1 Vascular Biology

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"Vascular Biology" applies to processes affecting arteries, veins, and other blood vessels. This chapter will focus on the physiology and pathophysiology of arteries. Vein function and dysfunction will be discussed in later chapters.

Anatomy and Function of Blood Vessels in Health

Arteries are grouped, in descending size, into large elastic arteries, smaller muscular arteries, and arterioles. Arterioles regulate blood flow into the capillaries, which are endothelial tubes designed to facilitate the exchange of nutrients and byproducts of metabolism. Veins function as low-pressure reservoirs and return blood to the heart.

Arteries have three layers: the intima, media, and adventitia (Fig. 1.1). The intima consists of the vascular endothelium, which is a single layer of cells and a thin layer of connective tissue, and is separated from the media by the internal elastic lamina made of elastin and fibrous tissue. The media consists of fibrous tissue, vascular smooth muscle, and elastin; the media is separated from the adventitia by the external elastic lamina. The adventitia consists of collagen and fibrous tissue that forms loose connective tissue.

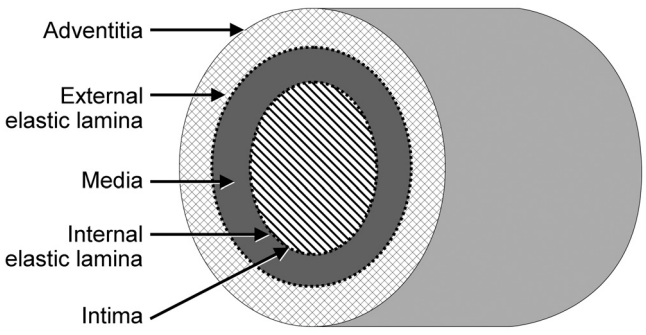

Fig. 1.1 Diagram showing the three layers of an artery.

Three Layers of Arteries

- Intima (single layer of endothelial cells)
- Media (vascular smooth muscle and connective tissue)
- Adventitia (loose connective tissue)

The connective tissue of large arteries contains more elastin, whereas smaller arteries have more collagen. The elastic properties of healthy large arteries, such as the ascending aorta, help to cushion the stroke volume, decrease the work of ejection by the left ventricle, and maintain pressure during diastole. The smaller arterioles and resistance arteries are able to regulate peripheral resistance by changing vascular smooth muscle tone to alter the lumen size.

- Elastic arteries (e.g., the aorta) cushion the stroke volume and reduce ventricular work
- Smaller, more muscular arteries regulate peripheral resistance and blood flow

Endothelial Function

The healthy endothelium is an autocrine and paracrine organ that produces substances that decrease vascular smooth muscle tone and inhibit inflammation and thrombosis. These substances include nitric oxide, prostacyclin, other endothelium-dependent vasodilators, and plasminogen activators. In disease states or after injury by factors such as abnormal strain, temperature, or risk factors for atherosclerosis, the endothelium produces substances that increase vascular tone, promote inflammation, and enhance thrombosis. These substances

include cytokines, growth factors, endothelins, and plasminogen inhibitors.

- Endothelium is an autocrine/paracrine organ
- The endothelium produces substances that affect vascular tone, inflammation, and thrombosis

Endothelium-Derived Vasodilators

The principal vasodilators produced by the endothelium include nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Of these, nitric oxide has a central role in mediating many functions of the endothelium aside from vasodilation.

Nitric Oxide

Nitric oxide is generated in the endothelium from the amino acid L-arginine by nitric oxide synthase (NOS). Nitric oxide production is accelerated by several physiologic stimuli, including shear stress at the endothelial surface (from blood flow) and in response to thrombin, serotonin, and acetylcholine (Fig. 1.2). These stimuli activate NOS by several mechanisms, including phosphorylation of the enzyme, increased intracellular calcium concentrations, and binding of calmodulin. NOS associates closely with invaginations in the endothelial luminal surface called caveolae (Fig. 1.3). A specific caveolar protein, caveolin-1, inactivates NOS by competing for binding with the calcium-calmodulin complex, which activates the enzyme.

