

Atherosclerosis

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Atherosclerosis is the leading cause of mortality and morbidity in developed nations. Through its major manifestations of myocardial infarction and stroke, it has also become a major cause of death in the developing world. Commonly known as “hardening of the arteries,” atherosclerosis derives its name from the Greek roots *athere-*, meaning “gruel,” and *-skleros*, meaning “hardness.” Recent evidence has demonstrated that chronic inflammation drives the atherosclerotic process and transduces traditional risk factors (such as hypercholesterolemia) into altered behavior of vascular wall cells, contributing to the disease and its thrombotic complications. The course of atherogenesis can smolder throughout adulthood, punctuated by acute cardiovascular events.

This chapter consists of two sections. The first part describes the normal arterial wall, the pathogenesis of atherosclerotic plaque formation, and the complications that lead to clinical manifestations of the disease. The second section describes findings from population studies that have identified specific risk factors for atherosclerotic events, thereby offering opportunities for prevention and treatment.

VASCULAR BIOLOGY OF ATHEROSCLEROSIS

Normal Arterial Wall

The arterial wall consists of three layers (Fig. 5-1): the **intima**, closest to the arterial lumen and therefore most “intimate” with the blood; the middle layer, known as the **media**; and the outer layer, the **adventitia**. A single layer of endothelial cells covers the intimal surface and provides a metabolically active barrier between circulating blood and the vessel wall. The media is the thickest layer of the normal artery. Boundaries of elastin, known as the internal and external elastic laminae,

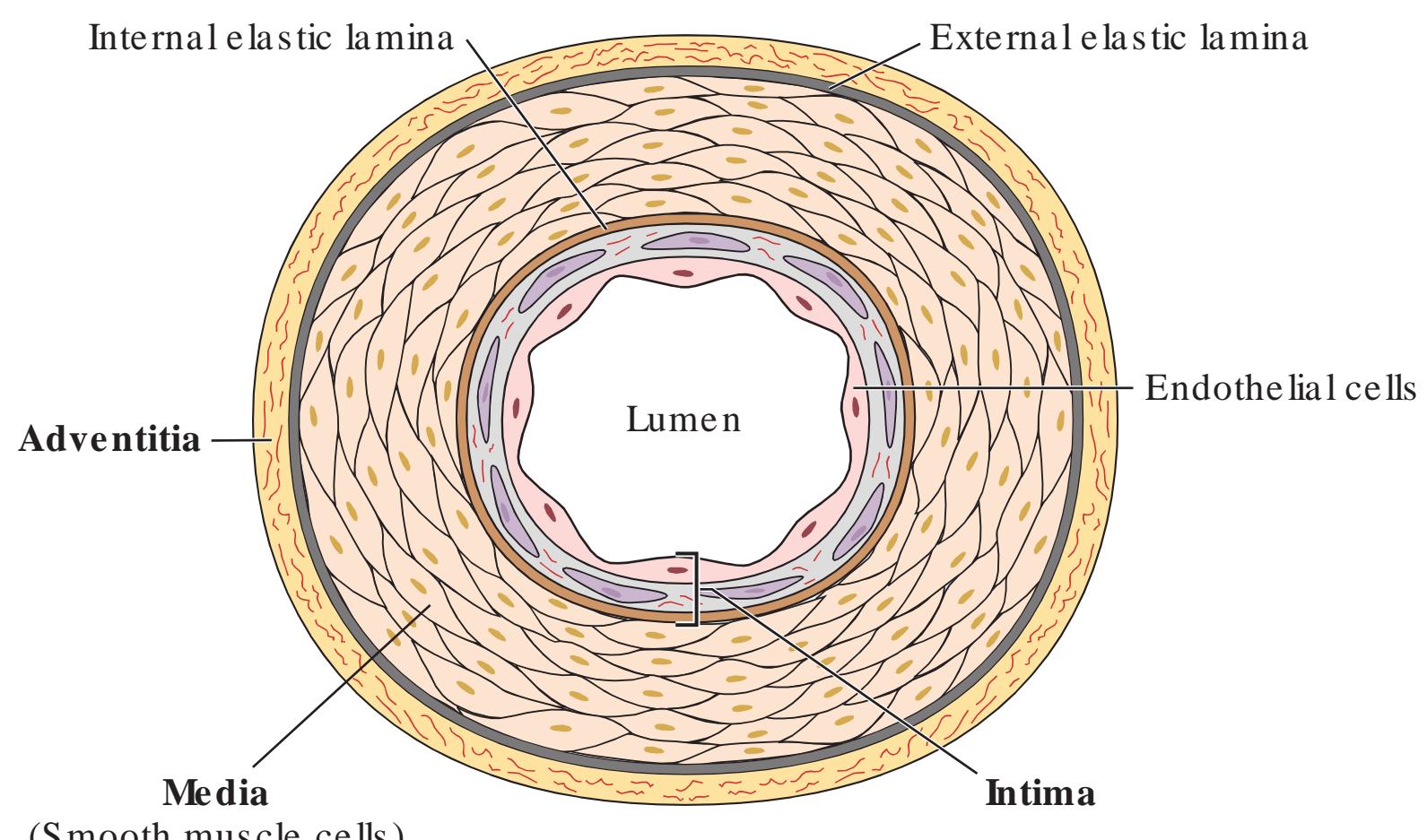


FIGURE 5-1. Schematic diagram of the arterial wall. The intima, the innermost layer, overlies the muscular media demarcated by the internal elastic lamina. The external elastic lamina separates the media from the outer layer, the adventitia. (Modified from Lieberman M Marks' Basic Medical Biochemistry: A Clinical Approach. 4th ed. Philadelphia, PA: Wolters Kluwer Health; 2013:649.)

separate this middle layer from the intima and adventitia, respectively. The media consists of smooth muscle cells (SMCs) and extracellular matrix and serves the contractile and elastic functions of the vessel. The elastic component, more prominent in large arteries (e.g., the aorta and its primary branches), stretches during the high pressure of systole and then recoils during diastole, propelling blood forward. The muscular component, more prominent in smaller arteries such as arterioles, constricts or relaxes to alter vessel resistance and therefore luminal blood flow (flow = pressure/resistance; see Chapter 6). The adventitia contains nerves, lymphatics, and blood vessels (*vasa vasorum*) that nourish the cells of the arterial wall.

Far from an inert conduit, the living arterial wall hosts dynamic interchanges between its cellular components—most importantly, endothelial cells, vascular SMC, and their surrounding extracellular matrix. An understanding of the dysfunction that leads to atherosclerosis requires knowledge of the normal function of these components.

Endothelial Cells

In a healthy artery, the endothelium performs structural, metabolic, and signaling functions that maintain homeostasis of the vessel wall. The tightly adjoined endothelial cells form a barrier that contains blood within the lumen of the vessel and controls the passage of large molecules from the circulation into the subendothelial space. As blood traverses the vascular tree, it encounters antithrombotic molecules produced by the normal endothelium that prevent it from clotting or that promote fibrinolysis (the breakdown of fibrin clots). Some of these molecules reside on the endothelial surface (e.g., heparan sulfate, thrombomodulin, and plasminogen activators; see Chapter 7), while other antithrombotic products of the endothelium enter the circulation (e.g., prostacyclin and nitric oxide [NO]; see Chapter 6). Although a net anticoagulant state normally prevails, the endothelium can also produce prothrombotic and antifibrinolytic molecules when subjected to various stressors.

Furthermore, endothelial cells secrete substances that modulate contraction of SMC in the underlying medial layer. These substances include vasodilators (e.g., NO and prostacyclin) and vasoconstrictors (e.g., endothelin) that alter the arteriolar resistance and therefore luminal blood flow. In a normal artery, the predominance of vasodilator substances results in net smooth muscle relaxation.

Endothelial cells can also modulate the immune response. In the absence of pathologic stimulation, healthy arterial endothelial cells resist leukocyte adhesion and thereby oppose local inflammation. However, endothelial cells respond to local injury or infection by expressing cell surface adhesion molecules, which attach mononuclear cells to the endothelium, and chemokines—substances that facilitate leukocyte recruitment to the site of

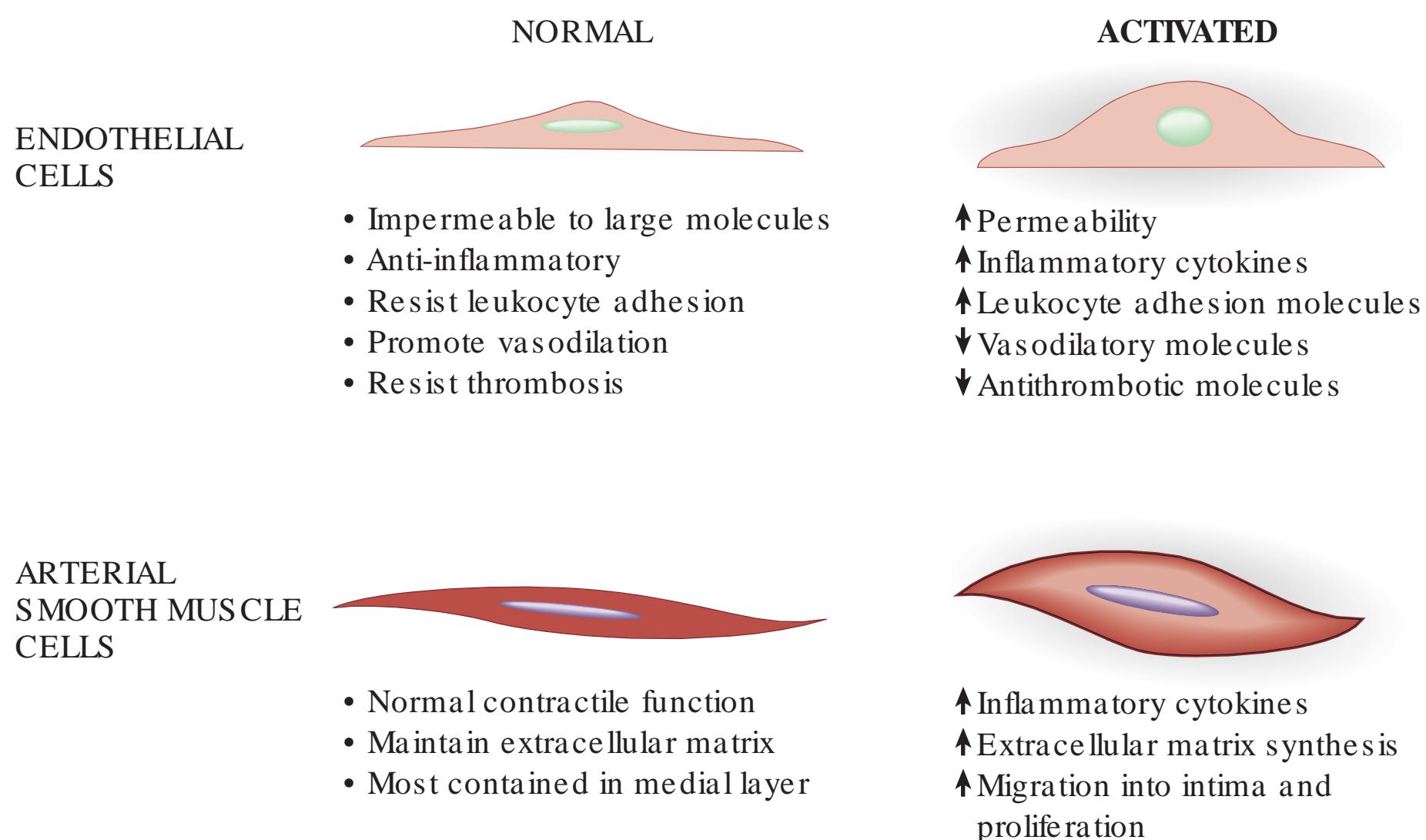


FIGURE 5-2. Endothelial and smooth muscle cell activation by inflammation. Normal endothelial and SMC maintain the integrity and elasticity of the normal arterial wall while limiting immune cell infiltration. Inflammatory activation of these vascular cells corrupts their normal functions and favors proatherogenic mechanisms that drive plaque development.

injury. These effects result in part by activation of the transcription factor nuclear factor kappa B (NF κ B.)

