

Inflammation and Atherosclerosis

Inflammation is a bodily response to tissue irritation or injury, intended primarily to facilitate restoration of tissue health. Toward this goal, the cellular and chemical tools of inflammation act in concert to eliminate harmful agents such as microbes or necrotic debris. If all goes well, inflammation is phased out within a few days, giving way to repair processes that eventually heal and reconstitute the sites of injury. However, if tissue health is not restored, either due to ineffective removal of offending agents or inadequate tissue repair, inflammation can persist indefinitely and become an obstructive chronic condition. In response to stable low-grade irritation, inflammation may linger on as a chronic response that continuously erodes the surrounding tissues. The lateral damage caused by this type of inflammation usually accumulates slowly, sometimes asymptotically for years, and if unabated, can lead to severe tissue deterioration. For example, the disabling defects seen in advanced stages of gingivitis and osteoarthritis are primarily the consequence of low-grade chronic inflammation in the gums and synovial joints, respectively. Accelerated tissue damage can result from chronic inflammation that has the potential to erupt episodically. This kind of reaction underlies many human diseases including inflammatory bowel disease and various forms of chronic lung disease.

Although chronic inflammation is a frequent cause of disability, it is not as life-threatening as some systemic inflammatory (anaphylactic) responses to stimuli such as drugs or toxins. For example, the aggressive systemic response to

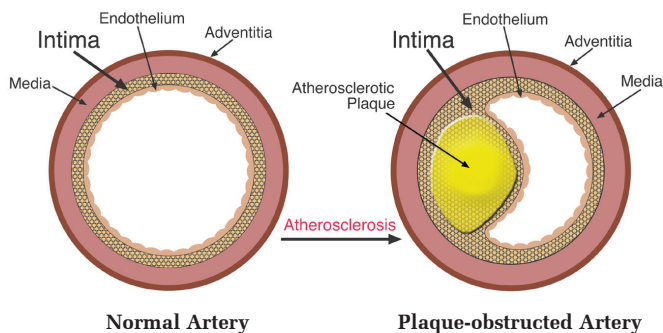
virulent microbial infection, or sepsis, is a leading cause of death in intensive care units, accounting for more than 250,000 deaths annually in the U.S. In extreme situations, inflammation may shift direction and turn relentlessly against the body's own tissues as if attempting to exterminate the host along with the offending agents. Such indifference toward the fate of the host suggests that the fundamental role of inflammation is to facilitate fitness of the species, which unfortunately does not always correlate with personal benefit. Thus, although critical for species survival, inflammation has considerable potential to plague aged or otherwise vulnerable individuals with severe torments.

A characteristic feature of inflamed tissues is the presence of an increased number of phagocytic cells, i.e. cells that are able to ingest particulate matter. Included among these are circulating polymorphonuclear leukocytes (PMNL) and monocytes, as well as monocyte-derived tissue macrophages. In general, PMNL are responsible for engulfing and killing invading microorganisms, whereas macrophages are predominantly involved with ingesting and degrading accumulated debris. The recognition signal for ingestion may be either the particle surface or certain serum proteins, called opsonins, which bind to the particle and render it ingestible. Normally, the immediate and early response to injury or acute inflammation is marked by an influx of PMNL (mainly neutrophils), whereas chronic inflammation is characterized by infiltration with mononuclear cells including macrophages, lymphocytes, and plasma cells. The central role of low-grade chronic

inflammation in the pathogenesis of conditions including atherosclerosis, colorectal cancer, and Alzheimer's disease has driven efforts to uncover hidden aspects of inflammation and to better cope with its ailments. Here we highlight the link between inflammation and atherosclerosis (ATH).

ATH is a vascular disease marked by fatty plaques in the intima of medium and large size arteries (Figure 1), and represents a leading cause of death in Western countries.

