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Katsiari CG, Bogdanos DP, Sakkas LI

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Inflammation and cardiovascular disease

Christina G Katsiari, Dimitrios P Bogdanos, Lazaros I Sakkas

ORCID number: Christina G Katsiari (0000-0002-4174-6576); Dimitrios P Bogdanos (0000-0002-9697-7902); Lazaros I Sakkas (0000-0002-7670-3314).

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Christina G Katsiari, Dimitrios P Bogdanos, Lazaros I Sakkas, Department of Rheumatology and Clinical Immunology, Division of Medicine, University of Thessaly, Larissa 41110, Greece

Corresponding author: Lazaros I Sakkas, Professor, FRCP (Hon), MD, PhD, Department of Rheumatology and Clinical Immunology, Division of Medicine, University of Thessaly, Panepistimiou 1, Larissa 41110, Greece. lsakkas@med.uth.gr

Telephone: +30-241-3502813

Abstract

Cardiovascular disease (CVD) has been associated with the so-called traditional risk factors, such as hypertension, hypercholesterolemia and cigarette smoking. Chronic inflammation, exemplified by elevated high sensitivity C-reactive protein, has been added to these risk factors for CVD as non-traditional risk factor. There are two aspects in this association. The first is whether inflammation plays a pathogenic role in traditional risk factors-mediated CVD or it is just an epiphenomenon. The second is whether chronic inflammation caused by an inflammatory disease has any impact on CVD. Accumulated data have shown that inflammation has a central and inciting role in the development of atherosclerosis leading to increased CVD risk. How inflammation contributes to CVD is a topic of continuous research where mechanisms involving both innate and adaptive immune pathways are involved. Endothelial dysfunction, oxidative stress in vascular endothelial cells, macrophage accumulation, formation of inflammasome, production of tumor necrosis factor (TNF)- α , IL-1 and IL-6 characterize the inflammatory process leading to atherogenesis. Recently clonal hematopoiesis of indeterminate potential represents a surprising and novel mechanism underlying atherogenesis. Data from chronic rheumatic inflammatory diseases exemplify the complexity of mechanisms leading to increased CVD, while they also provide evidence that anti-inflammatory biologic drugs, such as anti-TNF and anti-IL6 agents, could control atherogenesis and ameliorate CVD risk. Recent groundbreaking work using biologic anti-IL-1b therapy to treat men and women who have had a prior heart attack provides the best proof of the pathogenic contribution of inflammation in the development of CVD.

Key words: Cardiovascular disease; Coronary artery disease; Atherosclerosis; Inflammation; Innate immunity; Adaptive immunity; Biologic drugs

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Core tip: The association of inflammation with cardiovascular disease (CVD) has two

aspects. The first is whether inflammation plays a pathogenic role in traditional risk factors-mediated CVD or it is just an epiphenomenon. The second is whether chronic inflammation caused by an inflammatory disease has any impact on CVD. Chronic inflammation exemplified by elevated high sensitivity C-reactive protein has been added for risk factors for CVD. How inflammation contributes to CVD is a topic of continuous research. A trial showing that anti-IL1b monoclonal-antibody reduced cardiovascular events is the best proof of the pathogenic contribution of inflammation in atherosclerosis and CVD.

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INTRODUCTION

Cardiovascular diseases (CVD) encompass several entities such as coronary artery disease, cerebrovascular events, peripheral arterial disease, renal artery stenosis and aortic aneurysm. CVD are globally the leading cause of death^[1]. Coronary artery disease and stroke are the cause of 80% of CVD deaths in males and 75% in females^[1]. One major event underlying the development of a CVD is the presence of atheromatosis where cholesterol is indisputably recognized as an environmental and genetic driver of the disease^[2]. In contrast however to the notion that atherosclerosis represents a consequence of lipid accumulation as an ageing and degenerative process, the concept of inflammation is now in the center of current research addressing questions regarding which inflammatory mechanisms are involved as well as ways to intervene therapeutically^[3].

