REVIEW ARTICLE

MECHANISMS OF DISEASE

Inflammation, Atherosclerosis, and Coronary Artery Disease

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RECENT RESEARCH HAS SHOWN THAT INFLAMMATION PLAYS A KEY ROLE in coronary artery disease (CAD) and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. This review highlights the role of inflammation in the pathogenesis of atherosclerotic CAD. It will recount the evidence that atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree.

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A decade ago, the treatment of hypercholesterolemia and hypertension was expected to eliminate CAD by the end of the 20th century. Lately, however, that optimistic prediction has needed revision. Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and eastern Europe and the rising incidence of obesity and diabetes in the Western world.[1] Cardiovascular diseases cause 38 percent of all deaths in North America and are the most common cause of death in European men under 65 years of age and the second most common cause in women. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.

MAIN FEATURES OF ATHEROSCLEROTIC LESIONS

Atherosclerotic lesions (atheromata) are asymmetric focal thickenings of the innermost layer of the artery, the intima (Fig. 1). They consist of cells, connective-tissue elements, lipids, and debris.[2] Blood-borne inflammatory and immune cells constitute an important part of an atheroma, the remainder being vascular endothelial and smooth-muscle cells. The atheroma is preceded by a fatty streak, an accumulation of lipid-laden cells beneath the endothelium.[3] Most of these cells in the fatty streak are macrophages, together with some T cells. Fatty streaks are prevalent in young people, never cause symptoms, and may progress to atheromata or eventually disappear.

In the center of an atheroma, foam cells and extracellular lipid droplets form a core region, which is surrounded by a cap of smooth-muscle cells and a collagen-rich matrix. T cells, macrophages, and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows.[2,4,5] Many of the immune cells exhibit signs of activation and produce inflammatory cytokines.[5-8]

Myocardial infarction occurs when the atheromatous process prevents blood flow through the coronary artery. It was previously thought that progressive luminal narrowing from continued growth of smooth-muscle cells in the plaque was the main cause of infarction. Angiographic studies have, however, identified culprit lesions that do not cause marked stenosis,[9] and it is now evident that the activation of plaque rather