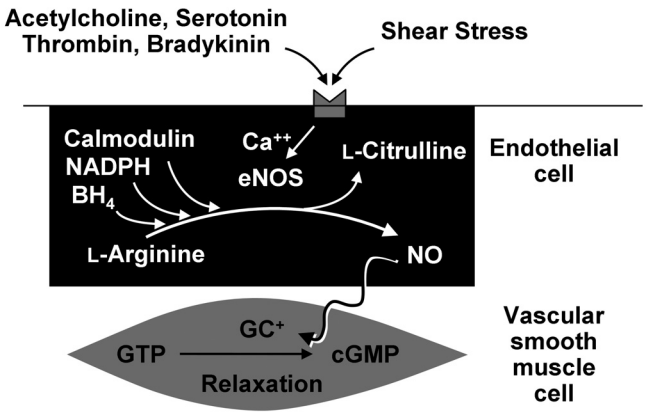

Fig. 1.2 The healthy endothelium responds to several different stimuli that increase nitric oxide (NO) production by increasing the activity of endothelial nitric oxide synthase (eNOS). eNOS function requires several cofactors, including tetrahydrobiopterin (BH_4), NADPH (nicotinamide adenine dinucleotide phosphate), and calmodulin. NO diffuses across the artery wall to activate guanylate cyclase (GC) in vascular smooth muscle; GC converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which relaxes smooth muscle and causes vasodilation. (From Kinlay S, Selwyn AP, Ganz P. Endothelium as a target of the risk factors in cardiovascular disease. In: Panza JO, Cannon RO III, editors. Endothelium, nitric oxide, and atherosclerosis: from basic mechanisms to clinical implications. Armonk [NY]: Futura Publishing Company, Inc.; 1999. p. 227-41. Used with permission.)

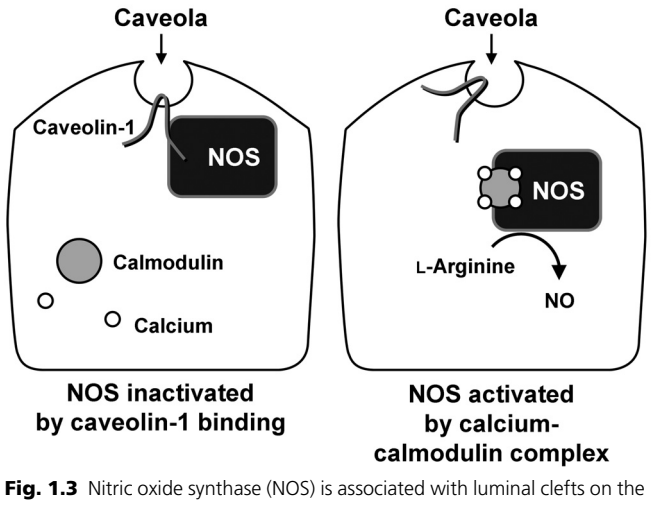

Fig. 1.3 Nitric oxide synthase (NOS) is associated with luminal clefts on the surface of endothelial cells called caveolae. Caveolin-1 is a caveolar protein that inactivates NOS. The calcium-calmodulin complex competes with caveolin-1 for binding to NOS and activates NOS to produce nitric oxide (NO). (From Kinlay S, Libby P, Ganz P. Endothelial function and coronary artery disease. Curr Opin Lipidol. 2001;12:383-9. Used with permission.)

Nitric oxide diffuses through the artery wall and enters vascular smooth muscle cells in the media, where it increases the activity of guanylate cyclase and the concentration of cyclic guanosine monophosphate (cGMP) (Fig. 1.2). The increased level of cGMP relaxes vascular smooth muscle and leads to vasodilation. Because shear stress is related to blood velocity, increased blood velocity also increases nitric oxide production and causes vasodilation, which in turn decreases blood velocity toward its original value. In contrast, decreased blood velocity decreases the stimulus for nitric oxide production, promotes vasoconstriction, and thereby increases blood velocity back toward its original value. In this way, the endothelium regulates vasomotor tone so as to keep blood velocity and shear stress at the endothelial surface within a narrow range. This regulation prevents sluggish blood flow that might promote thrombus formation and high shear that could injure the arterial intima.

- Shear stress, thrombin, serotonin, and acetylcholine are some factors that stimulate NOS
- NOS resides in endothelial clefts called caveolae
- Nitric oxide diffuses through the artery wall to activate guanylate cyclase and increase cGMP, which relaxes smooth muscle and dilates arteries

Prostacyclin

Prostacyclin is another endothelial product that induces

arterial dilation. It is produced from arachidonic acid by cyclooxygenase in response to shear stress or certain factors that also increase nitric oxide production. Prostacyclin activates adenylate cyclase to increase production of cyclic adenosine monophosphate (cAMP). In most vascular beds prostacyclin has only a small role in regulating vasomotor tone, but it is more important in inhibiting platelet aggregation.

- Prostacyclin activates adenylate cyclase to increase cAMP concentration

Other Endothelium-Derived Relaxing Factors

The existence of other endothelium-derived relaxing factors is supported by a residual vasodilation response to various stimuli after blocking nitric oxide and prostacyclin generation. One of these factors, EDHF, appears to be more important in the small arteries than the large conduit arteries; however, the structure of EDHF has yet to be identified. The lack of consistent inhibitors of EDHF that can be safely used in humans has thwarted its clinical study.

- EDHF appears to be a more important vasodilator of small arteries than of conduit arteries

Endothelium-Derived Vasoconstrictors

Although several locally produced substances can cause vasoconstriction, most are platelet-derived products, including serotonin and thrombin. However, the endothelium also produces substances that constrict vascular smooth muscle, of which the most important is endothelin.

