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T-cell receptors and ICAM-1 expression in renal allografts during rejection

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Abstract. Sixty-two biopsies taken from 38 kidney grafts were studied for 15 histological and 10 immunohistological parameters. The biopsies were divided into three groups, according to the clinical diagnosis at the time they were performed: group 1, rejection ($n = 43$); group 2, other causes of dysfunction ($n = 10$); and group 3, stable function ($n = 9$). Histological signs of acute rejection included diffuse interstitial infiltrate, tubular basement membrane damage, mononuclear leukocyte infiltration, and congestion of the peritubular capillaries. Immunoperoxidase staining with monoclonal antibodies to ten markers showed a statistically significant association between detection of T-cell receptor subunits alpha-beta (TcR2) and gamma-delta (TcR1) on infiltrating lymphocytes and of intercellular adhesion molecule-1 (ICAM-1) in tubular cells and acute rejection. These results suggest that T-cell receptors and ICAM-1 may be useful markers to differentiate acute rejection from renal graft dysfunctions due to other abnormalities.

Key words: T-cell receptors, kidney transplantation, rejection – Rejection, kidney, T-cell receptors – ICAM, expression, kidney transplantation, rejection

Alloantigens mismatched between a transplanted kidney and a recipient may trigger a cascade of immune reactions that start with the interaction of the donor-type antigen-presenting cell with the host CD4+ helper T cell [13]. CD8+ cytotoxic T-cell responses are generated [4, 14] and activated CD4+ and CD8+ T cells eventually produce lymphokines such as gamma interferon and interleukin-2 [6]. Clonal proliferation of antigen-reactive T cells may ensue, with a subsequent development of cytotoxic T cells. They lyse their targets via a series of events involving nonspecific adhesion, specific recognition, and triggering of the T-cell lytic machinery. Lymphokines generated in situ can attract and activate [12] other potential effector cells, such as natural killer (NK) cells and monocytes/macrophages. Moreover, they can induce or upregulate the expression of target cell antigens and adhesion molecules, such as HLA class I antigens and intercellular adhesion molecule-1 (ICAM-1) [2].

Characterization of the sequence of events triggered by mismatched alloantigens in renal transplant recipients may sharpen our ability to differentiate acute rejection of a kidney graft from other causes of renal dysfunction, thus improving therapeutic decisions and, thereby, the outcome of renal allografts and the survival of their recipients. We therefore, in the present study, performed a retrospective analysis of renal biopsies from three groups of transplant recipients, i.e., those who suffered from acute rejection, those who suffered from renal dysfunction caused by other mechanisms, and those who enjoyed a favorable clinical course.

Patients, materials, and methods

The recipient group included 14 females and 24 males with a mean age of 42.6 years (range 23–62 years). Two recipients had been transplanted with kidneys from living related donors; the remaining 36 recipients had been transplanted with kidneys from postmortal, unrelated donors after matching for maximal HLA compatibility via the Eurotransplant system. All patients were continuously treated with immunosuppressive therapy consisting of cyclosporin A (up to 12 mg/kg daily, according to serum levels) and prednisone (10 mg daily). In addition, patients were treated with methylprednisolone pulse therapy or antithymocyte globulin when they experienced episodes of acute graft rejection. The interval between renal transplantation and biopsy ranged from a minimum of 1 month to a maximum of 12 months.

Renal biopsies were taken with a 2-mm ultrasound-guided needle. Each sample was divided into two parts: one was fixed in 10% buffered formalin, embedded in paraffin, and used for conventional histology; the other one was snap-frozen in liquid nitrogen within 60 min after removal and stored at −70°C until used for immunohistochemistry. Characteristics of the monoclonal antibodies used are summarized in Table 1.

Three-micrometer thick sections of formalin-fixed tissues were stained with hematoxilin-eosin, silver methamine, or periodic acid-

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Schiff, following standard procedures [1]. Each section was analyzed for the parameters listed in Table 2.

Results were classified as extent of expression on components of graft or infiltrate. Thus, positive results meant more than 50% expression, weakly positive meant less than 50% expression, and negative meant no expression on either tissue or cells.