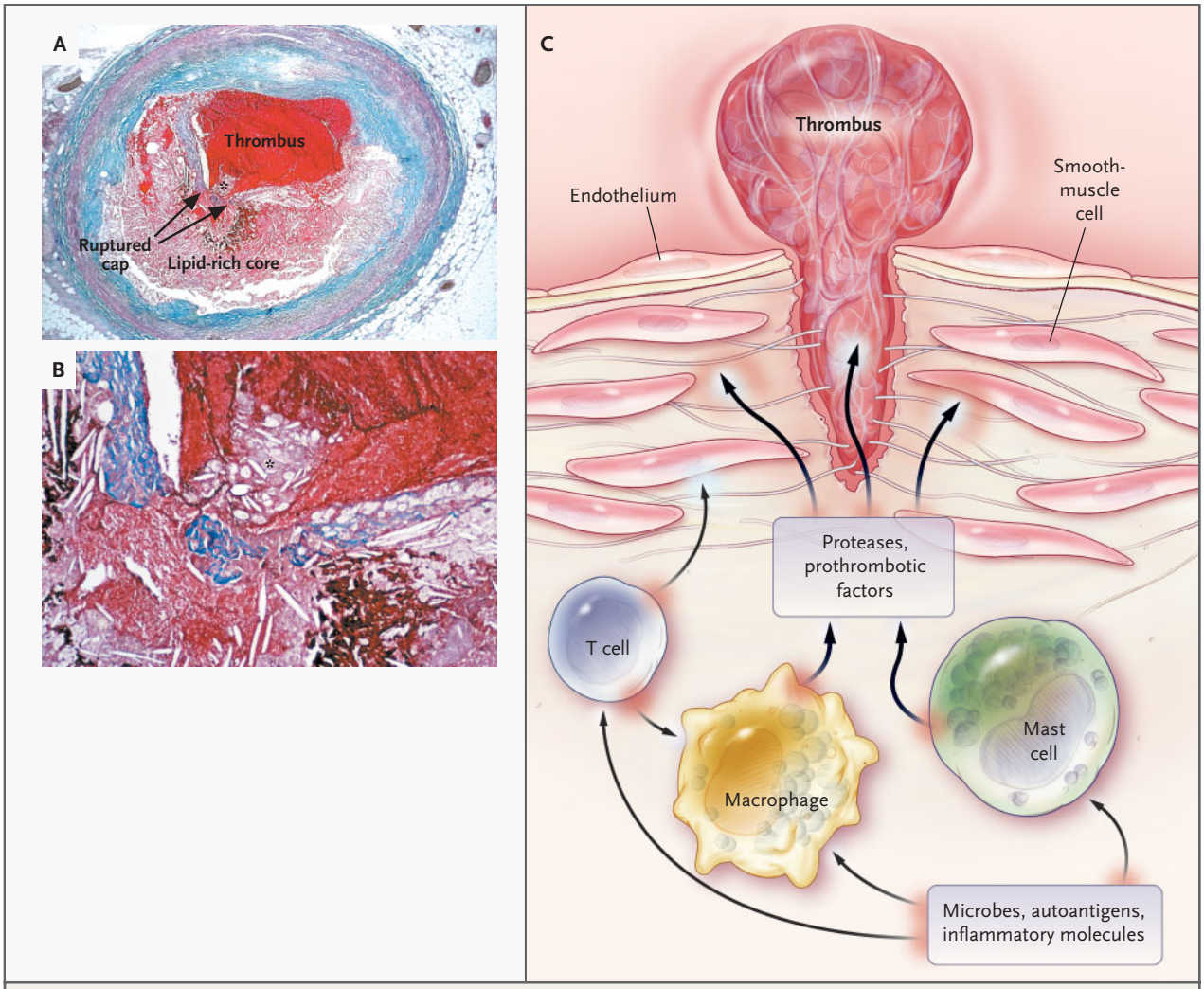

Figure 1. Atherosclerotic Lesion in a Human Artery.

Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus superimposed on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood. Trichrome stain was used, rendering luminal thrombus and intraplaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in Panel A indicated by the asterisk and shows that the contents of the atheromatous plaque have seeped through the gap in the cap into the lumen, suggesting that plaque rupture preceded thrombosis (the asterisk indicates cholesterol crystals). (Panels A and B courtesy of Dr. Erling Falk, University of Aarhus, Aarhus, Denmark.) Panel C illustrates the consequences of the activation of immune cells in a coronary plaque. Microbes, autoantigens, and various inflammatory molecules can activate T cells, macrophages, and mast cells, leading to the secretion of inflammatory cytokines (e.g., interferon-γ and tumor necrosis factor) that reduce the stability of plaque. The activation of macrophages and mast cells also causes the release of metalloproteinases and cysteine proteases, which directly attack collagen and other components of the tissue matrix. These cells may also produce prothrombotic and procoagulant factors that directly precipitate the formation of thrombus at the site of plaque rupture.

than stenosis precipitates ischemia and infarction (Fig. 1). Coronary spasm may be involved to some extent, but most cases of infarction are due to the formation of an occluding thrombus on the surface of the plaque.[10]

There are two major causes of coronary thrombosis: plaque rupture and endothelial erosion. Plaque rupture, which is detectable in 60 to 70 percent of cases,[11] is dangerous because it exposes prothrombotic material from the core of the plaque — phospholipids, tissue factor, and platelet-adhesive matrix molecules — to the blood (Fig. 1). Ruptures

preferentially occur where the fibrous cap is thin and partly destroyed. At these sites, activated immune cells are abundant.[7] They produce numerous inflammatory molecules and proteolytic enzymes that can weaken the cap and activate cells in the core, transforming the stable plaque into a vulnerable, unstable structure that can rupture, induce a thrombus, and elicit an acute coronary syndrome (Fig. 1). To understand how this can happen, we need to identify the key steps leading from a normal artery wall to a rupture-prone atherosclerotic plaque.

EVOLUTION OF THE RUPTURE-PRONE ATHEROSCLEROTIC PLAQUE

GENE-TARGETED MOUSE MODELS

Clinical investigations, population studies, and cell-culture experiments have provided important clues to the pathogenesis of atherosclerosis. However, experiments in animals are needed to dissect the pathogenetic steps and determine causality.[12] Atherosclerosis does not develop in laboratory mice under normal conditions. However, targeted deletion of the gene for apolipoprotein E (*apoE*-knockout mice) leads to severe hypercholesterolemia and spontaneous atherosclerosis. Atherosclerosis also develops in mice lacking low-density lipoprotein (LDL) receptors, especially when the mice are fed a fatty diet. One can use these knockout mice to study the relationship between hypercholesterolemia and atherosclerosis and to assess the effects of other genes and gene products on these conditions. By mating these mice with knockout mice lacking immunoregulatory genes, it is possible to clarify the role of immunologic and inflammatory mechanisms in atherosclerosis. Obviously, the findings in such models must be corroborated, as much as possible, by studies of human cells and tissues. Our current understanding of atherosclerosis therefore rests on a combination of research in animals and cell cultures, analysis of human lesions, clinical investigations of patients with acute coronary syndromes, and epidemiologic studies of CAD.