Endothelin is one of the most potent vasoconstrictors known. It was first discovered as a product secreted by endothelial cells. Endothelin is a peptide that is generated by successive cleavage of a large polypeptide ("big endothelin") within the endothelium. Three isotypes of endothelin have been described (endothelins 1, 2, and 3); however, endothelin-1 is the most abundant in vascular tissue. Endothelin-1 is also produced by activated macrophages and vascular smooth muscle cells, particularly in atherosclerosis.

Endothelin acts on the endothelin A receptors on vascular smooth muscle to stimulate vasoconstriction and vascular smooth muscle cell proliferation. Endothelin B receptors on the abluminal surface of endothelial cells mediate increased production of nitric oxide, but only in healthy cells. Nevertheless, the net action of endothelin-1 is vasoconstriction in most vascular beds.

Stimuli for endothelin production include thrombin, angiotensin II, and epinephrine. The production of endothelin is inhibited by nitric oxide and, conversely, endothelin inhibits the production of nitric oxide. Endothelin and nitric oxide participate in a "yin-yang" relationship to regulate vasomotor tone, with the net effect depending on the health of the endothelium.

- Endothelin-1 is one of the most potent vasoconstrictors known
- Endothelin-1 is produced by endothelial cells, activated macrophages, and vascular smooth muscle cells
- Endothelin-1 activates endothelin A receptors on vascular smooth muscle to stimulate vasoconstriction

Endothelium as a Regulator of Arterial Inflammation

Nitric oxide also is important for regulating inflammation associated with arterial injury. Nitric oxide inhibits the expression of monocyte chemoattractant protein (MCP)-1 and macrophage colony-stimulating factor (M-CSF). By inhibiting the transcription factor NF-κB, nitric oxide prevents the activation of several proatherogenic processes, including the expression of cellular adhesion molecules (Fig. 1.4). These processes are tightly controlled by the balance of antioxidants and pro-oxidant molecules in the cell. All stages of atherosclerosis exhibit activation of the endothelium, which releases the checks on the proatherogenic processes to increase the recruitment of inflammatory cells into the endothelium.

- Nitric oxide reduces inflammation by inhibition of MCP-1 and activation of NF-κB

Endothelium as a Regulator of Arterial Thrombosis

The final common pathway of many atherosclerotic processes is thrombus and occlusion of the arterial lumen. The healthy endothelium produces several antithrombotic substances, including heparans and the fibrinolytic tissue plasminogen activator. In atherosclerotic arteries, the balance of tissue plasminogen activators to inhibitors, such as plasminogen activator inhibitor (PAI), is reversed. Other factors that promote thrombus formation include decreased nitric oxide concentration in platelets, which promotes platelet activation.

Atherosclerotic Risk Factors and Abnormal Vascular Biology

Endothelial injury is a hallmark of early atherogenesis. Although physical injury such as balloon angioplasty or hypertension can disrupt the endothelium, many of the conventional atherosclerotic risk factors initiate athero-

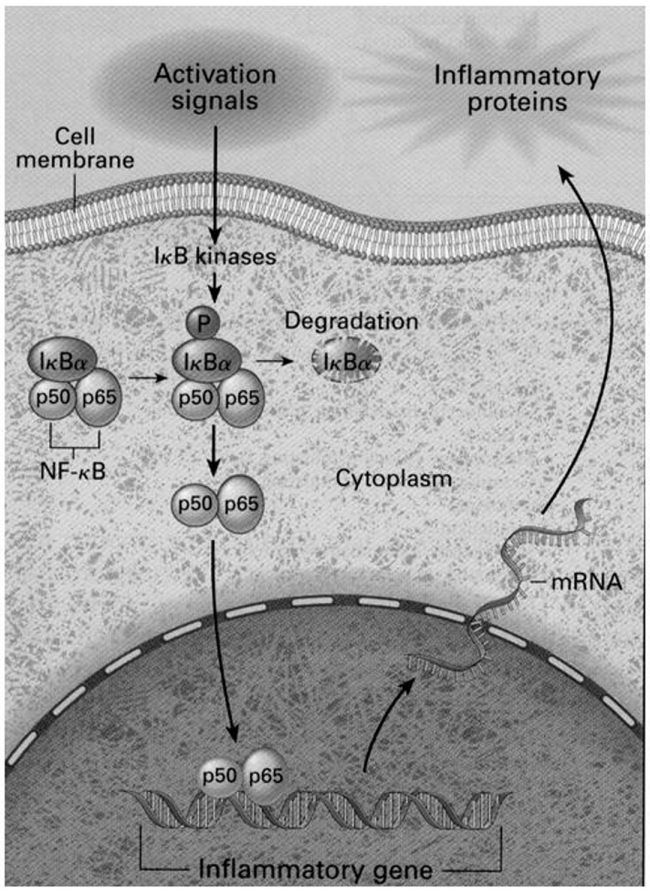

Fig. 1.4 The transcription factor NF-κB is kept inactive (by IκB) in the cytoplasm of healthy cells. Numerous activation signals, such as a decrease in nitric oxide bioavailability or increased oxidant stress, lead to activation of NF-κB, which then migrates to the nucleus and increases the transcription of many proinflammatory molecules. (From Barnes PJ, Karin M. Nuclear factor-κB: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med. 1997;336:1066-71. Used with permission.)

sclerosis by disturbing the normal homeostatic functions of the endothelium and vascular wall. Pathologic studies have tended to divide the stages of atherosclerosis into lesion initiation, fatty streak, fibroproliferative atheroma, and advanced lesions. However, the cellular events that lead to atherosclerosis occur at different rates and to different extents in different arterial segments of different people.

