

Immunomorphological characteristics of renal cell carcinoma

J. Markovic-Lipkovski¹, D. Brasanac¹, V. Todorovic¹, C.A. Müller² and G.A. Müller³

¹Institute of Pathology, University of Belgrade, Yugoslavia, ²Medical University Clinic, Section of Transplantation-immunology and Immunohematology, Eberhard-Karls University of Tübingen, Germany and ³Centre of Internal Medicine, Department of Nephrology and Rheumatology, Georg-August University, Göttingen, Germany

Summary. Immunomorphological characteristics of 27 renal cell carcinoma (RCC): 18 clear cell, 6 granular (chromophilic), 2 chromophobe, 1 spindle cell (sarcomatoid) as well as of 1 oncocytoma, were analyzed. The investigation was performed on cryostat sections by immunoperoxidase technique applying a panel of monoclonal antibodies which defined: proximal (TNE3, TN5, 5D9) and distal (TN8, TN9, 7C2) tubular antigens; intercellular adhesion molecule 1 (ICAM1); HLA class II (-DQ, -DR and -DP) antigens, intermediary filaments (cytokeratin and vimentin); and antigens on tumour infiltrating mononuclear leucocytes (TT1, TT2 and LeuM3 for CD4, CD8 and CD14 antigens, respectively). All RCC with exception of chromophobe co-expressed cytokeratin and vimentin. In addition, they were usually positive for all proximal and two distal tubular markers (TN8, TN9) indicating primitive cells which could differentiate into the epithelium of both parts of tubule system as the most probable originators of in RCC. Almost all RCC but the chromophobe aberrantly expressed HLA class II antigens which great variability from case to case. The presence of HLA-DR antigens was more intensive and widespread than of HLA-DQ and -DP antigens. Expression of ICAM1 mostly correlated with presence of HLA class II antigens, particularly with -DR on tumour cells of RCC. HLA-DR antigen expression was always more prominent than mononuclear cell infiltrate (among which macrophages prevailed over T cells) which could suggest that increased histocompatibility antigen expression precedes mononuclear cell influx.

In contrast to all other RCC, chromophobe tumours had quite distinct features revealing the most intense reaction with 7C2 (MAb that produced the weakest reaction with other tumour types), absence of vimentin and very weak reaction with antibodies for HLA class II Ag and ICAM1. Since oncocytoma has similar immuno-

histological properties it could be supposed that both tumours have common histogenesis.

Key words: Renal cell carcinoma, Histogenesis, Immunomorphology

Introduction

Renal cell carcinoma (RCC) could be presented by a broad spectrum of morphological variants (Thoenes et al., 1986). Therefore, it was of particular interest to investigate immunomorphological characteristics respecting distinct cell types or degree of malignancy of RCC. In order to give more input in understanding the origin of tumour cells in different RCC, monoclonal antibodies (MAbs), which recognize antigens presented on proximal or on distal tubular epithelial cells of adult kidneys, were applied. Previous results obtained by such investigations indicated proximal tubular epithelial cells (Grone et al., 1986; Oosterwijk et al., 1986; Bander, 1987) or more primitive cells which can differentiate towards proximal as well as distal tubular epithelium (Cohen et al., 1988; Droz et al., 1990) as the most probable site of origin of RCC. On the other hand, unlike normal adult kidney which express only cytokeratin on both parts of tubule system, tumour cell coexpress cytokeratin and vimentin, as do renal tubules (Van Muijen et al., 1987) during embryonal development. Recently, Thoenes et al. (1986) defined chromophobe type of RCC which expresses cytokeratin without concomitant vimentin expression (Pitz et al., 1987). In the present study further immunomorphological characteristics of this type of RCC were analyzed.

Controversial results have been published about presence of HLA class II antigens in RCC: from complete absence of those antigens on tumour cells (Droz et al., 1990), or their presence on a great number of RCC (Tomita et al., 1990a,b), to strict correlation between HLA class II antigen expression and degree of malignancy (Banner et al., 1990). Immunophenotyping

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of tumour infiltrating cells also gave inconsistent results: it revealed predominance of macrophages by some authors (Heinemann et al., 1987) or T lymphocytes by others (Banner et al., 1990; Tomita et al., 1990) with dominance of CD4+ or CD8+ cells.

All these, sometimes contradictory, results encouraged us to investigate immunophenotype of various types of RCC considering their possible site of origin, expression of intermediate filaments, ICAM1 and histocompatibility antigens, and also to characterize mononuclear leucocyte infiltrate.

Materials and methods

Renal Tissues

Kidney tissue was obtained from explanted kidneys with 27 RCC and 1 oncocytoma (Table 1). For comparison normal renal tissue was available from biopsies of 15 kidney grafts prior to transplantation. One part of each renal specimen was processed routinely for light-microscopical analysis. The other part of the kidney samples was put into cell culture medium (RPMI 1640, GIBCO-Europe, Karlsruhe, FRG) immediately after removal, snap frozen and stored in liquid nitrogen. Five µm thick frozen sections cut from each tissue were fixed in acetone for ten minutes after lyophilization for two hours and used for immunostaining.

Monoclonal antibodies

MAbs which defined some proximal and distal tubular antigens, HLA-class II antigens and intercellular adhesion molecule 1 (ICAM1), mononuclear leucocytes, as well as cytokeratin and vimentin were used in the present study.

For renal tubular antigens MAbs produced in our laboratory were applied (Müller and Müller, 1983): TN3, TN4 and 5D9 reacting mainly with proximal tubular antigens and MAbs TN8 TN9 and 7C2 reacting with distal tubular antigens of normal control kidneys (Müller et al., 1988; Markovic-Lipkovski et al., 1991). Monomorphic MAbs were applied to detect the expression of different HLA-class II antigens: Tü22 (anti-DQ), Tü34 (anti-DR) and B7/21 (anti-DP) (Ziegler and Milstein, 1979). In addition, a MAb specific for ICAM1 (CD54) (Rothlein et al., 1986) (Immunotech S.A.) was used. Identification of mononuclear leucocytes in tumor tissue was performed by using MAbs directed against surface antigens specific for T-/B-lymphocytes and macrophages as described previously (Markovic-Lipkovski et al., 1990). Intermediate filament polypeptides were identified by MAbs for cytokeratin and vimentin (DAKOPATTS). All specimens were stained with the MAb Wg/32.HL (anti HLA-ABC heavy chain) (Barnstable et al., 1978) as positive control and with the MAb W6/32.HK (inactive variant of W6/32.HL) (Ziegler and Milstein, 1979) as a negative control to assess nonspecific staining.

