Vascular Endothelium: Checkpoint for Inflammation and Immunity

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Vascular endothelial cells play a 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 endothelial cell activation or death.

There are three major classes of leukocytes, which differ in their physiological roles as well as in their fates after trafficking through vascular endothelium (Fig. 1). Granulocytes are important representatives of the innate immune system. They evade the blood stream to phagocytose invading microbes or dead tissue. They are not capable of recirculating and die within days of performing their task. Monocytes migrate into tissues, in which they settle and become resident macrophages. Macrophages process internalized microbes and present major histocompatibility complex (MHC) class II-bound antigen to lymphocytes. Under certain circumstances, macrophages differentiate into dendritic cells, the body’s most efficient and versatile antigen-presenting cells. Lymphocytes represent the antigen-specific immune system. Lymphocytes survey the body for the presence of antigens. Naive lymphocytes home in to secondary lymphoid organs to meet antigen-presenting cells and to become antigen-specific effector lymphocytes. Plasma cells and effector T lymphocytes leave the lymph node to reach the blood stream, from where they are recruited into peripheral tissue. Cytotoxic T lymphocytes (CTL) eliminate antigen-bearing cells through the perforin/granzyme, fas/fas ligand, or cytokine pathway. In peripheral tissues, helper T lymphocytes amplify macrophage function by release of activating cytokines. Anti-
bodies secreted by B cells greatly amplify the phagocytosis of foreign material through a process called opsonization.

On their way to sites of antigen challenge (microbial invasion, transplanted tissue, vaccine deposit) leukocytes have to cross vascular endothelial cells. Adhesion molecules in concert with chemokines play an essential role in leukocyte recruitment to secondary lymphoid organs as well as to peripheral tissue. Transmigration through the endothelium brings leukocytes into close contact with vascular cells. After this intimate interaction, leukocytes may further emigrate into parenchymal tissue. However, under certain circumstances the subendothelial space itself becomes a site of inflammation, such as in vasculitis, alloimmune vasculopathy, or arteriosclerosis. Endothelial cells are activated by proinflammatory cytokines to express adhesion molecules as well as high levels of antigen-presenting molecules (MHC class I and II). Adhesion molecules facilitate leukocyte recruitment. When endothelial cells express an antigen, they may become a direct target of leukocyte-derived effector molecules and finally succumb.

Adhesion molecules are involved in rolling, firm adhesion, and transmigration of leukocytes

The physiological role of leukocyte adhesion molecules has been elucidated by the study of a particular human disease: leukocyte adhesion deficiency (LAD). Patients with inherited LAD disorders suffer from recurrent, severe bacterial infections due to a failure to recruit granulocytes to the site of microbial invasion. CD18, the common β-chain of three intracellular adhesion molecule (ICAM)-1 ligands [lymphocyte function-associated antigen-1 (LFA)-1, Mac-1, and p150,95] is mutated in patients suffering from LAD-1 (15). As a consequence of this defect, ICAM-1 ligands are virtually absent on the surface of leukocytes, and firm adhesion to vascular endothelium (a prerequisite for granulocyte evasion into tissues) is impossible.

Patients with LAD have recurrent bacterial infections, suggestive of granulocyte dysfunction, but no obvious deficiency in antigen-specific immune responses. The recruitment of antigen-specific effector T cells to peripheral tissues is an important step in transplant rejection and graft vs. host disease, infection with intracellular pathogens (e.g., viruses), hypersensitivity reactions, and certain autoimmune disorders. Whereas the LFA-1/ICAM-1 interaction and CD15-E/P-selectin interaction are critical in neutrophil recruitment, lymphocyte recruitment to sites of antigen exposure involves additional or even redundant steps. This view is supported by the analysis of murine CD11a knockout lymphocyte (deficient in LFA-1) recruitment to secondary lymphoid organs (2). This study reveals a dominant role of LFA-1 in the recruitment to peripheral lymph nodes but not to the spleen. In addition, α4-integrins can compensate for the lack of LFA-1. Vascular endothelial cell adhesion molecule (VCAM)-1 is the preferred α4-integrin ligand in peripheral lymph nodes, whereas mucosa addressin cell adhesion molecule-1 is involved in recruitment to mesenteric lymph nodes and Peyer’s patches. VCAM-1 and ICAM-1, but not the selectins, have been shown to represent the dominant
molecules involved in CD8 T cell recruitment to peripheral sites of viral infection (1).