In summary, the normal endothelium provides a protective, nonthrombogenic surface with homeostatic vasodilatory and anti-inflammatory properties (Fig. 5-2).

Vascular Smooth Muscle Cells

SMC within the medial layer of normal muscular arteries have both contractile and synthetic capabilities. Various vasoactive substances modulate the contractile function, resulting in vasoconstriction or vasodilation. Such agonists include circulating molecules (e.g., angiotensin II), those released from local nerve terminals (e.g., acetylcholine), and others originating from the overlying endothelium (e.g., endothelin and NO). SMC also synthesize the collagen, elastin, and proteoglycans that form the bulk of the vascular extracellular matrix (see Fig. 5-2). In addition, SMC produce vasoactive and inflammatory mediators, including interleukin-6 (IL-6) and tumor necrosis factor (TNF).

In normal arteries, most SMC reside in the medial layer, although human arteries also contain some SMC in the intima, particularly in sites predisposed to atherosclerosis. During atherogenesis, medial SMC can migrate into the intima, proliferate, and augment synthesis of extracellular matrix macromolecules while they dampen contractile protein content.

Extracellular Matrix

In healthy arteries, fibrillar collagen, elastin, and proteoglycans make up most of the extracellular matrix in the medial layer. Interstitial collagen fibrils, constructed from intertwining helical proteins, possess great biomechanical strength, while elastin provides flexibility. Together these components maintain the structural integrity of the vessel, despite the high pressure within the lumen. The extracellular matrix also regulates the growth of its resident cells. Native fibrillar collagen, in particular, can inhibit SMC proliferation in vitro. Furthermore, the matrix influences cellular responses to stimuli—matrix-bound cells respond in a specific manner to growth factors and resist apoptosis (programmed cell death).

Atherosclerotic Arterial Wall

The arterial wall is a dynamic and regulated structure, but certain stimuli can disturb normal homeostasis and pave the way for atherogenesis. For example, as described later, vascular endothelial cells, as well as SMC, react readily to inflammatory mediators, such as IL-1 and TNF, and can produce them as well.

With the recognition that vascular wall cells respond to, and produce, proinflammatory agents, investigations into the role of “activated” endothelial and SMC in atherogenesis burgeoned. As a consequence, vascular endothelium and SMC joined classical inflammatory cells, such as mononuclear phagocytes and T lymphocytes, as key players in early atheroma formation and in advanced plaque progression. This fundamental research has identified several key components that contribute to the atherosclerotic inflammatory process, including endothelial dysfunction, accumulation of lipids within the intima, recruitment of leukocytes and SMC to the vessel wall, formation of foam cells, and deposition of extracellular matrix (Fig. 5-3), as described in the following sections. Rather than follow a sequential path, the cells of atherosclerotic lesions continuously interact and modify each other’s behavior, shaping the plaque over decades into one of many possible profiles. This section categorizes these mechanisms into three pathologic stages: the fatty streak, plaque progression, and plaque disruption (Fig. 5-4). In the arterial tree, lesions of all three stages can coexist, often side by side.

Fatty Streak

Fatty streaks represent the earliest visible lesions of atherosclerosis. On gross inspection, they appear as areas of yellow discoloration on the artery’s inner surface, but they neither protrude substantially into the arterial lumen nor impede blood flow. Surprisingly, fatty streaks exist in the aorta and coronary arteries of most people by age 20. They do not cause symptoms, and in some locations in the vasculature, they may regress over time. Although the precise initiation of fatty streak development is not known, observations in animals suggest that various stressors cause early endothelial dysfunction, as described in the next section.

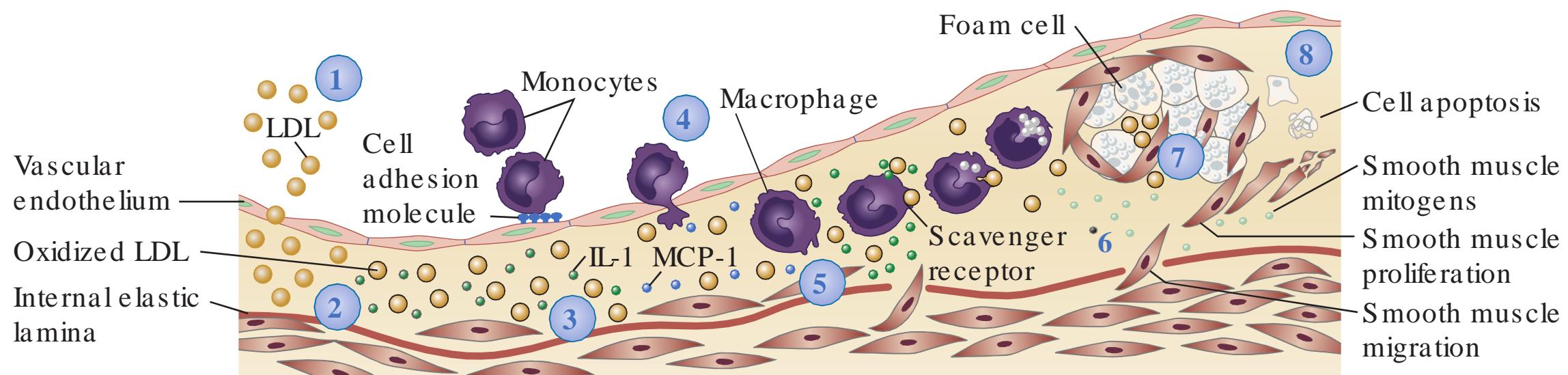


FIGURE 5-3. Schematic diagram of the evolution of atherosclerotic plaque. (1) Accumulation of lipoprotein particles in the intima. The darker color depicts modification of the lipoproteins (e.g., by oxidation or glycation). (2) Oxidative stress, including constituents of modified LDL, induces local cytokine elaboration. (3) These cytokines promote increased expression of adhesion molecules that bind leukocytes and of chemoattractant molecules (e.g., monocyte chemoattractant protein-1 [MCP-1]) that direct leukocyte migration into the intima. (4) After entering the artery wall in response to chemoattractants, blood monocytes encounter stimuli such as macrophage colony-stimulating factor (M-CSF) that augment their expression of scavenger receptors. (5) Scavenger receptors mediate the uptake of modified lipoprotein particles and promote the development of foam cells. Macrophage foam cells are a source of additional cytokines and effector molecules such as superoxide anion (O_2^-) and matrix metalloproteinases. (6) SMC migrate into the intima from the media. Note the increasing intimal thickness. (7) Intimal SMC divide and elaborate extracellular matrix, promoting matrix accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak evolves into a fibrofatty lesion. (8) In later stages, calcification can occur (not depicted) and fibrosis continues, sometimes accompanied by smooth muscle cell death (including programmed cell death or apoptosis), yielding a relatively acellular fibrous capsule surrounding a lipid-rich core that may also contain dying or dead cells. IL-1, interleukin 1; LDL, low-density lipoprotein. (Modified from Mann DL, Zipes D, Libby P, Bonow ROeds. Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier Saunders; 2015.)

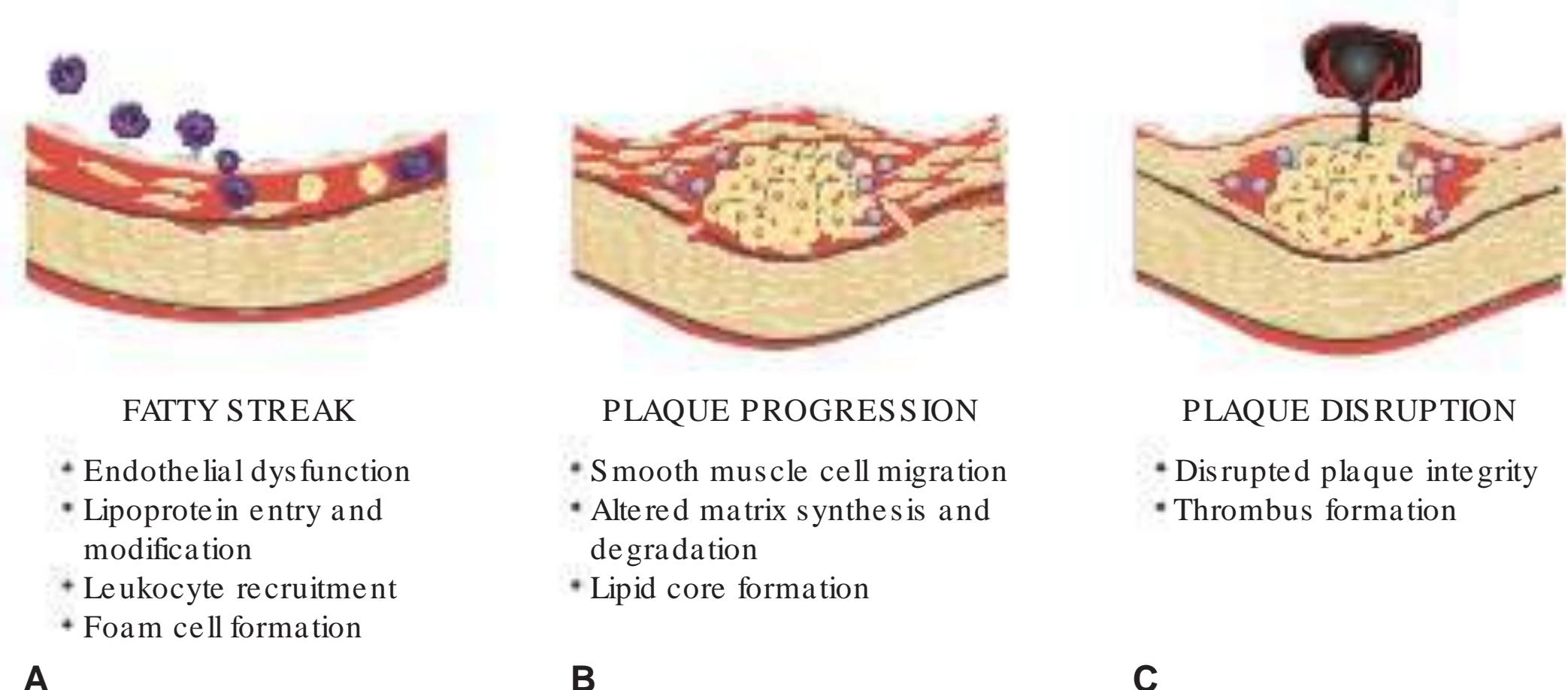
**A****B****C**

FIGURE 5-4. Stages of plaque development. **A.** The fatty streak develops as a result of endothelial dysfunction, lipoprotein entry and modification, leukocyte recruitment, and foam cell formation. **B.** Plaque progression involves migration of SMC into the intima, where they divide and elaborate extracellular matrix. The fibrous cap contains a lipid core. **C** Hemodynamic stresses and degradation of extracellular matrix increase the susceptibility of the fibrous cap to rupture, allowing superimposed thrombus formation. (Modified from Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1136.)

Such dysfunction allows entry and modification of lipids within the subendothelial space, where they serve as proinflammatory mediators that initiate leukocyte recruitment and foam cell formation—the pathologic hallmarks of the fatty streak (Fig. 5-3).

Endothelial Dysfunction

Injury to the arterial endothelium represents a primary event in atherogenesis. Such injury can result from exposure to diverse agents, including physical forces and chemical irritants.

