MECHANISMS OF DISEASE

Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy

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ATHEROSCLEROTIC LESIONS IN HUMANS TYPICALLY FORM OVER THE course of years to decades, one of the longest incubation periods among human diseases. Despite the chronicity of atherosclerosis, thrombotic complications — the most dreaded clinical consequences of this disease — occur suddenly, and often without warning. Our familiarity with the disease has generally led us to accept this apparent paradox without wonder. What mechanisms explain the abrupt transition from stable ischemic heart disease or asymptomatic atherosclerosis to acute coronary syndromes? This review examines our current understanding of the mechanisms underlying these syndromes. According to the traditional view, progressive stenosis narrows the lumen of an atherosclerotic coronary artery to such an extent that a small platelet thrombus could occlude the vessel completely. Thus, an occlusive thrombus complicating a high-grade stenosis would arrest flow and cause ST-segment elevation myocardial infarction. Acute coronary syndromes without ST-segment elevation would result from an incomplete or transient obstruction of flow in the culprit coronary artery at a site of critical stenosis.

These concepts have governed our traditional approaches to atherosclerosis therapy. Our diagnostic tools generally evaluate the ischemia that results from established, fixed stenosis (e.g., stress testing and perfusion scanning) or visualize the stenosis itself by means of arteriography. Our treatments have targeted the stenosis with the use of percutaneous intervention or bypass surgery.

PATHOGENESIS OF ACUTE CORONARY SYNDROMES

Findings from clinical and pathological studies have challenged these commonly held notions of the pathophysiological features of coronary atherosclerosis and its treatment.[1-4] Surprisingly, serial angiographic studies have revealed that the plaque at the site of the culprit lesion of a future acute myocardial infarction often does not cause stenosis that, as seen on the antecedent angiogram, is sufficiently severe to limit flow. Angiographic monitoring of responses to thrombolytic therapy has shown that after lysis of the offending thrombus, the underlying stenosis is often not the cause of the critical stenosis of the artery. In a prospective angiographic study involving patients undergoing percutaneous intervention for coronary artery disease, only half the subsequent events arose from lesions with sufficient stenosis to have warranted intervention at the time of revascularization.[5] Computed tomographic (CT) angiography, which permits evaluation of the arterial wall (not just the lumen), has shown that the characteristics of plaque associated with acute coronary syndromes include low attenuation (i.e., little or no calcification) and outward expansion of the artery wall, a process that tends to accommodate the growth of plaque while minimizing luminal encroachment.[6-8] Intravascular ultrasonography has shown that in acute coronary syndromes, the culprits often lie proximal to the sites of maximal stenosis — the traditional targets of revascularization therapies.[9]

This dissociation between the degree of stenosis and the propensity to provoke an acute coronary syndrome helps to explain why myocardial infarction often occurs without being heralded by the demand-induced symptoms of angina that would result from a high-grade stenosis.

Technologies that permit cross-sectional imaging of the coronary arteries, such as intravascular ultrasonography or CT angiography, underscore the pathological observation that the outward expansion of atherosclerotic arteries accommodates the growth of plaque for much of its life history.[2] Luminal stenosis occurs relatively late in the process of atherogenesis, when plaque growth outstrips the ability of the artery to compensate by expanding outward.[10,11] These findings support the distinction between the degree of stenosis and the size of a plaque. Compensatory enlargement (outward expansion) of the artery during plaque growth can conceal a considerable burden of atheroma by preventing stenosis and thereby obscuring signs and symptoms of ischemia. Sizable plaques can reside in the walls of affected arteries without being detected on arteriograms and without issuing any warning to the patient or physician.

Clinical data acquired during the current era of medical management of atherosclerosis have affirmed that invasive procedures for the treatment of stenoses generally do not prevent future thrombotic events more effectively than noninvasive treatments. The Occluded Artery Trial concluded that restoring coronary flow in the subacute phase of an acute coronary syndrome did not improve outcomes.[12] Similarly, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed overall that medical therapy provided as much protection from future acute coronary syndromes as did mechanical revascularization.[13] This assemblage of clinical data challenges the traditional view of the pathogenesis of acute coronary syndromes, which ascribes a leading role to critically stenotic lesions.