Immunoperoxidase staining of 3-μm thick sections of frozen tissue was performed as follows. The sections of tissue were cut and put on gelatinized glass slides and air-dried. The tissue was then incubated with acetone for a 10-min fixation period. Following three wash steps with phosphate-buffered saline (PBS), the sections were incubated for 30 min at room temperature with 50 μl of the appropriate dilution of the monoclonal antibody (Table 1). Following washing in PBS, the sections were incubated for 30 min at room temperature in 100 μl of horseradish peroxidase (HRP)-conjugated rabbit anti-mouse Ig (Dako, Glostrup, Denmark), diluted 1:60 in PBS containing 1% bovine serum albumin (BSA) and 20% normal human serum (NHS). The sections were again washed three times in PBS and incubated for 30 min at room temperature in 100 μl of swine anti-rabbit Ig (Dako, Glostrup, Denmark). Thereafter, wash steps were repeated three times and 5% 3-amino-9-ethylcarbazol in acetate buffer (37 ml 0.2 M acetic acid, 88 ml 0.2 M Na acetate, 125 ml distilled water), together with H_2O_2, was added for 5 min, followed by counterstaining with Mayer's hematoxylin.

Table 1. Characteristics of the monoclonal antibodies used

Antibody	Subclass	Source	Reactivity	Reference
DAKO-LCA	IgG2b	DAKO[a]	CD45	Eur J Immunol (1978) 8: 539–551
HB-44	IgG1	ATCC[b]	Monocytes	Proc Nat Acad Sci USA (1980) 77: 6764–6768
HNK-1	IgM	ATCC	CD16	J Immunol (1981) 127: 1024–1029
OKT-3	IgG2b	ATCC	CD3	Cell (1980) 19: 821–828
betaF1	IgG1	TCS[c]	TcR2	[20]
TcRgd1	IgG1	Dr. Borst[d]	TcR1	[21]
TS2/7	IgG1	TCS	VLA-1	J Biol Chem (1987) 262: 3300–3309
Ki-67	IgG1	DAKO	Prolif cells	J Histochem Cytochem (1989) 37: 1471–1479
CL 203.4	IgG1	Dr. Ferrone	ICAM-1	[29]
B8.11.2	IgG2b	Dr. Giphart[e]	HLA-DR	Proc Natl Acad Sci USA (1979) 76: 6567–6571

[a] Dakopatts, Glostrup, Denmark
[b] American Type Culture Collection, Rockville, Md., USA
[c] T Cell Sciences, Cambridge, Mass., USA
[d] The Netherlands Cancer Institute, Amsterdam, the Netherlands
[e] University of Leiden, Leiden, the Netherlands

The number of infiltrating cells staining positive with monoclonal antibodies to the first eight markers from Table 1 was scored as the number of stained cells in an area chosen at random over a surface of 0.625 mm^2, at a magnification of 400 ×, using a graticule in the eyepiece of the microscope. Sections smaller than 0.625 mm^2 were discarded. Not only was the number of positive-staining cells statistically evaluated, but also the presence or absence of positive-staining cells per se.

Staining with anti-HLA class II and anti-ICAM-1 monoclonal antibodies (Fig. 4) was classified according to the criteria outlined for the histological study. Each tissue specimen was scored by two independent observers without knowledge of the clinical diagnosis. To determine the differences among the three groups of biopsies, statistical analysis of the data was performed utilizing the chi-square test for the qualitative data and an analysis of variance for the quantitative data.

Results

Sixty-two renal biopsies obtained from 38 patients were divided into three groups according to the clinical diagnosis at the time the biopsy was performed. Group 1, classified as acute rejection, included 39 samples from 20 patients with an episode of dysfunction that responded to a full course either of methylprednisolone or of antithymocyte globulin and 4 samples from 4 patients who did not respond to immunosuppressive therapy and who progressively deteriorated for no other identified reason but acute rejection. Group 2, classified as other causes of dysfunction, included ten samples from six patients with renal dysfunction caused by either cyclosporin A toxicity ($n = 6$, documented by high cyclosporin A levels and a subsequent decrease in serum creatinine after lowering of the cyclosporin dosage), local infarction of the kidney, documented by renal scan ($n = 2$), infection ($n = 1$), or unknown reasons ($n = 1$, a combination of high gentamycin and cyclosporin levels). Group 3, classified as stable function, included nine samples from eight patients without renal dysfunction. Renal dysfunction was defined as a sustained rise in serum creatinine level of more than 20% above the mean of the previous (no less than 2-week) baseline levels or a decline in the rate of improvement of renal function.

