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Participation of Blood Vessel Cells in Human Adaptive Immune Responses

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Abstract

Circulating T cells contact blood vessels either when they extravasate across the walls of microvessels into inflamed tissues or when they enter into the walls of larger vessels in inflammatory diseases such as atherosclerosis. The blood vessel wall is largely composed of three cell types: endothelial cells lining the entire vascular tree, pericytes supporting the endothelium of microvessels and smooth muscle cells forming the bulk of large vessel walls. Each of these cell types interacts with and alters the behavior of infiltrating T cells in different ways, making these cells active participants in the processes of immune-mediated inflammation. In this review we will compare and contrast what is known about the nature of these interactions in humans.

Vascular Cells as Participants in Immune Responses

Immune-mediated inflammation of peripheral tissues depends upon local recruitment of circulating leukocytes into an extravascular site. In most instances, leukocytes are recruited across the wall of post-capillary venules, which are composed of a continuous, one cell thick inner lining of endothelial cells (ECs) supported by an incomplete outer layer of pericytes (PCs) located within the basement membrane to which the ECs are attached (Figure 1). Larger vessels are not directly involved in leukocyte trafficking into tissues, but may themselves be a target of inflammation, for example when arteries become involved by cell-mediated immune responses as occurs in atherosclerosis. In the arterial wall, the EC lining of the vessel is completely covered by vascular smooth muscle cells (SMCs), some of which are located within the vessel intima, consisting of the EC lining and the anatomic space immediately beneath the basement membrane of the ECs. However, most SMCs are densely concentrated in a multilayered, circumferentially oriented array within the vessel media, which surrounds and is separated from the intima by the internal elastic lamina. The arterial adventitia is external to the media and separated from it by the external elastic lamina. The adventitia contains fibroblasts, nerve endings, microvessels (known as vasa vasorum) and vascular stem cells. Some mononuclear leukocytes may also be present in each of these compartments that can increase dramatically in number with inflammation. It is increasingly appreciated that resident cell populations within the environment in which an immune

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response develops can play a major role in shaping the form of that immune response. While much of this emphasis has been on the roles played by parenchymal cells in peripheral tissues, cells of the blood vessel wall are also positioned to affect lymphocytes and recent observations have provided a deeper understanding of how blood vascular ECs, PCs and SMCs interact with infiltrating T cells in adaptive immune responses that occur near microvessels of inflamed peripheral tissues and within the wall of inflamed macrovessels. In this review we consider how these interactions impact the nature of the immune response, with focus on observations made with human cells and tissues. We discuss the issues surrounding the cell source in these experiments, and, when possible, emphasize conclusions based on in vivo observations. We caution against generalizing about the immunological functions of vascular cells, as in “ECs do the following but SMCs do something else.” While each vascular cell type displays specific characteristics that define it as an EC, PC or SMC, each of these populations may vary significantly in both phenotype and function depending on the anatomic location; i.e. their most defining feature is simply their anatomic position within the vessel wall. Heterogeneity among vascular cells arises from several causes (see Box 1). Additionally, major species differences in vascular cell immunological functions have led to much confusion in the literature (see Table 1). We also caution that conclusions from experiments with cultured cells often ignore the profound phenotypic alterations that result from removing cells from their natural context and exposing them to tissue culture conditions.

Interactions of T Lymphocytes with ECs

Transplantation immunologists were the first to investigate whether human ECs are capable of presenting (allo)antigens to T cells, resulting in T cell activation [1]. In situ, most human ECs basally express both class I and class II MHC molecules although the amount of expression may be less in some sites, especially larger arteries [2]. Class I MHC molecule expression decreases and class II MHC molecule expression largely disappears when human ECs are cultured or when human arterial segments are transplanted into immunodeficient xenogeneic mouse hosts, but in both cases, MHC molecule expression may be restored by exposure to human IFN- γ [3, 4]. IFN- γ treatment of human umbilical vein ECs concomitantly upregulates molecules required to load peptides on to class I and class II MHC molecules [5, 6], although not all of the known accessory molecules involved in these processes (e.g. tapasin or HLA-DM) have as yet been studied. Importantly, MHC-peptide complexes expressed by human EC can be recognized by resting antigen (or alloantigen)-specific human T cells in vitro [3, 7]. In other words, cultured human ECs have some capacity to act as antigen presenting cells (APCs).