The predisposition of certain regions of arteries (e.g., branch points) to develop atheroma supports the role of hydrodynamic stress. In straight sections of arteries, the normal laminar (i.e., smooth) shear forces favor the endothelial production of NO, which is an endogenous vasodilator, an inhibitor of platelet aggregation, and an anti-inflammatory substance (see Chapter 6). Moreover, laminar flow and high shear stress activates transcription factors such as Krüppel-like factor 2 (KLF2) that evokes an “atheroprotective” panel of endothelial functions and accentuates expression of the antioxidant enzyme superoxide dismutase, which protects against reactive oxygen species. Conversely, disturbed flow occurs near arterial branch points, causing low shear stress, which impairs these locally atheroprotective endothelial functions. Accordingly, arteries with few branches (e.g., the internal mammary artery) show relative resistance to atherosclerosis, whereas bifurcated vessels (e.g., the common carotid and left coronary arteries) contain common sites for atheroma formation.

Endothelial dysfunction may also result from exposure to a “toxic” chemical environment. For example, tobacco smoking, abnormal circulating lipid levels, and diabetes—all known risk factors for atherosclerosis—can promote endothelial dysfunction. Each of these stimuli increases endothelial production of reactive oxygen species—notably, superoxide anion—that interact with other intracellular molecules to influence the metabolic and synthetic functions of the endothelium. In such an environment, the cells promote local inflammation.

When physical and chemical stressors interrupt normal endothelial homeostasis, an activated state ensues, manifested by impairment of the endothelium’s role as a permeability barrier, the release of inflammatory cytokines, increased production of cell surface adhesion molecules that recruit leukocytes, altered release of vasoactive substances (e.g., prostacyclin and NO), and interference with normal antithrombotic properties. These undesired effects of

dysfunctional endothelium lay the groundwork for subsequent events in the development of atherosclerosis (see Figs. 5-2 and 5-3).

Lipoprotein Entry and Modification

The activated endothelium no longer serves as an effective barrier to the passage of circulating lipoproteins into the arterial wall. Increased endothelial permeability allows the entry of low-density lipoprotein (LDL) into the intima, a process facilitated by an elevated circulating LDL concentration in patients with hypercholesterolemia. In addition to high LDL concentrations in part from diet, several monogenic causes of elevated LDL exist, including mutations of the LDL receptor, of apolipoprotein B, and of PCSK9, a protease involved in regulation of the LDL receptor. Once within the intima, LDL accumulates in the subendothelial space by binding to proteoglycans in the extracellular matrix. This “trapping” increases the residence time of LDL within the vessel wall, where the lipoprotein may undergo chemical modifications that can promote the development of atherosclerotic lesions. Hypertension, a major risk factor for atherosclerosis, may further promote retention of lipoproteins in the intima by accentuating the production of LDL-binding proteoglycans by SMC.

Oxidation is one type of modification that befalls LDL trapped in the subendothelial space. It can result from the local action of reactive oxygen species and prooxidant enzymes derived from activated endothelial or SMC, or from macrophages that penetrate the vessel wall. In addition, the microenvironment of the subendothelial space sequesters oxidized LDL from antioxidants in the plasma. In diabetic patients with sustained hyperglycemia, glycation of LDL can occur—a modification that may ultimately render LDL antigenic and proinflammatory. These biochemical alterations of LDL act early and contribute to the inflammatory mechanisms initiated by endothelial dysfunction, and they may continue to promote inflammation throughout the life span of the plaque. In the fatty streak, and likely throughout plaque development, modified LDL (mLDL) promotes leukocyte recruitment and foam cell formation.

Leukocyte Recruitment

Recruitment of leukocytes (primarily monocytes and T lymphocytes) to the vessel wall is a key step in atherogenesis. The process depends on the expression of leukocyte adhesion molecules (LAMs) on the normally nonadherent endothelial luminal surface and on chemoattractant signals (e.g., monocyte chemotactic protein-1 [MCP-1]) that direct diapedesis (passage of cells through the intact endothelial layer) into the subintimal space. Two major subsets of LAM persist in the inflamed atherosclerotic plaque: the immunoglobulin gene superfamily (especially vascular cell adhesion molecule-1 [VCAM-1] and intercellular adhesion molecule-1 [ICAM-1]) and the selectins (particularly, E- and P-selectin). These LAMs and chemoattractant signals direct mainly monocytes to the forming lesion. Hypercholesterolemia favors accumulation in blood of a subset of monocytes that is characterized by expression of high levels of proinflammatory cytokines (e.g., IL-1 and TNF), distinguished in mice by expression of the cell surface marker Ly6c. Although outnumbered by monocytes, T lymphocytes also localize within plaques and direct the adaptive immune response.

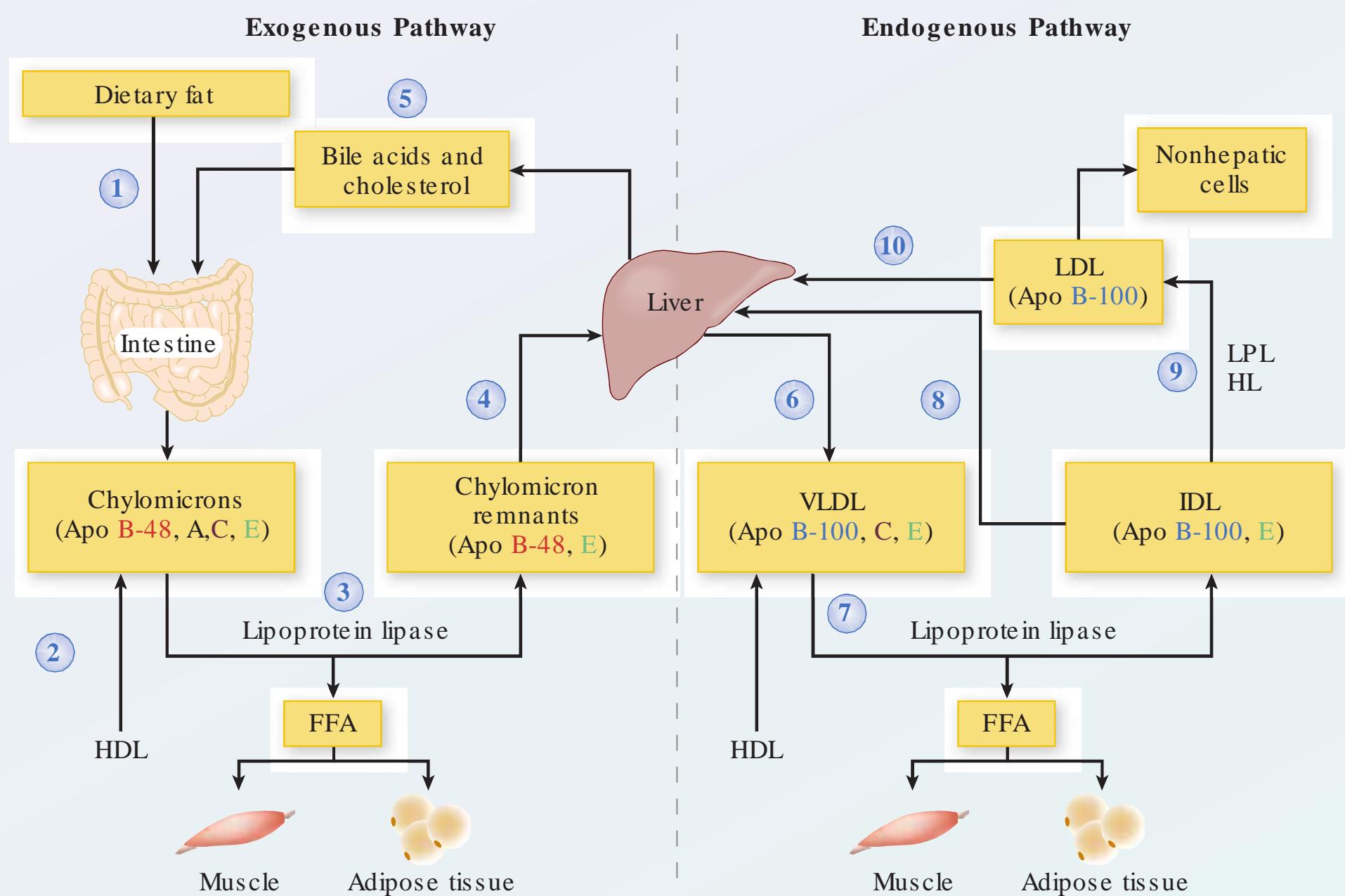
mLDL and proinflammatory cytokines can induce LAM and chemoattractant cytokine (chemokine) expression independently, but mLDL may also stimulate endothelial and SMC to produce proinflammatory cytokines, thereby reinforcing the direct action. This dual ability of mLDL to promote leukocyte recruitment and inflammation directly and indirectly persists throughout atherogenesis.

Foam Cell Formation

After monocytes adhere to and penetrate the intima, they differentiate into macrophages and imbibe lipoproteins to form foam cells. Foam cells do not arise from uptake of LDL cholesterol by classic cell surface LDL receptor-mediated endocytosis as described in Box 5-1

BOX 5-1 The Lipoprotein Transport System

Lipoproteins ferry water-insoluble fats through the bloodstream. These particles consist of a lipid core surrounded by more hydrophilic phospholipid, free cholesterol, and apolipoproteins (also called apoproteins). The apoproteins present on various classes of lipoprotein molecules serve as the “conductors” of the system, directing the lipoproteins to specific tissue receptors and mediating enzymatic reactions. Five major classes of lipoproteins exist, distinguished by their densities, lipid constituents, and associated apoproteins. In order of increasing density, they are **chylomicrons**, **very-low-density lipoproteins (VLDL)**, **intermediate-density lipoproteins (IDL)**, **low-density lipoproteins (LDL)**, and **high-density lipoproteins (HDL)**. The major steps in the lipoprotein pathways are labeled in the figure below and described as follows. The key apoproteins (apo) at each stage are indicated in the figure in parentheses.



Exogenous (Intestinal) Pathway

1. Dietary fats are absorbed by the small intestine and repackaged as chylomicrons, accompanied by apo B-48. Chylomicrons are large particles, particularly rich in triglycerides, that enter the circulation via the lymphatic system.
2. Apo E and subtypes of apo C are transferred to chylomicrons from HDL particles in the bloodstream.
3. Apo C (subtype CI) enhances interactions of chylomicrons with lipoprotein lipase (LPL) on the endothelial surface of adipose and muscle tissue. This reaction hydrolyzes the triglycerides within chylomicrons into free fatty acids (FFAs), which are stored by adipose tissue or used for energy in cardiac and skeletal muscle.
4. Chylomicron remnants are removed from the circulation by the liver, mediated by apo E.
5. One fate of cholesterol in the liver is incorporation into bile acids, which are exported to the intestine, completing the exogenous pathway cycle.

