JCI The Journal of Clinical Investigation

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J Clin Invest. 1997;99(1):3-8. https://doi.org/10.1172/JCI119129.

Perspective

Perspectives Series: Cell Adhesion in Vascular Biology

The Biology of PECAM-1

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Introduction

Platelet endothelial cell adhesion molecule-1 (PECAM-1) is a 130-kD member of the immunoglobulin (Ig) superfamily that is expressed on the surface of circulating platelets, monocytes, neutrophils, and selected T cell subsets. It is also a major constituent of the endothelial cell intercellular junction (1–3), where up to 10^6 PECAM-1 molecules (4) are concentrated. With a few minor exceptions, PECAM-1 is not present on fibroblasts, epithelium, muscle, or other nonvascular cells. Since its cloning nearly 10 yr ago (5, 6), much has been learned about the structure of this cell adhesion receptor and its function in vascular cells. The purpose of this brief Perspective is to review progress in the field of PECAM-1 biology, and to bring the reader up to date on current concepts about (*a*) the function of PECAM-1 in the different vascular cells in which it is expressed; (*b*) the molecular mechanisms by which PECAM-1 mediates cell–cell interactions; and (*c*) its role in bidirectional transmembrane signal transduction. In keeping with the intent of this series to discuss issues of cell adhesion in the context of human biology and pathophysiology, the potential clinical relevance of PECAM-1–mediated cellular interactions to thrombotic, inflammatory, and immunological diseases will be underscored at relevant points throughout the review.

Structure of the PECAM-1 gene and protein

PECAM-1 is encoded by a 75-kb gene that resides at the end of the long arm of chromosome 17 (7). The earliest reports of PECAM-1 in the literature described it variously as a myeloid differentiation antigen (8, 9) or as a homologue of platelet GPIIa (the integrin β_1 subunit) present within the plasma membrane of endothelial cells (1). After the determination of its primary structure in 1990 (6, 10, 11), however, PECAM-1 was assigned definitively to the growing family of type I transmembrane cell adhesion molecules that are members of the Ig superfamily (Ig-CAMs). The 574 amino acids that comprise the extracellular portion of this molecule are organized into six Ig-like homology domains, and typical of other members of the Ig superfamily, each of these is encoded by a single exon (12). After a short, single-pass transmembrane domain, PECAM-1 contains a 118–amino acid cytoplasmic domain that is both structurally and functionally complex, being encoded by eight different exons that can be alternatively spliced to yield PECAM-1 isoforms that variously contain or lack residues that serve as sites for palmitoylation, phosphorylation, and assembly of cytosolic signaling molecules (see cover of this issue for a schematic diagram of the PECAM-1 protein).

Functions of PECAM-1 in vascular cells

There is good evidence to suggest that PECAM-1 is a key participant in the adhesion cascade leading to extravasation of leukocytes during the inflammatory process. Muller et al. (13) were the first to show that pretreating monocytes or neutrophils with antibodies specific for PECAM-1 inhibited their emigration across an endothelial cell monolayer in a quantitative in vitro assay of transendothelial migration. Blocking endothelial cell junctional PECAM-1 also effectively inhibited leukocyte transmigration, indicating that PECAM-1 molecules on both the endothelial cell as well as the leukocyte side contributed to the transmigration process. The requirement for PECAM-1 in leukocyte recruitment appears to be operative in vivo as well, since antibodies to PECAM-1 have been shown to block the accumulation of neutrophils into the peritoneal cavity, the alveolar compartment, and human skin grafts in three different intact rat models of inflammation (14). An mAb to murine PECAM-1 has also been shown to be effective in reducing leukocyte emigration into the peritoneal cavity in a mouse model of acute peritonitis (15). In studies of direct potential relevance to human disease, two different groups have shown that antibodies to PECAM-1 reduce myocardial infarct size in both rat (16, 17) and feline models of ischemia-reperfusion injury (18). Together, these studies have combined to make agents that activate or antagonize the adhesive and/or signaling properties of PECAM-1 (see below) attractive potential therapeutics for the treatment of acute and chronic inflammatory conditions.

Functions mediated by PECAM-1 in other cells of blood or vascular origin have been less well worked out. Ohto et al. (8) reported that certain mAbs to PECAM-1 inhibit neutrophil and monocyte chemotaxis, but Muller et al. (13) observed no effect of the blocking anti–PECAM-1 mAb, hec7, on leukocyte migration into collagen gels in response to chemotactic stimuli. There is one report that transfection of PECAM-1 into NIH/3T3 cells actually diminishes the rate of cell migration (19), probably by virtue of its ability to stabilize intercellular contacts. PECAM-1 has also been implicated in T-lymphocyte function during the development of an alloimmune response,

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Received for publication 11 November 1996.

