Published in final edited form as:
Transplantation. 2008 November 27; 86(10): 1340–1348. doi:10.1097/TP.0b013e3181891d8b.

ENDOTHELIAL CELLS IN ALLOGRAFT REJECTION

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Abstract

In organ transplantation, blood borne cells and macromolecules (e.g. antibodies) of the host immune system are brought into direct contact with the endothelial cell (EC) lining of graft vessels. In this location, graft ECs play several roles in allograft rejection, including the initiation of rejection responses by presentation of alloantigen to circulating T cells; the development of inflammation and thrombosis; and as targets of injury and agents of repair.

Keywords

antigen presentation; inflammation; leukocyte; lymphocyte; antibody; complement

Introduction

In this review we will summarize the roles that graft endothelial cells (ECs) play in various stages of the rejection of allografts.

Endothelial Cells as Initiators of Rejection

T cells recognize allografts as non-self either by direct or indirect recognition of alloantigens (signal 1) (1,2). Direct recognition is initially dominant, involving many more T cell clones, whereas indirect recognition may become more important at later times. The adaptive immune response is altered by experience and at least half of all circulating T cells in an adult human are memory cells (3,4). Naïve and memory T cells have different requirements for activation (5–7) and patterns of recirculation (8). Memory cells are further subdivided into effector memory T cells that home to sites of inflammation and central memory T cells that recirculate through secondary lymphoid organs (8). Memory T cells generally have lesser requirements for costimulation (signal 2) and are less subject to modulation of their patterns of response by cytokines (signal 3) (9). They are also harder to immunosuppress, and to regulate (10). There is a high frequency of alloreactive memory T cells in humans that correlates with the outcome of clinical transplantation (11). As we will discuss shortly, memory T cells have a special relationship with ECs that will be described below.

Signals 1 and 2 are normally typically presented to naïve T cells by dendritic cells (DCs), referred to as “professional” antigen presenting cells (APCs). DCs increase their expression of MHC peptide complexes and co-stimulators (undergo “maturation”) in response to microbe-

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The authors have no conflicts of interest.

derived “pathogen-associated molecular patterns” (12) or signals released by injured cells (“damage-associated molecular patterns” or “alarmins”) (13). The latter may be more relevant in transplantation because ischemia/reperfusion (I/R) injury during organ transplantation releases alarmins, maturing DCs within the graft. Alarmins may also directly influence alloreactive memory T cell responses independently of DCs (14). In a rat kidney transplant model, graft-derived DCs (“passenger leukocytes") may be required to initiate graft rejection (15). In mice, allograft rejection by adoptively transferred naïve CD8+ T cells requires their activation within secondary lymphoid organs by graft-derived DCs (16), but rejection by adoptively transferred memory CD8+ T cells may occur in the absence of secondary lymphoid organs (17) and without a need for graft DCs (18). Passenger leukocyte depletion with antibody failed to prevent rejection of human kidneys although it is difficult to ascertain the completeness of depletion in this case. Nevertheless, these observations suggest that cells other than DCs may initiate allograft rejection perhaps through activation of alloreactive memory T cells (19). Several lines of evidence suggest that human (or mouse) ECs serve as this alternative initiator of rejection:

(1). In human allografts, vascular ECs basally express both class I and class II MHC molecules (20,21). (see Table I). In culture, human ECs reduce class I and completely lose expression of class II molecules; cytokines, including TNF, IFN-α, IFN-β and IFN-γ, can restore class I MHC molecule expression, but only IFN-γ restores class II expression (22). Human ECs also process protein antigens to peptides that can be recognized by T cell clones (23). It is unknown if human ECs process antigens differently from other cell types, although this has been suggested for viral antigens (24). However, CTL produced by culturing human CD8+ T cells with allogeneic B lymphoblastoid cells readily recognize allogeneic ECs, implying that common peptides are generated (25,26). Human ECs differ from mouse ECs in several respects relevant for antigen presentation (see Table II), and this must be considered when interpreting rodent transplant experiments.