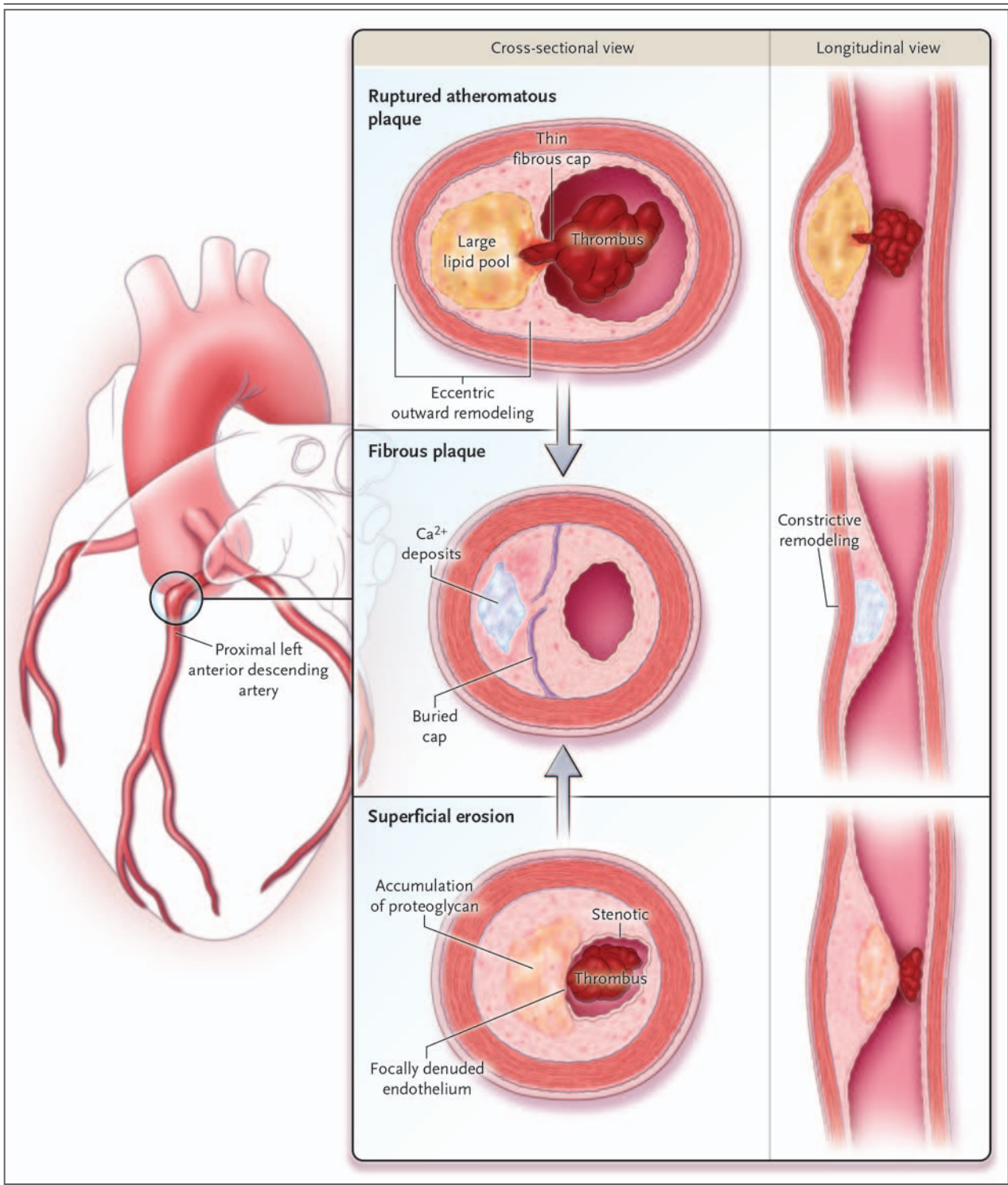### THROMBOTIC COMPLICATIONS OF ATHEROSCLEROSIS