LIPOPROTEIN RETENTION AND ACTIVATION OF IMMUNE CELLS

Role of Endothelial Activation, Adhesion Molecules, and Chemokines

Studies in animals and humans have shown that hypercholesterolemia causes focal activation of endothelium in large and medium-sized arteries. The infiltration and retention of LDL in the arterial intima initiate an inflammatory response in the artery wall[13,14] (Fig. 2). Modification of LDL, through oxidation or enzymatic attack in the intima, leads to the release of phospholipids that can activate endothelial cells,[14] preferentially at sites of hemodynamic strain.[15] Patterns of hemodynamic flow typical for atherosclerosis-prone segments (low average shear but high oscillatory shear stress) cause increased expression of adhesion molecules and inflammatory genes by endothelial cells.[16] Therefore, hemodynamic strain and the accumulation of lipids may initiate an inflammatory process in the artery.

The platelet is the first blood cell to arrive at the scene of endothelial activation.[17] Its glycoproteins Ib and IIb/IIIa engage surface molecules on the endothelial cell, which may contribute to endothelial activation. Inhibition of platelet adhesion reduces

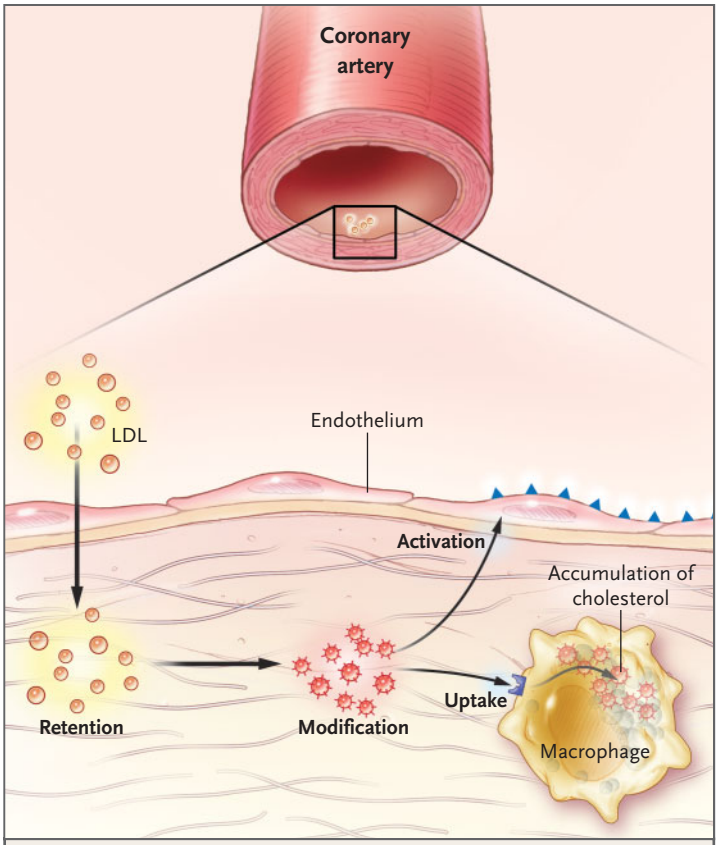

Figure 2. Activating Effect of LDL Infiltration on Inflammation in the Artery.
In patients with hypercholesterolemia, excess LDL infiltrates the artery and is retained in the intima, particularly at sites of hemodynamic strain. Oxidative and enzymatic modifications lead to the release of inflammatory lipids that induce endothelial cells to express leukocyte adhesion molecules. The modified LDL particles are taken up by scavenger receptors of macrophages, which evolve into foam cells.

