Lymphocyte Trafficking Mediated by Vascular Adhesion Protein-1
Implications for Immune Targeting and Cardiovascular Disease

J. Steven Alexander, D. Neil Granger

The trafficking, extravasation, and retention of lymphocytes within certain tissues (eg, lymph nodes) seem to be mediated by several classes of specialized adhesion glycoproteins that are expressed on the surface of unique endothelial cells (high endothelial venules [HEVs]) that exist in both the blood and lymph microvessels.1,2 The binding of these endothelial cell adhesion molecules to their corresponding ligands on lymphocytes (L-selectin, αβ2, αβ1, leukocyte function–associated antigen-1 [LFA-1], and CLA-1) tightly controls the kinetics and magnitude of lymphocyte margination, rolling, adhesion, and extravasation, thereby allowing these leukocytes to fulfill their immune surveillance functions and, in some tissues, mature into fully differentiated cells. During inflammation, the recruitment and retention of lymphocytes in affected tissues occur at an accelerated rate, because locally released mediators (eg, cytokines, chemokines, and oxidants) increase the expression of relevant adhesion molecules on both the endothelial cells and leukocytes.

Although much progress has been made in our understanding of the molecular determinants of lymphocyte–endothelial cell adhesion in the blood circulation, the identification and characterization of the glycoproteins that mediate this cell–cell adhesive interaction has tended to lag behind equivalent efforts made for neutrophil–endothelial cell adhesion.3–5 Nonetheless, the efforts to discover and characterize adhesive determinants on both leukocyte populations have led to the revelation that lymphocytes and neutrophils share several glycoproteins, including β2-integrins (CD11/CD18), and L-selectin. As a consequence of these observations, the initial models that were proposed to explain the coordinated recruitment of leukocytes to sites of inflammation assumed that neutrophils and lymphocytes followed the same sequential process and were mediated by a similar complement of adhesion molecules. With additional experimentation, it was realized that lymphocytes can use an assortment of unique adhesion molecules that selectively mediate their rolling and firm adhesion on HEVs. Furthermore, there is mounting evidence that supports the use of unique adhesion molecules for the vascular arrest of specific subpopulations of lymphocytes. An example of such a glycoprotein that selectively mediates the recruitment of CD8+ T lymphocytes is vascular adhesion protein-1 (VAP-1).

VAP-1, which was first described by Salmi and Jalkanen in 1992,6 has been proposed as a mediator of the selectin-independent adhesion of lymphocytes to endothelial cells in lymph nodes and at sites of inflammation.6–9 This endothelial adhesion molecule is now known to mediate the specific binding of CD8+ T cells, as well as natural killer (NK) cells, to peripheral lymph node HEVs independent of L-selectin, PSGL-1, and α4 integrins. Although VAP-1 does not function as an autonomous lymphocyte adhesive determinant, it cooperatively (with LFA-1, Mac-1, and L-selectin ligands) confers specific binding of CD8+ lymphocytes to lymph nodes and inflamed endothelia. CD4+ cells do not bind VAP-1, but use peripheral node addressins for trafficking.10 Together with peripheral node addressins, VAP-1 seems to be a major determinant of the flux of lymphocytes that occurs in some healthy vascular beds (eg, lymphoid tissue) and inflamed tissue. There is evidence that VAP-1, working in concert with intercellular adhesion molecule-1, can mediate the binding of tumor-infiltrating lymphocytes into hepatic carcinomas, suggesting that VAP-1 may also participate in defense against solid organ tumors.11

Structural and Functional Characteristics of VAP-1

VAP-1 is initially synthesized as a 180-kDa proform, which can be cleaved to an 84.6-kDa form with 6 possible N-glycosylation sites.12,13 This sialoglycoprotein is structurally distinct from other adhesion molecules, especially with regard to its unusual property of exhibiting copper-dependent monoamine oxidase activity.14,15 VAP-1 also contains an RGD site, usually assumed to mediate adhesion to integrin receptors, such as fibronectin, collagen, and laminin. Analysis of the VAP-1 gene reveals that it has 4 exons and 3 introns with multiple transcript initiation sites, indicating that there are several possible sites for modulation by inflammatory mediators.16

