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LABORATORY INVESTIGATION

Distribution of the major histocompatibility complex antigens in human and rat kidney

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Distribution of the major histocompatibility complex antigens in human and rat kidney. We have compared the distribution of the major histocompatibility complex (MHC) antigens in human and rat kidney using monospecific antisera to class I and II antigens of the MHC. FITC/TRITC double immunofluorescence was used to demonstrate these antigens in frozen sections and the *Staphylococcus aureus* Cowan I rosette assay on the cell surface. In both species, the MHC antigens were prominently present on the passenger leukocytes. Immunofluorescence analysis of human kidney demonstrated that the class I, β2-microglobulin (β2m), and class II antigens were present in the vascular endothelial cells and class I antigens in the renal tubular cells. The Staphylococcus assay demonstrated that these antigens were also exposed on the respective cell surfaces. In clear contrast, in the rat, class I, the β2m, and class II antigens were absent from the kidney vascular endothelium of large vessels and intertubular capillaries; however, large amounts of class II antigens were seen inside the proximal renal tubular cells. The Staphylococcus assay indicated that none or very little of these antigens were exposed on the kidney parenchymal cell surface. These differences may explain why rat renal transplants are relatively non-immunogenic and easily accepted, whereas human renal transplant recipients must be immunosuppressed ad infinitum.

Distribution des antigènes du complexe d'histocompatibilité principal du rein d'homme et de rat. Nous avons comparé la distribution des antigènes du complexe d'histocompatibilité principal (MHC) dans du rein d'homme et de rat en utilisant des antisérums monospécifiques des antigènes des classes I et II du MHC. Une double immunofluorescence FITC/TRITC a été utilisée pour démontrer ces antigènes dans des sections congelées et le dosage des rosettes de Staphylocoque doré Cowan I pour les démontrer à la surface cellulaire. Dans les deux espèces, les antigènes MHC étaient essentiellement présents sur les leucocytes de passage. L'analyse en immunofluorescence de rein humain a démontré que les antigènes de classe I, 1 β2-microglobuline (β2m) et de classe II étaient présents dans les cellules endothéliales vasculaires, et ceux de classe I dans les cellules tubulaires rénales. Le dosage Staphylocoque a démontré que ces antigènes étaient également exposés sur les surfaces cellulaires respectives. De facon clairement opposée, chez le rat, les antigènes de classe I, 1 β2m et de classe II étaient absents de l'endothélium vasculaire rénal des gros vaisseaux et des capillaires intertubulaires; cependant, de grandes quantités d'antigènes de classe II étaient visibles à l'intérieur des cellules tubulaires rénales proximales. L'essai Staphylocoque a indiqué qu'aucun ou très peu de ces antigènes étaient exposés à la surface des cellules parenchymateuses rénales. Ces différences pourraient expliquer pourquoi les greffons rénaux de rat sont relativement non immunogènes et facilement tolérés, alors que les receveurs de transplants rénaux humains doivent être immunodéprimés indéfiniment.

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Different types of allografts differ considerably in their acceptability. For example, kidney allografts across certain histocompatibility barriers in rats [1] and mice [2] may survive indefinitely, whereas skin allografts are rejected. Liver allografts are usually accepted without immunosuppression in the pig, but kidney and skin allografts have been rejected [3]. One striking example of this dichotomy is the behavior of renal allografts in rat and humans: Rat renal allografts are accepted nearly invariably after a short period of immunosuppression [4] and/or after elimination of the transplant passenger cells [5] whereas human renal allograft recipients must be immunosuppressed seemingly ad infinitum.

The major histocompatibility complex (MHC) antigens are the most important immunogens regulating allograft rejection. Considering the reported differences in the behavior of renal allografts in rat and humans, we found it interesting to compare—with the same methods—the distribution of the MHC antigens in these two organs. In addition to evaluating which anatomical components in rat and human kidney contain MHC products, we have analyzed which organelles express these antigens also on the cell surface.

Methods

Biopsy material

Two human kidneys procured, perfused, and stored in Eurocolins and three biopsy specimens from a macroscopically normal area from renal cancer specimens provided the human material. Rat kidneys were procured and perfused with phosphate-buffered saline (PBS) [6]. Renal tissue samples were frozen in liquid nitrogen; other pieces were immersed in RPMI-1640 tissue culture medium (Gibco Pharmaceuticals, Long Island, New York, USA) containing 5 g bovine serum albumin, and 1.2 g Hepes per 1 liter of medium for enzymatic disaggregation and cytological analysis (below).