Inflammation in arteries was observed centuries ago

Inflammation as an important factor in atherogenesis seemed to be a rather new concept when few years ago intense research interest appeared in the literature. If we search PubMed using both “inflammation” and “atherosclerosis” as key words, we can see an exponential increase of the number of articles on the subject: from around 80 articles found over an entire 20-years period between 1970 and 1990 to more than 12000 new publications since 2010. However, work by researchers and scholars have taught us that “arteriosclerosis”, inflammation and their in-between link had emerged over 200 years ago, as a long standing scientific discussion that actually evolved in active debate with legendary physician Rudolph Virchow as a strong advocate in favor of the significant role of the inflammatory process^[4]. Considering the almost complete absence of any discussion during the 20th century, it is incredible to realize that the argument around the topic had begun long before Virchow himself. Lobstein^[5,6] is credited as the first to use the term arteriosclerosis. Lobstein^[5,6] having observed inflammation in the internal layer of the aorta, attributed an earlier recognition of this disease to Aretaeus of Cappadocia, a Greek physician from the 1st century, although “it had been all forgotten over the last 18 centuries”. Undoubtedly, a connection between inflammation and atherosclerosis was explicitly made in the beginning of the 19th century as we can read in the writings of the English physician Joseph Hodgson: “...Thus the coats of arteries inflame and pass all the stages of adhesion, suppuration, or gangrene, in the same manner as the skin, a gland or a muscle”^[7].

During the last decades, the emergence of new imaging methods to assess sub-clinical atherosclerosis in epidemiologic and clinical studies^[8-10], combined with advances in molecular biology, prompted the re-emergence of the original theories of atherogenesis and a renewed interest in the putative role of inflammation.

CURRENT DEVELOPMENTS

Inflammation in atherosclerosis involves innate and adaptive immune mechanisms

Atherosclerosis begins with the accumulation of LDL in the subendothelial space of the vessel wall in places where endothelium displays abnormal permeability. A recently recognized mechanism enabling active transportation of LDL through the

endothelial cells involve activin receptor-like kinase 1 (Alk-1)^[11] and scavenger receptor class B type I (SR-BI)^[12]. Accumulated LDL can form bulky complexes and undergo protein modification through the action of lipoxygenases, myeloperoxidases and reactive oxygen species, which induces immune cell mediated phagocytosis^[13] initially by tissue macrophages and dendritic cells residing inside the arterial intima^[14]. Interestingly, it has been recently shown that before the development of atherosclerosis, circulating non-classical monocytes engulf oxidized LDL *via* scavenger receptor CD36 in an effort to protect the vasculature^[15]. Bone marrow derived monocytes on the other hand infiltrate the vascular wall where they differentiate to macrophages, which in turn uptake modified LDL. The formation of lipid droplets inside macrophages through the esterification of cholesterol results in the characteristic foam-like appearance of these cells. Although foamy macrophages were initially considered as the waste bin of lipids, it is now clear that they actively participate in the pathogenesis of atherosclerosis through several inflammatory interactions^[16,17]. It has been shown that the modification of cholesterol inside macrophages activates scavenger receptor CD36, which in turn trigger an array of immune responses downstream Toll-like-receptor (TLR) 4 and 6^[18]. At the same time our understanding of the molecular mechanisms underlying the inflammatory process in atherogenesis was broadened when it was shown that cholesterol crystals inside macrophages, activates caspase-1-activating NACHT, LRR and PYD domains-containing protein 3 (or cryopyrin) (NLRP3) inflammasome leading to the production and secretion of IL-1 and IL-18^[19]. Of note, detailed study using confocal reflection microscopy revealed the presence of cholesterol crystals in the atheromatic plaques inside macrophages as well as in the extracellular spaces found during the very early stages of atheromatosis, pointing towards the fact that the formation of cholesterol crystals drives inflammation rather than follows it^[19]. Moreover, it was later shown that activation of NLRP3 inflammasome is orchestrated by the function of scavenger receptor CD36, where macrophages lacking this receptor were unable to stimulate the production of IL-1^[20].

