Review paper

Endothelial adhesion molecules contribution to leukocyte recruitment into inflamed tissues

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Abstract

Adhesion of cells to each other and to the extracellular matrix is crucial for multicellular organisms in development and in the normal functioning of the immune system. One of the most studied aspects of cell adhesion is the accumulation of leukocytes in inflammation, an essential process for effective host defense against infection and injury. On their way to sites of antigen challenge (microbial invasion, transplanted tissue, vaccine deposit) circulating in blood leukocytes must adhere to the endothelium lining the postcapillary venules, penetrate the vessel wall and migrate to the site of tissue irritation. At each of these stages, specific adhesive interactions between leukocytes and the vessel wall (and subsequently the extracellular matrix) are important. This sequence of events can be vieved as a cascade reaction similar to the complement and coagulation cascades.

Key words: *endothelium, leukocytes, adhesion molecules, signalling, selectins, integrins, chemokines*

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Introduction

Recent studies confirmed active contribution of endothelial cells (ECs) to endothelial-leukocyte communication. This paper is not intended to be a global review but will focus on some aspects of leukocyte-endothelium interactions in inflammation.

Vascular ECs play an important, threefold role in the interaction with leukocytes. First, they are gatekeepers in leukocyte recruitment to inflammatory foci and lymphocyte homing to secondary lymphoid organs. Second, they modulate leukocyte activation. Finally, they are targets of leukocyte-derived molecules, resulting either in ECs activation or death.

It is increasingly recognized that vascular endothelia are heterogenous, in that the function and phenotype of endothelial cells is specialized according to their particular site [1–3]. Physiological lymphocyte circulation: adherence and transendothelial migration occurs in specialized postcapillary vascular sites, called high endothelial venules (HEVs), found in all secondary lymphoid organs. HEVs represent the most striking examples of tissue, whose specialized features are under the control of the local tissue environment. In contrast to the flat morphology of endothelia from other vessels, HEVs cells have a 'plump', cuboidal appearance and are characterized by a prominent Golgi complex, abundant polyribosomes and rough endoplasmic reticulum. In HEVs cells are connected by discontinous, spot-welded junctions, which facilitate the pasage of lymphocytes between adjacent cells, allowing massive lymphocyte extravasation. The HEVs cells contain multiple vesicular structures, among them Weibel Palade (W-P) bodies, involved in secretion. Moreover, they express on their surface functional addressins, which are specialized ligands for lymphocytes adhesion molecules. Extralymphoid sites of chronic inflammation are characterized by the presence of HEV-like postcapillary venules, morphologically and functionally similar to HEVs from lymphoid tissues. The presence of HEV-like cells and their degree of similarity to HEVs is related to the severity of the local inflammation in the perivascular area.

Endothelial cell activation

The multifunctional ability of endothelial cells (ECs) to control and mediate inflammation is now well recognized

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at both basic science and clinical levels. The quiescent endothelium maintains a status quo, but in the inflammatory process it undergoes a series of metabolic changes; the process is known as endothelial cell activation (ECA). When ECs are exposed to cytokines which mediate the inflammatory response „...there are quantitative changes in the level of expression of certain gene products (i.e. proteins) that, in turn, endow ECs with the new capacities that cumulatively allow ECs to perform new functions" [4]. There are five main changes associated with ECA: loss of vascular integrity, expression of ECs adhesion molecules, secretion of cytokines, prothrombotic changes and upregulation of lymphocyte adhesion molecules ligands. All these changes are mutually dependent and interactive. To an immunologist ECA means mainly: upregulation of MHC class II antigens, the production of certain cytokines and, last but not the least, the expression of cell adhesion molecules. This will now be discussed in the context of their mutual interactions in the process of the migration of leukocytes out of the blood vessel into inflamed tissue.

Leukocyte-endothelial interactions: four sequential steps of tethering, triggering, strong adhesion and transmigration into surrounding tissues comprise the classic paradigm of inflammatory cell recruitment. Specific families of adhesion molecules in concert with chemokines play an essential role in leukocyte transmigration to secondary lymphoid organs as well as to peripheral inflamed tissue [5].