Table 1. Grading, staging and histomorphology of RCC.

TUMOR TYPE	CASE No.	GRADING	STAGING	HISTOMORPHOLOGY
<i>Clear</i>	1	I	T1, Nx, Mx	Solid
	2	I	T2, N0, Mx	Solid
	3	I	T1, N0, Mx	Solid
	4	I	T2, N0, M0	Solid
	5	I	T2, Nx, Mx	Solid
	6	II	T2, Nx, Mx	Tubular
	7	II	T3, Nx, Mx	Tubular
	8	II	T2, Nx, Mx	Tubular/cystic
	9	II	T2, Nx, Mx	Tubular/cystic
	10	II	T2, Nx, Mx	Tubular, papillar
	11	II		Solid
	12	II		Solid/Tubular
	13	II	T2, Nx, M1	Solid
	14	II	T2, Nx, Mx	
	15	II	T2, N0, Mx	Solid
	16	II	T2, N0, Mx	Solid/cystic
	17	II	T1, Nx, Mx	Tubular/cystic
	18			
<i>Granular</i>	1	II		Solid/tubulo-papillar
	2	II	T3b, Nx, M1	Solid
	3	II	T2, N1, Mx	Solid
	4	II		Solid/cystic
	5		T3a, Nx, Mx	Solid
	6	II	T2, Nx, Mx	Solid, cystic
<i>Chromophobe</i>	1	II	T3a, Nx, Mx	Solid
	2	II	T2, N0, Mx	Solid
<i>Sarcomatoid</i>	1	III	T4	Solid

Immunostaining

Indirect immunoperoxidase staining was performed using MAbs as the first and a peroxidase-conjugated rabbit anti-mouse immunoglobulin (DAKOPATTS, FRG) as the second antibody layer, followed by counterstaining with Mayer's haematoxylin (Müller et al., 1985). Stained sections were light-microscopically assessed by two different investigators without knowledge of the clinical or histological diagnosis. Spread and intensity of staining by MAbs was scored semiquantitatively as follows: -, no reaction; 1, reaction in individual cells; 2, reaction in small group of cells; 3, reaction in about half of cells; 4, reaction in most of the cells; a) strong staining; b) weak staining.

Results

Among 27 cases of RCC studied, 18 were composed of clear cells, 6 of granular (chromophilic), 2 of chromophobe and 1 predominantly of spindle cells (sarcomatoid type).

1. Clear cell RCC (Table 2)

Monoclonal antibodies (TN3, TN4, 5D9) raised

Table 2. Immunomorphological characteristics of clear cell RCC.

CASE No.	TN3	TN4	5D9	TN8	TN9	7C2	CK	VIM.	ICAM1	-DQ	-DP	-DR
1	4a	4a	3a	3b	4a	2b	4b	4a	2b	2a	2b	3a
2	2a	2a	3a	4a	4a	2a	4b	4a	4a	4a	3a	4a
3	4a	4a	3a	4b	4a	2a	4b	3b	3a	3a	3a	4a
4	3a	3a	4a	4b	4a	3b	3a	4a	4a	2a	2a	3a
5	2b	2a	2a	3b	4b	2b	3a	3a	2a	2a	2a	3a
6	2b	2b	2b	4b	4a	-	4a	4a	4a	1a	2a	3a
7	4a	4a	4a	4a	4a	-	4a	4a	4a	2a	2a	4a
8	2a	1b	2a	-	-	-	3b	3b	3a	2b	2b	2a
9	2a	2a	2a	3a	3a	1a	4b	4a	4b	3a	3a	4a
10	4a	4a	4b	4a	4a	3b	3a	4a	4a	2b	2a	2a
11	3b	3b	3a	1a	3a	1b	3a	4a	1a	1a	1b	2b
12	2b	3b	3a	3b	4a	2a	3b	4a	3a	2a	3a	3a
13	3b	2b	1a	3b	4a	-	2b	3b	3a	2b	2b	3b
14	4a	4a	4a	3b	3a	-	4a	4a	3a	2a	2b	3b
15	3a	3a	3a	4a	4a	3a	3b	3a	3a	3a	2a	4a
16	3a	3a	3a	3b	4a	-	4b	4a	2a	1a	3a	3a
17	3b	-	3b	-	4b	3a	3a	4a	3a	1b	-	3a
18	3a	3a	3a	4b	4b	2a	3b	4a	4b	2a	2a	3a

-: no reaction; 1: reaction in individual cells; 2: reaction in small group of cells; 3: reaction in about half of cells; 4: reaction in most cells; a: strong staining; b: weak staining; CK: cytokeratin; VIM.: vimentin.

mainly against proximal tubule antigens gave positive cytoplasmic reaction with all 18 analyzed tumours of clear cell type, except 1 case which did not react with TN4 (Table 2). Distribution and intensity of staining varied from case to case and between different MABs as well. In 2 cases one of the markers prevailed (TN3 in case No. 13 and 5D9 in case No.2). 12 tumours revealed almost identical tissue distribution and intensity of staining with all antibodies to proximal tubular antigens. The staining was predominantly cytoplasmic like with MABs for proximal tubular antigens. The most consistent staining produced TN3 MAB (Fig. 1a). Reaction with MABs which recognize mainly distal tubular antigens (TN8, TN9, 7C2) was detected in all clear cell tumours except 1 (case No. 8). Domination of TN9 was observed in 7 cases. However, 7C2 gave weaker reaction than the other two MABs in most cases (in 6 tumours there was no staining with 7C2).

Anti-cytokeratin and anti-vimentin antibodies reacted with all tumours (Table 2) usually in a similar manner (Fig. 1b). In 7 tumours reaction was more prominent with anti-vimentin antibodies and in only 1 case with MAB to cytokeratin. In the remaining 10 cases both antibodies produced almost identical tissue distribution and staining pattern.