J. Clin. Invest.

0021-9738/97/01/0003/06 $2.00
Volume 99, Number 1, January 1997, 3–8

as Zehnder et al. (20) reported that an mAb directed against Ig-domain 6 of PECAM-1 inhibited T cell activation in a mixed lymphocyte reaction, while Behar et al. (21) noted a tendency for bone marrow transplant recipients unmatched for a Leu98Val polymorphism in PECAM-1 to develop acute graft-versus-host disease. Finally, despite the name platelet endothelial cell adhesion molecule-1, virtually nothing is known about the role that PECAM-1 plays in platelet function, though recent studies suggest that it may serve as an agonist receptor to modulate β_3 integrin function (to be discussed in greater detail below).

Mechanisms of PECAM-1–mediated adhesion

The first indication that PECAM-1 actually possessed adhesive activity was provided by the studies of Albelda et al. (22), who showed that although PECAM-1 was not present at intercellular junctions formed between PECAM-1–positive and PECAM-1–negative cells, it became strongly localized to cell–cell borders when adjacently transfected cells contacted one another. These findings led to the hypothesis that PECAM-1/PECAM-1 homophilic interactions are responsible for concentrating this molecule at endothelial cell intracellular junctions. Further support for a homophilic mechanism derived from the observation that murine L cell fibroblasts transfected with PECAM-1 acquire the ability to interact with one another in an aggregation assay. Finally, Sun et al. (23) have shown recently that purified, full-length PECAM-1 reconstituted into artificial phospholipid membranes interacts directly with other PECAM-1 molecules in a divalent cation-independent manner, a process that is completely inhibited by small Fab fragments of mAbs that bind to Ig-homology domains 1 and 2 of PECAM-1. That this amino-terminal region of the extracellular domain is physiologically relevant to PECAM-1–mediated cellular interactions is further supported by the finding that anti–PECAM-1 mAbs that block leukocyte transendothelial migration almost without exception epitope map to Ig-domains 1 or 2 (24, 25).

In addition to homophilic interactions, several studies have suggested that PECAM-1 may also be capable of interacting heterophilically with other components of the cell surface, as PECAM-1–transfected cells have been found to interact not only with each other, but also with nontransfected, PECAM-1–negative L cells in a heterotypic process that is dependent upon the presence of divalent cations (22, 26) and involves cell surface glycosaminoglycans (27). Two additional studies have implicated the integrin $\alpha_v\beta_3$ as another potential counterreceptor for PECAM-1 (28, 29). However, recent experimental observations cast doubt on there being physiologically important receptors for PECAM-1 other than PECAM-1 itself. First, neither heparin, heparin-sulfate, nor EDTA inhibit the interaction of purified PECAM-1, presented either as a full-length adhesion receptor incorporated into phospholipid membranes or as a high-affinity chimeric PECAM-1/IgG immunoadhesin (23), with human umbilical vein endothelial cells or PECAM-1–transfected L cell fibroblasts, both of which express abundant levels of glycosaminoglycans, including chondroitin-6-sulfate and heparan sulfate, on their surface. Second, despite having a near-consensus heparin-binding motif within Ig-domain 2 (22), neither cellular nor recombinant PECAM-1 binds glycosaminoglycans (30). Finally, blocking antibodies to $\alpha_v\beta_3$ prebound