Fine needle aspiration biopsy specimens of renal transplants

Fine needle aspiration biopsies (FNAB) were performed on renal allografts in the context of rejection episodes; part of each cytological specimen was used for the analysis of MHC antigen expression as described [7].

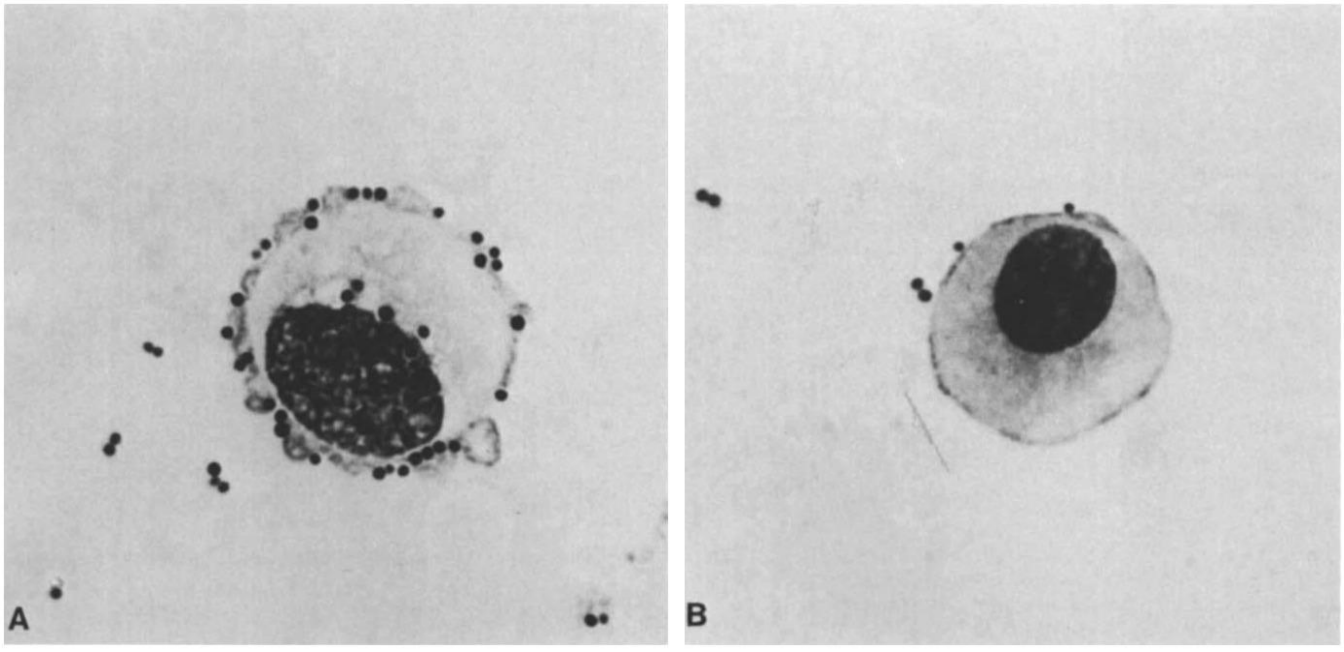

Fig. 1. *Binding of staphylococci by human renal endothelial cells* **(A)** *and lack of binding to renal tubular cells* **(B)** *after treatment with anti-class II.* (×1000)

Chemicals and media

Collagenase, type IV, and DNAse and Hepes buffers were obtained from Sigma Chemical Co. (St. Louis, Missouri, USA).

Antisera

The monoclonal mouse antibodies against the backbone molecule of class I (MAS 032), β2-microglobulin (β2m; MAS 018), and class II antigens (MAS 044) of the human HLA complex and to the backbone of class II antigen of the rat MHC (MAS 029 and MAS 043) were purchased from Sera-Lab Ltd., Crawley Down, Sussex, England. The specificity of these antibodies has been described [8].

Rabbit antisera to isolated molecules of rat class I antigen and β2m were received as a gift from Prof. P. Peterson, Uppsala University, Uppsala, Sweden. The specificity of these antisera also has been described [9].

