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EDITORIAL

Atherosclerosis: an Athero-Thrombo-Inflammatory Disease

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ABBREVIATIONS
CAD = coronary artery disease
CRP = C-reactive protein
GWAS = genome-wide associated studies
HDL = high density lipoprotein
IL = interleukin
LDL = low density lipoprotein
Lp (a) = lipoprotein a
Lp-PLA2 = lipoprotein associated phospholipase A2
MMPs = matrix metaloproteinases
ROS = reactive oxygen species
SMCs = smooth muscle cells
TGF = tissue growth factor
Th = T-helper (cells)

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ABSTRACT

Classical risk factors for the development of atherosclerosis include hypercholesterolemia, hypertension, smoking, and diabetes. When the atheromatous plaque erodes or ruptures, local thrombosis develops which leads to partial or complete vessel occlusion with its attendant potentially catastrophic consequences. Thus, the term athero-thrombotic disease has been adopted. However, inflammation is also a major contributor to the initiation and evolution of this process and has not been adequately addressed. The concept that atherosclerosis is an inflammatory disease has caused a paradigm shift in our understanding of its pathogenesis. Recent convincing evidence has accumulated that inflammation plays a fundamental role in atherothrombosis and the associated risk may be equal to that of hyperlipidemia. Based on this concept, new biomarkers and novel anti-inflammatory and immune therapies are being currently tested for managing atherosclerotic cardiovascular disease.

INTRODUCTION

Atherosclerosis is derived from the Greek words 'athera' (ἀθήρα) meaning soft gruel-like (porridge-/mush-/paste-like) fatty deposit and 'sclerosis' which means hardening. Atherosclerosis is a pathological process that affects large- and medium-sized arteries and causes coronary artery disease (angina pectoris and myocardial infarction), cerebrovascular disease (ischemic stroke and vascular dementia) and peripheral vascular disease (intermittent claudication and gangrene). Atherosclerosis is a chronic cumulative disease progressing over years. It is characterized by atherosclerotic plaques formed in the wall of the vessels, consisting of necrotic cores, calcified regions, accumulated modified lipids, inflamed smooth muscle cells (SMCs), endothelial cells, leukocytes, and foam cells.[1,2] Lesions begin early as fatty streaks and progress into pathologic lesions under the influence of both genetic and lifestyle insults. Classical risk factors include *hypercholesterolemia, hypertension, smoking* and *diabetes*. When the atheromatous plaque erodes or ruptures, the coagulation cascade is activated and local thrombosis occurs leading to partial or complete vessel occlusion locally or at a distance. Thus, the term athero-thrombotic disease has been adopted. However, inflammation is also a major contributor to the initiation and evolution of this process and has not been adequately addressed. The concept that atherosclerosis is an inflammatory

disease has caused a paradigm shift in our understanding of its pathogenesis.[1,3] It thus appears that the early stages of the disease process simulate chronic inflammation similar to that noted in other diseases in other organs, such as rheumatoid arthritis, liver cirrhosis or pulmonary fibrosis.[4-6] The early stages are also similar to the reaction observed in asthma (infiltration by T lymphocytes and monocytes, converted into macrophages, followed by proliferation of fibrous tissue).[5]

ATHEROSCLEROSIS: AN INFLAMMATORY DISEASE

Information that atherosclerosis is an *inflammatory disease* comes from several facts and findings.[1-4] There is immune activity in the atheromatous plaque, with the presence of T cells and macrophages, human leukocyte antigen, costimulatory factors, and cytokines. A systemic response is elicited with increase in C-reactive protein (CRP), interleukin (IL)-1, IL-6, and other antibodies. There is a genetic association detected between alleles of immune and inflammatory genes. There is information on immunopathogenesis of major effects of immune factors in model organisms. Inflammation in coronary arteries leads to release of inflammatory mediators into the circulation and triggers acute phase reaction in the liver.

