

Minor apolipoproteins contribute to the pleiotropic effects of high-density lipoprotein

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Abstract High-density lipoprotein (HDL) has several pleiotropic effects, including a role in the reverse cholesterol transport system. These include vasoprotective, anti-apoptotic, anti-inflammatory, antioxidant, and anti-thrombotic effects. Some of these properties may be ascribed to the minor apolipoproteins that associate with HDL. In particular, apolipoprotein M (ApoM) is a carrier of sphingosine 1-phosphate (S1P), which is a multifunctional bioactive lipid. ApoM bound to S1P exhibits a biased agonistic property for S1P1, which can exert beneficial effects on human health. The ApoM/S1P axis may be responsible for the protective effects of HDL in the pathogenesis of cardiovascular diseases, diabetes, infectious diseases, kidney diseases, liver diseases, autoimmune disorders, and Alzheimer's disease through its vasoprotective, anti-apoptosis, anti-thrombosis, and anti-fibrosis properties. In addition to ApoM, several minor apolipoproteins, such as ApoD, ApoL1, ApoH, ApoO, ApoF, and ApoJ, may contribute to the pleiotropic effects of HDL, because they are associated with human diseases other than atherosclerotic diseases. Of these, ApoD may be attributed to its anti-inflammatory properties, and ApoL1 to its anti-infectious effects. Although further studies are needed to elucidate the biological properties of these minor apolipoproteins, they may have diagnostic and therapeutic applications.

Keywords High-density lipoprotein (HDL), Pleiotropic effects, Apolipoprotein M (ApoM), Sphingosine 1-phosphate (S1P), Minor apolipoproteins

INTRODUCTION

High-density lipoprotein (HDL) is a protein that transports lipids, including cholesterol and phospholipids, as well as various apolipoproteins. The primary role of HDL is in the reverse cholesterol transport system (Rader and Hovingh 2014). HDL takes up excess cholesterol from peripheral tissues, such as endothelial vessels, and transfers it to low-density lipoprotein (LDL) and then to the liver. Cholesterol is subsequently secreted into the bile directly or following conversion to bile acids. Thus, low HDL cholesterol levels are an established risk factor for atherosclerotic disease

(Gordon *et al.* 1977).

In addition to the role of HDL in the reverse cholesterol transport system, HDL cholesterol (HDL-C) levels are associated with various human diseases other than atherosclerosis. For example, lower HDL-C levels are associated with outcomes of severe infectious diseases, the progression of kidney disease, morbidity of diabetes, and cancer prognosis. Considering the pathogenesis of these diseases, HDL may exhibit pleiotropic effects other than its role in the reverse cholesterol transport system (Endo *et al.* 2025; Men *et al.* 2025). An elegant series of basic experiments suggested the existence of vasoprotective, anti-apoptotic, anti-inflammatory, anti-oxidative, and anti-thrombotic effects of HDL (Brewer 2011).

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Regarding the underlying mechanisms for the effects of HDL, its components may contribute to these properties. HDL is composed of free cholesterol, cholesteryl ester, phospholipids, and other lipids, such as sphingolipids, as well as proteins. Of the proteins bound to HDL, apolipoprotein A-I (ApoA-I), apolipoprotein A-II, and apolipoprotein E (ApoE) are the major

components. Several other proteins, or minor apolipoproteins, are also present (Deng *et al.* 2022; Rosales *et al.* 2016) (Fig. 1). In this review, we discuss the potential roles of these minor apolipoproteins in the pleiotropic effects of HDL, with a focus on bioactive lipids and their association with human diseases.

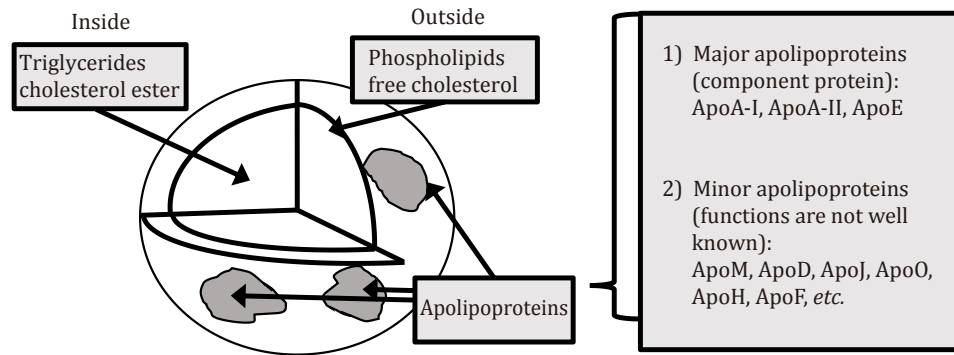


Fig. 1 Schematic figure for HDL components. A scheme for HDL components is shown

BIOACTIVE LIPIDS

Bioactive lipids are involved in various human diseases (Fig. 2). Eicosanoids, such as leukotrienes and prostaglandins, are primarily derived from arachidonic acids. They are considered first-generation lipid mediators, which are mainly produced by the cyclooxygenase (COX) enzymes. COX-1 is constitutively expressed and has an important role in homeostasis, whereas COX-2 is induced during inflammation. In human diseases, they have important roles in inflammation (Jo-Watanabe *et al.* 2019; Park 2026) (Fig. 2A). They represent therapeutic targets, of which COX-2 inhibitors are widely used (Qiang and Xu 2024; Yokomizo and Shimizu 2023). The lipid mediators derived from ω -3 fatty acids, such as EPA and DHA, are considered third-generation lipid mediators and include resolvins and marresines (Hirakata *et al.* 2019). They exert anti-inflammatory effects (Fig. 2B).

In addition to these lipid mediators, lysophospholipids are known as second-generation lipid mediators, and include sphingosine 1-phosphate (S1P), lysophosphatidic acids (LPA), and lysophosphatidylserine (LysoPS) (Kano *et al.* 2022; Takagi *et al.* 2022; Yatomi *et al.* 2018). Lysophospholipids are phospholipids with only one fatty acid. Therefore, they contain hydrophobic and hydrophilic parts, which can lyse cells at extremely high concentrations. Based on their

backbone, lysophospholipids may be divided into two classes, glycerolysophospholipids and sphingolysophospholipids (Fig. 2C). Glycerolysophospholipids are composed of a glycerol backbone. Depending on the functional group, they may be classified as LPA, lysophosphatidylcholine (LPC), LysoPS, lysophosphatidylinositol (LPI), lysophosphatidylglycerol (LPG), and lysophosphatidylethanolamine (LPE). Sphingolysophospholipids contain a sphingosine backbone. Of these, S1P is the most studied. It exerts various biological activities as described below. Specific G-protein coupled receptors have been identified for some of the lysophospholipids, including LPA1-6 for LPA, GPR34, P2Y10, and GPR174 for LysoPS, GPR55 for LPI and LPG, and S1P1-5 for S1P (Blaho and Chun 2018; Makide *et al.* 2014) (Fig. 2D). Overall, lysophospholipids have been well studied and represent potential therapeutic targets.

APOLIPOPROTEIN M (ApoM)

ApoM is an apolipoprotein with a molecular weight of ~21 kDa, and is associated with HDL (Xu and Dahlbäck 1999). Human ApoM has a slightly higher molecular weight because of glycation (Kobayashi *et al.* 2021). In humans, ApoM is primarily expressed in hepatocytes, followed by renal tubular cells (Xu and Dahlbäck 1999).

