Biology of the Impaired Endothelium

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The endothelium is a regulatory organ that mediates hemostasis, contractility, cellular proliferation, and inflammatory mechanisms in the vessel wall. Injury to the endothelium from hypertension, smoking, hyperlipidemia, and diabetes mellitus disrupts normal regulatory properties and results in abnormal endothelial cell function. Clinically, endothelial cell dysfunction can be manifested as vasospasm, thrombus formation, atherosclerosis, or restenosis. The normal hemostatic properties of the endothelium include the maintenance of a nonadhesive luminal surface, antithrombotic properties, anticoagulant properties, and fibrinolytic properties. The endothelial cell regulates smooth muscle cell contractility by the production of relaxing and constricting factors in response to physiologic stimuli. Endothelial cell injury is also an initial event in the development of atherosclerosis and restenosis by facilitating platelet adhesion and aggregation and by signaling the release of mitogens from platelets, macrophages, and endothelial cells, which stimulate smooth muscle cell proliferation. In addition, endothelial cells undergo morphologic and functional alterations in response to cytokine signals, which may contribute to the pathogenesis of vasculitis and atherosclerosis. In sum, the normal endothelium performs many regulatory functions which become altered when the endothelium is injured.

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The normal endothelium maintains a nonadhesive luminal surface and has fibrinolytic, anticoagulant, and antithrombotic properties [1,2]. A normal endothelial surface prevents the attachment of platelets. Platelet aggregation and adhesion are also normally inhibited by endothelial cell synthesis of prostacyclin (prostaglandin I_2) and endothelium-derived relaxing factor (EDRF) [3,4]. Antithrombotic and fibrinolytic properties of the endothelium are regulated by basal synthesis of tissue-type plasminogen activator (t-PA), which stimulates lysis of fibrin clots. Antithrombotic properties in the vessel wall are regulated through synthesis of antithrombin III, which binds to and inactivates thrombin, factor X, and other serine proteases [5]. Anticoagulant properties in the vessel wall are regulated by several pathways. The principal anticoagulant action of the endothelium is mediated through protein C and protein S [6]. The binding of thrombin to thrombomodulin serves to activate protein C; the latter, in turn, blocks factors Va and VIIIa. Antithrombin III inactivates thrombin and factor Xa, as well as endothelial cell serine proteases. The thrombin–thrombomodulin complex inactivates the procoagulant properties of thrombin, such as platelet activation. In addition, endothelial cell production of heparin-like glycosaminoglycans catalyzes the inactivation of coagulation proteases such as thrombin and factor X [7].

HEMOSTASIS

Normal hemostasis is disrupted when the vessel is injured. Subendothelial (collagen matrix) basement membrane is exposed. von Willebrand's factor is activated by thrombin to facilitate platelet adhesion and aggregation. Platelet-activating factor also contributes to primary hemostasis. Endogenous thrombolysis (t-PA) is inhibited by plasminogen activator inhibitor. Endothelial cell disruption also exposes tissue factor VII, which activates the extrinsic coagulation pathway, as well as factor XII, which stimulates the intrinsic coagulation pathway. Endothelial cell serine proteases also facilitate thrombus formation.

Endothelial cell injury stimulates primary hemo-

stasis by several mechanisms. Platelet adhesion occurs when platelets bind to the subendothelium via the platelet collagen receptor glycoprotein IA and to basement membrane by interactions with von Willebrand's factor and the glycoprotein IB receptor. Platelet aggregation follows when platelets bind to other platelets via the platelet glycoprotein receptor IIB IIIA. Platelet degranulation results in the release of vasoactive proteins from α granules, such as adenosine diphosphate (ADP), serotonin, thromboxane A_2, thrombin, and histamine, which further promote platelet aggregation, vasoconstriction, leukocyte chemostasis, and formation of a hemostatic plug.

