The process of leukocyte extravasation, a critical step in the inflammatory response, involves the migration of leukocytes from the bloodstream towards target tissues, where they exert their effector function. Leukocyte extravasation is orchestrated by the combined action of cellular adhesion receptors and chemotactic factors, and involves radical morphological changes in both leukocytes and endothelial cells. Thus, it constitutes an active process for both cell types and promotes the rapid and efficient influx of leukocytes to inflammatory foci without compromising the integrity of the endothelial barrier.

This article provides a review of leukocyte extravasation from both molecular and mechanical points of view, with a particular emphasis on the most recent findings on the topic. It includes a description of newly revealed steps in the adhesion cascade, such as slow rolling motion, intraluminal crawling and alternative pathways for transcellular migration, and discusses the functional role of novel adhesion receptors, the spatiotemporal organization of receptors at the plasma membrane, and the signaling pathways that control different phases of the extravasation process.

**Key words:** Inflammation. Extravasation. Leukocyte-endothelial interaction. Adhesion. Transmigration.

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**UPDATE**

**Cardiovascular Translational Medicine (V)**

**Molecular Basis of Leukocyte–Endothelium Interactions During the Inflammatory Response**

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The process of leukocyte extravasation, a critical step in the inflammatory response, involves the migration of leukocytes from the bloodstream towards target tissues, where they exert their effector function. Leukocyte extravasation is orchestrated by the combined action of cellular adhesion receptors and chemotactic factors, and involves radical morphological changes in both leukocytes and endothelial cells. Thus, it constitutes an active process for both cell types and promotes the rapid and efficient influx of leukocytes to inflammatory foci without compromising the integrity of the endothelial barrier.

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**Bases moleculares de las interacciones leucocito-endotelio durante la respuesta inflamatoria**

El proceso de extravasación leucocitaria, un paso crucial de la respuesta inflamatoria, implica la migración de los leucocitos desde la corriente sanguínea hasta los tejidos diana donde ejercen su función efectora. La extravasación de los leucocitos está orquestada por la acción conjunta de receptores de adhesión celular y factores quimiotácticos, e implica cambios morfológicos drásticos tanto en leucocitos como en células endoteliales. De este modo, constituye un proceso activo para ambos tipos celulares que promueve la rápida y eficiente llegada de los leucocitos a los focos inflamatorios sin comprometer la integridad de la barrera endotelial.

Este artículo revisa la extravasación leucocitaria, con especial hincapié en los hallazgos más recientes en este campo, tanto desde el punto de vista molecular como mecanístico. Incluye la descripción de nuevos pasos en la cascada de adhesión tales como el enlentecimiento del rodamiento, la locomoción intraluminal o la ruta alternativa de migración transcelular, así como el papel funcional de nuevos receptores de adhesión, la organización espaciotemporal de los receptores en la membrana plasmática y las rutas de señalización que controlan los diferentes estados del proceso de extravasación.

**Palabras clave:** Inflamación. Extravasación. Interacción leucocito-endotelio. Adhesión. Transmigración.

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Adhesion receptors play an essential physiological role in maintaining tissue integrity by regulating numerous processes such as cell activation, migration, growth, differentiation, and death. This regulation is achieved through direct signal transduction and modulation of intracellular signaling triggered by different growth factors. Cell-cell interactions are essential for regulating hematopoiesis and the inflammatory response. Adhesion molecules are therefore particularly implicated in a wide variety of cardiovascular disorders that involve inflammation, such as atherogenic processes and progression of atherosclerotic plaque, myocardial infarction, ischemia-reperfusion injury or transplant...
variable affinity, the high frequency of association-dissociation of interactions allows them to mediate labile and transient tethers between leukocytes and the endothelium.\(^{10,11}\) Tethering slows the speed of travel of the leukocytes and allows them to roll over the endothelial surface, favoring subsequent interactions mediated by integrins and their ligands and increasing leukocyte adherence. As a result, the leukocytes finally come to a halt on the vascular wall.\(^{12}\)

