Chapter 16
Lipoprotein(a) and Immunity

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Introduction

Lipoprotein(a) [Lp(a)] is an atherothrombogenic lipoprotein particle that differs in its composition and physicochemical and biological properties from other lipoproteins and contains a unique apolipoprotein(a) molecule [apo(a)]. The relationship between the immune system and lipid metabolism has been evaluated for many decades. An increased blood Lp(a) concentration is a proven risk factor for atherosclerotic cardiovascular disease (ASCVD). Lawn's hypothesis about Lp(a) as a repair factor remains relevant until today (Lawn et al. 1992). Recent studies suggest participation of humoral and cell immunity in wound healing and regeneration and in inflammatory diseases (Masoomikarimi and Salehi 2022; Eming et al. 2017). An elevated Lp(a) level in long-living persons suggests possible participation of immunological factors in both the physiological and pathophysiological Lp(a) pathways (Panza et al. 2007). It is assumed that with increased life expectancy and in the presence of "inflammaging," [Inflammaging is the long-term result of the chronic physiological stimulation of the innate immune system, which can become damaging during ageing—a period of life largely unpredicted by evolution (Franceschi et al. 2018)] Lp(a) may become a factor contributing to atherosclerosis and other inflammatory diseases (Franceschi et al. 2018).

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Lipoprotein(a) and IgG and IgM Autoantibodies (AAbs)

The production of immunoglobulins (Ig) by B cells is necessary for the recognition, neutralization, and removal of exogenous and endogenous pathogens and for maintaining homeostasis. The concept of "natural" antibodies synthesized by B1 cells with specificity to alien and native proteins was first proposed in 1908 by Ehrlich (Piro et al. 2008). Natural IgM antibodies are encoded by the germline cells, and they are present in the umbilical cord blood of newborns. It is assumed that the level of natural IgM antibodies is maintained constant throughout life (Holodick et al. 2017). The main biological functions of natural IgM are removal of apoptotic cells, protection from infection, and maintenance of tissue homeostasis (Reyneveld et al. 2020; Wang et al. 2016). The protective effect of IgM AAbs to oxidized LDL (low-density lipoprotein) (oxLDL) produced by B1 cells has been described in several studies and literature reviews (Tsimikas et al. 2012; van den Berg et al. 2018; Pattarabanjird et al. 2021). The presence of circulating Lp(a)-containing immune complexes in the plasma of patients with coronary heart disease (CHD), healthy donors, and patients with autoimmune diseases has been reported in several studies. Most of the immune complexes found in the plasma of healthy donors contained IgM AAbs against Lp(a), unlike patients with CHD (Wang et al. 2003; Sabarinath and Appukuttan 2015; Klesareva et al. 2016).

Recently, we have shown that the levels of IgM AAbs against Lp(a) were higher in patients without atherosclerosis or non-stenosing lesions of the coronary arteries (Afanasieva et al. 2016b). Such a protective function of these IgM AAbs was also present in patients with severe hypercholesterolemia (Klesareva et al. 2018). In a retrospective study of 1228 patients, the lower the IgM level of Lp(a) AAbs and the higher the concentration of Lp(a), the more vascular beds there were with stenosing atherosclerotic lesions (Tmoyan et al. 2021).

The autoimmune theory of atherosclerosis was formulated by Klimov more than 40 years ago. He showed that modified lipoproteins acquire autoantigenic properties and trigger an immune response to the "altered self" (Klimov 1990). The role of autoantigens is played by modified LDL, as well as lipoproteins containing oxidized phospholipids (Virella and Lopes-Virella 2008). Elevated plasma levels of IgG AAbs to oxLDL are associated with angiographically verified coronary atherosclerosis and progression of carotid lesions (Salonen et al. 1992). Previously, a direct relationship between the level of IgG AAbs against Lp(a) and the number of affected coronary arteries was demonstrated (Afanas'eva et al. 2014). The content of IgG AAbs against MDA (malondialdehyde)-LDL in the upper quartile was associated with the risk of cardiovascular events at a 10-year follow-up (Prasad et al. 2017). However, the role of Lp(a), as well as oxLDL, as possible specific autoantigen for B2 cells remains controversial (Ravandi et al. 2011). Nevertheless, studies aimed at using immunoglobulins specific to oxidized epitopes present on lipoproteins' and apoptotic cells' surfaces for the treatment of ASCVD are in progress (de Vries et al. 2021; Pluijmert et al. 2021; Ståhle et al. 2020).