Endogenous (Hepatic) Pathway

Because dietary fat availability is not constant, the endogenous pathway provides a reliable supply of triglycerides for tissue energy needs:

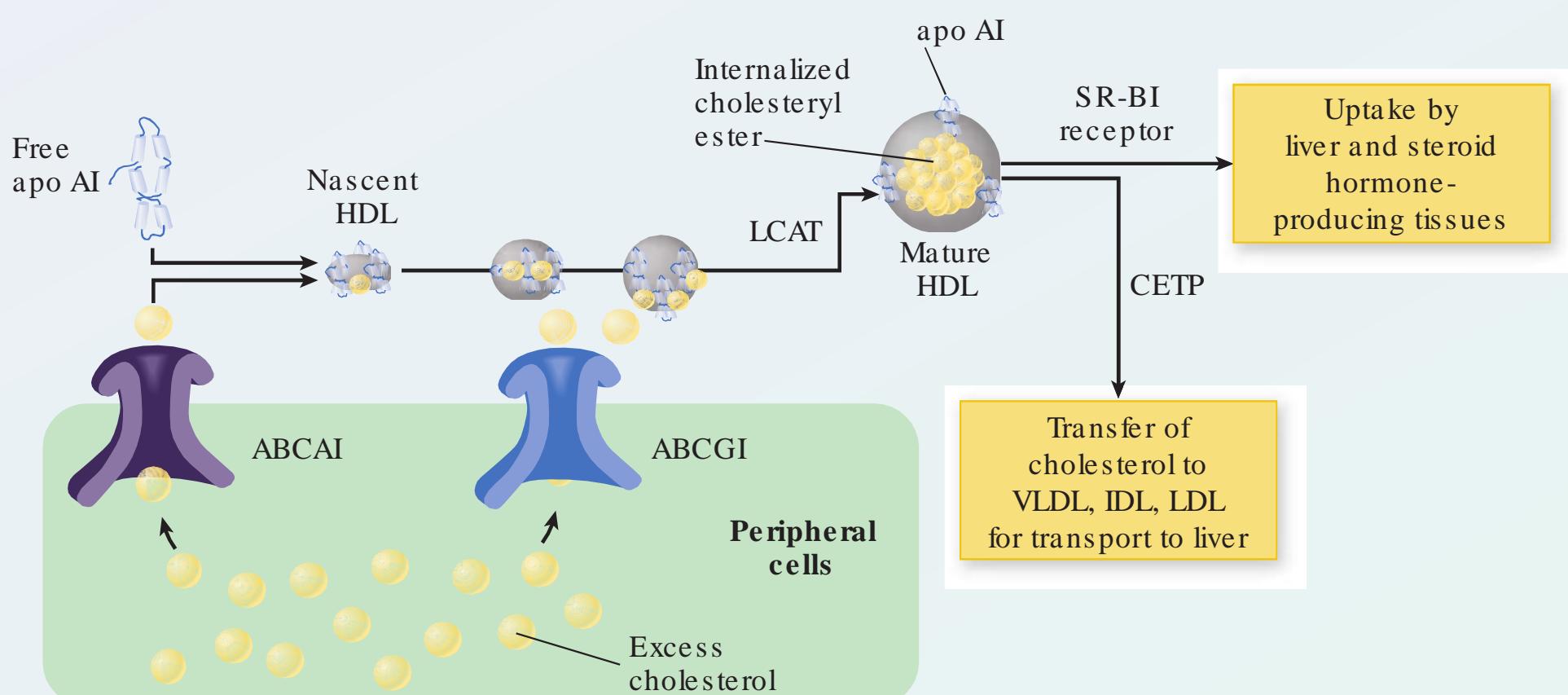
6. The liver packages cholesterol and triglycerides into VLDL particles, accompanied by apo B-100 and phospholipid. The triglyceride content of VLDL is much higher than that of cholesterol, but this is the main means by which the liver releases cholesterol into the circulation.

BOX 5-1 The Lipoprotein Transport System (continued)

7. VLDL is catabolized by LPL (similar to chylomicrons, as described in step 3), releasing fatty acids to muscle and adipose tissue. During this process, VLDL also interacts with HDL, exchanging some of its triglyceride for apo C subtypes, apo E, and cholestryl ester from HDL. The latter exchange (important in reverse cholesterol transport, as described in the next section) is mediated by cholestryl ester transfer protein (CETP).
8. Approximately 50% of the VLDL remnants (termed intermediate-density lipoproteins [IDL]) are then cleared in the liver by hepatic receptors that recognize apo E.
9. The remaining IDL is catabolized further by LPL and hepatic lipase (HL), which remove additional triglyceride, apo E, and apo C, forming LDL particles.
10. Plasma clearance of LDL occurs primarily via LDL receptor-mediated endocytosis in the liver and peripheral cells, directed by LDL's apo B-100 and apo E.

Cholesterol Homeostasis and Reverse Cholesterol Transport

Intracellular cholesterol content is tightly maintained by de novo synthesis, cellular uptake, storage, and efflux from the cell. The enzyme HMG-CoA reductase is the rate-limiting element of cholesterol biosynthesis, and cellular uptake of cholesterol is controlled by receptor-mediated endocytosis of circulating LDL (see step 10). When intracellular cholesterol levels are low, the transcription factor sterol regulatory element–binding protein (SREBP) is released from the endoplasmic reticulum. The active fragment of SREBP enters the nucleus to increase transcription of HMG-CoA reductase and the LDL receptor—which, through their subsequent actions, tend to normalize the intracellular cholesterol content.



Under conditions of intracellular cholesterol excess (as in the figure above), peripheral cells increase the transcription of the ATP-binding cassette A1 and G1 genes (ABCA1 and ABCG1, respectively). The ABCA1 gene codes for a transmembrane protein transporter that initiates efflux of cholesterol from the cell to lipid-poor circulating apo AI (which is synthesized by the liver and intestine), thus forming nascent (immature) HDL particles. ABCG1 facilitates further efflux of cholesterol to form more mature HDL particles. As free cholesterol is acquired by circulating HDL, it is esterified by lecithin cholesterol acyltransferase (LCAT), an enzyme activated by apo AI. The hydrophobic cholestryl esters move into the particle's core. Most cholestryl esters in HDL can then be exchanged for triglycerides in the circulation (via the enzyme CETP) with any of the apo B-containing lipoproteins (i.e., VLDL, IDL, LDL), which deliver the cholesterol back to the liver. HDL can also transport cholesterol to the liver and steroid hormone-producing tissues via the SR-B1 scavenger receptor.

(e.g., as occurs in normal hepatocytes), because the high cholesterol content in these cells suppresses expression of that receptor. Furthermore, the classic LDL receptor does not recognize modified LDL particles. Rather, macrophages rely on a family of “scavenger” receptors that preferentially bind and internalize mLDL. Unlike uptake via the classic LDL receptor, mLDL ingestion by scavenger receptors evades negative feedback inhibition and permits engorgement of the macrophages with cholesterol and cholesteryl ester, resulting in the typical appearance of foam cells. Although such uptake may initially provide benefit by sequestering potentially damaging mLDL particles, the impaired efflux of these cells as compared to the rate of influx, as well as local proliferation, leads to their accumulation in the plaque. This mitigates their protective role by fueling foam cell apoptosis and the release of proinflammatory cytokines that promote atherosclerotic plaque progression. During atherogenesis, the clearance of dead foam cells can become inefficient, thus promoting the accumulation of cellular debris and extracellular lipids, forming the lipid-rich center of a plaque (often termed the necrotic core).

Plaque Progression

Whereas endothelial cells play a central role in the formation of the fatty streak, SMC in the intima promote plaque progression by producing extracellular matrix that traps lipoproteins and adds to the bulk of the lesion. During decades of development, the typical atherosclerotic plaque acquires a distinct thrombogenic lipid core that underlies a protective fibrous cap. Not all fatty streaks progress into fibrofatty lesions, and it is unknown why some evolve and others do not.

Early plaque growth typically involves a compensatory outward remodeling of the arterial wall that preserves the diameter of the lumen and permits plaque accumulation without limitation of blood flow, hence producing no ischemic symptoms. Lesions at this stage can thus evade detection by angiography. Later plaque growth, however, can outstrip the compensatory arterial enlargement, restrict the vessel lumen, and impede perfusion. Such flow-limiting plaques can result in tissue ischemia, causing symptoms such as angina pectoris (see Chapter 6) or intermittent claudication of the extremities (see Chapter 15).

Many acute coronary syndromes (acute myocardial infarction and unstable angina pectoris) result when the fibrous cap of an atherosclerotic plaque ruptures, exposing prothrombotic molecules within the lipid core and precipitating an acute thrombus that suddenly occludes the arterial lumen. As described in this section, the extracellular matrix plays a pivotal role in fortifying the fibrous cap, isolating the thrombogenic plaque interior from coagulation substrates in the circulation.

Smooth Muscle Cell Migration

The transition from fatty streak to fibrous atheromatous plaque involves the migration of SMC from the arterial media into the intima, proliferation of the SMC within the intima, and secretion of extracellular matrix macromolecules by the SMC. Foam cells, activated platelets entering through microfissures in the plaque surface, and endothelial cells can all elaborate substances that signal SMC migration and proliferation (Fig. 5-5).

Foam cells produce several factors that contribute to SMC recruitment. For example, they release platelet-derived growth factor (PDGF)—also released by platelets and endothelial cells—which likely stimulates the migration of SMC across the internal elastic lamina and into the subintimal space, where they subsequently replicate. PDGF additionally stimulates the growth of resident SMC in the intima. Foam cells also release cytokines and growth factors (e.g., TNF, IL-1, fibroblast growth factor, and transforming growth factor- β [TGF- β]) that further incite SMC proliferation and/or the synthesis of extracellular matrix proteins. Furthermore, these stimulatory cytokines induce SMC and leukocyte activation, promoting further cytokine release, thus reinforcing and maintaining inflammation in the lesion.

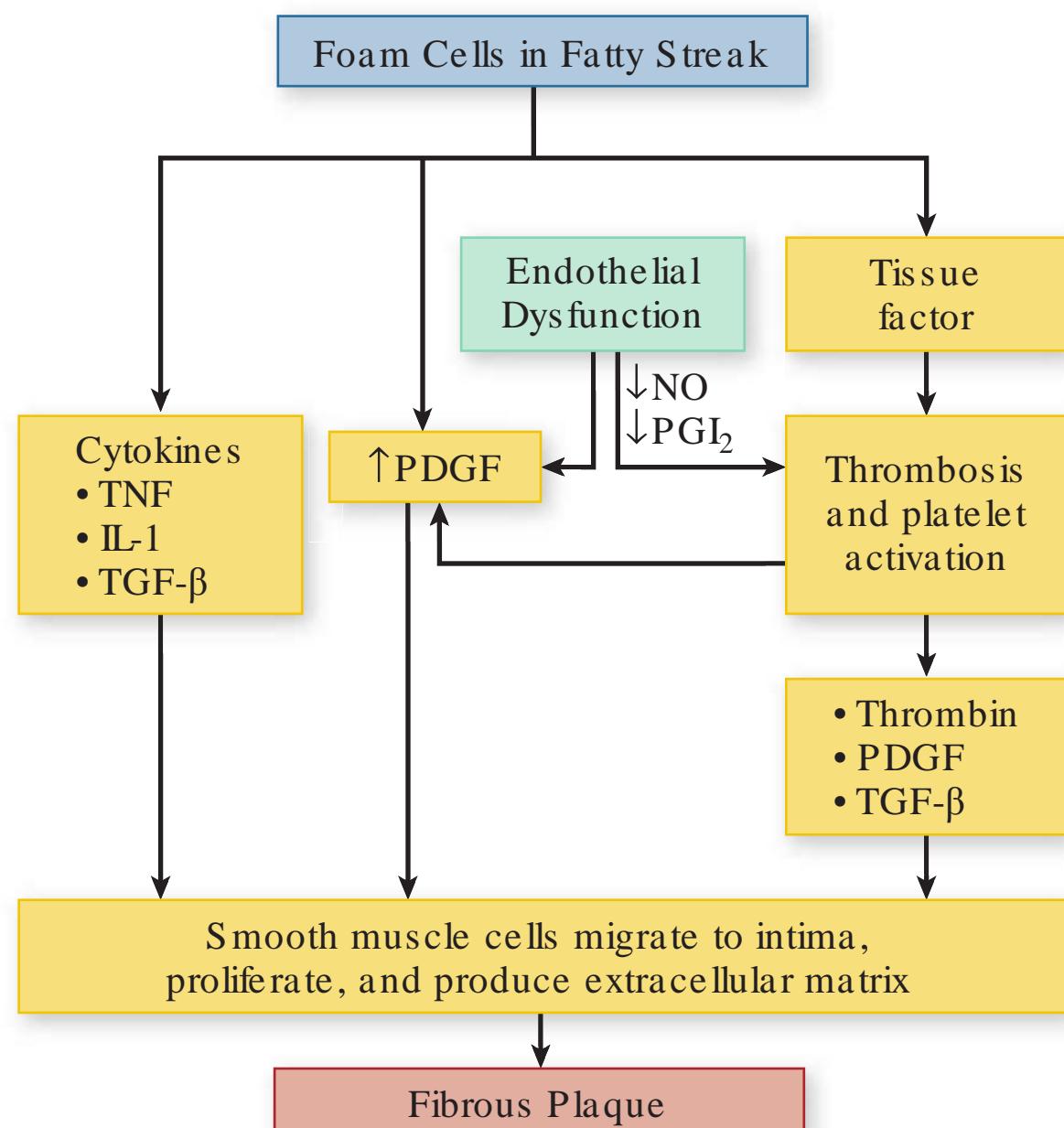


FIGURE 5-5. Progression from the fatty streak involves the migration and proliferation of SMC. Substances released from foam cells, dysfunctional endothelial cells, and platelets contribute to this process. IL-1, interleukin-1; NO, nitric oxide; PDGF, platelet-derived growth factor; PG₁, prostacyclin; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

According to the traditional concept, plaques grow gradually and continuously, but current evidence suggests that this progression may be punctuated by subclinical events with bursts of smooth muscle replication. For example, morphologic evidence of resolved intra-plaque hemorrhages indicates that breaches in plaque integrity can occur without clinical symptoms or signs. Such plaque disruptions expose tissue factor from foam cells to blood, which activates coagulation and microthrombus formation. Activated platelets within such microthrombi release additional potent factors—including PDGF—that can spur a local wave of SMC migration and proliferation.