The selectins (P, E, and L) are type 1 transmembrane glycoproteins that bind to fucosylated and sialylated hydrocarbons present in their ligands in a Ca\(^{2+}\)-dependent fashion. L-selectin is expressed by most leukocytes, whereas the E and P forms are expressed on endothelial cells activated by proinflammatory stimuli. P-selectin is also expressed by activated platelets (reviewed by Barreiro et al\(^{13}\)). In addition to the interaction of leukocyte selectin (L-selectin) with endothelial selectin (P- and E-selectin), the P-Selectin glycoprotein ligand-1 (PSGL1) protein is a major ligand of these 3 selectins. In fact, the binding of PSGL1 to P- and E-selectin promotes the interaction of leukocytes with the endothelium, whereas the binding of PSGL1 to L-selectin enables leukocyte-leukocyte interactions, whereby the adhered leukocytes facilitate the capture of other circulating leukocytes at sites where the endothelium is inflamed, regardless of whether these cells express ligands for endothelial selectins in a process denoted secondary recruitment.\(^{14}\)

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In addition to PSGL1, selectins can also bind to other glycoproteins such as CD44 or E-selectin-ligand-1 (ESL1) in the case of E-selectin. Each

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**Figure 1.** The adhesion cascade. The scanning electron microscope image shows a human endothelial monolayer treated with proinflammatory stimuli and perfused with human peripheral blood lymphocytes and monocytes at physiological flow (1.8 dyn/cm\(^2\)). Several unpolarized leukocytes have come into contact with the endothelium and have been captured during the rolling process. Also shown is a lymphocyte that has managed to firmly adhere to the endothelium and drastically changed its morphology from rounded to polarized.
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The integrins comprise a family of 24 heterodimeric receptors, each of which is composed of an α subunit and another β subunit. These molecules dynamically alter their adhesive properties through conformational changes (affinity) as well as through spatial redistribution on the cell surface (avidity). Recent observations predict the existence of 3 conformational states (bent conformation for low affinity, extended conformation with intermediate affinity, and extended conformation with high affinity). The most relevant integrins for leukocyte adhesion to the endothelium are members of the β2 subfamily, particularly LFA-1 (CD11a/CD18 or αLβ2) and myeloid-specific integrin Mac-1 (CD11b/CD18 or αMβ2), as well as integrins α4 VLA-4 (α4β1) and α4β7. Most of the ligands are transmembrane proteins that belong to the immunoglobulin superfamily. LFA-1 can bind to 5 intracellular adhesion molecules (ICAM-1 to ICAM-5), although the most important of these are ICAM-1 and ICAM-3. ICAM-1 is expressed on leukocytes, dendritic cells, and epithelial cells. In addition, expression is low on quiescent endothelial cells and increases with proinflammatory stimuli. ICAM-3 is expressed constitutively on all leukocytes. In addition to LFA-1, another ligand is the junctional adhesion molecule JAM-A, which is selectively concentrated on the apical region of the tight junctions of the endothelium and is partially redistributed to the apical surface of the endothelium with certain proinflammatory stimuli. On the other hand, Mac-1 interacts with ICAM-1, JAM-C, and the receptor for advanced glycation endproducts (RAGE). The integrin VLA-4 interacts with VCAM-1, which is an adhesion molecule that is expressed de novo after endothelial activation and also binds to JAM-B. VLA-4 also interacts with ADAM-28, fibronectin, osteopontin,
thrombospondin, the von Willebrand coagulation factor, and the invasin bacterial protein.48

Finally, αβ7 integrin, apart from interacting with VCAM-1 and fibronectin, specifically recognizes MAdCAM-1, a receptor expressed in the lymphoid tissues of the mucosa.19

**Modulation of Chemokine-Mediated Integrin Activity**

As tethering to the vascular endothelium occurs, the rolling velocity of the leukocytes slows and they are activated on encountering immobilized chemokines and integrin ligands exposed on the apical endothelial surface. This activation step enables the arrest of leukocytes and their subsequent firm adhesion to the endothelium under physiological flow conditions.49,50 Leukocyte activation implies a marked morphological change: the rounded circulating cell is transformed into a promigratory cell with polarized morphology, in which at least 2 regions can be identified, the cell front and the cellular uropod.51 The polarization of the leukocytes allows the cell to coordinate the intracellular forces to produce the necessary cell crawling during the extravasation process.52