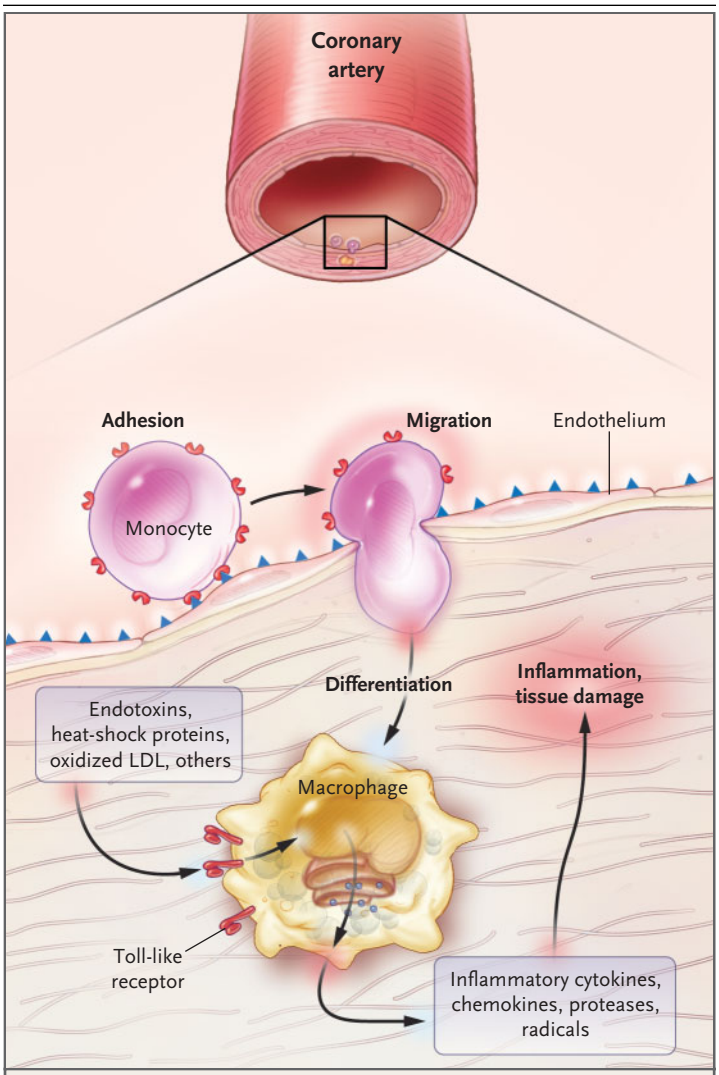

Figure 3. Role of Macrophage Inflammation of the Artery.

Monocytes recruited through the activated endothelium differentiate into macrophages. Several endogenous and microbial molecules can ligate pattern-recognition receptors (toll-like receptors) on these cells, inducing activation and leading to the release of inflammatory cytokines, chemokines, oxygen and nitrogen radicals, and other inflammatory molecules and, ultimately, to inflammation and tissue damage.

leukocyte infiltration and atherosclerosis in hypercholesterolemic mice.[17]

Activated endothelial cells express several types of leukocyte adhesion molecules, which cause blood cells rolling along the vascular surface to adhere at the site of activation.[18] Since vascular-cell adhesion molecule 1 (VCAM-1) is typically up-regulated in response to hypercholesterolemia, cells carrying counterreceptors for VCAM-1 (i.e., monocytes and lymphocytes) preferentially adhere to these sites (Fig. 2, 3, and 4).[19] Once the blood cells have attached, chemokines produced in the underlying intima stimulate them to migrate through the interendothelial junctions and into the subendothelial space (Fig. 2, 3, and 4). Genetic abrogation or pharmacologic blockade of certain chemokines and adhesion molecules for mononuclear cells inhibits atherosclerosis in mice.[20-24]

Macrophages in the Developing Plaque

A cytokine or growth factor produced in the inflamed intima, macrophage colony-stimulating factor, induces monocytes entering the plaque to differentiate into macrophages (Fig. 3). This step is critical for the development of atherosclerosis[25] and is associated with up-regulation of pattern-recognition receptors for innate immunity, including scavenger receptors and toll-like receptors.[26,27]

Scavenger receptors internalize a broad range of molecules and particles bearing molecules with pathogen-like molecular patterns.[26] Bacterial endotoxins, apoptotic cell fragments, and oxidized LDL particles are all taken up and destroyed through this pathway. If cholesterol derived from the uptake of oxidized LDL particles cannot be mobilized from the cell to a sufficient extent, it accumulates as cytosolic droplets. Ultimately, the cell is transformed into a foam cell, the prototypical cell in atherosclerosis.

Toll-like receptors also bind molecules with pathogen-like molecular patterns, but in contrast to scavenger receptors, they can initiate a signal cascade that leads to cell activation.[27] The activated macrophage produces inflammatory cytokines, proteases, and cytotoxic oxygen and nitrogen radical molecules. Similar effects are observed in dendritic cells, mast cells, and endothelial cells, which also express toll-like receptors. Bacterial toxins, stress proteins, and DNA motifs are all recognized by various toll-like receptors.[27] In addition, human heat-shock protein 60 and oxidized LDL particles may activate these receptors.[28,29] Cells in human atherosclerotic lesions display a spectrum of toll-like receptors,[30] and plaque inflammation may partly depend on this pathway. In support of this notion, genetic removal of a molecule in the toll-like receptor signaling pathway inhibits atherosclerosis in *apoE*-knockout mice.[31]

T-Cell Activation and Vascular Inflammation

Immune cells, including T cells, antigen-presenting dendritic cells, monocytes, macrophages, and mast

cells, patrol various tissues, including atherosclerotic arteries, in search of antigen.[32,33] A T-cell infiltrate is always present in atherosclerotic lesions (Fig. 4). Such infiltrates are predominantly CD4+ T cells, which recognize protein antigens presented to them as fragments bound to major-histocompatibility-complex (MHC) class II molecules (Fig. 4). CD4+ T cells reactive to the disease-related antigens oxidized LDL, heat-shock protein 60, and chlamydia proteins have been cloned from human lesions.[28,34,35]

A minor T-cell subpopulation, natural killer T cells, is prevalent in early lesions. Natural killer T cells recognize lipid antigens, and their activation increases atherosclerosis in *apoE*-knockout mice.[36] CD8+ T cells restricted by MHC class I antigens are also present in atherosclerotic lesions.[33] These cells typically recognize viral antigens, which may be present in the lesions (see below). Activation of CD8+ T cells in *apoE*-knockout mice can cause the death of arterial cells and accelerate atherosclerosis.[37]

When the antigen receptor of the T cell is ligated by antigen, an activation cascade results in the expression of a set of cytokines, cell-surface molecules, and enzymes. In inbred mice, two stereotypical responses can be elicited.[38] The type 1 helper T (Th1) response activates macrophages, initiates an inflammatory response similar to delayed hypersensitivity, and characteristically functions in the defense against intracellular pathogens. The type 2 helper T (Th2) response elicits an allergic inflammation. Although the Th1–Th2 system is more plastic in humans, the general pattern is similar.

