Pathogenesis of Atherosclerosis

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Atherosclerosis is a multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fuelled by lipids. Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players in the development of this disease. The most devastating consequences of atherosclerosis, such as heart attack and stroke, are caused by superimposed thrombosis. Therefore, the vital question is not why atherosclerosis develops but rather why atherosclerosis, after years of indolent growth, suddenly becomes complicated with luminal thrombosis. If thrombosis-prone plaques could be detected and thrombosis averted, atherosclerosis would be a much more benign disease. Approximately 76% of all fatal coronary thrombi are precipitated by plaque rupture. Plaque rupture is a more frequent cause of coronary thrombosis in men (~80%) than in women (~60%). Ruptured plaques are characterized by a large lipid-rich core, a thin fibrous cap that contains few smooth muscle cells and many macrophages, angiogenesis, adventitial inflammation, and outward remodeling. Plaque rupture is the most common cause of coronary thrombosis. Ruptured plaques and, by inference, rupture-prone plaques have characteristic pathoanatomical features that might be useful for their detection in vivo by imaging. This article describes the pathogenesis of atherosclerosis, how it begets thrombosis, and the possibility to detect thrombosis-prone plaques and prevent heart attack. (J Am Coll Cardiol 2006;47:C7–12) © 2006 by the American College of Cardiology Foundation

Atherosclerosis is by far the most frequent underlying cause of coronary artery disease, carotid artery disease, and peripheral arterial disease. Atherosclerosis alone is rarely fatal; it is thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque, that precipitates the life-threatening clinical events such as acute coronary syndromes and stroke (1–3). Therefore, the vital question is not why atherosclerosis develops but rather why none or only few among many plaques within a given person apparently pass through a thrombosis-prone and dangerous phase during a lifetime (Fig. 1) (4). That is what it is all about; preventing the development of thrombosis-prone plaques and, if they already are there, finding and treating those who harbor them and are at high risk of loosing myocardium, brain, and/or life. This viewpoint describes the pathogenesis of atherosclerosis with this ambitious goal in mind.

ATHEROGENIC STIMULI

Among the many cardiovascular risk factors, elevated plasma cholesterol level is probably unique in being sufficient to drive the development of atherosclerosis, even in the absence of other known risk factors (5). If all adults had plasma cholesterol levels <150 mg/dl, symptomatic disease would be rare. The other risk factors, such as hypertension, diabetes, smoking, male gender, and possibly inflammatory markers (e.g., C reactive protein, cytokines, and so on), appear to accelerate a disease driven by atherogenic lipoproteins, the first of which being low-density lipoprotein (LDL). How they do it is uncertain, but they may either increase the atherogenicity of LDL (e.g., particle size, number, and composition) or increase the susceptibility of the arterial wall (e.g., permeability, glycation, inflammation, and so on). The importance of risk factors beyond cholesterol is clearly documented by the great disparity in the expression of clinical disease among individuals with the same cholesterol level.

PROTECTIVE FACTORS

Alcohol, exercise, and high-density lipoprotein (HDL) and its major apolipoprotein, apoA-I, confer protection against diseases caused by atherothrombosis. Among other things, HDL/apoA-I prevents the atherogenic modifications of LDL and promotes “reverse cholesterol transport,” which slows plaque progression and may induce rapid regression, documented in experimental studies and suggested by serial intravascular ultrasound examinations of patients with acute coronary syndrome (6,7).

SUSCEPTIBILITY

The limited ability to predict clinical disease based on risk factor scores indicates that our knowledge about the individual susceptibility to atherogenic stimuli is inadequate (8–10). Experimental studies indicate that inactivation of genes coding for monocyte chemotactic protein-1 (MCP-1), its receptor on monocyte/macrophages (CCR2), and macrophage colony-stimulating factor has profound impact on the development of atherosclerosis in otherwise identical mice (5). Such disease susceptibility factors remain to be identified in humans.

