Inflammation and cardiovascular disease mechanisms

Peter Libby

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 inexcusable 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 1A; 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 VCAM-1 are prone to atherosclerosis because they cannot produce LDL receptor or apo E but engineered to express only VCAM-1. 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 apo E but engineered to express only 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).

1 From the Harvard Medical School and Brigham and Women’s Hospital, Boston, MA.
3 Reprints not available. Address correspondence to P Libby, Brigham and Women’s Hospital, 77 Avenue Louis Pasteur, NRB 741, Boston, MA 02115. E-mail: plibby@rics.bwh.harvard.edu.
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 chemotactic 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 atherosclerotic lesions. 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 athogenesis (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 chemotaxis (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
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 shows that extreme narrowing of the artery occurs as a result of plaque rupture and thrombosis. In coronary arterial thromboses, the underlying lesion often consists of 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.

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. In addition, mast cells in the plaque may release the MMP inducer TNF-α as well as the serine proteinases trypsin 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 anti-inflammatory 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 anti-inflammatory effect. However, lipid lowering is an anti-inflammatory 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 use 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 chemottractants. 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 pathophysiology 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.

The author had no conflict of interest to report.

**REFERENCES**

11. Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in


47. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64–70.


