Inflammation and cardiovascular disease mechanisms[1–3]

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ABSTRACT
The traditional view of atherosclerosis as a lipid storage disease crumbles in the face of extensive and growing evidence that inflammation participates centrally in all stages of this disease, from the initial lesion to the end-stage thrombotic complications. Investigators now appreciate that narrowing arteries do not necessarily presage myocardial infarction and that simply treating narrowed blood vessels does not prolong life. Although invasive approaches such as angioplasty and coronary artery bypass will remain necessary in some cases, we now understand that at least some of the cardiovascular benefits attributable to medical treatment and lifestyle modification (diet and physical activity) may result from reductions in inflammatory processes. *Am J Clin Nutr* 2006; 83(suppl):456S–60S.

KEY WORDS Myocardial infarction, atheroma, vascular cell adhesion molecule-1, VCAM-1, tumor necrosis factor-α, TNF-α, interleukin, endothelial cells, apolipoprotein, nitric oxide, CCR2, eotaxin, statin, CD40 ligand, platelet-derived growth factor, C-reactive protein

INTRODUCTION

Twenty or 30 y ago, we understood atherosclerosis as a bland lipid storage disease: lipid deposits formed on the surface of arteries and grew until they restricted and eventually blocked the blood supply to the tissues, resulting in a cardiovascular event, such as myocardial infarction (MI) or stroke. This traditional concept viewed atherosclerosis as analogous to the build-up of rust in a water pipe. We now understand better the mechanisms responsible for the initiation and development of atherosclerosis. Inflammation plays a key role, and we view arteries as highly organized organs comprised of living cells, not as inanimate conduits. We also recognize that atheromatous plaques develop within, rather than on, the arterial walls. Vascular events rarely result from inexorable plaque growth, but more often follow the rupture of a previously less prominent plaque, which results in clot formation, or thrombus. We further understand that atherosclerosis need not be an inevitable component of aging. Indeed, diet, lifestyle, and where appropriate, medication, can modify or forestall inflammatory processes and promote healthy aging.

INITIATION OF ATHEROSCLEROSIS

Inflammation participates in atherosclerosis from its inception and development to its ultimate endpoint, thrombotic complications. Normally, endothelial cells (ECs), which form the innermost surface of the artery wall, resist adhesion by leukocytes. However, triggers of atherosclerosis, such as consuming a high-saturated-fat diet, smoking, hypertension, hyperglycemia, obesity, or insulin resistance, can initiate the expression of adhesion molecules by ECs, thus allowing the attachment of leukocytes to the arterial wall (**Figure 1**A; 1). One likely culprit in this interaction between the endothelium and leukocytes is vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 binds monocytes and T lymphocytes, the types of leukocytes found in early atherosclerotic plaques. In rabbits fed an atherogenic diet, VCAM-1 is expressed by ECs in areas prone to lesion formation and also by ECs overlying early lesions (3). In such rabbits, VCAM-1 expression precedes the appearance of macrophages in the artery intima (the layer underneath the endothelium), and lesions appear after 3 wk (4). Despite similar cholesterol concentrations, lipoprotein profiles, and circulating leukocyte concentrations, mice prone to atherosclerosis because they cannot produce LDL receptor or apolipoprotein (apo) E but engineered to express only a poorly functioning form of VCAM-1 show a significant reduction in lesion formation compared with their VCAM-1–producing littermates (5).

What stimulates the expression of VCAM-1? In the case of an atherogenic diet, the initiating event is likely the accumulation of modified lipoprotein particles in the arterial intima. Oxidized lipids can induce VCAM-1 expression through a pathway mediated by nuclear factor-κB (6), as can proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α).

Interestingly, lesions tend to develop in specific areas only, likely because of the type of blood flow they experience. Laminar blood flow produces shear stress, which elicits several atheroprotective mechanisms, such as expression of a form of the antioxidant enzyme superoxide dismutase or increased nitric oxide synthase expression (7). The resulting increase in production of the vasodilator nitric oxide can limit VCAM-1 gene expression by inhibiting nuclear factor-κB activation and combating platelet clumping (8). Areas of the vasculature prone to lesion formation experience disturbed flow, and the lack of laminar flow may reduce the activity of such atheroprotective mechanisms. Cultured ECs subjected to disturbed flow exhibit increased expression of nuclear factor-κB compared with cells exposed to laminar flow (9).