AO anti-DA alloantibody was produced by skin grafting and hyperimmunization with DA lymphocytes and rendered class II specific by extensive adsorption over DA erythrocytes.

Rabbit antisera to Factor VIII-related antigen (FVIII R:Ag) and lysozyme (LZM) were purchased from Behringwerke (Marburg, Federal Republic of Germany). Rabbit antisera to vimentin, desmin and keratin have been characterized [10, 11]. Rabbit antisera to brushborder antigen and to Tamm-Horsfall antigen were gifts from Dr. Aaro Miettinen (Department of Serology and Bacteriology, University of Helsinki), and have been characterized earlier [12, 13]. Tetramethyl rhodamine isothiocynate (TRITC)-conjugated ulex europeus I agglutinin (TRITC-UEA I) was purchased from Vector Laboratories (Burlingame, California, USA). Fluorescein isothiocynate (FITC) coupled goat anti-mouse IgG was purchased from Cappel Laboratories (Cochranville, Pennsylvania, USA) and TRITC-coupled swine anti-rabbit IgG from Dakopatts (Copenhagen, Denmark).

Frozen section immunofluorescence

The frozen sections were cut, fixed in −20° acetone, exposed to mouse antibody (1:20), washed and exposed to FITC-coupled anti-mouse IgG (1:20). For double staining the sections were subsequently exposed to rabbit anti-vimentin, -keratin, or -FVIII RA:g or to TRITC-UEA I (1:20), washed and exposed to TRITC-coupled swine anti-rabbit IgG (1:20). The specimens were examined in a microscope (Zeiss Universal, Oberkochen, Federal Republic of Germany) equipped with an epi-illuminator IIIRS and filters for FITC and TRITC fluorescence.

Preparation of single cell suspension

After mechanical mincing and incubation (20 min/+37°C) in collagenase (0.2 mg/ml) and DNAse (0.2 mg/ml) medium, the dispersed cells were washed twice to remove traces of enzyme. This treatment does not affect the expression of subclass-specific surface markers of lymphoid cells, the distribution of cell surface glycoproteins [14], or the expression of the major locus MHC antigens on cell (lymphocyte) surface [15].

Staphylococcus rosette assay

A modification of the *Staphylococcus aureus* Cowan I rosette assay, based on the analysis of the rosette-forming cells from May-Grünwald-Giemsa (MGG) stained cytocentrifuged cell smears, was used [16, 17]. This modification makes it possible to identify morphologically the rosette-forming cell (Fig. 1). We have previously demonstrated that at a given antiserum con-

Table 1. Distribution of MHC antigens in frozen section immunofluorescence of human and rat kidney

	Kidney component and marker													
	Glomerulus			Tubuli		Vascular endothelium								
					Distal		Arterial			Venous				
	Vascular endothelium	Epithelium	Mesangium	Proximal	a-Tamm-Horsfall GP	Interstitial	L	M	S	L	M	S	Collecting ducts	Tissue macrophages
	UEA-I	a-keratin	a-desmin	a-BB		FVIII R:ag							a-keratin	a-vimentin a-LZM[a]
Humans														
MAB a class I[d]	+++	–	–	–	–	+++	++	++	++	++	++	++	–	+++
MAB a β2m	+++	–	–	–	–	+++	++	++	++	++	++	++	–	+++
MAB a class II	+++	–	–	–	–	+++	+	+	++	+	+	+	–	+++
Rat														
R a class I	–	–	–	–	–	–	–			–			–	+++
R a β2m	–	–	–	–	–	–	–			–			–	+++
MAB a-Ia														
MAS 029	+	–	–	+++	–	–	–			–			–	+++
MAS 043	+	–	–	+++	–	–	–			–			–	+++

Abbreviations: UEA, *Ulex europaeus* agglutinin; BB, brush border; FVIII R:ag, factor VIII-related antigen; LZM, lysozyme; L, large; M, medium; S, small; MAB, monoclonal antibody; R, rabbit.

[a] LZM positive cells were relatively few in number but all of them were obviously MHC expressing.

centration the number of bound staphylococci is directly proportional to the amount of cell-bound antibody [15].