HLA class II antigens, particularly -DQ and -DR, were present in all clear cell RCC with one exception obtained by anti HLA-DP antibody (Table 2). HLA-DR antigens were diffusely present, while expression of HLA-DP and -DQ antigens was usually confined to smaller groups of cells (Fig. 1c). In 3 cases a more prominent reaction produced anti -DQ than anti-DP MAB, while in 3 other cases the reverse relation was observed. ICAM1 was expressed in all cases, showing a reaction similar to HLA-DR antigens, which was usually more diffuse than the reaction with HLA-DP and -DQ

antigens. Interestingly, two types of staining with ICAM1 could be seen on renal tumour cells: apically (membranous) (Fig. 1d) and diffusely (cytoplasmic) (Fig. 1e).

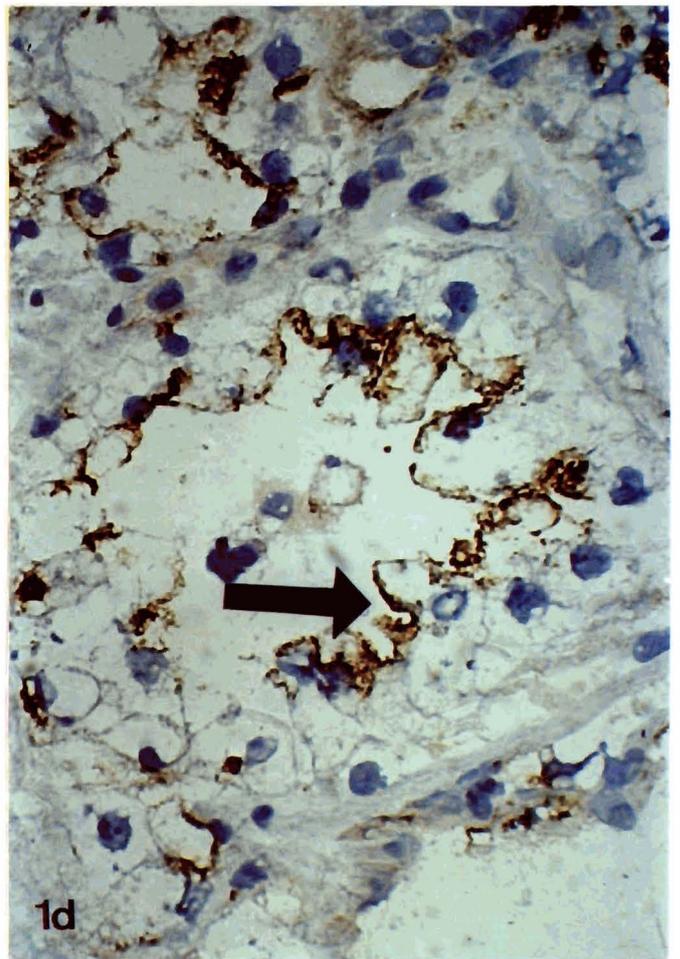
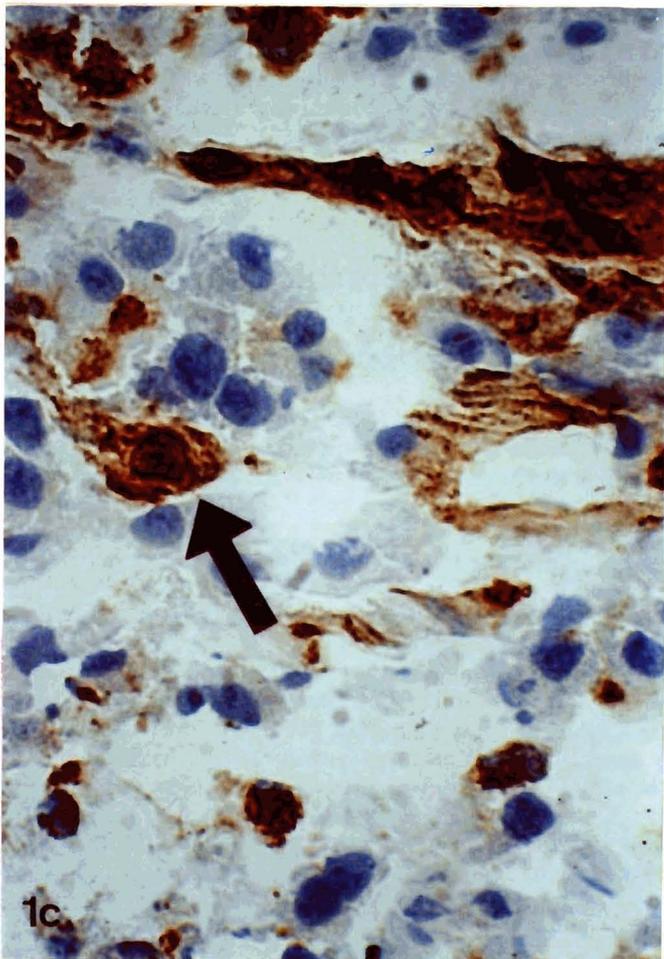
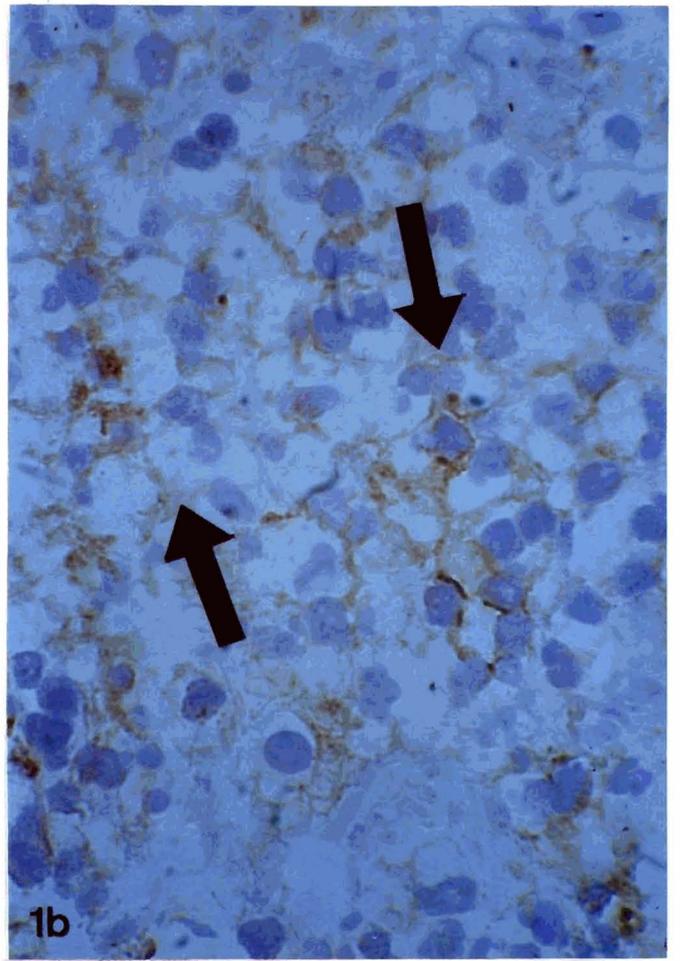
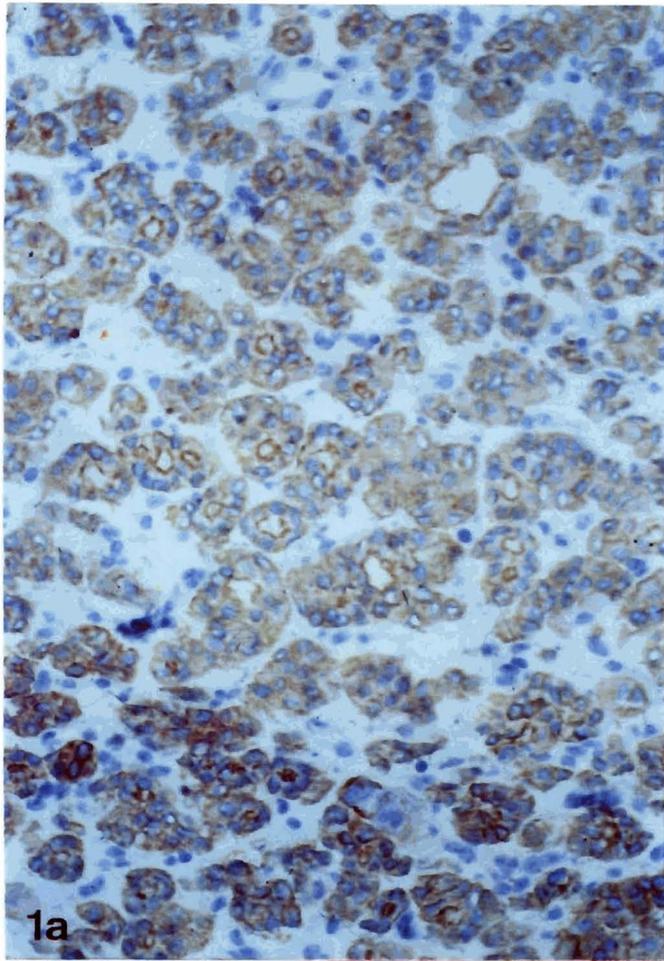
Analysis of tumour infiltrating mononuclear leucocytes revealed mild to moderate infiltration with CD14+ and CD4+ and/or CD8+ cells in 15 cases. In 12 tumours monocytes/macrophages were dominant infiltrating mononuclear leucocytes, but T-cells were never predominant. The CD4+ cells were more numerous than the CD8+ cells in one half of the cases, while the reverse ratio was observed in the other half. Although mononuclear infiltrating leucocytes expressed HLA-class II antigens to a great extent, the expression of HLA class II antigens on tumour cells was usually more widespread.