Figure 1- Schematic illustration of Normal and Blocked Arteries

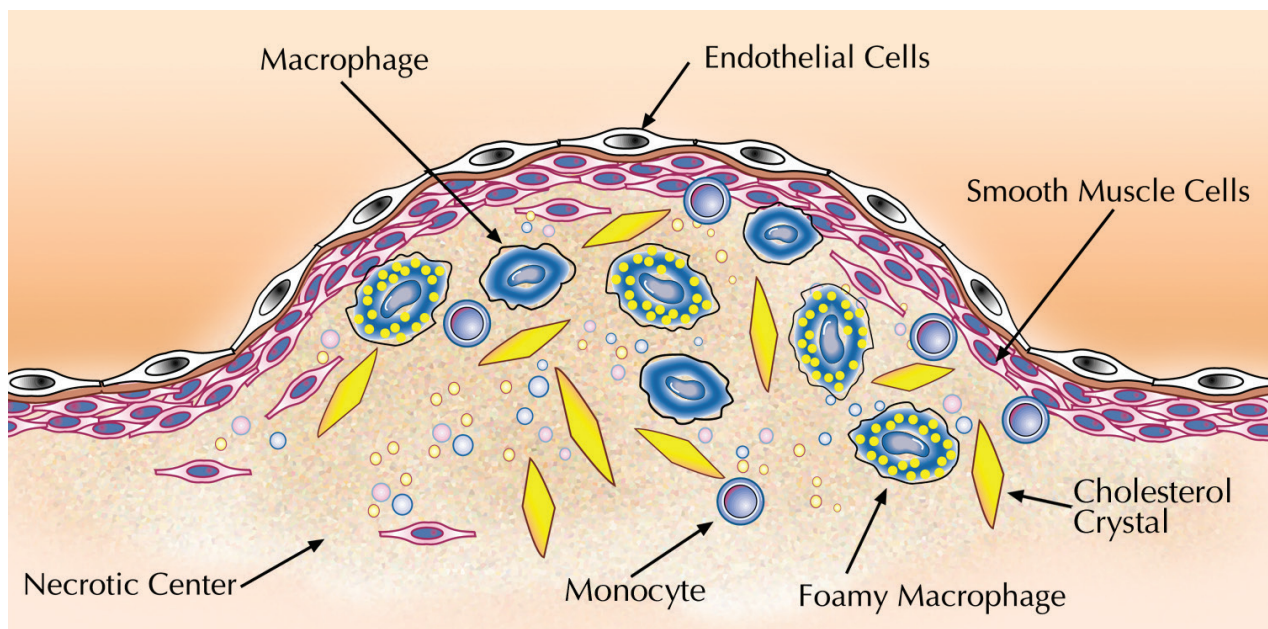


In addition to causing ischemia by obstructing blood flow in arteries that supply the heart, brain, kidneys, and lower extremities, atherosclerotic plaques can undergo disruption and precipitate thrombi (blood clots within the artery) that may lead to myocardial infarction (heart attack), cerebral infarction (stroke), or gangrene of the legs. A well-developed atherosclerotic plaque, or atheroma, consists of a fibrous cap overlying

a lipid mass, called the necrotic center (Figure 2). The superficial fibrous cap is composed primarily of smooth muscle cells (SMCs) and a relatively dense extracellular matrix (ECM) made of collagen, elastin, and proteoglycans. It also contains, especially beneath and to the side of the cap, macrophages, T lymphocytes, and foam cells. The latter are large lipid-laden cells derived predominantly from macrophages as a result of avid ingestion, via scavenger receptors, of modified lipids and lipoproteins (LPs). The necrotic center contains a mixture of lipids, mainly cholesterol and cholesteryl esters, as well as cellular debris, and modified fragments of apolipoprotein B (apoB). Since most of these substances are associated with LDL (the main extra-hepatic source of cholesterol), elevated plasma levels of LDL are considered a major risk factor for cardiovascular disease (CVD).