Inflammation is typically triggered when bacterial pathogens invade the organism. Both the innate (macrophages, endothelial cells and other cells) and the adaptive (T and B cells) immune systems are involved. Macrophages and T cells accumulate at sites of LDL retention in the forming atherosclerotic plaque, which is a site of immune inflammation. Toll-like receptors recognizing pathogen molecules trigger inflammation. Toll-like receptors can also recognize danger-associated endogenous molecules, like stress inducible cytosolic heat shock proteins, components of oxidized LDL, nucleic acids, etc. The innate immune response of macrophages is initiated by cholesterol crystals that activate a component of the innate immune system, the inflammasome, which is a multiprotein oligomer consisting of caspase 1, PYCARD (apoptosis-associated speck-like protein), NALP protein [a nucleotide oligomerization domain (NOD)-like receptor] and sometimes caspase 5, expressed in myeloid cells.[7] The activated T cell can instruct the B cell to make antibodies to its cognate antigen and activate the macrophage to promote inflammation.

Interleukin (IL)-1 consists of two distinct ligands, IL-1alpha and IL-1beta, with similar biological activities that signal through the IL-1 type I receptor (IL-1RI). A naturally occurring IL-1 receptor antagonist (IL-1Ra) binds to IL-1RI without initiating signal transduction and prevents IL-1 signaling, competitively inhibiting IL-1-mediated responses. Emerging evidence suggests that interleukin-1 (IL-1) may promote the formation of atheromatous lesions, enhance vascular inflammation, and trigger plaque destabilization.[8] Following acute myocardial infarction, IL-1 critically regulates the inflammatory response and is implicated in adverse remodeling by enhancing expression of matrix metalloproteinases. Furthermore, current available data also raise the possibility that IL-1 inhibitors (such as anakinra, a nonglycosylated recombinant human IL-1Ra) may be of clinical use in certain cardiovascular patients. On the other hand, lack of interleukin 1β or NLRP 3 inflammasome of innate immunity impressively reduces atherosclerosis. Finally, there is recent evidence for participation of mast cells in the process of atherosclerosis, as they release vasoactive substances and may be involved in several atherogenic actions, observations that may have some therapeutic implications.[3]

Activated T cells attach to the vascular surface via cell adhesion molecules and migrate into the intima. [9] When interacting with protein antigens (oxidized LDL, heat shock protein 60, and/or bacterial antigens), T helper (Th)-1 cells are formed which release pro-inflammatory markers and initiate a cascade of inflammation leading to atheromatous lesion formation and plaque vulnerability. Virtually, the atheroma is a Th1 lesion; Th1 cells are prevalent in human lesions; a local Th1 response to LDL autoantigen promotes atherosclerosis;[10] lack of Th1 cells reduces atherosclerosis in hypercholesterolemic mice. T helper 1-associated cytokines such as IL-1, interferon-γ, IL-6 and IL-12 within the atherosclerotic lesion, are proatherogenic and lead to enhanced activation and recruitment of T cells, macrophages and dendritic cells in the plaque. A disturbed balance between Th-1 and Th-2 cytokines has long been considered as the underlying cause of the autoinflammatory pathology in atherosclerosis. Th2 cytokines such as IL-5 and IL-10 are antiatherogenic and may counteract the Th1 cytokines. In general, both lack of innate (inflammasome) or adaptive immunity (B and T cells) in mice leads to dramatic reduction of atherosclerosis, without affecting cholesterol levels.

There is also a role of cytotoxic T cells in atherosclerosis. There is abundant T cell death in atherosclerotic plaque. CD8+ T cells kill target cells via cell-cell contact. A total of 30% of T cells in human plaques are CD8+ cells. Activation of CD8+ T cells to an artificial antigen on vascular smooth muscle cells is strongly pro-atherogenic in mice. CD137 ligand, a TNF-like molecule, which is also found in human atherosclerotic plaques, promotes recruitment and activation of cytotoxic CD8+ T cells.