2. Granular cell RCC (Table 3)

Proximal tubule antigens were present in all cases, with variable distribution and intensity of staining and with similar staining pattern, but usually less conspicuous, than in clear cell RCC. In 1 case reaction with TN3 was more prominent than with another two MABs, while the reverse holds for 5D9 in 2 other cases (Table 3).

Distal tubule antigens were detected in all cases, with more diffuse staining with TN9 in 1 case (Fig. 2a). An inverse relation between reaction with TN8/TN9 and with 7C2 was noticed. Regarded as a group, MABs against distal tubule antigens gave a stronger reaction in 3 cases, while the reaction with antibodies that recognize proximal tubule antigens prevailed in 3 further cases.

Cytokeratin and vimentin were coexpressed in all cases, with similar distribution and intensity of staining. Predominant reaction with anti-cytokeratin antibody was

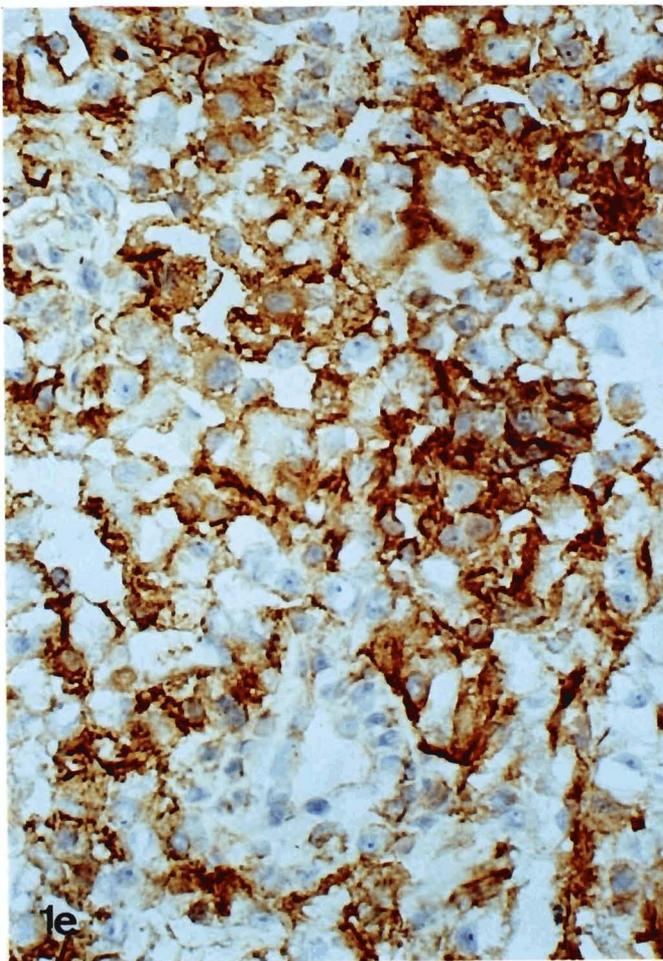


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Table 3. Immunomorphological characteristics of granular, chromophobe and sarcomatoid RCC and oncocytoma.