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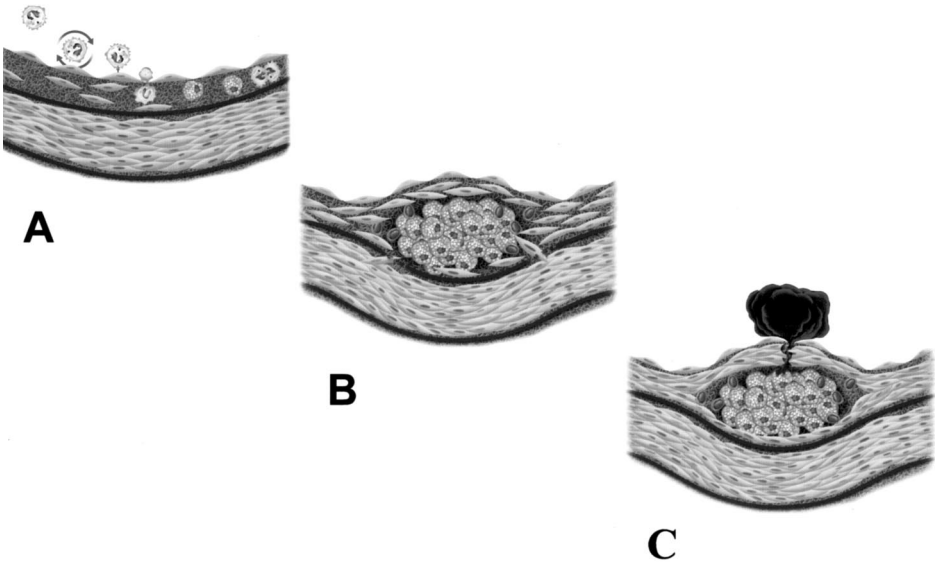

FIGURE 1. Participation of inflammation in all stages of atherosclerosis. A: Leukocyte recruitment to the nascent atherosclerotic lesion. Blood leukocytes adhere poorly to normal endothelium. When the endothelial monolayer becomes inflamed, it expresses adhesion molecules that allow leukocytes to adhere. Proinflammatory cytokines provide a chemotactic stimulus to adherent leukocytes to migrate into the intima. B: Monocytes transform into macrophages, express scavenger receptors, and engulf lipid particles, thus becoming the foam cells characteristic of atherosclerotic lesions. T lymphocytes join macrophages in the intima during lesion evolution and secrete cytokines and growth factors that can promote the migration and proliferation of smooth muscle cells. C: T lymphocytes also secrete cytokines that inhibit the production of collagen by smooth muscle cells and that stimulate macrophages to express collagen-degrading enzymes. This weakens the fibrous cap that protects the blood from the thrombogenic lipid core of the plaque. When the plaque ruptures, a thrombus forms that is responsible for most of the acute complications of atherosclerosis. Reproduced with permission from reference 2.

DEVELOPMENT OF THE FATTY STREAK

Once adhered to the arterial endothelium, monocytes penetrate the endothelial lining and enter the intima of the vessel wall by diapedesis between ECs, a process that requires a chemoattractant gradient, likely due in large part to monocyte chemoattractant protein-1 (MCP-1) (Figure 1B). Human and experimental atheroma overexpress MCP-1. This chemoattractant cytokine (chemokine) can recruit monocytes, the type of inflammatory white blood cell that characteristically accumulates in early atheromas. Mice susceptible to atherosclerosis as the result of inactivation of LDL receptors and also lacking the ability to express MCP-1 have 83% less lipid deposition and fewer macrophages in the walls of their aortas, despite consuming the same high-fat diet, than do MCP-1–producing mice (10). In a similar experiment, *apoE*$^{-}$/$^{-}$ mice also lacking the ability to express CCR2, the receptor for MCP-1, showed much less lesion development than did mice with a normal CCR2 gene, despite similar plasma lipid and lipoprotein concentrations (11).

Within the intima, monocytes mature into macrophages, exhibit increased expression of scavenger receptors, and engulf modified lipoproteins. Cholesterol esters accumulate in the cytoplasm, and the macrophages become foam cells, ie, lipid-laden macrophages that characterize the early stages of atherosclerosis. At the same time, the macrophages multiply and release several growth factors and cytokines, thus amplifying and sustaining proinflammatory signals.