The atherosclerotic lesion contains cytokines that promote a Th1 response (rather than a Th2 response).[8,39] Activated T cells therefore differentiate into Th1 effector cells and begin producing the macrophage-activating cytokine interferon-γ (Fig. 4). Interferon-γ improves the efficiency of antigen presentation and augments synthesis of the inflammatory cytokines tumor necrosis factor and interleukin-1.[38] Acting synergistically, these cytokines instigate the production of many inflammatory and cytotoxic molecules in macrophages and vascular cells.[33] All these actions tend to promote atherosclerosis. Indeed, in *apoE*-knockout mice lacking interferon-γ or its receptor, the development of atherosclerosis is inhibited.[40,41] Similarly, the extent of the disease is reduced when the Th1 pathway is inhibited pharmacologically[42] or genetically[43-45] in animals.

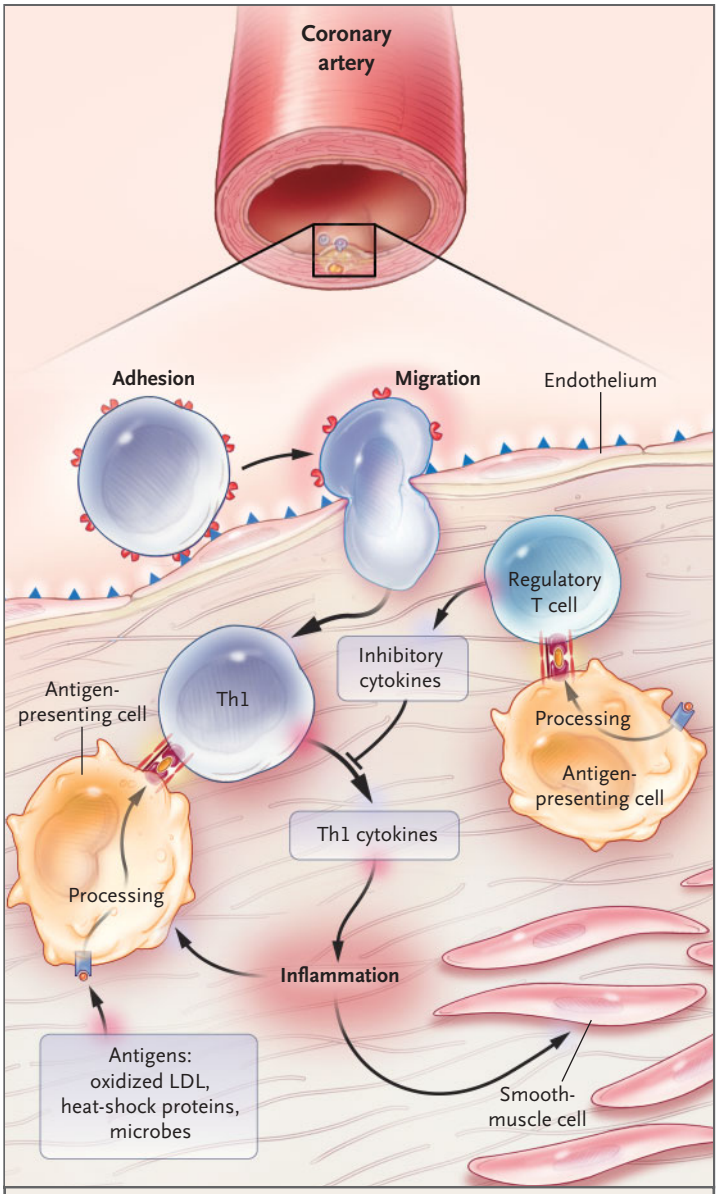

Figure 4. Effects of T-Cell Activation on Plaque Inflammation.
Antigens presented by macrophages and dendritic cells (antigen-presenting cells) trigger the activation of antigen-specific T cells in the artery. Most of the activated T cells produce Th1 cytokines (e.g., interferon-γ), which activate macrophages and vascular cells, leading to inflammation. Regulatory T cells modulate the process by secreting antiinflammatory cytokines (such as interleukin-10 and transforming growth factor β).