TUMOR TYPE	CASE No.	TN3	TN4	5D9	TN8	TN9	7C2	CK	VIM.	ICAM1	-DQ	-DP	-DR
<i>Granular</i>	1	2a	1a	1a	2a	4a	2a	4a	3a	1a	2a	2a	3a
	2	2a	2a	2a	4a	4a	1a	3a	4a	3a	3a	3a	4a
	3	4a	4b	3b	4b	4a	1a	4b	4a	4a	2a	2a	4a
	4	4a	4a	3a	4a	4a	2a	3a	3a	3a	3a	3a	4a
	5	4a	4a	4a	4a	4a	1b	4b	4a	3b	3a	2a	3a
	6	1a	1a	1a	3a	3a	2a	2a	4a	2a	4a	3b	4a
<i>Chromophobe</i>	1	1a	1a	1a	-	-	4a	4b	-	1b	1a	2a	1a
	2	2a	2b	1a	1a	1a	4a	4a	-	2a	1b	1a	2a
<i>Sarcomatoid</i>	1	1a	1a	-	3b	3b	-	1a	2a	4a	2a	3a	3a
<i>Oncocytoma</i>	1	2b	2b	2a	-	3b	4a	4b	-	2b	-	1b	2b

-: no reaction; 1: reaction in individual cells; 2: reaction in small group of cells; 3: reaction in about half of cells; 4: reaction in most cells; a: strong staining; b: weak staining; CK: cytokeratin; VIM.: vimentin.



seen in 1 case and with anti-vimentin antibody in 2 cases (Table 3).

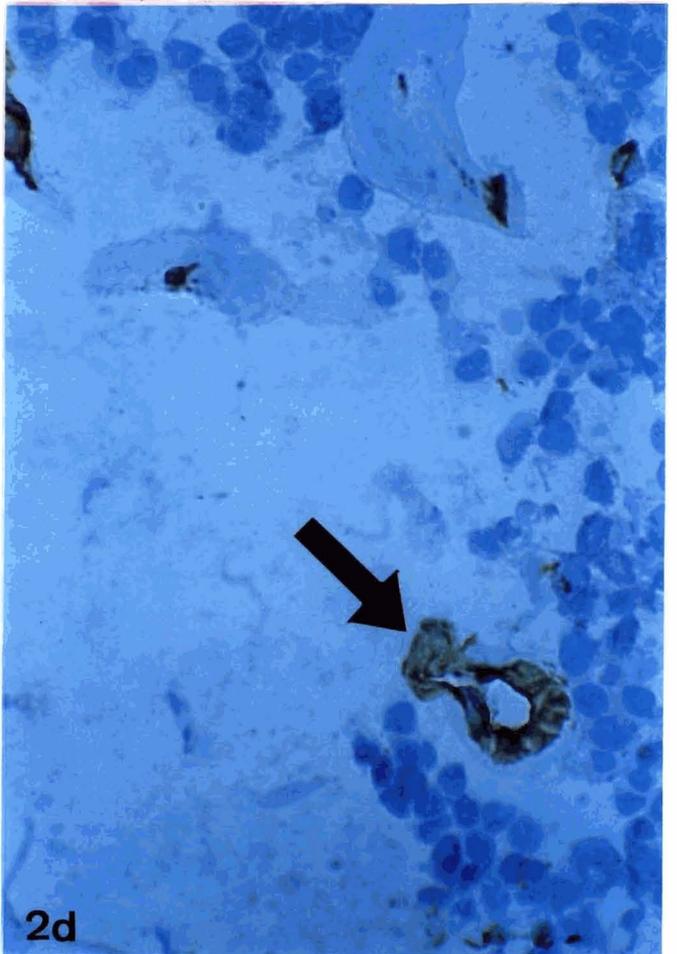
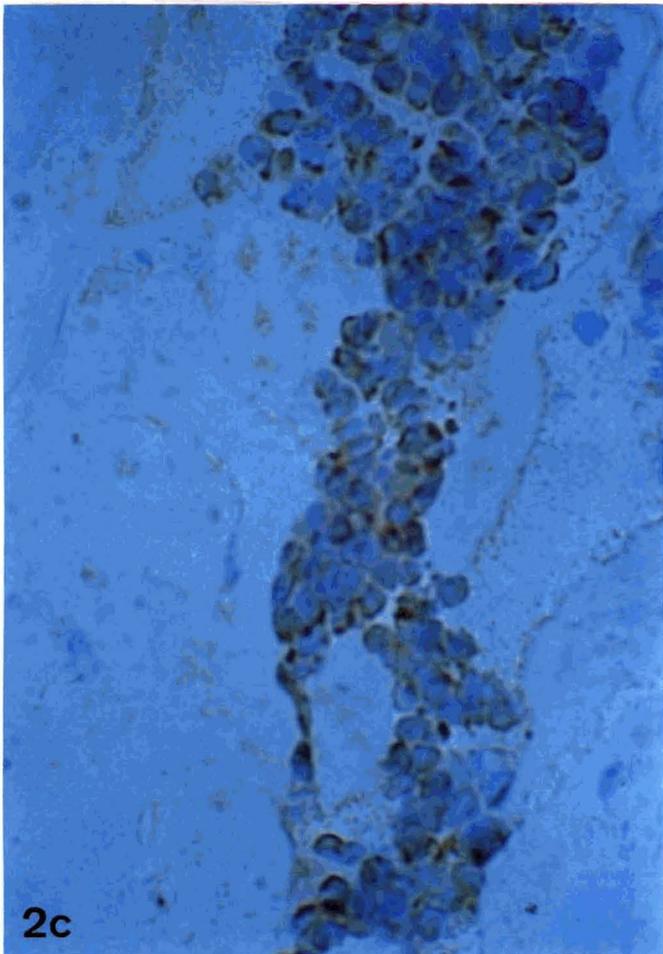
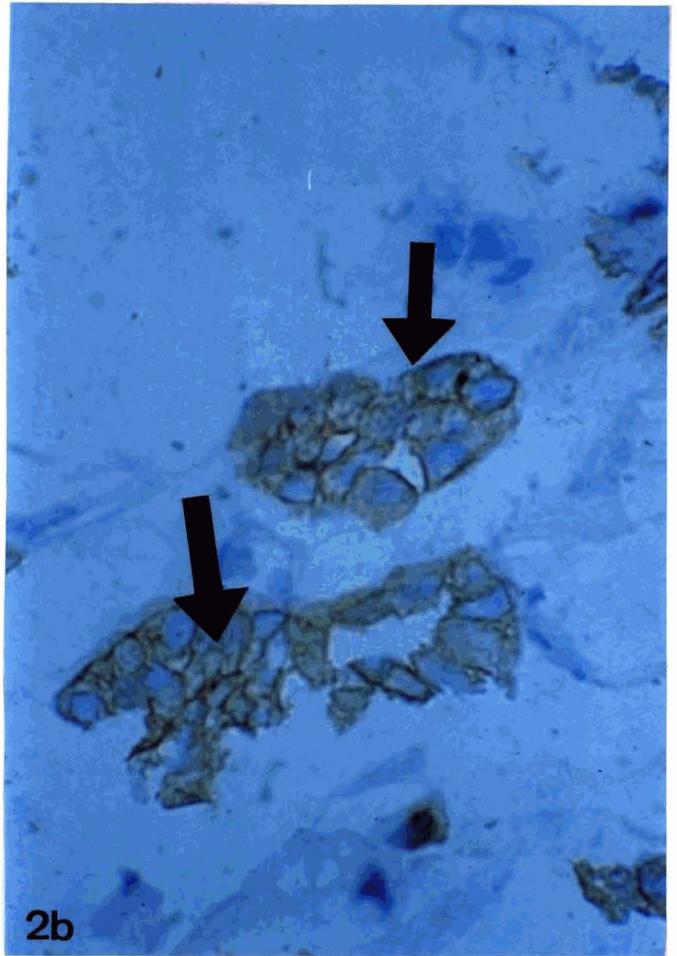
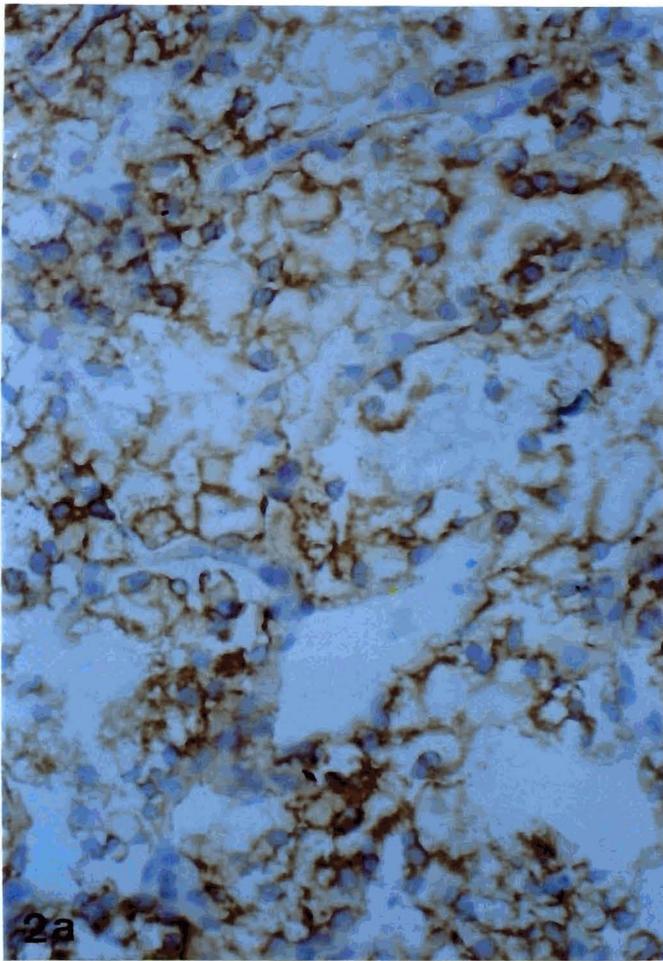
In 2 cases reaction with anti-HLA-DQ was more widespread than with anti-HLA-DP antibody. Expression of HLA-DR antigen was more prominent than that of -DP and -DQ, but less marked than among clear cell RCC. Positive staining with anti-DP and anti-DQ antibodies was usually confined to small groups of cells but with greater variations in distribution than in clear cell group of tumours (Table 3). ICAM1 revealed many cytoplasmic staining with great variations of distribution and intensity. ICAM1 expression was usually more prominent than HLA -DP/-DQ expression.