Selectins

Tethering and rolling along the vessel wall are the first steps in this process and are predominately mediated by the selectin family of adhesion molecules, found on both leukocytes and endothelium [for review see: 7]. The selectins are transmembrane glycoproteins that bind sialylated carbohydrate moieties present on mucin-type protein ligands. Three selectins have been identified: P-, E- and L-selectin. They possess a lectin domain at the NH2-terminus, which is central to the carbohydrate binding properties of the protein. This is followed by an EGF-like domain and various numbers of consensus repeat (CR) domains. The major structural difference between the selectins lies in the number of CR domains. In humans, P-selectin is the longest member of the family with nine CRs; E-selectin has six and L-selectin contains two CRs. The endothelial selectins are expressed at the lumenal surface of HEVs. Due to their shape, endothelial E- and P-selectins are extended beyond the surrounding glycocalyx, so allowing capture of circulating leukocytes that express the appropriate ligand molecule. P-selectin (CD62P, GMP-140, PADGEM, LECAM-3) is stored in the cytoplasm of ECs in W-P bodies and also in alpha granules of platelets. On activation of ECs the W-P bodies fuse with the ECs cell surface membrane, discharging their content and exposing P-selectin. Surface exposition of P-selectin is rapid and transient, peaking at 10 min and returning to normal by 20–30 min. Once expressed on the surface of endothelial cells, P-selectin is rapidly internalized by endocytosis. Platelets express much greater amounts of P-selectin than endothelium and bind endothelium via selectin dependent and independent mechanisms. Therefore, the platelet may also function as a bridge between the circulating leukocyte and endothelium. E-selectin (CD62E, ELAM-1, LECAM-2) is expressed exclusively by endothelial cells. Unlike P-selectin, E-selectin is not constitutively present in endothelial cells. Instead, E-selectin expression is transcriptionally regulated by mediators such as TNF-α and IL-1. Following stimulation with these cytokines, peak expression of E-selectin occurs in 4 h and then declines within 24 h. Once expressed on the cell surface, E-selectin is slowly internalized, and directed to lysosomes for degradation. L-selectin, (CD62L, LAM-1, LECAM-1, gp90MEL, DREG) constutively expressed by most leukocytes, mediates the initial capture and subsequent rolling of leukocytes along inflamed vascular endothelium under physiological shear flow. Further leukocyte activation induces rapid endoproteolytic cleavage of L-selectin from the cell surface, generating soluble L-selectin (sL-selectin).

Addressins

Each selectin recognizes specific carbohydrate motifs on either leukocytes or ECs, respectively. Ligands for selectins are called addresins [1]. Addressins represent mucin-type glycoproteins, characterized by a presence of sialylated (CD15s) and/or sulfated Lewis X or Lewis A carbohydrate epitopes. These are: glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), CD34 molecule and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on endothelia, and PSGL-1 on leukocytes. Peripheral lymph node addressins (PNAd's): GlyCAM-1 and CD34 present on HEVs of peripheric and mesenteric lymph nodes, act as tissue-specific ligands for L-selectin. (MAdCAM-1), found on HEVs of Peyer' Patches, mesenteric lymph nodes and lamina propria of the gut play similar role, but only in these mucosal-type tissues. Therefore, binding to MAdCAM-1 directs lymphocyte trafficking to gut, whereas interaction of PNAd's with lymphocyte L-selectin targets immune cells to peripheral lymph nodes. P-selectin glycoprotein ligand (PSGL-1), expressed by all leukocytes, is also able to bind to E-selectin. Interactions could also occur between PSGL-1 expressed on one leukocyte and L-selectin expressed on another. Constitutive E-selectin expression on dermal microvascular endothelial cells plays a critical role in mediating adhesive interactions of human skin-homing T cells and in pathologic accumulation of lymphocytes in skin. The major E-selectin ligand on human skin-homing T cells is cutaneous lymphocyte-associated antigen (CLA), a specialized glycoform of PSGL-1, defined by monoclonal antibody HECA-452. CLA initiates skin homing by mediating

E-selectin-dependent tethering and rolling within cutaneous venules. It is accepted, that the rolling is absolutely essential for strong adhesion. It has been demonstrated that in the absence of L-selectin, rolling leukocytes were not able to emigrate out of the HEVs. However, there are vascular beds including the liver, lung and heart which may not require rolling to recruit leukocytes. For example, the capillaries of the liver (sinusoids) are sufficiently narrow, such that during inflammation, leukocytes entering these vessels appear to stop without any apparent rolling. One potential explanation may be physical trapping due to activated, more rigid leukocytes and/or trapping of leukocytes in endothelial-swollen, diameter restrictive sinusoids [6].