However, the susceptibility to atherothrombosis differs not only among individuals with similar risk factor scores (individual susceptibility) but also among different arterial
segments from the same individual (arterial susceptibility). The endothelium is very sensitive to shear stress, and local hemodynamic conditions related to branching, low and oscillating shear, and reverse flow may offer some of the explanation for the fact that the coronary arteries are much more susceptible to atherosclerosis than the internal mammary arteries (11).

CELLULAR COMPONENTS OF ATHEROSCLEROSIS

Atherosclerosis is a chronic immunoinflammatory, fibroproliferative disease of large and medium-sized arteries fuelled by lipid (5,12,13). Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players in the development of this disease.

**Endothelial cells.** In lesion-prone areas, atherosclerotic lesions begin to develop under an intact but leaky, activated, and dysfunctional endothelium. Later, endothelial cells may vanish and de-endothelialized (denuded) areas appear over advanced lesions, with or without platelets adhering to the exposed subendothelial tissue (14).

Depending on size and concentration, plasma molecules and lipoprotein particles extravasate through the leaky and defective endothelium into the subendothelial space, where potentially atherogenic lipoproteins are retained and modified (e.g., oxidized) and become cytotoxic, proinflammatory, chemotactic, and proatherogenic. The mechanisms responsible for the atherogenic modification of LDL are unknown but could include oxidation mediated by myeloperoxidase, 15-lipoxygenase, and/or nitric oxide synthase (NOS) (5). Nitric oxide is a potent oxidant produced by both endothelial cells and macrophages that appears to exert both protective and atherogenic effects, depending on its source of production. Nitric oxide produced by endothelial NOS has vasodilator function and is potentially atheroprotective. In contrast, nitric oxide produced via the much higher capacity inducible NOS in macrophages, serving antimicrobial functions based on its potent oxidative properties, is potentially proatherogenic.

The endothelium becomes activated by atherogenic and proinflammatory stimuli, and the expression of adhesion molecules, primarily vascular cell adhesion molecule-1 (VCAM-1), are up-regulated, and monocytes and T cells are recruited. Besides VCAM-1, other adhesion molecules, such as intercellular adhesion molecule-1, E selection, and P selection, probably contribute to the recruitment of bloodborne cells to the atherosclerotic lesion (12,13).

Endothelial dysfunction as assessed clinically (impaired nitric oxide-mediated vasodilation) predicts clinical events caused by atherothrombosis, and it generally is assumed that this form of endothelial dysfunction equates with endothelial activation as described previously in which atheroprotective mechanisms are lost and atherothrombosis promoted. Regarding hard clinical end points, the anti-inflammatory and antithrombotic properties of the endothelium, however, may be more important than vasodilator function (15). It is indeed thought-provoking that the mere presence of atherogenic risk factors is associated with endothelial dysfunction not only in atherosclerosis-susceptible arteries but also in arteries that are relatively resistant to atherosclerosis (e.g., the brachial artery) and even in the microcirculation. Thus, impaired endothelium-mediated vasodilation is related to atherothrombosis but not necessarily causally.

**Leukocytes.** One of the earliest cellular responses in atherogenesis is the focal recruitment of circulating monocytes and, to a lesser extent, T lymphocytes (12,13). The persistence of this cellular response seems to underlie disease progression. B lymphocytes and plasma cells are rare in the intimal plaque but may be abundantly present in adventitia next to advanced intimal disease (16). Activated mast cells may be found both in plaque and adventitia, particularly in culprit lesions causing acute ischemic events (17). Neutrophils are rare in uncomplicated atherosclerosis but have been

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**Abbreviations and Acronyms**

- HDL = high-density lipoprotein
- LDL = low-density lipoprotein
- MCP-1 = monocyte chemotactic protein-1
- NOS = nitric oxide synthase
- VCAM-1 = vascular cell adhesion molecule-1

