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Editorial commentary: Arson in the artery: Who set the atheroma aflame?

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ABSTRACT

Inflammation drives the formation, evolution, and complication of atherosclerotic plaques. Yet, we have not yet captured the culprits who light the fire that burns within the atherosclerotic plaque. The arsonist remains at large. A rigorous analysis exculpates many of the usual suspects. Low-density lipoprotein (LDL) itself engenders little inflammation. Clinical trials do not support an actionable role of oxidized LDL in atherothrombosis. In contrast, triglyceride-rich lipoproteins do promote inflammation, and provide a promising target for intervention. Obese adipose tissue —especially visceral or ectopic lipid deposits — also incite inflammation. A newly recognized cardiovascular risk factor, clonal hematopoiesis provides a novel link between inflammatory pathways and atherosclerotic risk. Despite this progress, the jury is still out on who lit the plaque afire. The rigorous observer must still consider this an unsolved act of arson. We remain in "hot" pursuit of the causal culprit, the arsonist, and accomplices who set the artery wall ablaze.

It is no longer news that inflammation participates in the formation, evolution, and complication of atherosclerotic plaques [1]. A Google search now shows over 16 million "hits" when queried for the term "inflammation in atherosclerosis." This current acceptance represents a distinct departure from the situation three decades ago. In those days, most considered the atheroma a garbage heap of excess lipid, or a pile of proliferated smooth muscle cells [2,3]. We now have abundant experimental data that inculpate inflammation and immunity in atherogenesis. Clinical biomarker studies bridge these laboratory findings to patients and associated inflammation with cardiovascular risk. Closing the loop of causality, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that targeting inflammation with a surgical strike on one particular inflammatory mediator, administration of a monoclonal antibody that neutralized interleukin-1-beta (IL-1β), could limit recurrent events in a subset of survivors of acute coronary syndromes [4,5]. In this issue of *Trends in Cardiovascular Medicine,* P.K. Shah ably assembles the arguments that implicate inflammation in atherosclerosis and highlights the remaining translational challenge [6]. This paper outlines the usual list of pro-inflammatory stimuli that may instigate inflammation in atherosclerosis. Despite all these factors that fan the flames, we have not yet captured the culprits who set the fire that burns within the atherosclerotic plaque. The arsonist remains at large.

Most schemata of the initiation of atherosclerosis identified low-density lipoprotein (LDL), usually oxidatively or otherwise modified, as the instigator of the inflammatory response. LDL indisputably contributes to atherosclerotic risk. Overwhelming genetic, epidemiologic, biomarker, and intervention data establish an etiologic role beyond a doubt, satisfying modified Koch's postulates. If we maintained a cholesterol concentration in blood of a newborn, or that of animals that avoid sloth and gluttony, atherosclerosis would likely become an orphan disease.

Yet, is LDL a permissive cofactor, or is it an instigator of the inflammatory response within the artery wall? LDL itself engenders little inflammation [7,8]. Lowering LDL with an inhibitor of the Neiman-Pick C-Like Protein 1 (NPCL1) or of proprotein convertase subtilisin/kexin type 9 (PCSK9) does not reduce the high-fidelity biomarker of inflammation, C-reactive protein measured with a high-sensitivity assay (hsCRP). Statins both lower LDL and exert an independent anti-inflammatory action through well understood pathways. Inhibition of prenylation of small G proteins and augmented activity of transcription factors KLF2 among others account for this anti-inflammatory effect of statins independent of LDL lowering. Cholesterol crystals can coactivate the NLRP3 inflammasome in vitro. This supramolecular assembly activates the precursor of IL-1β, the target of the successful trial CANTOS. But the weak association of LDL with CRP does suggest that other factors operate in instigating inflammation in vivo.