Integrins

The engagement of selectins into leukocyte tethering triggers further intracellular signalling pathways that are essential for downstream actions of the leukocytes: strong adhesion, extravasation and migration through tissues. After a short period of rolling, leukocytes must be rapidly arrested on the vessel wall [8]. This arrest is exclusively mediated by a second family of adhesion molecules – integrins – localized on the leukocyte surface. Integrins are heterodimers, consisting of α and β subunits, which are classified according to their β subunit. There is substantial specialization between distinct vascular integrins. At least four leukocyte integrins mediate strong adhesion to endothelial cells. These are $\beta 2$ integrins CD11a/b/c on lymphocytes (CD11b is present also on neutrophils and monocytes) and $\beta 1$ integrin on lymphocytes and monocytes. Leukocyte function-associated antigen (LFA-1, $\alpha L\beta 2$, CD11a/CD18) and very late antigen (VLA-4, $\alpha 4\beta 1$, CD49d/CD29) are integrin-type cell adhesion molecules that are predominantly involved in leukocyte trafficking and extravasation. LFA-1 is exclusively expressed on leukocytes and interacts with its ligands, expressed on endothelial cells. LFA-1 is the major $\beta 2$ integrin on T lymphocytes and was the first integrin identified as a mediator of lymphocyte binding to normal and cytokine activated human umbilical vein ECs. Another important integrin is Mac-1 ($\alpha_M\beta 2$) integrin. All members of the $\beta 2$ family of integrins are thought to mediate neutrophil adhesion to activated ECs. VLA-4 is expressed on lymphocytes, monocytes, and eosinophils, but is not found on neutrophils.

Beta 2 integrins, which are members of the immunoglobulin gene superfamily bind to intercellular adhesion molecules: ICAM-1 and ICAM-2. ICAM-2 are constitutively expressed on all ECs. ICAM-1 are expressed at low levels on quiescent endothelium and their expression is increased after ECs activation by proinflammatory cytokines such as IL-1, TNF, or IFNγ. ICAM-1 and endothelial cell specific molecule-1 (ESM-1), a proteoglycan produced by endothelial cells under the control of inflammatory cytokines, both bind directly to LFA-1 onto the cell surface of human blood lymphocytes and monocytes, and may therefore influence both the recruitment of circulating lymphocytes to inflammatory sites and LFA-1-dependent leukocyte adhesion and activation.

The $\beta 1$ integrin VLA-4 recognizes and bind to vascular cell adhesion molecule 1 (VCAM-1) expressed on nonlymphoid endothelium. Belonging to Ig supergene family, VCAM-1 is not normally expressed on ECs but it is induced by IL-1, TNF, gram-negative bacterial lipopolysaccharide (LPS) and, in some cases, by IFN-γ. Besides VCAM-1, TNF alpha induces also the transcription of another ECs adhesion molecules: ICAM-1 and E-selectin, by activating the transcription factor NF-kappaB. Different combinations of cytokines can differentially modulate their induction. There are also differences in the ability to express these molecules between endothelium in large vessels and the microvasculature. Contact-mediated activation of endothelial cells (EC) by cytokine-stimulated T lymphocytes, induces release by ECs of monocyte chemotactic protein-1 (MCP-1), IL-8, and IL-6.

Integrin activation by chemokines

A unique feature of integrins is that their activity is dynamically regulated, independently of their level of surface expression. Circulating leukocytes maintain their integrins in nonadhesive state to avoid non-specific sticking to blood vessels. For firm adhesion support, the integrins must be activated, by chemokines, lipid mediators and other proinflammatory molecules presented on the surface of the endothelium. *In situ* activation of integrin avidity mediated by chemokine signaling can take place within seconds or subsecond time frames, resulting either in augmented reversible adhesions or immediate arrest on the vascular endothelium. This mechanism serves as a reversible checkpoint for tethered leukocytes to successful arrest on target endothelial sites. The activation of high integrin avidity to endothelial ligands results in firm integrin-mediated adhesion. Below thresholds of chemokine signals, reversible integrin-mediated tethering can be induced at leukocyte/endothelium contacts. These reversible contacts only slow down the rolling leukocyte, increasing the probability of subsequent encounters with chemokines and integrin ligands.

Lymphocytes cell-surface $\beta 2$ integrins (e.g. LFA-1) are triggered into their high affinity conformation by signaling through a chemokine receptors. Chemokines (***chemo****attractant cyto****kines***), a family of chemotactic cytokines, are well known by their capability of attracting inflammatory leukocytes (such as monocytes, activated T cells and neutrophils), mediate their chemotaxis and diapedesis [for reviews see: 8, 9]. In humans the chemokine system is organized in a redundant way. Some chemokines – such as stromal cell-derived factor-1α (SDF-1α), SLC (Exodus-2/6Ckine/TCA4) and macrophage inflammatory protein-3α (MIP-3α, ELC/Exodus-3) – are capable of triggering adhesion of most peripheral blood