If the progression of luminal stenosis to a critical narrowing does not cause many acute coronary syndromes, what mechanism produces these dramatic and sudden manifestations of chronic atherosclerosis? The long-standing focus on stenosis has diverted attention from autopsy studies conducted by generations of pathologists that have ascribed most fatal coronary events to a physical disruption of coronary arterial plaques (Fig. 1). Frank rupture of the plaque's fibrous cap causes the majority of these deaths; superficial erosion of a coronary artery accounts for most of the balance of fatal events. Autopsy studies have shown that erosion through the intima of a calcified nodule and intraplaque hemorrhage each trigger only a small percentage of acute coronary syndromes.[2,14]

Much of the work addressing the mechanisms of coronary thrombosis has focused on plaque rupture, the most common cause of fatal acute coronary syndromes. A fibrous cap typically overlies the lipid-rich center — also known as the necrotic core — of an atheromatous plaque (Fig. 1). This fibrous cap stands between the blood compartment, with its latent coagulation factors, and the lipid core, a portion of the plaque filled with thrombogenic material. Quantitative morphometric studies have identified the characteristics of plaques that have ruptured and caused a fatal myocardial infarction. Such plaques often, but not always, have thin fibrous caps (50 to 65 μm thick).[2,15] Ruptured plaques also tend to have large lipid cores and abundant inflammatory cells, as well as punctate or spotty calcification.[7,16] In a recent autopsy study,[17] a fibrous-cap thickness of less than 55 μm was identified as the best morphologic indicator of plaques that had caused fatal ruptures. More than 30% of these plaques were associated with a luminal stenosis of less than 75%, even when studied post mortem at pressures below physiological levels. Typically, the sites where plaques rupture and provoke fatal coronary events have few smooth-muscle cells.[18]

INFLAMMATION, COLLAGEN METABOLISM, AND PLAQUE RUPTURE AND THROMBOSIS

Extensive research has focused on the fibrous cap of the plaque because of its importance in the majority of fatal acute myocardial infarctions. This structure, which protects the plaque from rupture, owes its tensile strength to interstitial forms of collagen synthesized primarily by arterial smooth-muscle cells. The association between thinning of the fibrous cap and fatal plaque rupture led to the hypothesis that a defect in plaque collagen metabolism contributes to the

| Cross-sectional view | Longitudinal view |

Ruptured atheromatous plaque

Thin fibrous cap

Large lipid pool

Thrombus

Eccentric outward remodeling

Fibrous plaque

Ca²⁺ deposits

Constrictive remodeling

Buried cap

Superficial erosion

Accumulation of proteoglycan

Stenotic

Thrombus

Focally denuded endothelium

Proximal left anterior descending artery

depletion of this extracellular matrix protein, which has a critical role in strengthening the fibrous cap.[1] These considerations have engendered much interest in molecular mediators of collagen metabolism that may operate during atherogenesis. Since inflammatory cells accumulate at the site of ruptured plaques, and since biomarkers of inflammation predict acute coronary

Figure 1 (facing page). Characteristics of Atherosclerotic Plaques Associated with Various Presentations of Coronary Artery Disease.

Characteristic morphologic features of coronary atherosclerotic plaques are depicted in association with three clinical presentations. The anterior surface of the heart (left) shows a representative atherosclerotic plaque at a typical location in the proximal left anterior descending coronary artery. The cross-sectional and longitudinal views of the artery depict details of the lesion types, shown at the level of the plaque. The pair of images at the top shows an eccentric, positively remodeled atheromatous plaque with a thin fibrous cap that has ruptured and provoked the formation of a thrombus. The healing of such disrupted atheromatous plaques can promote evolution to a more fibrous plaque (shown in the middle pair of images). Such a stenotic, fibrous plaque can cause stable ischemic syndromes (e.g., demand angina pectoris) as a result of narrowing of the arterial lumen. In this situation, plaques can contain strata that show "buried caps," which result from a prior disruption of the fibrous cap that provoked the formation of thrombus, followed by healing, fibrosis, and often constrictive (inward) remodeling. This process can promote the progression of a nonocclusive, atheromatous, lipid-rich plaque to a stenotic, more fibrous, calcified plaque. The bottom pair of images shows a proteoglycan-rich plaque that has caused an occlusive thrombus as a result of superficial erosion of the intimal surface.