Chemokines govern leukocyte recruitment by activation of integrins

Leukocyte recruitment to peripheral tissues involves rolling, firm adhesion, and transmigration. Chemokines, synthesized at sites of inflammation or in secondary lymphoid organs, mediate rapid integrin activation through receptor-mediated activation of a pertussis toxin-sensitive α-subunit of G, (for review, see Refs. 5 and 10). This G protein-dependent step supports firm adhesion of leukocytes to endothelial adhesion molecules VCAM-1 and ICAM-1. Complementary to site-specific adhesion molecule expression, they play an important role in directing leukocyte subsets to sites of inflammation or antigen exposure. In contrast to adhesion molecule deficiencies, which lead to increased susceptibility for bacterial infections, chemokine deficiencies are not known to cause congenital human immunodeficiencies. This suggests that in humans the chemokine system is organized in a redundant way. This view is also confirmed by the promiscuous nature of most chemokine receptors. Granulocytes are activated by a variety of chemokines such as interleukin-8, platelet activating factor, complement component 5a, leukotriene B4, and so forth. Under flow conditions, monocytes are activated by macrophage chemoattractant protein (MCP)-1 and interleukin-8 and lymphocytes are activated by stromal cell-derived factor 1α, 6Ckine, and macrophage inflammatory protein (MIP)-3β to firmly adhere to cytokine-activated endothelial cells or purified ICAM-1. In a murine model of listeria infection, MIP-1α was shown to be critical in mediating protection against a lethal infection by sensitized CD8 T lymphocytes (7). The precise cellular source of chemokines is often unknown. However, activated vascular endothelial cells have been shown to synthesize and secrete interleukin-8, MCP-3, MCP-1, and others.

Chronic vascular inflammation: a rare disorder or a common disease?

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Chronic vascular inflammation: a rare disorder or a common disease?

After extravasation, leukocytes normally leave the perivascular area immediately to reach foci of antigen exposure or inflammation. In certain immune complex diseases, neutrophil granulocytes are recruited preferentially to the subendothelial and perivascular area, leading to so-called leukocytic vascuclitis. In solid organ transplantation and after allogeneic bone marrow/stem cell transplantation, vascular endothelial cells are antigen-bearing cells and therefore potential targets of alloantigen-specific lymphocytes. Under these circumstances, subendothelial lymphocytic infiltrates, called intimal arteritis or endothelialitis, are observed. It is not known which adhesion molecules and chemokines are involved in the accumulation of these predominantly CD8 lymphocytes in the intimal or peri- capillary space. In solid organ transplantation, acute endothelialitis is recognized to be the harbinger of severe transplant rejection (6). Generally, antigen-specific immune attack leads to the rapid antibody- or cell-mediated elimination of antigen-bearing cells. In the case of vascular endothelial cells, this would precipitate fibrinoid wall necrosis and thrombus formation and would severely compromise organ perfusion. Under immunosuppressive treatment, this fatal course can be slowed. However, persistent vascular lymphocytic inflammation is thought to sustain the development of transplant-associated arteriosclerosis or chronic graft vs. host disease.

A series of recently published experiments focus on interferon-γ as an important mediator of this chronic fibrotic vascuclopathy in solid organ transplantation. When allogeneic hearts were transplanted into interferon-γ-deficient murine recipients, the development of graft vascuclopathy was profoundly suppressed (13). Furthermore, the arteries showed virtually absent CD8 T cells and markedly reduced expression of VCAM-1 and ICAM-1. In a huSCID mouse model of transplant vascuclopathy, a human artery is interposed in the murine abdominal aorta. Human interferon-γ was shown to be suficient to induce intimal hyperplasia (16) indistinguishable from transplant-associated arteriosclerosis. This effect is presumably mediated through local expression of platelet-derived growth factor and its receptor.

To characterize the molecular events that are involved in lymphocyte-endothelial cell interactions during a perivascular immune reaction, we cultured purified CD8 T lymphocytes with allogeneic vascular endothelial cells in the presence of exogenous interleukin-2 (3). In this in vitro system we observed the differentiation of CD8 T lymphocytes into allospecific, MHC class I-restricted CTL. Furthermore, vascular endothelial cells supported the emergence of endothelial cell-selective CTL lines. By cloning these lines we were able to demonstrate that cell type selectivity is a stable property of endothelial-stimulated CTL and not a transient regulatory effect of the coculture (4). We further showed at the clonal level that these endothelial cell-stimulated cells persistently express certain early activation markers, such as interleukin-2 receptor (CD25), and an important costimulatory molecule, CD40L, a member of the tumor necrosis factor (TNF) family. This early activation phenotype has been confirmed in the polyclonal endothelial cell-stimulated CD8 T cells as well. Endothelial cell-stimulated CTL are poor secretors of cytokine, TNF, and interferon-γ, and therefore intact endothelial cells may suppress the proinflammatory activity of proinflammatory cytokines in the subendothelial microenvironment. Endothelial cells also profoundly suppress CD8 T cell activation by professional antigen-presenting cells. The physiological significance of endothelial cells as guardians of an anti-inflammatory vascular state adds a fascinating novel aspect to the manifold roles of these cells in maintaining tissue homeostasis.