Lp(a), such as LDL-like particles, also could be affected by modification of their protein and/or lipid compounds; such modifications activate humoral immune responses and create AAbs formation. Lp(a) AAbs immune complexes removed by macrophages can be transferred to foam cells.

The IgM and IgG antibody classes against Lp(a) detected in human serum appear to have not only different origins but also different functions. Natural IgM implies an evolutionary advantage to neutralize Lp(a) and to eliminate it. The appearance of autoantibodies of different IgG subclasses indicates the activation of adaptive immunity, which perceives Lp(a) as the antigen, and causes subsequent development of inflammatory reactions.

Lipoprotein(a) and Innate Immunity Cells

Monocytes and macrophages play a critical role in innate immunity (Libby et al. 2013) and have been the subject of numerous studies in connection with Lp(a). Lp(a) was detected in macrophage cell-rich areas of atherosclerotic plaques in humans according to morphology and immunohistochemistry studies (Sotiriou et al. 2006). On the other hand, individuals with elevated Lp(a) level exhibit enhanced accumulation of peripheral blood mononuclear cells in the arterial wall compared to individuals with normal levels of Lp(a) (van der Valk et al. 2016). Apo(a) stimulates the production of reactive oxygen species and matrix metalloproteinase-9 by collagen-adherent monocytes, and this effect was inversely associated with the molecular weight of apo(a) (Sabbah et al. 2019). Apo(a) also caused increased secretion of IL-8 by macrophages of the THP-1 and U-937 cell lines (Scipione et al. 2015). Monocytes isolated from subjects with elevated Lp(a) demonstrated an enhanced cell surface expression of chemokine receptors, adhesion molecules, and scavenger receptors (CCR7, CD62L, CD11b, CD11c, CD29, CD36, SR-A). Apo(a) upregulates the expression of the β2-integrin Mac-1 (CD11b/CD18), thereby facilitating cell adhesion and migration capacity. Several signaling cascades leading to altered gene expression profiles were found to contribute to Lp(a)-induced monocyte chemotactic activity (Scipione et al. 2015; Dzobo et al. 2022).

Besides displaying an activated and proinflammatory phenotype, monocytes isolated from individuals with elevated Lp(a) exhibited an increased secretion of proinflammatory cytokines (IL-1β, IL-6, TNFα) and a decrease in the anti-inflammatory cytokine IL-10 after stimulation via toll-like receptors. OxPLs associated with apo(a) as potent danger-associated molecular patterns (DAMPs) could be responsible for these effects (Koschinsky and Boffa 2022).

Apo(a) antisense treatment resulted in downregulation of proinflammatory gene expression in monocytes, including interferon (IFN)α, IFNγ, and toll-like receptor (TLR) pathways, and subsequent changes in monocyte phenotype and function, that is, a reduction in chemokine receptors CCR2 and CX3CR1 and transendothelial migratory capacity (Stiekema et al. 2020).

The number of circulating monocytes in apo(a) transgenic mice was four times higher than in wild-type mice and remained elevated for 3 weeks after Ca^{2+}-induced vascular damage (Huang et al. 2014). Also, Lp(a) affects the maturation of monocytes in humans (Schnitzler et al. 2020).

Monocytes are divided into three subpopulations, depending on the content of CD14 and CD16 surface markers, classical CD14++CD16−, intermediate CD14++CD16+, and nonclassical CD14+CD16++, while the latter two populations have the most pronounced proinflammatory and profibrotic potential. The participation of circulating monocytes in atherogenesis has been proven (Vergallo and Crea 2020), but the contribution of various subpopulations of monocytes to chronic inflammatory states is currently under discussion (Yang et al. 2014; Ożańska et al. 2020).