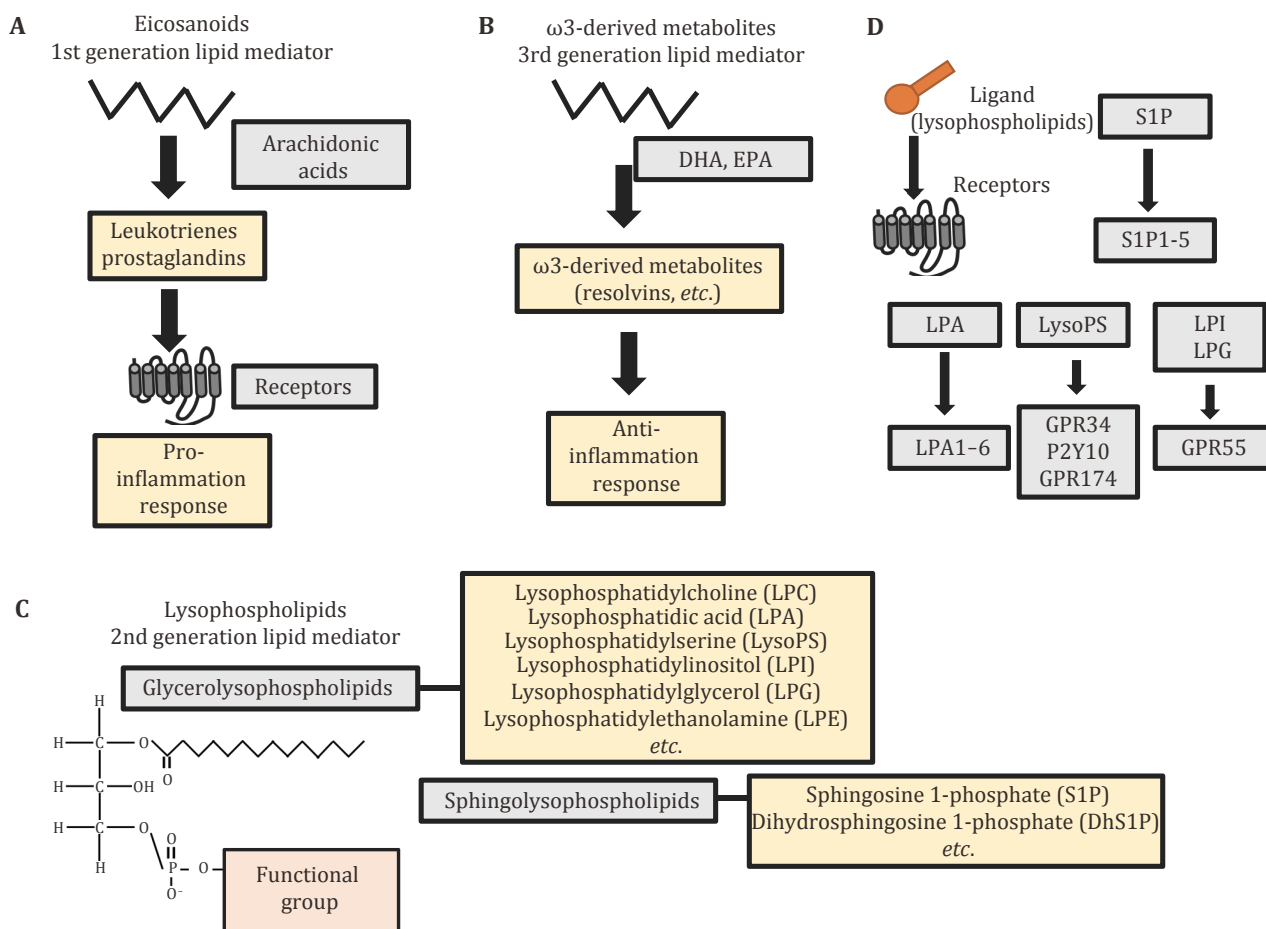


Fig. 2 Bioactive lipids. **A** First-generation lipid mediators. Eicosanoids, including prostaglandins and leukotrienes. **B** Third-generation lipid mediators. ω-3 fatty acid derivatives. **C** Second-generation lysophospholipids. Representative glycerolysophospholipids and sphingolysophospholipids are shown. **D** Receptors for lysophospholipid mediators are shown

Among the lysophospholipids, S1P is unique in that approximately two-thirds of plasma S1P is bound to HDL (Okajima 2002), whereas other lysophospholipids are normally distributed in the lipoprotein-depleted plasma (Kurano *et al.* 2019a), and bound to albumin (Kurano *et al.* 2019c) (Fig. 3A). Because S1P is involved in anti-apoptosis, vasoprotection, and cell proliferation, which partly overlap with the pleiotropic effects of HDL, S1P contributes to the pleiotropic effects of HDL (Kurano and Yatomi 2018; Xiong and Hla 2014) (Fig. 3B). However, the basis for the unique distribution of S1P has remained unclear. In 2011, Christoffersen *et al.* found that ApoM carries S1P on HDL (Christoffersen *et al.* 2011). ApoM has a pocket in its structure, which may contain S1P. This finding is very important for S1P biology, as it confirmed the contribution of S1P to the pleiotropic effects of HDL and enabled further studies of its functions *in vivo*. Exogenously administered S1P, using albumin as a vehicle, is rapidly degraded by lipid

phosphate phosphatase, whereas ApoM overexpression or knockout can modulate plasma S1P levels. ApoM also regulates S1P by preventing its degradation, and ApoM controls the total mass of S1P in the body (Kurano *et al.* 2013).

In addition to the effect of ApoM on the metabolism and amount of S1P, it influences the biological properties of S1P (Kano *et al.* 2022). Five S1P receptors have been identified. Of these, S1P1, S1P2, and S1P3 are ubiquitously expressed in whole body tissues. S1P1 and S1P3 have beneficial properties for human health, such as anti-apoptosis and vasoprotective effects, whereas S1P2 exerts harmful activity, such as a contraction response through the Rho/Rock pathway (Takuwa *et al.* 2012). Although all five S1P receptors are expressed in pancreatic β-cells, we found that the effects of S1P bound to ApoM on insulin secretion from pancreatic β-cells were inhibited only by VPC23019, an S1P1 and S1P3 antagonist, but not by JTE013, an S1P2 antagonist.

