



VASCULAR ENDOTHELIUM

Introduction

Historically viewed as a passive vascular lining, vascular endothelium plays important roles in the regulation of vascular tone, hemostasis, immune and inflammatory responses (1). These biological reactions involve close interactions between circulating cells and the endothelium. Research studies have shown that adhesion of leucocytes to the endothelial monolayer and transmigration through the vessel wall is an important component of physiological (for example, inflammation) or pathological (for example, atherosclerosis) processes. After adhesion to endothelial cells, which is mediated by specific ligand-receptor interactions, leucocytes actively penetrate the vessel wall via intercellular junctions. Many of these ligand receptor pairs have now been identified, providing insights into the processes controlling leucocyte migration.

Endothelial Adhesion Molecules

Two main classes of leucocyte receptors are expressed by endothelium: the selectins and the immunoglobulin (Ig) superfamily (2). The selectins, of which E- and P-selectin are expressed by endothelium, have affinity for carbohydrates (3). Binding is mediated by N-terminal lectin binding and epidermal growth factor homology domains (4). The Ig superfamily receptors (ICAM-1, ICAM-2 and VCAM-1) are composed of variable numbers of repeated immunoglobulin-like domains (5).

These molecules interact with the leucocyte 1 and 2 integrins (6). The synthesis, surface expression and avidity of these molecules are regulated by chemical mediators, in particular inflammatory cytokines and chemokines (7). Stimulation of the endothelium by thrombin or histamine induces the rapid release of P-selectin from intracellular storage. In contrast, expression of E-selectin, ICAM-1 and VCAM-1 is regulated at the level of gene transcription, and is induced by exposure of endothelial cells to stimuli such as interleukin-1, tumor necrosis factor or bacterial lipopolysaccharide (2). Therefore, the pattern of expression of adhesion molecules in response to inflammatory stimuli influences the time-course of leucocyte accumulation. E- and P-selectins mediate transient attachment (rolling) early in the course of an inflammatory response. In contrast, ICAM-1, ICAM-2 and VCAM-1 control firm adherence (7). Genetically deficient mice, lacking ICAM-1, E- and P-selectins, have provided important information on the specific contribution of these adhesive molecules in leucocyte rolling and extravasation in vivo (2). Once leucocytes have adhered, transmigration through the vessel wall involves other adhesive structures such as PECAM-1 or VE-cadherin (9).

Several of the genes encoding important endothelial proteins share common regulatory elements. For example, the genes encoding ICAM-1, VCAM-1 and E-selectin all contain AP-1 sites, the cognate recognition site for the c-fos (c-jun family) of transcription factors (10). Similarly, NF- κ B recognition elements are found in the promoter regions of the ICAM-1, VCAM-1 and E-selectin genes and in the genes encoding IL-6 and urokinase (11). By virtue of these overlapping control mechanisms, a single signaling pathway can produce up-regulation of several genes with the potential to switch the endothelial phenotype from anti-thrombotic and anti-inflammatory, to one predominantly pro-thrombotic and pro-inflammatory (10, 11).

Physiopathological Implications

Complex physiopathological stresses can alter regulatory functions of the endothelium. Adhesion of leucocytes to the endothelium is one of the most important events in the reaction to all forms of injury (10, 12, 13). Interaction of endothelial cells with activated leucocytes is associated with defective endothelium-dependent vasodilation, increase in vascular permeability and in activation of the coagulation cascade. Many leucocyte products, including reactive oxygen species, superoxide and inflammatory cytokines, impair endothelial function and create the potential for a positive feedback loop between inflammation and coagulation. Research reports have shown a role for these molecules in a number of pathological processes including atherosclerosis, transplant rejection, septic shock, late phase hypersensitivity reactions and reperfusion injury (2, 10).

Beside of its importance in understanding pathogenesis, current research work on adhesion molecules has potential future applications. Recent research studies suggest that the expression of these adhesion molecules may someday be a useful marker for active inflammation in many vascular diseases. Abrogation of endothelial adhesion, by interfering with blocking monoclonal antibodies or antagonist substances, may inhibit tissue injury (2, 12).

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