syndromes, studies (discussed below) have focused on the hypothesis that macrophages — and the mediators that they produce and that regulate their function — disrupt the collagen in the plaque in a manner that may jeopardize the integrity of the fibrous cap, thus precipitating an acute coronary syndrome.

A study of the control of collagen biosynthesis by human vascular smooth-muscle cells in culture revealed that exposure to interferon-γ, a product of activated T cells, strongly inhibited the ability of smooth-muscle cells to make the new collagen required to repair and maintain the integrity of the fibrous cap.[19] Even in smooth-muscle cells maximally stimulated with transforming growth factor β to produce interstitial collagen, interferon-γ reduced collagen synthesis to baseline levels or lower. Another study showed an inverse correlation between T-cell accumulation in human atherosclerotic plaques and the messenger RNA that encodes the precursor of interstitial collagen, an observation that supports the relevance in vivo of the profound inhibition of new collagen synthesis by a T-cell–derived mediator.[20]

The level of any macromolecule depends not only on its rate of synthesis but also on the rate at which it breaks down. Interstitial collagen is usually very stable and resists degradation by most proteolytic enzymes. Only a handful of human proteinases have interstitial collagenase activity capable of catalyzing the initial attack on fibrillar collagen. These enzymes belong to the matrix-metalloproteinase (MMP) family. The macrophage, a cell type that abounds in lesions that have caused fatal thrombi, overproduces all three human MMP interstitial collagenases — MMP-1, MMP-8, and MMP-13 — in plaques.[21-25] Moreover, plaques with features similar to those that have caused thrombotic complications display biochemical signatures of collagen cleavage in situ in macrophage-rich regions.[24] Studies of the regulation of MMP production by human macrophages have shown that the T-cell–derived cytokine CD40 ligand (CD154) boosts the production of interstitial collagenase by human macrophages.[26] Thus, cross-talk between adaptive immune cells (T cells) and the more numerous innate immune effector cells (macrophages) inhibits the synthesis and augments the degradation of interstitial collagen. These observations in human tissues and in isolated human cells provide a cellular and molecular mechanism linking inflammation to the thinning and weakening of the fibrous cap, which can precipitate plaque rupture, thrombosis, and acute coronary syndromes. Recent experiments show that the systemic inflammatory reaction to acute myocardial infarction can aggravate inflammation in the plaque, including increased protease activity.[27] This finding helps explain why recurrent thrombotic events tend to cluster in the aftermath of an acute coronary syndrome and often involve lesions not deemed responsible for the initial presentation.[5] It also clarifies why immediate revascularization, by limiting myocardial injury and consequent systemic inflammation, may reduce the risk of recurrent events, whereas revascularization after completion of an infarct does not generally confer such a benefit.

Another recently recognized regulator of plaque proteinase expression, local endothelial shear stress, also has clinical relevance to the formation of lesions prone to rupture. In pigs, regions of the coronary vasculature with low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps and exhibit enhanced expression of matrix-degrading proteinases, in-

Table 1. Interventions That Increase Collagen Content of Atherosclerotic Lesions in Studies in Animals.*

Intervention	Species	Source of Data
Reduction of dietary lipids	Rabbit	Aikawa et al.[31]
Treatment with statins	Rabbit	Fukumoto et al.[32]
Introduction of a mutation that renders resistance to collagenase	Mouse	Fukumoto et al.[33]
Induction of MMP-13 deficiency	Mouse	Deguchi et al.[34]
Induction of MMP-14 deficiency	Mouse	Schneider et al.[35]
Treatment with MMP-13 inhibitor	Mouse	Quillard et al.[36]

