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THE ROLE OF INFLAMMATION AND INFECTION IN CORONARY ARTERY DISEASE

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Key Words atherosclerosis, chronic inflammation, immune-mediated disease, acute coronary syndromes, *Chlamydia pneumoniae*

■ **Abstract** New insights into atherosclerosis, the most common disease affecting coronary arteries, may change therapeutic strategies from largely symptomatic to causal. Atherosclerotic plaques contain a lipid-related, immune-mediated inflammation, with release of secretory products capable of changing plaque morphology. Plaques prone to complications contain large numbers of inflammatory cells; stable plaques contain little inflammation. Similarly, atherectomy specimens from patients with coronary syndromes revealed more inflammatory cells in unstable than in stable patients. These observations, and the fact that acute coronary syndromes are associated with increased blood levels of inflammatory markers, have renewed interest in the possible relationship between infection and atherogenesis. Of all potential candidate antigens, *Chlamydia pneumoniae* presently is considered the most likely because a substantial number of patients with unstable syndromes contain *C. pneumoniae*-reactive T cells, both in blood and within the atherosclerotic plaque, suggesting enhancement of intraplaque inflammation.

INTRODUCTION

By far the most common cause of coronary artery disease is atherosclerosis. Over the past decade, a steady decline in mortality rates of acute myocardial infarction has been achieved, mainly as a result of the introduction of thrombolytic therapy in the early stages after infarction and also because of an explosive growth in interventional procedures such as percutaneous transluminal coronary angioplasty and coronary artery stent implantations. However, neither of these approaches affects the underlying atherosclerotic disease process. Indeed, the profile of mortality in ischemic heart disease has changed from acute myocardial infarction to chronic heart failure on the basis of the same disease. In this context, it is sobering to refer to the study of the global burden of disease, published in a series of four papers in *Lancet* in 1997 under the title "From What Will We Die in 2020?" The study

predicts that even then ischemic heart disease will rank number one among the causes of death (1).

Despite this rather grim outlook, some recently gained insights into the genesis of atherosclerotic arterial disease may provide a handle for a causal rather than a symptomatic therapeutic approach. This more optimistic point of view is based on the concept that atherosclerotic plaque biology is a dynamic process governed largely by an immune-mediated and lipid-related chronic inflammatory process (2). This review emphasizes these facets, focusing on coronary artery disease and its sequelae.

THE CLASSICAL CONCEPT OF ATHEROSCLEROSIS

In the classical concept, the atherosclerotic lesion is characterized as an elevated intimal plaque, which consists of fibrous tissue encapsulating a lipid core. It was recognized that these lesions contained smooth muscle cells, some of which could have phagocytosed lipids. Similarly, it was well known that macrophages were abundantly present, in particular surrounding the lipid core, known as the atheroma. The macrophages were considered to play an important role in phagocytosing lipids, and their function was seen mainly as scavenger cells attempting to remove the fat particles that had infiltrated the intima. It was recognized that these macrophages could "overeat," which resulted in cell death with spillover of fat, and that this process eventually produced the atheroma. Thus the pathogenesis of atherosclerosis was seen mainly as a lipid disorder with excessive influx of lipids into the arterial wall, with macrophages contributing to the eventual lesion by scavenging the lipids. There was little understanding of the mechanisms underlying the contribution of smooth muscle cells to the elevated lesion and certainly no understanding of macrophages as part of an inflammatory reaction.

This has all changed over the past decade. Currently, the major contributions relate to the role of intraplaque inflammation, with macrophages acting not only as scavenger cells but certainly also as immunocompetent cells interacting with other inflammatory cells such as lymphocytes and mast cells. This understanding provides the background for a much more rational approach to the disease.

INTRAPLAQUE INFLAMMATION

The introduction of immunohistochemical techniques to the study of atherosclerotic plaques has revealed the presence of macrophages and T lymphocytes (Figure 1), which colocalize, often with an intimate cell-to-cell contact (3, 4). A variable number of T cells, moreover, appear activated as revealed by the membrane expression of HLA-DR (4, 5). In addition to macrophages and T cells, atherosclerotic plaques contain accumulations of activated mast cells, with preference for the shoulder region of the lesions (6). All in all, these observations have led to an

understanding that atherosclerotic plaques contain an intraplaque immune-mediated cellular response.