The active, dimeric form of VAP-1 is restricted to endothelial cells. A trimeric form has been detected in smooth muscle cells. However, this molecule does not support lymphocyte adhesion; instead, it functions solely as an amine oxidase.17 VAP-1 has been demonstrated within the inflamed vasculature of skin, gut, liver, pancreas, and synovium.15,18,19 VAP-1 seems to be shed during some forms of liver (but not

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gut or joint) inflammation, which may result in the down-regulation of VAP-1–dependent lymphocyte binding.20

**Lymphocyte Binding to VAP-1**

Although it has been proposed that VAP-1–mediated lymphocyte binding may be regulated by shedding from the endothelial cell surface via differential glycosylation of the adhesion molecule and through posttranslational modifications, relatively little is known about the factors that influence and regulate this important controller of lymphocyte trafficking. In this issue of *Circulation Research*, Salmi et al21 have significantly extended our understanding of the potential role of VAP-1 in sustaining lymphocyte adhesion under physiologically relevant conditions of shear stress, and they describe a role for CD44 and sialic acid in its binding to lymphocytes. Using cultured endothelial cells transfected with VAP-1, Salmi et al demonstrated VAP-1–dependent adhesion of CD8+ T cells and NK cells under conditions of physiological shear stress. Importantly, VAP-1 mutants lacking either the RGD or monoamine oxidase motifs still sustained lymphocyte adhesion. Salmi et al also demonstrated that VAP-1 is specific for lymphocytes and will not sustain granulocyte binding to the endothelium. Lymphocyte binding also required L-selectin, LFA-1, and Mac-1 ligands but was critically dependent on VAP-1 expression. Revertants that lost the ability to express VAP-1 also lost the ability to bind lymphocytes. A novel and significant finding in the study is that engagement of CD44 on lymphocytes significantly increased VAP-1–dependent adhesion to the transfected endothelial cells, suggesting that this mobilizes the VAP-1 ligand. Additionally, treatment with sialidase to remove sialic acid from the lymphocytes dramatically enhanced VAP-1–dependent lymphocyte adhesion to the transfected endothelial cells. These findings raise the interesting possibility that CD44 functionally activates a VAP-1 ligand that enhances and regulates lymphocyte adhesion.

There is a growing body of evidence that implicates T lymphocytes in the initiation or progression of a variety of cardiovascular diseases and regional vascular disorders. Mononuclear cells, including T cells, have recently received attention as potential mediators of the vascular dysfunction associated with atherosclerosis.22 Similarly, there is evidence implicating lymphocytes in ischemic disorders, including ischemia-reperfusion injury23 and unstable angina.24 Likewise, T cells may contribute to the pathogenesis of transplant rejection25,26 and myocarditis.27 Therefore, the possibility exists that VAP-1 is a major regulator of the lymphocyte recruitment that is associated with these conditions and VAP-1 may be an important target for therapeutic intervention in at least some of these cardiovascular diseases.

**Future Directions**

The studies by Salmi et al21 have shed new light on the potential physiological and pathological significance of VAP-1 in inflammatory and cardiovascular diseases, but much of the evidence implicating this adhesion molecule in the process of lymphocyte recruitment in vivo remains circumstantial. Additional studies are needed to determine whether immunoneutralization of VAP-1 in vivo alters the trafficking of CD8+ cells in different regional vascular beds. Similarly, mice that are either genetically deficient or over-express VAP-1 should be developed and subsequently used to assess the importance of this adhesion molecule in lymphocyte trafficking. Both of these experimental strategies should reveal the qualitative and quantitative contributions of VAP-1 to the recruitment of lymphocytes in the healthy or inflamed microvasculature and should define the role of this adhesion molecule in immune function.

**References**


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