The high content of CD16+ monocytes is associated with unstable atherosclerotic plaques in the coronary arteries (Kashiwagi et al. 2010) and predicts the risk of cardiovascular events (Rogacev et al. 2012). In CHD patients, an increased content of intermediate monocytes CD14++CD16+ occurs with hyperlipoproteinemia(a) (Krychtiuk et al. 2015a), atherogenic dyslipidemia (Krychtiuk et al. 2015b), and dysfunctional high-density lipoproteins (Krychtiuk et al. 2014). The association of elevated Lp(a) concentration with absolute and relative content of CD14+CD16++ was shown in a retrospective study (Afanasieva et al. 2021). Since the function of this subpopulation is to remove "cellular debris," it is assumed that it contributes to elimination of excess Lp(a).

Neutrophil granulocytes are the largest population of circulating phagocytizing leukocytes capable of synthesizing a wide range of substances. Neutrophils and "neutrophil extracellular traps" (NETs) formed by them were found in atherosclerotic plaques of laboratory animals and humans (Afanasieva et al. 2021). NETs stimulate the production of IL-1 by macrophages and activate IL-17-producing T-helpers (Th17) in apoE-deficient mice, contributing to inflammation in the vessel wall (Döring et al. 2017). There are no data on the effect of Lp(a) or apo(a) on the formation of neutrophil traps. The absolute number of neutrophils and the neutrophil-lymphocyte index, as well as the concentration of Lp(a), was significantly higher in patients with stenosing atherosclerosis of various vascular beds (Tmoyan et al. 2021). The evaluation of the effect of Lp(a) on neutrophil activation is a promising avenue of further research.

The Role of Lipoprotein(a) and Proinflammatory Status in ASCVD Pathogenesis

Data on the association of increased Lp(a) concentration with systemic inflammation and its markers are ambiguous (Pirro et al. 2017). The risk of cardiovascular events associated with Lp(a) was significantly higher in the presence of "proinflammatory" genotype IL-1 (Naka et al. 2018) or elevated C-reactive protein level (Puri et al. 2020).

A higher lymphocyte count is associated with a higher apoB level; Lp(a) was inversely associated with basophil count in men but not in women according to a population study with 417,132 participants (Tucker et al. 2021). Low molecular weight apo(a) phenotype, reduced lymphocyte count, and increases in neutrophil granulocytes potentiated the risk of CHD in patients with type 2 diabetes (Suzuki et al. 2013).

The combination of a higher absolute monocyte count (>0.54 × 10^9 cells/mL) with elevated Lp(a) (≥30 mg/dL) is associated with higher risk of major adverse cardiovascular events (MACE) in patients with premature CHD manifestation (Afanasieva et al. 2022) (Fig. 16.1). An increase of Lp(a) concentration and the percentage of CD14++CD16+ monocytes potentiated risk of multivessel coronary disease (Afanasieva et al. 2021; Filatova et al. 2022) (Fig. 16.2).

A lower level of IgM AAbs against Lp(a) is negatively correlated with the concentration of sCD25 [the soluble form of the IL-2 receptor and a surrogate marker of T-cell activation (Brusko et al. 2009)] and associated with stenosing coronary atherosclerosis (Afanasieva et al. 2016b). This fact may serve as a confirmation of participation of both Lp(a) and T-cells in atherogenesis and also the immunomodulatory ability of IgM AAbs against Lp(a) (Wang et al. 2016).

Systemic inflammation accompanies age-related changes in lymphocyte subpopulations (Thomas et al. 2020). In patients with ASCVD, the number of naïve lymphocytes, including regulatory cells, decreases with age, while the level of effector populations, that is, Th1 and Th17, remains constant (Filatova et al. 2021). T-Lymphocytes with predominating Th1 are detected in atherosclerotic plaques (Saigusa et al. 2020). Th17, a subpopulation of CD4+ lymphocytes producing IL-17, also has a proatherogenic effect. Th17 cells participate in the immune response against their own and alien antigens by attracting myeloid cells to a place of inflammation, activating lymphocytes and secreting proinflammatory cytokines (Gao et al. 2010; Park et al. 2005). On the contrary, regulatory T-cells have anti-inflammatory activity and inhibit atherogenesis (Albany et al. 2019). Thus,

