New Insights into Inflammation in Atherosclerosis

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Submission: September 10, 2018; Published: September 19, 2018

Abstract

In this mini-review recent developments in the pathogenesis, pathophysiology, biomarkers and therapeutics in residual inflammation of atherosclerosis are discussed. New cellular pathways are discovered raising new interest in old therapeutics as colchicine and niacin. Biomarker studies call for more specific and sensitive markers. The recent CANTOS trial provided clinicians evidence that directly targeting inflammation by canakinumab is beneficial for the secondary prevention of cardiovascular disease. Whole genome and exome studies will lead to the discovery of new cellular pathways and treatments of residual atherosclerotic inflammation.

Introduction

Atherosclerosis is an inflammatory disease and a pivotal role for inflammation in the pathogenesis has been recognized in animal models and at the molecular level [1,2]. The recognition of atherogenesis as an active process rather than a cholesterol storage disease or a repository of calcium has highlighted some key inflammatory mechanisms [3]. Mononuclear macrophages contribute to all stages of this disease. Multiple lines of evidence have proven a causal role for low-density lipoprotein (LDL) cholesterol in atherosclerosis. However, even with intense LDL reductions, cardiovascular (CV) events still occur. Inflammation can explain some of this residual risk. After the first anti-inflammatory randomized controlled trial RCT with canakinumab proved for the first time that the presence of leukocytes within atherosclerotic arteries was described in the early 1960’s while macrophages, mast cells, monocytes, natural killer (NK) cells and dendritic cells, as well as non-specialized immune cells such as fibroblasts [11-13].

Lots of adhesion molecules or receptors for leukocytes expressed on the surface of the endothelial cell probably participate in the recruitment of leukocytes to the beginning atheroma. Proinflammatory cytokines can act at different stages. Interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha) can regulate the expression of adhesion molecules involved in early and late leukocyte recruitment. IL-1 and TNF-alpha can induce local production of growth factors, including fibroblast growth factors (FGFs) and platelet-derived growth factor (PDGF) which attract smooth muscle cells from the tunica media into the intima. Finally, other cytokines and growth factors may be important in the evolution to atheroma

Pathogenesis

Inflammation is a process that plays an important role in the initiation and progression of atherosclerosis [5]. The fundamental lesion of atherosclerosis is the atheromatous or fibro-fatty plaque which is a lesion that causes narrowing of the artery and predisposes to thrombosis, calcifies and causes weakening of the arterial wall resulting in aneurysmal dilatation [6]. Atherosclerosis is a chronic inflammatory and immune disease involving multiple cell types, including monocytes, macrophages, T-lymphocytes, endothelial cells, smooth muscle cells and mast cells [7]. The importance of monocytes and macrophages was noted in the early 1960’s while the presence of leukocytes within atherosclerotic arteries was described in the early 1980’s [8,9]. Macrophages, however, were the first inflammatory cell to be associated with atherosclerosis. Great effort has been devoted to elucidating the molecular mechanisms by which immune cells contribute to atherosclerosis [10]. The innate and adaptive immune systems have evolved to protect humans from pathogens such as bacteria, viruses, parasites, fungi and the presence of infection is detected by specialized cells, such as macrophages, mast cells, monocytes, natural killer (NK) cells and dendritic cells, as well as non-specialized immune cells such as fibroblasts [11-13].

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counteracts collagen production by smooth muscle cells [1,2]. Recently, investigators of Cedars-Sinai Medical Center identified a new cellular pathway that may help explain how arterial inflammation develops into atherosclerosis [14]. They used a bacterial infection to reveal a cascade of events that can lead to inflammation and atherosclerosis. Investigators focused on interleukin-1 beta (IL-1-beta) that helps rally the immune system against infection and injury, but it can also cause chronic inflammation. Using laboratory mice bearing a bacterial infection with Chlamydia pneumoniae, along with human cells cultured in a petri dish, the team discovered that several harmful processes related to IL-1-beta can lead to build up cholesterol in the arteries.

