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Invited critical review

HDL functionality and crystal-based sterile inflammation in atherosclerosis

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ABSTRACT

Change is inevitable. In early evolution, due to the limited availability of resources, the sole purpose of living organisms was to survive long enough to transmit their genes to the next generation. During their short lifetime, organisms used pathogen-associated and damage-associated molecular pattern pathways as an inflammatory response against pathogens (exogenous factors) and tissue damage (endogenous factors), respectively. Despite advances in human lifespan, it appears that an increasing number of diseases such as atherosclerosis are associated with inflammation. Excessive glucose, lipid and protein intake leads to the formation of endogenous crystals, i.e., cholesterol, which can induce a sterile inflammatory immune response that manifests as a vicious cycle. In this review, we evaluate the possible relationship between crystal-based sterile inflammatory response and HDL functionality.

Contents

1. Overview

Atherosclerosis is a chronic inflammatory disease starting with the accumulation of white blood cells and fatty materials such as cholesterol in the arterial wall [1]. Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as microbes, damaged cells, or irritants. Inflammation occurs in order to restore tissue homeostasis through the induction of various repair mechanisms. Chronic general or vascular inflammation is an essential requirement for the progression of atherosclerotic pathogenesis in patients. Inflammation of the arterial wall is a keystone in the pathogenesis of atherosclerosis. Still the factors that activate and sustain the inflammation remain elusive [1–4].

Abbreviations: HDL, high-density lipoprotein; oxLDL, oxidized-low density lipoprotein; PON 1, paraoxonase 1; ARE, arylesterase; CBSI, crystal-based sterile inflammation; NLRP3, nucleotide binding domain leucine-rich repeat receptor protein 3; IL-1β, interleukin 1 beta; IL-18, interleukin 18; TLR, Toll Like Receptor; NF-κB, Nuclear Factor kappa B; NO, Nitric oxide; eNOS, endothelial nitric oxide synthase; SAA, serum amyloid A; CRP, C-reactive protein; ROS, reactive oxygen species; NOX, nicotinamide adenine dinucleotide phosphate oxidase; VSMC, vascular smooth muscle cell; B2GPI, β2-glycoprotein I; Apo A1, apolipoprotein A-I.

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High-density lipoprotein (HDL) has been shown to have a diversity of functions that contribute to its atheroprotective effects: stimulation of macrophage cholesterol efflux; reverse cholesterol transport; and anti-inflammatory, antithrombotic, antiapoptotic, and anti-oxidative effects. *Functionality hypothesis* suggests that the measurement of HDL levels has no major relationship with how the HDL concentrations are being dynamically remodeled or the state of HDL capability. Impaired antioxidant and anti-inflammatory activities of HDL are associated with the lack of protection from atherosclerotic disease. Multiple mechanisms participate in the *HDL dysfunction*, comprising oxidative and inflammatory remodeling. *Healthy HDL* (H-HDL) has high levels of active antioxidant proteins and enzymes with high antioxidant potential and has anti-inflammatory activity. So, H-HDL can directly inhibit oxidation of low-density lipoprotein (oxLDL) or other targets containing phospholipids [5–8].

Oxidized LDL stimulates endothelial injury, monocyte adhesion, and platelet aggregation and inhibits apoptosis and endothelial nitric oxide synthase expression/activity, all of which promote the atherosclerotic process. So, oxLDL is pivotal in the development of atherosclerosis and represents a crucial proinflammatory stimulus. OxLDL not only enlarges atherogenesis but also induces vascular inflammation to stimulate the advance of atherosclerosis [9–11].

Nowadays, atherosclerosis is seen as an inflammatory disease of the arterial vessel, and it is, therefore, not surprising that the *dysfunctional HDL* is associated with an increased atherosclerotic risk. With these considerations in mind, we focus on an HDL-associated antioxidant enzyme, paraoxonase 1 (PON1), which has been shown to play an important role in protection against oxLDL. Many pathological processes associated with systemic inflammation are characterized by the presence of *dysfunctional HDL* or proinflammatory HDL, including dyslipidemia and gout [1,9,12,13].

However, detailed mechanisms and fundamental inductions of atherogenic inflammation remain inadequately outlined. For many years, the relationship between atherosclerotic disease risk and crystal-based sterile inflammation (CBSI), though strong and consistent, was suspected of being coincidental rather than causative [14]. Also, CBSI contributes to many common and serious human diseases. Therefore, that tie is markedly complex, involving a miscellaneous model that includes interactions between inflammatory processes and oxidative stress as well as atherosclerosis that remains only partly explained [15,16].

CBSI appears to be able to activate the immune response and in that framework has a mediating role in the inflammatory process via the inflammasome. The finest defined inflammasome is the nucleotide binding domain leucine-rich repeat receptor protein 3 (NLRP3) inflammasome, which comprises NLRP3, the ASC adaptor, and caspase-1 [17,18].