The chemokines bound to the glycosaminoglycans of the apical endothelial membrane act by signaling via the G protein coupled receptors (GPCR) located on the microvilli of the leukocyte, thereby inducing a wide range of “outside in” signals in a fraction of a second. These lead to multiple conformational changes in the integrins.53-55

The complexity and the short time period of the signaling mechanisms induced by the chemokines that control the activation of the integrins are consistent with the existence of compartmentalized and pre-formed protein networks (“signalosomes”) in the leukocytes.56 The presence of specific chemokines in different vascular beds helps orchestrate the selective recruitment of different leukocyte subpopulations to the inflammatory foci or to the secondary lymphoid organs.57 In addition, chemokines can exert a differential effect on specific integrins within the same microenvironment.58

**Modulation of Ligand-Mediated Integrin Affinity**

After chemokine-induced activation, the conformation of the integrins changes reversibly from the inactive (bent) form to the extended form with intermediate affinity. This event prepares the integrin for binding to its endothelial ligand. The integrins that contain an I domain inserted into their α subunits undergo a subsequent conformational change after binding to the ligand, culminating in the complete activation of the integrin and leukocyte arrest.59,60 Therefore, the high-affinity conformational state for immediate arrest of the leukocyte on the endothelium requires immobilized chemokines and the integrin ligands.53,62 However, the α4 integrins, which contain an I-like domain on the β chains, can spontaneously interact with their endothelial ligands without a prior chemotactic trigger.17

The signaling induced by the binding to the ligand leads to the separation of the cytoplasmic regions of the subunits of the integrin, thereby favoring its association with the cortical actin cytoskeleton. The α4 integrins are basically linked through paxillin while β2 integrins are linked through talin, filamin, and other structural molecules. In addition, the binding to the ligand increases the recruitment of additional integrins to increase the firm adhesion of the leukocyte in conditions of flow stress.53 This clustering of integrins depends on the release from their tether to the cytoskeleton—a process mediated by protein kinase C (PKC) and calpain—to increase their lateral mobility on the membrane.64 In addition, the role of Rap-1 and its activator CalDAG-GEFI have recently been described, as well as the coordinated action of kindlin-3 with talin in the activation of integrins to mediate the leukocyte firm adhesion in different types of hematopoietic cells.65,66 With regard to the spatial organization of the integrins, it has been shown that nanoclusters of LFA-1 not bound to its ligand are present and these enable the efficient formation of microclusters induced by binding to a ligand.57,68

On the other hand, several studies indicate that flow stress also regulates the integrins, reinforcing their bonds and even increasing their affinity.69,70 The integration of signaling derived from chemokines and the external forces to favor transmigration has been defined as the phenomenon of chemorheotaxis.71

**Regulation of Leukocyte Crawling by Integrins**

The signals implicated in the integrin-mediated firm adhesion of leukocytes to the endothelium have to be attenuated and the original contact has to be weakened enough to allow the migration of the leukocyte towards the appropriate site to start the process of endothelial transmigration. The β2 integrins seem to play an important role in crawling, as blockade of the integrin or its ligands leads to random migration, failure to position the cell at the interendothelial junctions, and defective diapedesis.72 In vivo studies using genetically modified mice lacking LFA-1 or Mac-1 clearly
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It has been observed that, after leukocyte arrest on the endothelium, the binding of VCAM-1 and ICAM-1 with their ligands triggers the reorganization of the endothelial cortical actin cytoskeleton and generates a 3-dimensional docking structure that surrounds the leukocyte and prevents leukocytes adhered in conditions of physiological flow from becoming unbound. This structure has a large accumulation of adhesion receptors, as well as the activated ezrin and moesin proteins. The endothelial docking structure is supported by the actin cytoskeleton, docking actin-bundling proteins such as actinin, proteins typical of focal adhesions such as talin, paxillin, and vinculin, and actin nucleating proteins. In addition, second messengers such as PI(4,5)P2 and the Rho/160ROCK signaling pathway are also important for generating and maintaining the endothelial docking structure (Figure 2).

