



Editorial

LDL Desialylation as a Trigger of Atherogenesis: Sialidase Inhibition as a Novel Anti-atherosclerotic Strategy



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The special issue of *Gene Expression*, entitled “Lipids and Inflammation in Health and Disease: Focus on Molecular Genetics”, highlights current advances in the roles of lipids in regulating inflammatory responses and the relationships between specific lipids and inflammation in health and disease.

Under normal conditions, phospholipids maintain cell membrane integrity and participate in intercellular communication.¹ Lipids have multiple functions in inflammatory processes. First, they can be enzymatically converted into prostaglandins and leukotrienes, potent signaling molecules that regulate the initiation, intensity, and resolution of inflammatory responses. Second, lipids provide an essential energy source for metabolically active immune cells during activation and proliferation.² Third, certain lipid species are susceptible to oxidative modification, and these oxidized lipids can drive chronic inflammation, contribute to the pathogenesis of inflammation-related diseases, including obesity, diabetes, and cardiovascular disease, and stimulate proinflammatory cytokine production by immune cells.^{3,4} Pro-resolving lipid mediators, including resolvins, help resolve inflammation and restore homeostasis.⁵ Thus, alongside other important factors, including aging, oxidative stress, mitochondrial mutations or dysfunction, and dysfunctional mitophagy, lipids play an important dual role in inflammation, as reflected in articles published in this Special Issue of *Gene Expression*.⁶⁻⁸

Lipids and inflammation contribute to the development of atherosclerotic lesions that can lead to myocardial infarction, stroke, and other vascular events. Previous studies identified low-density lipoprotein (LDL) particles in the blood of patients with atherosclerosis that had a lower sialic acid content than LDL from healthy individuals.⁹ This modified form was termed desialylated LDL. Desialylated LDL specifically refers to LDL particles that have lost sialic acid residues, which may represent an early and

fundamental modification. In contrast, modified LDL is a broader term encompassing desialylated LDL and LDL forms that have undergone subsequent modifications.

Experimental evidence indicates that neuraminidase activity can contribute to LDL desialylation.⁹ Furthermore, desialylated LDL differs from native LDL in multiple physical, chemical, and physiological properties. Specifically, desialylated LDL particles are smaller in diameter; contain lower levels of phospholipids, triglycerides, unesterified cholesterol, cholesteryl esters, and the antioxidant vitamin E; and exhibit greater density and a more negative surface charge than native LDL. Desialylated LDL may also be more prone to oxidation, disruption of the tertiary structure of apolipoprotein B (apoB), and self-association. A fundamental feature of desialylated LDL is its enhanced capacity to induce lipid accumulation in arterial cells, a property referred to as atherogenicity.¹⁰

The immune system may recognize modified LDL as foreign, leading to the production of antibodies against different modified forms of LDL. Antibodies against modified LDL have been detected in patients with atherosclerosis. These antibodies may form circulating immune complexes with modified LDL, which can exert proinflammatory and proatherogenic effects.¹¹ In addition to desialylated LDL, other forms of nonoxidatively modified LDL have been described.¹² Some of these forms of modified LDL share several characteristics, including increased atherogenicity, reduced size, increased negative charge, altered lipid composition, and greater oxidizability. These similarities suggest that modified LDL isolated using different methods may represent related particles that have undergone multiple modifications.

Multiple modifications of LDL can occur in plasma. In previous experimental work, native LDL and lipoprotein-depleted serum were mixed at the proportions present in the original plasma and incubated at 37°C to examine the sequence of LDL changes. The earliest change was a decrease in the sialic acid content of the native LDL fraction, followed by acquisition of the capacity to induce cholesterol accumulation in cultured subendothelial cells from intact human aortic intima. Later changes included reductions in phospholipids, neutral lipids, and α -tocopherol; increased negative charge; and the appearance of lipid

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peroxidation markers. No evidence of LDL acetylation was detected at any time point.¹⁰

These results support several important conclusions. LDL undergoes multiple modifications in plasma through a cascade of changes in lipoprotein particles, including desialylation, lipid loss, size reduction, increased electronegativity, and lipid peroxidation. Desialylation may be among the earliest LDL modifications and may be sufficient to render LDL atherogenic, whereas subsequent modifications may further enhance its atherogenicity. This concept is also supported by a study showing that exogenous GM3 has antiatherosclerotic effects *in vivo*.¹³ However, oxidized LDL should not be considered the sole important modification, because LDL oxidation may occur later in a multistep modification process and may not fully explain the early atherogenic properties of modified LDL.