(2), Cultured human ECs display functional co-stimulators that enhance T cell IL-2 production (27). While unable to express either CD80 or CD86, the principal costimulators required by naïve T cells, human ECs express other costimulators that are relevant for the activation of memory T cells. (see Table I).

(3). Human ECs cultured with resting allogeneic T cells in the absence of professional APCs stimulate IL-2 production by and proliferation of memory but not naïve T cells (4,7,27). This capacity distinguishes human ECs from most other cell types in peripheral tissues (28) as well as from DCs (see Table III). Once activated by ECs, memory T cells can subsequently respond to other cell types expressing relevant MHC molecules (28). Activation by ECs causes effector cytokine production from memory CD4+ T cells (29) and maturation of memory CD8+ T cells into cytolytic T lymphocytes (CTL), some of which are specific for EC targets (30). In mice, CD8+ but not CD4+ T cells proliferate to cultured allogeneic ECs (31,32). CD4+ T cell responses to cultured mouse ECs may largely involve activation of regulatory T cell populations (33). Significantly for transplant rejection, adoptive transfer of resting human effector memory T cells to an immunodeficient mouse host in the absence of professional APCs can injure allogeneic human ECs within a human skin graft (29).

Although human graft ECs are capable of directly activating T cells, ECs may play additional roles in the process of alloantigen recognition. First, EC may promote differentiation of monocytes into competent APCs (34) and may actually contribute to their differentiation into DCs (35). Second, host ECs may pick up graft antigens and present them to CD8+ T cells, displaying the property of "cross-presentation" sometimes proposed as unique to DCs (36).

The ability of ECs to stimulate alloreactive effector memory CD4+ T cells to secrete IFN-γ may have a special role in chronic allograft vasculopathy. This lesion, which is the major cause of late cardiac graft loss (and probably late renal graft loss as well) may depend on local IFN-γ production within the vessel wall (37). Histological analysis of these lesions in allograft coronary arteries suggests the persistence of graft ECs (38) in direct contact with subjacent host T cells (39). ECs may further contribute to chronic allograft vasculopathy by acting as a source of signals that induce bystander T cells to express inducible nitric oxide synthase, a signal that may help sustain alloresponses (40).

ECs as Participants in Rejection

Allograft rejection involves recruitment and activation of circulating leukocytes in response to co-ordinated changes in microvascular ECs (reviewed in (41)). Pro-inflammatory alterations in ECs is termed “activation” (41). Type I activation is mediated in response to ligands such as histamine or thrombin, and occurs independently of protein synthesis within minutes. Examples are NO or prostaglandin production or P-selectin translocation from storage organelles (Weibel-Palade bodies) to the cell surface. Type II activation is induced by cytokines such as TNF or IL-1, and involves transcription of new genes such as the adhesion molecules E-selectin, ICAM-1 and VCAM-1. Both responses may contribute to vascular leakiness, a cardinal feature of inflammation, although type II activation causes more sustained junctional changes and vascular leak. Key changes in activated venular ECs that contribute to leukocyte recruitment are expression of adhesion molecules that bind leukocytes and display of chemokines that activate the captured leukocytes. (see Table IV). The relevant EC adhesion molecules and activating chemokines responsible for leukocyte recruitment vary with particular leukocyte populations. Monocyte recruitment into rejecting human renal allografts may depend particularly upon EC selectins and the chemokines MCP-1 (CCL2) and RANTES (CCL5) that bind to chemokine receptors CCR1, CCR2 and CCR5 (42). Inflammatory T cells, especially those that have differentiated into effector memory T cells, more readily interact with VCAM-1 and with chemokines that bind to the receptor designated CXCR3, namely Mig (CXCL9) IP-10 (CXCL10) and ITAC (CXCL11) (43) and ENA-78 (CXCL5) (44). Both RANTES and IP-10 expression correlate with T cell infiltration into rejecting renal allografts (45,46). In vitro, T cells, but not monocytes, require shear stress to initiate transmigration (43,47). ECs may further contribute to leukocyte recruitment by forming a cup-like extension of the plasma membrane at sites of transmigration (48). This structure may form away from intercellular junctions allowing leukocytes to pass through the EC body.