Furthermore, both ICAM-1 and VCAM-1 cluster together in the endothelial docking structure, although one of them is not bound to its corresponding ligand. This joint clustering also proceeds independently of the anchoring to the actin cytoskeleton and of the formation of ICAM-1/VCAM-1 heterodimers, as this is due to the inclusion of VCAM-1 and ICAM-1 in microdomains rich in tetraspanins, which act as endothelial platforms for specialized adhesion (Figure 2). The tetraspanins are small proteins that delineate the different underlying mechanisms for each of these β integrins. Whereas firm adhesion is mediated by LFA-1, crawling depends on Mac-1; both processes contribute to an efficient migration. After activation by binding to a ligand, the integrins regulate different effectors of myosin contractility, actin-remodeling GTPases, and molecules implicated in the regulation of the microtubule network both at the cell front and in the uropod. Thus, the integration of signals generated at both cell poles leads to coordinated movement of the leukocyte.

**Functional Role of the Endothelial Adhesion Molecules VCAM-1 and ICAM-1 in Leukocyte Capture**

VCAM-1 and ICAM-1 molecules, both members of the immunoglobulin superfamily, are the main endothelial adhesion molecules implicated in the binding to integrins VLA-4 and LFA-1, respectively. ICAM-1 is scarcely expressed on the quiescent endothelium, whereas the expression of both molecules is induced after cell activation by proinflammatory cytokines such as interleukin (IL) 1 and tumor necrosis factor (TNF) α. In addition, binding of VCAM-1 and ICAM-1 to the actin cytoskeleton has been reported through 2 members of the ERM family, namely, ezrin and moesin. These molecules act as links between the membrane and the actin cytoskeleton, regulating cortical morphogenesis and cell adhesion.

The dynamics of VCAM-1 and ICAM-1 has been studied in human umbilical vein endothelial cells (HUVECs) activated with TNF during the process of leukocyte-endothelium interaction. It has been observed that, after leukocyte arrest on the endothelium, the binding of VCAM-1 and ICAM-1 with their ligands triggers the reorganization of the endothelial cortical actin cytoskeleton and generates a 3-dimensional docking structure that surrounds the leukocyte and prevents leukocytes adhered in conditions of physiological flow from becoming unbound. This structure has a large accumulation of adhesion receptors, as well as the activated ezrin and moesin proteins. The endothelial docking structure is supported by the actin cytoskeleton, docking actin-bundling proteins such as α actinin, proteins typical of focal adhesions such as talin, paxillin, and vinculin, and actin nucleating proteins. In addition, second messengers such as PI(4,5)P2 and the Rho/160ROCK signaling pathway are also important for generating and maintaining the endothelial docking structure (Figure 2). Furthermore, both ICAM-1 and VCAM-1 cluster together in the endothelial docking structure, although one of them is not bound to its corresponding ligand. This joint clustering also proceeds independently of the anchoring to the actin cytoskeleton and of the formation of ICAM-1/VCAM-1 heterodimers, as this is due to the inclusion of VCAM-1 and ICAM-1 in microdomains rich in tetraspanins, which act as endothelial platforms for specialized adhesion (Figure 2). The tetraspanins are small proteins that cross the membrane 4 times with lateral interaction of their second extracellular domain with other integral proteins of the membrane, regulate membrane function, and form multiple protein domains on the plasma membrane. They have
been implicated in several cell functions, including migration, homotypic and heterotypic cell-cell adhesion, and antigen presentation, viral infection, and gamete fusion.  

78-82 The use of innovative microscopy analytical techniques has enabled the characterization of the diffusive properties, organization at the nanoscale, and specific molecular interactions within the microdomains in live primary human endothelial cells. Such studies have provided convincing evidence of the existence of endothelial adhesion platforms as physical entities distinct from the lipid rafts in the plasma membrane.  

77 Scanning electron microscopy in samples treated with a specific peptide blocker of tetraspanins reveals the nanoclustering or avidity of VCAM-1 and ICAM-1 induced by the endothelial adhesion platforms as a new supramolecular organization mechanism that regulates the efficient adhesive capacity of both endothelial adhesion receptors to their counter-receptors, the leukocyte integrins.  

77 The functional relevance of the inclusion of ICAM-1 and VCAM-1 in tetraspanin microdomains in endothelial cells has been demonstrated through the use of an experimental strategy with interfering RNA targeting the tetraspanins CD9 and CD151 in primary human endothelial cells and through competitive blockade with glutathione-S-transferase (GST) fusion proteins that contain the second extracellular region of CD9.  

