

Atherosclerosis and Circulating Immune Complexes Containing Modified Low-Density Lipoprotein (LDL)

Nikolai Orekhov¹, Daria Borodko², Ulyana Rozhkova³, Stanislav Antonov⁴, Aleksandra Utkina⁵ and Sarah Alkhudhur^{6*}

¹*Institute for Atherosclerosis Research, 4-1-207, Osennyaya Street, 121609 Moscow, Russia*

²*Laboratory of Molecular Genetic Modeling of Inflammation, Institute of General Pathology and Pathophysiology, 8, Baltiiskaya Street, 125315 Moscow, Russia*

³*Institute for Atherosclerosis Research, 4-1-207, Osennyaya Street, 121609 Moscow, Russia*

⁴*Laboratory of Molecular Genetic Modeling of Inflammation, Institute of General Pathology and Pathophysiology, 8, Baltiiskaya Street, 125315, Moscow, Russia*

⁵*Department of Commodity Expertise and Customs Business, Plekhanov Russian University of Economics, 36, Streymyanny Lane, 115054 Moscow, Russia*

⁶*Faculty of Biology, Department of Immunology, Lomonosov Moscow State University, Moscow, Russian Federation*

¹*www.fuper@gmail.com*, ²*daria.borodko@gmail.com*, ³*ulyroz@gmail.com*, ⁴*vamore@inbox.ru*, ⁵*ytkinaas@yandex.ru* and ⁶*sarah.aj.95@mail.ru*

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ABSTRACT

Atherosclerosis remains the principal underlying pathology of cardiovascular disease, the leading cause of mortality worldwide [1]. While the association between elevated low-density lipoprotein (LDL) cholesterol and atherosclerotic risk is well-established, a more nuanced understanding has emerged over recent decades: native LDL is not inherently atherogenic [2]. Rather, it is the multiple enzymatic and non-enzymatic modifications that LDL particles undergo in the circulation that confer pathogenic properties [3]. Among the most significant developments in this field is the recognition that modified LDL (mLDL) serves as an autoantigen, triggering a humoral immune response that leads to the formation of circulating immune complexes (CICs) [4]. These mLDL-containing CICs possess potent proatherogenic and proinflammatory activities that far exceed those of uncomplexed modified lipoproteins [5]. This review examines the molecular characteristics of mLDL-CICs, the mechanisms by which they promote foam cell formation and vascular inflammation, and the clinical evidence supporting their role as both biomarkers and active participants in atherosclerotic disease progression. Particular attention is directed toward the composition of these complexes, the specific LDL modifications that confer immunogenicity, and the differential pathogenic outcomes associated with distinct complex types. The accumulating evidence positions mLDL-CICs as critical mediators linking lipid metabolism, immunity, and vascular pathology.

Keywords: *modified LDL-containing immune complexes (mLDL-CICs); atherosclerosis; oxidized low-density lipoprotein (oxLDL); macrophages; foam cells; Fcγ receptors; oxidative stress; vascular inflammation; cholesterol accumulation; cardiovascular disease.*

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1. INTRODUCTION

Cardiovascular diseases account for an estimated 17.9 million deaths annually, representing approximately 31% of all global mortality [1]. Atherosclerosis, the pathological process underlying the majority of these events, is a complex, progressive disorder characterized by the accumulation of lipids, inflammatory cells, and fibrous elements within the arterial wall [6]. The disease develops silently over decades, with clinical manifestations—myocardial infarction, stroke, or peripheral artery

disease—often appearing suddenly and catastrophically [7].

The lipid hypothesis of atherosclerosis, first proposed by Nikolai Anitschkow over a century ago, identified cholesterol accumulation in the arterial wall as the initiating event in lesion formation [8]. Subsequent epidemiological studies, most notably the Framingham Study, established elevated LDL cholesterol as a major cardiovascular risk factor [9]. Yet the relationship between circulating LDL levels and atherosclerotic disease is not

*Author for Correspondence: *sarah.aj.95@mail.ru*

straightforward. It has become increasingly apparent that not all LDL particles are equally atherogenic [10]. In the circulation of patients with atherosclerosis, LDL particles undergo a series of modifications—desialylation, oxidation, glycation, and others—that fundamentally alter their biological properties and confer atherogenicity [3, 11].

Perhaps more significantly, these modifications render LDL immunogenic. The immune system recognizes modified lipoproteins as foreign, generating specific autoantibodies that form immune complexes with circulating mLDL [4, 12]. These mLDL-containing CICs have emerged as particularly potent drivers of atherosclerosis, capable of inducing foam cell formation, promoting inflammation, and accelerating lesion progression through mechanisms distinct from those of uncomplexed modified LDL [5, 13].

This review synthesizes current understanding of mLDL-CICs in atherosclerosis, examining their formation, physicochemical properties, cellular effects, and clinical significance. We argue that mLDL-CICs represent not merely passive markers of disease but active pathogenic agents that bridge the traditional domains of lipid metabolism and immune function in atherosclerosis.

2. LDL MODIFICATIONS: FROM NATIVE PARTICLE TO AUTOANTIGEN

2.1 The Nature of Native LDL

Low-density lipoprotein particles are the primary carriers of cholesterol in human plasma. Each LDL particle consists of a hydrophobic core of esterified cholesterol and triglycerides surrounded by a phospholipid monolayer containing unesterified cholesterol and a single molecule of apolipoprotein B-100 (apoB-100) [14]. Notably, LDL particles are particularly enriched in free cholesterol, which can constitute up to 50% of the particle weight—a higher proportion than in any other lipoprotein fraction [15].