Table 2. Expression of cell surface markers in the three studied groups. pos, Number of biopsies within the group positive for the marker; tot, total number of biopsies within the studied group; CHI, chi square test

Target	Rejection		Other		Stable		
	pos/tot (%)	CHI 1vs2 *P*	pos/tot (%)	CHI 2vs3 *P*	pos/tot (%)	CHI 1vs3 *P*	F *P*
Leukocytes (CD45)	35/35 (100)	NS	9/9 (100)	NS	7/7 (100)	NS	
Monocytes/ macrophages	22/34 (64.7)	0.0286	1/7 (14.3)	NS	0/7 (0)	0.0042	
Natural killer cells (CD16)	34/34 (100)	NS	6/8 (75)	NS	4/7 (57.1)	NS	
Lymphocytes (CD3)	33/33 (100)	NS	8/8 (100)	NS	6/6 (100)	NS	
TCR/alpha-beta (TcR2)	32/34 (94.1)	0.0001	2/8 (25)	NS	2/7 (28.6)	0.0003	
TCR/gamma-delta (TcR1)	21/33 (63.6)	0.0093	1/8 (12.5)	NS	1/7 (14.3)	0.0493	
VLA-1	14/34 (41.2)	NS	1/8 (12.5)	NS	0/7 (0)	NS	
Proliferating cells	14/30 (46.7)	NS	1/8 (12.5)	NS	0/7 (0)	0.0456	

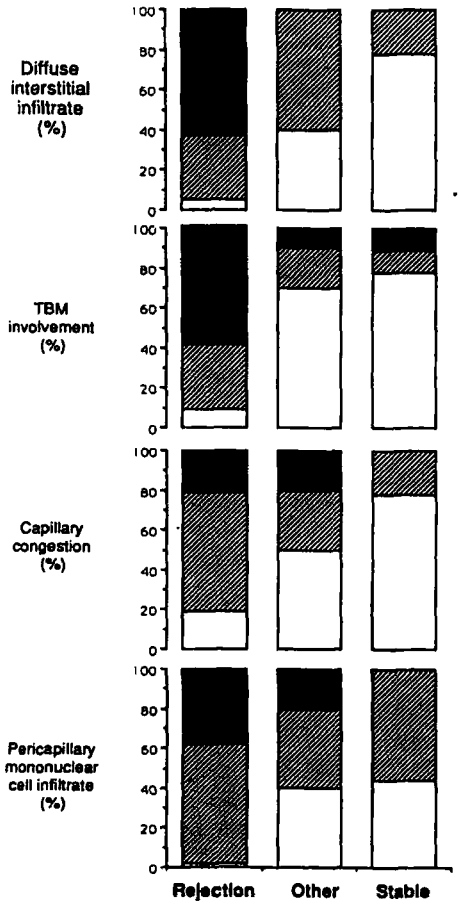

Fig. 1. Significant light microscopic features in biopsies taken during acute rejection ($n = 43$), during other causes of renal dysfunction ($n = 10$), and during stable renal function ($n = 9$). *Diffuse interstitial infiltrate*, damage to the tubular basement membrane *(TBM)*, *capillary congestion*, and *pericapillary mononuclear cell infiltrate* were significantly more often present ($P < 0.001$, chi-square for all parameters separately) in the rejection group. ■, Positive; ▨, weakly positive; □, negative

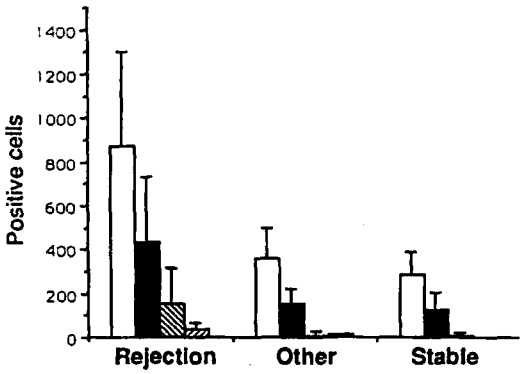

Fig. 2. The number of CD45- (□), CD3- (■), TcR2- (▧), and TcR1- (▨) *positive cells* infiltrating biopsies taken during *rejection* ($n = 35$), *other* causes of renal dysfunction ($n = 8$), and *stable* renal function ($n = 7$). Counts are expressed as cells per 0.625 mm^2 surface area (mean + 1 SD). There is a significant excess of CD45- and CD3-positive cells ($P < 0.001$, F test, analysis of variance) in the biopsies taken during rejection