To make its way of the immune system cell, IL-1-beta can use the same channels that are used by cholesterol to exit the cell. The result is a “traffic rush” on those channels that blocks the exit of artery damaging cholesterol and causes it to accumulate in the cell. Once it is released by the cell into the body, IL-1-beta suppresses a chemical receptor that enables niacin, or vitamin B3 to be used in the body. This action is harmful because niacin works by removing cholesterol from cells in the artery walls. When niacin is blocked, cholesterol can accumulate in the artery walls. The suppression of the niacin receptor has another negative effect. It reduces the number of chemical channels that cholesterol uses to exit the immune system cell, causing more cholesterol to be trapped inside. That is because the niacin receptor, besides enabling niacin, also increases these channels as part of its normal function [14].

These are important findings as drugs that inhibit IL-1-beta, such as canakinumab, have shown promise in combatting atherosclerosis and heart disease [4]. The Cedars study raises the possibility that by blocking the initial production of IL-1-beta, rather than just neutralizing it, a stronger positive effect could be obtained in these patients. A drug, colchicine, that blocks IL-1-beta production already exists, but is only FDA approved for gout and Familial Mediterranean Fever (FMF). Two clinical trials are underway to evaluate the drug’s potential for treating atherosclerosis [15]. Another aspect of the Cedar study is re-examination of using niacin therapy for atherosclerosis, which was long used until the 1980’s, when statin drugs were shown to be more effective at reducing cholesterol and cardiovascular risk [16].

Pathophysiology

Hypercholesterolemia is considered as one of the main triggers of atherosclerosis. The rise in plasma cholesterol levels causes changes in permeability of arterial endothelial cells, that allows the migration of lipids, particularly LDL-C particles inside the arterial wall. Circulating monocytes stick to the endothelial cells that express adhesion molecules, for example vascular adhesion molecule-1 (VCAM-1) and selectins, and subsequently migrate with the help of diapedesis into the subendothelial space [17]. Once they reach the subendothelial space, the monocytes gain macrophage characteristics and transform in foamy macrophages. LDL particles in the subendothelial space are oxidized and grow into strong chemo-attractants. These processes only heighten the buildup of massive intracellular cholesterol facilitated through the expression of scavenger’s receptors, including A, B1, C3d, C6d, for phosphatidylserine, and oxidized LDL by macrophages which bind the native and modified lipoproteins to anionic phospholipids. The end outcome is a cascade of vascular modifications which result in formation of a fatty streak, intimal thickening, fibroatheroma and plaque buildup. The clinical sequelae of atherosclerosis are vessel narrowing with symptoms such as angina pectoris and acute coronary syndromes [18].

About 50% of patients develop atherosclerosis in the absence of systemic hypercholesterolemia. Putative antigens as e.g. nicotine, heat shock proteins, components of plasma lipoproteins (Lp’s) and various microbial structures induce an inflammatory process that on its own may generate the atherosclerotic plaque formation [19]. Independently of systemic risk factors atherosclerosis develops preferentially at specific arterial sites such as branch points, outer wall of bifurcations, inner wall of curvatures and cardiac valves characterized by variations in shear stress or flow disturbances [20]. Blood pressure-derived tensile stress and in particular flow generated endothelial stress (ESS) shifts the endothelial cell function towards an atherosclerotic phenotype. Low ESS reduces NO (nitrous oxide)-dependent athero-protection and enhances the uptake and permeability of low-density lipoproteins. ESS promotes oxidative stress and inflammation in the endothelial cell by a process dependent on activation of the transcription factor nuclear factor kappa-B (NF-KB) and activation of sterol regulatory element binding proteins (SRBEPs), a family of endoplasmic reticulum (ER)-bound transcription factors that up-regulates the expression of genes encoding LDL receptors, cholesterol synthetase and fatty acid synthetase [21,22].

Genomic analysis revealed that in arterial regions with non-disturbed flow and normal ESS, the endothelial cell expresses various athero-protective genes and suppress several pro-atherogenic genes, generating stability and quiescence of the area [23,24]. Conversely, in regions with low and disturbed flow and low ESS the athero-protective genes are suppressed, whereas the pro-atherogenic genes are up-regulated thereby promoting atherosclerosis [25,26]. Hence in athero-susceptible sites the endothelial cells are primed or sensitized for atherogenesis, but additional risk factors are required to initiate the disease.