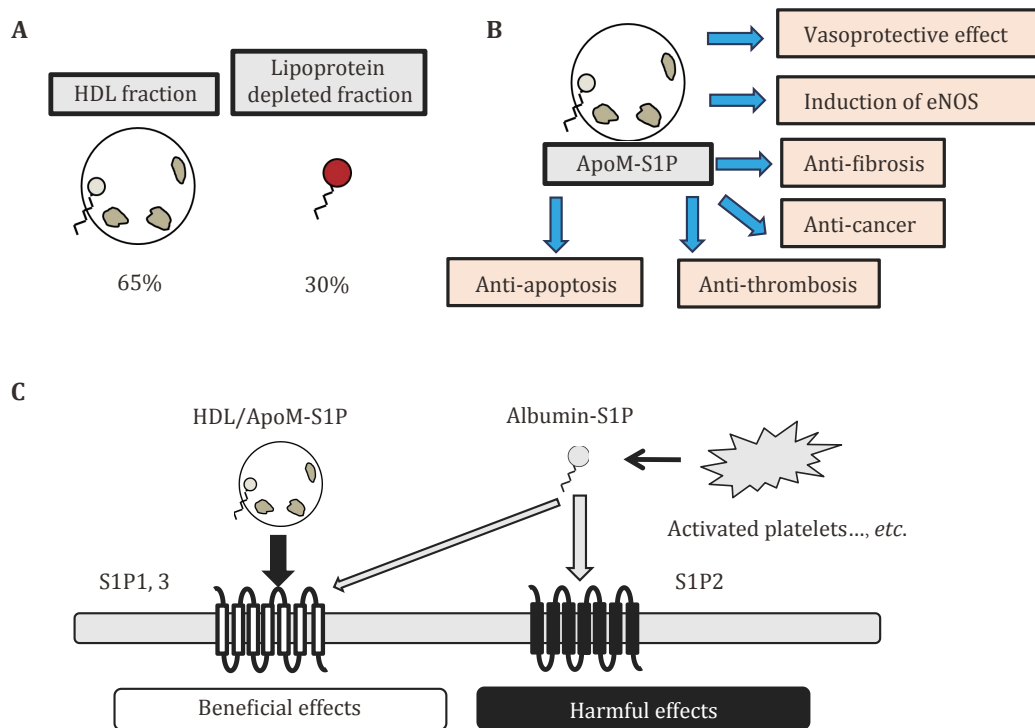


Fig. 3 Apolipoprotein M (ApoM) and sphingosine 1-phosphate (S1P). **A** Distribution of S1P in plasma. **B** ApoM-S1P contributes to the pleiotropic effects of HDL. **C** Differences in the agonistic properties for S1P receptors between ApoM-bound S1P and albumin-bound S1P

This suggests that S1P bound to ApoM exerts an agonistic effect through S1P1 and/or S1P3, but not S1P2 (Kurano *et al.* 2014) (Fig. 3C). These effects of S1P bound to ApoM have also been observed *in vivo*. For example, ApoM overexpression ameliorated IgA nephropathy, which was reversed with VPC23019, but not JTE013 (Kurano *et al.* 2019b). In 2015, Hla *et al.* demonstrated that S1P bound to ApoM is an S1P1 agonist (Galvani *et al.* 2015). Because the binding sites for S1P of S1P1 exist in the membranous position of S1P1 (Fujiwara *et al.* 2007; Hanson *et al.* 2012), and S1P bound to ApoM, but not S1P to albumin, increases the membranous content of S1P (Kurano *et al.* 2023b), S1P bound to ApoM may selectively activate S1P1 (Fig. 3C).

ApoM may be involved in the epidemiological associations between HDL-C and human diseases. HDL-C levels are negatively associated with atherosclerotic diseases (Gordon *et al.* 1977). Although this association has been attributed to the role of HDL in the reverse transport system (Rader and Hovingh 2014), the vasoprotective roles of HDL may also be involved. In animal models, S1P bound to ApoM protects against myocardial infarction and cerebral infarction, by maintaining endothelial cell barrier function and exerting anti-inflammatory and anti-hypertensive effects (Swendeman *et al.* 2017). In this paper, it is notable

that the therapeutic application of an engineered ApoM was demonstrated in mice.

In diabetes, HDL-C levels are negatively associated with insulin resistance, primarily through the decreased production of HDL and the suppression of lipase activity in obesity (Yanai *et al.* 2022). Interestingly, HDL-C levels are associated with the occurrence of type-2 diabetes (Haase *et al.* 2015; Schmidt *et al.* 2005; Wilson *et al.* 2007). Recent studies have suggested that ApoM/S1P is partly responsible for these effects. Palmitate suppresses ApoM expression through PPAR β/δ (Luo *et al.* 2014). The activities of PPAR are modulated during diabetes. It regulates ApoM and S1P levels in a bell-shaped manner, with the greatest levels of ApoM observed when PPAR γ is mildly activated (Kurano *et al.* 2018a). Insulin and leptin also suppress ApoM expression (Luo *et al.* 2005; Nojiri *et al.* 2014). In humans, serum ApoM levels are higher in individuals with type-2 diabetes, and ApoM polymorphisms are associated with type-1 diabetes (Kurano *et al.* 2020). In addition, ApoM is positively regulated by HNF1, and its mutation results in MODY3 (Mughal *et al.* 2013; Richter *et al.* 2003). During the pathogenesis of diabetes, S1P promotes insulin secretion from pancreatic β -cells and their survival through S1P1. It may promote insulin secretion because it prevents apoptosis, increases the expression of Pdx-1, and attenuates ER stress (Kurano

et al. 2014). Along with its effects on insulin secretion, S1P-bound ApoM may attenuate insulin resistance (Kurano *et al.* 2020; Yu *et al.* 2020). It also activates the PI3K–AKT pathway, which overlaps with the insulin signal. In addition, S1P bound to ApoM protects mitochondrial function by increasing SIRT1 protein levels through the activation of S1P1 (Kurano *et al.* 2020; Yu *et al.* 2020).

HDL-C levels are associated with the progression of kidney diseases. In the subjects with chronic kidney diseases, in which a decrease in renal function occurs more rapidly in subjects with lower HDL-C levels (Hanai *et al.* 2012; Russo *et al.* 2016; Tu *et al.* 2010). The S1P1 pathway protects against kidney injuries (Awad *et al.* 2006), whereas the S1P2 pathway facilitates kidney injuries (Liu *et al.* 2012). ApoM bound to S1P ameliorated the phenotypes of IgA nephropathy (Kurano *et al.* 2019b) and diabetic nephropathy (Kurano *et al.* 2023b) model mice through the suppression of mesangial expansion and fibrosis, as well as the protection of mitochondrial function through S1P1. In contrast, ApoM expressed in renal tubular cells did not alter the phenotype of cisplatin-induced kidney injuries (Bisgaard *et al.* 2024). In renal-specific ApoM transgenic mice, however, because circulating ApoM and S1P were increased, but not enough to prevent kidney injuries, the role of circulating ApoM, which is mainly derived from the liver, remains unclear. In humans, serum ApoM levels were lower in subjects with diabetic nephropathy and associated with the progression of renal dysfunction over five years (Kurano *et al.* 2023b). A similar association of ApoM with poor prognosis was observed in subjects with type-1 diabetes (Baker *et al.* 2022). Interestingly, urinary ApoM levels were higher in patients with acute kidney disease (Svarrer *et al.* 2016). Although urinary ApoM is taken up again through tubular megalin (Faber *et al.* 2006), its significance in the pathogenesis of kidney disease should be determined.

HDL-C levels are lower in patients with severe infectious diseases and associated with prognosis (Apalama *et al.* 2025; Gordon 2004; Tsai *et al.* 2009). Several studies have also demonstrated that serum ApoM levels are lower in patients with severe infectious diseases, especially sepsis (Kumaraswamy *et al.* 2012; Palmiere *et al.* 2015). During the COVID-19 pandemic, serum ApoM levels were found to be lower in individuals infected with SARS-CoV-2, and those with a poor prognosis had even lower levels (Marfia *et al.* 2021). The overexpression of ApoM protects against death and organ injuries resulting from the administration of lipopolysaccharide, whereas ApoM

knockout had the opposite effect (Kurano *et al.* 2018b). The protective mechanisms of ApoM/S1P in lipopolysaccharide-induced septic mouse models included decreased apoptosis through S1P1 or S1P3 (Kurano *et al.* 2018b). Its anti-inflammatory properties are controversial and may depend on the experimental model (Kurano *et al.* 2018b; Wang *et al.* 2019; Zhu *et al.* 2018). In addition to the protective properties of ApoM/S1P, studies suggest that ApoM/S1P exerts anti-DIC effects. A decrease in platelet counts and an increase in PAI-1, as well as the existence of thrombosis in the kidneys stained with PTAH, were inhibited by ApoM/S1P (Kurano *et al.* 2018b). Protection against NETosis through S1P4 may be involved (Kurano *et al.* 2023c), whereas the prothrombin time was somewhat elongated in ApoM-overexpressing mice administered lipopolysaccharides. Further studies indicated that this does not result from the aggregation of DIC, but from the suppression of thrombin secretion from hepatocytes through ARID5B, which is regulated by ApoM (Kurano *et al.* 2025b).