The results of the histological analysis of the samples in the three groups of patients are as follows. The presence of focal infiltrate, hemorrhage, and fibrosis did not correlate with the presence of acute rejection as defined above. Nor did such features as arterial intima proliferation, arterial media proliferation, arterial wall diameter, arterial hyalinosis or glomerular thrombosis, ischemia, or cellularity show any relationship to the presence of acute rejection. However, diffuse interstitial infiltrate, damage to the tubular basement membrane, capillary congestion, and mononuclear infiltrates around capillaries were features seen significantly more often in the biopsies taken during acute rejection than those taken in the other two situations (Fig. 1).

The results of the immunoperoxidase staining of the renal biopsy samples with monoclonal antibodies to markers characteristic of cell types, to T-cell receptors, and to an antigen associated with cell proliferation are as follows. Neither the number of CD16- and VLA-positive cells nor the number of proliferating cells correlated with the presence of rejection. As can be seen in Fig. 2, the number of CD45- and CD3-positive cells was related to the presence of rejection (analysis of variance, $P < 0.01$). Analysis of the presence of "mere positivity" showed that this qualitative parameter gave additional information. As can be seen in Table 2, the presence of monocytes/macrophages, TcR1- and TcR2-positive lymphocytes, and proliferating cells could be found significantly more often during rejection.

In the biopsies from patients without rejection, ICAM-1 was present on glomerular and intertubular capillaries and weakly present on arteriolar and venular endothelial cells. Bowman's capsule stained positive for ICAM-1. During rejection, ICAM-1 expression in the glomeruli increased significantly ($P < 0.001$) compared with the stable situation; however, the difference between biopsies taken during rejection and during episodes with other causes of renal dysfunction was not statistically significant. Tubular ICAM-1 expression was significantly more often present during rejection in comparison to the group with stable function ($P < 0.001$) and that with renal function impairment due to other causes ($P < 0.001$; Fig. 3). An example of tubular ICAM-1 staining is shown in Fig. 4.

In the control biopsies without rejection, HLA class II staining was strongest for glomerular and endothelial capillaries. Weaker staining of venular endothelial cells was observed and arteriolar endothelium did not stain. However, in half of the biopsies, tubuli were positive as well. Although the percentage of biopsies with HLA class II positive tubuli was higher in the rejecting group, the difference was not statistically significant (Fig. 3).

Discussion

The clinician dealing with renal transplantation usually makes the diagnosis of acute rejection on the basis of a well-described combination of clinical and histological findings [1, 10, 24, 31]. However, the presence of similar histological signs in clinically sound grafts [5, 18], as well as a diminishing abundance of infiltration in later rejections, due to fibrosis, and the influence of the immunosup-

pressive regimen [19] on the magnitude of infiltrating cells, have cast severe doubt on the validity of these criteria. Therefore, several investigations have evaluated the usefulness of a number of immunological markers in the diagnosis of renal allograft rejection [3, 6, 8, 11, 27–29]. Although the results have been promising, none of the markers is being used routinely to differentiate renal dysfunctions caused by graft rejection from other causes.

In the present study, we analyzed the usefulness of 15 of the most commonly used histological parameters [1], of the composition of the cell infiltrate, and of the expression of ICAM-1 and HLA-DR antigens in the diagnosis of renal graft rejection. In agreement with findings in the literature [1, 10, 24, 31], of the histological parameters investigated, diffuse interstitial infiltration of leukocytes, damage to the tubular basement membrane, and mononuclear leukocytes infiltrating the peritubular capillary wall were found to be the most discriminating.