Results

Distribution of the MHC antigens in frozen section immunofluorescence

The distribution of the MHC antigens in frozen section immunofluorescence is demonstrated in Table 1 and Figure 2. In humans certain structures within the glomeruli and the intertubular parenchyma displayed a strong staining with monoclonal antibodies to class I, β2m, and class II antigens of the human MHC complex. None of the remaining parenchymal components displayed any reactivity. Double staining with TRITC-UEA I identified the intra-glomerular antibody-binding structures as the glomerular vascular endothelial cells [18, 19], and double staining with anti-keratin and anti-desmin demonstrated that the glomerular epithelium or mesangium did not contain significant amounts of these antigens. Double staining with TRITC-UEA I and anti-factor VIII R:Ag identified the intensively stained intertubular structures as intertubular vascular endothelial cells [18, 19]. The vascular endothelium of larger vessels, including the arterioli and venae, bound these antibodies somewhat weaker. In addition, the glomerular tufts and the intertubular spaces contained some solitary cells reactive with anti-LZM [20]. These cells were also anti-class I and anti-class II positive but could be visualized only with difficulty because of their overlapping with the vascular endothelium. These cells probably represent the fixed mononuclear phagocytes of the renal parenchyma.

In rat no significant binding of rabbit anti-class I and -β2m to the parenchymal structures (including the vascular endothelium) was observed. Monoclonal antibodies to the class II antigen did not react with the vascular endothelium of large vessels or intertubular capillaries; however, the glomerular endothelial cells were class II positive. Anti-class II bound strongly to some tubular cells and to solitary cells in the kidney parenchyma, in particular within the glomerular tufts and between the tubuli. Double staining with anti-brushborder antigen demonstrated that the strongly binding tubular components were proximal tubular cells [13]. Double-staining with anti-lysozyme identified some of the positive cells in glomerular tufts as mononuclear phagocytes [21]; most of the class II positive glomerular cells, however, were FVIII R:Ag positive endothelial cells.

Binding of anti-MHC sera on disaggregated kidney components

Human. In humans (Table 2) the anti-class I antibody bound to the passenger lymphocytes, monocytes, and macrophages as well as to the endothelial and (weaker) to kidney tubular cells. The average binding by the kidney vascular endothelial cells was 130, 40 and 50% of the mean binding by the (passenger) lymphocytes in specimens obtained by organ procurement, surgical biopsy, or by the FNAB, respectively.

The anti-class II antibody bound to the passenger lymphocytes, monocytes, and macrophages; the binding of macrophages were approximately two times stronger than the mean binding to lymphocytes. Also, the renal vascular endothelial cells bound to this antibody; the average binding to endothelial cells was approximately 60, 40 and 120% of the binding to the (passenger) lymphocytes in specimens obtained by procurement, surgical biopsy, and FNAB, respectively. No significant binding of anti-DR antibody to renal tubular cells was observed.

Rat. In rat, rabbit anti-class I, rabbit anti-β2m and AO anti-DA antisera had a very similar reaction pattern. A positive reaction was obtained by the passenger lymphocytes, monocytes, and macrophages (Table 2) and a weak though still significant reaction by the passenger erythrocytes and granulocytes (not shown). A weak reaction was recorded by the proximal and distal tubular cells and the endothelial cells; this reaction was less distinct than, for example, that by the passenger erythrocytes. The reaction pattern of rabbit anti-

