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Review

Lipoprotein(a) and inflammation: A dangerous duet leading to endothelial loss of integrity

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ABSTRACT

Lipoprotein(a) [Lp(a)] is an enigmatic lipoprotein whose ancestral useful properties have been gradually obscured by its adverse pro-atherogenic and pro-thrombotic effects, that culminate into an increased risk of ischemic cardiovascular events. Although plasma Lp(a) levels are largely determined on a genetic basis, multiple factors have been reported to interfere with its plasma levels. Inflammation is one of these factors and it is believed to promote pro-atherogenic and pro-thrombotic changes leading to increased cardiovascular disease risk. The influence of inflammation on plasma Lp(a) levels is variable, with studies reporting either increased, reduced or unchanged Lp(a) expression and plasma concentrations following exposure to pro-inflammatory stimuli. The complex association between inflammation and Lp(a) is further amplified by additional findings showing that Lp(a) may promote the expression of a plethora of pro-inflammatory cytokines and induces the endothelium to switch into an activated status which results in adhesion molecules expression and inflammatory cells invasion into the arterial wall. In this picture, it emerges that increased plasma Lp(a) levels and inflammation may coexist and their coexistence may exert a deleterious impact on endothelial integrity both at a functional and structural level. Also, the detrimental duet of inflammation and Lp(a) may interfere with the physiological endothelial repair response, thus further amplifying endothelial loss of integrity and protective functions. A fundamental understanding of the interaction between Lp(a) and inflammation is critical for our comprehension of the mechanisms leading to the derangement of endothelial homeostasis and vascular dysfunction.

Contents

Abbreviations: Lp(a), lipoprotein(a); LDL, low-density lipoprotein; apoB100, apolipoprotein B100; apo(a), apolipoprotein(a); CVD, cardiovascular disease; LDL-C, LDL-cholesterol; HDL-C, high-density lipoprotein cholesterol; K, kringle; PCSK9, proprotein covertase subtilisin/kexin type 9; OxLDL, oxidized LDL; OxPL, oxidized phospholipid; LPS, lipopolysaccharide; IAVI, isolated aortic valve interstitial; CAVD, calcific aortic valve disease; ATX, autotaxin; NF-κB, nuclear factor-κB; MCP-1, monocyte chemoattractant protein-1; TGF-β, transforming growth factor-β; ICAM-1, intercellular adhesion molecule-1; HUVEC, human umbilical vein endothelial cell; IL, interleukin; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; COX-2, cyclooxygenase-2; LAL, lysosomal acid lipase; CRP, C-reactive protein; VAP-1, vascular adhesion protein-1; MTX, methotrexate; NO, nitric oxide; EMP, endothelial microparticle; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; AT1, angiotensin-1; Stat3, signal transducer transactivator-3; NADP(H), nicotinamide adenine dinucleotide phosphate; TX, thromboxane; PGI2, prostaglandin I2; ADMA, asymmetric dimethylarginine; hsCRP, high sensitivity CRP; ROS, reactive oxygen species; ACh, acetylcholine; EPC, endothelial progenitor cell; VEGF-R1, vascular endothelial growth factor receptor-1; SDF-1, stromal cell derived factor-1; MLC, myosin light chain; bFGF, basic fibroblast growth factor; FMD, flow-mediated dilatation.

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1. Introduction

Lipoprotein(a) [Lp(a)] is a cholesterol-rich low-density lipoprotein (LDL) particle with one molecule of apolipoprotein B100 (apoB100) and one apolipoprotein(a) [apo(a)]. Lp(a) is probably involved in wound healing; in this regard, apo(a)'s affinity for fibrin, its stimulating effect on cell division and its ability to carry cholesterol might be useful for tissue repair. However, this original function does not seem to be essential anymore, given that the individuals with low or null concentrations of plasma Lp(a) manifest no deficiency syndrome or disease [1,2].

Elevated plasma Lp(a) levels is now considered an independent risk factor for athero-thrombotic cardiovascular disease (CVD), particularly in subjects with high LDL-cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C) levels [3]. Accordingly, pro-thrombotic effects of Lp(a) have been described to be due to a structural homology between apo(a) and plasminogen and plasmin. Also, pro-atherogenic effects of Lp(a) have been reported extensively [4]. Although the exact mechanisms linking Lp(a) to atherosclerosis are still poorly clarified, there is sufficient evidence showing that Lp(a) can enter arterial wall, promotes intimal cholesterol deposition and stimulates endothelial cell activation and vascular wall inflammation [4].

Apo(a) structure comprises a serine-protease domain, similar to that of plasminogen, and two additional plasminogen-like highly glycosylated domains (*i.e.*, kringles). One kringle is similar to the kringle V (KV) of plasminogen, the other, kringle IV (KIV), includes 10 different types in apo(a) (KIV types 1–10). KIV type 2 occurs repeatedly, from 10 to 40 times in the apo(a) structure. The number of KIV repetitions is genetically determined, resulting in 34 different apo(a) isoforms [5].