CONTRACTILITY

The healthy endothelium regulates vascular contractility and promotes vascular relaxation. The endothelium contains receptors for various pharmacologic stimuli, including thrombin, vasopressin, acetylcholine, and platelet granulation products [8]. Receptor binding stimulates endothelial cell synthesis and release of EDRF, which acts locally on smooth muscle cells to stimulate production of cyclic guanosine monophosphate (cGMP) which, in turn, mediates relaxation [9]. Although more investigation is needed, there is convincing evidence that EDRF encompasses a group of substances, one of which is probably nitrous oxide [9,10]. Other non-receptor-mediated stimuli, such as shear stress and calcium ionophore, also initiate EDRF release [11]. Endothelial cells promote smooth muscle cell relaxation through the local production of prostacyclin which causes an increase in cyclic adenosine monophosphate (cAMP), resulting in vasodilation.

These vasodilator mechanisms are counterbalanced by vasoconstrictor substances produced by the endothelium. For example, endothelin is a potent vasoconstrictor produced by the endothelial cells in response to hypoxia and other stimuli [12]. The exact physiologic role of endothelin in normal and atherosclerotic conditions is now under evaluation.

A complex series of events occurs when the endothelium is injured. Since receptor-mediated stimulation of EDRF is disrupted, physiologic and pharmacologic stimuli produce a direct effect on smooth muscle cells, resulting in vasoconstriction. For example, vasoconstriction is routinely observed following coronary angioplasty [13]. Vasospasm surrounding an atherosclerotic plaque may occur due to deficient release of EDRF, and

probably accounts for some angina experienced by patients with coronary artery disease.

CELLULAR PROLIFERATION

Injury to the endothelium may initiate the development of atherosclerosis [14]. Circulating monocytes adhere to the injured vessel surface and migrate into the intima, take up extracellular lipid as macrophages, and develop into foam cells. Growth factors, released by platelets, endothelial cells, and macrophages, promote smooth muscle cell migration into the intima and proliferation. Macrophages and proliferating smooth muscle cells engage in collagen matrix synthesis. Abnormal cellular proliferation, in combination with calcium deposition and thrombus formation, results in the development of an atherosclerotic plaque. Balloon injury following angioplasty initiates a similar process of pathologic cellular proliferation, which becomes manifest over several months as restenosis [15]. Release of mitogens by activated endothelium, platelets, and mononuclear cells may be associated with a change in medial smooth muscle cells. The smooth muscle cell is normally refractory to growth factors and does not synthesize collagen matrix. When the blood vessel is injured, the smooth muscle cell may undergo a 'phenotypic' change to a synthetic cell where it becomes noncontractile, responsive to growth factors, and capable of connective tissue synthesis [16].

IMMUNITY AND INFLAMMATION

The endothelium is responsive to a number of cytokines, including the interferons (α, β, and λ), tumor necrosis factor-α, interleukin-1, and interleukin-6 [17]. These products of the immune system can induce changes in endothelial cell structure and function by a process termed endothelial activation. Endothelial cells become activated by the binding of leukocytes, monocytes, and lymphocytes to the endothelium by adhesion molecules. For example, interleukin-1 can induce the synthesis of endothelial leukocyte adhesion molecule-1 (ELAM-1), which stimulates neutrophil adhesion to endothelial cells [18]. Interferon-λ stimulates intracellular adhesion molecule 1 (ICAM-1) expression, which in turn promotes lymphocyte attachment and a local immune response. The adhesion of mononuclear cells to endothelial cells by adhesion molecules is a process that is central to vascular inflammation and a response to immune injury [19,20]. These mechanisms may also be responsible, in part, for the accelerated atherosclerosis observed in cardiac transplant arteries.

In conclusion, the endothelium is a highly active and reactive tissue that regulates hemostasis, vascular contractility, cellular proliferation, and immunity and inflammation. As our understanding of the endothelium expands, new therapeutic modalities are likely to emerge, based on recombinant DNA technology [21,22].

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