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**Figure 1.** Plaque heterogeneity within a given patient. (A) Cross section of a coronary artery cut just distal to a bifurcation. The atherosclerotic plaque to the left (circumflex branch) is fibrotic and partly calcified, whereas the plaque to the right (marginal branch) is lipid-rich with a nonoccluding thrombus superimposed. (B) Higher magnification of the plaque-thrombus interface reveals that the fibrous cap over the lipid-rich core is extremely thin, inflamed, and ruptured with a real defect—a gap—in the cap. Both arteries contain contrast medium injected postmortem. Trichrome stain, staining collagen blue and thrombus red.
described in thrombosed coronary plaques, probably recruited as a response to plaque rupture (18).

The mere adhesion to the endothelium is, of course, not enough for blood-borne cells to arrive in the lesion, transendothelial migration also is required. As to that, one or more chemokines (chemotactic cytokines) are necessary. Experimental studies indicate that the most important atherogenic chemoattractants are oxidized LDL and MCP-1 (12). Monocyte chemotactic protein-1 is a powerful chemokine and its receptor on monocyte/macrophages (CCR2) may be up-regulated enormously during plaque development, from ~3,000/cell in the resting state to >60,000/cell when stimulated. Monocyte chemotactic protein-1 attracts potently both monocytes and T cells (but not neutrophils and B cells) and most likely plays a fundamental role in the recruitment of these cells. Endothelial cells, smooth muscle cells, and macrophages all contribute to overexpression of MCP-1 in atherosclerosis. Thus, once within the intima, monocyte-derived macrophages may recruit themselves by secreting MCP-1. Cytokines (e.g., interleukin-8) also may play a role in monocyte-macrophage trafficking (5).

Within intima, the monocytes differentiate into macrophages and internalize the atherogenic lipoproteins via so-called scavenger receptors, of which SR-A and CD36 have been demonstrated to play quantitatively significant roles in experimental atherosclerosis. The development of lipid-loaded macrophages containing massive amounts of cholesteryl esters (foam cells) is a hallmark of both early and late atherosclerotic lesions. With continuing supply of atherogenic lipoproteins, the macrophages eat until they die because, in contrast to the native LDL receptor, scavenger receptors are not down-regulated by cellular cholesterol accumulation. The death of macrophages by apoptosis and necrosis contributes to the formation of a soft and destabilizing lipid-rich core within the plaque. On the other hand, macrophages may under appropriate conditions (low LDL and high HDL) shrink by effluxing cellular cholesterol to extracellular HDL via membrane transporters, the initial step in "reverse cholesterol transport" (5–7). Aside from their scavenger function, macrophages also possess destabilizing and thrombogenic properties by expressing matrix-degrading proteolytic enzymes (e.g., matrix metalloproteinases) and tissue factor (12). Thus, these innate protective cells initially recruited to combat cytotoxic lipids, turn into devastating friendly fire during the progression of atherothrombosis.

Immune activation is ongoing in atherosclerotic lesions (13,19). Although lymphocytes are not required for the development of atherosclerosis, the immune system modulates the progression of the disease. There are a number of candidate antigens in the lesion that could be responsible for immune activation, including modified LDL, heat-shock proteins, beta-2-glycoprotein I, and microbial antigens. Of these, the most extensive data support an important role for oxidized LDL, which is abundantly present in atherosclerotic plaques, where it is recognized by T cells (13,19). The up-regulated expression of the immune mediator CD40 and its ligand CD154 by all cell types present in advanced atherosclerotic lesions promotes lesion formation in atherosclerosis-prone mice (13).

**Smooth muscle cells.** Only endothelial cells, macrophages, and a few T cells participate in the development of the early and asymptomatic foam-cell lesion, the fatty streak. In disease progression, the immunoinflammatory response is joined by a fibroproliferative response mediated by intimal smooth muscle cells. These cells are responsible for healing and repair after arterial injury. If the atherogenic stimuli persist over the course of years, as they often do, the reparative response may become so voluminous and dominating that lumen is lost, blood flow is reduced, and ischemia sets in (Fig. 2) (20). Nevertheless, smooth muscle cells and the collagen-rich matrix they produce do confer stability to plaques, protecting them against much more ominous consequences; plaque rupture and thrombosis (21).