Because desialylation appears to be the initial step in the multistep LDL modification process in blood, this observation suggests that sialidase activity is present in plasma. Several genes encode neuraminidases, or sialidases, that may contribute to LDL desialylation in atherosclerosis. The human neuraminidase family includes *NEU1*, *NEU2*, *NEU3*, and *NEU4*. Among these, *NEU3* is of particular interest because it is a major plasma membrane-associated sialidase that is active at neutral pH and has been implicated, together with *NEU1*, in LDL desialylation and early atherogenesis.⁹ *NEU1* is primarily lysosomal but may also contribute to extracellular desialylation under inflammatory conditions. Future genome-wide and functional studies may identify polymorphisms in *NEU1*, *NEU3*, or related genes that influence LDL sialylation status and susceptibility to atherosclerosis.

We have studied the role of desialylated LDL in atherogenesis for more than 35 years. Despite the accumulated evidence, clinical confirmation of the proposed key role of LDL desialylation in atherogenesis and related cardiovascular diseases remains lacking. Because sialidase activity in the blood represents a potential pharmacological target, the effects of sialidase inhibitors on atherosclerosis-related indices have been investigated both *in vitro* and *in vivo*.^{9,14} In *ApoE*^{−/−} mouse models, pharmacological inhibition of neuraminidases has been shown to delay fatty streak formation and reduce atherosclerotic lesion size without affecting plasma cholesterol or LDL levels.⁹

These findings support cautious optimism about sialidase inhibition as a potential anti-atherosclerotic strategy, but this approach should remain investigational. Any clinical application will require standardized assays for LDL sialylation, independent validation of the association between LDL desialylation and vascular outcomes, careful evaluation of inhibitor specificity and safety, and rigorous clinical studies with clinically meaningful end points.

The proposed mechanistic link between sialidase inhibition and anti-atherosclerotic effects may involve multiple interconnected pathways. First, by preserving the sialic acid content of LDL, sialidase inhibitors may prevent atherogenic modifications of LDL that promote its aggregation and retention within the arterial intima.⁹ Second, sialylated LDL may exhibit reduced binding to arterial proteoglycans, thereby limiting subendothelial lipoprotein accumulation, which is a critical early step in lesion formation.¹⁵ Third, desialylated LDL has been reported to promote macrophage responses and foam cell formation, linking lipoprotein

modification to proinflammatory cytokine production and vascular inflammation.⁹ Thus, preventing desialylation may attenuate this inflammatory cascade and influence both lesion initiation and progression, although this possibility requires further translational validation.

Interestingly, epigallocatechin-3-gallate has been reported to influence histone modifications, including histone acetylation and methylation, in human endothelial cells.¹⁶ Thus, agents that affect both lipoprotein modification and inflammatory epigenetic programs may be relevant to the interplay between lipids and inflammation. These observations exemplify the interplay between lipids and inflammation in atherosclerosis and may inform preventive and therapeutic strategies.

Overall, LDL desialylation illustrates the broader theme of this Special Issue: lipid biology and inflammation are deeply interconnected and shaped by molecular, genetic, metabolic, and immune mechanisms. The articles in this issue emphasize that understanding these connections may provide new insights into chronic inflammatory and cardiometabolic diseases. Future work should clarify how lipid modification, inflammatory signaling, mitochondrial dysfunction and genetic regulation interact in specific disease contexts and how this knowledge can be translated into safe and effective therapeutic strategies.

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Conflict of interest

ANO has served as an editorial board member of *Gene Expression* since June 2023. The authors declare no other conflicts of interest.

Author contributions

Drafting the manuscript (VAM), reviewing and editing the manuscript (NAO, AVC, ANO), and approval of the final manuscript for publication (VAM, NAO, AVC, ANO).

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