In 2004, the American Heart Association endorsed a recommendation, based on five major clinical trials of LDL-lowering therapy (with statins), to significantly reduce the desired baseline levels of LDL from 130 mg/dL to less than 100 mg/dL for persons at moderate to high risk for heart disease (1). Since then, supporting evidence for the benefit of cholesterol-lowering regimens has continued to grow, based on studies showing high plasma LDL concentrations to be proatherogenic *in vitro* and *in vivo* (2) and countless other investigations unequivocally

Figure 2- Schematic illustration of Atherosclerotic Plaque

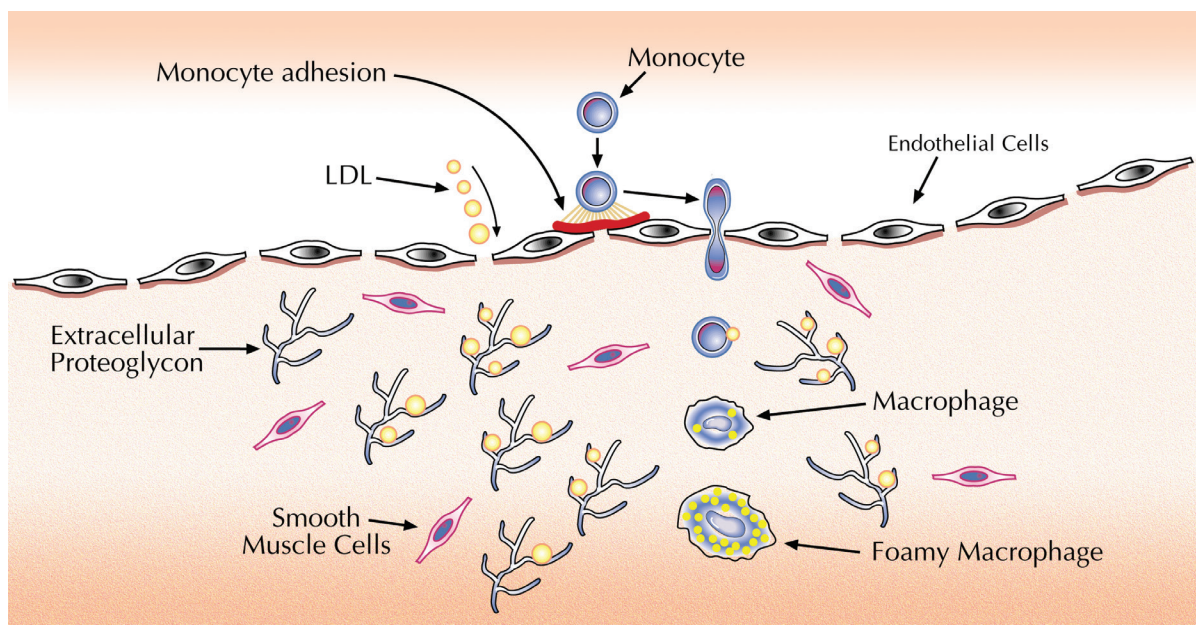


establishing LDL as a cause of atherosclerotic CVD (3). Despite these findings, the utility of LDL as a biomarker has long been complicated by the fact that plasma concentrations of LDL are insufficient and sometimes misleading predictors of future cardiovascular events (4). Instead, the atherogenic potential of LDL and other LPs is influenced to a larger extent by variations in particle size and apoprotein content. For example, HDL (the good cholesterol) and LDL (the bad cholesterol) are very similar in terms of size, density, and lipid composition, but contain different apoprotein constituents. An observational study found that people with homozygosity for a certain genetic variation at the human CETP gene have larger LDL particles, and that this genotype is associated with exceptional longevity and a markedly reduced risk of CVD, regardless of LDL levels (5). On the other hand, association of apoprotein(a) with LDL generates a more atherogenic particle called Lp(a), which is now considered an independent risk factor for acute coronary events in both men and women (6). Notably, evidence from both clinical trials and basic research suggests that statin therapy significantly reduces the baseline levels of inflammatory mediators (e.g. C-reactive protein) independently of LDL lowering (7). Thus, the anti-inflammatory properties of statins, although initially unexpected, could be a major contributing factor toward their clinical efficacy in reducing the rates of cardiovascular events.