Lesion Initiation

Endothelial Dysfunction

Endothelial dysfunction is an early feature of atherosclerosis related to all of the conventional cardiovascular risk factors. This is primarily a functional disorder of the endothelium, wherein production and bioavailability of nitric oxide in the artery wall are decreased. Nitric oxide is decreased in regions of low shear stress, such as disturbed blood flow at bifurcations or bends in the artery.

Low-Density Lipoprotein Retention and Oxidative Modification

Low-density lipoprotein (LDL) cholesterol permeates the endothelial cell layer and enters the subendothelial cell matrix. Elevated plasma levels of LDL increase the rate of delivery and retention of LDL in the artery wall. Although very little of the circulating LDL is oxidized, once LDL is in the artery wall, reactive oxygen species deplete antioxidants and oxidize fatty acids on the LDL surface. Elevated glucose levels can also lead to glycosylation of proteins in the artery wall and to advanced glycosylated end products (AGEs). Both modified (oxidized) LDL and AGEs in the artery wall activate the overlying endothelial cells.

- Endothelial dysfunction is an early feature of atherosclerosis
- Endothelial dysfunction results in less nitric oxide in the artery wall
- High plasma LDL concentration increases retention and oxidation of LDL in the artery wall
- Elevated plasma glucose can lead to AGEs in the artery wall
- Oxidized LDL and AGEs activate endothelial cells

High-Density Lipoprotein and Reverse Cholesterol Transport

High-density lipoprotein (HDL) is a significant protective factor for atherosclerosis. HDL contains several antioxidants, including paraoxonase, which may prevent the oxidation of LDL cholesterol.

Reverse cholesterol transport from peripheral tissues to the liver occurs by passive or active transport. HDL can absorb cholesterol passively from the plasma membrane of cells. Active transport occurs by interaction of apolipoprotein A1 on nascent HDL with the ATP-binding cassette transporter A1 (ABCA1) on peripheral tissues, including macrophages. Cholesterol can be removed from mature HDL by HDL-specific scavenger receptors on the liver (SR-B1 receptor). Cholesterol in HDL may be exchanged for triglycerides in intermediate-density lipoprotein (IDL) by cholesterol ester transfer protein (CETP). Transferred cholesterol can be returned to the liver (uptake by the LDL receptor) or delivered to peripheral tissues.

A rare genetic defect in apolipoprotein A1 (ApoA1 Milano) leads to very efficient transfer of cholesterol from the ABCA1 transporter on peripheral tissues and is thought to accelerate reverse cholesterol transport. Recombinant forms of ApoA1 Milano can also enhance this effect and are being developed for therapeutic use. Partial inhibitors

of CETP block cholesterol transfer from HDL to other lipoproteins and may also increase reverse cholesterol transport with obvious therapeutic potential.

- HDL protects against atherosclerosis
- HDL particles have antioxidants and promote reverse cholesterol transport
- HDL returns cholesterol to the liver by direct receptor uptake (SR-B1) and indirectly via transfer to IDL, which is taken up by the LDL receptor on the liver
- CETP inhibitors partially block cholesterol transfer from HDL to IDL and may increase reverse cholesterol transport

Endothelial Cell Activation and Cellular Adhesion Molecules

Endothelial cell activation and the progressive increase in reactive oxidant species in the artery wall (oxidant stress) inhibits the production of nitric oxide by endothelial cells and rapidly converts nitric oxide in the artery wall to inactive metabolites such as peroxynitrate. The decrease in nitric oxide activates transcription factors such as NF-κB, which move into the nucleus to increase the transcription of genes that produce cytokines and cellular adhesion molecules (CAMs) (Fig. 1.4).

CAMs, such as the selectins, intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM), are expressed on the luminal surface of endothelial cells. They interact specifically with integrins expressed on the surface of monocytes and T cells (Fig. 1.5). Selectins bind to monocytes to promote a slow rolling of monocytes on the endothelial surface (rolling stage). Selectin binding is followed by firmer interactions between integrins and VCAM or ICAM (adhesion). CAMs, together with chemokines (e.g., MCP-1, oxidized LDL), then promote transmigration of the monocytes through the junctions between endothelial cells into the intima of the artery wall (migration) (Fig. 1.5). This process initiates and promotes inflammatory cell recruitment into the wall.