Native LDL, however, does not induce lipid accumulation in cultured vascular cells [2]. This observation, initially puzzling, led to the crucial insight that LDL must undergo modification to become pathogenic [3]. The search for these modifications has revealed a complex cascade of changes that occur spontaneously in the circulation, particularly in the proatherogenic environment associated with cardiovascular risk factors [16].

2.2 Desialylation: The Primary Modification

Among the various modifications LDL undergoes, desialylation—the removal of terminal sialic acid residues from carbohydrate chains—appears to be the earliest and most consequential [17]. Sialic acid is a critical structural component of native LDL, capping the biantennary sugar chains of ApoB-100 and the carbohydrate moieties of

associated gangliosides [18]. The enzyme trans-sialidase, whose activity is elevated in atherosclerotic patients, catalyzes this desialylation [19].

The importance of desialylation is underscored by quantitative findings. In healthy individuals, desialylated LDL constitutes only 5-10% of the total LDL pool. In patients with coronary artery disease, however, this fraction can increase dramatically, accounting for up to 60% of circulating LDL [20]. This striking elevation suggests that desialylation is not merely an incidental phenomenon but a central feature of the atherogenic process [21]. The structural consequences of desialylation are profound. Removal of sialic acid exposes terminal galactose residues, which can be recognized by lectins and serve as markers for altered lipoproteins [22]. The desialylated particle is smaller, denser, and more electronegative than its native counterpart—characteristics that facilitate its entry into the arterial wall and its retention within the subendothelial space [23].

2.3 The Cascade of Multiple Modifications

Desialylation does not occur in isolation. Rather, it initiates a sequence of progressive modifications that transform the LDL particle into a multiply modified entity (mmLDL). Ex vivo experiments have delineated this temporal cascade with remarkable precision [24]:

Within one hour of incubation with serum from atherosclerotic patients, LDL undergoes desialylation. By three hours, desialylated LDL begins to induce lipid retention in cultured cells. At six hours, reductions in neutral lipid and phospholipid content become evident, accompanied by particle size diminution. By 36 hours, the particles acquire increased electronegativity. Between 48 and 72 hours, tocopherol is lost, susceptibility to copper oxidation increases, and lipid peroxidation end products accumulate [24].

This temporal sequence has important implications for understanding the pathogenesis of atherosclerosis. Desialylation—the initiating event—renders the particle more susceptible to subsequent modifications, including oxidation, glycation, and aggregation [25]. The multiply modified LDL that emerges from this process possesses a constellation of properties that promote lipid retention, inflammation, and immune activation [26].

Of particular note is the relationship between desialylated LDL and the small, dense LDL (sdLDL) subfraction, which is strongly associated with cardiovascular risk [27]. The sdLDL subfraction displays a profound deficiency in sialylation compared to larger, more buoyant LDL particles, and this deficiency correlates directly with its increased atherogenicity [28]. Similarly, electronegative LDL (LDL(-)), which is elevated in atherosclerotic patients, is highly enriched with desialylated particles [29].

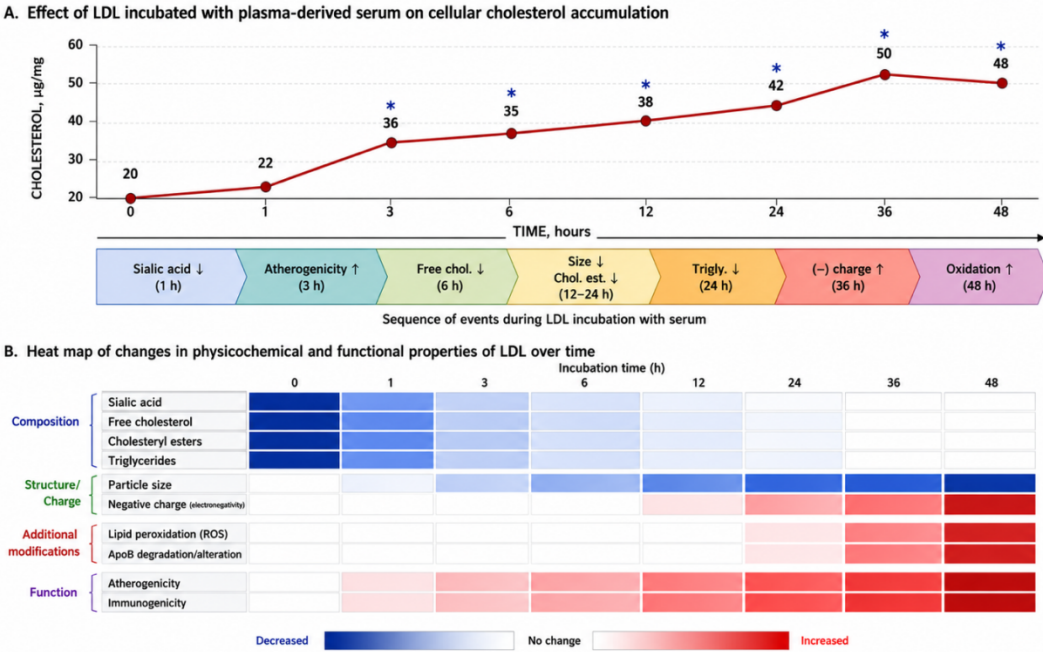


Fig. 1. Cascade of multiple modification of LDL during incubation with serum.