In addition to the diseases described above, an elegant series of experiments demonstrated that ApoM/S1P protects against other human diseases. ApoM/S1P has protective roles in liver diseases through the facilitation of hepatic regeneration and the suppression of fibrosis (Ding *et al.* 2016). ApoM/S1P also protects against autoimmune diseases through the enhancement of endothelial integrity (Burg *et al.* 2018) and perhaps through the suppression of lymphocyte-mediated inflammation (Blaho *et al.* 2015). Moreover, a recent study demonstrated that ApoM/S1P protects against Alzheimer's disease by promoting the proliferation and polarization of ependymal cells in the brain (Choi *et al.* 2025). In humans, serum ApoM levels were higher in patients with liver injuries, hepatocellular carcinoma (Jiang *et al.* 2008), and rheumatic arthritis (Huang *et al.* 2014), whereas they were lower in individuals with activated SLE (Tydén *et al.* 2019). Although the reports are limited, ApoM levels in the cerebrospinal fluid (CSF) were lower in patients with Alzheimer's disease (Khoonsari *et al.* 2016). Because some studies have indicated a role for ApoM in the pathogenesis of cancer, its negative association with HDL-C levels (Loosen *et al.* 2022) may be explained by the ApoM/S1P axis (Mu *et al.* 2021; Zhou *et al.* 2022).

APOLIPOPROTEIN D (ApoD)

HDL exhibited anti-inflammatory effects in a series of experimental studies; however, the underlying mechanisms remain unclear. Genome-wide association

studies were conducted in the Japanese population to identify single-nucleotide polymorphisms associated with serum C-reactive protein (CRP) levels as well as other lipid parameters (Kurano *et al.* 2016). Apolipoprotein D (ApoD) is associated with CRP (Kurano *et al.* 2023a). In basic experiments, ApoD overexpression protected against inflammation caused by lipopolysaccharide or a high-fat diet. ApoD modulates lipid mediators in an anti-inflammatory direction. ApoD increased eicosapentaenoic acid and docosahexaenoic acid, as well as their metabolites. It

also increased anti-inflammatory lysophospholipids, such as S1P, and decreased pro-inflammatory LPA and LPI. ApoD binds to some of these lipid mediators, whereas it increases ApoM, an S1P carrier, and decreases autotaxin, an enzyme that produces LPA. In addition, ApoD suppresses osteopontin expression, which may also act as an anti-inflammatory modulator (Fig. 4A). In humans, serum ApoD levels were higher in diabetic subjects and negatively correlated with serum osteopontin and autotaxin levels, as well as IL-6 and TNF- α levels (Kurano *et al.* 2023a).

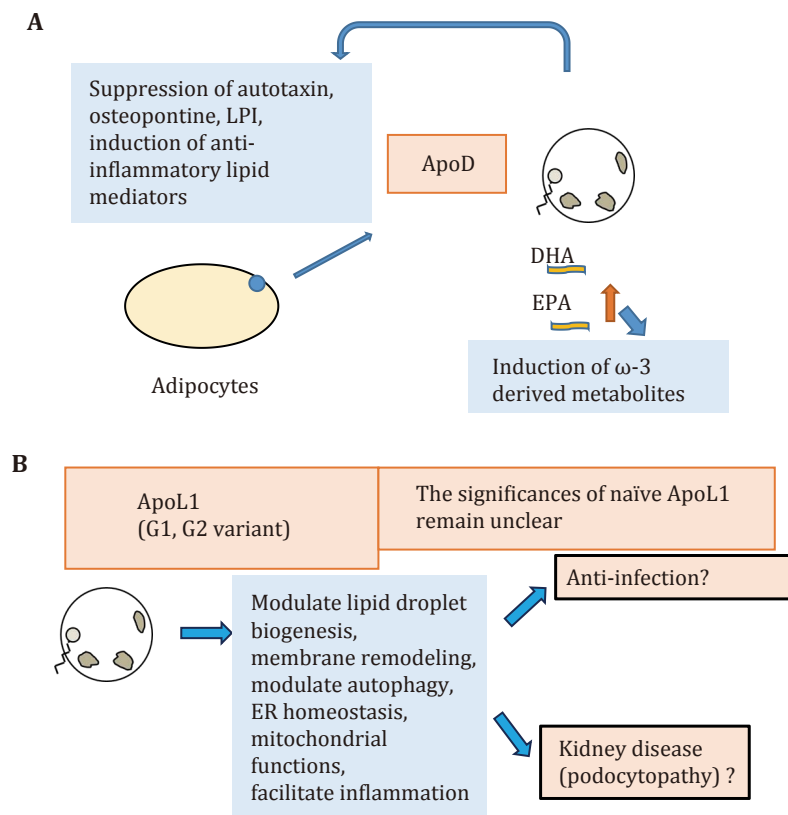


Fig. 4 Apolipoprotein D (ApoD) and apolipoprotein L1 (ApoL1) and their biological properties. Putative biological properties of ApoD (**A**) and ApoL1, particularly G1 and G2 variants (**B**), are shown

In other human studies, serum or plasma ApoD levels were associated with women who later developed pre-eclampsia (Dong *et al.* 2025) or gestational diabetes (Faurø *et al.* 2025). Better overall survival in breast cancer patients (negative) (Gao *et al.* 2025), risk of large-for-gestational-age infants (negative), aortic disease in obese individuals (positive) (Wang *et al.* 2024), poor prognosis of coronary arterial disease (positive) (Annema *et al.* 2022), cerebral amyloid angiopathy (up) (Kuiperij *et al.* 2020), and schizophrenia (up) (Mahadik

et al. 2002) have been reported. In the CSF and brain, ApoD levels are associated with multiple sclerosis (up) (Reindl *et al.* 2001), schizophrenia (up) (Thomas *et al.* 2001), and Alzheimer's disease (up) (Kalman *et al.* 2000). Based on these reports, it remains controversial whether ApoD has anti-inflammatory or pro-inflammatory properties and whether its modulation is responsible for the pathogenesis of human diseases or compensatory changes.

APOLIPOPROTEIN L1 (ApoL1)

Apolipoprotein L1 (ApoL1) is known for its association with kidney diseases, especially in African individuals. A genome-wide association study suggested that its variant can explain the risk of kidney diseases in this population (Freedman *et al.* 2018). Compared with the wild-type genotype (G0), the G1 or G2 variants are associated with an increased risk of kidney diseases, including local segmental glomerulosclerosis, human immunodeficiency virus (HIV)-associated nephropathy, lupus nephritis, sickle cell nephropathy, and solidified glomerulosclerosis, as well as rapid failure of transplanted kidneys from donors with APOL1 renal-risk genotypes (Freedman *et al.* 2018). These kidney diseases are classified as APOL1-mediated kidney diseases. Individuals with ApoL1 variants are resistant to *Trypanosoma*, which may cause the natural selection of ApoL1 variants in the African population (Pays *et al.* 2023). The natural roles of ApoL1 have not been fully elucidated (Fig. 4B), whereas ApoL1 variants cause podocytopathy. APOL1 may participate in lipid droplet biogenesis (Adeva-Andany *et al.* 2023) and membrane remodeling associated with inflammation (Pays 2024). It is reportedly bound to phosphatidic acid (PA) and cardiolipin (CL) as well as the phosphoinositides (PIPs), including PI4P, and cholesterol (Uzureau *et al.* 2020; Wan *et al.* 2008). In addition, ApoL1 damages cells by disturbing the endolysosomal and autophagic system, mitochondrial function, ER homeostasis, and promoting inflammation (Höffken *et al.* 2025).