- Activated endothelial cells exhibit increased activity of the proinflammatory transcription factor NF-κB
- CAMs, including selectins, ICAM, and VCAM, are expressed on the lumen surface of endothelial cells
- The sequence of leukocyte recruitment includes rolling (selectin binding), adhesion (CAM binding), and migration (CAM and cytokine assisted)

Fatty Streak

Like many other cell types, monocytes (which are recruited into the arterial intima and transform into macrophages)

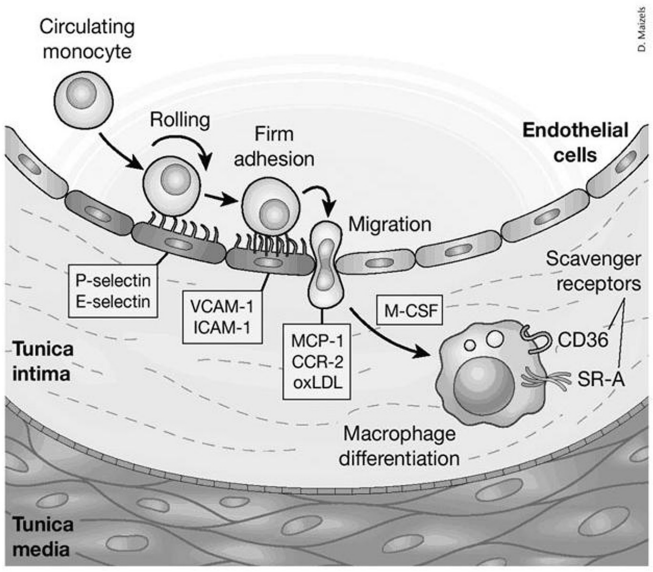

Fig. 1.5 Recruitment of monocytes and lymphocytes into the vessel wall occurs by a coordinated process mediated by selectins (P-selectin, E-selectin) and cellular adhesion molecules (ICAM-1, VCAM-1) on the surface of activated endothelial cells. The three steps are rolling, adhesion, and migration of leukocytes. CCR, chemokine receptor; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; oxLDL, oxidized low-density lipoprotein. (From Li AC, Glass CK. The macrophage foam cell as a target for therapeutic intervention. Nat Med. 2002;8:1235-42. Used with permission.)

have LDL receptors that recognize native LDL and facilitate its uptake in a regulated fashion according to a cell's needs. However, macrophages have scavenger receptors that recognize oxidized LDL; these have a central role in atherosclerosis because they allow the macrophage to take up LDL in an unregulated manner. Retention and oxidation of LDL in the artery wall leads to engorgement of monocytes with oxidatively modified LDL and to formation of foam cells, the hallmarks of the fatty streak (Fig. 1.6). Activated monocytes amplify this process by expressing chemokines (MCP-1) and cytokines (M-CSF).

Foam cells also express angiotensin II receptors and are capable of promoting LDL oxidation. Angiotensin II increases the production of the free radical superoxide by stimulating oxidases on vascular smooth muscle cells. Thus, angiotensin II increases oxidant stress within the artery wall, which promotes atherogenesis.

The macrophage response to oxidized LDL forms part of the rapidly responding innate immunity. Scavenger receptors recognize a diverse range of ligands associated with pathogens and foreign bodies, and other features of the innate defense system, such as C-reactive protein and IgM antibodies to oxidized LDL, are found in atherosclerotic plaques. Although these responses are necessary for eliminating pathogens, the macrophage response has deleterious effects—increased atherosclerotic risk factors.

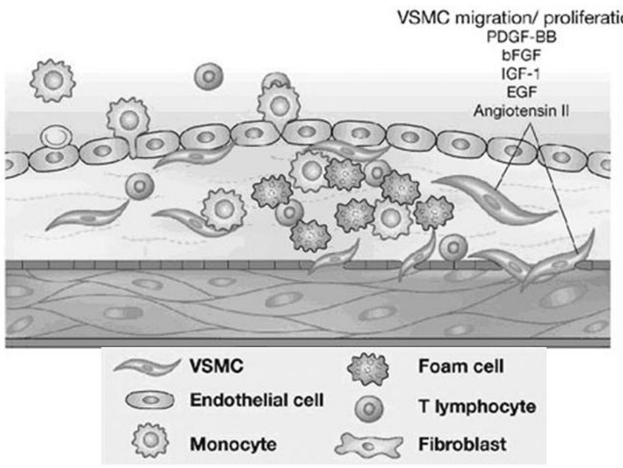

Fig. 1.6 Foam cell formation and the migration of vascular smooth muscle cells (VSMCs) into the intima mark the beginning of the fatty streak. bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; IGF-1, insulin-like growth factor-1; PDGF-BB, platelet-derived growth factor BB. (From Dzau VJ, Braun-Dullaeus RC, Sedding DG. Vascular proliferation and atherosclerosis: new perspectives and therapeutic strategies. Nat Med. 2002;8:1249-56. Used with permission.)