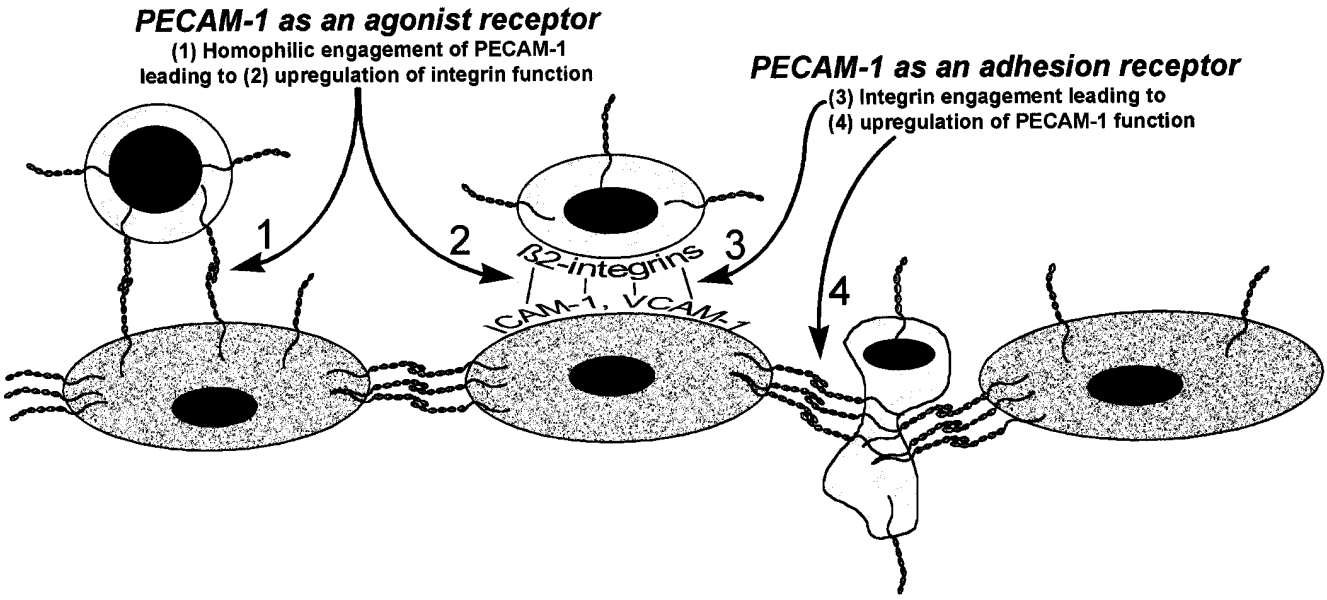

Figure 1. Dual functional roles for PECAM-1 in leukocyte–endothelial cell interactions. Two non-mutually exclusive receptor functions are depicted. On the left, homophilic engagement of PECAM-1 molecules between circulating leukocytes and the underlying endothelial cell monolayer (*1*) initiates intracellular signal transduction events that result in the upregulation of leukocyte integrin affinity, facilitating subsequent interactions with endothelial cell counterreceptors (*2*). Integrin-mediated cellular interactions (*3*), in turn, amplify cytosolic signal transduction pathways, some of which result in the phosphorylation of PECAM-1 and the binding of additional signaling molecules, some of which modulate the affinity of PECAM-1 and enable transendothelial migration (*4*). While good experimental evidence exists for many of these events, others are tentative assumptions, based on paradigms already established for other adhesion receptor signal transduction pathways, which remain to be proven. The depicted ability of PECAM-1 homophilic interactions to mediate leukocyte transendothelial migration, while at the same time maintaining the permeability barrier established by the monolayer of endothelial cells, is adapted from a model originally proposed by Muller et al. (13).