Activated T cells also contribute to plaque evolution. Cells of the T helper 1 subtype (Th1) produce proinflammatory cytokines that promote plaque progression and instability, while lymphocytes of the T helper 2 subtype (Th2) and regulatory T cells (Treg) produce factors, including TGF-β and IL-10, which can inhibit SMC proliferation and potentially mitigate plaque growth.

Extracellular Matrix Metabolism

As the predominant collagen-synthesizing cell type, SMC favor fortification of the fibrous cap. Net matrix deposition depends on the balance of its synthesis by SMC and its degradation, mediated in part by a class of proteolytic enzymes known as matrix metalloproteinases (MMP). While PDGF and TGF-β stimulate production of interstitial collagens by SMC, the Th1-derived cytokine interferon-γ (IFN-γ) inhibits SMC collagen synthesis. Furthermore, inflammatory cytokines stimulate local foam cells to secrete collagen- and elastin-degrading MMP, thereby weakening the fibrous cap and predisposing it to rupture (Fig. 5-6).

Plaque Disruption

Plaque Integrity

The tug-of-war between matrix synthesis and degradation continues over decades but not without consequences. Death of smooth muscle and foam cells, either owing to excess inflammatory stimulation or by contact activation of apoptosis pathways, liberates cellular contents, contributing imbibed lipids and cellular debris to the growing lipid core. The size of the lipid

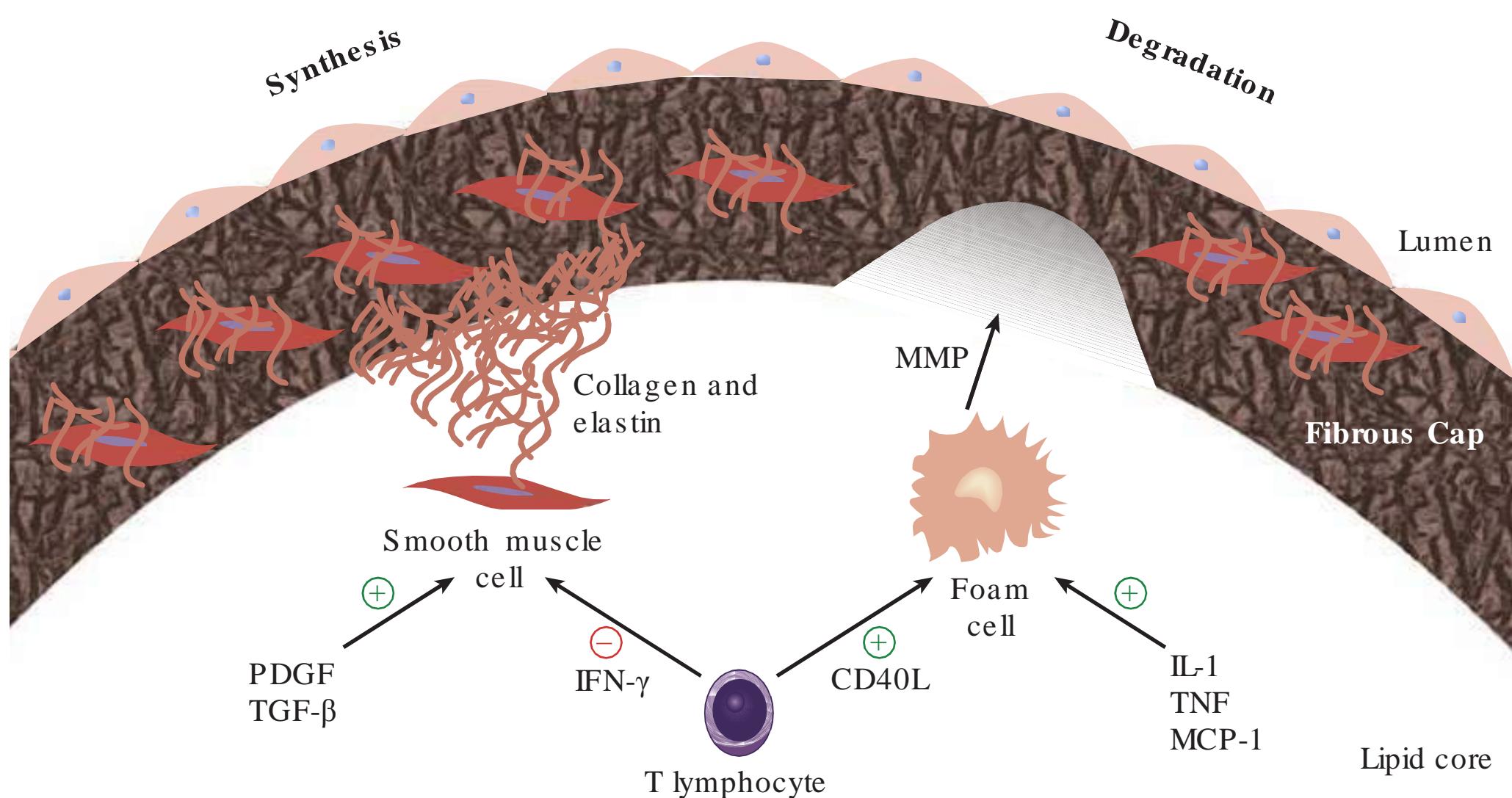


FIGURE 5-6. Matrix metabolism underlies fibrous cap integrity. The net deposition of extracellular matrix is the result of competing synthesis and degradation reactions. Smooth muscle cells synthesize the bulk of the fibrous cap constituents, such as collagen and elastin. Foam cells elaborate destructive proteolytic enzymes, such as the collagen-degrading matrix metalloproteinases (MMP) and the elastolytic cathepsins. T-lymphocyte-derived factors favor destruction of the fibrous cap. All plaque residents, however, contribute to the cytokine milieu of the plaque, providing multiple activating and inhibitory stimuli as shown. IFN- γ , interferon- γ ; IL-1, interleukin-1; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; TGF- β , transforming growth factor- β ; TNF, tumor necrosis factor. (Modified from Libby P. The molecular bases of acute coronary syndromes. Circulation. 1995;91:2844–2850; Young JL, Libby P, Schönbeck U. Cytokines in the pathogenesis of atherosclerosis. Thromb Haemost. 2002;88:554–567.)

core has biomechanical implications for the stability of the plaque. With increasing size and protrusion into the arterial lumen, mechanical stress focuses on the plaque border abutting normal tissue, called the shoulder region.

The structure of the fibrous cap contributes to plaque integrity. Whereas lesions with thick fibrous caps may cause pronounced arterial narrowing, they have less propensity to rupture. Conversely, plaques that have thinner caps (and often appear less obstructive by angiography) tend to be fragile and more likely to rupture and incite thrombosis. Current clinical terminology describes the extreme spectrums of integrity as “stable plaques” (marked by a thick fibrous cap and small lipid core) or “vulnerable plaques” (marked by a thin fibrous cap, rich lipid core, extensive macrophage infiltrate, and a paucity of SMC; Fig. 5-7). Despite the common use of these terms, this distinction vastly oversimplifies the heterogeneity of plaques and may overestimate the ability to foresee a plaque’s “clinical future” based on structural information. Most plaques with the so-called “vulnerable” morphology do not actually cause clinical events; hence, attempts to specifically identify such plaques may not direct therapy in an effective manner. Moreover, a substantial minority of fatal thrombi in coronary arteries arise from matrix-rich plaques with intact fibrous caps, a morphology that may arise from superficial erosion of the lesion by mechanisms that are not well understood.

Thrombogenic Potential

Rupture of atherosclerotic plaque does not inevitably cause major clinical events such as myocardial infarction or stroke. As described in the previous section, small nonocclusive thrombi may incorporate into the plaque, stimulating further smooth muscle growth and extracellular matrix deposition (see Fig. 5-7). The balance between the thrombogenic

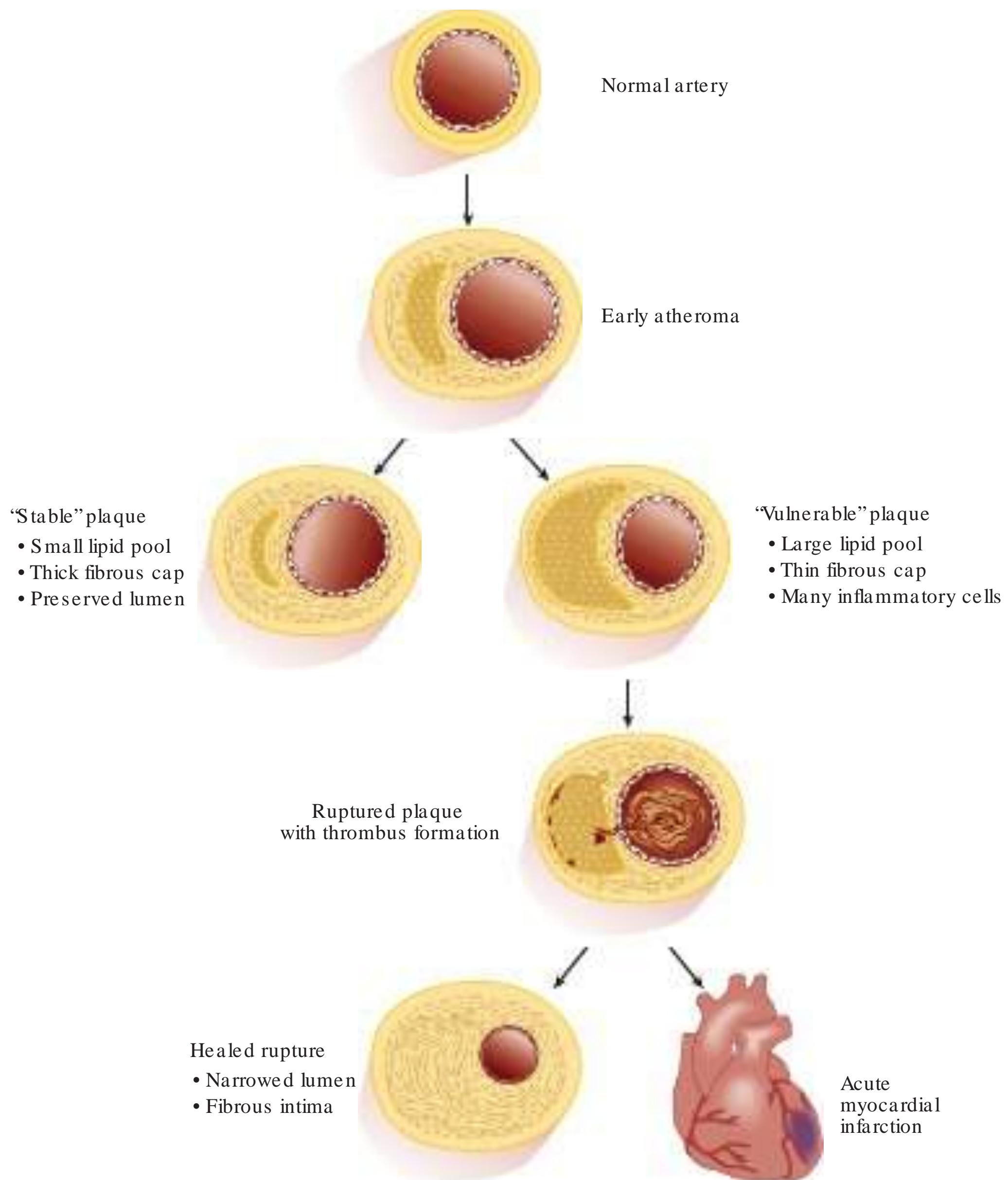


FIGURE 5-7. Stable versus vulnerable plaques. Stable plaque is characterized by a small lipid core and a thick fibrous cap, whereas vulnerable plaque tends to have a large lipid core and a relatively thin fibrous cap. The latter is subject to rupture, resulting in thrombosis. A resulting occlusive clot can cause an acute cardiac event, such as myocardial infarction. A lesser thrombus may resorb, but the wound-healing response stimulates smooth muscle cell proliferation and collagen production, thereby thickening the fibrous cap and narrowing the vessel lumen further. (Modified from Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868–874.)

