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Adhesion molecules and rejection of renal allografts

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Adhesion molecules and rejection of renal allografts. Despite an increasing amount of immunohistochemical and molecular biology data relating to the pathogenesis of kidney transplant rejection, the pathological diagnosis of this condition still rests on routine light microscopy. The detection of changes in expression and distribution of adhesion molecules in renal allograft biopsies may open a new era of increased accuracy of rejection diagnosis. Of the various adhesion molecule reactivities, peritubular capillary VCAM-1 staining appears to be the most specific finding for chronic rejection. This same staining reaction is seen in acute rejection, but may have less specificity in that setting.

There has been substantial progress recently in the understanding of adhesion molecules and their complex interactions in human disease [1, 2]. The involvement of these molecules in the rejection of transplanted organs has been an area of special interest [3, 4].

The transplanted kidney is an ideal natural laboratory for the study of involvement of adhesion molecules in renal diseases. Repeat biopsies are frequently performed throughout the course of the transplant, and these may identify recurrent disease at an earlier time than it would be possible to observe the same process in the native kidney. In addition, diseases may progress more quickly in a single tranplanted kidney than they would in native kidneys, thus allowing the identification of more stages of the disease in a shorter time period. Focal glomerulosclerosis, a condition that may recur within minutes in the transplanted kidney, is one disease that has been studied in this manner [5].

Kemeny et al [5] found that podocytes show altered integrin distribution in idiopathic focal glomerular sclerosis that changes in the course of the disease. They postulated that podocytes lose their adhesive phenotype in early FSGS, which may contribute to the detachment of podocytes from the GBM.

Studies on involvement of adhesion molecules in ischemia-reperfusion injury [6] are particularly relevant to the transplanted kidney, where ischemic injury leads to shedding of live tubular cells into the urine which is an order of magnitude greater than that observed in the ischemically-damaged native kidney [7].

Probably the most interesting area of investigation in which adhesion molecules have been studied in the transplanted kidney is in acute and chronic rejection [8–12]. This communication will briefly review the functional significance and the diagnostic and therapeutic utility of adhesion molecule expression in acute and chronic renal transplant rejection.

Acute rejection

Acute rejection of renal allografts involves many interrelated processes, including recognition of alloantigens, activation and proliferation of allospecific T cells, recruitment, interaction, and migration of effector inflammatory cells, all resulting in target cell damage by cytolytic or delayed hypersensitivity mechanisms. Recently, it has become increasingly apparent that various adhesion molecules play pivotal roles in these processes [13–18]. Indeed, treatment with antibodies against several adhesion molecules can reverse or even prevent acute rejection in animal models and clinical studies [14, 18–21].

Functional significance of adhesion molecules in acute allograft rejection

The adhesion molecules mediating various processes in acute rejection and their ligands are summarized in Tables 1 to 5. It should be noted that many adhesion molecules are expressed by several cell types and thus may mediate more than one function [13–18]. Although numerous synonyms exist for some adhesion molecules, only the most recent and widely accepted names and abbreviations are used herein [13–18, 22].

Antigen presentation

It is well known that specific recognition of the alloantigen-MHC complex on antigen presenting cells by the T cell receptor-CD4 (or CD8) complex results in activation of T lymphocytes only if secondary stimulatory signals are provided by additional contacts between antigen presenting cells and T cells [13, 23]. This accessory stimulatory contact is provided by the pairs of adhesion molecules listed in Table 1 [13–18]. Aside from the dendritic reticulum cells ("professional" antigen presenting cells), any cell with constitutive or induced expression of MHC molecules may assume this function. However, whether the antigen presentation results in activation of allospecific T-cells depends on whether antigen presenting cells express the appropriate adhesion molecules for secondary signaling [23].

Inflammatory cell-endothelial cell interactions

During acute rejection, inflammatory cells, including T lymphocytes, must come in contact with endothelial cells, which not only

Table 1. Adhesion molecules and antigen presentation

T cells	Antigen presenting cells
LFA-1	ICAM
VLA-4	VCAM-1
CD28	B7 and B70
CTLA-4	B7 and B70
LFA-2	LFA-2

Modified from Truong et al [12].

Table 2. Adhesion molecules and endothelial-inflammatory cell interaction

Inflammatory cells	Endothelial cells
Glycoproteins and glycolipids	E-selectin
Glycoproteins and glycolipids	P-selectin
PECAM-1	PECAM-1
L-selectin	GlyCAM-1
CD44	Hyaluronate
VLA-4	VCAM-1
LFA-1	ICAM-1
LFA-2	LFA-3

Modified from Truong et al [12].