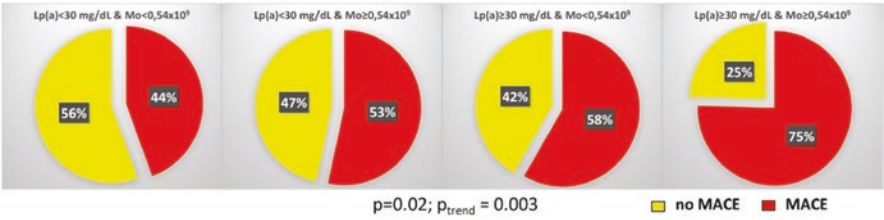

Fig. 16.1 The proportion of major adverse cardiovascular events (MACE) in patients with premature coronary heart disease depending on blood monocyte count and lipoprotein(a) concentration. Two-hundred *adult patients with early* coronary heart disease *manifestation (before 55 years in men and 60 years in women) were enrolled, median follow-up 12 years. MACE, nonfatal myocardial infarction, ischemic stroke, coronary artery bypass grafting, and hospitalization for unstable angina* (Afanasieva et al. 2022)

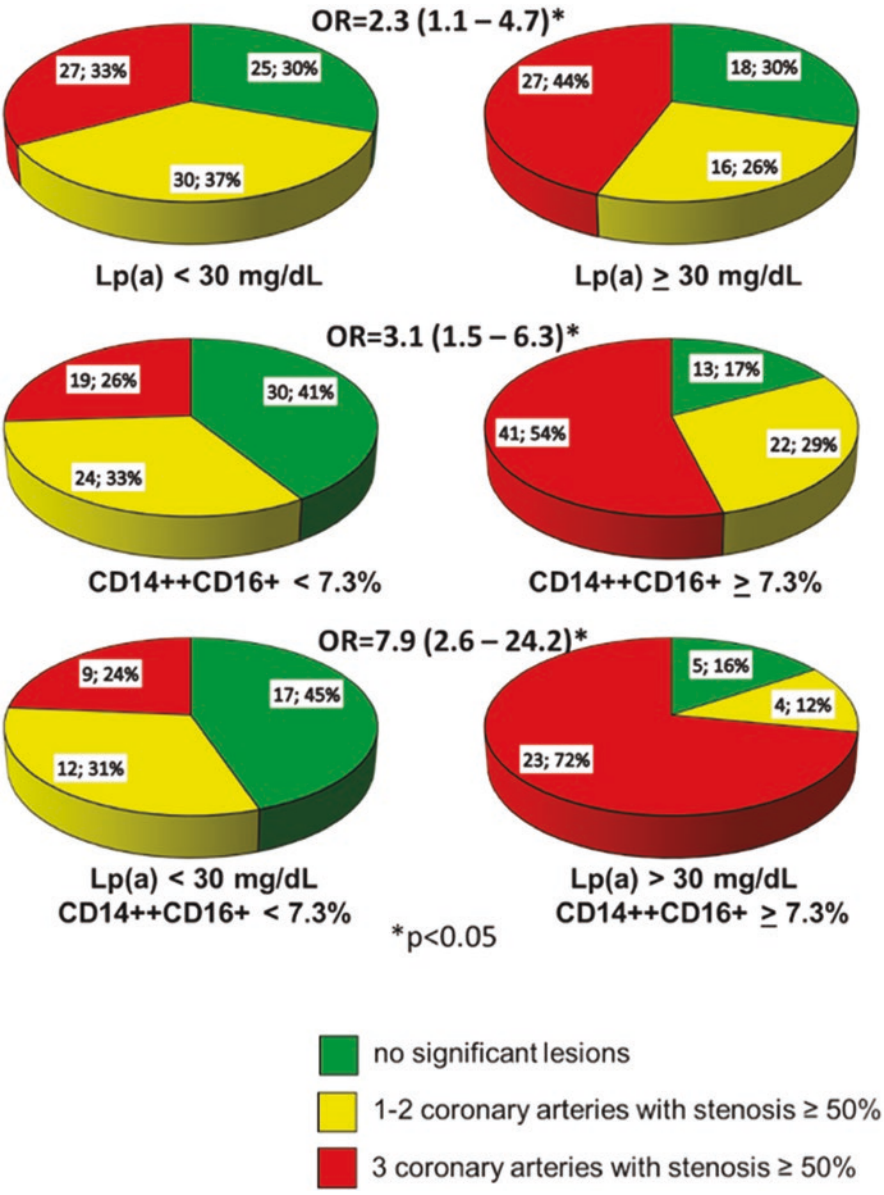

Fig. 16.2 Association of lipoprotein(a), CD14++CD16+ intermediate monocyte subpopulation, and their association with coronary atherosclerosis severity (n = 150). *Odds ratio (OR) of triple vessel disease* vs *no significant, and 1–2-vessel disease was calculated according to logistic regression analysis adjusted for age, sex, type 2 diabetes, and hypertension* (Afanasieva et al. 2021)

age-related deficiency of regulatory cells and a shift of the immune balance toward effector populations may contribute to atherosclerosis progression.

Activation and increased amounts of Th17 are related to the progression of atherosclerosis and risk of coronary events (Liuzzo et al. 2013). The ratio of circulating Treg/Th17 is reduced in patients with severe coronary atherosclerosis (Potekhina et al. 2015). The concentration of Lp(a) is not associated with the content of various T-cell subpopulations (Afanasieva et al. 2016a, b). However, an increased content of circulating Th17 (% of CD4+ lymphocytes), as well as a reduced content of Treg or IL-10 CD4+-producing cells along with Lp(a) concentrations above 12 mg/dL, is associated with severe coronary atherosclerosis (Afanasieva et al. 2016b) and carotid atherosclerosis progression (Afanasieva et al. 2016a). Thus, the increased concentration of Lp(a) and proinflammatory status with some shifts in immunity could potentiate atherosclerosis progression.