and fibrinolytic potential of the plaque, and the fluid phase of blood, determines whether disruption of the fibrous cap leads to a transient, nonobstructive mural thrombus or to a completely occlusive clot.

The probability of a major thrombotic event reflects the balance between the competing processes of clot formation and dissolution by fibrinolysis. Inflammatory stimuli found in the plaque microenvironment (e.g., CD40L) elicit tissue factor, the initiator of the extrinsic coagulation pathway, from many plaque components including SMC, endothelial cells,

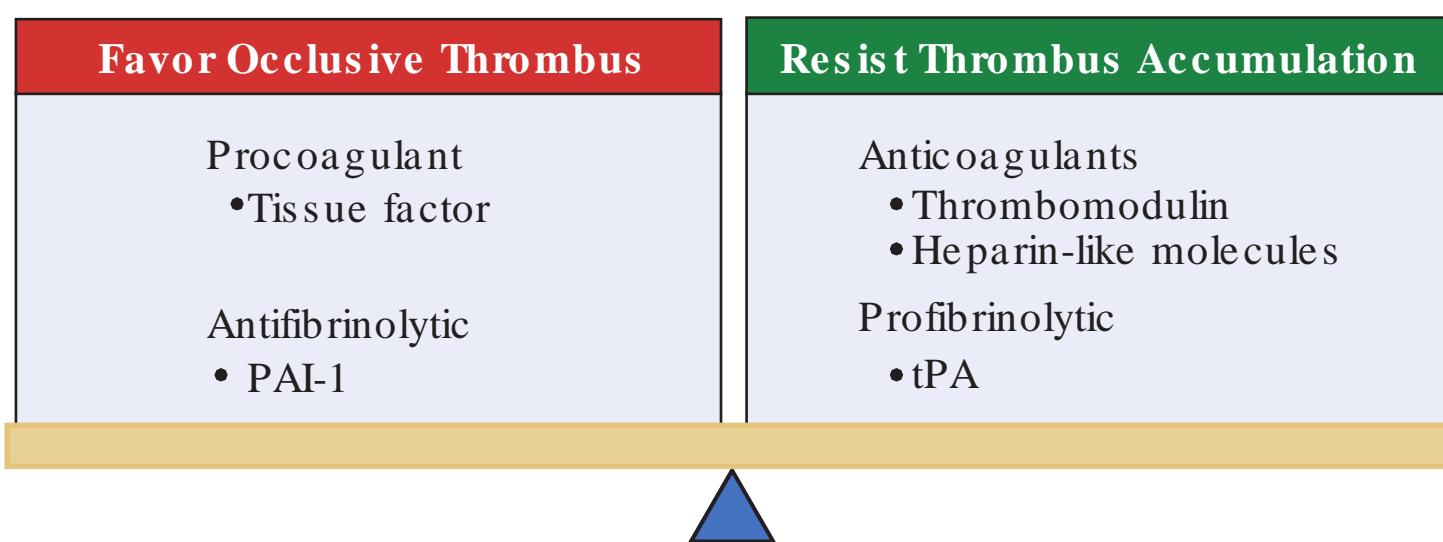


FIGURE 5-8. Competing factors in thrombosis. The clinical manifestations of plaque disruption rely not only on the stability of the fibrous cap but also on the thrombogenic potential of the plaque core. The balance of physiologic mediators dictates the prominence of the thrombus, resulting in either luminal occlusion or resorption into the plaque. PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator.

and macrophage-derived foam cells. Beyond enhancing expression of the potent procoagulant tissue factor, inflammatory stimuli further support thrombosis by favoring the expression of antifibrinolytics (e.g., plasminogen activator inhibitor-1) over the expression of anticoagulants (e.g., thrombomodulin, heparin-like molecules) and profibrinolytic mediators (e.g., tissue plasminogen activator; Fig. 5-8). Moreover, as described earlier, the activated endothelium also promotes thrombin formation, coagulation, and fibrin deposition at the vascular wall.

A person's propensity toward coagulation may be enhanced by genetics, comorbid conditions (e.g., diabetes), and/or lifestyle factors (e.g., smoking, visceral obesity). Consequently, the concept of the "vulnerable plaque" has expanded to that of the "vulnerable patient," to acknowledge other contributors to a person's vascular risk.

Complications of Atherosclerosis

Atherosclerotic plaques do not distribute homogeneously throughout the vasculature. They usually develop first in the dorsal aspect of the abdominal aorta and proximal coronary arteries, followed by the popliteal arteries, descending thoracic aorta, internal carotid arteries, and renal arteries. Therefore, the regions perfused by these vessels most commonly suffer the consequences of atherosclerosis.

Complications of atherosclerotic plaques—including calcification, rupture, hemorrhage, and embolization—can have dire clinical consequences due to acute restriction of blood flow or alterations in vessel wall integrity. These complications, which are discussed in greater detail in later chapters, include the following:

- Calcification of atherosclerotic plaque, which may increase its fragility.
- Rupture or ulceration of atherosclerotic plaque, which exposes procoagulants within the plaque to circulating blood, causing a thrombus to form at that site. Such thrombosis can occlude the vessel and result in infarction of the involved organ. Alternatively, the thrombus can organize, incorporate into the lesion, and add to the bulk of the plaque.
- Hemorrhage into the plaque owing to rupture of the fibrous cap or of the microvessels that form within the lesion. The resulting intramural hematoma may further narrow the vessel lumen.
- Embolization of fragments of disrupted atheroma to distal vascular sites.
- Weakening of the vessel wall: the fibrous plaque subjects the neighboring medial layer to increased pressure, which may provoke atrophy and loss of elastic tissue with subsequent expansion of the artery, forming an aneurysm.
- Microvessel growth within plaques, providing a source for intraplaque hemorrhage and further leukocyte trafficking.

The complications of atherosclerotic plaque may result in specific clinical consequences in different organ systems (Fig. 5-9). When lesion growth eventually outstrips the compensatory outward enlargement of the plaque, the lesion can narrow the vessel lumen and, in the case of the coronary arteries, cause intermittent chest discomfort on exertion (angina pectoris). In contrast, plaque that does not compromise the vessel lumen but has characteristics of vulnerability (e.g., a thin fibrous cap, a large lipid core, spotty calcifications) can rupture, leading to acute thrombosis and myocardial infarction (see Chapter 7). Such nonstenotic plaques are often numerous and dispersed throughout the arterial tree, and because they do not limit arterial flow, they do not produce symptoms and often evade detection by exercise testing or angiography.

The description presented here of atherogenesis and its complications can explain the limitations of widely employed treatments. For example, percutaneous intervention (angioplasty and stent placement) of symptomatic coronary stenoses effectively relieves angina pectoris, but does not necessarily prevent future myocardial infarction or prolong life, with the exception of patients in the early phase of an acute ST-elevation myocardial infarction, as described in Chapter 7. This disparity likely reflects the multiplicity of nonocclusive plaques at risk of precipitating thrombotic events. It follows that lifestyle modifications and drug therapies that curb the risk factors for plaque formation, and lessen features associated with “vulnerability,” provide a critical foundation for preventing progression and complications of atherosclerosis.

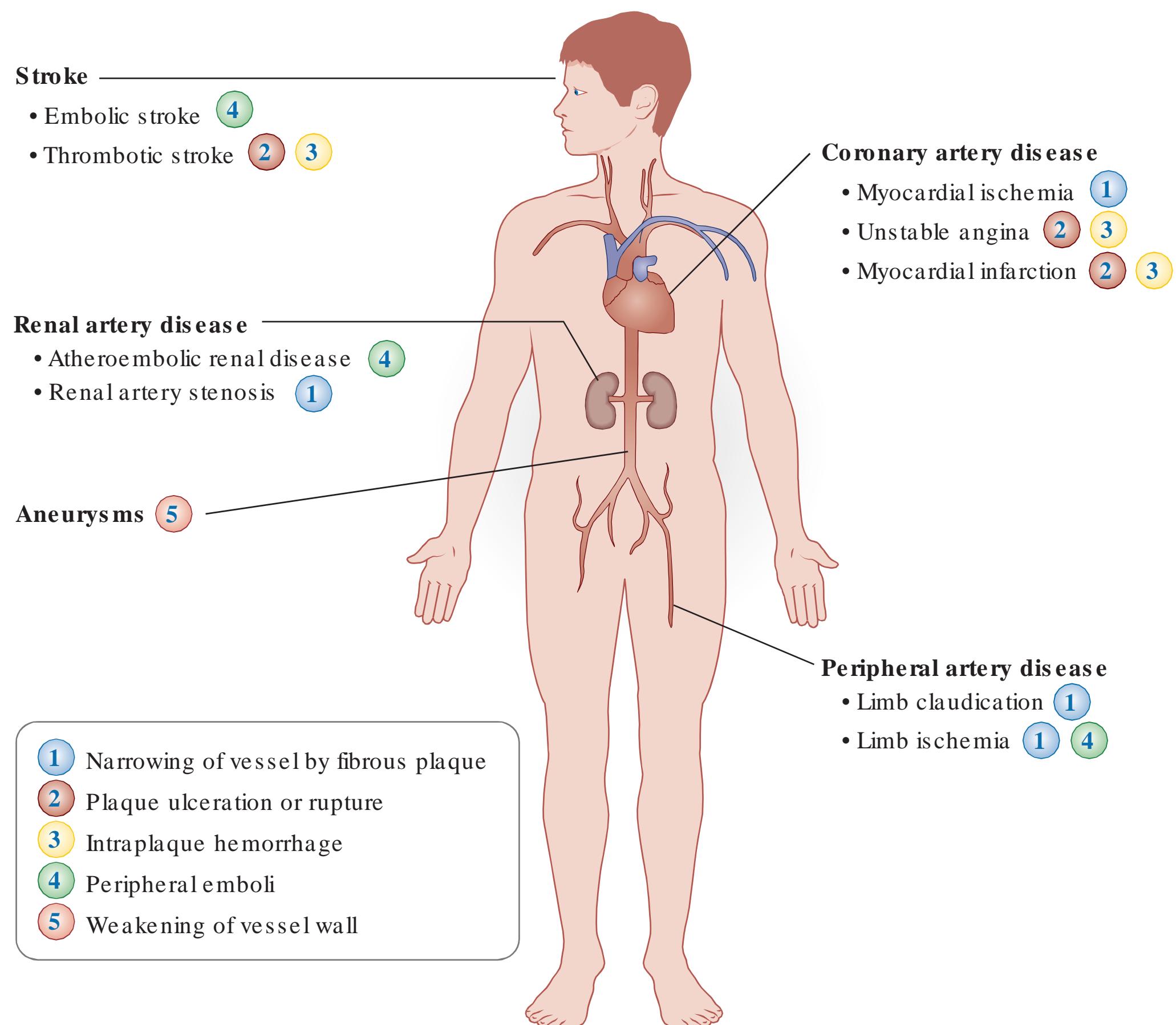


FIGURE 5-9. Clinical sequelae of atherosclerosis. Complications of atherosclerosis arise from the mechanisms listed in the figure.