* MMP denotes matrix metalloproteinase.

cluding interstitial collagenases.[28,29] In humans, regions of low shear stress in coronary arteries are more likely to cause acute coronary events than regions of high shear stress.[30]

Despite their appeal, the initial data that supported the contribution of proteinases to the pathogenesis of acute coronary syndromes depended primarily on association, and evidence that altered collagen metabolism determines the collagen content of the fibrous cap remained speculative. Insights furnished by the study of experimental preparations that permit gain-of-function and loss-of-function manipulation now support a causal role for altered collagen metabolism in the collagen content of plaque (Table 1). In mice with a genetic susceptibility to diet-induced atherosclerosis, further mutation of a gene that encodes the precursor of interstitial collagen, rendering it resistant to MMP collagenases, yielded an accumulation of collagen in the plaque.[33] In other experiments, genetic inactivation of collagenolytic enzymes or their activators increased the collagen content of plaque.[34,35] Although such germline manipulations permit exquisite selectivity, the congenital absence of an enzyme could confound the interpretation of the results owing to the possibility of compensatory changes in other pathways. Moreover, the genetic approach does not permit analysis of the influence of collagenolysis on aspects of plaque structure that relate to rupture in lesions that have already formed. A recent study has therefore used pharmacologic inhibition of interstitial collagenase to test this hypothesis. Indeed, oral administration of a selective inhibitor of a principal interstitial collagenase, MMP-13, in mice yielded an increase in the collagen content

of the fibrous cap in established atherosclerotic plaques.[36]

The combined studies of plaque in humans and animals support the concepts formulated in the early 1990s.[1] Decreased synthesis and increased breakdown of collagen, controlled by inflammatory signals, reduce the content of this critical extracellular matrix macromolecule in plaques. The resultant friable fibrous cap may render plaques susceptible to rupture and thrombosis (Fig. 2). Yet, a weakened fibrous cap alone does not suffice to precipitate plaque rupture, and not all plaques that rupture have thin fibrous caps.[37] Additional contributors to the triggering of plaque rupture may include coronary vasospasm and punctate calcifications. Recent computational analyses indicate that microcalcifications within the atherosclerotic intima can result in a striking increase in circumferential stress and could thus contribute to plaque rupture.[16]

When the fibrous cap ruptures, allowing blood to come into contact with thrombogenic material in the plaque's lipid core, thrombosis can ensue. When a plaque is disrupted, tissue factor, a potent procoagulant produced by macrophages in the plaque's core, triggers thrombin generation and platelet activation and aggregation.[38,39] The same proinflammatory signal that augments collagenase production — CD154 — also induces the expression of tissue factor in human mononuclear phagocytes (Fig. 2).[26] Thus, inflammatory cells and mediators not only regulate collagen synthesis and breakdown but also increase the thrombogenic potential of the atherosclerotic plaque. These dual actions explain the strong links between inflammation and the thrombotic complications of atherosclerosis.[40]