In addition to the associations of ApoL1 variants with kidney diseases and *Trypanosoma* infection in humans as described above, serum ApoL1 levels are positively associated with frontotemporal dementia (Katzeff *et al.* 2020) and a high risk for type-2 diabetes (Croyal *et al.* 2022). However, there are few studies describing the significance of the quantity of ApoL1 in kidney diseases, which warrants further study.

APOLIPOPROTEIN A4 (ApoA4)

Along with ApoM, ApoD, and ApoL-1, other minor apolipoproteins are associated with HDL. Although their properties have not been elucidated, some have been demonstrated to be associated with human diseases.

Apolipoprotein A4 (ApoA4) was shown to carry S1P in addition to ApoM in the special conditions where ApoM and Albumin are deleted. In ApoM- and

albumin-knockout mice, Obinata *et al.* found that S1P is associated with ApoA4 in plasma (Obinata *et al.* 2019), although the contributions of ApoA4 to the binding of S1P to HDL might be small in human subjects and wild-type mice. Serum ApoA4 levels were associated with flow-mediated dilation (Li *et al.* 2022), suggesting that it protects endothelial function. Although the underlying mechanisms remain unclear, clinical studies suggest that ApoA4 is associated with maternal disturbance (Matsuo *et al.* 2024), Alzheimer's disease (down) (Lu *et al.* 2023; Zhang *et al.* 2022), obstructive sleep apnea (up) (Tang *et al.* 2021), schizophrenia (down) (Li *et al.* 2021), chronic kidney diseases (up) (Kronenberg *et al.* 2002; Stangl *et al.* 2015), progression of chronic kidney diseases (positive) (Boes *et al.* 2006), peripheral artery diseases (negative) (Dittrich *et al.* 2019), liver fibrosis (up) (Wang *et al.* 2017), seasonal allergic rhinitis (up) (Makino *et al.* 2010), cardiovascular diseases in hemodialysis patients (down) (Omori *et al.* 2010), and chronic pancreatitis (down) (Koga *et al.* 1985). In type-2 diabetic patients, serum ApoA4 levels were higher compared with normal subjects, but decreased in those with diabetic foot syndrome (Ji *et al.* 2023a). For individuals with aneurysmal subarachnoid hemorrhage, a low concentration of ApoA4 in HDL is associated with its lack of anti-inflammatory effects (de Azúa-López *et al.* 2023). The anti-inflammatory properties of ApoA4 were also demonstrated in an animal experiment (Roula *et al.* 2020).

APOLIPOPROTEIN H (ApoH)

Apolipoprotein H (ApoH) exists mainly as a free form, while a smaller amount of ApoH was reportedly in chylomicrons, VLDL, LDL and HDL (Gambino *et al.* 1999; Polz and Kostner 1979). Considering the important roles and associations with human diseases, ApoH in HDL might somehow contribute to the pleiotropic effects of HDL. ApoH is also called 2-glycoprotein I, and is a cofactor for the binding of antiphospholipid antibodies (APA) to anionic phospholipids, such as phosphatidylserine or cardiolipin (Valesini and Shoenfeld 1992). The binding capacity is influenced by the genetic variation of ApoH (Kamboh and Mehdi 1998; Schwarzenbacher *et al.* 1999). ApoH polymorphisms are associated with a susceptibility to recurrent pregnancy loss in women with antiphospholipid syndrome (Deng *et al.* 2023). Although ApoH polymorphisms are associated with antiphospholipid syndrome, the association of serum ApoH levels with this syndrome has not been established.

In addition to its potential involvement in the pathogenesis of thrombosis, ApoH reportedly inhibits ferroptosis through the PI3K–AKT–SREBP pathway and increases monounsaturated fatty acid-containing phospholipid levels (He *et al.* 2024). Serum ApoH is associated with gestational diabetes (up) (Faurø *et al.* 2025), poor outcomes in severe influenza infection (down) (Garcinuño *et al.* 2024), acute myeloid leukemia (up) (Jajula *et al.* 2024), fatty liver (down) (Liu *et al.* 2023, 2024b), type-2 diabetes (up) (Croyal *et al.* 2022), hepatocellular carcinoma (down) (Liu *et al.* 2024a), sepsis (down) (Yu *et al.* 2024), and clinical phenotypes of Crohn's disease (Gazouli *et al.* 2013).

APOLIPOPROTEIN F (ApoF)

Apolipoprotein F (ApoF) is a natural inhibitor of cholesteryl ester transfer protein (CETP). Interestingly, it does not completely inhibit CETP activity, but reportedly inhibits CETP activity associated with LDL (Liu and Morton 2020). Although the modulation of specific bioactive lipids by ApoF has not been determined, CETP overexpression attenuates the distribution of cholesterol as well as other bioactive lipids, including S1P, among lipoproteins (Kurano *et al.* 2017). For example, the overexpression of CETP increased the S1P content in VLDL and LDL, whereas it decreased that in HDL. These alterations appear to be harmful to human health. The overall effects of S1P on the activation of eNOS in vascular endothelial cells and insulin secretion from β -cells are enhanced. The biological effects of S1P may be more pronounced when bound to ApoB-containing lipoproteins than HDL (Kurano *et al.* 2017). In addition to S1P, CETP overexpression modulates other glycerol-lysophospholipids (Kurano *et al.* 2019a), which suggests that ApoF can regulate the pleiotropic properties of lipoproteins indirectly by modulating bioactive lipids.

In clinical studies, ApoF levels are associated with severe COVID-19 (up) (Souza Junior *et al.* 2021), schizophrenia (up) (Li *et al.* 2021), hepatic steatosis (down) (Deprince *et al.* 2023), and type-2 diabetes (up) (Croyal *et al.* 2022). Compared with other minor apolipoproteins, there have been fewer clinical studies to date.

APOLIPOPROTEIN O (ApoO)

Apolipoprotein O (ApoO) is another minor apolipoprotein that is predominantly bound to HDL. ApoO was identified as a novel apolipoprotein that is elevated in

the heart of human diabetic subjects (Lamant *et al.* 2006; Turkieh *et al.* 2014). Although the detailed role of ApoO in the pleiotropic effects of HDL is unknown, ApoO increases the degree of phospholipid unsaturation by inhibiting NRF2 and CYB5R3 to activate autophagy and apoptosis by regulating the p38 signaling pathway, and to cause mitochondrial degenerative changes (Chen *et al.* 2024; Liu *et al.* 2022; Turkieh *et al.* 2014). In humans, however, few studies have determined an association between ApoO and diseases; however, plasma ApoO levels were shown to be higher in subjects with acute coronary syndrome (Yu *et al.* 2012).

APOLIPOPROTEIN J (ApoJ)

Apolipoprotein J (ApoJ) is also known as clusterin. It is present on circulating HDL, whereas ApoJ is a component of lipoproteins in the central nervous system, as well as ApoE (Calero *et al.* 2000). Although the properties of ApoJ have not been fully elucidated, several studies suggest that ApoJ has various biological effects. ApoJ plays a role in AD pathogenesis through various processes, such as aggregation and clearance of A β , neuroinflammation, lipid metabolism, and the regulation of neural cell death and survival (Foster *et al.* 2019; Matsubara *et al.* 1995; Xie *et al.* 2005). In addition to its physiological roles in the CNS, ApoJ may also be involved in the pathogenesis of human diseases. ApoJ aggravates hepatic fibrosis by activating STAT3 signaling (Liu *et al.* 2025). It also regulates muscle glucose metabolism and insulin sensitivity through low-density lipoprotein receptor-related protein-2 (LRP2), which is coupled with insulin receptor signaling (Seo *et al.* 2020).