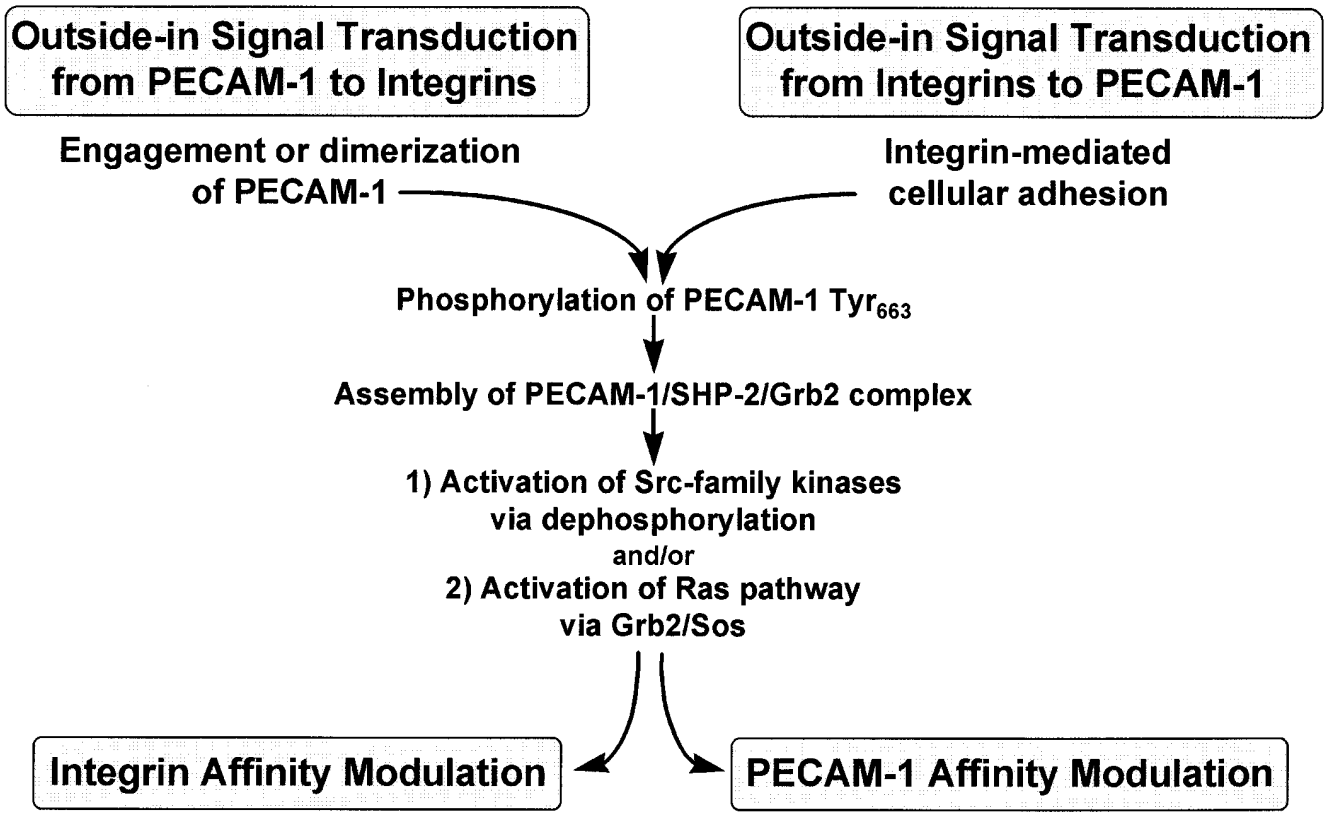

Figure 2. Proposed model for transmembrane signaling through PECAM-1. Antibody-induced dimerization of PECAM-1 has been shown recently to affect the phosphorylation state of its cytoplasmic domain, creating a docking site for one or more signaling molecules. At the same time, engagement or dimerization of PECAM-1 on the surface of lymphocytes, endothelial cells, or platelets results in the upregulation of integrin function (outside-in signaling from PECAM-1 to integrins). PECAM-1 not only modulates integrin function, but is itself affected by integrins, as integrin-mediated cellular contact leads directly to tyrosine phosphorylation of the PECAM-1 cytoplasmic domain (outside-in signaling from integrins to PECAM-1). The signaling molecules that mediate bidirectional cross-talk between integrins and PECAM-1 are just now beginning to be identified and may involve elements of the pathway shown schematically in this figure.

to cells that abundantly express this integrin have no effect on the subsequent binding of PECAM-1 proteoliposomes or PECAM-1/IgG, while an mAb to PECAM-1 Ig-domain 1 bound to these same cells completely abolishes their binding (23). Together, these studies argue that the mechanism by which introduction of PECAM-1 into cells promotes interactions with PECAM-1–negative cells must be an indirect one. As will be discussed below, there is now increasing evidence that, at least in some cell types, PECAM-1 functions as an agonist receptor, and that its activation initiates specific signal transduction pathways that result in secondary adhesion events mediated by non–PECAM-1 receptors.

PECAM-1 transmits signals into and receives signals from the cell interior

The first experimental evidence that PECAM-1 might be involved in outside-in signal transduction came from the studies of Tanaka et al. (31), who showed that antibody-induced dimerization of PECAM-1 on the surface of T cells resulted in their increased adherence to the β_1 integrin substrates VCAM-1 (via $\alpha_4\beta_1$) and fibronectin (via $\alpha_5\beta_1$). Monovalent Fab fragments of PECAM-1 mAbs were ineffective, suggesting that dimerization of PECAM-1 on the cell surface might be responsible for the observed upregulation of β_1 integrin function. Since that time, affinity modulation of β_1 integrins induced by cross-linking PECAM-1 has been reproduced in $CD34^+$ hematopoietic progenitor cells (32), and β_2 integrin function has been shown to be modulated by PECAM-1 dimerization in lymphokine-activated killer cells (33), monocytes and neutrophils (34), and natural killer cells (35). The ability of PECAM-1 to mediate outside-in signal transduction has been extended recently to β_3 integrins on platelets by the studies of Varon and co-workers, who showed that the binding of $F(ab')_2$ fragments specific for PECAM-1 Ig-domain 6 results in the transformation of the resting $\alpha_{IIb}\beta_3$ complex into an activated conformational state and augments platelet adhesion and aggregation (Varon, D., D.E. Jackson, B. Shenkman, and P.J. Newman, manuscript in preparation). Finally, DeLisser and colleagues (36, 37) have shown that L cells transfected with PECAM-1 isoforms missing all or parts of their cytoplasmic domain are unable to associate with nontransfected L cells (i.e., they lose heterophilic binding ability), consistent with the hypothesis that PECAM-1–mediated signal transduction, which presumably requires the cytoplasmic domain to relay signals from the extracellular domain into the cytosol, is required for heterotypic L cell aggregation. Taken together, it seems likely that PECAM-1 dimerization or engagement may be capable of transducing signals into the cell, a process that may mimic ho-

mophilic PECAM-1/PECAM-1 interactions that are thought to occur between leukocytes and endothelial cells during the process of transendothelial migration. The dual functional roles proposed for PECAM-1, serving as both an agonist receptor as well as an adhesion receptor in vascular cells, are depicted in Fig. 1.