The top graph demonstrates the effect of LDL incubated with plasma-derived serum at 37°C on total cholesterol content (in µg/mg of cellular protein) in cells cultured from uninvolved intima of human aorta. Sialylated LDL was isolated by lectin chromatography and incubated with autologous plasma-derived serum. Cells were incubated with 100 mg/ml LDL for 24 h. Data are the means of three determinations ± S.E.M. *Significant difference from non-incubated LDL, $p < 0.05$. The bottom diagram shows the sequence of events occurring with native LDL in the plasma. “Already after 1 h of incubation the sialic acid content is decreased while the proportion of desialylated LDL increases. After 3 h of incubation LDL starts anifesting atherogenic properties. Within a 6-24-h interval, a fall in the levels of all major classes of lipids is observed, which in turn causes a reduction in the particle size. An increase in the electronegative charge is observed after 36 h of incubation while the first signs of lipid peroxidation and apo B degradation appear only after 48 h.”. Adapted from Tertov, V.V.; Kaplun, V.V.; Sobenin, I.A.; Orekhov, A.N. Low-density lipoprotein modification occurring in human plasma. *Atherosclerosis*, 1998, 138(1), 183-195. [http://dx.doi.org/10.1016/S0021-9150\(98\)00023-9](http://dx.doi.org/10.1016/S0021-9150(98)00023-9)

2.4 Immunogenicity of Modified LDL

The structural alterations induced by LDL modification have a critical consequence: they render the particle immunogenic. Laboratory-modified LDL preparations—copper-oxidized LDL (oxLDL), malondialdehyde-modified LDL (MDA-LDL), advanced glycation end

product-modified LDL (AGE-LDL), and others—readily induce antibody formation in experimental animals [30]. More importantly, autoantibodies recognizing these modified forms are present in human sera, indicating that similar modifications occur in vivo [31].

The characterization of human autoantibodies to mLDL has revealed important features of this immune response. When whole human serum is subjected to affinity chromatography using immobilized oxLDL or AGE-LDL, the predominant antibody isotype is IgG, specifically subtypes 1 and 3, followed by IgM and, in much smaller concentrations, IgA [32]. The presence of these antibodies in the circulation implies that LDL is recognized as an autoantigen—a self-molecule that has been sufficiently altered to breach immune tolerance [33].

The specificity of these autoantibodies provides insight into the nature of the immunogenic epitopes. IgG fractions isolated from circulating immune complexes of patients react most strongly with MDA-LDL, oxLDL, and AGE-LDL [34]. Further analysis reveals that MDA-lysine is the major immunogenic epitope of oxLDL, while CML-lysine serves as the primary epitope of AGE-LDL [35]. Importantly, laboratory-modified lipoproteins often contain multiple epitopes, some of which are shared between different modifications [36]. This cross-reactivity reflects the complexity of the modification process and suggests that LDL molecules modified in vivo may bear multiple antigenic determinants [37].

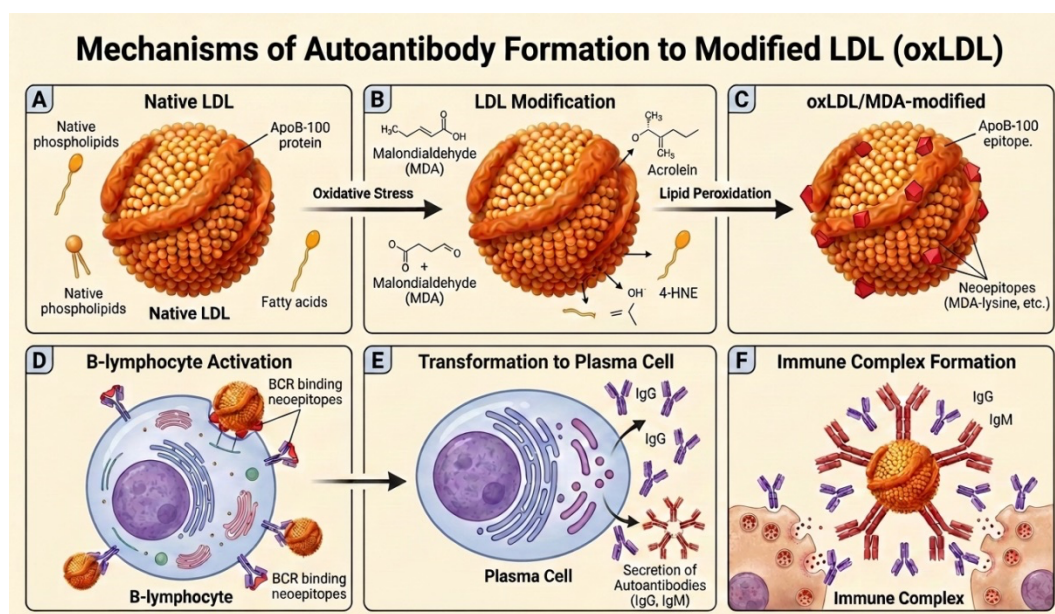


Fig. 2. Formation of autoantibodies to modified LDL

A-B: Modification Pathway that shows the progression of LDL as it undergoes modifications such as oxidative stress and lipid peroxidation (producing MDA). These changes create "neoepitopes" on the ApoB-100 surface that are no longer recognized as self.