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The hypothesis that oxidized LDL drives this disease derived from concordant chemical and experimental studies of compelling weight [9]. Yet, each and every therapeutic attempt to retard LDL oxidation or limit oxidative stress in the artery wall has failed in rigorous clinical trials. Such interventions range from all antioxidant vitamins studied, through a variety of phospholipase inhibitors, to the potent lipophilic antioxidant succinobucol [10]. Moreover, recent studies indicate that native LDL more potently stimulates the adaptive immune response through T cell activation than does an oxidized form of this atherogenic lipoprotein [11]. Hence, we lack evidence to make a strong case that oxidized LDL sparks the flame that burns in the human atherosclerotic plaque.

Obese adipose tissue – especially visceral or ectopic lipid deposits – does raise CRP [12]. Weight reduction limits the elevation of this biomarker of inflammation. But even when fully adjusted for weight, CRP still correlates with increased cardiovascular risk. In the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) an apparently well population selected for above-median CRP (2 mg/L) showed that about a quarter of participants did not have a BMI above 25 [13]. Thus, factors beyond obesity must contribute to the inflammation that drives atherosclerotic risk.

Infection could obviously trigger an inflammatory response [1]. Strong preclinical and some seroepidemiologic evidence support infections, e.g. Chlamydia species, in atherosclerotic risk. But all of the adequate antibiotic trials in secondary prevention have failed to show event reduction. Acute infections can raise oxygen requirements (e.g. through tachycardia and fever) and limit oxygen delivery (e.g. hypotension, hypoxemia). These factors could favor a Type 2 “demand” myocardial ischemic event. The procoagulant and antifibrinolytic state associated with the acute-phase response to infection might also favor thrombosis, and hence Type 1 myocardial infarctions. But an inciting role for infection in atherogenesis has evaded proof. A large trial underway will test if a more potent vaccination protocol for influenza can limit events in individuals with cardiovascular risk [14]. This study could answer a pressing clinical question. Yet, it would still not establish an initial role for viral infection in atherosclerosis.

The protective action of high-density lipoprotein (HDL) in atherosclerosis has come under considerable question [15,16]. Human genetic analyses and a consistent failure of several independent pharmacologic interventions that raise HDL cholesterol have controverted a wealth of observational and experimental data that link low HDL to a causal action in cardiovascular protection. On the other hand, triglycerides, which tend to rise as HDL falls, have gained support as a marker of increased risk for cardiovascular complications. The triglyceride measurement serves as a biomarker for a class of lipoproteins known as triglyceride-rich lipoproteins (TGRL) or as remnant particles. Strong human genetic evidence now supports a causal role for TGRL in atherosclerotic events [16]. Analyses of observational data that do not adjust triglycerides for HDL further support a causal contribution of TGRL to atherosclerotic risk. The cholesterol content of TGRL, rather than the triglycerides themselves, likely drive the atherosclerotic risk caused by this class of particles [17]. A study in progress, PROMINENT, will test whether a novel selective PPAR-α modulating agent, pemafibrate, will mitigate the excess risk of cardiovascular events associated with hypertriglyceridemia [18].

A heightened interest in the intestinal microbiome has kindled substantial recognition of the interaction with our endogenous microbial population with cardiovascular conditions. In situations that compromise epithelial barrier function, leaks of bacterial products that can activate pattern-recognition receptors and serve as pathogen-associated molecular patterns (PAMPs) might instigate or potentiate inflammatory processes in the artery wall and elsewhere, as discussed by Shah [6]. Studies performed several decades ago demonstrated the ability of bacterial lipopolysaccharide, the endotoxic principal of Gram-negative bacteria, to potentiate inflammation within artery walls and aggravate inflammation in experimentally induced atherosclerotic lesions [19,20]. The current concept of trained immunity underscores the possible participation of episodic exposure to pro-inflammatory stimuli such as PAMPs in sustaining inflammatory responses within tissues [21]. Thus, while infectious agents may not directly cause inflammation during atherogenesis, infection may aid atherogenesis and contribute to precipitating thrombotic complications of the disease [1].