One key mediator of this transformation and proliferation, macrophage colony-stimulating factor (M-CSF), is also overexpressed in experimental and human atherosclerotic plaques (12, 13). Mice prone to atherosclerosis as a result of reduced expression of the LDL receptor or the *apoE* gene and also lacking the ability to express M-CSF show retarded plaque development with markedly reduced macrophage accumulation compared with that in mice able to express normal M-CSF concentrations (14, 15).

T lymphocytes, the cells of the adaptive immune response, also participate critically in atherogenesis (Figure 1C). A trio of interferon-γ–inducible chemokines, γ-IP-10, MIG, and I-TAC, beckon these lymphocytes to enter the inflamed artery wall (16). These chemokines interact with the CXCR3 receptor, which is highly expressed by T lymphocytes in the atherosclerotic plaque.

Several additional adhesion molecules, chemokines, cytokines, and growth factors participate in this process. For example, interaction between IL-8 and its receptor, CXCR2, can also contribute to lesion formation in mice (9, 17). There are also some surprises. The atherosclerotic plaque overexpresses eotaxin, which is traditionally associated with eosinophil chemoattraction (18). Eotaxin binds to the receptor CXCR3, which localizes predominantly in macrophage-rich areas, thus suggesting that eotaxin modulates macrophage function in the plaque. Small numbers of mast cells inhabit the plaque as well, and these also express CXCR3. Therefore, eotaxin may mediate mast cell migration to the site of the lesion (18). VCAM-1, MCP-1, and M-CSF, however, appear to be the key mediators in the initiation and development of the initial lesion of atherosclerosis, the fatty streak. They also illustrate some of the complex tapestry of inflammatory signaling that leads to atherosclerotic plaque development.

PROGRESSION TO COMPLEX PLAQUE

In today's society, in which sloth and gluttony are unfortunately prevalent, the initiation of the atherosclerotic process can occur early in life. Indeed, 1 in 6 American teenagers already has pathologic intimal thickening in their coronary arteries (19). Autopsy studies of soldiers killed during the Korean and Vietnam wars and of trauma victims have shown that atherosclerosis

begins early in life (20), although its symptoms and complications may typically manifest later, in midlife. Thus, atherosclerosis smolders beneath the clinical horizon, often for decades, evolving from the fatty streak seen in teenagers to the complex plaque that causes cardiovascular complications in adults.

Human endothelial cells exposed to *Escherichia coli* endotoxin, a proinflammatory stimulus, express IL-1β and IL-1α messenger RNA (21), which raises the possibility that vascular ECs are not merely passive responders to immunologic stimuli from leukocytes but are actively involved in the process. Since then, a range of cytokines expressed by vascular wall cells has been identified, including IL-1β, IL-1α, TNF-α, TNF-β, IL-6 (an important messenger cytokine), and the very factors important to the recruitment and activation of the monocytes, ie, M-CSF, MCP-1, and IL-18.

Another proinflammatory cytokine, CD40 ligand (CD154), can contribute to this phase of atherogenesis as well. Interruption of CD40/CD154 signaling can slow the initiation of atherosclerosis (22), but how does interruption of this key mediator of inflammation affect the progression of atherosclerosis once atherosclerotic lesions are established? To answer that question, LDL-receptor–deficient mice were fed a high-cholesterol diet for 13 wk, which resulted in the creation of lesions (23). Administration of an antibody to CD154 then halted CD40 signaling. The progression of atherosclerosis was then analyzed after an additional 13 wk. In 2 control groups (one group of mice received rat immunoglobulin and another received saline only), atherosclerotic lesion size showed severe disease progression, increasing 4- to 5-fold over the 13-week baseline. However, lesion progression in mice treated with anti-CD154 virtually halted and was reduced significantly compared with that in the control groups (23). This finding illustrates how inflammation influences the progression of atherosclerosis and that muting inflammatory signaling not only prevents the formation of new lesions but also halts the evolution of existing atherosclerosis.