- Monocytes recruited into a plaque mature into macrophages
- Macrophages engorge with modified LDL by scavenger receptor uptake in an unregulated manner and become foam cells
- Chemokines (e.g., MCP-1) and cytokines (e.g., M-CSF) amplify this process
- Angiotensin II increases superoxide production on vascular smooth muscle cells

Fibroproliferative Atheroma

Cytokines, growth factors, and the renin-angiotensin system all stimulate growth of the plaque and the development of more advanced atherosclerotic features.

Cytokines and Signal Amplification

Monocytes recruited early into the plaque produce growth factors and cytokines that stimulate the recruitment of other cell types into the intima, including T cells, B lymphocytes, fibroblasts, and vascular smooth muscle cells. Neutrophils and granulocytes are not features of atherosclerosis.

Smooth muscle cells migrate from the media into the intima and produce extracellular matrix molecules such as collagen I and III, fibronectin, and proteoglycans. These molecules provide biomechanical strength, interact with integrins, and influence plaque stability.

- Monocytes, macrophages, T cells, B cells, fibroblasts, and smooth muscle cells are found in the fibroproliferative atheroma
- Smooth muscle cells produce collagen that provides biomechanical strength to the plaque

T Cell Entry

Lymphocytes interact closely with other cell types to influence plaque development. Both T cells and B cells are recruited into atherosclerotic plaques and form part of the acquired immune response in atherosclerosis. Macrophages activate T cells by presenting antigens (e.g., oxidized LDL) to specific T-cell receptors, with costimulatory signals produced by interactions between CD40 ligand and CD40 on both cells. Interferon-γ, produced by T cells, can regulate the expression of scavenger receptors on macrophages, inhibit the production of matrix by smooth muscle cells, and increase the expression of proteases such as metalloproteases that degrade collagen in the plaque.

- Macrophages activate T cells by presenting antigens (e.g., oxidized LDL) to T-cell receptors
- T cells produce interferon-γ, which inhibits matrix production by smooth muscle cells and increases metalloprotease production by macrophages

Neovascularization

Neovascularization heralds the development of more complex plaques that are associated with clinical events. In normal blood vessels, the vasa vasorum is confined to the adventitia and outer artery wall. During early atherosclerosis development, the vasa vasorum proliferates and forms a disordered network and ultimately extends through the media into the intima (Fig. 1.7). Neovascularization of the intima is associated with focal collections of inflammatory cells and may be a source of intraplaque hemorrhage that could contribute to plaque growth and stenoses.

- More complex plaques have disordered proliferation of the vasa vasorum
- Disruption of these vessels might contribute to intraplaque hemorrhage

Vascular Remodeling and Proteases

Extracellular matrix and collagen in plaque are susceptible to several proteases, including the metalloproteases, which are abundant in plaque, particularly with macrophages. Loss of nitric oxide and the oxidation of nitric oxide to peroxynitrate decrease the activity of the tissue inhibitors of

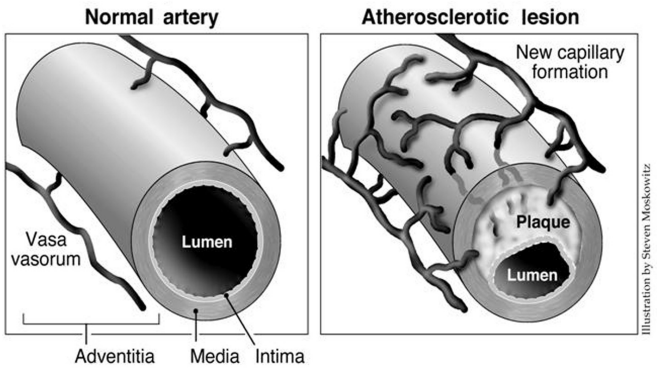

Fig. 1.7 Neovascularization of plaque occurs by disordered growth of penetrating arteries from the vasa vasorum and can potentially lead to intraplaque rupture. (From Moulton KS. Plaque angiogenesis and atherosclerosis. Curr Atheroscler Rep. 2001;3:225-33. Used with permission.)

metalloproteases. The subsequent proteolysis of collagen and fibrous tissue in the plaque promotes plaque instability and the development of complex plaques with thin fibrous caps.

The activation of matrix metalloproteases may prevent the development of flow-limiting lesions in the early stages of atherosclerosis. During atherosclerosis development, the artery remodels to accommodate the growing atherosclerotic plaque and enlarges to preserve the artery lumen (Fig. 1.8). This compensatory enlargement was initially described in cross-sectional pathologic studies and preserves the arterial lumen until plaque exceeds approximately 40% of the total cross-sectional area of the artery. Remodeling also occurs in the opposite direction (negative remodeling) and may contribute to stenoses that limit blood flow. Positive remodeling is associated with greater expression of matrix metalloproteases than negatively remodeled plaques.