Along with the autoinflammatory nature of atherosclerosis exemplified by abnormal macrophage polarization^[17], activation of TLRs-mediated pathways and aberrant inflammasome activation and IL-1 production, adaptive immune responses have also a role in the regulation of atherogenesis. Pro-inflammatory T cell subsets (Th1 and Th17) facilitate the progression of atheromatosis through the secretion of interferon- γ , tumor necrosis factor (TNF) and IL-17. On the other hand T regulatory cells (Tregs) have a protective effect through cytokines such as IL-10 and TGF β ^[21,22]. Recently, an interesting hypothesis has been proposed placing atheromatosis inside the broad spectrum of "autoimmune diseases". In particular, although modified oxidized LDL is usually suggested as the responsible antigen provoking T cell polyclonal activation, several data derived from animal studies support the idea that a break of tolerance to native, unaltered apolipoprotein B may represent the trigger for lymphocyte abnormal responses^[22].

Inflammatory cell death and atherosclerosis

Destabilization of the atheromatic plaque constitutes a critical step regarding the risk of acute cardiovascular events^[23]. Although a lot is to be learned about the mechanisms underlying the transformation of an atheromatic plaque from stable to unstable, the development of the necrotic core represents a key event. The necrotic core is created from dead macrophages within the plaque which were not cleared^[24]. During the early stages of plaque formation, macrophage apoptosis represents a protective mechanism leading to reduced cellularity and cholesterol burden within the lesion assuming that efferocytosis (phagocytosis of the dead cells) is intact. In case efferocytosis is impaired or overwhelmed, apoptotic debris starts to accumulate, which can lead to secondary necrosis^[25]. Impaired efferocytosis appear to stem from different abnormalities including aberrant expression of CD47, which leads to reduced recognition of apoptotic cells, as well as impaired expression of crucial surface receptors such as MerTK^[26]. Impaired efferocytosis will lead to secondary necrosis. *In situ* necrotic material is furthermore added through necroptosis of macrophages. Necroptosis which represents a programmed form of inflammatory cell death is thought to be driven by unrelenting cell exposure to lipoproteins and mediated by mixed lineage kinase domain-like pseudokinase (MLKL) and receptor-interacting serine/threonine-protein kinases (RIPK)^[27,28].

The inflammatory link between hematopoiesis and atherosclerosis

Analogous to monoclonal gammopathy of undetermined significance, representing a potential precursor of multiple myeloma, clonal hematopoiesis of indeterminate potential (CHIP) has been recently described as a condition subsequent to somatic mutations within bone marrow cells that could lead to hematologic neoplasia^[29].

Apart from increased risk for developing hematologic cancer, the presence of CHIP has been recently and surprisingly associated with increased risk of CVD: risk of myocardial infarction and stroke increased by 2 fold and risk of premature atherosclerosis in patients younger than 50 years old increased by 4-fold compared to control subjects without CHIP^[30]. Mutations in each of *TET2*, *DNMT3A*, *ASXL1*, and *JAK2* genes were found to be associated with CVD. The effect and underlying mechanisms of *TET2* mutations, which represent one of the most frequently mutated genes linked to CHIP, was further tested in a murine model of atherosclerosis. It was found that loss of Tet2 function accelerated atherosclerosis while in parallel increased macrophage responses to native LDL, including release of inflammatory chemokines, production of IL-1b and activation of inflammasome^[30,31].

Rheumatic diseases as a complex paradigm of the contribution of inflammation to CVD

The link between increased cardiovascular risk and continuous mild elevation of C-reactive protein (CRP), as a marker of persistent low grade systemic inflammation, was initially described in the general population^[32-34]. Rheumatoid arthritis (RA), the prototype systemic inflammatory joint disease, characterized by high levels of CRP and other inflammatory cytokines, leads to increased mortality mainly due to CVD^[35]. In fact, RA has been recently recognized as an independent risk factor for CVD, analogous to diabetes mellitus^[36,37]. Cytokines such as TNF- α and IL-6 have central role in the pathophysiology of RA. The direct impact of such cytokines on human arterial endothelial cells (HAECs) greatly supports their role in atherogenesis. In particular, TNF- α induced upregulation of scavenger receptors (SR) LOX-1 and SR-A^[38] in HAECs and THP-1/macrophages cell line^[39]. IL-6 also induced upregulation of SR-A in HAECs and macrophage while both TNF- α and IL-6 led to the accumulation of oxidized LDL in THP-1/macrophages transforming them to foam cells^[38,39]. Thus, the contribution of systemic inflammation to the increased CVD risk in patients with RA appears to be true but the exact impact in addition to traditional risk factors is still under investigation, where RA-related complications can furthermore act as confounding factors. For instance, in consequence of inflamed joints and increased disease burden, patients with RA display decreased activity, are subjected to increased steroid exposure and are characterized by sarcopenic obesity where loss of muscle mass is combined with increased abdominal fat^[40,41]. All these factors could also have an impact to CVD risk. It should be also added that CVD risk in patients with RA, apart from increased atherosclerosis, is also related to non-ischaemic heart disease stemming from conditions such as myocarditis, left ventricular diastolic dysfunction and pulmonary hypertension^[42,43].