In addition to recognition of MHC-peptide complexes (signal 1), the activation of resting T cells also depends upon additional signals provided by antigen-independent membrane protein co-stimulators (signal 2). Human EC cultured from a variety of different vessel sources express a number of costimulator molecules, the receptors for which are increased on activated or memory T cells, including LFA-3 (CD58, the ligand for T cell CD2) [8–10], OX40-L (CD252) [10, 11], 4-1BB-L (CD137) (22), ICOS-L (CD275, also known as B7-H2) [10, 12, 13] and GITR-L (no CD number as yet assigned) [14, 15]. ICOS-L expression is generally low but increases markedly in response to inflammatory cytokines such as TNF or IL-1 [10, 12, 13]. Of note, cultured human ECs typically lack both B7-1 and -2 (CD80 and CD86, respectively) [10, 16–18], ligands for T cell activating receptor CD28 and for inhibitory receptor CTLA-4 (CD152), a finding that is consistent with examination of human tissues by immunostaining [19]. There have been a few reports of CD80 and/or CD86 expression on human ECs cultured from certain vascular beds with specialized features such as brain capillaries [20, 21], liver sinusoids [22], or pancreatic islets [23]; expression on liver sinusoidal ECs has also been reported in situ in the setting of fulminant

hepatic failure [24]. While CD80 and CD86 are often viewed as the prototypic costimulators of T cell activation, they are most critical for activation of naïve T cells and less so for memory T cells. Furthermore, it has recently been demonstrated that human ICOS-L (but not mouse ICOS-L) can signal through CD28, potentially substituting for CD80 or CD86 [25]. Human ECs also express CD40 [26–28], often described as a costimulator of T cell activation, although it is uncertain if engagement of the CD40 ligand (CD154) on T cells actually delivers a costimulatory signal to the T cell. In addition to these molecules that positively contribute to T cell activation by serving as a signal 2, cultured human ECs also express ligands that deliver inhibitory signals that limit T cell activation, sometimes called negative co-stimulators, such as PD-L1 (CD274, also known as B7-H1) and PD-L2 (CD273, also known as B7-DC), both of which are inducible by IFN- γ on human EC [29, 30]. In situ, the expression of PD-L1 or PD-L2 has been observed on hepatic sinusoidal EC in the setting of chronic inflammation [31–33] and PD-L1 may induced on human dermal microvessels following injection of IFN- γ and TNF [29]. Overall, the expression patterns of co-stimulators by human ECs, especially after exposure to cytokines such as IFN- γ and/or TNF, are suggestive of a capacity to activate resting memory but perhaps not resting naïve T cells.

Human T cells responses in vitro are typically assessed using cells isolated from peripheral blood and the types of human T cell responses that may be studied are limited by the frequency of T cells in human blood specific for any given antigen. For protein antigens, the frequency has been estimated at 10–100 per million naïve T cells, rising to about 1,000 to 10,000 per million memory T cells after immunization [34]. The number capable of recognizing a specific peptide is somewhat lower. However, if a specific peptide antigen is known and the T cells have expanded in vivo due to infection, immunization or autoimmunity, antigen-specific cells can be detected using peptides bound to soluble self-MHC oligomers (generally tetramers) [35]. In many cases the peptide is not known and an alternative strategy used in human immunology is to analyze an allogeneic response. Most peptide-specific, self-MHC restricted T cells will cross-react with allogeneic cells from many different donors. The antigen in this case is some peptide complexed to a non-self MHC molecule. Different alloreactive T cells recognize the same non-self-MHC molecule but are specific for different peptides. Because each allogeneic stimulator cell expresses many different peptides bound to its MHC molecules (although each individual MHC molecule may only bind one peptide at a time) and because each different peptide-MHC complexes may activate different responding T cells, the overall frequency of alloreactive T cells is high, approaching 2–3% of both the circulating CD4+ and CD8+ T cell populations [36]. In adults, about half of each of these subsets are naïve and half are memory T cells, and the frequency of T cells that cross-react to recognize allogeneic cells is equivalent in the naïve and memory populations, the latter having formed in response to previous infections [37]. This frequency of alloreactive T cells is sufficiently great to be detected by assays of T cell proliferation, of cytokine production or activation antigen expression. An even greater proportion of human T cells can be stimulated in an in vitro assay by using bacterial superantigens (5–10% of the total T cells) or by using polyclonal activators such as the plant lectin phytohemagglutinin (PHA) or an antibody to CD3 proteins associated with the T cell receptor (TCR) for antigen, the latter two stimuli approaching 100% T cell activation. Superantigens or polyclonal activators produce little T cell response in the absence of co-stimulators or antibodies that mimic co-stimulators.

