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Inflammation, infection and atherosclerosis

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ABSTRACT

Atherosclerotic cardiovascular disease is a leading cause of death in much of the world. Adoption of a healthy lifestyle and cholesterol lowering are the key measures used to prevent major complications of atherosclerosis. Recent data have identified a critical role for inflammation mediated through activation of both innate and adaptive immune pathways in the pathophysiology of atherosclerosis opening up opportunities for development of anti-inflammatory interventions that could supplement risk factor modification and lipid lowering as an approach to further reducing the burden of atherosclerotic cardiovascular disease.

Introduction

Atherosclerotic cardiovascular disease is a highly prevalent condition throughout much of the world contributing significantly to morbidity, mortality and healthcare costs.

Atherosclerosis affects medium and large size arteries eventually compromising the lumen leading to ischemic syndromes affecting the heart, brain and limbs. Acute cardiovascular events such as unstable angina, acute myocardial infarction, many cases of sudden cardiac death usually result from thrombosis superimposed on a ruptured atherosclerotic plaque or plaque with superficial endothelial erosion [1,2]. Thromboembolic events emanating from disrupted atherosclerotic plaques in the carotid arteries result in ischemic stroke.

Atherosclerosis is a complex disease process involving entry and subsequent accumulation of atherogenic lipoproteins in the subendothelium and subsequent deposition of extracellular matrix, immune and inflammatory cells (monocytes-macrophages, T cells, dendritic cells and mast cells), smooth muscle cells, immunoglobulins, necrotic cellular debris and neo-vasculature with intraplaque hemorrhage resulting in the formation of an atherosclerotic plaque [3]. A large body of evidence from pre-clinical and clinical studies have demonstrated that in addition to dyslipidemia, inflammation resulting from activation of innate immunity as well as adaptive immunity plays an important role in the initiation, progression and destabilization of atherosclerotic plaques [4]. In fact, Rudoplh Virchow suggested a role for inflammation in atherosclerosis as far back as the 19th century: “In some, particularly violent cases the softening manifests itself even in the arteries not as the consequence of a really fatty process, but as a direct product of inflammation.” [5].

Gene deletion experiments have shown that disruption of inflammatory genes reduces atherosclerosis independent of alteration in circulating lipid levels [6]. Enhanced atherosclerosis in chronic immune-inflammatory disease such as rheumatoid arthritis, psoriasis and SLE provide indirect support for the role of chronic inflammation in atherosclerotic cardiovascular disease. Recent observations also suggest that in addition to active inflammation, inadequate resolution of acute vascular inflammation may also play a role in perpetuating chronic smoldering inflammation that characterizes atherosclerosis [7].

Thrombosis superimposed on an atherosclerotic plaque usually results from rupture of the fibrous cap exposing tissue factor containing lipid-rich necrotic core of the plaque to circulating blood triggering the activation of clotting cascade with thrombin generation, platelet aggregation and thrombus formation; however nearly 30% of thrombi occur on intact proteoglycan rich atherosclerotic plaques with only superficial endothelial erosion [1,2]. Plaque rupture is generally attributed to collagen depletion in the fibrous cap of the plaque resulting from matrix degradation by matrix degrading metalloproteinases (MMP) secreted by inflammatory cells, predominantly macrophages, in the plaque [8]. Excessive death of matrix synthesizing smooth muscle cells also contributes to collagen depletion in the fibrous cap. The mechanism of plaque erosion is less well understood. Apoptosis of endothelial cells and a local prothrombotic phenotype has been implicated and attributed to neutrophil mediated injury, through NETosis, and release of myeloperoxidase and interaction with TLR-2 on endothelium and local platelet mediated neutrophil activation [2,9,10].