SUPERFICIAL EROSION OF PLAQUES

Superficial erosion of coronary atheromata causes approximately 20 to 25% of cases of fatal acute myocardial infarctions.[2] Observations made with the use of optical coherence tomography support the relevance of findings in autopsy studies to clinical acute coronary syndromes.[41-44] This anatomical substrate for coronary thrombosis occurs more frequently in women than in men and in persons with certain risk factors, such as hypertriglyceridemia. Many lesions that cause coronary thrombosis because of superficial erosion lack prominent inflammatory infiltrates; such plaques exhibit proteoglycan accumulation (Fig. 1).
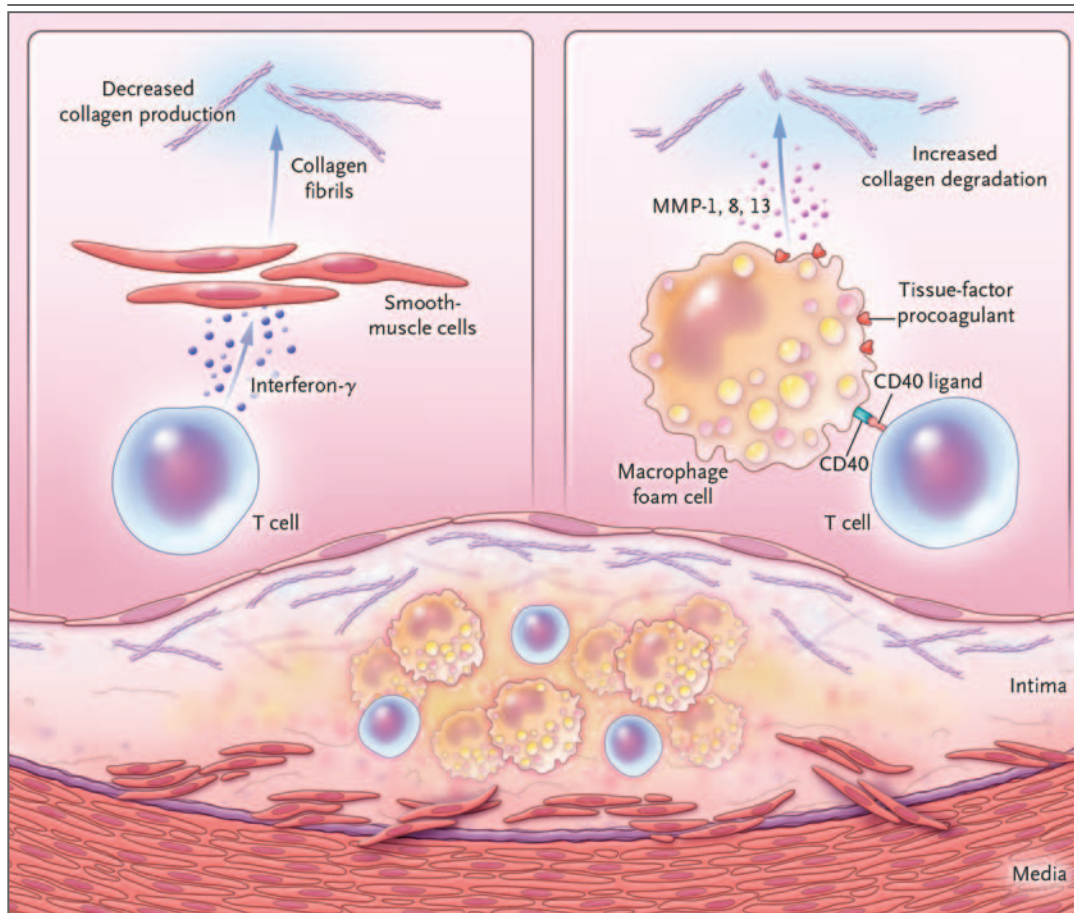
Figure 2. Inflammatory Pathways Predisposing Coronary Arteries to Rupture and Thrombosis.

A cross-section of an atheromatous plaque at the bottom of the figure shows the central lipid core that contains macrophage foam cells (yellow) and T cells (blue). The intima and media also contain arterial smooth-muscle cells (red), which are the source of arterial collagen (depicted as triple helical coiled structures). Activated T cells (of the type-1 helper T-cell subtype) secrete cytokine interferon-γ, which inhibits the production of the new, interstitial collagen that is required to repair and maintain the plaque's protective fibrous cap (upper left). The T cells can also activate the macrophages in the intimal lesion by expressing CD40 ligand (CD154), which engages its cognate receptor (CD40) on the phagocyte. This inflammatory signaling causes overproduction of interstitial collagenases (matrix metalloproteinases [MMPs] 1, 8, and 13) that catalyze the initial rate-limiting step in collagen breakdown (top right). CD40 ligation also causes macrophages to overproduce tissue-factor procoagulant. Thus, inflammatory signaling puts the collagen in the plaque's fibrous cap in double jeopardy — decreasing synthesis and increasing breakdown — rendering the cap susceptible to rupture. Inflammatory activation also boosts tissue-factor production, which triggers thrombus formation in the disrupted plaque. These are the mechanisms through which inflammation in the plaque can precipitate the thrombotic complications of atherosclerosis, including acute coronary syndromes.