ATHEROSCLEROSIS RISK FACTORS

In the early 20th century, most viewed atherosclerosis as an inevitable process of aging. But in 1948, the landmark Framingham Heart Study began to examine the relationship between specific attributes and cardiovascular disease, establishing the concept of atherosclerotic risk factors. Among later studies, the Multiple Risk Factor Intervention Trial (MRFIT) screened more than 325,000 men, offering an opportunity to correlate risk factors with subsequent cardiovascular disease and mortality. Of the major risk factors, those that are not correctable include advanced age, male gender, and heredity—that is, a history of coronary heart disease among first-degree relatives at a young age (before age 55 for a male relative or before age 65 for a female relative). Risk factors for atherosclerosis amenable to modification include undesirable concentrations and composition of circulating lipids (dyslipidemia), tobacco smoking, hypertension, diabetes mellitus, and lack of physical activity and obesity (Table 5-1).

In addition to these standard predictors, certain biologic markers associated with the development of cardiovascular events have been undergoing rigorous evaluation as “novel” risk markers. These include elevated circulating levels of the special lipoprotein particle Lp(a) and certain markers of inflammation, including the acute-phase reactant C-reactive protein (CRP). Furthermore, recent genome-wide association studies (GWAS) have sought to identify variants in genetic loci associated with increased cardiovascular risk.

The following sections address these risk factors and biologic markers.

Genetics

Genetic predisposition, as reflected by family history, comprises a major risk factor for atherosclerosis. While directly causative genes remain elusive, recent GWAS have identified a number of loci associated with atherosclerotic disease. The strongest connection with CAD and myocardial infarction localizes to chromosome 9p21.3. This region contains genes that code for two cyclin-dependent kinase inhibitors that can regulate the cell cycle and may participate in TGF- β inhibitory pathways. Other associations with CAD include SORT-1 that encodes a molecule implicated in lipoprotein trafficking. Such findings promise eventually to enhance identification, prevention, and treatment of atherosclerotic disease.

Genetic studies have also shown that loss of function mutations in the gene that encodes the enzyme PCSK9 (proprotein convertase subtilisin/kexin type 9) augment LDL receptor levels on cell surfaces, boosting LDL clearance, and yielding lower LDL concentrations in blood. Individuals with loss of function variants in PCSK9, thus exposed to lower levels of LDL from childhood than those with the typical genotype, appear protected from atherosclerotic events. This observation has spurred the ongoing development of biological agents that limit PCSK9 action.

TABLE 5-1 Common Cardiovascular Risk Factors

Modifiable risk factors

- Dyslipidemia (elevated LDL, decreased HDL)
- Tobacco smoking
- Hypertension
- Diabetes mellitus, metabolic syndrome
- Lack of physical activity

Nonmodifiable risk factors

- Advanced age
- Male sex
- Heredity

Traditional Risk Factors

Dyslipidemia

A large and consistent body of evidence establishes abnormal circulating lipid levels as a major risk factor for atherosclerosis. Observational studies have shown that societies with high consumption of saturated fat and prevalent hypercholesterolemia have greater mortality from coronary disease than countries with traditionally low saturated fat intake and low serum cholesterol levels (e.g., rural Japan and certain Mediterranean nations). Similarly, data from the Framingham Heart Study and other cohorts have shown that the risk of ischemic heart disease increases with higher total serum cholesterol levels. The coronary risk is approximately twice as high for a person with a total cholesterol level of 240 mg/dL compared with a person whose cholesterol level is 200 mg/dL.

In particular, elevated levels of circulating LDL correlate with an increased incidence of atherosclerosis and coronary artery disease. When present in excess, LDL can accumulate in the subendothelial space and undergo the chemical modifications that further damage the intima, as described earlier, initiating and perpetuating the development of atherosclerotic lesions. Thus, LDL is commonly known as “bad cholesterol.” Conversely, elevated HDL particles (often called “good cholesterol”) associate with protection against atherosclerosis, often attributed to HDL’s ability to transport cholesterol away from the peripheral tissues back to the liver for disposal (termed “reverse cholesterol transport”) and its putative antioxidative and anti-inflammatory properties. Elevated serum LDL may persist for many reasons, including a high-fat diet or abnormalities in the LDL receptor clearance mechanism. Patients with genetic defects in the LDL receptor, which leads to a condition known as familial hypercholesterolemia, cannot remove LDL from the circulation efficiently. Heterozygotes with this condition have one normal and one defective gene coding for the receptor. They display high plasma LDL levels and develop premature atherosclerosis. Homozygotes who completely lack functional LDL receptors may experience vascular events, such as acute myocardial infarction, as early as the first decade of life.

Increasing evidence also implicates triglyceride-rich lipoproteins, such as VLDL and IDL, in the development of atherosclerosis. However, it remains undetermined whether these particles participate directly in the disease or simply keep company with low levels of HDL cholesterol. Of note, poorly controlled type 2 diabetes mellitus commonly associates with the combination of hypertriglyceridemia and low HDL levels.

Lipid-Altering Therapy

Strategies that improve abnormal lipid levels can limit the consequences of atherosclerosis. Many large studies of patients with coronary disease show that dietary or pharmacologic reduction of serum cholesterol can prevent cardiovascular events.

Lifestyle modifications that may be beneficial include avoidance of tobacco, maintenance of healthy diet and weight, and augmented physical activity. Yet, even intensive lifestyle modification may not be sufficient to prevent cardiovascular events in individuals with long established atherosclerotic risk factors. Hence, many individuals require pharmacologic agents to optimize cardiovascular outcomes. The major groups of lipid-altering agents (see Chapter 17) include HMG-CoA reductase inhibitors (also known as “statins”), niacin, fibric acid derivatives, cholesterol intestinal absorption inhibitors, and bile acid-binding agents. Of these, the statins have emerged as the key LDL-lowering drugs that reduce cardiovascular events in broad categories of patients. These agents inhibit the rate-limiting enzyme responsible for cholesterol biosynthesis. The resulting reduction in intracellular cholesterol concentration promotes increased LDL receptor expression and thus augments clearance of LDL particles from the bloodstream. Statins also lower the rate of VLDL synthesis by the liver (thus lowering circulating triglyceride levels) and raise HDL by an unknown mechanism.

Major clinical trials evaluating statin therapy have demonstrated reductions in ischemic cardiac events, the occurrence of ischemic strokes, and mortality rates in individuals both with and without a history of prior atherosclerotic cardiovascular events. Based on previous guideline recommendations, many clinicians use specific serum LDL targets to adjust the dose of statin therapy. However, in 2013, the American College of Cardiology and American Heart Association issued updated guidelines that advocate a different approach. Based on evidence from multiple randomized controlled clinical trials, the new recommendations focus therapy on groups of patients most likely to benefit from lipid-lowering therapy (Table 5-2) and recommends dosages of statins that were employed in such trials, rather than titrating dosages based on serum lipoprotein levels. In particular, such studies have affirmed that more intense doses of statins improve outcomes in acute and chronic coronary heart disease more than lower-dose regimens.

The clinical benefits of statins likely derive from several mechanisms. Lowering LDL can limit lipid accumulation in atherosclerotic plaques and forestall the biological consequences detailed earlier in this chapter. Other potentially beneficial actions (so-called “pleiotropic effects”) include reduced inflammation, a driver of atherosclerosis and its complications. These pleiotropic effects likely result from activation of the transcription factor KLF2 and interference with prenylation of small G proteins implicated in the regulation of inflammatory functions of vascular cells and leukocytes. Clinical trials have provided data that support an anti-inflammatory action of statins by showing reductions in plasma levels of CRP, a serum marker of inflammation described later. Such analyses cannot separate the LDL-lowering effect of statins from their anti-inflammatory mechanisms because of the prominent role of LDL in initiating inflammatory cascades. Nonetheless, accumulating clinical and experimental data suggest that at least part of the benefit of statins derives from mechanisms other than LDL lowering.

Other classes of drugs that lower LDL (e.g., niacin, fibrates, inhibitors of bile acid, or cholesterol absorption from the gut) do not share the efficacy of statins in reducing clinical events. These agents are now primarily prescribed to patients who do not tolerate statins or when LDL cholesterol reduction is not adequate on statin therapy alone.

TABLE 5-2
American College of Cardiology/American Heart Association Recommended Groups for Statin Therapy

Patient Type	Recommendation
Clinical atherosclerotic cardiovascular disease (ASCVD) already present (i.e., history of CAD, stroke, or peripheral vascular disease)	High-intensity statin ^a
LDL cholesterol ≥ 190 mg/dL	High-intensity statin ^a
Diabetics (age 40–75 with LDL 70–189 mg/dL) and 10-year cardiac risk ^c $\geq 7.5\%$	High-intensity statin ^a
10-year cardiac risk ^c $< 7.5\%$ without clinical ASCVD	Moderate-intensity statin ^b
Nondiabetics (age 40–75 with LDL 70–189 mg/dL) without clinical ASCVD but with 10-year cardiac risk ^c $\geq 7.5\%$	Moderate-to-high intensity statin ^{a,b}

^aHigh-intensity statin is intended to lower LDL cholesterol $\geq 50\%$ (e.g., atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily); for patients aged ≥ 75 , or if at risk of statin adverse effect, consider moderate-intensity statin instead.

^bModerate-intensity statin is intended to lower LDL cholesterol 30%–50% (e.g., atorvastatin 10–20 mg daily, rosuvastatin 5–10 mg daily, or simvastatin 20–40 mg daily).

^cThe 10-year ASCVD risk for fatal or nonfatal myocardial infarction or stroke can be estimated using the online calculator at <http://my.americanheart.org/cvriskcalculator>

CAD, coronary artery disease.

While elevated serum HDL appears to protect against atherosclerosis, recent clinical trials have failed to show clinical benefit of pharmacologically raising HDL in contemporary treated patients. For example, the prospective placebo-controlled AIM-HIGH and HPS2-THRIVE studies demonstrated that niacin (the most effective available agent to raise serum HDL) did not reduce cardiac event rates in patients who had already achieved desirable LDL levels on statin therapy. In addition, recent clinical studies of two experimental drugs that greatly raise HDL cholesterol (known as cholesteryl ester transfer protein [CETP] inhibitors) showed no clinical benefit. Similarly, clinical trials of drug therapies that reduce elevated triglyceride levels (i.e., using fibrates or omega-3 supplements) have not shown significant improvement in cardiovascular event rates. Such drugs are now used primarily to reduce severely elevated levels of serum triglycerides to prevent the associated complication of pancreatitis.

Tobacco Smoking

Numerous studies have shown that tobacco smoking predisposes to atherosclerosis and ischemic heart disease. Even low level smoking leads to adverse outcomes, but the heaviest smokers have the greatest risk of cardiovascular events. Tobacco smoking could promote atherosclerotic disease in several ways, including enhanced oxidative modification of LDL, decreased circulating HDL levels, endothelial dysfunction owing to tissue hypoxia and increased oxidant stress, increased platelet adhesiveness, increased expression of soluble LAMs, inappropriate stimulation of the sympathetic nervous system by nicotine, and displacement of oxygen by carbon monoxide from hemoglobin. Extrapolation from animal experiments suggests that smoking not only accelerates atherogenesis but also increases the propensity for thrombosis—both components of the “vulnerable patient.”