Table 3. Adhesion molecules and transendothelial migration of inflammatory cells

Inflammatory cells	Endothelial cells
LFA-1	ICAM-1
VLA-4	VCAM-1

Modified from Truong et al [12].

present alloantigens and are, themselves, targets for immune-mediated injury, but also constitute a barrier through which inflammatory cells must transmigrate in order to localize in the renal interstitium [13–18]. The necessary contact is mediated by the pairs of adhesion molecules listed in Table 2. Interactions of VLA-4/VCAM-1 and LFA-1/ICAM-1 are of indisputable importance in acute rejection and have been thoroughly evaluated in the tissue diagnosis of rejection [24–26]. Although other adhesion/ligand pairs play crucial roles in inflammation, whether they facilitate acute rejection or whether their identification in tissue sections has a diagnostic role remains unclear [13–18, 23–26].

Transendothelial migration of inflammatory cells

Allospecific or non-specific inflammatory cells must migrate through capillaries to infiltrate the interstitium, an important feature of acute cellular rejection. This highly complex process likely depends on the interplay of many factors, including cytokines, chemotactic factors, and adhesion molecules [27, 28]. The role of specific adhesion molecules in this process has been partly elucidated [13, 27, 28]. LFA-1/ICAM-1 interaction appears crucial to this process Table 3, as T cell clones from LFA-1 deficient individuals bind normally to cultured endothelial monolayers, but migrate through cultured endothelial cells at only about half the rate of normal lymphocytes [29]. In addition, monoclonal antibodies against LFA-1 markedly reduce lymphocyte migration [30]. Recently, transendothelial migration of human monocytes has been shown to be mediated by VLA-4 [31].

Table 4. Adhesion molecules and interstitial localization of inflammatory cells

Inflammatory cells	Interstitial cells, extracellular matrix
LFA-1	ICAM-1 (on interstitial fibroblasts)
VLA-4	Receptors on extracellular matrix
VLA-1 to VLA-6	Receptors on extracellular matrix
CD44	Hyaluronate

Modified from Truong et al [12].

Table 5. Adhesion molecules and mediation of binding of cytotoxic T cells or natural killer cells to target cells

Inflammatory cells	Target cells
VLA-4 (activated T cells)	VCAM-1 (activated tubular and endothelial cells)
CD44 (lymphocytes)	Hyaluronate (on target cells?)
LFA-1 (leukocytes, natural killer cells)	ICAM-1 (activated tubular and endothelial cells)
Mac-1 (macrophages, granulocytes, natural killer cells)	ICAM-1 (activated tubular and endothelial cells)
LFA-2 (T cells, natural killer cells)	LFA-3 (tubular and endothelial cells)

Modified from Truong et al [12].

Interstitial localization of inflammatory cells

The dynamics of inflammatory cells in the renal interstitium are poorly understood (Table 4). The role of adhesion molecules in interstitial inflammation is mostly conjectural, based on knowledge of adhesion molecules expressed by inflammatory cells and their ligands found on fibroblasts and extracellular matrix proteins. For example, LFA-1 on T-lymphocytes can bind to ICAM-1 induced on interstitial fibroblast-like cells during rejection. VLA-4 and VLA-5 on activated T cells can bind fibronectin, and VLA-1, VLA-2, VLA-3, VLA-5, and VLA-6 may bind various other extracellular matrix proteins, including collagens and laminin [22].

Binding of cytotoxic T-cells and natural killer cells to target cells

Effector cells mediate damage to the rejected kidney through many mechanisms, one of which is lysis of target cells by CD8+ T lymphocytes or natural killer cells. Cell to cell contact, which may be provided by the pairs of adhesion molecules listed in Table 5, is necessary for these cells to deliver the "cytolytic hit" [32]. These specific adhesion molecule interactions may explain, at least in part, the attachment of CD8 T cells to activated endothelial cells in producing endothelialitis and the infiltration of these lymphocytes between tubular epithelial cells with resultant tubulitis. Both endothelialitis and tubulitis are characteristically seen in acute rejection [33].

Several studies have reported prevention or reversal of acute rejection in animals or humans by treatment with antibodies against various adhesion molecules, including ICAM-1 and LFA-1. These fascinating observations confirm the crucial role of adhesion molecules in the diverse biological processes leading to acute rejection [18–21].

Table 6. Staining patterns for adhesion molecules in normal and rejecting kidney

	ICAM-1		VCAM-1		E-selectin		P-selectin		PECAM-1	
	Normal	Rejection	Normal	Rejection	Normal	Rejection	Normal	Rejection	Normal	Rejection
Glomerular endothelial cells	+	+	−	−	−	−	±	±	+	+
Mesangial cells	−	−	−	−	−	−	−	−	−	−
Podocytes	−	−	−	−	−	−	−	−	−	−
Parietal epithelial cells	+	+	+	+	−	−	−	−	−	−
Tubular cells	±	++	±	++	−	−	−	−	−	−
Peritubular capillary endothelial cells	+	+	±	++	−	±	±	±	±	±
Endothelial cells of larger vessels	+	+	±	+	−	±	±	±	+	+

Modified from Truong et al [12].