Several pathophysiologic observations in both humans and animals have led to the hypothesis of response-to-injury for atherosclerosis, and recent data emphasize *endothelial dysfunction* rather than denudation, as the initiating stage in a chronic inflammatory atherosclerotic process (Fig. 1).[1,3] Possible causes of such endothelial dysfunction may comprise elevated and modified (oxidized or glycated) LDL; free radicals from cigarette smoking, hypertension, and diabetes mellitus; genetic abnormalities; increased homocysteine; infectious agents such as herpesviruses or *Chlamydia pneumonia*; and combinations

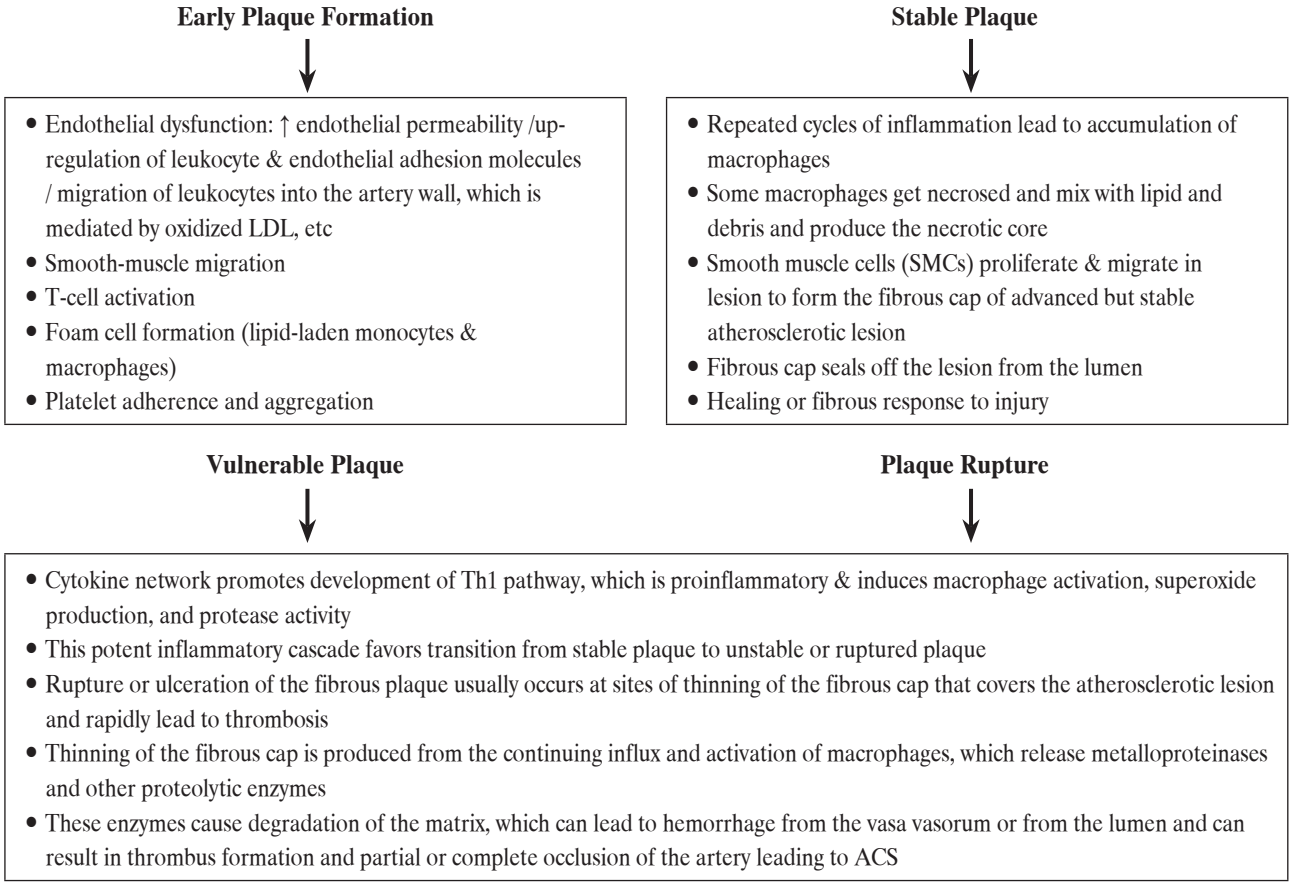

FIGURE 1. Role of the Deleterious Effect of Inflammation in Atherosclerosis (see text for discussion). ACS = acute coronary syndromes; LDL = low dense lipoprotein; SMCs = smooth muscle cells; Th = T helper (cells).

of these or other factors.[1]

Lipoprotein (a) resembles LDL but possesses a unique glycoprotein apolipoprotein a (apo a) group and exists in different isoforms with kringle domains that are similar to those found in plasminogen. An elevated level of Lp (a) is a risk factor for atherosclerosis because it promotes inflammation. Its activity appears to be facilitated by increased levels of homocysteine and LDL and by diabetes. Lp (a) induces proinflammatory molecules via its apo a, among which is the tissue factor that is also prothrombotic. Animal studies show that apo a decreases the amount of plasmin and tissue growth factor beta (TGF-β), whose physiologic role is to limit inflammatory responses and prevent the migration and proliferation of smooth muscle cells.

Inflammation can also be implicated in the occurrence of plaque rupture and development of thrombosis, which can lead to acute myocardial infarction (Fig. 1).[1,11] When activated in the intima, the T lymphocytes produce pro- inflammatory cytokines, inducing production of extracellular matrix-degrading metaloproteinases (MMPs) (which weaken the fibrous cap of the plaque) and of the potent procoagulant tissue factor (which initiates the coagulation cascade). Inflammation also inhibits the production or promotes degradation of collagen and hence further influences the strength and stability of the fibrous cap. Thus, inflammation contributes to all phases of atherosclerosis, from its initiation to its ultimate complication of thrombosis (Fig. 1, Table 1). Presence of multiple types of vulnerable plaques suggests that atherosclerosis is a diffuse inflammatory process. [11]

GENETIC STUDIES