C: B-Cell Recognition—Specific B-lymphocytes identify these neoepitopes as damage-associated molecular patterns, initiating the adaptive immune response.

D-E: Plasma Cell Transformation & Secretion: Upon activation, B-cells differentiate into Plasma Cells, which secrete specific IgG and IgM autoantibodies directed against the modified LDL.

F: Immune Complex Formation— The final stage shows the formation of mLDL-CICs—circulating immune complexes created when autoantibodies bind to modified LDL particles. These complexes represent a "mechanistic link" between dyslipidemia and chronic inflammation.

3. FORMATION AND PHYSICOCHEMICAL PROPERTIES OF MLDL-CONTAINING IMMUNE COMPLEXES

3.1 Discovery and Historical Context

The involvement of immune complexes containing lipoproteins in atherosclerosis was first suggested in 1970 by Beaumont and colleagues, who reported massive hyperlipidemia and accelerated atherosclerosis in a patient with IgA myeloma who's monoclonal IgA functioned as an autoantibody against LDL [38]. In 1978, Fust and coworkers documented the presence of LDL antibodies and immune complexes in patients with cardiovascular disease [39].

These early observations laid the groundwork for systematic investigation. Subsequent studies demonstrated that anti-LDL antibodies bind preferentially to modified LDL rather than native LDL, strongly suggesting that the antibodies are generated in response to the appearance of

modified lipoproteins in the circulation [40]. The higher affinity of autoantibodies for desialylated LDL and MDA-LDL compared to native LDL provides compelling evidence that these antibodies are not merely cross-reactive with naturally occurring structures but are specifically induced by modified lipoprotein antigens [41].

3.2 Isolation and Characterization

Tertov and colleagues developed a method for isolating LDL-containing CICs from serum using polyethylene glycol 6000 precipitation, followed by chromatographic separation [42]. This approach revealed that LDL-CICs differ markedly from native LDL in their physicochemical properties [43].

The LDL particles within CICs have significantly lower sialic acid content—that is, they are desialylated. They also show reductions in neutral lipids, phospholipids, and neutral sugars. The particles are smaller in diameter, possess higher hydrated density, and exhibit increased electrophoretic mobility, indicating greater electronegativity [44]. These characteristics closely parallel those of the multiply modified (desialylated) LDL fraction described independently, confirming that LDL-CICs are enriched in modified lipoprotein species [45].

Of particular significance is the observation that the LDL content of circulating immune complexes correlates strongly with the blood concentration of desialylated LDL but not with total LDL levels [46]. This finding indicates that it is predominantly desialylated LDL that forms complexes with autoantibodies and reinforces the conclusion that the affinity of circulating anti-LDL autoantibodies is higher for modified LDL than for native LDL [47].

The immunoglobulins within these complexes are predominantly IgG of subtypes 1 and 3 [48]. Antibodies isolated from immune complexes demonstrate higher affinity constants than those remaining free in the

circulation, suggesting that the antibodies involved in immune complex formation represent a higher-affinity subset of the anti-mLDL antibody population [49].

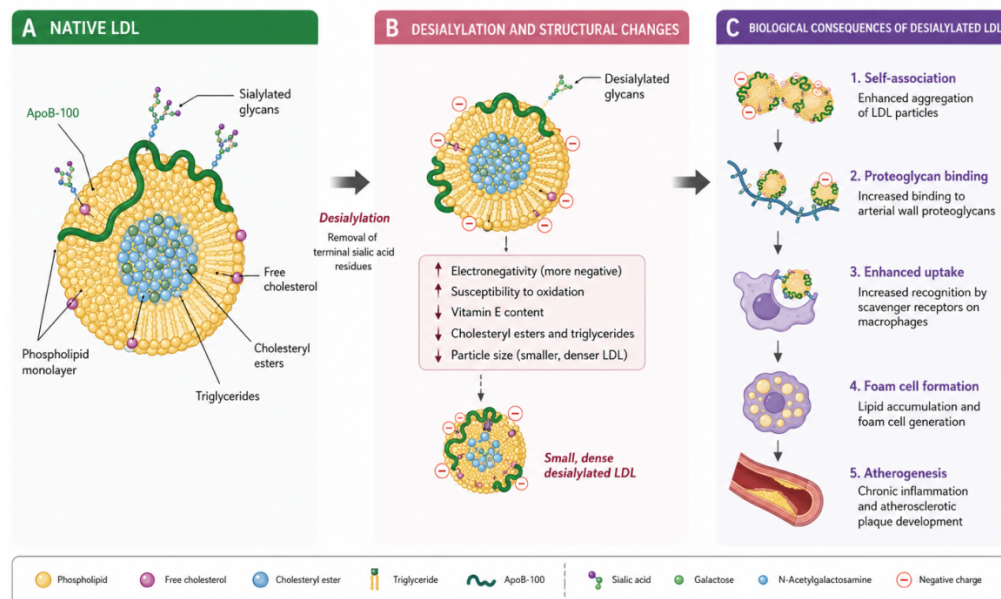


Fig. 3. Structural and physicochemical differences between native LDL and desialylated LDL.

