. 1983) may suggest that Wilms' tumours do not contain epithelial tumour components corresponding to the proximal tubules which have microvilli and that these epithelial tumour components rather exhibit distal tubular differentiation, as judged by the identification of epithelial membrane antigen and Tamm-Horsfall protein (Yeger et al. 1986; Fleming et al. 1985). Our study, however, clearly showed the existence of CALLA, the antigen for proximal tubules and glomeruli, in Wilms' tumour which formed glomeruloid structure. CALLA could only be detected in glomeruloid structure and in the connecting tubular structure scattered in CALLA-negative epithelial and blastemal tumour cells. In contrast, these CALLA-positive glomeruloid structures were BA-1 nonreactive while this antibody stained the majority of epithelial and blastemal components. This is concordant with the observation obtained in developing nephrons where BA-1 reactivity disappeared in glomeruli when they developed accompanying the aquisition of CALLA. Consistant with this, the existence of epithelial tumour components corresponding to the proximal tubules in Wilms' tumour has been reported by using the antiserum raised against proximal tubular brush border antigen (Wallace and Nairn 1972) and by monoclonal antibodies against 1-3-Fucosyl N-acetyl lactosamine (Fleming and Brown 1987). Thus it is now very clear that Wilms' tumours do contain metanephric tissues corresponding to the proximal tubules and glomeruli which can be demonstrated both by histological examination and by immunohistochemical methods. These observations strongly suggest that although Wilms' tumour shows a variety of histological appearances, a differentiation mechanism, comparable with that involved in normal nephrogenesis, is conserved in tumour cells which controls the expression of antigens as well as the formation of functional structure. Similar observation in Wilms' tumor was very recently reported by Fleming and Symes (1987).

The results described in this study establish that monoclonal antibodies have value in the analysis of the histogenesis of Wilms' tumour. Comparing normal nephrogenesis and that of Wilms' tumour may be useful in studying the cellular differentiation mechanism involved in the development of human kidney. Furthermore Wilms' tumour xenotransplanted to nude mice is an excellent system to study such a differentiation mechanism; the differentiating capability of human tumours is well maintained in the system.

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