The mechanisms of superficial erosion have received much less attention than those involved in the rupture of the fibrous cap. The programmed cell death (i.e., apoptosis) of endothelial cells could contribute to their desquamation.[45] Oxidative stress can promote endothelial apoptosis. In particular, hypochlorous acid — the product of myeloperoxidase, an enzyme released by activated leukocytes associated with atheromata — can initiate apoptosis of endothelial cells.[46] As these cells undergo apoptosis, they produce the procoagulant tissue factor. The oxidant hypochlorous acid may thus initiate or propagate endothelial cell loss and local thrombosis in coronary arteries. Endothelial cells can also express proteinases that may sever their tethers to the underlying base-

Table 2. Favorable Effects of Lipid Lowering in Experimentally Produced Atherosclerotic Plaques.

Reduces inflammation (lowers levels of macrophages, cytokines, and chemokines and expression of leukocyte adhesion molecules)

Reduces expression of interstitial collagenase (MMP-1)

Increases levels of interstitial collagen

Lowers levels of oxidized low-density lipoprotein

Reduces production of reactive oxygen species

Increases expression of endothelial nitric oxide synthase

Reduces thrombotic potential (reduced tissue factor content and activity)

Increases fibrinolytic potential (reduced level of plasminogen activator inhibitor-1)

ment membrane.[45] Modified low-density lipoprotein (LDL), for example, can induce the expression of the enzyme MMP-14 by human endothelial cells.[47] MMP-14 can activate MMP-2, an enzyme that degrades basement-membrane forms of nonfibrillar collagen (type IV). The mechanisms of superficial erosion merit attention in future investigations; they are much less well understood than the mechanisms underlying the fracture of the plaque's fibrous cap.

THERAPEUTIC IMPLICATIONS OF NEW MECHANISTIC INSIGHTS

Although revascularization procedures that target occlusive coronary stenosis relieve anginal symptoms, they have not consistently reduced the risk of an acute coronary syndrome or death from coronary artery disease. In stark contrast, contemporary medical therapy — notably, statin treatment — has prevented both first and recurrent acute coronary syndromes in broad categories of patients. Curiously, even though these medical interventions reduce events, they have little effect on the degree of stenosis as assessed on angiography and result in only modest reductions in atheroma volume as assessed on intravascular ultrasonography.[48] Can the new insights into the mechanisms of acute coronary syndromes, described above, illuminate these clinical findings and explain how medical treatment reduces the thrombotic complications of atherosclerosis?

Event reduction that is out of proportion to the shrinkage of stenoses has led to the hypothesis that lipid lowering alters qualitative characteristics of atheromata — that such treatment causes modest quantitative improvement in lumen

caliber but may qualitatively limit the propensity of plaques to rupture and their thrombogenicity. These changes in the biologic features of plaque are now considered to confer "stabilization," a feature that distinguishes lipid-lowering interventions from those that address luminal stenosis without altering the molecular and cellular processes inculpated in the triggering of thrombotic complications.[49] A comprehensive series of studies in rabbits and mice tested this hypothesis. One series of investigations in rabbits with experimentally induced atherosclerosis lowered lipid levels by means of diet alone, a "lifestyle" intervention. A combination of arterial injury and an atherogenic diet provoked the development of fibrofatty aortic plaques in rabbits. After a period of lesion generation, the rabbits were switched to a low-fat, low-cholesterol diet or were kept on a diet that maintained dyslipidemia. The lipid-lowering diet reduced the content of inflammatory cells, augmented interstitial collagen accumulation, and reduced tissue factor antigen and activity in concert with other effects that contrast with the features of human plaques prone to rupture and thrombosis (Table 2).[31,50]