Desialylation of LDL removes terminal sialic acid residues, leading to increased negative charge, oxidative susceptibility, and self-association. These changes promote arterial retention, macrophage uptake and foam cell formation, thereby accelerating atherogenesis.

3.3 Quantity and Relationship to Circulating LDL

Quantitative studies have revealed that the LDL component of immune complexes constitutes no more than 2% of the total circulating LDL pool [50]. This small fraction might seem inconsequential. Yet, paradoxically, this minor component appears to be fundamental to the atherogenic properties of whole serum. In cell culture experiments, immune complexes isolated from patient sera produce atherosclerosis-related changes comparable to those induced by the whole serum from which they were derived [51].

The removal of LDL-CICs from the serum of coronary heart disease patients eliminates the atherogenic properties of that serum in cell culture assays [52]. This finding provides compelling evidence that the pathogenic activity of patient sera is largely attributable to the immune complex fraction, despite its quantitative insignificance relative to total LDL.

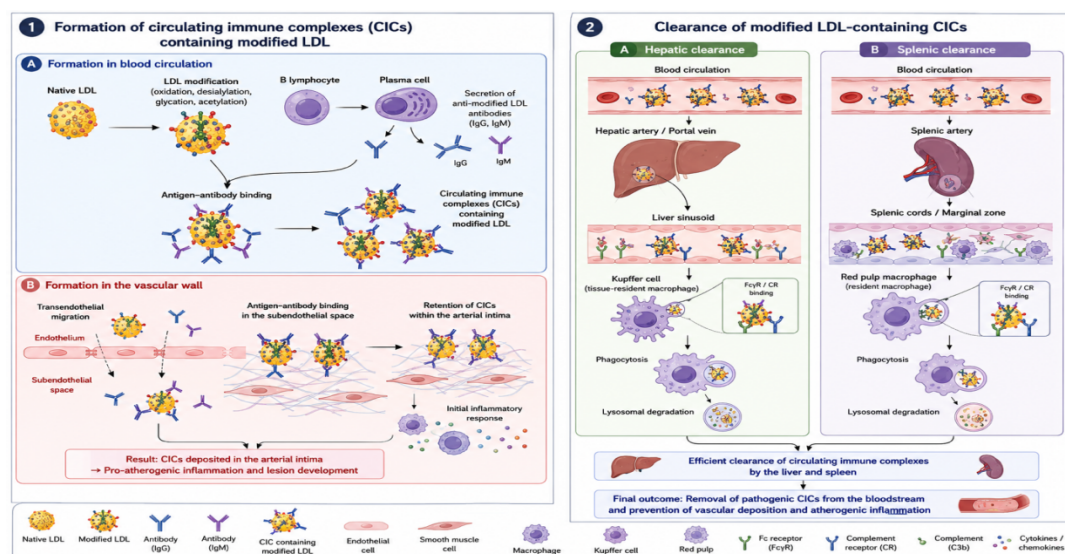


Fig. 4. Formation and clearance of CICs containing modified LDL in the blood and/or vascular wall.

4. CELLULAR MECHANISMS OF ATHEROGENICITY

4.1 Foam Cell Formation and Cholesterol Accumulation

The most direct evidence for the atherogenic role of mLDL-CICs comes from studies of their effects on cultured cells. Incubation of macrophages with LDL-containing immune complexes leads to dramatic accumulation of cholesterol, particularly esterified cholesterol, transforming these cells into foam cells—the hallmark of early atherosclerotic lesions [53].

Klimov and colleagues demonstrated that mouse macrophages cultured in the presence of immune complexes containing LDL and anti-LDL antibodies show markedly increased uptake of LDL [54]. Incubation of human peritoneal macrophages with autologous LDL-containing immune complexes similarly results in foam cell transformation [55]. The cholesterol content of macrophages incubated with LDL immune complexes

increases approximately 60-fold compared to control macrophages [56].

The mechanism of this enhanced cholesterol uptake involves Fc receptor-mediated endocytosis rather than the classical LDL receptor pathway [57]. When LDL immune complexes bind to Fcγ receptors on macrophages, they are internalized efficiently, delivering large amounts of cholesterol to the cell [58]. This mechanism is particularly significant because it circumvents the normal feedback regulation that controls LDL receptor expression. In fact, the engagement of Fc receptors by LDL immune complexes paradoxically leads to overexpression of LDL receptors, further amplifying cholesterol uptake [59].

The importance of Fc receptor engagement is demonstrated by experiments using F(ab')₂ fragments of anti-LDL antibodies. Immune complexes prepared with these fragments, which lack the Fc domain necessary for Fc receptor binding, fail to induce the same atherogenic responses as intact antibody complexes [60].