Lipoprotein(a) as a Carrier of Inflammatory Mediators

Differences in the physicochemical and immunochemical properties of LDL and Lp(a) have been noted for a long time (Zawadzki et al. 1988). The apo(a) moiety has a binding site for oxidized phospholipid (oxPL) that determines its proinflammatory effects on immune cells (Koschinsky and Boffa 2022).

Proteomic analysis shows that Lp(a) may serve as a carrier of many protein molecules, and their spectrum differs in Lp(a) and LDL (Bourgeois et al. 2020a; von Zychlinski et al. 2011, 2014). These proteins can participate in the processes of oxidation, cell proliferation and intercellular interactions, immunomodulation and activation of the complement system, and blood clotting (Bourgeois et al. 2021).

Such a variety of proteins can provide Lp(a) particles with the ability to participate in the response to injury or damage. Possible ways that Lp(a) participates in activation of the immune system via its plasma components are shown in Fig. 16.3.

The complement components C3 and C4 associated with Lp(a) could determine the interaction of Lp(a) with innate and acquired immunity. The complex of Lp(a) with α2 macroglobulin can interact with low-density lipoprotein receptor-related protein 1 (LRP-1) and can not only contribute to the internalization of Lp(a) with high molecular weight isoforms of apo(a) (März et al. 1993) but also induce the migration of myeloid cells, such as monocytes and neutrophils.

Lp(a) constitutes the main pool of lipoprotein-associated proprotein convertase subtilisin/kexin type 9 PCSK9 (Tavori et al. 2016). There is evidence of the modulating effect of PCSK9 on cell immunity (Liu and Frostegard 2018; Kim et al. 2019). Also, PCSK9 can regulate the number of CD36 and LRP-1 receptors (Shapiro et al. 2018), which are expressed by hematopoietic cells, participating in the processes of hemostasis, inflammation, and tissue regeneration. The binding of PCSK9 to CD36 (Qi et al. 2021) can be recognized as a “danger signal” of innate immunity (Silverstein 2021).