83 Therefore, the inclusion of ICAM-1 and VCAM-1 in tetraspanin domains is necessary for these domains to function properly in stringent dynamic conditions such as flow stress. VCAM-1 and ICAM-1 are not the only adhesion receptors that interact with tetraspanin microdomains, others such as JAM-A, PECAM-1, ICAM-2, or CD44 also do so. It could therefore be postulated that the tetraspanin microdomains act as specialized platforms that constitutively organize the appropriate adhesion receptors in the membrane for fast kinetics and efficient leukocyte extravasation.  

77 The endothelial adhesion receptors VCAM-1 and ICAM-1 are able to transmit signals after binding to the ligand. The VCAM-1 molecule is implicated in opening the interendothelial junctions to facilitate leukocyte extravasation. In fact, VCAM-1 induces the activation of NADPH oxidase (possibly NOX2) and production of reactive oxygen species (ROS) dependent on GTPase rac activity, with the subsequent activation of matrix metalloproteinases and loss of adhesion mediated by VE-cadherin due to phosphorylation of β-catenin by Pyk-2.  

84-88 thereby favoring the extravasation process. On the other hand, VCAM-1 and ICAM-1 are able to induce a rapid increase in Ca^2+ concentration, leading to the activation of Src kinase and the subsequent phosphorylation of cortactin.  

90-93 ICAM-1 can also activate RhoA, inducing the formation of stress fibers and the phosphorylation of focal adhesion kinase (FAK), paxillin, and p130Cas, which in turn are implicated in signaling routes involving c-Jun N-terminal kinase (JNK) and p38.  

94-97 This increases endothelial permeability and is associated with increased transendothelial leukocyte migration. The induction of c-fos and rhoA transcription has also been reported via ICAM-1.  

96 Finally, ICAM-1 can induce its own expression and that of VCAM-1, acting as a regulating mechanism to facilitate leukocyte transmigration.  

86 INTEGRINS AND THEIR LIGANDS DURING ENDOTHELIAL TRANSMIGRATION

During endothelial transmigration, the endothelial junctions are partially dismantled to avoid damage to the monolayer or substantial changes in permeability. Thus, the leukocyte membranes and the endothelium remain in close contact during diapedesis and, afterwards, the endothelial membranes reseal their links. 

Once the leukocytes have reached an appropriate site for transmigration (preferably the intercellular junctions), they deploy exploratory pseudopods between 2 adjacent endothelial cells. The pseudopods then transform into a lamella that moves across the open space on the monolayer. During this process, the LFA-1 molecule is the integrin with the predominant role. This molecule is quickly relocalized to form a ring-shaped cluster at the contact interface between the leukocyte and endothelium, where it interacts with ICAM-1  

98 and, in some other cell models, with JAM-A.  

100 When the transmigration process is over, LFA-1 is finally concentrated in the uropod.  

101 Other proteins implicated in the transmigration process are ICAM-2, JAM-B, JAM-C, PECAM-1 (CD31), ESAM, and CD99. Many of these are able to interact both homophilically and heterophilically maintaining the interendothelial junctions or the leukocyte-endothelial interactions.  

102-105 In the leukocyte transmigration process, in addition to the classic diapedesis route, in which the leukocytes cross the interendothelial junctions (paracellular route), there is increasing evidence of an alternative route in which the leukocytes can migrate through individual endothelial cells (transcellular route) without perturbing the interendothelial junctions. This process takes place preferentially in the microvasculature, the blood-brain barrier, or high endothelial venules of the secondary lymphoid organs rather than in the macrovasculature.  

106-108 Recent observations on the mechanism of this transcellular migration process
indicate that, initially, the leukocytes generate invasive podosomes dependent on Src kinase and Wiskott–Aldrich syndrome protein (WASP) activity to palpate the endothelial surface. These podosomes subsequently develop into the transcellular pore. In the endothelium. It is necessary membrane fusion regulated by calcium and SNARE-containing complexes, as well as new membrane supply by vacuole-vesicular organelles. It has been also reported the translocation of ICAM-1 to caveolae after leukocyte adhesion and the subsequent formation of a kind of multivesicular channel containing ICAM-1 and caveolin-1 around a leukocyte pseudopod that penetrates through the endothelial cell. Both proteins, ICAM-1 and caveolin, follow the path of the entire leukocyte, moving towards the basal endothelial membrane.