The smooth muscle cell is the principal connective tissue-producing cell in the normal (the "soil") and diseased (atherosclerotic) intima (21). Because of the repairing and protective capabilities of smooth muscle cells, their recruitment, proliferation, and synthetic activities are considered beneficial, whereas senescence, impaired function, and/or death of these cells most likely are detrimental, suggested by the local loss of smooth muscle cells where plaques tear apart (rupture). It is unknown why smooth muscle cells are lacking at rupture sites, but apoptotic cell death could play an important role (22,23).

**SPECIAL FEATURES OF ATHEROSCLEROTIC PLAQUES**

**Lipid-rich core.** Early in atherogenesis, the atherogenic lipoproteins are cleared from the intima by the scavenging macrophages, giving rise to intracellular lipid accumulation (foam cell formation). This in-principle protective function may be overwhelmed and turned into a detrimental disease-
causing pathway when the foam cells die and leave the lipid behind as a soft, destabilizing, and rather inert necrotic (atheromatous) core within the plaque (Fig. 1).

Atherogenic lipoproteins also may be retained and accumulate within intima without first passing through foam cells (24). The lipid-rich atheromatous core is avascular, hypocellular, soft-like gruel, and totally devoid of supporting collagen. Its size is, of course, critical for the stability of a plaque.

**Cell death.** During the progression of atherosclerosis, endothelial cells, macrophages, and smooth muscle cells die by apoptosis or necrosis (the former probably prevails). Disintegration of foam cells and loss of smooth muscle cells may have detrimental consequences, leading to the formation of a destabilizing lipid-rich core and a fragile and rupture-prone fibrous cap (22). Furthermore, apoptosis contributes dramatically to the high tissue factor activity and thrombogenicity of the lipid-rich core (25). The paradoxical observation that a plaque may grow even though cell death appears to exceed cell proliferation is probably because cell death is mediated by influx (recruitment) of new cells rather than local cell division. During regression of atherosclerosis induced by cholesterol lowering in animals, inflammatory cells (macrophages) disappear, but their fate remains elusive. Many macrophages appear to die within the lesion, but others probably emigrate from regressive plaques (26).

**Calcification.** Focal calcification in atherosclerotic plaques is very common and increases with age (27). The total amount of calcification—the coronary artery calcium score—is a genuine marker of coronary plaque burden and provides prognostic information beyond that provided by traditional risk factor scoring (28). Plaque calcification is to some extent active and controlled, resembling calcification in bone, and both lipid and connective tissue may calcify. In coronary arteries, calcification is almost always caused by atherosclerosis; medial calcification (Mönckeberg’s calcinosis) is exceedingly rare. Clinical observations suggest that culprit lesions responsible for acute coronary syndromes generally are less calcified than plaques responsible for stable angina, and the pattern of plaque calcification also differs (29,30).

**Neovascularization and intraplaque hemorrhage.** Angiogenesis is frequent in advanced atherosclerosis. It is probably a marker of ongoing disease activity and may thus characterize high-risk plaques (31–34). Endothelial proliferation and sprouting usually originates from vasa vasorum in adventitia and extends through media into the base of the plaque, where neovascularization is most conspicuous. The new microvessels are fragile, leaky, and express cellular adhesion molecules (VCAM-1, intercellular adhesion molecule-1), resulting in local extravasation of plasma proteins, erythrocytes (bleeding), and inflammatory cells. Thus, angiogenesis and inflammation often coexist and could mediate rapid plaque progression (31–34). Regardless of the integrity of the plaque surface, extravasated erythrocytes are common in neovascularized areas, but there is no convincing evidence that these low-pressure bleedings may precipitate rupture of the plaque surface and/or acute luminal thrombosis (35). Neovascularization disappears with plaque regression induced by cholesterol lowering in animals.