All three approaches described above have been used to examine the ability of cultured human ECs to act as APCs. Cultured human ECs from all vessel sources tested have proven to be capable of activating allogeneic resting memory CD4+ or CD8+ T cells to express activation antigens, to synthesize and secrete IL-2 and effector cytokines and to proliferate [3, 16, 38–43], but in these same assays, ECs generally cannot activate naïve T cells [10, 16, 43]. In contrast, allogeneic “professional” APCs, such as B cells, monocytes or dendritic

cells (DC), can readily activate both memory and naïve T cells. In assays with CD4⁺ T cells, the cultured human ECs are generally pre-treated with IFN- γ to re-induce class II MHC expression [16, 39, 41] or, alternatively, the ECs may be transduced with CIITA, the transcription factor that mediates class II MHC molecule expression in response to IFN- γ [44]. Antibodies that block interactions with MHC or costimulator molecules, especially LFA-3, reduces or completely eliminates T cell activation by allogeneic EC [10, 16, 40, 43]. The frequency of memory T cells that respond to allogeneic ECs is generally a few fold lower than that responding to allogeneic professional APCs [16], and in the case of CD8⁺ T cells, the size of proliferating alloreactive clones stimulated by ECs are also smaller [45]. Both effects can be explained by a preferential ability of ECs to activate effector memory T cells over central memory T cells [46] as the former cells are fewer in number and have less replicative potential than the latter. The capacity of ECs to present antigen to only a subset of T cells requires that in vitro conditions are optimized, for example to re-induce expression of class II MHC molecules on the EC, in order to detect limited proliferation and this may explain why some groups have reported that human ECs fail to induce CD4⁺ T cell proliferation [47–49]

Activated T cells undergo a process of differentiation, during which they acquire effector functions; this process is more rapid for effector memory than for naïve or central memory T cells. In the case of CD8⁺ T cells, differentiation often leads to acquisition of the ability to kill those cells that express the class I MHC-peptide complex that is recognized by their TCR. Cultured human ECs can induce differentiation of resting allogeneic CD8⁺ memory, but not naïve T cells into functional cytotoxic T lymphocytes (CTL) [50]. Unexpectedly, the specificity of such CTLs is often limited to EC targets [51, 52]. This restriction may relate to differences in the identity of the peptides loaded into class I MHC molecules by ECs compared to those loaded by professional APCs [53]; however, this difference in peptide loading may arise from loss of IFN- γ -inducible immunoproteasomal subunits in cultured ECs (a change that occurs concomitantly with downregulation of MHC molecule expression) and thus may not occur in vivo where ECs are exposed to IFN- γ . It is unclear if human ECs can cross-present peptides, i.e. load peptides derived from endocytosed proteins into class I MHC molecules. The capacity to cross-present, should it exist, would allow ECs to interact with circulating CD8⁺ T cells specific for viruses that do not normally infect ECs. In the case of CD4⁺ T cells, effector functions are largely defined by effector cytokine production and CD4⁺ T effector cells can further differentiate into various T helper (Th) subsets that produce different sets of characteristic cytokines to better control specific types of infections. There is little evidence that cultured human ECs normally bias this response towards any particular Th subset, but injured ECs produce cytokines, such as IL-1 α , that favor IL-17 production from CD4⁺ T cells [54]. It has been reported that cultured human ECs may be induced to express the surface proteins ILT3 and 4 (possibly in response to IL-10) and these proteins preferentially favor differentiation of T cells into a regulatory subset [55], but this finding has been disputed [56]. It is currently unclear if human ECs can efficiently activate regulatory T cells and, if so, which subset.