Recent genome-wide associated studies (GWAS) have identified novel loci associated with coronary artery disease (CAD) or myocardial infarction. Interestingly, recent studies identified novel inflammation-related loci associated with CAD risk, including a region near the major histocompatibility complex (MHC) on chromosome 6p21 and the chemokine ligand 2 (CXCL2) on chromosome 4, encoding an atheroprotective chemokine.[12-14] Both GWAS and candidate gene

TABLE 1. Factors Determining Atheromatous Plaque Vulnerability, Rupture and Myocardial Infarction

Large lipid necrotic core	Role of core as a vulnerability factor still debated	Some have found larger pool of extractable lipid in symptomatic than in asymptomatic patients		
Thin fibrous cap	Its resistance depends on presence of functioning SMCs & related extracellular matrix that maintains the fibrous cap			
Inflammatory activity in the plaque	Evolution of atheromas modulated by innate & adaptive immune responses	When selective recruitment/ activation of Th1 T cells is triggered in plaque, a potent inflammatory cascade is initiated	Th1 T cells release IFN-γ, playing a crucial role in atherosclerosis	IFN-γ activates macrophages, promotes pro-coagulant protein & MMP secretion, inhibits SMC proliferation, & downregulates α-actin & collagen expression
Adventitia Inflammation	Lymphocytes, macrophages, & mast cells have been found in contact with sensory nerve fibers			
Diffuse inflammation & vulnerability	Presence of multiple vulnerable plaques in coronary tree	Presence of active multicentric inflammatory infiltrate in coronary vessels in fatal MI	Increased MPO activity in coronary vessels in unstable angina	Activated T cells found in peri-MI area & remote regions in patients with a first MI
Expression of factors that weaken the fibrous cap	Cell migration into the lesion (T cells, foam cells, macrophages)	Proliferation of elements in the lesion (cells, matrix-degrading enzymes, cytokines, growth factors, oxidative excess)	Impaired NO function/ Production & degradation of the extracellular matrix (proteases/ MMPs, cytokines, ROS)	Apoptosis of smooth muscle cells
Physical forces acting on fibrous cap	Circumferential force (induced by blood pressure)	Shear stress	Vasospasm	
Newly formed microvessels (vasa vasorum) / Neoangiogenesis	These vessels are weak and could be responsible for intraplaque hemorrhage			
Intraplaque hemorrhage	From cracks or fissures at luminal surface at its thinnest portion, or from rupture of vasa vasorum	Contributes to growth of the lipid necrotic core	Facilitates a more rapid progression & rupture of plaque	