lymphocyte subpopulations. Other chemokines trigger adhesion of only particular specialized subsets. That adhesion-triggering requires occupancy of a treshold number of chemokine receptors per cell that is much higher than that necessary for mediating chemotaxis. Functionally distinct T cell subsets exhibit specific chemokine receptor profiles that regulate their tissue localization. Granulocytes are activated by several chemokines, among them interleukin-8 (IL-8), platelet activating factor, complement component 5a and leukotriene B4. Under shear stress conditions, monocytes are activated by MCP-1 and IL-8, and lymphocytes are activated by SDF-1α, SLC, and MIP-3α. The precise cellular source of chemokines is often unknown. However, activated vascular endothelial cells have been shown to synthesize and secrete IL-8, MCP-3, MCP-1, and others. Chemokines can also direct migration of adherent cells across the endothelium, and control segregation of cells into specific microenvironments within tissues [6, 9]. Tissue-selective trafficking of memory and effector T and B lymphocytes is mediated by unique combinations of adhesion molecules and chemokines: TECK/CCL25 in small intestine, CTACK/CCL27 in skin, or MEC/CCL28 in diverse mucosal sites. Constitutively expressed chemokines may help determine the character of local immune responses and contribute to the systemic organization of the immune system [9, 10].

A proposed mechanism for the integrin activation is as follows: leukocytes tethered by endothelial selectins or selectin ligands form microvillar contacts (tethers) with endothelial integrin ligands. Physiological *in situ* activation of integrins is mediated by immobilized chemokines/chemoattractants, displayed on the tips of endothelial microvilli in sites of immune cell extravasation. Due to leukocyte preference for surface-bound over soluble chemokines, upregulation of leukocyte integrin avidity by chemokines is therefore predicted to take place mainly *in situ* i.e. at the emigration site. The signal is passed through the G-protein-coupled receptors (GPCRs), catalyzing GDP/GTP exchange on the G-protein alpha-subunit. GPCRs are a family of seven transmembrane helical proteins [11]. Once activated by an extracellular signal, GPCRs trigger the intracellular signal transduction cascade by activating a heterotrimeric G protein [11]. Chemokine signals transmitted via GPCRs, elicit a variety of events resulting in enhanced integrin clustering and patching. Macroclustering of the integrin on the cell surface is a prerequisite for high LFA-1 avidity. The different types of LFA-1 clusters may generate intermediate or high avidity [12]. The manner by which affinity, microclustering and macroclustering changes are acquired by particular leukocyte integrins, can result in firm binding to one cell type but not to another.

The temporal nature of chemokine-stimulated integrin avidity may require additional adhesion strengthening steps to take place at leukocyte/endothelial contacts, shortly after leukocyte arrest. Numerous costimulatory molecules including CD2, CD7, CD28, CD14 and other immunoregulatory receptors, could be involved in integrin avidity modulation at endothelial contacts. However, these integrin effectors appear mainly to trigger late adhesion strengthening and spreading events. Only memory and activated T cells adhere to ECs and home to sites of inflammation. Memory T cell extravasation is accompanied by their phenotypic and functional changes induced by the interactions with the ECs: up-regulation of certain adhesion (CD11a, CD49d), activation (CD69), and costimulatory (CD86) receptors. These effects appear to be mediated by αLβ2 integrin-CD54 interactions [13].

The function of integrins in leukocyte adhesion to the vasculature is controlled primarily by expression patterns of endothelial integrin ligands, chemokine receptors on specific leukocyte types, and site-specific chemokines and costimulatory ligands. In addition to these crucial expression-regulated factors, there is growing evidence for the tight control of integrin avidity modulation by the cell cytoskeleton. Integrin outside-in signaling is promoted at the leukocyte contact with the endothelial integrin ligands through anchorage to the actin cytoskeleton and a buildup of integrin complexes, whose link integrin to actin, causing remodeling and microtubule reorganization, necessary for cell spreading and contractility on endothelial surfaces [14].

Leukocytes do not roll or adhere on arterial endothelium. This is due not only to high shear forces, but also because the arterioles lack sufficient adhesion molecule expression to support the rolling. Nevertheless, there is a growing body of evidence that certain stimuli including cigarette smoke, oxidized LDL, prolonged stimulation with TNF, or high cholesterol diet do induce leukocyte-arterial endothelium interactions.

Summarizing, an initial slowing of leukocytes on the vascular endothelium, mediated by selectins, is followed by activation of β2 integrins on leukocytes exposed to cytokines and pro-inflammatory mediators. Once activated the leukocyte integrins bind to counterreceptors on the endothelium, leading to adherence of the leukocyte. Finally, the chemokine-induced integrin activation signals must be reversed, to allow firmly arrested leukocytes to migrate from the site of arrest and extravasate the vessel wall.