PLAQUE RUPTURE

The development of atheromatous plaques would not be such a major health issue were it not for plaque rupture and thrombosis. In coronary arterial thromboses, the underlying lesion often does not produce critical arterial narrowing. Indeed, serial angiogram data show that extreme narrowing of the artery occurs weeks or months before MI in only $\approx$15% of cases (24). Additionally, coronary arteries can enlarge and compensate for the developing plaque, thus preserving the flow of blood to the myocardium (25). This mechanism becomes overwhelmed only when the stenosis occupies >40% of the arterial lumen (25).

We now know that physical disruption of the atherosclerotic plaque, most often a fracture of the fibrous cap that ordinarily protects the blood from contact with the lipid core, causes most acute coronary syndromes, resulting in thrombus formation and sudden expansion of the lesion, perhaps to the extent that blood flow through the affected artery becomes compromised or even completely blocked. Given the critical importance of such events in clinical practice, our group has investigated the role of inflammation in plaque disruption, with a particular focus on the structure of the fibrous cap.

The fibrous cap owes its biomechanical strength and stability to interstitial collagen. One characteristic of plaques that have ruptured and caused fatal thrombosis is their tendency toward thin fibrous caps (26–28). Inflammation interferes with the integrity of the interstitial collagen matrix in 2 ways: by blocking the creation of new collagen fibers and by stimulating the destruction of existing collagen. In the arterial wall, collagen is produced mostly by smooth muscle cells, stimulated by transforming growth factor-β, platelet-derived growth factor, and, to a lesser extent, IL-1. However, the cytokine interferon-γ, which is produced by T lymphocytes in the plaque, inhibits both basal collagen production and the stimulatory effects of transforming growth factor-β, platelet-derived growth factor, and IL-1 (29).

T lymphocytes also participate in the inflammatory processes that promote the destruction of existing collagen in vulnerable plaques. CD40 ligand and IL-1 produced by T-lymphocytes promote the production of collagen-degrading enzymes by macrophages, including members of the matrix metalloproteinase MMP family, specifically MMP-1, MMP-8, and MMP-13 (30, 31). In addition, mast cells in the plaque may release the MMP inducer TNF-α as well as the serine proteinases tryptase and chymase, which can activate MMP proenzymes (32, 33). Other causes of physical disruption of the fibrous cap are possible, but these appear to be the most common.

T lymphocytes also promote the thrombogenicity of the lipid core through the expression of CD40 ligand, which stimulates macrophage production of tissue factor, a potent procoagulant that, once exposed to factor VII in the blood, initiates the coagulation cascade (34). Therefore, inflammation promotes not only the initiation of the atherosclerotic lesion but also its progression to complex plaque; the weakening of the fibrous cap, which renders the plaque prone to rupture; and finally, boosting of the thrombogenicity of the lipid core.

COMBATING THE PROBLEM

To combat the problem of atherosclerosis, we must address the classic risk factors for cardiovascular disease with interventions such as diet, physical activity, and smoking cessation (a fundamental but often neglected component). Initiating and maintaining these lifestyle changes are not easy tasks. Fortunately, the statin class of drugs is particularly effective at reducing cardiovascular events, even in those with average LDL concentrations.

Many studies, in broad categories of individuals, have shown that lipid-lowering drugs reduce cardiovascular events by between 25% and 38% (6, 35, 36). Paradoxically, however, the effect of statins and other lipid-lowering therapies on the extent of stenosis caused by a plaque is much smaller, on the order of a few percent (10). Although cardiologists have traditionally focused on the actual stenosis, the dissociation between the extent of stenosis and cardiovascular disease risk reiterates that the functional state of the atherosclerotic plaque, not merely its size or the degree of luminal encroachment, determines the likelihood of acute coronary syndromes.

If statins do not shrink plaques significantly, how do they reduce cardiovascular disease risk? The burgeoning evidence linking inflammation to all phases of atherosclerosis suggests that lipid lowering may itself comprise an antiinflammatory therapy. Some evidence supports this suggestion. In plaques induced experimentally in rabbits, a low-cholesterol diet can quell inflammation and stabilize the atherosclerotic plaque. Indeed, a low-cholesterol diet not only strengthens the fibrous cap, as shown by collagen accumulation, but also reduces core thrombogenicity, with marked lowering of tissue factor (37, 38).