Biomarkers

The value of circulating biomarkers in predicting coronary artery disease is not fully elucidated. Chronic inflammation in cardiovascular disease (CVD) appears to be associated with the oxidative-antioxidative homeostasis, resulting in accumulation of oxidized LDL in the arterial wall [27]. Endogenous antioxidant enzymes such as glutathione peroxidase (GSH-Px) play a major role in maintaining oxidative homeostasis acting as the first-line defense against free radicals [28]. The oxidative process perpetuates an inflammatory response in the subendothelial space as activated cells secrete pro-inflammatory molecules. Expression of TNF-alpha and IL-1 by endothelial cells and monocytes triggers a response
involving monocyte chemo-attractant protein-1 (MCP-1) which promotes monocyte recruitment, macrophage activation and signal expression [27,29]. Other cytokines, among them IL-10 and IL-6 are released in the process of atherosclerosis development [30-32]. C-reactive protein (CRP) synthesis is increased in the liver. CRP activates the complement system that promotes phagocytosis which allows clearance of necrotic tissues in the atherosclerotic plaque and perpetuates the inflammatory response [33,34]. Within this inflammatory response, metabolism biomarkers, e.g., insulin, leptin and adiponectin also play an important role. Adiponectin correlates with lower risk of CAD events, probably through inhibiting TNF-alpha action in endothelial cells, while increased leptin concentration is associated with CVD [35-37].

**High-Sensitivity CRP**

The prognostic value of hsCRP in atherosclerosis is unclear, particularly in statin users. Cainzos et al. [38] evaluated 6757 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) with a median follow-up of 13.2 years. Higher levels of hsCRP were associated with a higher risk of all study endpoints in the unadjusted Cox proportional hazard regression analysis except atrial fibrillation. Among non-users of statins hsCRP only remained associated with venous thromboembolism (VTE) after adjusting for ASCVD risk factors, and did not improve risk prediction either, although it was strongly associated with incident heart failure (HF): (HR for hsCRP>2mg/l vs<2mg/l;3.99,95%CI;2.02,7.90) and all cause death (HR;1.52,95%CI;1.11,2.08) in multivariate analysis and hsCRP significantly improved prediction of HF (area under the curve (AUC) basic model 0.741,AUC basic+ hsCRP 0.788).The authors conclude that the utility of hsCRP for ASCVD prediction was modest. On the other hand, hsCRP was associated with incident VTE in statin non-users, and all-cause mortality and HF in statin users in the latter, hsCRP improved the prediction of incident HF events [38].

**Interleukines**

Cenari et al. [39] have provided important insights into the role of IL-1-beta in mice studies. They demonstrated that IL-1-beta has an impact on atherosclerotic calcification and propose Rac2 (RAS family small GTPase2) as a key signaling molecule that regulates Rac1 mediated IL-1-beta production by bone marrow derived cells of the immune system. Using apolipoprotein E knockout (ApoE-/-) mice fed high fat diet they showed that advanced plaque calcification is associated with increased IL-1-beta and decreased Rac2 levels. They have generated mice with systemic deletion of the gene for Rac2 crossed with ApoE-/- mice and used these to show that calcification is driven by hematopoietic cells that produce IL-1-beta. Finally in a retrospective small clinical trial of patients with coronary artery disease, the authors showed that Rac2 is decreased whereas IL-1-beta and sudden cardiac disease was increased in these patients. These results suggest IL-1-beta may be useful as a biomarker and predictor of calcification risk and cardiovascular end points in patients with coronary artery disease, but the true impact of IL-1-beta on calcification and CVD risk requires further study [39,40]. In a MESA cohort of 668 patients with non-alcoholic fatty liver disease (NAFLD), IL-6 was independently associated with the prevalence and severity of subclinical atherosclerosis. Further research into the longitudinal effects of NAFLD on progressive CVD will determine whether IL-6 is a useful marker of NAFLD-related atherosclerosis [41,42].

In the Tromso Study the association between 28 blood biomarkers and the formation and progression of carotid plaque was studied in a cohort of 703 participants a large biomarker panel was measured in blood at baseline. Carotid ultrasound was assessed both at baseline and 6 years follow-up. Adjusted for traditional risk factors only IL-6 was an independent predictor of plaque progression (OR;1.44,95% CI;1,12-1.85 per SD increase in IL-6 level. The authors concluded that IL-6 is an independent predictor of plaque progression [43].