Mixed, usually scant, mononuclear cell infiltrate was present in all cases, with macrophages dominating in 3 and with lymphocytes dominating in 2 cases. Among T cells CD4+ were more numerous in 3 and CD8+ in 1 case. Distribution and intensity of staining with LeuM3, TT1 and TT2 were variable but, in general, reaction was more diffuse than in clear cell groups of tumours.

3. Chromophobe RCC (Table 3)

Two RCC were composed of chromophobe cells. Among antibodies against tubular antigens the most prominent reaction was observed with 7C2-MAB for distal tubule antigens which produced the weakest reaction in other renal cell tumours (Fig. 2b) (Table 3). Cytokeratin was diffusely present but without simultaneous expression of vimentin (Figs. 2c,d). HLA class II antigens and ICAM1 were detected in both cases of chromophobe RCC, but in a markedly more restricted manner than in the other tumour types. Mononuclear cell infiltrate was rather scant.

Fig. 1. a. Clear cell RCC. Widespread and intensive staining with antibody for proximal tubule. MAb TN3. b. Clear cell RCC. Expression of vimentin on tumour cells. MAb to vimentin. c. Clear cell RCC. HLA-DR positive tumour cells. MAb Tu 36. d. Clear cell RCC. Apically, expression of ICAM1 on tumour cells of cystic type RCC. MAb to CD54. e. Clear cell RCC. Diffuse expression of ICAM1 on tumour cells of compact type RCC. MAb to CD54. a, x 100; b, x 260; c, d and e, x 400



4. Undifferentiated (sarcomatoid) RCC (Table 3)

In 1 tumour, spindle shaped cells dominated. More diffuse reaction with MAb to distal tubule antigens (except with 7C2 which produced no reaction) was observed. Anti-cytokeratin and anti-vimentin antibodies reacted with a small number of cells. HLA class II antigens showed very strong and widespread expression (Table 3). The reaction with anti -DR was more diffuse than anti-DP/DP antibodies as in clear cell RCC. In addition, ICAM1 was also diffusely present. The majority of inflammatory cells represent monocyte/macrophages. T lymphocytes usually infiltrate RCC with slight predominance of CD4 + subject.