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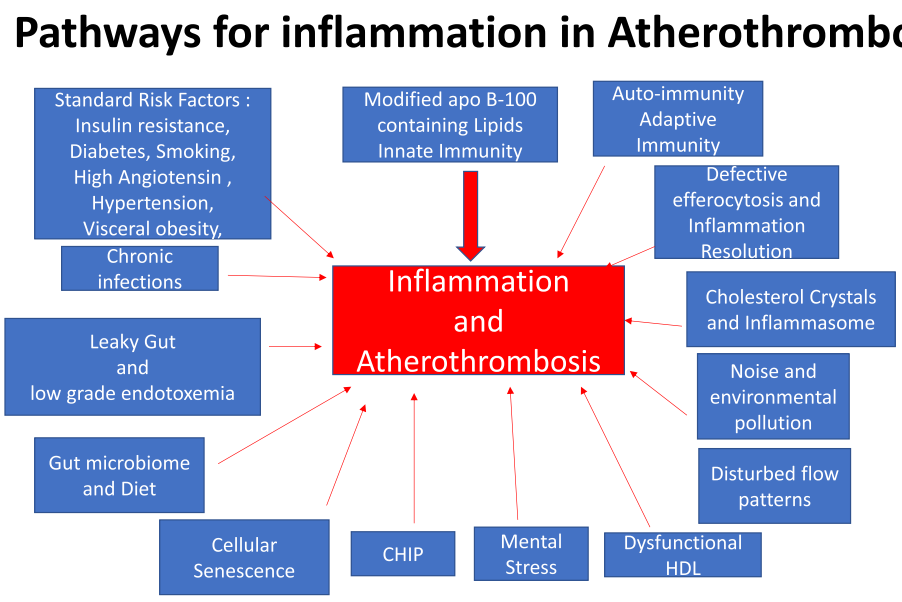

Fig. 1. Schematic summarizes the multiple pathways linking inflammation to athero-thrombosis. CHIP (Clonal hematopoiesis of indeterminate potential).

What triggers inflammation in atherosclerosis?: (Fig. 1)

Several studies have implicated a number of pathways for vascular inflammation in atherosclerosis but the primary initial trigger is likely the subendothelial retention and modification of atherogenic lipoproteins. The various pathways for inflammation are discussed below:

Lipid entry, subendothelial retention and modification: It is generally accepted that one of the earliest events in atherogenesis is entry of apoB100 containing lipoproteins(LDL, VLDL, IDL, Lpa) into the arterial subendothelium where lipoproteins get trapped by interaction with subendothelial proteoglycans through a charge-based interaction and or sphingomyelinase action. Retention of lipoproteins is followed by modification (aggregation, oxidation, glycation) of lipoproteins creating pro-inflammatory lipids that activate the overlying endothelium creating a pro-inflammatory endothelial phenotype. Endothelial activation involves increased adhesive interaction with circulating bone marrow and spleen derived monocytes from expression of adhesion molecule such as vascular cell adhesion molecule −1 (VCAM) and intercellular adhesion molecule (ICAM-1). In addition, induction of chemotactic molecules monocyte chemotactic protein −1 (MCP-1) and CCL5(RANTES) lead to mononuclear cell recruitment into the subendothelium [6]. Monocytes enter the arterial wall and turn into foam cells by ingesting lipid through non-downregulatable scavenger receptors(SRA and CD36) and become macrophages and foam cells; some foam cells are also derived from local medial smooth muscle cells. Foam cells are unable to exit the lesion, in part, due to reduced expression of CCR7 [11,12]. Monocytes-macrophages multiply under the proliferative influence of macrophage colony stimulating factor (MCSF) expressed in the vascular wall. This acute inflammatory reaction is initially a defense mechanism by the innate immune system in response to lipid retention but foam cells are unable to migrate out of the lesion leading to persistent and chronic smoldering inflammation. A variety of monocyte phenotypes have been described in murine models ranging from M1 or classically activated pro-inflammatory cells to M2 or alternatively activated anti-inflammatory or pro-resolving cells and other shades of grey in between. The corresponding circulating monocytes in humans include CD14+CD16− and CD14low−CD16+ subsets. Pro-inflammatory monocyte-macrophages are implicated in atherogenesis whereas alternatively activated monocyte-macrophages may play a role in resolution of inflammation and healing. Recent studies have suggested that there is considerably more monocyte phenotypic diversity in the vessel wall than the more simplistic dogma of pro-inflammatory (M1) and pro-resolving (M2) subsets.

Cholesterol crystals and NLRP 3 Inflammasome activation: Besides modified atherogenic lipoproteins, formation of *cholesterol crystals* in the plaque and their subsequent ingestion by macrophages, activates NLRP-3 inflammasome leading to secretion of inflammatory cytokines IL-1 beta and IL-18 that perpetuate inflammation and progression of atherosclerosis [13–15]. Inflammasome activation requires a priming signal that can be provided by activation of innate immune signaling pathway, involving TLR-4 and MYD88 by ox-LDL or neutrophil derived NETS; the priming signal increases the transcription of pro-IL-1 beta and pro- IL-18; the second signal is provided by the cholesterol crystals that leads to activation of inflammasome with activation of caspase1 that converts pro-IL-1 beta and Pro-IL18 into the active cytokines that are secreted [15]. Recent studies have highlighted the importance of mitochondrial DNA alterations and TWIK2 Potassium efflux channel in the lipid induced activation of the inflammasome [15].