MI = myocardial infarction; MMPs = matrix metaloproteinases; MPO = myeloperoxidase; NO = nitric oxide; ROS = reactive oxygen species; SMC = smooth muscle cell; Th = T helper (cells)

studies lend support to the hypothesis that proinflammatory pathways, involving both innate and adaptive immunity, play a causal role in CAD. The ABO locus, also linked to CAD risk by the GWAS approach, is related to multiple phenotypes, including plasma interleukin-6 (IL-6) levels. Relevant to inflammation, the 9p21 CAD risk locus appears to play a role in interferon-gamma signalling. Candidate gene studies also support a causative role of inflammation pathways in atherosclerosis. Of note, a common loss of function coding variant in the IL-6 receptor gene (IL6R) is associated with a reduction in CAD risk.[13]

ATHEROPROTECTION

However, not all immunity is pro-atherogenic. There is a defense mechanism fighting back. Pro-atherogenic immunity can be modulated by inhibitory stimuli. LDL immunization or immunomodulatory intravenous immunoglobulin reduce atherosclerosis. Subpopulations of B and T cells are atheroprotective. As discussed earlier, Th2 cytokines such as IL-5 and IL-10 are antiatherogenic and may counteract the Th1 cytokines. Transforming growth factor beta (TGF-β) derived from T-cells has a protective effect. Regulatory T-cells use TGF-β to suppress atherosclerosis. Thus, several therapeutic opportunities may emerge by taking advantage of knowledge expansion regarding blocking antibodies to LDL/oxidized LDL, targeting T regulatory cells for atheroprotective vaccination, blocking inflammatory mediators (cytokines, leukotrienes) and/or immune activation (CD137, etc) or using anti-inflammatory cytokines as atheroprotecive agents. Interleukin-1 has been implicated to promote the formation of atheromatous lesions, enhance vascular inflammation, and trigger plaque destabilization, raising the possibility that IL-1 inhibitors, such as anakinra, a nonglycosylated recombinant human IL-1Ra, may be clinically useful agents to protect patients with CAD.[8] High density lipoprotein cholesterol (HDL) inhibits oxidation of LDL and blocks the proinflammatory effects of oxidized LDL. HDL provides protection against atherosclerosis by promoting the activity of antioxidant enzymes. Animal studies also show that the key protein of HDL, apolipoprotein A-I, may prevent the oxidation of LDL.

BIOMARKERS

Thus, there is compelling evidence that atherosclerosis should be regarded as an inflammatory disease principally triggered by LDL accumulation. However, inflammation is an independent risk factor. This notion that inflammation is heavily involved in atherosclerosis has spurred the discovery and adoption of inflammatory biomarkers for cardiovascular risk prediction (Table 2).[15-17] Most of the biomarkers associated with atherosclerosis are indeed indicators of inflammatory