This implies that inflammatory mediators can be released, such as growth factors, cytokines, and other proteins, which could regulate a variety of processes affecting what components make up the atherosclerotic plaque. (In fact, the analogy with other immune-mediated chronic inflammatory diseases, such as rheumatoid arthritis, is tempting.) If so, the secretory products of activated immunocompetent cells may induce breakdown of extracellular matrix components, producing sites of plaque vulnerability, whereas other secretory substances may stimulate repair mechanisms, such as smooth muscle cell growth and production of extracellular matrix components, eventually leading to fibrosis. One may think of the cells as releasing breakdown and repair factors onto a balance scale; the balance may be tipped one way, leading to plaque instability and plaque complications, or the other way, leading to plaque stabilization (7).

MECHANISMS AFFECTING PLAQUE STABILITY

It has been shown unequivocally that plaque vulnerability relates to intraplaque inflammation. Not only are sites of plaque rupture or plaque surface erosion associated with distinct accumulations of inflammatory cells (8), but the study of atherectomy specimens obtained from patients presenting with stable angina, unstable angina, and acute myocardial infarction has shown that a direct relationship exists between the number of inflammatory cells and the severity of the coronary syndrome (9). Similarly, the number of T lymphocytes expressing interleukin-2 (IL-2) receptor activity, a marker for recent-onset activation, increases significantly with the severity of the coronary syndrome (9). The mechanisms involved, affecting the integrity of the fibrous cap of the atherosclerotic plaque, are potentially manifold and, to this end, macrophages, T cells, and mast cells should be further investigated.

To put the role of T cells in perspective, it is important to provide a brief summary of their functional characteristics relevant to their potential role in inflammatory processes. Functional subpopulations are recognized on the basis of their ability to secrete discrete patterns of cytokines. T-helper-1 (Th1) cells produce interferon- γ (IFN- γ), IL-2, and lymphotoxin, responsible for distinct cell-mediated immune responses intended to eradicate intracellular pathogens. T-helper-2 (Th2) cells produce IL-4 and IL-5, considered important in promoting humoral immune responses. In this context, therefore, it is important that within atherosclerotic plaques a Th1-like environment prevail (10–12). As a consequence, IFN- γ produced within the intraplaque inflammation may affect plaque morphology by inhibiting the proliferation of smooth muscle cells and by decreasing their capability for extracellular matrix synthesis. In addition, IFN- γ enhances the recruitment of immunocompetent cells by upregulating adhesion molecule expression on endothelial cells, so it may play a role in the continuation of a smoldering inflammation. It also appears that other cytokines, such as IL-1 and tumor necrosis

factor α (TNF- α), may induce apoptosis of smooth muscle cells, thus introducing another pathway that may lead to impaired extracellular matrix synthesis (13).

The role of macrophages in the context of plaque destabilization is their release of matrix metalloproteinases (MMPs). Plaque macrophages, particularly when loaded with lipids (foam cells), produce several MMPs, including interstitial collagenase (MMP-1), stromelysin (MMP-3), and the gelatinases MMP-2 and MMP-9. The secretion of these proteinases is controlled by inflammatory cytokines, such as TNF- α and IL-1, again highlighting the intricate interaction between macrophages and T cells. Recent studies, moreover, have claimed a role for mast cells also in orchestrating the release of these proteinases (6, 14). In fact, as with macrophages and T cells, the number of activated mast cells in coronary atherectomy specimens correlates directly with the severity of the coronary syndrome (15). Hence, one may consider a functional role for mast cells in these conditions because they may release the neutral proteases tryptase and chymase, both capable of degrading extracellular matrix components. However, the number of TNF- α -positive mast cells also increases with the severity of the coronary syndrome, colocalizing with MMP-9-positive macrophages, which suggests that activated mast cells are involved in the release of matrix-degrading enzymes by macrophages. Although several natural tissue inhibitors of MMPs, such as tissue inhibitors of metalloproteinases 1–3 (TIMP 1–3), are also produced in plaques, the net effect appears to favor tissue breakdown as shown by in situ zymography of human plaque tissues (16).