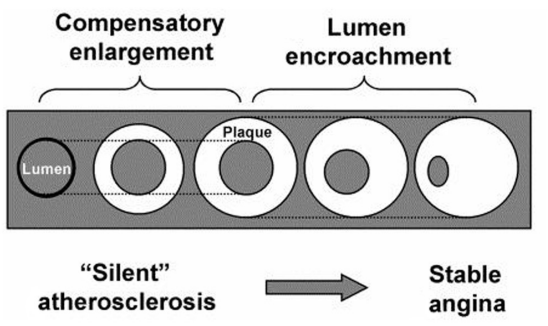

Fig. 1.8 Compensatory enlargement of the artery accommodates atherosclerosis early in its natural history. However, once plaque exceeds approximately 40% of the cross-sectional area of an artery, there is no further enlargement of the vessel, and atherosclerosis encroaches on the lumen. (From Popma JJ, Sawyer M, Selwyn AP, et al. Lipid-lowering therapy after coronary revascularization. Am J Cardiol. 2000;86 Suppl 2:18H-28H. Used with permission.)

Local blood flow and biomechanical forces may regulate vascular remodeling. Laminar flow tends to produce a greater shear stress on the surface of the endothelium than disturbed flow. Regions of low shear stress (on the outer aspects of a bifurcating artery) tend to have greater atheroma and endothelial cell activation than areas of higher shear stress. Areas of higher shear stress are also more likely to exhibit positive remodeling than areas of low shear stress.

- Oxidant stress and T cells stimulate macrophages to produce metalloproteases
- Metalloproteases break down collagen, a process that promotes plaque instability
- During the early stage of plaque growth, the artery is able to prevent lumen encroachment by compensatory enlargement (positive remodeling)
- Positive remodeling is associated with abundant expression of metalloproteases
- Negative remodeling (shrinkage of the lumen) probably contributes to the development of flow-limiting stenoses

Advanced Lesions

Chronic ischemic syndromes during exertion are related to flow-limiting stenoses, whereas acute ischemic syndromes such as the acute coronary syndromes are more often related to thrombosis of disrupted plaques that are minimally narrowed. Several features of advanced plaques cause acute complications related to flow disruption.

Lipid Pool

Unregulated accumulation of cholesterol by macrophages and vascular smooth muscle cells leads to cell apoptosis and release of the cell contents into the extracellular space of the intima. Autopsy studies of acute coronary syndrome have generally identified two types of culprit lesions. The most common form consists of a plaque with a necrotic lipid pool and an overlying thin fibrous cap that has fractured (Fig. 1.9). These plaques typically rupture at the shoulder or edge, where biomechanical forces and inflammatory cell activity are concentrated. A smaller proportion of the lesions result from endothelial cell erosion without frank rupture of the plaque. Loss of endothelial cells can occur by apoptosis induced by inflammatory mediators or by breakdown in the collagens that fix endothelial cells to the underlying matrix.

- Apoptosis of macrophages and vascular smooth muscle cells contributes to the development of the necrotic lipid core of a plaque

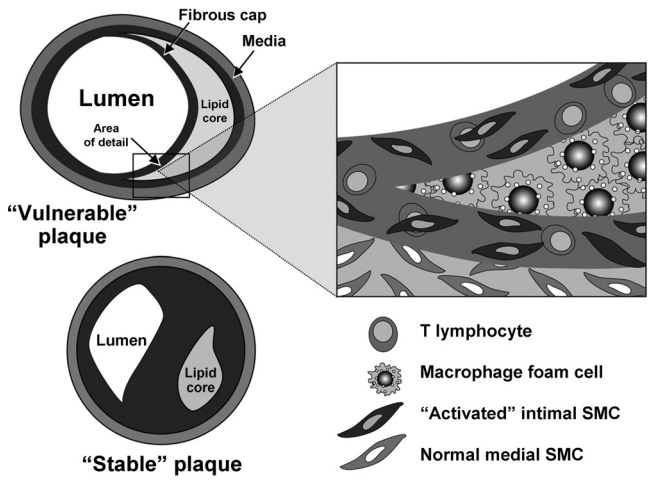

Fig. 1.9 Advanced plaques include the "vulnerable plaque" with inflammatory cell activity and a thin fibrous cap overlying a large lipid pool, which causes only minimal lumen narrowing. Plaques typical of stable exertional angina tend to be rich in fibrous tissue and calcium with a narrow lumen. SMC, smooth muscle cell. (From Libby P. Molecular bases of the acute coronary syndromes. Circulation. 1995;91:2844-50. Used with permission.)