Patients with other chronic rheumatic diseases were also found to have increased CVD risk, namely systemic lupus erythematosus, ankylosing spondylitis and psoriatic arthritis^[44-46]. TNF- α and recently IL-17 have been recognized as significant mediators in the pathogenesis of spondylarthropathies. It was shown that IL-17 and particularly in combination with TNF- α promote pro-inflammatory, pro-coagulant and pro-thrombotic effects in blood vessels. For instance, in primary endothelial cells, IL-17 up-regulated 248 pro-inflammatory genes, and when combined with TNF- α this number increased to 9803^[47]. In addition, IL-17 up-regulated genes critical for coagulation, such as tissue factor, whereas supernatants from IL-17-treated endothelial cells induced strong platelet aggregation^[47].

Targeting inflammation to cure CVD

Attenuation of inflammation should logically diminish the incidence of atherosclerosis and CVD. However, drugs that combat inflammation do not necessarily protect against CVD. On the contrary, potent anti-inflammatory agents such as steroids and non-steroidal anti-inflammatory drugs (NSAIDs) bare warnings regarding associated cardiovascular risk. However, which is their cumulative result on CVD when used in the context of chronic inflammation needs careful consideration. Regarding the use of steroids, a meta-analysis with more than 100000 participants, including a large number of patients with RA, showed that the use of glucocorticosteroids is clearly linked with increased incidence of cardiovascular events^[48]. Things are more complicated when NSAIDs, including selective inhibitors of cyclooxygenase-2 (COX-2) are examined. Rofecoxib for example was withdrawn from the market due to cardiovascular harm, while celecoxib - another COX-2 inhibitor - appears to be much safer^[49]. Interestingly, celecoxib has been shown to have a protective effect on vasculature^[50]. Diverse effects between different NSAIDs however are proposed to stem from differential actions involving COX-2 independent pathways^[51]. In particular, contrary to naproxen and ibuprofen, celecoxib activates COX-2-independent AMPK-CREB-Nrf2 pathways resulting in significant anti-inflammatory effects including inhibition of TNF- α -mediated NF- κ B signaling, and

IL-1 β induction of IL-6^[51].

Successful control of inflammation and disease activity in patients with RA and other rheumatic diseases using conventional and biologic disease modifying anti-rheumatic drugs (DMARDs) appears in some studies to coincide with decreased risk of CVD. Indeed, a recent meta-analysis showed that anti-TNF- α biologic treatment, as well as use of methotrexate - a conventional DMARD - are associated with reduced risk of cardiovascular events^[52]. Moreover, TNF inhibitors showed decreased risk of myocardial infarction when compared to methotrexate and other conventional DMARDs^[53]. In an elegant study in patients with psoriasis and psoriatic arthritis, where men had significantly higher total carotid plaque progression as assessed by ultrasound, TNF-inhibitor treatment was associated with reduced atherosclerosis progression in men but not in women^[54]. Also in PsA patients, aortic vascular inflammation, assessed by 18F-FDG PET CT scan, was reduced in men and women treated with TNF inhibitors^[54]. It should be noted that focal vascular inflammation, assessed by 18F-FDG PET CT scan, precedes calcium deposition, a marker of atherosclerotic plaque progression^[55]. These results provide evidence that TNF-inhibitors decrease vascular inflammation and thus may inhibit atherosclerosis progression but do not explain the difference of TNF- α inhibitor effect on carotid plaque progression between men and women.