Clinical studies have indicated that ApoJ is associated with central nervous diseases. ApoJ levels in cerebrospinal fluids are decreased in Alzheimer's disease (Ko *et al.* 2022) and elevated in Parkinson's disease (Paslawski and Svenningsson 2023). In addition to its measurement in the cerebrospinal fluid, serum ApoJ levels are associated with cognitive disorders (Romagnoli *et al.* 2021). Higher plasma ApoJ is also reportedly associated with poor prognosis of intracerebral hemorrhage (Wu *et al.* 2022) and a higher risk for type-2 diabetes (Croyal *et al.* 2022). ApoJ levels in synovial and systemic fluids may also have translational potential as a biomarker of early repair responses in rheumatoid arthritis or osteoarthritis (Kalvaityte *et al.* 2022).

OTHER PROTEINS

Other proteins are present in HDL that are not usually called apolipoproteins. For example, paraoxonase 1 (PON-1) is known for its contribution to HDL function. HDL may exert anti-oxidative effects, and PON-1 is considered an important protein transported by HDL and contributes to its anti-oxidative effects (Ceron *et al.* 2014; Martinelli *et al.* 2013). Reduced PON-1 activity has been associated with cardiovascular diseases (Camps *et al.* 2009; Rasic-Milutinovic *et al.* 2012). The anti-oxidative properties of PON-1 are attributed to its role in the hydrolysis of toxic oxon metabolites. In addition, PON-1 increased the LysoPS levels indirectly, while direct enzymatic hydrolysis has not been confirmed (Shimura *et al.* 2025). The role of LysoPS remains to be fully elucidated, although it has been reported to modulate the immune system, particularly lymphocytes and macrophages (Yaginuma *et al.* 2023). Therefore, PON-1 may contribute to the pleiotropic effects of HDL by attenuating LysoPS.

Recent studies have suggested that CRP is not just a mere biomarker, but also a bioactive protein (Ji *et al.* 2023b). We recently found that CRP modulates lipid mediators in a pro-inflammatory direction (Kurano *et al.* 2025a). In addition, although we did not describe it in the previous paper, we also observed that CRP overexpression modulates the level of lipid mediators of lipoproteins, including HDL (Fig. 5). Because CRP is an established biomarker for inflammation as well as a risk factor for cardiovascular disease (Kawase Ishihara *et al.* 2015; The Emerging Risk Factors Collaboration 2012), it may have several roles in modulating the pleiotropic effects of HDL, especially related to its anti-inflammatory properties. Concordantly, the HDL contents of LPC, LPA, LPI, and LPG, which are deemed to possess pro-inflammatory properties, are increased in the CRP-overexpressing mice (Fig. 5), while these modulations might be caused only in inflammation and CRP is not an integrated structural component of HDL. Further investigations are required to elucidate the possible roles of CRP.

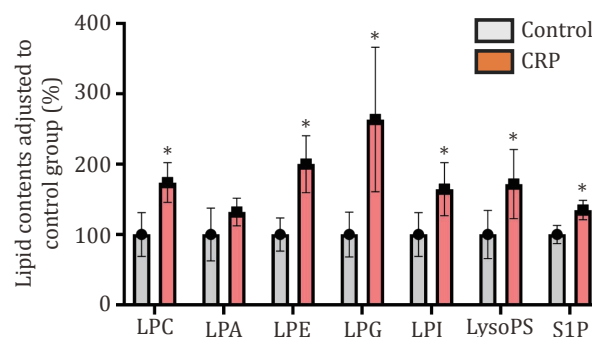


Fig. 5 Modulations of lysophospholipids in HDL by CRP. The modulations of the contents of lysophospholipids in HDL by the overexpression of CRP in mice are shown. * represents the significant difference. The detail methods are shown in our previous paper (Kurano *et al.* 2025a)

SUMMARY

This review discussed the possibility that minor apolipoproteins may contribute to the pleiotropic properties of HDL, as their presence has been detected in clinical and basic studies. The underlying mechanisms of these molecules involve the modulation of bioactive lipids, particularly the association between ApoM and S1P. Although further basic and clinical studies are necessary, minor apolipoproteins may be useful for diagnostic and therapeutic applications. ApoM and other minor apolipoproteins may also represent novel markers for various human diseases (Tables 1 and 2). With respect to therapeutic applications, Hla *et al.* produced an engineered S1P chaperone (Swendeman *et al.* 2017), which was based on ApoM, recombinants or liposomes that may be used for the treatment of various diseases.

Table 1 Potential use of ApoM for human diseases as biomarkers

Disease	Potential use as biomarkers
Cardiovascular diseases	Low levels of ApoM suggest impaired anti-atherosclerotic properties of HDL
Diabetes	Low levels of ApoM suggest susceptibility to advanced diabetic nephropathy
Infectious diseases	Low levels of ApoM suggest poor prognosis and disease severity
Kidney diseases	Low levels of ApoM suggest poor outcomes in chronic kidney diseases

Table 2 Potential use of minor apolipoproteins other than ApoM as biomarkers for human diseases

Disease	Potential use as biomarkers
ApoD	
Coronary artery disease	High levels of ApoD suggest the necessity for more intensive care because of a potentially poor prognosis
Alzheimer's disease	High levels of CSF ApoD are a possible diagnostic or risk biomarker for Alzheimer's disease
ApoL1	
Renal diseases	Variants of ApoL1 are a risk for renal diseases
Trypanosoma infection	Variants of ApoL1 confer resistance to Trypanosoma infection
ApoH	
Antiphospholipid syndrome	Polymorphisms of ApoH are associated with susceptibility to antiphospholipid syndrome
Infectious disease	Low levels of serum ApoH may be associated with severe infectious diseases, such as sepsis and its consequent pro-coagulant conditions
ApoJ	
Alzheimer's disease	Low levels of CSF ApoJ are possible diagnostic or risk biomarkers for Alzheimer's disease

Abbreviations

ApoA-I	Apolipoprotein A-I
ApoA4	Apolipoprotein A4
ApoD	Apolipoprotein D
ApoE	Apolipoprotein E
ApoF	Apolipoprotein F
ApoH	Apolipoprotein H
ApoJ	Apolipoprotein J
ApoL1	Apolipoprotein L1
ApoM	Apolipoprotein M
ApoO	Apolipoprotein O
COX	Cyclooxygenase
CRP	C-reactive protein
CSF	Cerebrospinal fluids
HDL	High-density lipoprotein
LPA	Lysophosphatidic acids
LPC	Lysophosphatidylcholine
LPE	Lysophosphatidylethanolamine
LPG	Lysophosphatidylglycerol
LPI	Lysophosphatidylinositol
LysoPS	Lysophosphatidylserine
PON-1	Paraoxonase 1
S1P	Sphingosine 1-phosphate

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Compliance with Ethical Standards

Conflict of Interest Makoto Kurano, Kazuhisa Tsukamoto, Shengyi Liu, Teruhiko Yoshida and Yutaka Yatomi declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