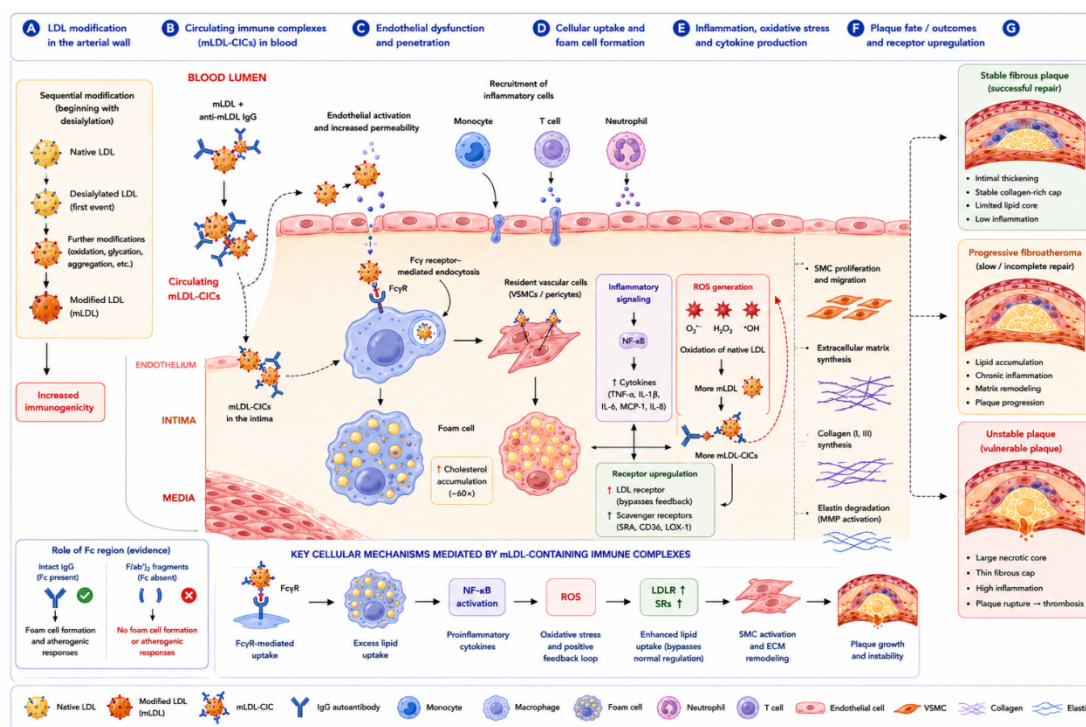


Fig. 5. Mechanisms of participation of modified LDL in atherosclerosis.

Native LDL undergoes atherogenic modifications in the subendothelial space, leading to increased endothelial permeability, lipid infiltration, and recruitment of inflammatory cells. Modified LDL is taken up by macrophages and resident cells, forming foam cells. These events promote extracellular matrix remodeling, smooth muscle cell activation, and the development and progression of atherosclerotic lesions.

4.2 Proinflammatory Signaling

Beyond direct cholesterol delivery, mLDL-CICs activate proinflammatory signaling cascades in monocytic cells. Treatment of human monocytic THP-1 cells or peripheral

blood monocytes with LDL immune complexes enhances their ability to bind and take up native LDL, an effect dependent on Fc receptor engagement [61]. Activation also stimulates mRNA expression for scavenger receptors, further increasing the cells' capacity for lipid uptake [62].

Perhaps even more significantly, activation of monocytic cells with lipoprotein immune complexes stimulates the generation of reactive oxygen intermediates [63]. These reactive species can, in turn, oxidize exogenous LDL, perpetuating a cycle of LDL modification, immune

complex formation, and inflammatory activation [64]. This mechanism provides a direct link between immune complex formation and the oxidative stress that characterizes atherosclerotic lesions [65].

4.3 Effects on Apoptosis and Plaque Vulnerability

Recent studies have revealed that the effects of mLDL-CICs extend beyond foam cell formation to influence the stability of atherosclerotic plaques. The composition of the immune complex—specifically, the nature of the LDL modification within the complex—appears to modulate downstream cellular responses [66].

Immune complexes containing oxLDL induce both cell proliferation and mild to moderate macrophage apoptosis. In contrast, complexes containing MDA-LDL induce more

marked macrophage apoptosis but do not stimulate proliferation [67]. Furthermore, MDA-LDL immune complexes induce the release of higher levels of matrix metalloproteinases and tumor necrosis factor (TNF) than oxLDL immune complexes [68].

These differential effects have important implications for plaque biology. High levels of TNF are likely to promote apoptosis, while elevated matrix metalloproteinase activity may contribute to thinning of the fibrous cap of the atheromatous plaque [69]. The combination of macrophage apoptosis and fibrous cap thinning is a well-recognized characteristic of vulnerable plaques—those prone to rupture and responsible for the majority of acute cardiovascular events [70].

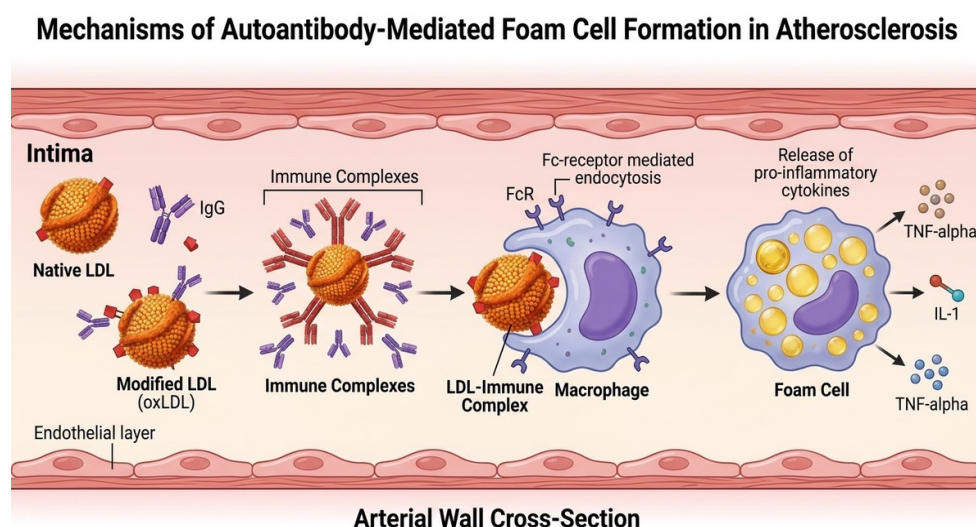


Fig. 6. The Proatherogenic Role of mLDL-CICs in the Arterial Wall.