EC functions related to antigen presentation and leukocyte recruitment may be linked. Antigen-activated T cells are a major source of cytokines that mediate type II EC activation, including TNF and lymphotoxin (LT, also called LTα or TNFβ). Antigen-activated T cells may also activate ECs through a contact-dependent pathway utilizing CD154 (49). EC antigen presentation to effector memory T cells may trigger T cell diapedesis involving the cytokine-inducible transmembrane chemokine fractalkine (CX3CL1) and its receptor (CX3CR1) on effector memory T cells (50).

ECs may also contribute to graft vessel thrombosis that can exacerbate graft injury (51). Resting ECs keep blood fluid (41) by preventing platelet activation and displaying tissue factor pathway inhibitors and inhibitors of thrombin, such as heparan sulfates (51). If thrombin is generated, resting ECs capture the active enzyme on thrombomodulin and use it to activate protein C, which degrades clotting factors. ECs also produce plasminogen activators that lead to lysis of fibrin thrombi. Type II activated EC synthesize express pro-coagulant molecules. At the same time EC injury (see below) abrogates EC anti-coagulant properties. Although thrombosis may be observed in acute cell-mediated rejection (ACR), it is more characteristically associated with antibody-mediated rejection (AMR) (52).

ECs as Targets of Rejection

Allograft ECs are a primary target of rejection. Cells and molecules that contribute to rejection through their actions on ECs include:

(1). Cytolytic T Lymphocytes (CTL)

Direct recognition of a specific complex of peptide and non-self class I MHC molecules on graft EC by host CTL is a major mechanism of ACR in immunosuppressed patients, leading to graft cell apoptosis (53,54). The presence of CTL and CTL-specific mRNAs in biopsies correlates with ACR (55). CTL generated from CD8+ memory T cells by co-culture with allogeneic ECs may only kill ECs (30), and EC-selective CTL have been recovered from rejecting grafts (56). EC lysis by CTL involves either T cell ligands that engage death receptors (DRs, see below) on ECs or granule exocytosis of effector molecules (57). Both pathways require cell-cell contact and are initiated by recognition of non-self class I MHC/peptide complexes. Granule exocytosis deposits perforin and granzyme B from the CTL on the target cell surface. Perforin facilitates entry of granzyme B, a serine protease that cleaves and activates pro-capsase 3, an effector of apoptosis. The activation and activity of caspase 3 may be held in check by X-linked Inhibitor of Apoptosis Protein (x-IAP). Granzyme B also cleaves and activates pro-caspase 8, which may cleave and activate pro-caspase 3, and may also cleave and activate the cytosolic protein Bid. Activated Bid interacts with Bax, a pro-apoptotic member of the Bcl-2 family, inducing Bax to dimerize in the outer mitochondrial membrane and initiate release of proteins that promote cell death, including cytochrome c, Apoptosis Inducing Factor (AIF) and Second Mediator of Apoptotic Cell death (SMAC, also known as Diablo). This Bax-mediated release reaction is antagonized by anti-apoptotic members of the Bcl-2 family, including Bcl-2 itself. SMAC/Diablo prevents x-IAP from inhibiting caspase 3 activation. Cytochrome c interacts with Apoptotic Protein Activating Factor-1 (APAF-1) to activate procaspase 9, an alternative activator of caspase-3. AIF leads to cell death independent of caspases. CTL-mediated killing of cultured human ECs depends granule exocytosis and can be inhibited by overexpression of Bcl-2, implying a role for mitochondrial release of SMAC-Diablo in this cell type (58).