The interleukin 17A pathway is required for increased vascular inflammation in both nascent and advanced atherosclerosis in mice with renal impairment. IL-17A blockade in established atherosclerotic lesions normalized macrophage content in mice with renal impairment [44]. Human IL-17 receptor A is central for IL-17A signaling similar to mouse [45]. Blocking antibodies for both are now approved for clinical use [46,47]. Studies investigating their anti-atherosclerotic effects in patients with chronic kidney disease (CKD) have not be performed yet. Interleukin-18 (IL-18) is a pleiotropic proinflammatory cytokine which belongs to the IL-1 family. This cytokine is among the more recently recognized cytokines to be involved in the development of various cardiovascular diseases. At one end, studies indicate that IL-18 is a key player that orchestrates the inflammatory cascade associated with the pathogenesis of atherosclerosis whereas others show circulating IL-18 levels to be a prognostic marker [48].

**suPAR**

Recently, Diedrichsen and coworkers examined the association and prognostic role of a systemic marker named soluble urokinase Plasminogen Activator Receptor (suPAR) in major cardiovascular event (MACE)-[49,50]. They studied a large cohort of 1179 participants older than 50 years of age (49% of the study cohort, males and females (52,4%) at moderate to high CV risk or with a history of previous CV event (61,9%) of the study cohort reported MACE at enrollment. At unadjusted analysis suPAR as well as hsCRP was significantly associated with MACE. Progressive adjustment for traditional CV risk factors and a marker of subclinical atherosclerosis, such as coronary artery calcification, CAC, did not change the independent association of both markers of inflammation of MACE [49]. However, the risk associated of high serum levels of suPAR and hsCRP was only modest (HR;95% CI;1,20 (1,04-1,38) and 1,03 (1,003-1,05) for high suPAR and hsCRP, respectively and as far as suPAR is concerned especially driven by a larger risk observed in women [49]. suPAR originates from urokinase Plasminogen Activator Receptor (suPAR) which is a glycosyl-phosphatidylinositol (GPI) linked membrane protein expressed by various cells of the immune system, including monocytes, macrophages and T-lymphocytes, and other cell lines such as endothelial cells, keratinocytes, fibroblast and smooth muscle cells [50].
Additionally, uPAR has been identified in certain tumor cells. Hence numerous medical conditions characterized by different degrees of activation of the immune system may lead to increased levels of suPAR. This may occur during infections as e.g. pneumonia, sepsis and autoimmune disease as well as in patients with solid tumors [50]. Current data also suggest that suPAR may be elevated in CV disease. However, considering the complicated biology and mechanisms responsible for suPAR release in the blood stream one may wonder what are the sensitivity and specificity for chronic vascular inflammation? Obviously, there is a call for a specific and sensitive inflammation biomarker in atherosclerosis [51,52].

**Therapeutics**

Several drugs have been developed to target IL-1 signaling. Anakinra, an IL-1 receptor antagonist, down regulates signaling through both IL-1-alpha and IL-1-beta isoforms and is used to treat rheumatoid arthritis [53]. Canakinumab is a fully human IL-1-beta neutralizing antibody [53]. In terms of CVD prevention canakinumab was particularly attractive since known atherosclerosis risk factors up-regulate IL-1-beta via the NLRP3 inflammasome. Additionally, canakinumab may be less likely to impair host immune function since signaling via IL-1 alpha remains intact. In a pilot study performed in preparation for CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) among 556 diabetic individuals at risk for CVD, canakinumab led to significant decrease in hsCRP, fibrinogen, and IL-6 with no impact on LDL-C or other lipid measures [54]. CANTOS was a randomized, double blind, placebo-controlled trial of canakinumab in 10.061 patients with a history of MI and hsCRP>2mg/l [4]. Such patients with “residual inflammatory risk” rather than “residual cholesterol risk” are a common and very high-risk group [55,56]. Three different doses of subcutaneous canakinumab were used:50,150 and 300 mg given every 3 months. The primary endpoint was a composite of non-fatal MI, non-fatal stroke or cardiovascular death (MACE). There was an additional pre-specified secondary endpoint of MACE along with hospitalization for unstable angina requiring revascularization (MACE+).