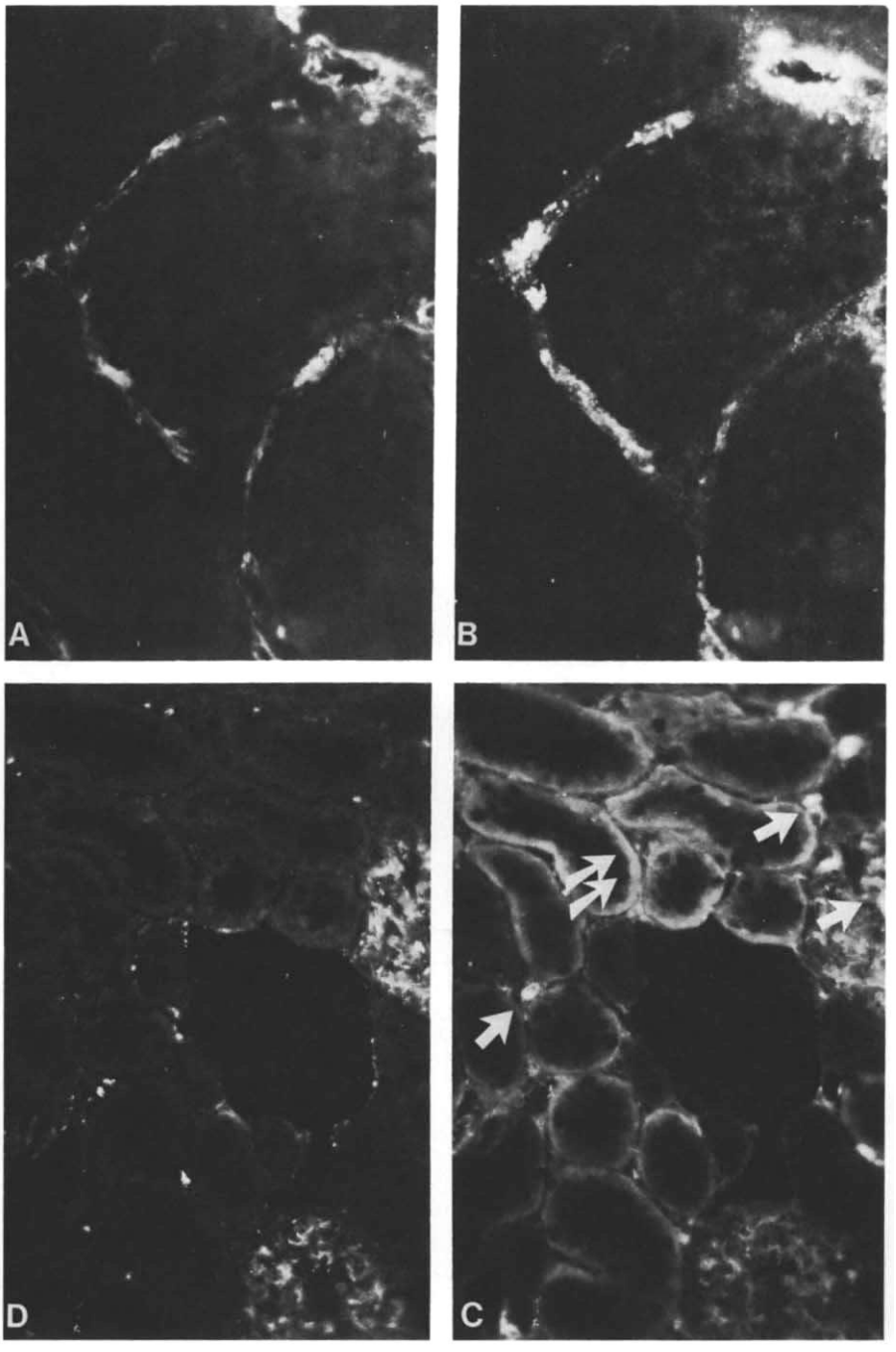

Fig. 2. *Double indirect immunofluorescence of frozen sections of human and rat kidney with hybridoma antibodies against class II* (**A, C**) *and rabbit anti-FVIII R:Ag* (**B, D**). The bright peritubular capillary staining of human kidney with anti-class II (**A**) codistributes with FVIII R:Ag reactivity (**B**). In rat kidney some scattered anti-class II reactive cells (**C**) are seen in peritubular areas and glomeruli (*arrows* in **C**). In addition some tubules, which were also reactive in double staining with anti-brushborder antigen, appeared to express Ia-like material (*double arrow* in **C**). Glomerular endothelial cells express FVIIIR:Ag in **D** partially codistributing with Ia positivity in **C**. (Magnifications: **A** and **B**, ×320; **C** and **D**, ×200)

class II, of the two monoclonal antibodies directed to class II antigens of the rat MHC, and erythrocyte-adsorbed AO anti-DA were again concordant. The passenger lymphocytes, monocytes, and macrophages (Table 2), but not the passenger erythrocytes and granulocytes (not shown), gave a positive reaction. No significant reaction was observed with any one of the renal parenchymal components.