- Adeva-Andany MM, Funcasta-Calderón R, Fernández-Fernández C, Ameneiros-Rodríguez E, Vila-Altesor M, Castro-Quintela E (2023) The metabolic effects of APOL1 in humans. *Pflugers Arch* 475(8): 911–932
- Annema W, Gawinecka J, Muendlein A, Saely CH, Drexel H, von Eckardstein A (2022) Elevated levels of apolipoprotein D predict poor outcome in patients with suspected or established coronary artery disease. *Atherosclerosis* 341: 27–33
- Apalama ML, Begue F, Tanaka S, Cournot M, Couret D, Meilhac O, Pokeerbox MR (2025) High-density lipoproteins and COVID-19: preparing the next pandemic. *J Lipid Res* 66(5): 100779. <https://doi.org/10.1016/j.jlr.2025.100779>
- Awad AS, Ye H, Huang L, Li L, Foss Jr FW, Macdonald TL, Lynch KR, Okusa MD (2006) Selective sphingosine 1-phosphate 1 receptor activation reduces ischemia-reperfusion injury in mouse kidney. *Am J Physiol Renal Physiol* 290(6): F1516–F1524
- Baker NL, Hammad SM, Hunt KJ, Semler A, Klein RL, Lopes-Virella MF (2022) Plasma apoM levels and progression to kidney dysfunction in patients with type 1 diabetes. *Diabetes* 71(8): 1795–1799
- Bisgaard LS, Christensen PM, Oh J, Torta F, Füchtbauer EM, Nielsen LB, Christoffersen C (2024) Kidney derived apolipoprotein M and its role in acute kidney injury. *Front Pharmacol* 15: 1328259. <https://doi.org/10.3389/fphar.2024.1328259>
- Blaho VA, Galvani S, Engelbrecht E, Liu C, Swendeman SL, Kono M, Proia RL, Steinman L, Han MH, Hla T (2015) HDL-bound

- sphingosine-1-phosphate restrains lymphopoiesis and neuro-inflammation. *Nature* 523(7560): 342–346
- Blaho VA, Chun J (2018) 'Crystal' clear? Lysophospholipid receptor structure insights and controversies. *Trends Pharmacol Sci* 39(11): 953–966
- Boes E, Fliser D, Ritz E, König P, Lhotta K, Mann JF, Müller GA, Neyer U, Riegel W, Riegler P, Kronenberg F (2006) Apolipoprotein A-IV predicts progression of chronic kidney disease: the mild to moderate kidney disease study. *J Am Soc Nephrol* 17(2): 528–536
- Brewer Jr HB (2011) The evolving role of HDL in the treatment of high-risk patients with cardiovascular disease. *J Clin Endocrinol Metab* 96(5): 1246–1257
- Burg N, Swendeman S, Worgall S, Hla T, Salmon JE (2018) Sphingosine 1-phosphate receptor 1 signaling maintains endothelial cell barrier function and protects against immune complex-induced vascular injury. *Arthritis Rheumatol* 70(11): 1879–1889
- Calero M, Rostagno A, Matsubara E, Zlokovic B, Frangione B, Ghiso J (2000) Apolipoprotein J (clusterin) and Alzheimer's disease. *Microsc Res Tech* 50(4): 305–315
- Camps J, Marsillach J, Joven J (2009) The paraoxonases: role in human diseases and methodological difficulties in measurement. *Crit Rev Clin Lab Sci* 46(2): 83–106
- Ceron JJ, Tecles F, Tvarijonaviciute A (2014) Serum paraoxonase 1 (PON1) measurement: an update. *BMC Vet Res* 10: 74. <https://doi.org/10.1186/1746-6148-10-74>
- Chen J, Hu J, Guo X, Yang Y, Qin D, Tang X, Huang Z, Wang F, Hu D, Peng D, Yu B (2024) Apolipoprotein O modulates cholesterol metabolism via NRF2/CYB5R3 independent of LDL receptor. *Cell Death Dis* 15(6): 389. <https://doi.org/10.1038/s41419-024-06778-4>
- Choi BJ, Hong JY, Park MH, Park KH, Han WH, Yoon HJ, Jung HY, Kim KY, Lee SA, Lim EY, Hur JW, Song IS, Jeon SY, Choi M-K, Christoffersen C, Kim H-J, Kim SH, Schuchman EH, Bae J-S, Jin HK (2025) HDL-bound S1P affects the subventricular niche and early neuropathological features of Alzheimer's disease. *Nat Commun* 16(1): 5728. <https://doi.org/10.1038/s41467-025-60750-0>
- Christoffersen C, Obinata H, Kumaraswamy SB, Galvani S, Ahnström J, Sevvana M, Egerer-Sieber C, Muller YA, Hla T, Nielsen LB, Dahlbäck B (2011) Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. *Proc Natl Acad Sci USA* 108(23): 9613–9618
- Croyal M, Wargny M, Chemello K, Chevalier C, Blanchard V, Bigot-Corbel E, Lambert G, Le May C, Hadjadj S, Cariou B (2022) Plasma apolipoprotein concentrations and incident diabetes in subjects with prediabetes. *Cardiovasc Diabetol* 21(1): 21. <https://doi.org/10.1186/s12933-022-01452-5>
- de Azúa-López ZR, Pezzotti MR, González-Díaz Á, Meilhac O, Ureña J, Amaya-Villar R, Castellano A, Varela LM (2023) HDL anti-inflammatory function is impaired and associated with high SAA1 and low APOA4 levels in aneurysmal subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 43(11): 1919–1930
- Deng S, Xu Y, Zheng L (2022) HDL structure. In: Zheng L (ed.) *HDL metabolism and diseases*. Singapore: Springer, pp 1–11
- Deng X, Sang Q, Zhang R, Mu J, Bao S (2023) The association of APOH and NCF1 polymorphisms on susceptibility to recurrent pregnancy loss in women with antiphospholipid syndrome. *J Assist Reprod Genet* 40(7): 1703–1712
- Deprince A, Hennuyer N, Kooijman S, Pronk ACM, Baugé E, Lienard V, Verrijken A, Dirinck E, Vonghia L, Woitrain E, Kloosterhuis NJ, Marez E, Jacquemain P, Wolters JC, Lalloyer F, Eberlé D, Quemener S, Vallez E, Tailleur A, Kouach M, Goossens JF, Raverdy V, Derudas B, Kuivenhoven JA, Croyal M, van de Sluis B, Francque S, Pattou F, Rensen PCN, Staels B, Haas JT (2023) Apolipoprotein F is reduced in humans with steatosis and controls plasma triglyceride-rich lipoprotein metabolism. *Hepatology* 77(4): 1287–1302
- Ding B-S, Liu CH, Sun Y, Chen Y, Swendeman SL, Jung B, Chavez D, Cao Z, Christoffersen C, Nielsen LB, Schwab SR, Rafii S, Hla T (2016) HDL activation of endothelial sphingosine-1-phosphate receptor-1 (S1P₁) promotes regeneration and suppresses fibrosis in the liver. *JCI Insight* 1(21): e87058. <https://doi.org/10.1172/jci.insight.87058>
- Dittrich J, Beutner F, Teren A, Thiery J, Burkhardt R, Scholz M, Ceglarek U (2019) Plasma levels of apolipoproteins C-III, A-IV, and E are independently associated with stable atherosclerotic cardiovascular disease. *Atherosclerosis* 281: 17–24
- Dong Y, Lee C-L, Li J, Liu X, Zeng Q, Zhong J, Zhang Q, Wu T, Ng VWY, Lee CKF, Burton GJ, Ng EHY, Yeung WSB, Cheung K-W, Chiu PCN (2025) Maternal causation of early-onset pre-eclampsia: excessive endometrial gland-derived apolipoprotein D induces placental ferroptosis and developmental abnormalities. *J Biomed Sci* 32(1): 103. <https://doi.org/10.1186/s12929-025-01199-7>
- Endo Y, Sasaki K, Ikewaki K (2025) Beyond high-density lipoprotein-cholesterol: unraveling the complexity of high-density lipoprotein functionality. *J Atheroscler Thromb* 32(11): 1359–1367
- Faber K, Hvidberg V, Moestrup SK, Dahlbäck B, Nielsen LB (2006) Megalin is a receptor for apolipoprotein M, and kidney-specific megalin-deficiency confers urinary excretion of apolipoprotein M. *Mol Endocrinol* 20(1): 212–218
- Faurø KK, Obel LM, Christesen HT, Jensen DM, Jensen TK, Glintborg D, Andersen MS, Overgaard M (2025) Apolipoprotein profile in early pregnancy and the link to gestational diabetes mellitus: insights from Odense child cohort. *Endocr Pract* 31(6): 805–812
- Foster EM, Dangla-Valls A, Lovestone S, Ribe EM, Buckley NJ (2019) Clusterin in Alzheimer's disease: mechanisms, genetics, and lessons from other pathologies. *Front Neurosci* 13: 164. <https://doi.org/10.3389/fnins.2019.00164>
- Freedman BI, Limou S, Ma L, Kopp JB (2018) *APOL1*-associated nephropathy: a key contributor to racial disparities in CKD. *Am J Kidney Dis* 72(5 Suppl 1): S8–S16
- Fujiwara Y, Osborne DA, Walker MD, Wang D-A, Bautista DA, Liliom K, Van Brocklyn JR, Parrill AL, Tigyi G (2007) Identification of the hydrophobic ligand binding pocket of the S1P₁ receptor. *J Biol Chem* 282(4): 2374–2385
- Galvani S, Sanson M, Blaho VA, Swendeman SL, Obinata H, Conger H, Dahlbäck B, Kono M, Proia RL, Smith JD, Hla T (2015) HDL-bound sphingosine 1-phosphate acts as a biased agonist for the endothelial cell receptor S1P₁ to limit vascular inflammation. *Sci Signal* 8(389): ra79. <https://doi.org/10.1126/scisignal.aaa2581>
- Gambino R, Rui G, Pagano G, Cassader M (1999) The binding of apolipoprotein H (β_2 -Glycoprotein I) to lipoproteins. *Prostaglandins Other Lipid Mediat* 57(5–6): 351–359
- Gao W, Yao Y, Gao Q, Zhao T, Li H (2025) Impact of serum lipids on prognosis in breast cancer patients: a systematic review and meta-analysis. *World J Surg Oncol* 23(1): 234. <https://doi.org/10.1186/s12957-025-03875-2>
- Garcinúño S, Lalueza A, Gil-Etayo FJ, Diaz-Simon R, Lizasoain I, Moraga A, Diaz-Benito B, Naranjo L, Cabrera-Marante O, Pleguezuelo DE, Ruiz-Ruigomez M, Ayuso B, Arrieta E, Folgueira D, Paz-Artal E, Cueto C, Lumbreras C, Serrano A, Serrano M (2024) Immune dysregulation is an important factor in the underlying complications in Influenza infection. ApoH, IL-8 and IL-15 as markers of prognosis. *Front Immunol*