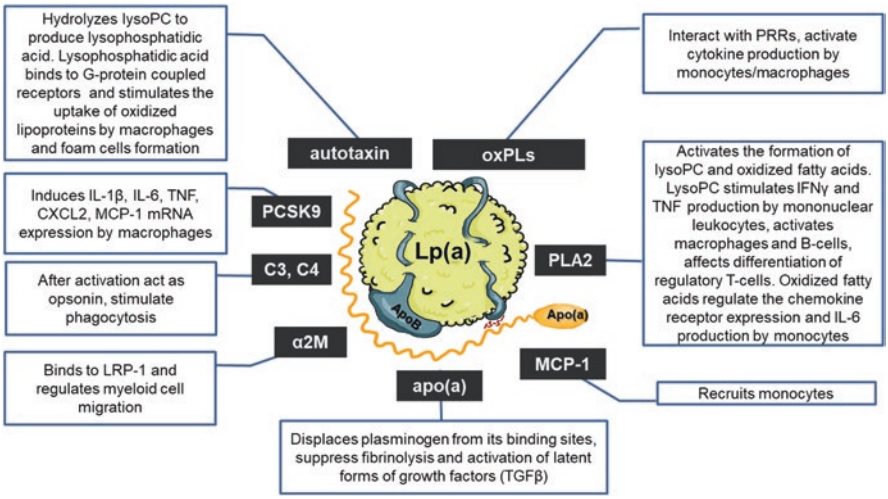

Fig. 16.3 Possible mechanisms of lipoprotein(a) contribution to immune cell activation. *lysoPC* lysophosphatidylcholines, *LPARs* LPA receptors or G-protein-coupled receptors, *IL-1β* interleukin 1β, *IL-6* interleukin 6, *TNF* tumor necrosis factor, *CXCL2* chemokine (C–X–C motif) ligand 2, *MCP-1* monocyte chemoattractant protein 1, *mRNA* messenger RNA, *LRP-1* low-density lipoprotein receptor-related protein 1, *TGFβ* transforming growth factor beta, *IFNγ* interferon γ, *PRRs* pattern recognition receptors, *oxPL* oxidized phospholipids, *PLA2* phospholipase A2, *α2M* alpha-2-macroglobulin, *PCSK9* proprotein convertase subtilisin/kexin type 9, *C3 and C4* complement components 3 and 4, and *apo(a)* apolipoprotein(a)

Lp(a) as a possible carrier of autotaxin and a source of lysophosphatidic acid is associated with calcification and aortic valve stenosis (Bouchareb et al. 2015; Bourgeois et al. 2020b). The lysophosphatidic acid participates in the differentiation and homing of T-lymphocytes (Zhang et al. 2012; Knowlden and Georas 2014). Both facts suggest another possible mechanism of Lp(a) action on the immune system.

An association of MCP-1 with Lp(a) via oxidized phospholipids of Lp(a) has been described (Wiesner et al. 2013). The attachment of Lp(a) containing MCP-1 at the site of injury can lead to increased recruitment of monocytes. Thus, proteins associated with the Lp(a) particle as well as oxPL may explain its proinflammatory properties.

Many properties of Lp(a), as well as its biological roles, remain a mystery despite more than 50 years of research. Lp(a) is able to carry affected areas not only the cholesterol necessary for the synthesis of new cells but also biologically active components that attract phagocytes of the innate immune system. It can be assumed that the original role of Lp(a) as a factor in damage repair and transport systems has largely been lost at the present time. An increased concentration of Lp(a) set against the background of genetic, epigenetic, and environmental variables has become a powerful risk factor for atherosclerotic cardiovascular diseases. We designed an immunosorbent for specific Lp(a) apheresis and proved that specific Lp(a), but not

LDL, removal by extracorporeal treatment can lead to stabilization and even regression of atherosclerotic lesions in coronary and carotid arteries (Pokrovsky et al. 2016, 2020). This study was the first direct clinical observation and confirmation of Lp(a) atherogenicity in humans (Pokrovsky et al. 2017). The elucidation of molecular and cellular mechanisms of Lp(a) involvement in inflammatory remodeling of the arterial wall engaging the Lp(a) immunity axis is a promising direction for the development of new therapeutic approaches.

Lp(a) is an extremely interesting polymolecular complex, and as we learn more about it, it is clear the less we understand about its enormous functional range and its capacity to interact with and influence important pathways, such as immunity, inflammation, thrombosis, and oxidation.

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