Fortunately, smoking cessation can reverse some of the adverse outcomes. People who stop smoking greatly reduce their likelihood of coronary heart disease, compared with those who continue to smoke. In one study, after 3 years of cessation, the risk of coronary artery disease for former smokers became similar to subjects who never smoked.

Hypertension

Elevated blood pressure (either systolic or diastolic) augments the risk of developing atherosclerosis, coronary heart disease, and stroke (see Chapter 13). The association of elevated blood pressure with cardiovascular disease does not appear to have a specific threshold. Rather, risk increases continuously with progressively higher pressure values. Systolic pressure predicts adverse outcomes more reliably than does diastolic pressure, particularly in older persons.

Hypertension may accelerate atherosclerosis in several ways. Animal studies have shown that elevated blood pressure injures vascular endothelium and may increase the permeability of the vessel wall to lipoproteins. Cyclic circumferential strain, increased in hypertensive arteries, can enhance SMC production of proteoglycans that bind and retain LDL particles, promoting their accumulation in the intima and facilitating their oxidative modification. Angiotensin II, a mediator of hypertension (described in Chapter 13), acts not only as a vasoconstrictor but also as a stimulator of oxidative stress (through activation of NADPH oxidases, a source of superoxide anion, O_2^-) and as a proinflammatory cytokine. Thus, hypertension may also promote atherogenesis by contributing to a prooxidant and inflammatory state.

Antihypertensive Therapy

Like dyslipidemias, treatment of hypertension should start with lifestyle modifications but often requires pharmacologic intervention. The Dietary Approaches to Stop Hypertension (DASH) studies demonstrate that a diet high in fruits and vegetables, with dairy products low

in fat and an overall reduced sodium content, significantly improves systolic and diastolic blood pressures. Regular exercise can also reduce resting blood pressure levels. Many medications effectively lower blood pressure, as described in Chapters 13 and 17.

Diabetes Mellitus and the “Metabolic Syndrome”

Diabetes mellitus affects an estimated 170 million people worldwide, a prevalence projected to grow 40% worldwide by 2030. In the United States alone, 18.2 million people have diabetes, and projections suggest that one in every three children born in 2000 will eventually develop the condition. With a three- to fivefold increased risk of acute coronary events, 80% of diabetic patients succumb to atherosclerosis-related conditions, including coronary heart disease, stroke, and peripheral artery disease.

The predisposition of diabetic patients to atherosclerosis may relate in part to accompanying dyslipidemia, to nonenzymatic glycation of lipoproteins (which enhances uptake of cholesterol by scavenger macrophages, as described earlier), or to the associated prothrombotic tendency and antifibrinolytic state. Diabetics frequently have impaired endothelial function, gauged by the reduced bioavailability of NO, and increased leukocyte adhesion. Tight control of serum glucose levels in diabetic patients reduces the risk of microvascular complications, such as retinopathy and nephropathy. Yet demonstration of a reduction of macrovascular outcomes, such as myocardial infarction and stroke, by glycemic control remains much more elusive. Indeed, studies have suggested that intense glucose lowering may even augment the incidence of adverse cardiovascular events. In contrast to the uncertain benefits of intense glycemic control for macrovascular events, treatment of hypertension and dyslipidemia in diabetic patients convincingly reduces the risk of cardiac and cerebrovascular complications.

The **metabolic syndrome** (also known as the “insulin resistance syndrome”) refers to a cluster of risk factors, including hypertension, hypertriglyceridemia, reduced HDL, hyperglycemia, and visceral obesity (excessive adipose tissue in the abdomen). This constellation associates with a high risk for atherosclerosis in both diabetic and nondiabetic patients, and using currently accepted criteria, 25% of Americans have this condition. The presence of insulin resistance in this syndrome appears to promote atherogenesis long before affected persons develop overt diabetes.

Lack of Physical Activity

Exercise may mitigate atherogenesis in several ways. In addition to its beneficial effects on the lipid profile and blood pressure, exercise enhances insulin sensitivity and endothelial production of NO. Observational studies of both men and women indicate that even modest activities, such as brisk walking, for as little as 30 minutes per day can protect against cardiovascular mortality.

Estrogen Status

Cardiovascular disease dominates other causes of mortality in women, including breast and other cancers. Before menopause, women have a lower incidence of coronary events than men. After menopause, however, men and women have similar rates. This observation suggests that estrogen (the levels of which decline after menopause) may have atheroprotective properties. Physiologic estrogen levels in premenopausal women raise HDL and lower LDL. Experimentally, estrogen also exhibits potentially beneficial antioxidant and antiplatelet actions and improves endothelium-dependent vasodilation.

Early observational studies suggested that hormone therapy reduced the risk of coronary artery disease in postmenopausal women, prompting many physicians to prescribe such medications for cardiovascular prevention purposes. However, the Heart and Estrogen/Progestin

Replacement Study demonstrated an association between such hormone use and an early increased risk of vascular events in women with preexisting coronary disease. Subsequent randomized primary prevention studies from the Women's Health Initiative were terminated prematurely because estrogen-plus-progestin treatment increased cardiovascular risk by 24% overall, with a striking 81% higher risk during the first year of therapy. Because currently available clinical trial data do not show that gonadal hormone therapy lowers cardiovascular events and that it may actually be harmful, such therapy should not be commenced for the sole goal of reducing cardiovascular risk.

Biomarkers of Cardiovascular Risk

Despite identification of the well-established risk factors just described, one out of five cardiovascular events occurs in patients lacking these attributes. In conjunction with growing knowledge about the pathogenesis of atherosclerosis, several novel markers of risk have emerged. These biomarkers serve three primary roles: (1) as a means to help stratify the risk of atherosclerotic disease and thus guide the choice of therapies, (2) as clinical measures to assess treatment effects, and (3) as potential targets of new therapeutic regimens.

Lipoprotein (a)

Lipoprotein (a), referred to as Lp(a) and pronounced "L-P-little-a," independently predicts cardiovascular events in some studies. Lp(a) is a variant of LDL whose major apolipoprotein (apo B-100) links by a disulfide bridge to another protein, apo(a). Apo(a) structurally resembles plasminogen, a plasma protein important in the endogenous lysis of fibrin clots (see Chapter 7). Thus, the detrimental effect attributed to Lp(a) may relate to competition with normal plasminogen activity. Lp(a) is able to enter the arterial intima, and *in vitro* studies have shown that it encourages inflammation and thrombosis.

Lp(a) levels in the population are skewed and not normally distributed, showing a trailing prevalence of the higher levels. Not all population studies support a link between Lp(a) and cardiovascular events, though people with the highest Lp(a) levels do appear to have increased risk. Recent GWAS and Mendelian randomization analyses also support a causal link between Lp(a) and cardiovascular events.

Diet and exercise have little impact on Lp(a) levels. Of current lipid-lowering agents, niacin has the greatest effect on Lp(a), lowering its concentration by as much as 20%. However, thus far, there is no evidence that reduction of Lp(a) by drug therapy improves cardiovascular outcomes.

G-Reactive Protein (CRP) and Other Markers of Inflammation

Because the pathogenesis of atherosclerosis involves inflammation at every stage, markers of inflammation have undergone evaluation as predictors of cardiac risk. Recall that the process of lipoprotein entry and modification in the vessel wall triggers the release of cytokines, followed by leukocyte infiltration, more cytokine release, and smooth muscle migration into—and proliferation within—the intima. Involved cytokines (e.g., IL-6) incite increased hepatic production of acute-phase reactants, including CRP, fibrinogen, and serum amyloid A.

Of these molecules, CRP has shown the greatest promise as a marker of low-grade systemic inflammation associated with atherosclerotic disease. Large studies of apparently healthy men and women indicate that those with higher basal CRP levels have increased risk of adverse cardiovascular outcomes, independent of serum cholesterol concentrations and other traditional risk markers. Multiple prospective studies affirm that CRP measured by a highly sensitive assay (hsCRP) independently predicts myocardial infarction, stroke, peripheral artery disease, and sudden cardiac death. Although it serves as a marker of risk not captured by traditional algorithms, CRP itself does not mediate atherogenesis.

Recent data support the use of CRP levels to potentially guide therapy. For example, the prospective JUPITER trial studied 17,800 healthy individuals with above-median levels of CRP who did not have elevated LDL and demonstrated a reduced incidence of major cardiovascular events in patients who were treated with statin therapy, compared to those who received a placebo.

Given the critical role of inflammation in atherogenesis, ongoing clinical trials are testing available and novel anti-inflammatory medications for the prevention of recurrent cardiovascular events among patients with coronary disease.

Outlook

Despite accumulating knowledge of the pathogenesis of atherosclerosis and its clinical sequelae, this disease remains a major cause of death throughout the world. Although improvements in cardiovascular care have reduced age-adjusted mortality from this condition, it will continue to grow as a menace as the population ages and as developing countries embrace the adverse dietary and activity habits of a Western lifestyle. Ongoing research of the biology of atherosclerosis, as well as advances in therapeutic procedures and medications, will undoubtedly continue to further our abilities to combat this condition. Yet we have not fully capitalized on what we already know—that much cardiovascular risk is modifiable. Effective control of the risk factors described earlier remains a critical component to tame this global scourge. It is here that the relationship between the patient and health care provider, and the role of medical professionals as community leaders advocating healthy lifestyles, remain of cardinal importance.

SUMMARY

- Atherosclerosis is the leading cause of mortality and morbidity in developed nations and has become a major cause of death in the developing world.
- The arterial wall consists of the intima (closest to the arterial lumen), the media (the middle layer), and the adventitia (the outer layer).
- The normal endothelium provides a protective, nonthrombogenic surface with homeostatic vasodilatory and anti-inflammatory properties.
- Early in atherogenesis, injurious stimuli activate endothelial and smooth muscle cells, which recruit inflammatory cells to the vessel wall.
- Atherosclerotic plaques form over decades and can display features associated with clinical stability, or a propensity to provoke thrombotic events (“vulnerable” plaques).
- Clinical atherosclerotic events result from narrowing of the vessel lumen, aneurysm formation, or plaque disruption with superimposed thrombus formation.
- Common manifestations of atherosclerosis include angina pectoris, myocardial infarction, stroke, and peripheral artery disease.
- Modifiable risk factors for atherosclerosis include dyslipidemia, smoking, hypertension, and diabetes.
- Nonmodifiable risk factors include advanced age, male sex, and a family history of premature coronary disease.
- Novel biomarkers, such as high-sensitivity C-reactive protein (hsCRP), may prove useful in defining risk.

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Additional Reading

- Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet.* 2015;385:1397–1405.
- Cook NR, Paynter NP, Eaton CB, et al. Comparison of the Framingham and Reynolds risk scores for global cardiovascular risk prediction in the multiethnic women's health initiative. *Circulation.* 2012;125:1748–1756.
- Gimbrone MA, Jr., Garcia-Cardena G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. *Cardiovasc Pathol.* 2013;22:9–15.
- Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell Metab.* 2011;14:575–585.
- Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2012;32:2045–2051.
- Libby P. Mechanisms of acute coronary syndromes. *N Engl J Med.* 2013;369:883–884.
- Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature.* 2011;473:317–325.
- Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. *Cell.* 2011;145:341–355.
- Schunkert H, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet.* 2011;43:333–338.
- Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med.* 2012;366:1108–1118.
- Steinberg D. In celebration of the 100th anniversary of the lipid hypothesis of atherosclerosis. *J Lipid Res.* 2013;54:2946–2949.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation.* 2013;129:S1–S45. DOI: 10.1161/01.cir.0000437738. 63853.7a.
- Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: A rationale for increased efforts to understand its pathophysiology and develop targeted therapies. *J Am Coll Cardiol.* 2012;60:716–721.