(2). Natural Killer (NK) cells

NK cells infiltrate grafts shortly after transplantation (59) and typically recognize targets by a combination of activating and inhibitory receptors (60). Activating receptors recognize ligands such as the Fc portions of antibodies, enabling antibody-dependent cell-mediated cytotoxicity (ADCC), or molecules such as MHC class I-related antigen-A-1 (MICA-1). ADCC may be a major component of acute AMR in which ECs are primary targets of alloantibody (see below). NK cell inhibitory receptors often recognize specific allelic forms of class I MHC molecules complexed to self-peptides but cannot recognize allogeneic cells that lack these molecules (“absent self”). In the absence of inhibitory signals, host NK cells will recognize and kill allogeneic ECs (61). NK cell-mediated EC killing has been invoked as a primary pathway of hyperacute and accelerated acute rejection of xenografts (62) and has been proposed to play a role in chronic allograft vasculopathy (63). A role for NK cells in ACR of allografts is less clear. NK cell killing utilizes the same mechanisms as CTL, namely engaging DR ligands and granule exocytosis of effector molecules.

(3). Macrophages

Monocytes infiltrate kidneys undergoing ACR or AMR and differentiate into macrophages, which contribute to rejection (64). Macrophages have been associated with capillary regression during development by inducing EC apoptosis (65); similar events may occur during rejection. EC injury by macrophages may involve multiple effector mechanisms including elaboration of TNF, TRAIL, reactive oxygen species (ROS) and NO. The expression of these effectors can

be enhanced by IFN-γ-mediated macrophage activation (66). Macrophages may undergo an alternative pathway of activation, differentiating into "M2 cells" that are distinct from IFN-γ-activated "M1 cells". M2 cells are associated with tissue repair but may also promote fibrosis in late graft loss (66).

(4). Neutrophils

Neutrophils are usually the first cell type recruited into inflammatory responses and their paucity in the infiltrates associated with ACR is striking. It is possible that they are transiently recruited at the very earliest stages of the acute rejection process and have disappeared by the time biopsies are taken. This idea is supported by the observation that E-selectin expression by ECs in human cardiac biopsies, which is important for neutrophil recruitment, is transient and predictive of imminent rejection and absent during rejection responses (67,68). Neutrophils are more common in AMR or in non-immune injury to ECs (see below) and reduction of neutrophil infiltrates in the peri-operative period reduces subsequent T cell-mediated rejection of mouse cardiac allografts (69). Injury of EC depends on neutrophil activation and neutrophils may be activated by cytokines, chemokines, antibodies and complement products. Activated neutrophils may release both ROS and degradative enzymes that contribute to killing of microbes; these effector molecules are also capable of injuring or killing ECs.

(5). Death receptor ligands

DRs are members of the TNF receptor superfamily that contain an intracellular protein-protein interaction domain called a death domain (DD) (70,71). DRs expressed on ECs include TNFR1 (also known as DR1), Fas (also known as DR2), DR3, TRAIL-R1 (also known as DR4) and TRAIL-R2 (also known as DR5). TNFR1 binds both TNF and lymphotoxin, made primarily by activated leukocytes, whereas DR3 binds TNF-like molecule 1A (TL1A), which is made by ECs and activated leukocytes (72). TNF, LT and TL1A are found in rejecting allografts (73). Fas binds FasL, whereas the two TRAIL receptors bind TRAIL. These membrane-associated ligands are expressed on activated effector cells, such as CD4+ effector T cells, CD8+ CTL, NK cells or macrophages, and can mediate cell-cell contact-dependent killing. In most cells, DR-initiated killing involves activation of DR-linked pro-caspase 8. This has been shown to occur in cultured human ECs and is enhanced by IFN-γ treatment which increases pro-caspase 8 expression (74). IFN-γ also allows TNFR1 to initiate a caspase-independent death pathway in ECs that is initiated by the lysosomal enzyme cathepsin B and involves Bid-independent release of AIF from mitochondria (75).