Plasma Lp(a) levels are largely determined via variation in the apo(a) gene [1,4]. The number of KIV type 2 repeats are inversely correlated with plasma Lp(a) levels. In a Mendelian randomization study, it has been described that subjects in the lowest quartiles of KIV-2 repeats, had a higher multivariable-adjusted risk of myocardial infarction than subjects in the highest quartile, thus supporting the causal association between elevated Lp(a) levels and increased cardiovascular risk [6].

Also, some influence on plasma Lp(a) levels has been attributed to additional non-genetic factors, including estrogens, testosterone, growth hormone, thyroid function, renal failure, peroxisomal disorders, alcohol consumption, nicotinic acid, aspirin, coenzyme Q10, lipoprotein apheresis, proprotein convertase subtlisin/kexin type 9 (PCSK9) inhibition, and HIV-1 protease inhibitors [7–11]. Additionally, there is some evidence showing that inflammation may interfere either positively or negatively with plasma Lp(a) levels [1,12–15].

Inflammation is widely recognized to be an important contributing factor to atherosclerosis development and progression, and to increased CVD risk [16–20]. In this regard, there is ample pre-clinical and clinical evidence confirming that inflammation plays a pivotal role in many steps of atherogenesis by promoting, among the others, endothelial activation, dysfunction and loss of integrity, failure of endothelial repair capacity, intimal lipid deposition, plaque formation and instability [16,21–23]. The detrimental link between inflammation and atherosclerotic CVD risk is further supported by those studies showing that attenuation of inflammation is generally paralleled by improvement of surrogate indicators of arterial function (*e.g.*, endothelial function, aortic stiffness, ratio of endothelial microparticles to endothelial progenitors) [18,21], and cardiovascular prognosis [24].

While there is sufficient evidence that inflammation may increase plasma Lp(a) levels, data have emerged suggesting that a bidirectional regulatory loop involves Lp(a) and inflammation; thus, the evidence showing a dichotomous effect of inflammation on plasma Lp(a) levels [1,12–15] has been integrated by the observations that Lp(a) may be pro-inflammatory in most cases, while exerting anti-inflammatory effects in other conditions [25].

Irrespective of the nature of the interaction between inflammation and Lp(a), there is evidence supporting the hypothesis that this detrimental duet might sustain and amplify the switch from the beneficial reactive activation of the endothelium to an unfavorable exhaustion of this protective response; finally, it leads to endothelial dysfunction, fragmentation, detachment and loss of repair activity, triggers inflammatory signalling cascades, thus promoting ultimately inflammation and endothelial injury perpetuation.

In this review, we report evidence exploring the bidirectional link between Lp(a) and inflammation and discuss modes of dysregulation of endothelial homeostasis by this unfavorable duet, focusing on the processes leading to the loss of endothelial integrity and the failure of endothelial repair.

2. Lipoprotein(a) and inflammation: a bidirectional link

2.1. Lp(a) triggers inflammation

Previous studies have established a close link between lipoproteins and inflammation [16]. In the vascular wall, oxidized LDLs (OxLDLs) trigger both directly and indirectly a detrimental sequence of pro-inflammatory events leading to atherosclerosis development, progression and complications [26]. On entrance and possible trapping within the arterial intima, triglyceride-rich lipoprotein degradation by lipoprotein lipase liberates free fatty acids and monoacylglycerols, both of which are able to generate local inflammation [27]. Diacylated and triacylated lipoproteins can be recognized by toll-like receptors, a type of pattern-recognition receptors that responses against invading microbes, activating early innate recognition and host inflammatory response [28,29]. Also, lipoprotein exposure to reactive oxygen species generates diverse oxidized phospholipids (OxPLs) which are able to contribute to the initiation and the amplification of the inflammatory response. Specifically, OxPLs present on OxLDLs are able to elicit strong pro-inflammatory cytokine and chemokine responses in murine macrophages and human monocytes [30]; they can alter also intracellular redox status and activate pro-inflammatory genes, leading to vessel wall inflammation [31].

Although oxidized lipids and non-HDLs are generally believed to promote inflammation both locally and systemically, they may also acquire a protective phenotype attenuating inflammation. Thus, during endotoxemia, lipoproteins may exert direct anti-inflammatory effects by neutralizing lipopolysaccharide (LPS) [32]. Also, increased levels of OxPLs on circulating lipoproteins during diet-induced dyslipidemia mitigate the pro-inflammatory cytokine response of dendritic cells and impair their capacity to instruct protective T-cell differentiation programs [33].