Cultured human ECs can also activate T cells by “presenting” a superantigen [57]; superantigens bind to class II MHC molecules on an APC so, as in alloantigen presentation to CD4⁺ T cells, presentation of superantigen by cultured human ECs to either CD4⁺ or CD8⁺ T cells requires re-induction of class II MHC molecule expression. Superantigen presentation, like alloantigen presentation, depends upon costimulators expressed by the EC. Similarly, human ECs provide costimulators that are needed for T cell activation by PHA and nearly all T cells respond to this stimulus [9, 58]. Interestingly, PHA allows human EC to activate resting naïve T cells despite the absence of B7–1 or B7–2 signals [58]. Finally, ECs do not effectively support T cell activation by anti-CD3 antibodies. This is because CD3 antibodies are most effective when bound to the cell surface of an APC or otherwise

immobilized and cultured human ECs lack Fc receptors and therefore cannot bind anti-CD3 antibodies. Transduction of ECs with an Fc receptor, such as CD32a, allows anti-CD3 antibody binding and thereby permits effective activation of nearly all human T cells [56]. Like the superantigen and PHA response, anti-CD3 antibody activation of human T cells depends upon EC costimulators.

What is the *in vivo* relevance of EC presentation of antigen to circulating memory T cells? There are two non-exclusive hypotheses. First, memory T cells may periodically require low level TCR stimulation to survive. The display of self-MHC molecules bearing self-protein-derived peptides on the surface of microvascular ECs could provide such a signal. There are as yet no data to our knowledge that directly support this idea. Second, ECs display of microbe-derived peptides could provide a homing signal to effector memory T cells of recurrent infection, initiating a rapid recall response at the site of a recurrent infection (or to a transplanted organ, which the immune system perceives as being infected). The mechanism by which the majority of circulating effector memory T cells are recruited into a site of peripheral inflammation is similar to that observed for other leukocyte populations (reviewed in [59]), namely capture (tethering) and subsequent rolling on E-selectin or VCAM-1 (both expressed by venular EC in response to TNF or IL-1), activation by inflammatory chemokines bound to heparan sulfate on the EC surface (including specific inflammatory chemokines synthesized by EC in response to a variety of cytokines), followed by firm adhesion to endothelial ICAM-1 or VCAM-1, migration to the regions of the intracellular junctions of the ECs and ultimately transendothelial migration via a paracellular or transcellular pathway [60]. Unlike other leukocytes, tethered T cells also require shear stress, provided by flowing blood, to fully activate high affinity LFA-1 binding to ICAM-1, and will only rapidly (within 5–10 minutes) transmigrate if shear stress is present [61, 62]. Furthermore, the only subset of freshly isolated T cells capable of such rapid transendothelial migration in response to inflammatory chemokines are effector memory T cells [62]. This process is independent of antigen presentation and TCR signaling. In support of the idea that TCR signals may also contribute to T cell recruitment, presentation of antigen by cultured human ECs that engage the TCR of freshly isolated effector memory T cells under conditions of shear stress will cause T cells to arrest and transmigrate across the EC monolayer in the absence of inflammatory chemokines [63–66]. Because very few human T cells can be engaged by a single peptide antigen, even after immunization, or even by an allogeneic MHC molecule, it is necessary to use a superantigen bound to class II MHC or anti-CD3 mAb bound to a transduced Fc γ IIa receptor (CD32a) in order to observe the effect of TCR signals upon trans-EC migration. The kinetics of T cell transmigration in response to a TCR signal is somewhat slower than that induced by inflammatory chemokines and requires a minimum of 30 minutes instead of 5–10 minutes, but also requires shear stress. Both pathways may utilize ICAM-1 but the TCR pathway requires additional interactions involving EC proteins including fractalkine (also known as CX3CL-1), PECAM-1 (CD31), CD99 and the two shared ligands for the T cell adhesion molecules DNAM-1 (CD226) and Tactile (CD96), also known as polio virus receptor (CD155) and nectin-2 (CD112). TCR recognition, while requiring fractalkine signaling for transmigration, renders effector memory T cells unresponsive to inflammatory chemokines [63]. This suggests that individual effector memory T cells can be recruited to an inflammatory site in response to either TCR signals or to inflammatory chemokines, but not both. We propose that that TCR-based recruitment of circulating effector memory T cells is very early step in a recall response, bringing in antigen-specific “pioneer T cells” that release cytokines, such as TNF and IFN- γ . These cytokines then fully activate venular ECs to efficiently recruit T cells via the conventional chemokine pathway that is antigen-independent. Chemokine signals can cause human CD8⁺ T cells to express inducible nitric oxide synthase (i-NOS) whereas TCR signals activate cytokine transcription and cell cycle entry while suppressing i-NOS expression [67, 68]. Consequently, human T cell infiltrates in