In the kidney TNFR1 is expressed basally on glomerular and vascular ECs and is downregulated during ACR or ischemia/reperfusion (I/R) injury (76). Transcripts and protein for DR3 are induced in vascular ECs (and renal tubular epithelial cells) in human kidney allografts undergoing either ACR or I/R injury (77). TNFR1 signaling appears responsible for TNFR1 downregulation (78). Signaling through TNFR2, which is not a DR and which is minimally expressed in normal kidney, upregulates TNFR2 expression on ECs and on tubular epthelial cells (78). Whereas TNFR1 signals lead to inflammation and apoptosis, TNFR2 signals promote proliferation and repair (78). Signals that induce DR3 are unknown and signals through DR3 are initiated by binding of TL1A (72). TL1A protein is synthesized by ECs in normal human kidney and synthesis is increased in rejection (73). In organ cultures of normal human kidney and wild-type mice, TL1A activates NF-κB, induces caspase-3 and apoptosis, and upregulates TNFR2 in TEC. In DR3 null mice, TL1A does not induce NF-κB or caspase-3 activation but still upregulates TNFR2, suggesting there is a second receptor for TL1A (73).

(6). Antibodies and complement

AMR is characterized by monocyte margination against EC and by capillaries containing thrombi and fibrinoid arterial necrosis (52). Antibody and complement components are present

on the EC surface, and C4d deposition is now taken as evidence of AMR (79) but the lectin pathway of complement activation, which can be triggered by ischemia, could also lead to endothelial C4d deposits. The diagnosis of AMR is supported by detection of circulating antibodies that recognize graft ECs (54). Such antibodies most often react with HLA-A, B, C and DR antigens, but circulating anti-EC antibodies that react with non-HLA alloantigens have been detected in patients (80). Some non-HLA alloantigens are shared by ECs and monocytes but not lymphocytes (E-M antigens), and some are only found on ECs (E antigens). MICA on renal endothelium is also a potential target for AMR. AMR to ECs may involve complement and complement-induced inflammation and/or NK cells, which recognize bound antibodies via Fc receptor and mediate ADCC (81).

In addition to killing ECs via complement activation or targeting NK cells for ADCC, alloantibodies may activate ECs. Anti-MHC antibodies activate ECs to degranulate Weibel-Palade bodies, leading to release of IL-8 and display of P-selectin. In culture and in humans skin grafts placed on immunodeficient mice, F(ab)' fragments of an HLA-A,B,C antibody can exert such effects despite their inability to engage Fc receptors or active complement (82). Anti-class I antibodies may also be mitogenic for ECs, although the role of this response to allograft rejection is unclear. Activation of the complement system may also affect ECs independent of antibody, causing perturbation in EC barrier function retraction of EC plasma membrane from the underlying substrate, release of preformed von Willebrand factor and P-selectin from Weibel-Palade bodies to the cell surface, and production of cytokines including IL-α, IL-8 and MCP-1 (83). The combination of C5a and antibody binding can cause ECs to shed anti-coagulant heparan sulfates (84). ECs express a variety of complement receptors and complement regulatory proteins that may modulate these responses (85,86). There is little evidence to date that any of these are actively regulated in allograft rejection. Deposition of complement membrane attack complex on ECs usually does not, by itself, kill ECs but may induce endothelial microparticle (EMP) formation and thrombosis (see below) (87).

(7). Non-immune injuries

Hemodynamic factors combined with mediators such as cytokines have profound effects on EC injury. Disturbances in flow patterns in atherosclerosis, post-surgical, intimal hyperplasia and I/R injury or infection (e.g., with cytomegalovirus) can influence EC-T cell interactions through expression of alarmins and adhesion molecules promoting rejection (88–90). These responses may explain why renal allografts from living-related donors which are healthy, generally have a higher graft survival than cadaver donor transplants, involving injured kidneys.

(8). Thrombosis

Injury to ECs from whatever cause may lead to graft vessel thrombosis. Circulating procoagulant EMPs, which are shed plasma membrane components, are markers of vascular damage produced by EC apoptosis or deposition of the complement membrane attack complex, but are also generated in response to thrombin, collagen, and/or shear stress (91,92). EMPs impair EC function in vitro, diminishing acetylcholine-induced vasorelaxation and NO production, and increasing superoxide production (93). At the same time, cytokine-activated EC lose some anti-coagulant properties, such as expression of thrombomodulin and acquire pro-coagulant properties such as expression of tissue factor and fibrinogen-like protein 2 (41). As noted earlier, EC injury and type II-activation may thus combine to promote thrombosis.