Extravasation

Following strong adhesion to endothelium, leukocytes migrate across endothelial barriers under shear flow into the parenchymal tissue. Extravasation of leukocytes into tissues through tight junctions of endothelial cells is mediated by integral membrane protein: platelet and endothelial cell adhesion molecule-1 (PECAM-1), and further perivascular migration through the extracellular matrix occurs *via* β1 integrins [15]. Leukocytes enter sites of inflammation by squeezing through the borders between endothelial cells that line postcapillary venules at that site. This rapid process, called transendothelial migration (TEM) or diapedesis, is completed within 90 s after a leukocyte arrests on the endothelial surface. In this time, the leukocyte

moves in ameboid fashion across the endothelial borders, which remain tightly apposed to it during transit. During TEM, PECAM is targeted to segments of the junction across which monocytes are in the act of migration [16].

Under certain circumstances the subendothelial space itself becomes a site of inflammation, such as in vasculitis, alloimmune vasculopathy, or arteriosclerosis. Endothelial cells activated by proinflammatory cytokines express adhesion molecules, but also a high levels of antigen-presenting molecules (MHC class I and II). As a consequence, they may become a direct target of cytotoxic lymphocytes and finally succumb. Dermal microvascular ECs display high levels of class I and class II MHC molecules, the only known purpose of which is to present antigenic peptides to lymphocytes. Upon contact with activated T cells or their secreted products (cytokines), dermal ECs themselves become activated, revealing inducible leukocyte adhesion molecules such as E-selectin, ICAM-1, and VCAM-1; that can determine In addition to host defence, endothelial-leukocyte interactions contribute to pathological inflammatory conditions such as reperfusion injury after ischaemia, autoimmunity, graft rejection and allergic reactions [17].

Soluble adhesion molecules

Soluble adhesion molecules: sE-selectin and sL-selectin can be assumed to derive from activated endothelial cells and leukocytes, respectively, mostly because of enzymatic cleavage from cell surfaces. Soluble L-selectin, present in human sera, retains ligand-binding activity. Due to slow sL-selectin turnover (the t(1/2) of sL-selectin >20 h), during chronic inflammation serum sL-selectin level may increase, even up to 20-fold, as compared to normal level. It has been observed, that the presence of sL-selectin decreased lymphocyte migration to peripheral lymph nodes with dose-dependent inhibition occurring with increasing sL-selectin concentrations. This means that increased sL-selectin levels present in certain pathologic conditions may adversely affect leukocyte migration [18]. Soluble P-selectin is cleaved from both platelets and endothelial cells. It can be also directly synthesized in human as the product of an alternatively-spliced transcript. Soluble ICAM-1 and VCAM-1 may derive from many different cells [19]. Soluble adhesion molecules can readily be measured in blood and other body fluids, using commercially available kits for each of the selectins, ICAM-1 and VCAM-1. A large literature now exists on the levels these adhesion molecules achieve in inflammatory diseases, both in relation to clinical disease state and in relation to conventional markers of the acute phase response (e.g. C-reactive protein (CRP), erythrocyte sedimentation rate). However, in many clinical situations levels of soluble adhesion molecules correlate with the acute phase response, and may not provide additional information to the clinician [19].

Future research

Diseases characterized by acute inflammation and neutrophil infiltration show increased expression of E and P-selectin, whereas in chronic lymphocytic inflammation there is increased VCAM-1 expression. One of a potential target for immunosuppression is blocking of LFA-1 and VLA-4 binding sites with their proper ligands. Elucidation of the avidity modulation of integrins at particular endothelial contact zones may introduce new targets for therapeutic intervention of pathological processes of leukocyte emigration at various vascular beds. There is now a considerable literature on the effects in animal models of therapeutic targeting adhesion molecules with antibodies, and on the effects of individual and combined gene deletions. As a generalization, attempts to interfere into chronic relapsing inflammatory diseases (e.g. inflammatory bowel disease, psoriasis, multiple sclerosis) are proving to be more successful than interventions for severe acute inflammation. Much work has been performed to establish which inflammatory clinical situations can be modified by targeting adhesion molecules or chemokines. So far, few, if any, of the clinical trials have delivered positive results. There are now clinical trial data suggesting significant benefits for targeting the $\alpha 4$ integrin subunit with the humanised monoclonal antibodies in multiple sclerosis and also in Crohn's disease [18, 19].

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