Canakinumab is an anti-IL-2 β monoclonal antibody that has been recently developed initially for the treatment of hereditary Cryopyrin-Associated Periodic Syndromes, which represent a subset of hereditary autoinflammatory diseases and is now used for a number of other autoinflammatory diseases such as juvenile idiopathic arthritis among others. In a recent groundbreaking study, canakinumab was however tested in another population. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), a randomized double-blind placebo-controlled trial of over 10000 patients with previous myocardial infarction and high sensitive CRP above 2 mg/L, showed that at median follow up of 3.7 years, canakinumab (150 mg/3 mo) significantly reduced cardiovascular events independent of lipid levels^[56]. Although, a previous study had unexpectedly shown that mice lacking IL-1 receptor display advanced atherosclerosis^[57], and thus disrupting our linear thinking regarding the pro-inflammatory atherogenic effects of IL-1, CANTOS, a large prospective trial, is the best proof of the pathogenic contribution of inflammation in atherosclerosis and CVD in humans to date.

CONCLUSION

Inflammation holds an integral role in atherogenesis and consequent CVD. Numerous mechanisms have been identified (Figure 1). It is expected that different mechanisms may not equally contribute to the development of CVD. Moreover, distinct clinical states may involve separate pathways. The ability to accurately assess the mechanisms underlying CVD risk in each patient represents a true challenge, which currently is only partially evaluated. Knowing which mechanism(s) are crucial among different groups of patients will guide us when and how to intervene. Several drugs used in clinical practice such as monoclonal antibodies, which specifically aim different targets involved in inflammatory interactions, may prove valuable tools towards the control of CVD.

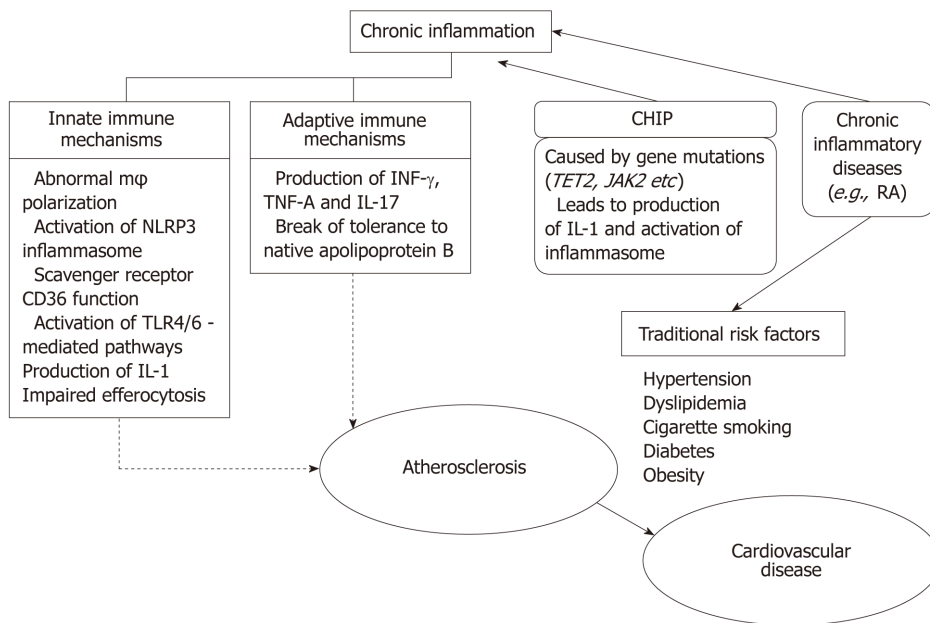


Figure 1 Inflammation and cardiovascular disease. A selection of different mechanisms that have been shown to link inflammation with atherosclerosis and cardiovascular disease along with traditional risk factors, are depicted. Mφ: Macrophage; NLRP3: NACHT, LRR and PYD domains-containing protein 3 (or cryopyrin); TLR: Toll-like receptor; CHIP: Clonal hematopoiesis of indeterminate potential; RA: Rheumatoid arthritis.

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