Discussion

The results of this investigation are compatible with several previous studies and demonstrate significant differences in the distribution of the major histocompatibility complex antigens on the different cellular components of human and rat kidney. As shown earlier by Paul, van Es, and Baldwin [21]; von Willebrand, Parthenais, and Häyry [15]; Häyry, von Willebrand, and Andersson [22]; and others [23–25], the class I MHC antigens in human kidney are distributed over a fairly wide range and are present, in addition to the passenger cells, also on the tubular and vascular endothelial cells of the kidney. The class II antigens are present on most of the endothelial cells of the vascular tree as their distribution nearly completely overlaps with UEA I [19]. The class II antigens are most prominent in the glomerular and intertubular capillary endothelium. The Staphylococcus assay demonstrated that they are

Table 2. Binding of staphylococci by disaggregated human and rat kidney passenger and parenchymal cells, after treatment with anti-class I and II antibody

Antiserum	Origin of tissue specimen	N	Average number of staphylococci per cell (±SD)					
			Passenger cells			Parenchymal cells		
			Lymphocytes	Monocytes	Macrophages	Endothelial cells	Small (proximal) tubular cells	Large (distal) tubular cells
Human[a]								
MAB a class I (MAS 032)	Procured kidney	(2)	11.2	6.6	—[b]	15.3	13.1	5.5
	Surgical biopsy	(3)	6.7 ± 0.3	4.9 ± 2.0	7.3 ± 2.0	2.5 ± 0.6	2.4 ± 0.9	—
	FNAB specimen	(4)	10.1 ± 2.3	ND	ND	5.2 ± 0.5	4.4 ± 1.1	—
MAB a class II (MAS 044)	Procured kidney	(2)	5.0	10.0	—	2.8	0.6	—
	Surgical biopsy	(3)	6.3 ± 0.9	6.1 ± 2.9	9.3 ± 1.2	2.5 ± 0.5	0.8 ± 0.1	—
	FNAB	(4)	2.5 ± 1.5	ND	ND	3.0 ± 2.5	0.9 ± 0.9	—
Rat[c]								
R a class I	Procured kidney	(2)	5.9	5.1	4.8	1.8	1.4	0.3
R a β2m	Procured kidney	(2)	5.5	5.2	5.3	1.6	0.9	0.3
R a class II	Procured kidney	(2)	4.2	4.9	4.2	0.8	0.2	0.2
MAB a class II (MAS 029)	Procured kidney	(2)	4.2	4.6	5.4	0.7	0.8	0.0
MAB a class II (MAS 043)	Procured kidney	(2)	4.7	4.9	6.4	0.5	0.4	0.1
AO a DA I + II[d]	Procured kidney	(2)	6.5	5.8	6.3	1.1	1.0	1.1
AO a DA II[e]	Procured kidney	(2)	4.0	4.9	3.7	0.3	0.9	0.2

[a] The background of control antibody varied between 0.1 and 0.6 staphylococci per cell.
[b] The — indicates that no or too few cells of this type were present in the specimen for reliable analysis.
[c] The background of corresponding control sera varied, depending on the cell type and the serum, between 0.0 and 1.0 Staphylococci per cell.
[d] Non-adsorbed.
[e] Adsorbed extensively with DA RBC.

also exposed on the cell surface. This is in striking contrast to rat kidney, where none of the parenchymal cells carried the class II antigens on the cell surface. As shown by adsorption experiments with kidney homogenate [26, 27], the rat kidney carries substantial amounts of the class II antigen. In contrast to humans, most of the class II antigen in a rat kidney is localized intracellularly in the brushborder antigen-expressing proximal tubular cells [13], as Hart and Fabre [28] suggested. However, practically none of the antigen is exposed on the cell surface.

An interesting delineation of these findings is made when they are related to the present knowledge on the immunogenicity of renal structures in vivo. It is well-known that human renal allografts are nearly invariably rejected in the absence of immunosuppression and that the strength of rejection follows the MHC disparity at least to a certain extent. In attempts to increase the renal allograft survival by donor pretreatment in humans, the success has been variable [29, 30]. In clear contrast, the rat kidney parenchymal cells express very little immunogenic potential [31] and elimination of passenger component by treatment of the graft donor with cytotoxic drugs, nearly invariably results in a distinct prolongation of graft survival without further immunosuppression [4]. Even a rat kidney is immunosensitive, however, as shown in the experiments of Lechler and Batchelor [5]: If a recipient rat carrying a successfully enhanced renal transplant is exposed to the donor strain dendritic cells, the graft is promptly rejected. Thus, although (intracellular) class II antigens of the rat kidney are, as expected [32], non-immunogenic, the vascular endothelial cells of human kidney, known to be preserved after successful transplantation [33] seem to provide subsequent stimuli for graft rejection even after the passenger component has been replaced by host type [34].

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