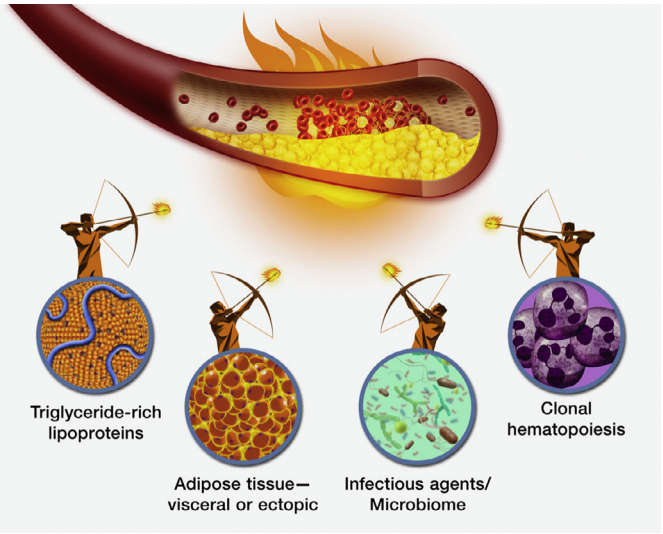

Fig. 1. Some non-standard risk factors implicated in inciting inflammation in atherothrombosis.

The recent recognition that clonal hematopoiesis can drive atherosclerotic events opens a new vista linking leukocytes with this arterial disease [22,23]. With age, humans accumulate clones of leukocytes in peripheral blood that arise from somatic mutations in bone marrow stem cells. The mutations that cause clonal hematopoiesis belong to a family of driver genes associated with the development of acute leukemia. Clonal hematopoiesis is common. Septuagenarians have a 10-20% chance of having a clone of mutant leukocytes in peripheral blood. The risk for atherosclerotic complications conferred by clonal hematopoiesis does not depend on conventional cardiovascular risk factors. Mouse experiments affirm causality of mutations that cause clonal hematopoiesis in atherogenesis. The inflammasome to IL-1β to IL-6 pathway likely drives a pro-inflammatory response in animals with clonal hematopoiesis mutations [23,24]. Mice with these mutations exhibit elevated concentrations of pro-inflammatory chemokines implicated in leukocyte accumulation within plaques. The emergence of clonal hematopoiesis as a novel cardiovascular risk factor furnishes a further link between inflammatory pathways and atherosclerotic risk.

Despite all of the progress reviewed here and the paper by Shah, the jury is still out on who lit the plaque afire. The rigorous observer must still consider this an unsolved act of arson. We remain in “hot” pursuit of the causal culprit, the arsonist and accomplices who set the artery wall ablaze (Fig. 1).

In addition to numerous classical risk factors, a number of less well-established stimuli may contribute to inflammation within the atheroma. Triglyceride-rich lipoproteins, traditionally disregarded as an independent atherosclerotic risk factor, cannot only deliver cholesterol to the artery wall but can exert pro-inflammatory functions. Visceral or ectopic depots of adipose tissue (e.g. adventitial or pericardial fat) can elaborate cytokines

that can produce an "echo" within the arterial plaque or furnish an “outside-in” signal that could stimulateinflammatory activation of intrinsic vascular cells and of leukocytes that accumulate within the lesion. The products of infectious agents either at sites of infection or from the endogenous microbiome can serve as pathogen-associated molecular patterns (PAMPs) that engage pattern-recognition receptors on cells within atherosclerotic lesions. Gram-negative bacterial endotoxin provides one common example, but microbial agents can elaborate many more PAMPs. Metbolites produced by the microbiota may also aggravate atherogenesis. Clonal hematopoiesis can drive systemic inflammation as well as local inflammatory responses within the plaque augmenting atherothrombotic risk. The relative contributions and a causal role for in arterial inflammation of these non-traditional risk factors remains to be determined.

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