What might be the mechanism by which PECAM-1 engagement leads to downstream signal transduction events that result in integrin activation and heterotypic cellular activation? Like many protein-tyrosine kinase receptors (including those for PDGF, FGF, VEGF, NGF, and M-CSF), the extracellular domain of PECAM-1 is comprised of Ig-like domains. However, the PECAM-1 cytoplasmic domain does not contain a catalytic kinase domain and therefore is unable to become activated by receptor autophosphorylation after ligand (i.e., PECAM-1) binding has occurred. However, previous studies have shown that PECAM-1 can become tyrosine phosphorylated in both human platelets (38) and in cultured endothelial cells (39), and we have found recently that, when phosphorylated, Tyr_{663} within the cytoplasmic domain of PECAM-1 becomes a specific docking site for the Src-homology 2 (SH2) domains of the protein-tyrosine phosphatase, SHP-2 (40). SHP-2 is a ubiquitously expressed protein-tyrosine phosphatase that contains two SH2 domains at the amino terminus of the protein, followed by a catalytic phosphatase domain, and a carboxyl-terminal region that can itself become tyrosine phosphorylated (41–44). SHP-2 has been found previously to associate with several autophosphorylated receptor-tyrosine kinases, including the platelet-derived growth factor receptor (43–45) and the epidermal growth factor receptor (43, 44, 46). Though the precise way in which the association of SHP-2 with the cytoplasmic domain of PECAM-1 might lead to downstream signaling in vascular cells has not been worked out yet, SHP-2 in other cell types has been implicated as a multifunctional signaling molecule, acting both as a phosphatase to activate nearby Src family kinases and/or as an upstream mediator of $p21^{ras}$ activation via its ability to bind the Grb2/Sos complex (for reviews on the role of SHP-2 in signaling see references 47–49).

In addition to its role in activating integrins via outside-in signal transduction, PECAM-1 also appears to be able to respond to integrin-mediated cell–cell and cell–matrix interactions. Lu et al. (39) have shown recently that engagement of integrins on cultured endothelial cells results in dephosphorylation of PECAM-1 (39), whereas Jackson et al. (40) have shown that integrin-mediated interactions result in an *increase* in tyrosine phosphorylation of PECAM-1 in aggregating human platelets. While the differences in observed phosphorylation state of PECAM-1 in these two cell types in response to integrin engagement are not well understood, it is likely that the relative balance of kinase and phosphatase activity controls the phosphorylation state not only of PECAM-1, but of other cellular receptors as well. A schematic diagram of the proposed involvement of PECAM-1 in signal transduction in blood and vascular cells is shown in Fig. 2.

Conclusions

Recent studies on the adhesive and signaling properties of PECAM-1 have impacted our understanding of its role in vascular cell biology in important and exciting ways. Definition of the specific regions of the extracellular domain that mediate PECAM-1 homophilic interactions as well as the elucidation of the specific molecular events that take place during signal transduction events involving PECAM-1 remain important avenues of future investigation. As our knowledge of the basic cellular and molecular mechanisms by which PECAM-1 exerts its adhesive and cell modulatory effects improves, so should our understanding of the relative role that this novel cell adhesion receptor plays in thrombosis, hemostasis, immunity, and the inflammatory response.

Acknowledgments

I am indebted to both past and present members of my laboratory who have made significant contributions to many of the studies reviewed herein, including Richard Gumina, Denise Jackson, Nancy Kirschbaum, Chao-Yan Liu, Cathy Paddock, Kim Piotrowski, Qi-Hong Sun, Ronggang Wang, and Christopher Ward. I am also grateful to Drs. Steven Albelda, Horace DeLisser, and William Muller for many years of fruitful and enjoyable collaboration, and for their constant stream of insights and suggestions.

This work was supported in part by grants HL-40926 and HL-44612 from the National Institutes of Health. Dr. Newman is the recipient of an Established Investigator Award from the American Heart Association.