**Vascular remodeling and luminal stenosis.** During plaque development, remodeling of the artery takes place, in which the flow-limiting potential of the intimal plaque may be attenuated (expansive remodeling) or accentuated (constrictive remodeling) by reactive changes in the underlying vessel wall. Plaques assumed to be rupture-prone (so-called inflamed thin-cap fibroatheroma) and those responsible for

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**Table 1.** Worldwide, 1,114 (76%) of 1,460 Fatal Coronary Thrombi Were Precipitated by Plaque Rupture

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yrs)*</th>
<th>n</th>
<th>Rupture</th>
<th>Study†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital, —</td>
<td>—</td>
<td>19</td>
<td>19 = 100%</td>
<td>Chapman, 1965</td>
</tr>
<tr>
<td>Hospital, —</td>
<td>—</td>
<td>17</td>
<td>17 = 100%</td>
<td>Constantinides, 1966</td>
</tr>
<tr>
<td>Hospital, AMI + SCD</td>
<td>58</td>
<td>40</td>
<td>39 = 98%</td>
<td>Friedman et al., 1966</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>62</td>
<td>88</td>
<td>71 = 81%</td>
<td>Bouch et al., 1970</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>66</td>
<td>91</td>
<td>68 = 75%</td>
<td>Sinapius, 1972</td>
</tr>
<tr>
<td>Coroner, SCD</td>
<td>53</td>
<td>20</td>
<td>19 = 95%</td>
<td>Friedman et al., 1973</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>67</td>
<td>76</td>
<td>69 = 91%</td>
<td>Hori et al., 1978</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>67</td>
<td>49</td>
<td>40 = 82%</td>
<td>Falk, 1983</td>
</tr>
<tr>
<td>Coroner, SCD</td>
<td>&lt;65</td>
<td>32</td>
<td>26 = 81%</td>
<td>Tracy et al., 1985</td>
</tr>
<tr>
<td>Medical exam, SCD</td>
<td>&lt;70</td>
<td>61</td>
<td>39 = 64%</td>
<td>El Fawal et al., 1987</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>—</td>
<td>83</td>
<td>52 = 63%</td>
<td>Yutani et al., 1987</td>
</tr>
<tr>
<td>Coroner, —</td>
<td>—</td>
<td>85</td>
<td>71 = 84%</td>
<td>Richardson et al., 1989</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>63</td>
<td>20</td>
<td>12 = 60%</td>
<td>van der Wal et al., 1994</td>
</tr>
<tr>
<td>Coroner, SCD</td>
<td>—</td>
<td>202</td>
<td>143 = 71%</td>
<td>Davies, 1997</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>69</td>
<td>291</td>
<td>218 = 75%</td>
<td>Arbusini et al., 1999</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>61</td>
<td>61</td>
<td>56 = 92%</td>
<td>Shi et al., 1999</td>
</tr>
<tr>
<td>Hospital, AMI</td>
<td>69</td>
<td>100</td>
<td>81 = 81%</td>
<td>Kojima et al., 2000</td>
</tr>
<tr>
<td>Medical exam, SCD</td>
<td>48</td>
<td>125</td>
<td>74 = 59%</td>
<td>Virmani et al., 2000</td>
</tr>
</tbody>
</table>

| Total AMI + SCD            | 1,460      | 1,114 = 76% | Worldwide |

*Mean. †For details, see Falk et al. (41).
— = not reported; AMI = acute myocardial infarction; SCD = sudden coronary death.
Table 2. Features Associated With Plaque Rupture