Despite the observation that the inflammatory process favors tissue degradation, there is also evidence for an evolution toward tissue repair. The release of growth factors and cytokines capable of stimulating the proliferation and synthetic capacity of smooth muscle cells is the main driving force to this end. This process results in the deposition of extracellular matrix components, such as proteoglycans and collagens. The growth factors involved include transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). These factors are produced by dysfunctioning endothelial cells as well as macrophages, but they may also be released by a thrombus attached to the plaque surface (17). The increase in extracellular matrix gradually leads to an increase in plaque volume, which in the coronary artery leads to a gradual narrowing of the lumen. Initially, enlargement of the vessel wall compensates for the narrowing (18, 19), but in long-standing cases the narrowing eventually becomes clinically relevant. At the same time, however, this repair process has a beneficial effect on plaque integrity. The production of collagens serves to encapsulate the lipid core, which may stabilize the plaque.

Given the fact that intraplaque inflammation is essentially a lipid-related process, one may anticipate that lipid-lowering strategies could have a beneficial effect by swinging the net effect of the inflammation-related secretory products toward repair rather than tissue breakdown. Indeed, animal experiments have confirmed this notion, whereas lipid-lowering trials in humans have revealed a significant decrease in the number of acute coronary events, suggesting a change toward plaque stabilization (20).

INTRAPLAQUE INFLAMMATION AND INFECTION

The possible role of infection in atherosclerotic disease is attracting much attention (for recent reviews, see 21, 22). A possible relationship between infectious diseases and the genesis of atherosclerosis is intriguing, but as yet much remains hypothetical. It is important to distinguish between a potential role for infectious diseases in the genesis of atherosclerosis per se and the possibility that infection may enhance a smoldering inflammatory process in an atherosclerotic plaque already generated. Too often this distinction is not made, which confounds matters rather than illuminating them. The general consensus now is that at the onset of atherogenesis, endothelial cell dysfunction is a key factor, allowing an influx of lipids and attracting inflammatory cells. However, the mechanisms underlying these phenomena remain largely hypothetical. A variety of associated risk factors have been incriminated, such as smoking, hypercholesterolemia, hypertension, and diabetes mellitus. More recently, additional factors have been identified, including homocystinemia, raised plasma levels of lipoprotein (a), hypercoagulability, and genetic markers such as angiotensin-converting enzyme polymorphisms. At the same time, the concept of a primary (auto)immune disease causing endothelial cell dysfunction has attracted interest, and in this context the option of a role for infectious diseases has been established. However, no convincing data yet support the latter hypothesis.

Furthermore, the mechanisms involved in the process of immune activation within the arterial wall also remain speculative. One mechanism could operate by way of the innate immune system. The influx of modified lipoproteins such as oxidized low-density lipoprotein (OxLDL) and their uptake by macrophages may lead to a non-antigen-specific immune activation in which the phenotypic transformation of blood monocytes into foam cells is associated with a change in functional status, manifested by the release of growth factors, cytokines, and enzymes. Specific immune activation by way of the adapted immune system may also play a role in atherosclerotic disease. In fact, a number of studies have shown increased levels of antibodies against OxLDL as well as increased antibody titers of infectious agents. Most often incriminated are cytomegalovirus and the bacteria *Helicobacter pylori* and *Chlamydia pneumoniae*. At present, *C. pneumoniae* is the most suspected. A serological relationship between myocardial infarction and coronary artery disease on the one hand and plasma antibodies against *C. pneumoniae* on the other hand was first described by Saikku et al (23), but since then several groups have confirmed these observations (for a review, see 24). In addition, *C. pneumoniae* has been demonstrated in human atherosclerotic lesions using different techniques, including electron microscopy, immunohistochemistry (Figure 2), and polymerase chain reaction (PCR), and the organisms have also been cultured from atherosclerotic plaques (25, 26). Although immunohistochemical studies demonstrate the presence of *C. pneumoniae* in atherosclerotic plaques in the majority of cases, there are marked differences from the results obtained with PCR. This could relate to differences in the sensitivity or specificity of both methods. There appears to be no association between the type of lesion and the presence

of *C. pneumoniae*; mild lesions are as likely to be positive for the presence of *C. pneumoniae* as are severe lesions (27). However, the frequency of *C. pneumoniae* in atherosclerotic plaques appears increased when compared with normal vessels (28).