5. Oncocytoma (Table 3)

One case of oncocytoma showed very weak staining with all renal tubular markers with the exception of 7C2 which gave a prominent reaction (Table 3). There was no co-expression of cytokeratin and vimentin since strong presence of cytokeratin was associated with absence of vimentin. The expression of ICAM1 and HLA-DR, -DP antigens was mild and, however, HLA-DQ antigen was not detected at all. No mononuclear leucocytic infiltration was seen in tumour tissue.

Discussion

Classification of RCC is mainly based on the cytological characteristics of the tumour cells: clear cell, chromophile (basophile s. granular and eosinophile), chromophobe, spindle cell (sarcomatoid) and oncocytic (Thoenes et al., 1986). In the present study immunohistochemical investigation of the RCC with monoclonal antibodies to proximal and distal tubular antigens, cytokeratin and vimentin, HLA class II (-DR, -DQ and -DP) antigens and ICAM1 revealed that usual types of RCC, with exception of chromofobe, have similar immunomorphological characteristics.

Our results showed that RCC expressed markers present on both, proximal and distal tubular epithelial cells of adult kidneys. These antigens are present, although in different proportions, in all cases of RCC independently of cell types or degree of malignancy even on spindle cell carcinoma. These findings indicate that RCC retains tissue specific antigens during tumour progression showing the cancer's tissue of origin. However, the type of tubular epithelial cells (proximal or distal) from which the RCC originates could not be determined from our results. Previous attempts to establish origin of cells in RCC gave various results, some of them pointed to proximal tubule epithelial cells (Grone et al., 1986; Bander, 1987) while others were in

favour of primitive cells (Cohen et al., 1988; Droz et al., 1990). Tumour cells of all RCC that we studied here, with the exception of chromophobe and oncocytic, usually expressed cytokeratin and vimentin cells in different proportions. Since coexpression of cytokeratin and vimentin was observed on normal renal tubules during foetal development (Tomita et al., 1990a,b) our results support the hypothesis (Droz et al., 1990) that primitive cells, with capability to differentiate towards both proximal and distal tubule epithelium, might be the cells that originate RCC.

The application of monoclonal antibodies we investigated revealed obvious differences between RCCs of various cell types and of chromophobe cell tumours. Interestingly, chromophobe RCC have similar immunophenotype characteristics as oncocytoma. They showed an intense reaction with MAb 7C2, recognizing some epitopes on distal tubular epithelial cells, that gave negative or weak reaction in all other types of RCC. In contrast, all other tissue differentiating antigens were negative in both types of tumours. In addition, chromophobe RCC, like oncocytoma, revealed no vimentin, as has already been published, (Pitz et al., 1987; Lazzaro et al., 1991) and only a weak reaction with ICAM1 and HLA class II antigens associated with very conspicuous mononuclear leucocytic infiltration. The question is still open as to whether the similar immunomorphological characteristics of these two tumours with quite different biological behaviour indicate that chromophobe type of RCC has a specific histogenesis which could be in connection with oncocytoma (Van Krieken et al., 1988) as was already suggested (Pitz et al., 1987).

Cell surface molecules play a central role in regulating cell development and growth. It is possible that appearance of abnormal surface molecule on tumour cells is responsible of their malignant growth (Gogusev et al., 1993). According to previous works (Müller et al., 1989) tubular epithelial cells of healthy adult kidneys did not express ICAM1 (Bishop and Hall, 1989; Müller et al., 1991) and HLA class II antigens, with the exception of -DR antigen, which could be variably present on proximal tubular cells. Aberrant expression of ICAM1 and HLA class II antigens on proximal tubular cells was detected in some pathological conditions (Müller et al., 1989, 1991; Jevnikar et al., 1990; Markovic-Lipkovski et al., 1991). Study of HLA class II antigen expression in RCC has given, so far, various, even contradictory, results. Some authors reported a high percentage of RCCs with the presence of HLA class II antigens (Tomita et al., 1990a,b), while the others found them less regularly (Heinemann et al., 1987; Banner et al., 1990), or did not find them at all (Droz et al., 1990). We detected HLA class II antigens in all analyzed cases, but

Fig. 2. **a.** Granular cell RCC. Intensive reaction of tumour cells with MAb to distal tubular antigens. MAb TN9. **b.** Chromophobe cell RCC. Reaction with distal tubular marker. MAb 7C2. **c.** Chromophobe cell RCC. Cytokeratin positive tumour cells. MAb to cytokeratin. **d.** Chromophobe cell RCC, same case as Fig. 2c. Absence of vimentin on tumour cells, but presence on blood vessels. MAb to vimentin. a and b, x 400; c and d, x 100

with different number of tumour positive cells, ranging from few to almost all. Variable results obtained from different groups could be due to application of different MABs. In the present study ICAM1 was detected on tumour cells in all analyzed RCC, with slightly greater variations in distribution and intensity of staining among granular cell tumours. Interestingly, it was observed that ICAM1 on tumour cell could have membranous or cytoplasmic localization, while in kidneys with glomerulonephritis ICAM1 is usually apically localized (Müller et al., 1991). Expression of ICAM1 correlated with expression of HLA-class II antigens, particularly -DR antigen, in each case of RCC. In contrast to already published data (Reuter, 1990), there was no correlation between degree of ICAM1 and HLA class II antigen expression with staging or grading of RCC. Although tumour cells showed concomitant ICAM1 and HLA class II antigen expression, it is still not clear whether these antigens could have any role in host immunoreponse to RCC.

In contrast to chromophobe, mononuclear leucocytic infiltration was present in all other RCCs. Analysis of T-lymphocytes and macrophages revealed domination of the latter in almost all cases (more distinctly among clear cell RCCs.). The number of HLA class II antigens and ICAM1-positive mononuclear infiltrating cells (lymphocytes and macrophages) was considerably smaller than the number of tumour cells which expressed the same molecules and could indicate that increased histocompatibility antigen and ICAM1 expression is the primary event, followed by mononuclear cell influx as a consequence. Regrettably, no clear correlation between degree of the expression of any of HLA class II antigens or ICAM1 and amount of mononuclear cells was observed. Thus, a connection between their appearance in RCC could not be certainly established as was previously suggested (Reuter, 1990).

Our findings emphasize some immunomorphological characteristics of distinct RCC types, but the complicated network between their immunomorphology and different biological activity has to be further investigated.