ECs Resistance to Injury and Repair

ECs can acquire resistance to injury by up-regulating a number of cytoprotective genes such as hemoxygenase-1 (HO-1), A20, Bcl-2, and Bcl-x_L, which protect cells from cytokine-mediated apoptosis (94). Many of these gene products are regulated by NF-κB and are induced by TNF. Induction of protective genes may contribute to resistance against AMR, a phenomenon called “accommodation.” (94). Accommodated grafts function without rejection despite the presence of recipient-specific antibodies. Although many genes contributing to resistance to injury are regulated by NF-κB, activation of the serine/threonine kinase Akt via the PI3K signaling pathway and/or of ERK-1,2 in response to TNF (95) or growth factors, (96–98) can also contribute to cytoprotection. IL-11 and IL-6, which signal via STAT3, have also been shown to render EC resistant to immune-mediated injury (99,100).

Graft vessels containing injured ECs may undergo repair. For injuries of limited extent, neighboring ECs may simply spread to cover the defect and then divide. In cases of more extensive vessel injury (e.g., vascular rejection), vessels of transplant recipients may display endothelial chimerism through replacement of damaged donor endothelium by host-derived precursors (101). The percentage of recipient ECs in the peritubular capillaries correlates with the type of renal transplant rejection, being predominantly found in vascular rejection. It is likely that ECs are lost from the vessel as a result of rejection and are replaced by circulating endothelial progenitor cells (EPCs) that have the capacity to differentiate into mature ECs. The markers that define circulating EPCs are controversial and true EPCs must be distinguished from hematopoietic cells that stimulate angiogenesis but do not give rise to long-lived ECs (102). The signals that recruit EPCs are also unknown, but both VEGF (103) and SDF-1 (104) are thought to be important. Both may be detected in allografts.

Conclusions

We have reviewed evidence that graft ECs are critical players in all stages of the host response to allografts, contributing to the initiation and effector phases of rejection. We have also noted that ECs may resist injury or contribute to repair. Despite these central roles performed by ECs, it is striking that none of the existing therapeutic strategies to improve the outcome of transplantation have focused on improving EC health or function. Development of such strategies may not only protect the graft, but may also improve the cardiovascular health of the host, a major complication of current transplantation medicine.

Acknowledgements

Supported by grants from National Institute for Health Research and British Heart Foundation to JRB and grants from the NIH (HL036003, HL051014, HL062188 and HL070295) to JSP.

Abbreviations

ACR, acute cell-mediated rejection
ADCC, antibody-dependent cell-mediated cytotoxicity
AIF, apoptosis inducing factor
AMR, antibody-mediated rejection
APC, antigen presenting cell(s)
APAF-1, apoptotic protease activating factor-1
CTL, cytolytic T cell(s)
DC, dendritic cell(s)
DD, death domain
DR, death receptor
EC, endothelial cell(s)

EMP, EC-derived microparticles
EPC, endothelial progenitor cell(s)
HO, hemoxygenase
ICAM-1, intercellular adhesion molecule-1
IL, interleukin
MCP-1, monocyte chemoattractant protein-I
MICA-1, MHC class I-related antigen A-1
NK, natural killer
ROS, reactive oxygen species
SMAC, second mediator of apoptotic cell death
TL1A, TNF-like molecule 1A
TNF, tumor necrosis factor
TNFR, TNF receptor
TRAIL, TNF-related apoptosis-inducing ligand
VCAM-1, vascular cell adhesion molecule-1
x-IAP, X-linked inhibitor of apoptosis protein