TABLE 2. Biomarkers of Atheromatous Plaque Inflammation

Markers of Inflammation	Metabolic Markers	Lipid Markers	Markers of Plaque Neovascularization & Thrombosis	Markers of Endothelial Dysfunction	Oxidative Stress Markers
CRP	Insulin	LDL-C	Angiogenic cytokines (placental growth factor, stroma-derived factor 1)	NO	MPO
Pentraxin 3	Glucose	HDL-C	Nicotine	ADMA	
Soluble CD40 ligand	Adipokines (leptin, resistin)	oxLDL-C	Tissue factor	Soluble vascular adhesion molecules	
TNF	Inflammatory cytokines (TNF)	Small dense LDL-C		vWF	
Cellular adhesion molecules (ICAM-1, VCAM-1	Adiponectin (vasoprotective)	Lp(a)		Endothelial progenitor cells	
Cytokines (IL-1, IL-18)		Lp-PLA2			
Metalloproteinases					

ADMA = asymmetric dimethylarginine; CRP = C-reactive protein; HDL-C = high density lipoprotein cholesterol; ICAM = intercellular adhesion molecule; LDL-C = low density lipoprotein cholesterol; Lp(a) = lipoprotein a; IL = interleukin; Lp-PLA2 = lipoprotein phospholipase A2; MPO = myeloperoxidase; NO = nitric oxide; oxLDL-C = oxidized LDL cholesterol; TNF = tumor necrosis factor; VCAM = vascular cell adhesion molecule; vWF = von Willebrand factor

response.[11] Current inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), adiponectin, soluble CD40 ligand, myeloperoxidase, lipoprotein associated phospholipase A2 (Lp-PLA2), pentraxin-3, cytokines such as IL-6 and IL-18, proteases such as matrix metalloproteinase-9, are informative and have generated considerable attention, but their use as a screening method is debated. Among them, CRP has emerged as a leading biomarker of inflammation for clinical application.

ANTI-INFLAMMATORY THERAPIES

Furthermore, *anti-inflammatory therapies,* e.g. TNF blockers, methotrexate, statins, etc, will need to be considered and evaluated for their effect on cardiovascular disease.[18] Half of coronary events are explainable by the presence of traditional risk factors (hypercholesterolemia, hypertension, smoking, diabetes and metabolic syndrome), however, the other half may be related to vascular inflammation, infectious agents or other hitherto unknown factors. Thus, although hypercholesterolemia is important in about half the patients with cardiovascular disease, other factors need to be considered. Atherosclerosis does not result merely from accumulation of lipids. Recent evidence has established the important role and contribution of inflammation in the pathogenesis of atherosclerosis. We need to selectively modify the deleterious components of arterial inflammation and enhance the protective elements, particularly in those other half of patients with cardiovascular disease who do not have hypercholesterolemia.[1] Some standard therapies for CAD prevention (e.g. statins) have anti-inflammatory effects that might contribute to their clinical benefit; however, prospective studies are necessary to test directly the benefits and safety of specific therapies targeting the inflammatory process.

Antioxidants, such as vitamins A, C, and E are known to have anti-inflammatory effects on cells.[19] Antioxidants seem to reduce fatty streaks in arteries of animals and enhance the resistance of human LDL (in vitro) to oxidation. High doses of vitamin E (α-tocopherol) reduce the release of proinflammatory cytokines and decrease adhesion of monocytes to endothelium. Vitamin E has been shown to reduce CRP levels in individuals with risk factors and in patients with cardiovascular disease. Several biological functions of vitamin E which appear to improve the imbalance between oxidative stress and antioxidant status, at least in plasma (but not in plaques) could account for its protective effect against the development of atherosclerosis. It has been proposed that flavonoids may act in the arterial wall to suppress LDL oxidation caused by macrophages and inflammatory responses, resulting in a decline of CAD. Different classes of flavonoids can be found in citrus fruits, herbs, legumes, fruits and vegetables. Flavonoids in plants (soybean) and in red wine decrease reactive oxygen species (ROS) production and maintain or enhance the balance between nitric oxide (NO) synthase and endothelin-1 in the endothelium, thus helping to maintain normal vascular cell functions. Atherosclerosis is lessened in animals fed diets containing soy protein compared with those fed diets with animal protein.