This figure illustrates how mLDL-CICs act as "active participants in atherogenesis" within the vascular environment, contributing to the development of atherosclerotic plaques. Intimal entrapment: mLDL (oxLDL) particles become trapped in the subendothelial space (intima), where they form immune complexes with IgG antibodies. Fc receptor-mediated uptake: Unlike native LDL, these immune complexes have "potent proatherogenic properties", inducing foam cell formation. The diagram shows a macrophage using its Fc receptors (FcRs) to engulf mLDL-CICs. Foam cell formation & inflammation: Following endocytosis, the macrophage becomes a lipid-laden foam cell. This process promotes inflammation through the release of pro-inflammatory cytokines (such as TNF- α and IL-1) and the generation of reactive oxygen species. Plaque progression: The accumulation of foam cells and sustained inflammatory signaling directly contribute to plaque progression, instability, and cardiovascular events.

This observation suggests that the specific composition of mLDL-CICs may influence not only the extent of atherosclerosis but also the clinical presentation. Patients whose immune complexes react strongly with antibodies

to MDA-LDL appear to be at heightened risk of acute vascular events, particularly myocardial infarction, while those with complexes reacting strongly with oxLDL antibodies show progressive atherosclerosis as measured by intima-media thickness and coronary calcification scores [71].

5. CLINICAL EVIDENCE AND DIAGNOSTIC UTILITY

5.1 Association with Atherosclerotic Disease

The clinical significance of mLDL-CICs is supported by extensive evidence. Anti-LDL autoantibodies and LDL-containing immune complexes have been detected in the blood of patients with various cardiovascular diseases and in atherosclerotic lesions themselves [72]. Deposits of immune complex components have been identified in vascular atherosclerotic lesions, confirming that these complexes are not merely circulating markers but participate directly in the disease process [73].

Patients with angiographically confirmed coronary atherosclerosis show elevated levels of IgG class autoantibodies against modified LDL compared to healthy subjects [74]. The titer of LDL-CICs in blood serum

correlates significantly with the progression of atherosclerosis in vivo [75]. This correlation has been observed across multiple studies and appears to be independent of traditional lipid parameters [76].

5.2 Predictive Value for Cardiovascular Events

The predictive value of mLDL-CICs for cardiovascular events has been examined in several clinical studies. Elevated levels of mLDL in circulating immune complexes are strong predictors of cardiovascular disease [77]. In diabetic patients, mLDL-CIC levels also predict other significant complications, including nephropathy and retinopathy, suggesting that the pathogenic mechanisms involving immune complex formation may extend beyond the vasculature [78].

Importantly, the predictive value of mLDL-CICs appears to exceed that of conventional lipid parameters. The cholesterol content of circulating immune complexes has been proposed as a possible risk factor for coronary atherosclerosis with diagnostic value superior to other measured serum lipid parameters [79].

5.3 Implications for Diabetes

The role of mLDL-CICs is particularly well-studied in type 1 diabetes, where advanced glycation end products are generated at accelerated rates due to chronic hyperglycemia [80]. AGE-modified LDL is a potent immunogen, and AGE-LDL immune complexes are elevated in diabetic patients [81].

In this population, mLDL-CICs may serve as biomarkers for macrovascular disease [82]. The presence of AGE-LDL antibodies and immune complexes in diabetic patients is associated with increased risk of cardiovascular complications, suggesting that the AGE modification pathway contributes importantly to the accelerated atherosclerosis observed in diabetes [83].

6. CONTROVERSIES AND CONFLICTING EVIDENCE

The pathogenic role of mLDL-CICs, while supported by substantial evidence, is not universally accepted. One significant controversy concerns the interpretation of autoantibody levels. Some studies have reported that autoantibodies to modified LDL may have protective effects, perhaps by facilitating clearance of modified lipoproteins or by blocking their uptake by macrophages [84]. In contrast, other studies—reviewed extensively here—support a pathogenic role for these antibodies [85].

A recent study examining antibodies to MDA-LDL in 253 subjects—including healthy individuals, patients with preclinical atherosclerosis, and patients with coronary artery disease—found that plasma levels of IgG antibodies to MDA-LDL were significantly reduced in patients with coronary artery disease compared to healthy individuals and those with preclinical atherosclerosis [86]. In vitro, these antibodies were shown to reduce MDA-LDL cytotoxicity and its ability to induce cholesterol ester accumulation in macrophages [87]. These findings suggest

that anti-lipoprotein antibodies may, in some circumstances, have a protective effect by preventing foam cell formation.