References

1. van Mourik, J.A., O.C. Leeksma, J.H. Reinders, P.G. de Groot, and J. Zandbergen-Spaargaren. 1985. Vascular endothelial cells synthesize a plasma membrane protein indistinguishable from platelet membrane glycoprotein IIa. *J. Biol. Chem.* 260:11300–11306.

2. Muller, W.A., C.M. Ratti, S.L. McDonnell, and Z.A. Cohn. 1989. A human endothelial cell-restricted externally disposed plasmalemmal protein enriched in intercellular junctions. *J. Exp. Med.* 170:399–414.

3. Albelda, S.M., P.D. Oliver, L.H. Romer, and C.A. Buck. 1990. EndoCAM: a novel endothelial cell-cell adhesion molecule. *J. Cell Biol.* 110:1227–1237.

4. Newman, P.J. 1994. The role of PECAM-1 in vascular cell biology. *In* Platelet-Dependent Vascular Occlusion. G.A. Fitzgerald, L.K. Jennings, and C. Patrono, editors. The New York Academy of Sciences, New York. 165–174.

5. Newman, P.J., M.P. Doers, and J. Gorski. 1987. Molecular cloning of a 130 kD membrane glycoprotein expressed on human platelets, umbilical vein endothelial cells, and human erythroleukemia (HEL) cells. *J. Cell Biol.* 105:53*a*. (Abstr.)

6. Newman, P.J., M.C. Berndt, J. Gorski, G.C. White, S. Lyman, C. Paddock, and W.A. Muller. 1990. PECAM-1 (CD31) cloning and relation to adhesion molecules of the immunoglobulin gene superfamily. *Science (Wash. DC).* 247:1219–1222.

7. Gumina, R.J., N. Kirschbaum, P.N. Rao, P. vanTuinen, and P.J. Newman. 1996. The human PECAM1 gene maps to 17q23. *Genomics.* 34:229–232.

8. Ohto, H., H. Maeda, Y. Shibata, R. Chen, Y. Qzaki, M. Higashihara, A. Takeuchi, and H. Tohyama. 1985. A novel leukocyte differentiation antigen: two monoclonal antibodies TM2 and TM3 define a 120-kd molecule present on neutrophils, monocytes, platelets, and activated lymphoblasts. *Blood.* 66:873–881.

9. Goyert, S.M., E.M. Ferrero, S.V. Seremetis, R.J. Winchester, J. Silver, and A.C. Mattison. 1986. Biochemistry and expression of myelomonocytic antigens. *J. Immunol.* 137:3909–3914.

10. Stockinger, H., S.J. Gadd, R. Eher, O. Majdic, W. Schreiber, W. Kasinrerk, B. Strass, E. Schnabl, and W. Knapp. 1990. Molecular characterization and functional analysis of the leukocyte surface protein CD31. *J. Immunol.* 145: 3889–3897.

11. Simmons, D.L., C. Walker, C. Power, and R. Pigott. 1990. Molecular cloning of CD31, a putative intercellular adhesion molecule closely related to carcinoembryonic antigen. *J. Exp. Med.* 171:2147–2152.

12. Kirschbaum, N.E., R.J. Gumina, and P.J. Newman. 1994. Organization of the gene for human platelet/endothelial cell adhesion molecule-1 (PECAM-1) reveals alternatively spliced isoforms and a functionally complex cytoplasmic domain. *Blood.* 84:4028–4037.

13. Muller, W.A., S.A. Weigl, X. Deng, and D.M. Phillips. 1993. PECAM-1 is required for transendothelial migration of leukocytes. *J. Exp. Med.* 178:449–460.

14. Vaporciyan, A.A., H.M. DeLisser, H. Yan, I.I. Mendiguren, S.R. Thom, M.L. Jones, P.A. Ward, and S.M. Albelda. 1993. Involvement of platelet endothelial cell adhesion molecule-1 in neutrophil recruitment in vivo. *Science (Wash. DC).* 262:1580–1582.

15. Bogen, S., J. Pak, M. Garifallou, X. Deng, and W.A. Muller. 1994. Monoclonal antibody to murine PECAM-1 (CD31) blocks acute inflammation in vivo. *J. Exp. Med.* 179:1059–1064.

16. Gumina, R.J., J. Schultz, Z. Yao, D. Kenny, D.C. Warltier, G. Gross, and P.J. Newman. 1995. Antibody to PECAM-1 reduces myocardial infarct size. *J. Invest. Med.* 43:312*a*. (Abstr.)