a humanized mouse model of arterial allograft rejection contain both proliferating T cells that express cytokines and conventional activation antigens and non-proliferating T cells that express i-NOS [68]. Inhibition of i-NOS in this setting inhibits the magnitude of the T cell infiltrate [68], an effect explained by the capacity of NO, the product of i-NOS, to inhibit apoptosis of activated human T cells following IL-2 withdrawal [69]. It has also been described that ECs can induce a state of “pre-activation” in memory CD4⁺ T cells in an antigen-independent manner defined by transcription factor activation and the upregulation of certain adhesion and co-stimulatory receptors that serve to increase T cell motility and proliferative responses to subsequent antigenic stimulation.[70–72]. Thus, ECs modulate the phenotype and function of populations of T cells that are recruited to sites of inflammation via both antigen-specific and antigen-independent mechanisms.

Interactions of T Lymphocytes with SMCs

Human SMCs in situ appear to express lower amounts of both class I and class II MHC molecules than do EC [4] but achieve similar levels of expression when cultured and treated with IFN- γ [41]. Incubation of resting memory T cells with cultured human SMCs, typically isolated from aorta, saphenous vein or umbilical artery, results in early evidence of TCR engagement, such as CD25 expression, but the T cells do not produce cytokines or proliferate [39, 41, 73]. This failure can be attributed to two specific differences of SMCs from ECs. First, SMCs lack expression of at least two costimulators expressed by EC, OX40-L and ICOS-L [73]. Second, IFN- γ -treated SMCs express very high amounts (perhaps 100-fold that of EC) of indoleamine 2,3 dioxygenase (IDO) [74]. IDO degrades tryptophan, an amino acid essential for T cell activation [75]. Combined inhibition of IDO and expression of exogenous OX40-L (but not ICOS-L) enables SMC to activate resting CD4⁺ and CD8⁺ memory T cells [73]. Although SMC lack the capacity to mediate the initial activation of resting T cells, they are not immunologically inert. T cells activated by allogeneic ECs are capable of responding to allogeneic SMCs from the same donor [41]. Therefore, as the major cell population present within the arterial wall, SMCs may present antigens to infiltrating T cells previously activated by ECs or other APCs. Furthermore SMCs are probably the principal source of IL-1, IL-6 and TGF- β within the arterial wall [44, 76]. Paracrine effects of SMCs on T cells are probably more significant within the vessel media than the intima for two reasons. First, there are more SMCs in the vessel media than the vessel intima and they are more densely packed. Second, the media is further away from the vessel lumen and is largely unperfused by capillaries. The net result of increased SMC number and limited fluid exchange by diffusion or perfusion is that SMCs control the environment of the media and through a combination of IDO expression and TGF- β secretion and accumulation [74, 76], medial SMCs create a zone of medial immunoprivilege that impairs anti-viral responses [77] as well as allo-immune responses [74, 76]. Breakdown of this system may result in T cell invasion, SMC death and loss of integrity of the arterial wall, consequences of which may be inflammatory aneurysms and arterial rupture.

Interactions of T Lymphocytes with PCs

There have been few studies of the immunological properties of human PCs. Human PCs cultured from placental microvessels express lower amounts of MHC molecules and positive costimulators but higher amounts of negative costimulators than do EC [15]. IDO expression in these PCs is much lower than in SMCs and more like that of ECs [15]. Co-culture of resting allogeneic CD4⁺ T cells with human placental PC results in early expression of CD25 and CD69, indicative of MHC recognition, but fails to induce cytokine production or proliferation [15]. However, unlike similar experiments with SMC [41], T cells cultured with allogeneic PCs are resistant to restimulation by allogeneic ECs from the same donor [15]. This change is accompanied by expression of genes associated with T cell anergy and

can be prevented by blocking recognition of MHC molecules or of PD-L1 and PD-L2 expressed by the PCs. The induction of anergy by PCs is also minimized if the T cells are first activated by allogeneic ECs. In other words, PCs are not likely to anergize T cells that have recognized their cognate antigen on the EC surface as they have been recruited, but may deliver signals that inhibit the subsequent antigen-specific activation of chemokine-recruited T cells. The unique distribution and immune functions of PCs, as opposed to SMCs may be of great importance in host defense as microvessels are major sites of memory T cell trafficking into peripheral tissues.