References

- Bander N.H. (1987). Monoclonal antibodies in urologic oncology. *Cancer* 60, 658-667.
- Banner B.F., Burnham J.A., Bahnson R.R., Ernstoff M.S. and Auerbach H.E. (1990). Immuno-phenotypic markers in renal cell carcinoma. *Mod. Pathol.* 3, 129-134.
- Barnstable C.J., Bodmer W.F., Brown G., Galfré G., Milstein C., Williams A.F. and Ziegler A. (1978). Production of monoclonal antibodies to group A erythrocytes, HLA and other human cell surface antigens-new tools for genetic analysis. *Cell* 14, 19-20.
- Bishop G.A. and Hall B.M. (1989). Expression of leucocyte and lymphocyte adhesion molecules in the human kidney. *Kidney Int.* 36, 1078-1085.
- Cohen C., McCue P. and Derose P. (1988). Histogenesis of renal cell carcinoma and renal oncocytoma. An immunohistochemical study. *Cancer* 62, 1946-1951.
- Droz D., Zachar D., Charbit L., Gogusev J., Chretien Y. and Iris L. (1990). Expression of the human nephron differentiation molecules in renal cell carcinomas. *Am. J. Pathol.* 137, 895-905.
- Gogusev J., Augusti M., Chretien Y. and Droz D. (1993). Interleukin-6 and TNF production in human renal cell carcinoma. *Kidney Int.* 44, 585-592.
- Grone H.J., Weber K., Helmchen U. and Osborn M. (1986). Villin - A marker of brush border differentiation and cellular origin in human renal cell carcinoma. *Am. J. Pathol.* 124, 294-302.
- Heinemann D., Smith P.J.B., Symes M.O. (1987). Expression of histocompatibility antigens and characterisation of mononuclear cell infiltrates in human renal cell carcinomas. *Br. J. Cancer* 56, 433-437.
- Jevnikar A.M., Wuthrich R.P., Takei F., Xu H., Brennan D.C., Glimchen L.H. and Rubin-Kelley V.E. (1990). Differing regulation and function of ICAM-1 and class II antigens on renal tubular cells. *Kidney Int.* 38, 417-425.
- Lazzaro B., Conick P. and Morbier Katz S. (1991). Renal cell carcinoma vs. renal oncocytoma. Report of a case with overlap features and review of the literature. *Urology* 37, 52-56.
- Markovic-Lipkovski J., Müller C.A., Risler T., Bohle A. and Müller G.A. (1990). Association of glomerular and interstitial mononuclear leukocytes with different forms of glomerulonephritis. *Nephrol. Dial. Transpl.* 5, 10-17.
- Markovic-Lipkovski J., Müller C.A., Risler T., Bohle A. and Müller G.A. (1991). Mononuclear leukocytes, expression of HLA class II antigens and intercellular adhesion molecule 1 in focal segmental glomerulosclerosis. *Nephron* 59, 286-293.
- Müller C.A. and Müller G.A. (1983). Characterisation of renal antigens on distinct parts of the human nephron by monoclonal antibodies. *Klin. Wochenschr.* 61, 893-902.
- Müller C., Ziegler A., Müller C., Hadam M., Waller H.D., Wernet P. and Müller G. (1985). Divergent expression of HLA-DC/MB, DR and -SB region products on normal and pathological tissue as detected by monoclonal antibodies. *Immunobiology* 169, 228-249.
- Müller G.A., Müller C.A., Markovic-Lipkovski J., Kilper R.B. and Risler T. (1988). Renal, major histocompatibility complex antigens and cellular components in rapidly progressive glomerulonephritis identified by monoclonal antibodies. *Nephron* 49, 132-139.
- Müller C.A., Markovic-Lipkovski J., Risler T., Bohle A. and Müller G.A. (1989). Expression of HLA-DQ, -DR, -DP antigens in normal kidney and glomerulonephritis. *Kidney Int.* 35, 116-124.
- Müller G.A., Markovic-Lipkovski J. and Müller C.A. (1991). Intercellular adhesion molecule-1 expression in human kidneys with glomerulonephritis. *Clin. Nephrol.* 36, 203-208.
- Oosterwijk E., Rutter D.J. and Wakka J.C. (1986). Immunohistochemical analysis of monoclonal antibodies to renal antigens. Application in the diagnosis of renal cell carcinoma. *Am. J. Pathol.* 123, 301-309.
- Pitz S., Moll R., Storkel S. and Thoenes W. (1987). Expression of intermediate filament proteins in subtypes of renal cell carcinomas and in renal oncocytomas. Distinction of two classes of renal cell tumours. *Lab. Invest* 56, 642-653.
- Reuter V.E. (1990). Antigen expression in renal cell-carcinoma. Correlation with histological grade, pathological stage and development of distant metastasis. *Eur. Urol.* 2, 4-5.
- Rothlein R., Dustin M.L., Marlin S.D. and Springer T.A. (1986). A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. *J. Immunol.* 137, 1270-1275.
- Thoenes W., Störkle St. and Rumpelt H.J. (1986). Histopathology and

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- classification of renal cell tumours (adenomas, oncocytomas and carcinomas). The basic cytological and histological elements and their use for diagnostics. *Pathol. Res. Pract.* 181, 125-143.
- Tomita Y., Nishiyama T., Fujiwara M. and Sato S. (1990a). Immunohistochemical detection of major histocompatibility complex antigens and quantitative analysis of tumour-infiltrating mononuclear cells in renal cell cancer. *Br. J. Cancer* 62, 354-359.
- Tomita Y., Nishiyama T., Watanabe H., Fujiwara M. and Sato S. (1990b). Expression of intercellular adhesion molecule-1 (ICAM-1) on renal cell cancer: possible significance in host immune responses. *Int. J. Cancer* 46, 1001-1006.
- Van Krieken J.H.J.M., Oosterwijk E., Lycklama A., Nijeholt A.A.B. and Ruiter D.J. (1988). Renal oncocytoma: a report of two cases with immunohistochemical evaluation. *Hum. Pathol.* 19, 460-464.
- Van Muijen G.N.P., Ruiter D.J. and Warnaar S.O. (1987). Coexpression of intermediate filament polypeptides in human fetal and adult tissues. *Lab. Invest.* 57, 359-364.
- Ziegler A. and Milstein C. (1979). A small polypeptide different from β 2-microglobulin associated with a human cell surface antigen. *Nature* 279, 243-244.

Accepted March 10, 1995