Among study participants the mean age was 61 years and nearly 75% were male. Approximately 40% had a history of diabetes and 81% had undergone percutaneous or surgical revascularization. More than 93% were receiving lipid lowering therapy at baseline with a mean entry LDL-C of 82mg/dl and 95% of individuals were taking either an antplatelet or an anticoagulant. The median hsCRP at baseline was 4,2mg/dl. Treatment with canakinumab led to a significant decrease in both hsCRP and IL-6. At 48 weeks, median hsCRP was reduced by 26-41% in a dose-dependent manner. Similarly, at 12 months median IL-6 was reduced by 19-38%. Drug treatment had no impact on LDL-C or HDL-C, had a modest 4-5% increase in median triglyceride (TG) levels [4]. Study participants were followed for a median of 3.7 years. Individuals receiving either the 150 or 300 mg dose of canakinumab experienced a 15% reduction in MACE (p=0,007).

There was a non-significant 7% reduction in the primary endpoint for those receiving the 50mg dose. Similar significant reductions in MACE+ were seen in the higher dose groups (17%; p=0,006) with a non-significant 10% reduction in the 50 mg group. Subgroup analyses showed no evidence of effect modification by sex, age, history of diabetes, smoking history, body mass index, or baseline levels of lipids or hsCRP [57]. In a pre-specified analysis canakinumab efficacy was found to differ considerably based upon the magnitude of inflammation reduction achieved by individual trial participants. Individuals with hsCRP concentration <2mg/l after the first dose of canakinumab experienced a 25% reduction in MACE (p<0,0001) compared to a non-significant 5% in reduction in those with on-treatment hsCRP levels>2mg/l.

These differences persisted even after adjusting for potential confounders, including baseline hsCRP and LDL-C as well as clinical risk factors, including age, sex, smoking history, hypertension and diabetes and BMI, and were consistent in causal inference analysis.

In addition, individuals with a reduction in hsCRP<2mg/l also experienced a 31% reduction in cardiovascular death (p=0,0004) and all-cause mortality (p<0,0001). Those with on-treatment hsCRP levels>2mg/l did not have a significant reduction in these endpoints. Within the overall trial, the number needed to treat (NNT) for the 5 year composite endpoint of MI, stroke, coronary revascularization or all-cause mortality was 24 [57]. This number was 16 for those with on-treatment hsCRP levels <2mg/l and 57 for individuals with on-treatment hsCRP levels>2mg/l. Overall canakinumab was tolerated well with identical discontinuation rates compared to placebo. Mild neutropenia and thrombocytopenia were slightly more common in those treated with canakinumab. Rates of death to infection or sepsis were low but more likely in the canakinumab group (incidence rate 0.31 vs 0.18 per 100 person-years; p=0.02). In terms of types of infections, only pseudomembranous colitis was more common in the treatment group. No opportunistic infections were observed, demonstrating canakinumab is not a clinically immunosuppressive intervention.

Further demonstrating this issue, random allocation to canakinumab as compared to placebo in CANTOS resulted in large and highly significant dose-dependent reduction in cancer fatality, incident lung cancer and fatal lung cancer [58]. With the publication of the CANTOS results, clinicians have definitive evidence that directly targeting inflammation is beneficial for the secondary prevention of cardiovascular disease. Beyond CANTOS, there are several ongoing trials of other anti-inflammatory agents including low dose methotrexate n the Cardiovascular Inflammation Reduction Trial, [59] colchicine in the LoDoCo2 and COLCOT trials [15], as well as proposed trials involving other modulators of IL-1,II-6 and the NLRP3 inflammasome.

**Conclusion**

Even with intense LDL-C reduction a residual inflammatory cardiovascular risk remains. New cellular pathways that may help
explain how arterial inflammation develops into atherosclerosis are explored. IL-1-beta plays an important role in these pathways raising new interest in therapeutics as colchicine and niacin. With the CANTOS trial results, clinicians have evidence that directly targeting inflammation by canakinumab is beneficial for the secondary prevention of cardiovascular disease. The research in biomarkers of inflammation in atherosclerosis calls for more specific and sensitive markers. Whole genome and exome studies will soon lead to the discovery of new cellular pathways and treatments of residual atherosclerotic inflammation. Atherosclerosis has shown it is definitely more than an arterial cholesterol deposit disease.

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How to cite this article: Michael A N. New Insights into Inflammation in Atherosclerosis. Glob J Endocrinol Metab 2(4). GJEM.000547.2018. DOI: 10.31031/GJEM.2018.02.000547