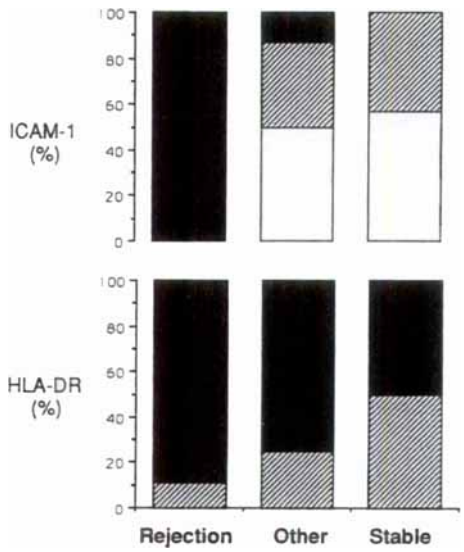

Fig. 3. Tubular *ICAM-1* and *HLA-DR* expression during *rejection* ($n = 36$), *other* episodes of renal function deterioration ($n = 8$), and *stable* renal function ($n = 8$). ICAM-1 expression is significantly more often present during rejection episodes ($P < 0.0001$, chi-square), while the differences for HLA-DR are not significant

Immunoperoxidase staining of cell infiltrates with monoclonal antibodies specific for leukocytes, lymphocytes, NK cells, and monocytes/macrophages confirmed previous observations [11, 28] that lymphocytes account for 30%–50% of the leukocyte population. However, analysis of cell infiltrates for their composition and for the expression of VLA and of the MoAb Ki-67-defined proliferation antigen did not provide any useful information for the diagnosis of renal graft rejection. Our results are in agreement with those of Seron et al. [28] with regard to the lack of a diagnostic value of the composition of cell infiltrate, but they differ from theirs with regard to the expression by interstitial cells of the proliferation antigen identified by the MoAb Ki-67. The latter investigators stained renal biopsies with MoAb Ki-67 using a method of gold enhancement of the diaminobenzidine reaction product and they found proliferating cells in the interstitium of kidneys in 15 out of 18 rejection episodes. Therefore, they concluded that identification of proliferating cells could be a useful marker to differentiate rejection from other causes of graft dysfunction. The discrepancy between Seron et al.'s results and our own may reflect the difference in sensitivity of the histochemical procedures used in the two studies, since the use of gold salt may increase the sensitivity of the immunoperoxidase techniques. An alternative possibility that cannot be excluded is the existence of a real difference in the characteristics of the patient population investigated by Seron et al. [28] and by ourselves.

Staining with monoclonal antibodies specific for the beta [25] and for the delta chain [34] of the T-cell receptor showed, for the first time, an increase in the number of CD3-positive cells expressing TcR1 and TcR2, respectively, in renal biopsies from patients with graft rejection. The percentage of TcR1-positive T cells in the renal biopsies during rejection was, on the average, 8.9%. Similar per-