It also appears that not only humoral responses against *C. pneumoniae* but also cell-mediated immunity, by way of antigen-specific T cells, may play a role in atherosclerosis. The frequency of *C. pneumoniae*-responsive T cells in the peripheral blood is increased in patients with coronary heart disease (29), whereas T cell lines isolated from abdominal aneurysms respond to *C. pneumoniae* antigens (30). Recently, T cell lines and clones isolated from carotid atherosclerotic lesions obtained in surgery also showed a positive response for *C. pneumoniae* (31). Our own observations confirm these findings (31a). We generated T cell lines and clones from surgically removed atherosclerotic lesions obtained from patients with acute atherosclerotic disease and were able to demonstrate that about half the cells responded to *C. pneumoniae*. These findings are a strong indication that a causal relationship may indeed exist between *C. pneumoniae* and the inflammatory process within destabilized atherosclerotic plaques.

However, it also appears that only a percentage of individuals present such a particular response, indicating clearly that antigenic stimuli other than *C. pneumoniae* have to be taken into account. This notion may help explain the observation that patient trials using antibiotics directed against *C. pneumoniae* produced beneficial effects in one study but not in the other (32, 33).

The question remains whether *C. pneumoniae* can be incriminated in atherogenesis at the very start of the disease or whether it provides additional stimuli to change a smoldering inflammation into a recently activated one. At this stage, no conclusive data support either concept, but the fact that the peripheral blood of patients with coronary syndromes contains *C. pneumoniae*-responsive T cells, with levels increasing with the severity of clinical syndromes, suggests that *C. pneumoniae* may play a role in these syndromes. However, we certainly have not reached a stage where it appears appropriate to start treating a general population of individuals with atherosclerosis with specific anti-*C. pneumoniae*-directed or any other antibiotics.

CONCLUDING REMARKS

At this stage the evidence is overwhelming that intraplaque inflammation is of crucial importance for plaque stability. Given the fact that the chronic inflammatory process is an immune-mediated and lipid-related process, one may anticipate that lipid-lowering strategies may change the balance from an unstable pathway toward a more stabilized situation. This could explain the favorable results in some lipid-lowering trials where the main effect was not so much a decrease in plaque size as a significant decrease in acute events. One may consider this the result of a stabilizing pathway, with an increase in extracellular matrix and a decrease in

lipid-related inflammation. Experimental studies have shown that at least in animal models this is the case.

It is also fair to state that at this stage there is only circumstantial evidence that infection may play a role in atherosclerotic disease. Nevertheless, *C. pneumoniae* is a likely candidate for recent-onset activation of a smoldering inflammatory intraplaque process, leading to plaque destabilization and, eventually, plaque complications such as rupture and surface erosion. At this stage, however, specific antigen-directed antibiotic treatment of a general atherosclerotic diseased population appears unjustified.

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Figure 1 An atherosclerotic plaque in a carotid artery stained with monoclonal antibodies against CD68 (macrophages, *panel A*) and CD3 (T lymphocytes, *panel B*) using a streptavidin-biotin complex technique. Note the presence of large numbers of macrophages and T lymphocytes in the fibrous cap covering the atheroma. (From Reference 21 with permission.)

Figure 2 High-power magnification of an inflammatory infiltrate in a carotid atherosclerotic plaque stained with an antibody specific for *C. pneumoniae*. Note the presence of mononuclear cells that stain positive for *C. pneumoniae*. (From Reference 21 with permission.)

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