If arterial stenosis, the traditional marker of cardiovascular disease, is not considered the decisive factor in overall

cardiovascular disease risk, the question arises of how best to monitor a patient's vulnerability to a cardiovascular event. Several proinflammatory markers associate with cardiovascular disease risk, including IL-6, TNF-α, and, most prominently, the downstream acute-phase reactant C-reactive protein (CRP) (39–42). CRP has many advantages as a marker: it is stable, has negligible circadian variation, and is easily and reliably measured (43). If lipid-lowering therapy is antiinflammatory and statins decrease lipid concentrations and reduce cardiovascular disease risk, statin therapy should produce a parallel decrease in CRP as well. Indeed, that is exactly what happens: CRP concentrations decrease 15–50% with statin therapy (44–52). This is a class effect; the entire family of lipid-lowering drugs decreases inflammation.

If reduced CRP truly measures a patient's likelihood of a cardiovascular complication, the rate of cardiovascular events should decrease as well. A recent paper reported exactly that: in patients with acute coronary syndrome undergoing statin therapy, individuals with CRP concentrations <2 mg/L showed a lower risk of recurrent MI or death from cardiovascular causes than did those with higher concentrations (2.8 compared with 3.9 events per 100 person-years; $P = 0.006$) (53). This benefit appears in considerable measure independent of the well-known effect of statin therapy on cholesterol concentration. Thus, the clinical benefit of statins appears related to their antiinflammatory effect. However, lipid lowering is an antiinflammatory therapy in and of itself, and this activity is central to the clinical benefit of statin therapy.

CLINICAL CHOICES

The best approach to treating coronary artery disease is controversial and sometimes pits angioplasty and stenting against coronary bypass surgery. However, comparing these end-stage interventions as alternative choices for routine therapy is a colossal admission of failure. Indeed, although revascularization can effectively relieve angina, it poorly prevents MI or prolongs life (54). We must find new approaches to combat this disease. For many years, cardiologists focused on the stenosis. Stenotic lesions are easy targets because patients have symptoms, and measuring blood flow or imaging a blocked artery is easy as well. However, the more common nonstenotic lesion masks MI. As we have seen, nonstenotic lesions, which are hidden in the artery wall without causing discrete stenosis, more often cause acute complications. Clinically, we certainly often need to used revascularization strategies to relieve compromised tissue blood flow. We must, however, couple such therapies with systemic interventions including lifestyle modification and appropriate drug therapy. Perhaps most importantly, we need to prevent cardiovascular complications in individuals without signs and symptoms of compromised blood flow. Health professionals must identify overtly healthy individuals who are at increased risk of first cardiovascular events and introduce effective approaches to prevention. Reducing inflammation is one effective way to prevent cardiovascular complications.

CONCLUSION: A CENTRAL ROLE FOR INFLAMMATION IN ATHEROSCLEROSIS

Inflammation is central to cardiovascular disease. It often begins with inflammatory changes in the endothelium, which begins to express the adhesion molecule VCAM-1. VCAM-1 attracts monocytes, which then migrate through the endothelial layer under the influence of various proinflammatory chemoattractants. Once within the arterial intima, the monocytes continue to undergo inflammatory changes, transform into macrophages, engulf lipids, and become foam cells. T lymphocytes also migrate into the intima, where they release proinflammatory cytokines that amplify the inflammatory activity. Through these inflammatory processes, the initial lesion of atherosclerosis, the fatty streak, is formed.

Furthermore, inflammation is central to the progression from fatty streak to complex plaque. As the plaque evolves, T cells activate macrophages by either cyto-signaling or contact through CD40 ligation to secrete a panoply of molecules, including cytokines and MMPs, that make up the collagen that forms the fibrous cap, which ordinarily protects the plaque. As a result, the fibrous cap becomes thin and friable and can rupture, thus creating a thrombus that can lead to an MI or other complications.

This sequence of events differs greatly from the former perspective of cardiovascular disease as a lipid storage problem. We now know that critical stenoses do not cause most MIs. Our assessment and management of cardiovascular disease risk must evolve in step with a deepened understanding of pathophysiologic mechanisms. Inflammatory markers such as CRP merit careful consideration for inclusion in our risk assessment algorithms. Lifestyle modification and proven medical therapies must join stenting and coronary bypass surgery. If we are to embrace fully our new appreciation of inflammation in the initiation and development of atherosclerosis, we must reduce new biological insights to practice to aid in the identification of individuals at risk of cardiovascular events, with the goal of lessening our dependence on late-stage and invasive treatments.

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