Advances in cardiovascular research have established a fundamental role for inflammation in all stages of ATH and shown retention of apoB-containing LPs in the intima of arterial walls to be a key initiating event in atherogenesis (Figure 3) (8). The retention of atherogenic lipoproteins results primarily from ionic interactions between positively charged residues of apoB and negatively charged moieties of arterial extracellular proteoglycans (9). ApoB is a very large protein (MW 513 kDa) and the predominant apoprotein constituent of LDL. The principal proteoglycan-binding domain of apoB was identified as a stretch of 11 basic amino-acid residues that span from residue 3359 through residue 3369 (10). A single point mutation, which changes lysine-3363 to glutamic acid, generates a mutated apoB protein that possesses normal LDL-receptor-binding capacity but impaired ability to interact with proteoglycans. Transgenic mice carrying this mutation were found to be significantly more resistant to experimental ATH than control mice, demonstrating the critical role of lipoprotein retention by proteoglycans (9). The cascade of events elicited by binding of LDL to intimal extracellular proteoglycans, which ultimately leads to thrombosis, is a topic of active research. The emerging picture is outlined below.

LDL plays a vital physiological role in supplying peripheral cells with cholesterol, which is an indispensable constituent of cellular membranes.

Figure 3- Schematic illustration of early events in ATH



En route to delivering cholesterol to arterial cells, LDL can be intercepted and retained by extracellular proteoglycans, which render it susceptible to modification. Sphingomyelinase and lipoprotein lipase are two key enzymes implicated in this process (11). Arterial endothelial cells and SMCs respond to irritation by modified LDL by secreting leukocyte adhesion molecules (e.g. VCAM-1) and chemokines (e.g. MCP-1), which facilitate trafficking of circulating monocytes into the intima. The recruited monocytes perpetuate a local inflammatory response, digest some modified LDL, and become macrophages. Locally expressed cytokines such as M-CSF augment the expression of macrophage scavenger receptors, leading to increased uptake of modified LDL and formation of macrophage foam cells. The conversion of macrophages to foam cells is accompanied by the secretion of “messenger” cytokines (e.g. IL-6), which stimulate hepatic expression of acute-phase proteins, including C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1). These proteins, which play a central role in mediating both acute and chronic inflammatory responses, can accelerate the evolution of atherosclerotic lesions by promoting T-cell activation and infiltration into the atheroma. Activated T lymphocytes secrete cytokines that elicit transformation of SMCs from the contractile to the proliferative state. Proliferating SMCs express elastin and collagen-degrading enzymes, which enable them to penetrate through the ECM of the growing plaque. Normally, following the expansion of SMCs, the cells restore the characteristic dense ECM of their tissue by synthesizing increased amounts of matrix constituents. However, in the atheroma, this synthesis can be halted by T-cell-derived γ -interferon, causing the fibrous cap to gradually become thinner, weaker, and more susceptible to rupture. When the plaque rips open, procoagulants such as tissue factor and thromboxane A₂, along with necrotic debris, cholesterol and other plaque contents, come into contact with the blood, and thrombosis ensues.

Experimental data suggest that elevated baseline levels of circulating inflammatory mediators are associated with increased cardiovascular risk and

can predict adverse outcomes in persons with suspected acute coronary syndromes. To date, a variety of inflammatory biomarkers have proven to have predictive value for future vascular events, including acute phase proteins (e.g. CRP, SAA, and fibrinogen), cell adhesion molecules (e.g. sICAM, and selectins), and proinflammatory cytokines (e.g. IL-6, TNF- α , MCP-1, and placental growth factor). For example, multiple studies have demonstrated that baseline levels of CRP are a reliable measure of underlying ATH and a strong predictor of future myocardial infarction and stroke. Consequently, basal levels of CRP of <1, 1-<3, and \geq 3 mg/L have been defined as low, moderate, and high cardiovascular risk, respectively (12).

In summary, insights gained from the link between inflammation and ATH have considerable potential to yield improved therapeutic and diagnostic tools to better prevent ATH and manage its severe complications.

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