17. Gumina, R.J., J.E. Schultz, Z. Yao, D. Kenny, D.C. Warltier, P.J. Newman, and G.J. Gross. 1996. Antibody to platelet/endothelial cell adhesion molecule-1 reduces myocardial infarct size in a rat model of ischemia-reperfusion injury. *Circulation.* In press.

18. Murohara, T., J.A. Delyani, S.M. Albelda, and A.M. Lefer. 1996. Blockade of platelet endothelial cell adhesion molecule-1 protects against myocardial ischemia and reperfusion injury in cats. *J. Immunol.* 156:3550–3557.

19. Schimmenti, L.A., H.-C. Yan, J.A. Madri, and S.M. Albelda. 1992. Platelet endothelial cell adhesion molecule, PECAM-1, modulates cell migration. *J. Cell. Physiol.* 153:417–428.

20. Zehnder, J.L., M. Shatsky, L.L.K. Leung, E.C. Butcher, J.L. McGregor, and L.J. Levitt. 1995. Involvement of CD31 in lymphocyte-mediated immune responses: importance of the membrane-proximal immunoglobulin domain and identification of an inhibiting CD31 peptide. *Blood.* 85:1282–1288.

21. Behar, E., N.J. Chao, D.D. Hirake, S. Krishnaswamy, B.W. Brown, J.L. Zehnder, and F.C. Grumet. 1996. Polymorphism of adhesion molecule CD31 and its role in acute graft-versus-host disease. *N. Engl. J. Med.* 334:286–291.

22. Albelda, S.M., W.A. Muller, C.A. Buck, and P.J. Newman. 1991. Molecular and cellular properties of PECAM-1 (endoCAM/CD31): a novel vascular cell-cell adhesion molecule. *J. Cell Biol.* 114:1059–1068.

23. Sun, Q., H.M. DeLisser, M.M. Zukowski, C. Paddock, S.M. Albelda, and P.J. Newman. 1996. Individually distinct Ig homology domains in PECAM-1 regulate homophilic binding and modulate receptor affinity. *J. Biol. Chem.* 271: 11090–11098.

24. Yan, H., J.M. Pilewski, Q. Zhang, H.M. DeLisser, L. Romer, and S.M. Albelda. 1995. Localization of multiple functional domains on human PECAM-1 (CD31) by monoclonal antibody epitope mapping. *Cell Adhesion and Communication.* 3:45–66.

25. Liao, F., H.K. Huynh, A. Eiroa, T. Greene, E. Polizzi, and W.A. Muller. 1995. Migration of monocytes across endothelium and passage through extracellular matrix involve separate molecular domains of PECAM-1. *J. Exp. Med.* 182:1337–1343.

26. Muller, W.A., M.E. Berman, P.J. Newman, H.M. DeLisser, and S.M. Albelda. 1992. A heterophilic adhesion mechanism for platelet/endothelial cell adhesion molecule 1 (CD31). *J. Exp. Med.* 175:1401–1404.

27. DeLisser, H.M., C.Y. Yan, P.J. Newman, W.A. Muller, C.A. Buck, and S.M. Albelda. 1993. PECAM-1 (CD31)-mediated cellular aggregation involves cell surface glycosaminoglycans. *J. Biol. Chem.* 268:16037–16046.

28. Piali, L., P. Hammel, C. Uherek, F. Bachmann, R.H. Gisler, D. Dunon, and B.A. Imhof. 1995. CD31/PECAM-1 is a ligand for $\alpha_v\beta_3$ integrin involved in adhesion of leukocytes to endothelium. *J. Cell Biol.* 130:451–460.

29. Buckley, C.D., R. Doyonnas, J.P. Newton, S.D. Blystone, E.J. Brown, S.M. Watt, and D.L. Simmons. 1996. Identification of avb3 as a heterotypic ligand for CD31/PECAM-1. *J. Cell. Sci.* 109:437–445.

30. Sun, Q., C. Paddock, G.P. Visentin, and P.J. Newman. 1996. PECAM-1 is not a heparin-binding protein. *Mol. Biol. Cell.* 7:434*a*.

31. Tanaka, Y., S.M. Albelda, K.J. Horgan, G.A. Van Seventer, Y. Shimizu, W. Newman, J. Hallam, P.J. Newman, C.A. Buck, and S. Shaw. 1992. CD31 expressed on distinctive T cell subsets is a preferential amplifier of β_1 integrin-mediated adhesion. *J. Exp. Med.* 176:245–253.

32. Leavesley, D.I., J.M. Oliver, B.W. Swart, M.C. Berndt, D.N. Haylock, and P.J. Simmons. 1994. Signals from platelet/endothelial cell adhesion molecule enhance the adhesive activity of the very late antigen-4 integrin of human $CD34^+$ hemopoietic progenitor cells. *J. Immunol.* 153:4673–4683.