It is intriguing to speculate that immunoregulatory events are also involved in a much more common vascular disorder: arteriosclerosis (Fig. 2). In the western world, ~50% of people die from arteriosclerosis-related disease. An important role for activated inflammatory cells, T lymphocytes and macrophages in particular, has been proposed at all stages of the...
disease (14). It is remarkable that inflammatory genes and leukocyte adhesion molecules are upregulated in the fibrous cap of atherosclerotic plaques compared with the tunica media of the artery (12). Of a series of transcription factors, early growth response gene-1 (egr-1) was elevated in these lesions. Its binding sites can be found in the promoter regions of a series of injury response genes, and it induces transcription of growth factors [PDGF-A and -B, transforming growth factor-β1], cytokines (TNF, interleukin-2), cell cycle regulators (e.g., p53), and adhesion molecules (e.g., ICAM-1) in reporter assays in vitro. It is hypothesized that a deregulated inflammatory response is involved in arteriosclerosis and drives lesion progression or destabilization. This hypothesis is supported by the fact that CD40L can be detected in atherosclerotic lesions. CD40L is an important activator molecule of dendritic cells and B cells, initiating antigen-specific immune responses and isotype switch of immunoglobulins involved in affinity maturation. CD40L deficiency causes a rare form of immunodeficiency, the X-linked hyper-IgM syndrome. Patients with this disease suffer from recurrent bacterial and fungal infections, suggesting a combined B and T lymphocyte defect. In atherosclerotic lesions, CD40L is not only detected in leukocytes but also in endothelial and smooth muscle cells (11). Inhibition of CD40-CD40L interaction stops lesion progression in murine models of arteriosclerosis. CD40 signaling in endothelial cells mediates expression of procoagulant tissue factor and therefore challenges one of the tissue-protecting qualities of vascular endothelium: to provide an anticoagulant endovascular surface. The presence of proinflammatory signaling molecules in lesions of chronic vascular diseases such as transplant-associated vasculopathy and arteriosclerosis still does not prove that they are initiating the disease. These molecules might just be coincidentally present in lesions of arteriosclerosis and not even actively involved in the pathological process of lipid accumulation, vessel wall degeneration, and remodeling. Unless drugs can selectively target these proinflammatory mediators, and unless clinical trials will prove the efficacy of these drugs in reducing morbidity and mortality, their significance in sustaining human disease remains a fascinating hypothesis.

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References


Myocardial Stretch Induces Changes in Contractility: An Autocrine/Paracrine Mechanism Triggered by Local Release of Angiotensin II and Endothelin

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Abstract

The Frank-Starling mechanism is well known, and it states that if the length of the muscle was increased, there were corresponding rapid and slow increases in developed force. In isolated strips of ventricular myocardium, they showed that if the length of the muscle was increased, there were corresponding rapid and slow increases in developed force. The slow force response (SFR) to stretch is a non-inotropic response that involves release of angiotensin II, release/increased formation of endothelin, activation of the renin-angiotensin system, and stimulation of the sympathetic nervous system. These actions allow the heart to increase its output after the increase in arterial pressure. The heart dilatation induced by clamping the heart outflow was accompanied by a decrease in heart rate and stroke volume. Von Anrep (15) showed in 1912 that a decrease in heart rate and stroke volume induced by an increase in arterial pressure is due to a decrease in heart rate and stroke volume. The decrease in heart rate and stroke volume after an increase in arterial pressure is due to the decrease in heart rate and stroke volume. The decrease in heart rate and stroke volume after an increase in arterial pressure is due to the decrease in heart rate and stroke volume. The decrease in heart rate and stroke volume after an increase in arterial pressure is due to the decrease in heart rate and stroke volume. The decrease in heart rate and stroke volume after an increase in arterial pressure is due to the decrease in heart rate and stroke volume. The decrease in heart rate and stroke volume after an increase in arterial pressure is due to the decrease in heart rate and stroke volume. The decrease in heart rate and stroke volume after an increase in arterial pressure is due to the decrease in heart rate and stroke volume.