In addition, the intermediate filament protein vimentin also seems to play an important role in the transcellular route. The in vivo presence of dome-shaped endothelial structures that cover the leukocyte during transendothelial migration have also recently been described. These observations seem to indicate that the endothelial docking structures might become domes that completely envelope the leukocytes on the luminal face of the endothelium, thereby allowing rupture of the basolateral membrane without compromising the endothelial barrier function.

**ANTIADHESION-BASED THERAPIES**

The advances in our knowledge of the molecular mechanisms that underlie cell migration and the extravasation cascade have allowed molecular targets to be identified for antiadhesion therapy for inflammation. Monoclonal antibodies against the $\alpha_4$ and $\alpha_6$ chains have shown a clear beneficial effect in different animal models of inflammatory and autoimmune states, as well as in human diseases such as multiple sclerosis, inflammatory bowel disease, and psoriasis. Similar results have been obtained in animal models with different VLA-4 synthetic peptides.

The promising results obtained in these animal studies have encouraged formation of to different groups and pharmaceutical companies dedicated to developing new drugs for clinical trials. Thus, a humanized anti-VLA-4 monoclonal antibody has shown a clear therapeutic effect in relapses of multiple sclerosis and Crohn disease. Other potential uses of this type of therapeutic monoclonal antibody would be in inflammatory and/or autoimmune diseases that are widespread in the general population, such as rheumatoid arthritis, asthma, and type 1 diabetes mellitus.

As in the case of VLA-4, the anti-LFA-1 antibody has been shown to have a significant therapeutic effect in humans, as a humanized monoclonal anti-$\alpha_4$ antibody has been approved to treated moderate to severe psoriasis.

There is no doubt that the therapeutic monoclonal antibodies directed against adhesion molecules or costimulators represent an important step forward in treating inflammation and autoimmune diseases. However, biological agents, such as monoclonal antibodies against $\alpha_4$ and $\alpha_6$ leukocyte integrin chains are directed against receptors with a range of different biological functions: the generation of immune response, differentiation of lymphocytes into Th1/Th2, the effector phase of immune cells, and the extravasation of leukocytes to the inflammatory foci, among others. In addition, it is evident that some monoclonal antibodies may act as agonist molecules, thereby generating intracellular signals after binding to their antigen. Thus, long-term administration of these types of drugs could have unexpected and even undesirable consequences. It would be very important to take into account all information derived from both basic studies and preclinical research to enable the appropriate design of future clinical trials with this type of biologic agent (reviewed González Amaro et al).

A large number of anti-inflammatory therapies against different target molecules in the endothelium have also been investigated. The efficacy of blockade of P-selectin to prevent damage caused during ischemia-reperfusion processes (transplantation, thrombosis, stroke, etc) as well as the beneficial effects of anti-ICAM-1 antibodies for preventing restenotic lesions in animals have been investigated and, as a result, they are emerging as possible therapeutic targets in humans. There are also numerous studies of chronic autoimmune or inflammatory diseases in which therapies based on anti-TNF, anti-VCAM-1, or anti-ICAM-1 have been applied. Recent research points to tetraspanins and, specifically, CD9, as a potential general anti-inflammatory target that could regulate the adhesive function of multiple adhesion receptors and be more effective than individual inhibition of each one separately. However, the tetraspanin CD9 is ubiquitously expressed throughout the organism, and so the release of CD9 blockers should be done locally and restricted to the area of inflammation. Prior studies on knock-out mice lacking expression of CD9 and other tetraspanins are necessary to clarify whether this hypothesis is plausible. Indeed, recently, the role of the endothelial tetraspanin CD81 was described as a possible diagnostic and therapeutic marker of atherogenes in humans. The expression of CD81 on the luminal surface of the endothelium increases in the initial states of the
disease, and so this molecule could play a crucial role in the formation of atherosclerotic plaque by favoring adhesion of monocytes in the stage prior to the triggering of the inflammatory response.\textsuperscript{121}

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