33. Piali, L., S.M. Albelda, H.S. Baldwin, P. Hammel, R.H. Gisler, and B.A. Imhof. 1993. Murine platelet endothelial cell adhesion molecule (PECAM-1/CD31) modulates b2 integrins on lymphokine-activated killer cells. *Eur. J. Immunol.* 23:2464–2471.

34. Berman, M.E., and W.A. Muller. 1995. Ligation of platelet/endothelial cell adhesion molecule 1 (PECAM-1/CD31) on monocytes and neutrophils increases binding capacity of leukocyte CR3 (CD11b/CD18). *J. Immunol.* 154: 299–307.

35. Berman, M.E., Y. Xie, and W.A. Muller. 1996. Roles of platelet endothelial cell adhesion molecule-1 (PECAM-1, CD31) in natural killer cell transendothelial migration and β_2 integrin activation. *J. Immunol.* 156:1515–1524.

36. DeLisser, H.M., J. Chilkotowsky, H. Yan, M. Daise, C.A. Buck, and S.M. Albelda. 1994. Deletions in the cytoplasmic domain of platelet-endothelial cell adhesion molecule-1 (PECAM-1, CD31) result in changes in ligand binding properties. *J. Cell Biol.* 124:195–203.

37. Yan, H., H.S. Baldwin, J. Sun, C.A. Buck, S.M. Albelda, and H.M. DeLisser. 1995. Alternative splicing of a specific cytoplasmic exon alters the binding characteristics of murine platelet/endothelial cell adhesion molecule-1 (PECAM-1). *J. Biol. Chem.* 270:23672–23680.

38. Modderman, P.W., A.E.G.K. von dem Borne, and A. Sonnenberg. 1994. Tyrosine phosphorylation of P-selectin in intact platelets and in a disulfide-linked complex with immunoprecipitated $pp60^{c\text{-}src}$. *Biochem. J.* 299:613–621.

39. Lu, T.T., L.G. Yan, and J.A. Madri. 1996. Integrin engagement mediates tyrosine dephosphorylation on platelet-endothelial cell adhesion molecule 1. *Proc. Natl. Acad. Sci. USA.* 93:11808–11813.

40. Jackson, D.E., C.M. Ward, R. Wang, and P.J. Newman. 1996. The protein-tyrosine phosphatase, SHP-2, binds PECAM-1 and forms a distinct signaling complex during platelet aggregation: evidence for a mechanistic link between PECAM-1- and integrin-mediated signal transduction. *Blood.* 88:438*a*.

41. Freeman, R.M., J. Plutzky, and B.G. Neel. 1992. Identification of a human src homology 2-containing protein tyrosine-phosphatase: a putative homolog of *Drosophila* corkscrew. *Proc. Natl. Acad. Sci. USA.* 89:11239–11243.

42. Ahmad, S., D. Banville, Z. Zhao, E.H. Fischer, and S.-H. Shen. 1993. A widely expressed human protein-tyrosine phosphatase containing *src* homology 2 domains. *Proc. Natl. Acad. Sci. USA.* 90:2197–2201.

43. Feng, G.-S., C.-C. Hui, and T. Pawson. 1993. SH2-containing phosphotyrosine phosphatase as a target of protein-tyrosine kinases. *Science (Wash. DC).* 259:1607–1610.

44. Vogel, W., R. Lammers, J. Huang, and A. Ullrich. 1993. Activation of a phosphotyrosine phosphatase by tyrosine phosphorylation. *Science (Wash. DC).* 259:1611–1614.

45. Kuhne, M.R., A. Pawson, G.E. Leinhard, and G. Feng. 1993. The insulin receptor substrate 1 associates with the SH2-containing phosphotyrosine phosphatase Syp. *J. Biol. Chem.* 268:11479–11481.

46. Lechleider, R.J., R.M. Freeman, and B.G. Neel. 1993. Tyrosyl phosphorylation and growth factor receptor association of the human corkscrew homologue, SH-PTP2. *J. Biol. Chem.* 268:13434–13438.

47. Stone, R.L., and J.E. Dixon. 1994. Protein-tyrosine phosphatases. *J. Biol. Chem.* 269:31323–31326.

48. Feng, G., and T. Pawson. 1994. Phosphotyrosine phosphatases with SH2 domains: regulators of signal transduction. *Trends Genet.* 10:54–58.

49. Streuli, M. 1996. Protein tyrosine phosphatases in signaling. *Curr. Opin. Cell Biol.* 8:182–188.

"Cell Adhesion In Vascular Biology"

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