Diagnostic utility of adhesion molecule expression in acute renal allograft rejection

Although numerous adhesion molecules are implicated in acute rejection, only a few of them have been evaluated for diagnostic use. Most thoroughly studied are ICAM-1 and VCAM-1, whereas significantly less information is available for E-selectin, P-selectin, and PECAM-1. The diagnostic use of these molecules centers around their immunohistochemical detection in graft biopsies. Rare studies have supplemented immunohistochemical analysis with *in situ* hybridization [24, 34]. Studies analyzing the corresponding mRNAs by Northern hybridization or polymerase chain reaction have not been attempted and likely would not have the same diagnostic utility since changes in message level would not be site specific. As implied above, some adhesion molecules are expressed by multiple cell types (such as ICAM-1 on monocytes, mesangial cells, lymphocytes, endothelial cells, tubular epithelial cells), some of which may have up-regulated expression in disease processes other than rejection, which can affect the transplanted kidney. It is the change in expression of these molecules at specific renal compartments that provide the diagnostic clues. This information is best provided by immunohistochemistry. Staining patterns with monoclonal antibodies to the various pertinent adhesion molecules in the normal kidney and renal allograft with rejection are outlined in Table 6.

ICAM-1

All studies agree that ICAM-1 is strongly expressed constitutively in endothelial cells of the normal kidney, and is not phenotypically altered during acute rejection [24–26, 35–40]. In contrast, the normal tubules are either completely negative or display weak staining of rare proximal tubules in up to 65% of cases. Acute rejection is associated with diffuse staining of proximal tubules, predominantly the brush border, and focal staining of distal tubules and collecting ducts. The diagnostic utility of ICAM-1 expression is somewhat lessened since biopsies of grafts without rejection or grafts with stable function also sporadically express increased tubular ICAM-1 [37, 38]. Nevertheless, staining for ICAM-1 has been used for differentiating acute rejection from cyclosporine A nephrotoxicity [41].

VCAM-1

The glomerular endothelial cells in normal kidney do not express VCAM-1 and remain negative in acute rejection [34, 36–38, 42–45]. In contrast, the endothelial cells of peritubular capillaries or large vessels display negative or very weak, focal staining in normal kidney, but become strongly and diffusely positive during acute rejection. The changes of tubular VCAM-1 expression in acute rejection are similar to that of ICAM-1 except that the staining is basolateral rather than luminal (brush border). Some preliminary reports indicate overlapping patterns of VCAM-1 staining between rejecting and stable grafts [37, 38].

E-selectin

Expression of E-selectin is not seen in normal kidney, but is observed focally in endothelium of peritubular capillaries and large vessels during rejection [25, 26, 36–38].

P-selectin

P-selectin appears to be focally expressed in endothelial cells of normal kidneys and is not detectably altered during acute rejection [38].

PECAM-1

Immunohistochemical staining for this adhesion molecule strongly decorates all endothelial cells in normal kidney. During acute rejection, up to 17% of cases paradoxically display focal loss of staining, which may be related to endothelial damage [26]. Another preliminary study, however, indicated increased PECAM-1 staining in acute rejection [25].

Current data on adhesion molecules in serum, as opposed to tissue expression, are meager and, in general, indicate a lack of diagnostic implication. Specifically, serum level of ICAM-1, VCAM-1, and E-selectin was shown to correlate with serum creatine but not with diagnostic categories. Moreover, increased serum VCAM-1 has been noted in CMV infection in renal transplant recipients [16, 39, 40].

Adhesion molecules and their ligands in chronic rejection

Little work has been done thus far in this field. Duijvwestijn et al [46] found increased expression of ICAM-1 and its ligands in a subpopulation (7 of 52) of glomeruli in a rat model of chronic rejection. They suggested that the positive glomeruli may play an important role in the development of chronic rejection.

Hill, Main and Atkins [10] and von Willebrand et al [47] found that peritubular capillary VCAM-1 staining was the most specific finding for chronic rejection in human kidneys. They postulate that the up-regulation of VCAM-1 may be one of the important etiologic factors in the development of chronic rejection. VCAM-1 appears to be the most diagnostically relevant adhesion molecule in chronic rejection.

Conclusion

The study of adhesion molecules not only provides significant insight into the mechanisms leading to acute and chronic renal allograft rejection, but also opens new venues for therapeutic manipulation. Although acute rejection is frequently associated with distinctive changes in the tissue expression of several adhesion molecules, the precise role of these changes in the differential diagnosis of acute rejection awaits further studies.

Standard approaches to the diagnosis of acute and chronic transplant rejection do not employ immunochemical or molecular biology techniques [48, 49]. It is hoped that with further investigation of adhesion molecules, their detection may begin a new phase of increased accuracy of rejection diagnosis.

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