Dysfunctional HDL: Several experimental studies and clinical observations have shown that unlike healthy HDL, dysfunctional HDL that loses its beneficial properties (promoting cholesterol efflux, anti-inflammatory effect and antioxidant effect) in some clinical states is associated with increased inflammation and atherosclerosis [16]. Dysfunctional HDL is created by oxidative damage to apo A-1 such as may occur in response to exposure to myeloperoxidase or mast cell derived tryptase, changes in composition of HDL cargo with acquisition of proinflammatory molecules (Symmetrical Dimethyl Arginine, Apo CIII, Serum amyloid A) or loss of anti-inflammatory/antioxidant and atheroprotective molecules(paraoxonase, apo A-1, Clustrin) [16]. Dysfunctional HDL has been detected in many clinical conditions such as renal failure, acute inflammatory conditions, chronic immune-inflammatory states, diabetes, coronary artery disease, exposure to environmental pollutants [16]. Dysfunctional HDL may contribute to ongoing inflammation although cause and effect of dysfunctional HDL and inflammation is not entirely clear.

Chronic infections, Gut microflora, low grade endotoxemia and atherosclerosis: A number of experimental and clinical investigations have implicated bacteria such as Chlamydia pneumoniae, Porphyromonas gingivalis and H.pylori in atherosclerosis and plaque inflammation [17,18]. Both direct infection of the arterial wall as well as proinflammatory and prothrombotic effects of remote infections and molecular mimicry have been implicated in this relationship [17,18]. Despite serologic and epidemiologic evidence suggesting a relationship between chlamydia pneumonia infection and ASCVD, adequately powered clinical trials of antibiotics targeting chlamydia pneumonia have failed to reduce cardiovascular events raising serious questions about a causal link [17]. Indirect vascular effects of non-vascular infections, such as influenza, or pneumonia, urinary tract infections and skin infection leading to inflammation, have also been implicated in athero-thrombosis. Observational and randomized studies have shown benefits of the flu vaccine in reducing acute cardiovascular events triggered by influenza [17]. Chronic HIV infection has also been implicated in accelerating atherothrombotic cardiovascular events through dysregulation of the immune system [19].

Recently, several studies have causally implicated gut microflora in a variety of mmuno-inflammatory diseases including atherosclerosis [20]. Certain gut bacteria produce Trimethylamine Lyase, an enzyme that converts dietary carnitine and phosphatidylcholine (common components of western diet) into Trimethylamine (TMA) which when absorbed into the circulation is oxidized to Trimethylamine oxide (TMAO) by hepatic enzyme Flavin Mono-oxygenase (FMO) [20]. TMAO increases foam cell formation and atherosclerosis in animal models and also activates platelet-mediated thrombogenesis [19]. Circulating TMAO levels have been correlated with increased prevalence of CAD and increased risk of future cardiovascular events in human subjects [20]. Mice harboring high levels of choline-metabolizing bacteria are more susceptible to diet-induced metabolic disease. Inhibition of gut microflora or its enzymes have reduced experimental atherosclerosis but to date no human clinical trials have been completed in this arena [20]. Modulation of microbial metabolism through dietary intervention or direct supplementation might therefore provide an effective strategy, either alone or in combination with established therapies, for prevention of cardiovascular diseases, especially athero-thrombosis.

Other metabolites derived from gut microbiome include short chain fatty acids(SCFA). SCFA have been linked to cardiovascular risk factors, mostly in animal models, but a clear pathogenetic link of SCFA to human cardiovascular disease and cardiovascular events remains unclear [20].

Recent studies suggest that low-grade subclinical endotoxemia is correlated with the occurrence of chronic low-grade inflammatory diseases, like atherosclerosis, in humans and animal models [21–23]. Sustained low grade subclinical endotoxemia enhances murine atherosclerosis through programming monocytes into a non-resolving inflammatory state through disruption of an integrated feedback circuit [23].

Furthermore, low grade chronic endotoxemia from Gram negative bowel bacteria and a leaky gut has also been shown to induce chronic low grade inflammation and increased atherogenesis in murine models further suggesting that remote infection can have vascular inflammatory effects that can modulate atherogenesis.