Concluding remarks

As noted in the opening sections of this review, how many of the blood vessel cell properties described in this review are general for vascular cells at different anatomic locations is unclear (see Box 1). Some atypical human ECs, such as those that line liver sinusoids, may be tolerizing rather than activating, perhaps through induction of T cell apoptosis [78]. It is unclear if all human vascular SMCs behave the same way and very little is currently known about the immunological properties of human PCs from sources other than placenta. It is also uncertain what immunological properties are exhibited by vascular cells that are derived during repair from stem cells. In culture, human EPCs that are differentiated into ECs become indistinguishable from conventional ECs in their ability to activate allogeneic T cells [79]. PCs may be closely related to MSCs [80], which are being evaluated for their immunosuppressive potential in various clinical settings [81]. In this review, we have focused on human vascular cells and have compared these findings with results from experiments in other species in Table 1. Suffice it to say that such comparisons show many fundamental differences.

What may we conclude at the present time about the effects of human vascular cells upon the adaptive immune response? First, antigen presentation by ECs may be an important contributor to preserving and activating immunological memory. Second, the vessel wall is formed from cells in addition to ECs that also can interact with T cells. In the arterial wall, SMCs considerably outnumber ECs and understanding how the immune system interacts with blood vessels requires that these less studied cell types, at least from an immunological perspective, also be taken into account. SMCs have little effect on infiltrating T cells individually, but the mass of SMC present in the arterial media creates a zone of immunoprivilege. PCs, confined to the microvasculature, appear to inhibit the activation of recruited effector memory T cells that have not as yet encountered their cognate antigen, such as those recruited by inflammatory chemokines, possibly inducing clonal anergy. In contrast, T cells that have been recruited by antigen presentation on ECs are resistant to PC-induced anergy. The differences among the immunological properties of these vascular cell types are summarized in Table 2. Finally, we must acknowledge the limitations of current studies for definitively addressing these questions. Cell culture systems have been the principal source of information about immunological properties of human vascular cells, but new experimental approaches, such as humanized mouse systems [82, 83], will be needed to fully elucidate how cells of the human vessel wall modulate the adaptive immune response in vivo.

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Box 1. Heterogeneity of vascular cells

ECs, SMCs and PCs each share common features that define them as a cell type but also display profound heterogeneity defined by anatomic position within the vascular tree. This diversity, which may affect the immunological function of these vascular cells, arises from several causes. First, some heterogeneity among vascular cells can be attributed to distinct embryological origins. Most ECs, independent of anatomic location, can trace their lineage back to angioblasts arising in the lateral and posterior mesoderm, including the aorto-gonadal-mesonephric regions, but there are exceptions, for example the origin of the ECs of the coronary artery system from precursors within the epicardium [84]. SMCs, on the other hand, are very heterogeneous in origin and may arise from local mesenchyme, from ECs, or, in the case of thoracic aorta, from neural crest cells [85]. The differing propensity of SMCs from varied origins to respond to inflammatory stimuli and pathological vascular remodeling is best exemplified in the privileged status of the internal mammary artery as a bypass graft for coronary artery disease. The origins of PCs have not been traced and are presumed to arise from local mesenchyme. The PCs at several anatomic locations, e.g. the mesangial cells of the renal glomeruli or the stellate cells of the liver sinusoids, are so phenotypically different from the PCs associated with other capillaries as to be considered as PCs only on the basis of their perivascular location. Second, vascular cells further differentiate from each other by their environment. Environmental influences include the exposure to physical forces imparted by blood flow, such as shear stress or stretch, the chemical composition, oxygen content and pH of the blood plasma, and by local tissue cues provided by parenchymal cells. In general, arterial ECs are less responsive to inflammatory cytokines than venous ECs [86]. However, ECs exhibit their greatest diversity among the capillary beds that form in distinct anatomic locations, ranging from the highly impermeant capillaries of the brain vs. the porous capillary tufts within the renal glomeruli or the sinusoids of the liver [87, 88]. The impermeance of brain capillaries to fluid or blood proteins depends on signals provided by astrocytes [89]. A third source of heterogeneity may be imposed by pathological and repair processes. Differentiated vascular cells may replicate during the response to injury but resident vascular stem cells may also contribute to repair. MSC located in the medial-adventitial border of arteries or in the PC layer of microvessels, may serve to replace SMCs or PCs [90]. EPCs perhaps residing within the endothelial lining itself [91], may give rise to new ECs during vessel repair or wound healing. Both MSCs and EPCs may be also be found in and disseminated via the circulation (caution is needed, however, because many of the cell populations that have been described in the literature as circulating EPCs are actually pro-angiogenic leukocytes that promote vessel repair but are not capable of giving rise to true ECs [92]). Vascular repair may not be perfect. For example, in the case of cirrhotic livers, the capillaries that reform in the response to injury may take on the form of continuous capillaries rather than the sinusoids of a healthy organ [93]. It is not known if replacement vascular cells recapitulate the immune functions of the original vascular cells at a particular site. A fourth and highly significant source of heterogeneity that has led to much confusion in the literature are species differences. Rodent ECs significantly differ from human ECs in their patterns of expression of molecules that interact with lymphocytes and consequently behave quite differently in various immunological assays (ref [94]. Fifth and finally, cell culture can significantly alter vascular cell phenotype [86]. Much of the information relating to how vascular cells interact with lymphocytes has been derived from cell culture models, and the behaviors of cultured cells can differ dramatically from those of cells in vivo.

