the intima. Lipoprotein particles in the extracellular space of the intima, particularly those retained by binding to matrix macromolecules, may undergo oxidative modifications. Considerable evidence supports a pathogenic role for products of oxidized lipoproteins in atherogenesis. Lipoproteins sequestered from (plasma) antioxidants in the extracellular space of the intima become particularly susceptible to oxidative modification, giving rise to hydroperoxides, lysophospholipids, oxysterols, and aldehydic breakdown products of fatty acids and phospholipids. Modifications of the apoprotein moieties may include breaks in the peptide backbone as well as derivatization of certain amino acid residues. Local production of hypochlorous acid by myeloperoxidase associated with inflammatory cells within the plaque yields chlorinated species such as chlorotyrosyl moieties. Considerable evidence supports the presence of such oxidation products in atherosclerotic lesions.

Leukocyte Recruitment Accumulation of leukocytes characterizes the formation of early atherosclerotic lesions (Fig. 291e-1). Thus, from its very inception, atherogenesis involves elements of inflammation, a process that now provides a unifying theme in the pathogenesis of this disease. The inflammatory cell types typically found in the evolving atheroma include monocyte-derived macrophages and dendritic cells, T and B lymphocytes, and mast cells. Hypercholesterolemia augments the portion of particularly proinflammatory monocytes in blood that preferentially enter the nascent atheroma in mice. A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell probably participate in the recruitment of leukocytes to the nascent atheroma. Proinflammatory cytokines can augment the expression of leukocyte adhesion molecules.

Laminar shear forces such as those encountered in most regions of normal arteries also can suppress the expression of leukocyte adhesion molecules. Sites of predilection for atherosclerotic lesions (e.g., distal to flow dividers) often have low shear stress and/or disturbed flow. Ordered, pulsatile laminar shear of normal blood flow augments the production of nitric oxide by endothelial cells. This molecule, in addition to its vasodilator properties, can act at the low levels constitutively produced by arterial endothelium as a local anti-inflammatory autacoid, e.g., limiting local adhesion molecule expression. Exposure of endothelial cells to laminar shear stress increases the transcription of Krüppel-like factor 2 (KLF2), which augments the activity of numerous salutary endothelial functions including nitric oxide synthase. Laminar shear stress also stimulates endothelial cells to produce superoxide dismutase, an antioxidant enzyme. These examples indicate how hemodynamic forces may influence the cellular events that underlie atherosclerotic lesion initiation and potentially explain the favored localization of atherosclerotic lesions at sites that experience disturbed flow or low shear stress.

Once captured on the surface of the arterial endothelial cell by adhesion receptors, the leukocytes penetrate the endothelial layer and take up residence in the intima. In addition to products of modified lipoproteins, cytokines (protein mediators of inflammation) can regulate the expression of adhesion molecules involved in leukocyte recruitment. For example, interleukin 1 (IL-1) and tumor necrosis factor (TNF) induce or augment the expression of leukocyte adhesion molecules on endothelial cells. Because products of lipoprotein oxidation can induce cytokine release from vascular wall cells, this pathway may provide an additional link between arterial accumulation of lipoproteins and leukocyte recruitment. Chemoattractant cytokines appear to direct the migration of leukocytes into the arterial wall.

Foam-Cell Formation Once resident within the intima, the mononuclear phagocytes mature into macrophages and become lipid-laden foam cells, a conversion that requires the uptake of lipoprotein particles by receptor-mediated endocytosis. One might suppose that the "classic" LDL receptor mediates this lipid uptake; however, humans or animals lacking effective LDL receptors due to genetic alterations (e.g., familial hypercholesterolemia) have abundant arterial lesions and extraarterial xanthomata rich in macrophage-derived foam cells. In addition, the exogenous cholesterol suppresses expression of the LDL receptor; thus, the level of this cell-surface receptor for LDL decreases under conditions of cholesterol excess. Candidates for alternative receptors that can mediate lipid loading of foam cells include a number of macrophage "scavenger" receptors, which preferentially endocytose modified lipoproteins, and other receptors for oxidized LDL or very low-density lipoprotein (VLDL). Monocyte attachment to the endothelium, migration into the intima, and maturation to form lipid-laden macrophages thus represent key steps in the formation of the fatty streak, the precursor of fully formed atherosclerotic plaques.