- Most plaques responsible for acute coronary syndromes feature a large lipid core and fracture of an overlying thin fibrous cap
- Endothelial cell erosion contributes to a smaller number of culprit lesions in acute coronary syndromes

Thrombosis

Thrombus occludes the artery lumen in some cases of plaque rupture and is the final common pathway leading to acute ischemic syndromes. Disruption of the endothelial layer exposes the subendothelial tissues and necrotic lipid core, both of which are highly thrombogenic. Tissue factor, a product of foam cells, is also abundant in the lipid core of ruptured plaques and promotes thrombus formation. The endothelium of advanced plaques is dysfunctional and less able to produce nitric oxide, prostacyclins, tissue plasminogen activator, and heparan sulphate. Depletion of these substances activates platelets and thrombotic pathways. Other factors that promote thrombus formation include increased vasomotor tone that may decrease blood flow and elevated circulating plasma PAIs (e.g., PAI-1).

- Disruption of plaque exposes the underlying thrombogenic subendothelial tissues to blood
- Factors that contribute to thrombosis include vasomotor dysfunction, elevated inhibitors of thrombolysis (e.g., PAI-1), and activation of platelets

Calcification

Calcification of the artery wall is a feature of advanced atherosclerosis. Calcification is an active process closely related to remodeling in bone and may be related to intraplaque hemorrhage. Arterial calcification is more often associated with stable plaques than with those with a greater inflammatory component.

- Calcification of arteries is an active process related to remodeling in bone

Asymptomatic Plaque Rupture

Asymptomatic plaque rupture with superficial thrombus is often seen at autopsy. Persons who die suddenly of an acute coronary syndrome due to an identified ruptured plaque often have many more plaques that have ruptured and are clinically silent. Subclinical plaque rupture can contribute to the growth of atherosclerosis and the development of flow-limiting lesions.

Risk Factor Modification

Reversal of several risk factors for atherosclerosis decreases the progression of atherosclerosis and the risk of clinical events. This risk reversal is best studied for LDL reduction by pharmacologic and non-pharmacologic means.

Decreasing LDL cholesterol levels by dietary and pharmacologic methods improves endothelial function and promotes plaque stability. For example, intensive lowering of LDL in humans by apheresis can rapidly improve endothelial vasomotor function within hours. LDL lowering also decreases the density and activity of inflammatory cells in plaque by decreasing recruitment and increasing apoptosis of inflammatory cells. LDL lowering also inhibits various pro-thrombotic pathways, including the tissue factor pathway, within plaque. In most studies of LDL lowering, plaque regression is minimal, indicating that plaque stabilization is the main benefit of lowering of LDL level.

- Risk factor modification, particularly LDL lowering, improves endothelial function, reduces inflammation, and decreases pro-thrombotic factors in plaque
- LDL lowering has little effect on the size of atheroma but has important effects on plaque stabilization

Conclusion

Atherosclerosis is an active process that involves en-

dothelial dysfunction, inflammation, and thrombosis. An understanding of the cellular processes and the effects of therapies has in turn helped our understanding of the clinical complications and prognosis and has helped in the development of new treatment strategies designed to prevent clinical events.

Questions

1. Which of the following statements is most correct?
- **a.** Endothelial cells migrate into the media during atherosclerosis initiation.
- **b.** Nitric oxide is produced by endothelial cells.
- **c.** Endothelin is a potent vasodilator.
- **d.** Elastic arteries regulate peripheral resistance.
- **e.** The adventitia contains abundant smooth muscle and connective tissue.

2. Which statement is false?
- **a.** Prostacyclin inhibits platelet activation.
- **b.** Nitric oxide inhibits many pro-inflammatory pathways.
- **c.** The endothelium produces tissue plasminogen activator.
- **d.** LDL is oxidized in the artery wall.
- **e.** HDL increases cholesterol deposition in peripheral tissues.

3. Which of the following statements is most true?
- **a.** An increase in endothelial nitric oxide activates the transcription factor NF-κB.
- **b.** ICAM is most responsible for monocyte rolling on endothelial cells.
- **c.** The fatty streak is characterized by foam cells.
- **d.** The chemokine MCP-1 blocks monocyte migration into the artery wall.
- **e.** All of the above are true.

4. Features of advanced atherosclerotic plaques include:
- **a.** Neovascularization of plaque
- **b.** Lipid pools
- **c.** T cells
- **d.** Metalloproteases
- **e.** All of the above

5. Which of the following statements are true?
- **a.** Neutrophils are abundant in early atherosclerotic plaques.
- **b.** T cells stimulate macrophages to produce metalloproteases.
- **c.** Therapies that lower LDL cholesterol substantially decrease plaque size.
- **d.** Calcification of arteries generally occurs as a passive process of deposition.
- **e.** Circulating PAIs such as PAI-1 are increased in patients with atherosclerosis and may promote thrombus formation.

6. Which of the following statements is most true?
- **a.** Compensatory enlargement of atherosclerotic arteries refers to the enlargement of the vessel lumen over time.
- **b.** Laminar blood flow imparts a higher shear stress on the endothelium compared with regions of disturbed blood flow.
- **c.** Negative remodeling of arteries contributes to the shrinkage of atherosclerotic plaques.
- **d.** Metalloproteases are more often associated with atherosclerotic plaques in regions of negatively remodeled arteries.

Suggested Readings

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