This apparent contradiction—between studies supporting pathogenic and protective roles for anti-mLDL antibodies—may be resolved by considering several factors. First, the nature of the antibody response matters: isotype (IgG vs. IgM), affinity, and epitope specificity likely influence whether a given antibody population promotes or inhibits atherogenesis [88]. Second, the concentration of antibodies relative to antigen may determine whether immune complexes form and whether they are cleared efficiently [89]. Third, the specific LDL modification involved may be critical, as the same antibody may have different effects depending on the antigen [90]. Fourth, the phase of the disease (early vs. advanced) may influence whether immune responses are predominantly protective or pathogenic [91].

The observation that antibodies involved in immune complex formation have higher affinity than those remaining free in the circulation [49] suggests that high-affinity antibodies are more likely to participate in pathogenic processes. The balance between protective and pathogenic antibodies may therefore depend on the characteristics of the antibody response and the efficiency of immune complex clearance.

7. THERAPEUTIC IMPLICATIONS AND FUTURE DIRECTIONS

7.1 Targeting mLDL-CICs as a Therapeutic Strategy

The pathogenic role of mLDL-CICs opens possibilities for therapeutic intervention. If these complexes are directly involved in promoting atherosclerosis, then strategies to reduce their formation or enhance their clearance might be expected to have beneficial effects [92].

One approach involves inhibiting the modification of LDL. Desialylation, identified as the primary and earliest modification, is catalyzed by trans-sialidase. Pharmacological inhibition of this enzyme could potentially prevent the cascade of LDL modifications that lead to immune complex formation [93]. Such an approach would target the earliest steps in the pathogenic pathway.

Another strategy involves modulating the immune response to modified LDL. If certain antibody populations are protective while others are pathogenic, then selective modulation of the immune response might be feasible [94]. Induction of regulatory immune responses, perhaps through immunization with modified LDL epitopes, represents a promising but unproven approach [95]. Immunotherapy directed at atherosclerosis antigens is an area of active investigation [96].

7.2 Diagnostic Applications

The strong association between mLDL-CIC levels and atherosclerotic disease suggests that these complexes could serve as valuable diagnostic and prognostic biomarkers [97]. Traditional lipid parameters, while

useful, have limitations. The measurement of mLDL-CICs could provide additional information about the actual pathogenic activity of the immune system in individual patients [98].

The diagnostic potential is particularly relevant for early detection of atherosclerosis. Because the disease develops silently for decades, markers that identify early, preclinical disease could enable intervention before clinical events occur [99]. mLDL-CICs, which appear to be involved in early lesion formation, could fill this role [100].

7.3 Future Research Directions

Several questions warrant further investigation. First, the mechanism by which LDL becomes immunogenic requires additional elucidation. While desialylation appears to initiate the process, the precise epitopes recognized by pathogenic antibodies and the pathways by which immune tolerance is breached remain incompletely understood [101].

Second, the relationship between different types of LDL modifications and clinical outcomes deserves further study. The observation that oxLDL-CICs and MDA-LDL-CICs have differential effects on cellular responses and clinical presentation [71] suggests that characterization of the specific modifications present in immune complexes could provide more accurate prognostic information [102].

Third, the balance between pathogenic and protective antibody responses requires further investigation. Understanding the factors that determine whether a given immune response promotes or inhibits atherosclerosis could lead to more rational therapeutic approaches [103].

Fourth, the potential for modulating mLDL-CIC formation or clearance therapeutically merits exploration in preclinical models [104–106].

8. CONCLUSION

The recognition that circulating immune complexes containing modified LDL play a central role in atherosclerosis represents a significant advance in understanding this complex disease. Native LDL is not inherently atherogenic; rather, it is the multiple modifications that LDL undergoes in the circulation—beginning with desialylation—that confer pathogenicity. These modifications render LDL immunogenic, triggering a humoral immune response that produces specific autoantibodies. The immune complexes that form between modified LDL and these antibodies possess potent proatherogenic properties, inducing foam cell formation through Fc receptor-mediated uptake, promoting inflammation through reactive oxygen species generation, and potentially contributing to plaque instability through differential effects on apoptosis and matrix remodeling.

The clinical evidence supporting the role of mLDL-CICs in atherosclerosis is substantial. Elevated levels of these complexes are found in patients with atherosclerotic disease, correlate with disease progression, and predict cardiovascular events. The diagnostic and prognostic value

of mLDL-CIC measurement may exceed that of traditional lipid parameters, particularly for the detection of preclinical atherosclerosis.

Significant questions remain, particularly regarding the balance between protective and pathogenic immune responses and the potential for therapeutic modulation. The observation that some autoantibodies may have protective effects while others promote disease suggests that simple measurement of total anti-mLDL antibody levels may be insufficient; more detailed characterization of antibody specificity, affinity, and isotype may be needed.

Despite these uncertainties, the evidence supports the view that mLDL-CICs are not merely passive markers of disease but active participants in atherogenesis. They bridge the traditional domains of lipid metabolism and immune function, providing a mechanistic link between dyslipidemia and the chronic inflammation that characterizes atherosclerosis. As such, they represent promising targets for both biomarker development and therapeutic intervention.

The continued investigation of mLDL-CICs promises to deepen our understanding of atherosclerosis and to open new avenues for its diagnosis, prevention, and treatment. The integration of lipid biology, immunology, and clinical cardiovascular medicine in this field exemplifies the interdisciplinary approach needed to address the complex challenges of atherosclerotic disease.

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