ATHEROMA EVOLUTION AND COMPLICATIONS

Although the fatty streak commonly precedes the development of a more advanced atherosclerotic plaque, not all fatty streaks progress to form complex atheromata. By ingesting lipids from the extracellular space, the mononuclear phagocytes bearing such scavenger receptors may remove lipoproteins from the developing lesion. Some lipid-laden macrophages may leave the artery wall, exporting lipid in the process. Lipid accumulation, and hence the propensity to form an atheroma, ensues if the amount of lipid entering the artery wall exceeds that removed by mononuclear phagocytes or other pathways. Macrophages also proliferate in plaques in response to hematopoietic growth factors overexpressed in lesions, another aspect of the dynamic regulation and flux of cells during atherogenesis.

Export by phagocytes may constitute one response to local lipid overload in the evolving lesion. Another mechanism, reverse cholesterol transport mediated by high-density lipoproteins (HDLs), probably provides an independent pathway for lipid removal from atheroma. This transfer of cholesterol from the cell to the HDL particle involves specialized cell-surface molecules such as the ATP binding cassette (ABC) transporters. *ABCA1*, the gene mutated in Tangier disease, a condition characterized by very low HDL levels, transfers cholesterol from cells to nascent HDL particles and ABCG1 to mature HDL particles. "Reverse cholesterol transport" mediated by these ABC transporters allows HDL loaded with cholesterol to deliver it to hepatocytes by binding to scavenger receptor B1 or other receptors. The liver cell can metabolize the sterol to bile acids that can be excreted. Thus, macrophages may play a vital role in the dynamic economy of lipid accumulation in the arterial wall during atherogenesis.

Some lipid-laden foam cells within the expanding intimal lesion perish. Some foam cells may die as a result of programmed cell death, or *apoptosis*. This death of mononuclear phagocytes results in the formation of the lipid-rich center, often called the *necrotic core*, in established atherosclerotic plaques. Impaired clearance of dead foam cells (efferocytosis) in plaques may hasten lipid core formation. Macrophages loaded with modified lipoproteins may elaborate microparticles or exosomes (which may contain regulatory microRNAs), cytokines, and growth factors that can further signal some of the cellular events in lesion complication. Whereas accumulation of lipid-laden macrophages characterizes the fatty streak, buildup of fibrous tissue formed by extracellular matrix typifies the more advanced atherosclerotic lesion. The smooth-muscle cell synthesizes the bulk of the extracellular matrix of the complex atherosclerotic lesion. A number of growth factors or cytokines elaborated by mononuclear phagocytes can stimulate smooth-muscle cell proliferation and production of extracellular matrix. Cytokines found in the plaque, including IL-1 and TNF, can induce local production of growth factors, including forms of platelet-derived growth factor (PDGF), fibroblast growth factors, and others, which may contribute to plaque evolution and complication. Other cytokines, notably interferon γ (IFN-γ) derived from activated T cells within lesions, can limit the synthesis of interstitial forms of collagen by smooth-muscle cells. These examples illustrate how atherogenesis involves a complex mix of mediators that in the balance determines the characteristics of particular lesions.

The accumulation of smooth-muscle cells and their elaboration of extracellular matrix probably provide a critical transition, yielding a fibrofatty lesion in place of a simple accumulation of macrophage-derived foam cells. For example, PDGF elaborated by activated platelets, macrophages, and endothelial cells can stimulate the migration of smooth-muscle cells normally resident in the tunica media into the intima. Such growth factors and cytokines produced locally can