Cytokines of the Th2 pathway can promote antiatherosclerotic immune reactions.[46] However, they may also contribute to the formation of aneurysms by inducing elastolytic enzymes.[47] Therefore, switching the immune response of atherosclerosis

from Th1 to Th2 may not necessarily lead to reduced vascular disease.

T-cell cytokines cause the production of large amounts of molecules downstream in the cytokine cascade (Fig. 5). As a result, elevated levels of interleukin-6 and C-reactive protein may be detected in the peripheral circulation. In this way, the activation of a limited number of immune cells can initiate a potent inflammatory cascade, both in the forming lesion and systemically.

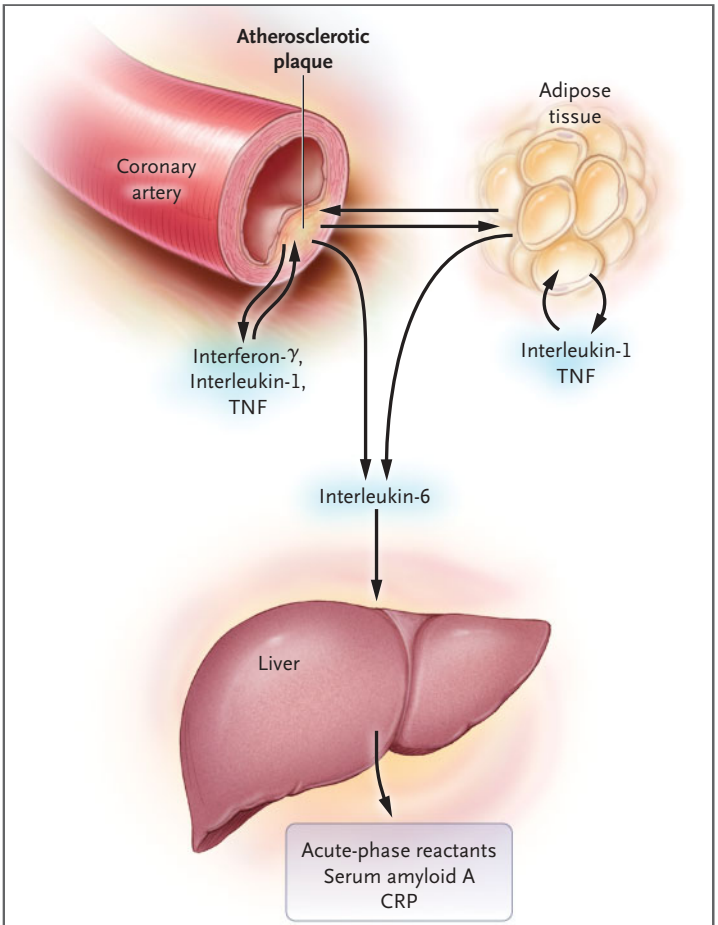

Figure 5. The Cytokine Cascade.

Activated immune cells in the plaque produce inflammatory cytokines (interferon-γ, interleukin-1, and tumor necrosis factor [TNF]), which induce the production of substantial amounts of interleukin-6. These cytokines are also produced in various tissues in response to infection and in the adipose tissue of patients with the metabolic syndrome. Interleukin-6, in turn, stimulates the production of large amounts of acute-phase reactants, including C-reactive protein (CRP), serum amyloid A, and fibrinogen, especially in the liver. Although cytokines at all steps have important biologic effects, their amplification at each step of the cascade makes the measurement of downstream mediators such as CRP particularly useful for clinical diagnosis.

Antiinflammatory Factors and Disease Activity

Powerful regulators built into the immune network act as protective factors in atherosclerosis. They include two antiinflammatory cytokines, interleukin-10 and transforming growth factor β (TGF-β). Antibody responses and metabolic factors can also contribute to immune regulation. Gene targeting or pharmacologic inhibition of interleukin-10 aggravates atherosclerosis in hypercholesterolemic mice and exacerbates coronary thrombosis.[48-50] Abrogation of TGF-β signaling in T cells elicits a dramatic phenotype, with rapid development of large, unstable atherosclerotic lesions.[51] These effects indicate that T-cell–mediated immunity is under tonic inhibition by TGF-β and interleukin-10; removal of these brakes on atherosclerosis accelerates the process.