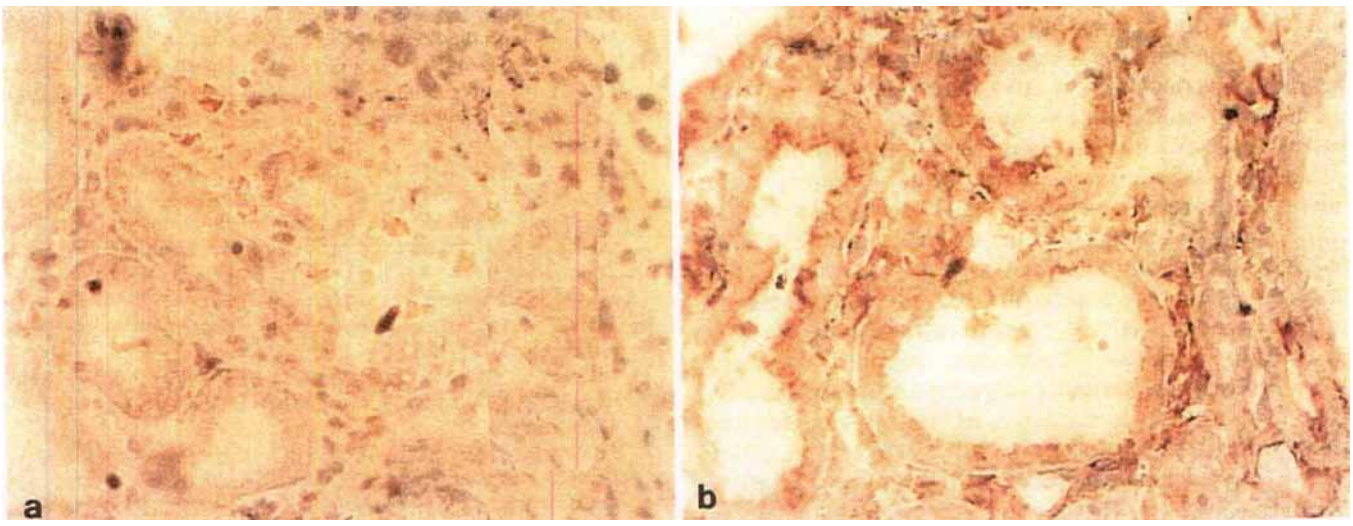

Fig. 4 a, b. Immunoperoxidase staining with the anti-ICAM-1 MoAb CL 203.4 of frozen sections of renal biopsies. **a** Biopsy taken from functionally stable allograft (immunoperoxidase staining $\times 100$). **b** Biopsy taken during clinically defined acute rejection episode (immunoperoxidase staining $\times 250$). Differential staining is mainly restricted to the proximal tubular cells

centages have been found in other inflammatory infiltrates in nonlymphoid tissues [25]. Only in granulomatous inflammatory infiltrates have higher percentages been observed [21]. TcR1-positive T cells cultured from transplanted hearts in humans have been reported not to be cytotoxic [15]. Thus, the function of TcR1-positive cells in allografts is not known. From Fig. 2 it is clear that the sum of the number of TcR1- and TcR2-positive T cells in the biopsies from the three studied patient groups is less than the number of CD3-positive cells. In preliminary experiments (data not shown) applying beta F1 and TcRgd1 monoclonal antibodies on peripheral blood mononuclear cells (PBLs) from healthy controls, the same phenomenon was observed. FACS analysis of the same PBLs using the WT31 instead of the beta F1 monoclonal antibody revealed a significantly higher number of TcR2-positive cells, resulting in the disappearance in the gap between the sum of the TcR1- and TcR2-positive cells and the number of CD3-positive cells.

Thus, counting of beta F1-stained sections results in false, low values for TcR2-positive cells. Unfortunately, other more sensitive monoclonal antibodies reacting with TcR2-positive cells in tissue sections are, to our knowledge, unavailable at this time.

Adhesion molecules have been shown to play an important role in the interaction of cytotoxic T cells with their targets [2, 7, 9, 32]. Furthermore, our group has recently shown that antilymphocyte function-associated molecule-1 (LFA-1) monoclonal antibodies inhibit the donor-specific lysis of proximal tubular epithelial cells [20, 33]. Therefore, we tested renal biopsies for the expression of ICAM-1, which is the ligand of LFA-1, and we compared its expression with that of HLA class II antigens. Like ICAM-1 [23], HLA class II antigens are not normally expressed on renal tubular cells [22] and are susceptible to modulation by cytokines [16, 17, 33]. Furthermore, it has been suggested that the appearance of HLA class II antigens on renal tubular cells might be a useful marker to differentiate between rejection and other causes of renal graft dysfunction [2]. In agreement with the results recently reported by Faull and Russ [9], we detected ICAM-1 in tubular cells during renal allograft rejection.

ICAM-1 expression is significantly associated with rejection. This conclusion is at variance with that by Faull and Russ [9], who question the usefulness of this marker for the diagnosis of renal graft rejection, since they detected it in several biopsies without apparent rejection. However, the number of biopsies with rejection studied by us ($n = 36$) is considerably larger than the number in Faull and Russ's study ($n = 8$). This may explain why, in our study, statistical significance ($P < 0.001$) could be reached in the absence of ICAM-1-negative tubules in biopsies taken during rejection. We recognize that our results need to be confirmed in a larger, prospective study in which biopsies are taken irrespective of renal function and therapy. Until the results of such a study are known, classical histological abnormalities, such as diffuse interstitial infiltrates, tubular basement membrane involvement, capillary congestion, and pericapillary mononuclear cell infiltrate, will certainly increase the likelihood of rejection. Tubular ICAM-1 expression may be at least as valuable for the clinician, as it was the most sensitive marker for rejection in this study. Thus far, the absence of tubular ICAM-1 expression seems to exclude rejection.

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