Figure 1.

Small and large vessel sites for recruitment of circulating leukocytes. (A) A typical microvessel is composed of a single, continuous layer of endothelial cells supported by an incomplete layer of pericytes. Both cell types are surrounded by a common basement membrane. (B) The wall of a large artery contains a luminal layer of endothelial cells attached to an underlying basement membrane but without the presence of pericytes. The endothelium together with a variable layer of subendothelial connective tissue that may contain phenotypically-modified smooth muscle cells constitutes the vessel intima. The intima is surrounded by the vessel media which consists of concentric layers of densely-packed, concentrically arranged smooth muscle cells separated by elastic laminae. The relatively thick internal elastic lamina marks the boundary between intima and media, whereas the external elastic lamina marks the boundary between media and adventitia. The adventitia contains fibroblasts, vascular stem cells, nerve endings, and, in larger vessels, nutrient microvessels called vasa vasorum. These various constituents of the vessel wall may interact with leukocytes during their trafficking to extravascular sites of inflammation. In the inflamed or atherosclerotic artery, the vasa vasorum may, through the process of angiogenesis, give rise to penetrating microvessels that cross the media and nurture inflammatory cells that accumulate within the intima (not shown).

Table I

Differences in immune functions of human and murine vascular cells.

Attributes	Human	Mouse	Refs.
MHC molecules	Class I and II basal expression	Class I basal expression	[2–4, 95]
Co-stimulators	LFA-3 plays non-redundant role	LFA-3 absent	[8–10, 96]
	CD80 and CD86 generally absent	CD80 expressed	[97]
	PD-L1 and PD-L2 expressed	PD-L1 only expressed	[30]
	ICOS-L activates ICOS and CD28	ICOS-L activates ICOS only	[25]
Ag presentation	EC activate CD4+ memory Th cells	EC do not activate CD4+ T-reg cells only	[38–46, 98, 99]
	EC differentiate memory CD8+ T cells to become CTL	EC differentiate naïve and memory CD8+ T cells to become CTL	[50–52, 100]
	SMC/PC do not activate T cells	SMC/PC activate naïve CD4+ T cells	[15, 41, 101, 102]
T cell recruitment	P-selectin basally expressed in EC	P-selectin inducible by TNF in EC	[103]

Table II

Differences in immune functions of human vascular cell types.

Attributes	EC	SMC	PC	Refs.
MHC molecules	Class I, II basal expression	Class I, II <EC in vivo	Class I, II <EC in vivo	[2–4]
Co-stimulators	Several constitutive and inducible	OX40-L and ICOS-L absent	OX40-L and ICOS-L poorly induced	[15, 73]
	PD-L1 and –L2 moderately induced	PD-L1 and –L2 moderately induced	PD-L1 and –L2 highly induced	[15, 73]
Cytokines	IL-6 production modest	IL-6 production high	Not determined	[104]
Inhibitors	IDO activity modest	IDO activity high	IDO activity modest	[15, 74]
Ag presentation	Activate resting memory T cells	Stimulate recently activated T cells	Stimulate recently activated T cells	[15, 41]
Immunogenicity	Pro-immunogenic	Medial immunoprivilege	Induce clonal anergy in resting cells	[15, 46, 50]