Indeed, CBSI can induce NLRP3 inflammasome activation with interleukin (IL-1β and IL-18) production. Two signals are required for full NLRP3 activation, including, first, a Toll Like Receptor (TLR)-dependent activation of Nuclear Factor kappa B (NF-κB), resulting in the upregulation of NLRP3 and pro-IL-1 β priming expression (activators: cellular proteins, oxide lipids and lipoproteins, nucleic acids, and extracellular matrix), and, second, an NLRP3 activating signal, which comprises multiple exogen molecules (activators: microbes, asbestosis, silica, and metal particles, titanium dioxide) and endogenous activator molecules (cholesterol, uric acid, calcium pyrophosphate, calcium oxalate, extracellular ATP, and high glucose) [19–23].

One possible role for these activator molecules is that they may serve as biological links bridging the progression from chronic inflammation into an *HDL-dsyfunctionality* response in the later stages of atherosclerosis. The H-HDL particle may serve as a reservoir or transporter of anti-inflammatory proteins and antioxidant enzymes that restrict inflammasome induced IL-1β production to specific sites.

Furthermore, previous researchers reported that HDL is an additional factor that prevents an unbalanced release of inflammatory cytokines [24]. This role of H-HDL seems especially important in diseases that are characterized by increased endogen crystalline levels and in which IL-1β and IL-18 have important roles, such as atherosclerosis [25]. Now, the challenge for both clinical chemistry researchers as well as clinicians is to attempt to extend and integrate this new mechanistic insight into atherogenesis in order to identify preventive approaches or drug able targets in the pathway. Therefore, we hypothesize that increasing PON1 activity may provide protection against the development of oxLDL and may decrease inflammasome related IL-1B and IL-18 cytokine production. The goal of this paper is to summarize the recent data on CBSI (especially cholesterol crystals) and to make connections between separate findings to figure out the full picture. We will particularly focus on CBSI and search for clues for the impact of *HDL-functionality* on the atherosclerotic process.

2. Crystal-based sterile inflammation

Inflammation is a protective host response required for resistance to infection. Regardless, chronic inflammation that occurs in response to tissue injury in the absence of a pathogen is considered sterile and can contribute to tissue damage. For example, sterile physical damage, such as a burn or bruise, evokes acute inflammation, which consists of the four canonical signs of inflammation: redness, pain, heat and swelling. These four cardinal signs were described as early as three thousand years ago by Aulus Cornelius Celsus [26].

The inflammatory features of atherosclerosis are adequately established, but the factor(s) that inspire inflammation in the artery wall remains largely unknown. Microbe-free animals are susceptible to atherosclerosis, suggesting that endogenous substances trigger the sterile inflammation [27,28].

Why endogen molecules such as *cholesterol crystals* (ChCrs) and uric acid crystals (UACs) trigger inflammation and are associated with the co-morbidity of atherosclerosis? The reasons have been unclear, but recent studies provide new insights into these issues.

The CBSI in hypercholesterolemia, hyperuricemia, silicosis and asbestosis is thought to derive from the inability of cells to destroy the ingested aggregates leading to successive rounds of apoptosis and the re-ingestion of the crystalline material (Fig. 1) [23]. The immune system recognizes when endogenous molecules such as uric acid (UA) or cholesterol (Ch) change their physical state from soluble to crystalline [23]. These processes likely have evolved to recognize the so-called sterile tissue damage. The mechanisms that are at play to identify sterile tissue damage can also bring on chronic inflammatory reactions if the danger signals occur inveterate or are not efficiently absolved, such as seen in the arteries of hypercholesteremic individuals [29,30].

Although crystal-based, various particles are structurally quite distinct; they stimulate entirely inflammation-equivalent pathways. Immune cells in the tissues, such as tissue macrophages of dendritic cells can recognize these danger signals and alert other immune cells via the production of cytokines [31]. For example, crystalline substances can induce inflammation by stimulating the caspase-1-activating NLRP3 inflammasome, which terminates in cleavage and secretion of IL-1β. The inflammasomes are literally a different type of cytosolic multiprotein complex that serves as a sensor of either microbe invasion or cellular stress and work via triggering caspase-1-mediated processing of pro-IL-1β to IL-1β [1–3,31].

The essential configuration of inflammasome complexes includes two or three essential components depending on the Nod-like receptor (NLR) member in query because most of the work on atherosclerosis has focused on the NLRP3 inflammasome. Based on this novel mechanistic link between CBSI and IL-1β release, it is important to once more reassess how the atherogenic environment stimulates immune cells to produce IL-1β [1,3,16].

CBSI is a major component of atherosclerosis, and studies have shown that IL-1β is a potent proinflammatory and atherogenic cytokine. Furthermore, IL-1β promotes the secretion of many other cytokines as

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