Other studies showed that statin treatment caused similar reductions in inflammatory-cell content and collagenase levels and augmented collagen accumulation in atheromata of Watanabe heritable hyperlipidemic rabbits.[32,51] Because rabbits of this strain — characterized by mutated LDL receptors — have only modestly reduced LDL cholesterol levels when treated with statins, these studies indicate that statins have a stabilizing effect on plaques that extends beyond their lipid-lowering action.[52]

Observations in humans support the concept, established in animals, that lipid lowering can increase the fibrous nature of plaques — a change that should confer resistance to rupture. Imaging studies suggest that plaques have a more fibrous character in patients receiving treatment with statins than in those not receiving such treatment.[53-56] Statin therapy is also associated with reduced lipid content and indexes of macrophage activity and more fibrous atheromata as assessed on magnetic resonance imaging in both rabbits and humans.[57-59] These studies in humans affirm the clinical relevance of the studies in animals described above and the classic observations of Armstrong and colleagues regarding the "regression" of atheroscle-

rotic lesions in nonhuman primates after dietary restriction of lipids.[60]

Despite the remarkable benefits of statin therapy, patients appropriately treated with this class of agents are still at considerable risk for acute coronary syndromes[61] — hence the need to make further inroads against this residual burden of disease. The advent of novel strategies for lowering LDL cholesterol levels below those achievable with statins alone (e.g., inhibition of serum proprotein convertase subtilisin/kexin 9 [PCSK9]) provides considerable promise in this regard.[62,63] Therapies that target other aspects of the lipid profile have proved disappointing when put to the test, despite extensive preclinical and clinical biomarker data. Clinical trials of interventions that address levels of high-density lipoprotein (HDL) cholesterol have shown no benefit (e.g., the cholesteryl ester transfer protein [CETP] inhibitors tested thus far, and niacin).[64-67] Similarly, recent large-scale trials of fibrates, agents that substantially lower triglyceride levels and modestly raise HDL cholesterol levels, in patients with type 2 diabetes mellitus have not shown a reduction in cardiovascular events.[68,69]

Given the role of inflammation in the pathophysiological aspects of plaque rupture, several studies are assessing the use of antiinflammatory therapies other than statins to reduce the risk of a recurrent acute coronary syndrome. A recent clinical trial of low-dose colchicine (0.5 mg per day) in patients with stable ischemic heart disease has shown a reduced incidence of acute coronary syndromes.[70] This trial was relatively small (532 patients, with a total of 55 events), and the investigators did not use a double-blind design and did not report levels of inflammatory biomarkers, which might have provided a glimpse into the possible mechanisms underlying the ef-fects of colchicine. Nevertheless, these encouraging results should prompt a larger-scale, double-blind trial of this inexpensive agent, which has a long history of clinical use and a well-known and acceptable risk profile. Two large clinical trials are testing the use of darapladib, a small molecular inhibitor of a lipoprotein-associated phospholipase, to reduce clinical events.[71,72] Although this intervention has the potential for antiinflammatory actions, in a phase 2 trial it did not reduce levels of C-reactive protein but did limit lipid core size, a characteristic that may render plaques susceptible to rupture.[73] Other interventions under investigation include antibody neutralization of the proinflammatory cytokine interleukin-1β or the use of low-dose methotrexate on a weekly basis, treatments currently used successfully for other inflammatory conditions.[74,75]

SUMMARY

Our understanding of the pathogenesis of acute coronary syndromes has undergone a veritable revolution in the past 20 years. We now understand in molecular and cellular terms how most serious thrombotic complications of coronary atherosclerosis occur. In particular, inflammatory pathways have emerged as important drivers of plaque disruption and thrombosis. This insight into the pathophysiological features of acute coronary syndromes expands the scope of treatment of this disease beyond the traditional focus on reducing stenoses. The laboratory and clinical data summarized here should help us both to understand how contemporary therapies can reduce the risk of these events and to make further inroads against the residual burden of disease in the future.

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