Age-related Clonal hematopoiesis of indeterminate potential (CHIP) and inflammation: Advancing age is an important risk factor for atherosclerotic cardiovascular disease. Certain age -related somatic hematopoietic mutations are associated with increased risk of hematologic malignancy, cardiovascular and all cause mortality [24,25]. The most common mutations involve loss of function variants of Dnmt3a and TET-2 genes. Loss of function mutations of TET-2 gene are associated with enhanced activation of NLRP-3 inflammasome pathway increasing inflammation, and increased risk of cardiovascular disease in humans [24,25]. This could be one potential mechanism by which advancing age results in enhanced inflammation and atherogenesis.

Senescent cellular phenotype and inflammation: Atherosclerotic plaques contain a subset of foam cells, endothelial cells and vascular smooth muscle cells with that bear markers of senescence (short telomeres, expression of Beta Gal gene, P16-^{Ink4A}, P53 and P21 genes) exhibiting a senescence associated secretory phenotype (SASP) which is characterized by secretion of inflammatory and extracellular matrix degrading molecules that contribute to atherogenesis and potential plaque instability [26]. Genetic and pharmacological removal of senescent cells reduces atherosclerosis and features of plaque instability in hyperlipidemic mice implying a role for senescent cells in atherogenesis and plaque instability [26]. Removal of senescent cells by senolytic agents may emerge as a novel therapeutic intervention in chronic inflammatory diseases including atherosclerosis.

Adaptive immunity and atherogenesis: Experimental studies have shown that adaptive immune response, orchestrated by antigen presenting cells and T-cell subtypes to various auto-antigens (LDL, oxLDL, apo B100, HSP 60, Betamicroglobulin), can provoke a pro-inflammatory response that promotes atherogenesis [4,27,28]. This is mediated through polarization of naïve T-cells into Th-1 and Th-17 phenotypes with secretion of inflammatory cytokines such as interferon gamma, TNF alpha, IL-17 [4,27,28]. On the contrary, activation of a regulatory -T cell response is associated with inhibition of atherosclerosis mediated through secretion of anti-inflammatory cytokines IL-10 and TGF beta [4,27,28].In human atherosclerosis, oxidized LDL reactive T-cells have been previously identified in atherosclerotic plaques suggesting that adaptive immune response to lipid antigens may also play a role in human atherogenesis [4,27,28]. Humoral response to LDL-related antigens have also been observed in animal and human models of atherosclerosis. Accelerated atherosclerosis observed in chronic auto-immune diseases such as SLE, RA and psoriasis are consistent with role of adaptive immunity in atherogenesis [4,27,28]. These observations have raised the tantalizing possibility that immunemodulation, using a vaccine or an antibody, may be a potential approach to reducing inflammation and atherogenesis [27,28].

***Abnormal flow patterns and shear-stress as triggers of local inflammation*:** Arterial sites of predilection for plaque development include branch points and curvatures characterized by low or oscillating shear stress [29]. Experimental studies have suggested that such athero-promoting flow patterns are sensed by shear-stress responsive elements in endothelial genes, leading to inhibition of expression of protective genes such as KLF-2 leading to transcriptional activation of inflammatory, vasoconstrictor and prothrombotic genes which can all promote atherogenesis [29]. On the other hand, flow patterns associated with athero-resistant arterial sites are characterized by high shear-stress and activation of KLF-2 transcription factor leading to suppression of inflammatory and prothrombotic genes in the endothelium [29].

Mental stress and inflammation: Experimental studies have shown that mental stress, such as when provoked by an acute myocardial infarction, can activate sympathetic nervous system mediated stimulation of hematopoetic stem cells and inflammatory monocytes in bone marrow and spleen which can lodge in arterial wall and promote atherosclerotic plaque inflammation and plaque progression [30–33]. Clinical observations provide support for the potential relevance of mental stress induced inflammation [32,33].