Current evidence supports the use of *statins* as an anti-inflammatory intervention in atherosclerosis due to both LDL-lowering and direct anti- inflammatory effect. Analysis of the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy– Thrombolysis In Myocardial Infarction 22) study, suggested such dual mechanism of benefit of statin therapy, LDL-lowering, and a direct anti-inflammatory effect independent of LDL-lowering, reflected by reduction of high-sensitivity CRP (hsCRP).[3,20] Specifically, within the PROVE IT–TIMI 22 trial, clinical outcomes were best among statin-treated patients who not only achieved LDL-C levels below 70 mg/dl, but who also achieved hsCRP levels below 2 mg/l.[3,20]

Recently, the U.S. National Institutes of Health (NIH) decided to launch an international multi-center trial, the Cardiovascular Inflammation Reduction trial *(CIRT)*, to determine whether an anti-inflammatory drug can reduce heart attacks, stroke and deaths due to cardiovascular disease in individuals at high-risk.[21-23] These are patients with a history of myocardial infarction within the past 5 years, and who also have diabetes type 2 or metabolic syndrome. The trial will randomly assign patients to low-dose *methotrexate* (10-20 mg weekly) for 3-4 years or placebo. CIRT will enroll 7,000 patients at 350-400 sites across the US and Canada over the next 2.5 years and will follow them for 2-4 years (average 2.5 years). Site selection will begin in November 2012, and patient recruitment will start in March 2013.

IMMUNIZATION

Finally, considering atherosclerosis as an autoimmune disease, *vaccination* can provide an alternative treatment for atherosclerosis.[18,24] Thus, immune therapies are on the horizon as the next frontier in the battle against atherosclerosis. Nilsson and collaborators are in the process of developing the peptide vaccine CVX-210, in a subcutaneous and a nasal version, which is made up of fragments of apolipoprotein B, the protein permanently associated with LDL, and they are in the planning stage of Phase I trials for the subcutaneous form.[24] On the other hand, for passive immunization in atherosclerosis, there are monoclonal antibodies in development, targeting oxidized LDL. This includes BI-204 monoclonal antibody, which is in Phase II trials. A promising vaccination strategy will be one that results in plaque stabilization in addition to reducing plaque development. Since atherosclerosis prevails at a very young age but only manifests itself later in life, the majority of individuals will benefit from a vaccination strategy early in life that prevents the development of lesions, while patients

already afflicted by the disease will benefit from strategies that focus on plaque stabilization.

CONCLUSION

Despite the irrefutable utility of traditional risk factors (hypercholesterolemia, diabetes, hypertension and smoking) in assessing the risk of and guiding our approach to atherosclerosis, we are still left with an incomplete picture. Indeed, as many as half of cardiovascular events occur in individuals with plasma cholesterol concentrations below the recommended levels of 200 mg/dL for total cholesterol and 130 mg/dL for LDL cholesterol. Recent evidence of the involvement of inflammation in atherosclerosis has spawned new interest in understanding and solving the enigma of atherosclerosis, which plagues the world. Thus, attention has been focused on this exciting pathophysiological mechanism of atherosclerosis which may provide additional information for cardiovascular risk stratification, prediction and cardiovascular disease management. Shedding further light and providing new insight into the mechanism of this unrelenting disease will help evaluate the role of emerging biomarkers in the clinical management of atherosclerosis and targeting novel therapies. Indeed, evidence has accumulated that inflammation plays a fundamental role in atherothrombosis and the risk of CAD associated with inflammation could be equal to that of hyperlipidemia. Future, randomized trials applying the inflammatory hypothesis of atherothrombosis will directly test novel anti-inflammatory therapies in high risk patients and provide eagerly awaited information regarding their efficacy.

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