<table>
<thead>
<tr>
<th>Structural</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Large and soft lipid-rich core</td>
<td></td>
</tr>
<tr>
<td>Thin and collagen-poor fibrous cap</td>
<td></td>
</tr>
<tr>
<td>Cellular</td>
<td></td>
</tr>
<tr>
<td>Lack of SMCs at rupture site</td>
<td></td>
</tr>
<tr>
<td>Accumulation of MACRs at rupture site</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td></td>
</tr>
<tr>
<td>Impaired matrix synthesis (SMC-related)</td>
<td></td>
</tr>
<tr>
<td>Increased matrix breakdown (MACR-derived MMPs)</td>
<td></td>
</tr>
<tr>
<td>Remodeling</td>
<td></td>
</tr>
<tr>
<td>Expansive (outward) vascular remodeling</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Adventitial inflammation and neovascularization</td>
<td></td>
</tr>
</tbody>
</table>

MACR = macrophage; MMP = matrix metalloproteinase; SMC = smooth muscle cell.

acute coronary syndromes usually are relatively large and associated with expansive remodeling, which tends to preserve a normal lumen. In contrast, plaques responsible for stable angina usually are smaller but, nevertheless, often are associated with more severe luminal narrowing because of concomitant constrictive remodeling (36). Smoking and diabetes mellitus have been linked to constrictive remodeling but, otherwise, the reason for these different modes of remodeling is unknown. Experimental studies indicate that processes in adventitia could play a decisive role in remodeling.

Plaque rupture. The term plaque rupture is used for “A plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid-rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque” (37). This is the most common cause of coronary artery thrombosis.

Nonfatal thrombosis. Plaque rupture is not a rare event in the development of coronary atherosclerosis. It is particularly frequent and often multiple in acute coronary syndromes (38). Rupture of the plaque surface is followed by variable amounts of hemorrhage into the plaque and luminal thrombosis, causing sudden and rapid but often clinically silent progression of the lesion. It is probably the most important mechanism underlying the episodic (versus linear) progression of coronary lesions observed by serial angiography (39,40).

Fatal thrombosis. A recent extensive review of the literature revealed that plaque rupture is responsible for 76% of all fatal heart attacks caused by coronary thrombosis worldwide (Table 1) (41). The remaining 24% are caused by plaque erosion and other less well-defined mechanisms. Plaque rupture is a more frequent cause of coronary thrombosis in men (~80%) than in women (~60%). Except for gender and menopause, no particular risk factors consistently have been connected with a particular type of coronary plaque or mechanism of thrombosis.

Pathoanatomical features of ruptured plaques and, by inference, plaques assumed to be rupture-prone (vulnerable) are shown in Table 2, and potential targets for their detection by imaging are highlighted in Figure 3.

Fibrin and platelets. During atherogenesis, multiple sites of endothelial denudation and plaque rupture develop and heal. When subendothelial tissue is exposed, platelets adhere and fibrin forms. The magnitude of this thrombotic response depends on the thrombogenic stimulus; plaque rupture probably is much more thrombogenic than plaque erosion. In the pathogenesis of arterial thrombosis, platelet aggregation is responsible for the initial flow obstruction but fibrin formation is necessary for the subsequent stabilization of the platelet-rich thrombus. Thus, both platelets and fibrin may accumulate over ruptured and eroded plaques.

Contribution of bone marrow-derived cells. Bone marrow-derived macrophages play a critical role in the initiation and progression of atherosclerosis. However, conventional wisdom says that endothelial cells and intimal smooth muscle cells reside within the arterial wall and proliferate, migrate, and secrete what might be needed for expedient healing and repair after injury (21). Therefore, it came as an incredible
surprise when experimental studies suggested that many of the healing smooth muscle cells originated in the bone marrow and were brought to the injured vessel wall with the circulating blood (42). Supportive human observations also have been published, and the challenge is to use this potential in the retardation and stabilization of atherosclerosis in humans (43,44). Mobilization of atheroprotective cells from the bone marrow and promoting their homing to thrombosis-prone plaques may be a new way to stabilize atherosclerosis against thrombosis and its devastating consequences.

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REFERENCES