Insulin resistance, obesity, Renin-Angiotensin 2, hypertension, and smoking: Other well known risk factors for atherosclerotic CVD including insulin resistance/diabetes mellitus, Angiotensin II signaling and hypertension, visceral obesity and smoking are known to enhance inflammation and this effect may explain the

potential causal link between these risk factors and atherogenesis [34–38]. Insulin resistance is a major contributor to the development of type 2 diabetes mellitus. Insulin resistance is associated with chronic inflammation, particularly manifest in visceral adipose tissue, liver, pancreatic beta cells, induced by various pro-inflammatory and/or oxidative stress mediators such as interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, multiple chemokines and adipocytokines [35–38]. Chronic exposure of pro-inflammatory mediators stimulates the activation of cytokine signaling proteins which ultimately block the activation of insulin signaling receptors in β-cells of pancreatic islets [35–38]. Both innate immune as well as adaptive immunity have been implicated in the pathogenesis of diabetes mellitus [35–39].

Recent studies have also identified a role for T-cells and the adaptive immune response in mediating angiotensin and DOCA induced hypertension in murine models [34].

Malfunctioning efferocytosis and inflammation-resolution response: Acute inflammatory response to infectious or non-infectious injury is mediated by innate immune activation which serves to neutralize these injurious invasions of the host and once their job is done, inflammation resolving mechanisms are activated to conclude the mission. However, failure of these inflammation resolving mechanisms may contribute to persistent and chronic inflammation and diseases such as atherosclerosis [7]. Cell death by apoptosis is a common feature of atherosclerotic plaques and apoptotic debris is cleared by a subset of pro-resolving macrophages by a process called efferocytosis; defective efferocytosis leads to accumulation of apoptotic cells followed by secondary necrosis which creates a pro-inflammatory state [7]. Thus defective efferocytosis contributes to persistent inflammatory state and increased atherogenesis and necrotic core expansion. [7]. Recent studies have shown that a “don’t eat me signaling molecule” CD47 is overexpressed in murine and human atherosclerotic plaques; CD47 inhibits efferocytosis and that inhibition of CD47 in a murine model enhances efferocytosis and reduces atherosclerosis [40]. Resolution of inflammation is also modulated by several other mediators that include arachidonic acid-derived lipoxins, omega-3 fatty acid eicosapentaenoic acid-derived resolvins, docosahexaenoic acid-derived resolvins, protectins, and maresins [7].

Several observations suggest that an imbalances between inflammation resolving mediators and inflammation promoting mediators are associated with chronic inflammatory conditions such as atherosclerosis. Potential modulators of this imbalance remain largely unknown. A better understanding of such modulators may provide new therapeutic opportunities against atherosclerosis.

Noise, sleep deprivation and environmental pollution: Exposure to noise, especially aircraft noise, sleep deprivation and exposure to environmental particulate matter all seem to increase oxidative stress, induce endothelial dysfunction and inflammation ultimately increasing risk of hypertension, glucose intolerance and atherosclerosis [41]. However, no interventional data are available to verify the causality of these associations.

Conclusions and perspectives

A large body of experimental data support the role of inflammation orchestrated by innate and adaptive immunity in atherosclerosis and its complications. Lipid retention and modification is likely the main early trigger for inflammation but other pathways and mediators as outlined above are also likely to play an important role in atherogenesis and its complications. Despite compelling mechanistic and preclinical data, it has been sobering to learn about the failure of some interventions targeting inflammation such as inhibitors of pro-inflammatory phospholipases (Darapladib and Veraspladib), a MAP kinase inhibitor and low dose methoterexate in human subjects [42–45]. More recent studies have provided favorable results with low dose Colchicine in preliminary trials and larger studies of Colchcine are currently ongoing. Recent data from the CANTOS clinical trial showing cholesterol independent cardiovascular benefits of anti-IL1 beta antibody, Cannakinumab, treatment provided the first proof of concept in favor of the inflammatory hypothesis in humans opening the door for development of even more effective and safe anti-inflammatory interventions [46]. Acute inflammation starts as a defense mechanism to neutralize infectious and noninfectious injurious triggers but chronic non-resolving inflammation can be deleterious. Anti-inflammatory interventions will need to be selective in that they abrogate chronic persistent inflammation without interfering with the defensive effects of acute inflammation. CANTOS trial showed modest overall cardiovascular benefits with anti-IL1 b antibody but resulted in an excess of fatal infections. That reinforces the need for safer, more effective and targeted anti-inflammatory interventions. Novel compounds that target the inflammasome (such as MCC950) [47,48], pro-inflammatory senescent cells (senolytic agents such as Fisetin) [49], as well as vaccines targeting LDL related antigens [27,28] hold promise for reducing inflammation but clinical validation with appropriate event-based clinical trials will be required to confirm efficacy and safety.

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