Antibody-producing B cells, although not numerous in lesions, contribute to antiatherosclerotic activity, perhaps as a result of specific antibodies against plaque antigens, binding of antibodies to inhibitory Fc receptors, or cytokines produced by B cells. Spleen B cells are particularly effective inhibitors of atherosclerosis,[52] possibly because certain natural antibodies produced by some of these cells recognize phosphorylcholine, a molecule present in oxidized LDL, apoptotic cell membranes, and the cell wall of *Streptococcus pneumoniae*.[53] These antibodies may contribute to the elimination of oxidized LDL and dead cells as well as to the defense against pneumococcal infections. Interestingly, persons who have undergone splenectomy have increased susceptibility not only to pneumococcal infections but also to CAD.[54]

Cross-Talk between Inflammation and Metabolism

The balance between inflammatory and antiinflammatory activity controls the progression of atherosclerosis. Metabolic factors may affect this process in several ways. Obviously, they contribute to lipid deposition in the artery, initiating new rounds of immune-cell recruitment. Furthermore, the adipose tissue of patients with the metabolic syndrome and obesity produces inflammatory cytokines, particularly tumor necrosis factor and interleukin-6 (Fig. 5).[55,56] "Adipokines" — cytokines of the adipose tissue, including leptin, adiponectin, and resistin — may also influence inflammatory responses throughout the organism.[55] Finally, molecules generated during lipid peroxidation in atherosclerotic disease can induce protective as well as inflammatory reactions, for instance, by binding to nuclear receptors that control inflammatory genes.[14,57]

INFECTIONS AND CAD

Several studies have linked infections to atherosclerosis and CAD. Elevated titers of antibodies against chlamydia were found in patients with CAD,[58] and it was speculated that this microbe causes atherosclerosis. However, *Chlamydia pneumoniae* infection does not cause atherosclerosis in animals, although it may stimulate disease progression and plaque activation.[59,60] This could be due either to a direct action in plaques or to remote signaling by inflammatory mediators.[61] Molecular mimicry between *C. pneumoniae* antigens and human molecules may contribute to the activation of inflammation.[62] However, several recent secondary-prevention trials, including two reported in this issue of the *Journal*, failed to prevent acute coronary syndromes by administering antibiotics targeting *C. pneumoniae*, suggesting that *C. pneumoniae* infection is not a predominant cause of these syndromes.[63-66]

Herpes family viruses may also contribute to CAD. Cytomegalovirus is found in lesions, can modulate immune-cell as well as vascular-cell activity, and increases experimental atherosclerosis.[67-69] Clinical data imply an important role for cytomegalovirus in transplantation-related arteriosclerosis causing graft rejection.[70] More studies will be needed to determine whether the virus is involved in more common forms of CAD. Since several types of pathogens may contribute to CAD, it is unlikely that a single microbe causes atherosclerosis. Instead, the total burden of infection at various sites may affect the progression of atherosclerosis and elicit clinical manifestations.[71]

ACUTE CORONARY SYNDROMES

MECHANISMS OF PLAQUE RUPTURE

What causes a silent atherosclerotic lesion to rupture? Activated macrophages, T cells, and mast cells at sites of plaque rupture[5,7,72] produce several types of molecules — inflammatory cytokines, proteases, coagulation factors, radicals, and vasoactive molecules — that can destabilize lesions (Fig. 1). They inhibit the formation of stable fibrous caps, attack collagen in the cap, and initiate thrombus formation.[73-76] All these reactions can conceivably induce the activation and rupture of plaque, thrombosis, and ischemia.

Two types of proteases have been implicated as key players in plaque activation: matrix metalloproteinases (MMPs) and cysteine proteases.[77,78] Several members of these families of enzymes occur in the plaque and may degrade its matrix. MMP activity is controlled at several levels: inflammatory cytokines induce the expression of MMP genes, plasmin activates proforms of these enzymes, and inhibitor proteins (tissue inhibitor of metalloproteinase) suppress their action. Similarly, cysteine proteases are induced by certain cytokines and checked by inhibitors termed "cystatins."[78] Several of these molecules play decisive roles in the formation of aneurysms, as shown by experiments in gene-targeted mice. However, mechanistic studies in models of atherosclerosis have yielded complex results, with certain MMPs reducing rather than increasing the size of the lesions. At the same time, these enzymes clearly affect the composition of plaque. Therefore, they may represent future therapeutic targets. Study of plaque rupture in animal models should be helpful in determining the role of these proteases in the activation of plaque and myocardial infarction.

SYSTEMIC INDICATORS OF INFLAMMATION

The inflammatory process in the atherosclerotic artery may lead to increased blood levels of inflammatory cytokines and other acute-phase reactants (Fig. 5). Levels of C-reactive protein and interleukin-6 are elevated in patients with unstable angina and myocardial infarction, with high levels predicting worse prognosis.[79-81] The levels of other inflammatory markers are also elevated in these patients, including fibrinogen, interleukin-7, interleukin-8, soluble CD40 ligand, and the C-reactive protein–related protein pentraxin 3.[82-85] Levels of C-reactive protein are elevated in patients with unstable angina, a condition that is probably dependent on coronary thrombosis of atherosclerotic plaques, but not in those with variant angina caused by vasospasm.[86] Therefore, elevated C-reactive protein levels in patients with acute coronary syndromes likely reflect inflammation in the coronary artery rather than in the ischemic myocardium.[86] Activated T cells are also present and subgroups of inflammatory T cells are increased in the blood of patients with acute coronary syndromes.[87,88] Collectively, these findings suggest that inflammatory immune activation in coronary arteries initiates acute coronary syndromes, with circulating levels of inflammatory markers reflecting the clinical course of the condition.