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Table I

Molecules Expressed by Human Endothelial Cells Relevant for Antigen Presentation

Category	Molecule	Comment	Rels
MHC	HLA-A,B,C	Constitutive; increased by IFN-α,β,γ TNF	(20,21)
	TAP1,2	Constitutive; increased by IFN-α,β,γ TNF	(105)
	LMP2,7	Constitutive; increased by IFN-α,β,γ TNF	(105)
	HLA-DR, DP, DQ	Basal and induced further by IFN-γ	(106)
	Invariant Chain	Basal and induced further by IFN-γ	(106)
Costimulators	LFA-3 (CD58)	Constitutive (Ig superfamily)	(107)
	PDL-1	Constitutive; increased by IFN-γ (Ig superfamily)	(108)
	PDL-2	Constitutive; increased by IFN-γ (Ig superfamily)	(108)
	ICOS-Ligand	Constitutive; increased by TNF (Ig superfamily)	(109)
	4-1BB Ligand	Constitutive; increased by IFN-γ (TNF superfamily)	(7)
	CD40	Constitutive; increased by IFN-γ and TNF (TNFR superfamily)	(110)
	Ox40-Ligand	Constitutive (TNF superfamily)	(7)
	GITR-Ligand	Induced by TNF (TNF superfamily)	(108)
Cytokines	IL-1α	Constitutive; increased by IL-1, TNF	(111)
	IL-6	Induced by IL-1, TNF	(112)
Other	Indolamine 2,3 dioxygenase	Induced by IFN αβγ	(113)

Table II

Some Molecular Difference between Human and Mouse Endothelial Cells Relevant for Rejection

Molecule	Human	Mouse	Rel
Class II MHC	basal and inducible	absent	(114)
LFA-3	constitutive	absent	(114)
CD80	absent	constitutive and inducible	(114)
P-selectin	constitutive and mobilizable	cytokine inducible	(114)
IL-8	inducible	absent	(114)
Activation of CD4+ T cells	central and effector memory cells	regulatory cells only	(29,32)
Activation of CD8+ T cells	memory cells only	naïve and memory cells	(4,31)

Table III

Some Comparisons of Antigen Presentation by Human Endothelial Cells (115) vs. Human Dendritic Cells (116)

Property	Endothelial Cell	Dendritic Cell
Phagocytosis	absent (in vitro only)	present (when immature)
Pinocytosis	active	active
MHC expression	basal; regulated by cytokines	regulated by maturation
Cross presentation	probable	yes
Costimulation	LFA-3 dominant; no B7 (CD80, CD86);	B7 (CD80, CD86) dominant
Adhesion	selective for memory T cells	Cluster with naïve T cells
Activation of T cells	selective for (effector) memory T cells	Preferential with naïve T cells

Table IV

Some Molecules Expressed by Human Endothelial Cells Relevant for Inflammation/Rejection

Category	Molecules	Comment	Rels
Leukocyte Adhesion	E-selectin	Induced by TNF, IL-1	(117)
	ICAM-1	Constitutive; increased by TNF, IL-1 IFN-γ	(118)
	VCAM-1	Induced by TNF, IL-1, IL-4, IL-13	(119,120)
	P-selectin	Constitutive: sequestered until translocated	(121)
	ICAM-2	Constitutive	(122)
Leukocyte Transmigration	PECAM-1	Constitutive	(123)
	CD99	Constitutive	(124)
Leukocyte Activation	Platelet activating factor	Synthesized in response to thrombin, histamine	(125)
	IL-8, Gro-α	Induced by TNF, IL-1	(126,127)
	IP-10	Induced by IFN-γ	(129)
	ITAC	Induced by IFN-γ	(129)
	Mig	Induced by IFN-γ	(130)
	ENA-78	Induced by IL-1	(44)
	MCP-1	Induced by TNF, IL-1, IFN-γ IL-4, IL-13	(131,132)
	Rantes	Induced by TNF plus IFN-γ	(133)
	Eotaxin 3	Induced by IL-4	(134)
	Fractalkine	Induced by TNF, IL-1, IFN-γ	(135)
Vasoactive	Cyclo-oxygenase 2	Induced by TNF, IL-1	(136)
	Endothelial NOS	Constitutive; decreased by TNF	(137)
Procoagulant	Tissue factor	Induced by TNF, IL-1, CD40L	(138,139)
	Heparan sulfate	Shed by Ab + C'	(84)
	Thrombomodulin	Constitutive; decreased by TNF, CD40L	(139,140)