INFLAMMATORY MARKERS AND THE RISK OF CAD

Although the degree of active inflammation is increased in activated plaques of patients with acute

coronary syndromes, smoldering inflammation characterizes silent plaques. Such lesions may also release inflammatory mediators into the systemic circulation (Fig. 5). A moderately elevated C-reactive protein level on a highly sensitive immunoassay is an independent risk factor for CAD in a healthy population.[89,90] Whether this test should be used to screen asymptomatic persons is a matter of debate.[90] Other measures of acute-phase reactants, including the erythrocyte sedimentation rate and levels of fibrinogen and other plasma proteins, also provide information about the inflammatory risk of CAD,[91] as do levels of circulating, soluble adhesion molecules such as soluble intercellular adhesion molecule 1, soluble VCAM-1, and soluble P-selectin, which are shed by activated cells.[92]

The fact that several different inflammatory markers, with different biologic activities, contribute to the statistical risk of CAD makes it unlikely that C-reactive protein or any of the other markers actually causes the disease. Instead, they all reflect the local inflammatory process in the artery and, perhaps, other tissues (e.g., adipose tissue) (Fig. 5). Further research will be needed to clarify the role of these molecules as markers of risk as well as contributors to disease progression.

THERAPEUTIC OPPORTUNITIES

The knowledge that atherosclerosis is an inflammatory disease offers new opportunities for the prevention and treatment of CAD. Powerful immunosuppressant or antiinflammatory agents could represent attractive treatments for acute coronary syndromes.[93] For long-term prevention of atherosclerosis, a more specific approach is desirable, such as vaccination with disease-related antigens.[94] Experimental results in both these areas are encouraging.

The immunosuppressive drugs cyclosporine and sirolimus block the activation of T cells and, at high levels, smooth-muscle proliferation.[95] They inhibit intimal lesions,[95,96] and sirolimus-coated stents are currently used to prevent restenosis after angioplasty.[97] Whether this family of compounds can be used in acute coronary syndromes is not known.

Antiinflammatory compounds include cyclooxygenase-2 inhibitors and other inhibitors of eicosanoid synthesis. The situation is complex, however, since enzymes inhibited by such compounds are also involved in the production of prothrombotic eicosanoids by platelets and endothelial synthesis of antithrombotic eicosanoids. The recent findings of an increased incidence of cardiovascular events in patients treated with the cyclooxygenase-2 inhibitor rofecoxib (Vioxx)[98] demonstrate the complexity of eicosanoid biology and indicate the need for a cautious approach to the use of this type of antiinflammatory compounds in patients with cardiovascular disease.

Remarkably, lipid-lowering statins have antiinflammatory properties.[99-101] They are among the most important of the pleiotropic effects of statins (i.e., effects not directly dependent on reduced cholesterol levels). These properties likely result from the ability of statins to inhibit the formation of mevalonic acid. Downstream products of this molecule include not only the end product, cholesterol, but also several isoprenoid intermediates that are used by lipids to attach to several intracellular signaling molecules.[99] The enzymatic addition of isoprenoids to intracellular proteins controls the activity of many signaling pathways, including those of cell division and antigen presentation. In addition, reduced cholesterol levels in membranes of cells exposed to statins may interfere with the clustering of T-cell–antigen receptors during immune activation.[102]

Several beneficial effects of statins may be due to antiinflammatory activity. For instance, atorvastatin ameliorates experimental autoimmune encephalomyelitis,[103] and a recent clinical trial demonstrated that atorvastatin has beneficial effects in patients with rheumatoid arthritis.[104] This may be due to the capacity of statins to inhibit antigen-dependent T-cell activation.[105] Other important targets include endothelial nitric oxide production and fibrinolysis, both of which are enhanced by statins, and platelet activity, which is reduced.[99] Inhibition of inflammation adds to lipid lowering as beneficial effects of statins on CAD, as recently demonstrated in two clinical trials of patients with atherosclerosis and CAD. In these studies, reduction of inflammation (reflected by C-reactive protein levels) through statin therapy improved the clinical outcome independently of the reduction in serum cholesterol levels.[106,107]

Finally, vaccination is an attractive approach to induce protective immunity.[94] In experiments in animals, atherosclerosis was reduced by vaccination with oxidized LDL, bacteria containing certain modified phospholipids, or heat-shock protein 60.[53,108-112] This may be due to the induction of protective antibodies or T cells. However, better antigen preparations must be developed and more

mechanistic knowledge obtained before this approach can be tested in humans.

In conclusion, new knowledge about inflammation in CAD has provided surprising insights into its pathogenesis, has offered new opportunities for diagnosis and prediction, and may lead to new treatments for this life-threatening disease.

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