- 15: 1443096. <https://doi.org/10.3389/fimmu.2024.1443096>
- Gazouli M, Anagnostopoulos AK, Papadopoulou A, Vaiopoulou A, Papamichael K, Mantzaris G, Theodoropoulos GE, Anagnou NP, Tsangaris GT (2013) Serum protein profile of Crohn's disease treated with infliximab. *J Crohns Colitis* 7(10): e461–470
- Gordon BR (2004) Poor outcomes associated with low lipid and lipoprotein levels. *Crit Care Med* 32(3): 878–879
- Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR (1977) High density lipoprotein as a protective factor against coronary heart disease. *The Framingham Study. Am J Med* 62(5): 707–714
- Haase CL, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R (2015) HDL cholesterol and risk of type 2 diabetes: a mendelian randomization study. *Diabetes* 64(9): 3328–3333
- Hanai K, Babazono T, Yoshida N, Nyumura I, Toya K, Hayashi T, Bouchi R, Tanaka N, Ishii A, Iwamoto Y (2012) Gender differences in the association between HDL cholesterol and the progression of diabetic kidney disease in type 2 diabetic patients. *Nephrol Dial Transplant* 27(3): 1070–1075
- Hanson MA, Roth CB, Jo E, Griffith MT, Scott FL, Reinhart G, Desale H, Clemons B, Cahalan SM, Schuerer SC, Sanna MG, Han GW, Kuhn P, Rosen H, Stevens RC (2012) Crystal structure of a lipid G protein-coupled receptor. *Science* 335(6070): 851–855
- He X, Zhang J, Huang M, Wang J, Yang S, Yu X, Xu Y, Yang W (2024) Serum apolipoprotein H determines ferroptosis resistance by modulating cellular lipid composition. *Cell Death Dis* 15(10): 718. <https://doi.org/10.1038/s41419-024-07099-2>
- Hirakata T, Yokomizo T, Matsuda A (2019) The roles of omega-3 fatty acids and resolvins in allergic conjunctivitis. *Curr Opin Allergy Clin Immunol* 19(5): 517–525
- Höffken V, Braun DA, Pavenstädt H, Weide T (2025) A cell biologist's view on APOL1: what we know and what we still need to address. *Cells* 14(13): 960. <https://doi.org/10.3390/cells14130960>
- Huang Y, Liu Y, Jiang L, Sun R, Zhang H, Liu R, Xu N (2014) Apolipoprotein m (APOM) levels and APOM rs805297 G/T polymorphism are associated with increased risk of rheumatoid arthritis. *Joint Bone Spine* 81(1): 32–36
- Jajula S, Naik V, Kalita B, Yanamandra U, Sharma S, Chatterjee T, Bhanuse S, Bhavsar PP, Taunk K, Rapole S (2024) Integrative proteome analysis of bone marrow interstitial fluid and serum reveals candidate signature for acute myeloid leukemia. *J Proteomics* 303: 105224. <https://doi.org/10.1016/j.jprot.2024.105224>
- Ji J, Zhao X, Huang J, Wu X, Xie F, Li L, Wang T, Mi S (2023a) Apolipoprotein A-IV of diabetic-foot patients upregulates tumor necrosis factor α expression in microfluidic arterial models. *Exp Biol Med (Maywood)* 248(8): 691–701
- Ji S-R, Zhang S-H, Chang Y, Li HY, Wang M-Y, Lv J-M, Zhu L, Tang PMK, Wu Y (2023b) C-reactive protein: the most familiar stranger. *J Immunol* 210(6): 699–707
- Jiang J, Zhang X, Wu C, Qin X, Luo G, Deng H, Lu M, Xu B, Li M, Ji M, Xu N (2008) Increased plasma apoM levels in the patients suffered from hepatocellular carcinoma and other chronic liver diseases. *Lipids Health Dis* 7: 25. <https://doi.org/10.1186/1476-511X-7-25>
- Jo-Watanabe A, Okuno T, Yokomizo T (2019) The role of leukotrienes as potential therapeutic targets in allergic disorders. *Int J Mol Sci* 20(14): 3580. <https://doi.org/10.3390/ijms20143580>
- Kalman J, McConathy W, Araoz C, Kasa P, Lacko AG (2000) Apolipoprotein D in the aging brain and in Alzheimer's dementia. *Neurol Res* 22(4): 330–336
- Kalvaityte U, Matta C, Bernotiene E, Pushparaj PN, Kiapour AM, Mobasher A (2022) Exploring the translational potential of clusterin as a biomarker of early osteoarthritis. *J Orthop Translat* 32: 77–84
- Kamboh MI, Mehdi H (1998) Genetics of apolipoprotein H (β 2-glycoprotein I) and anionic phospholipid binding. *Lupus* 7 Suppl 2: S10–S13
- Kano K, Aoki J, Hla T (2022) Lysophospholipid mediators in health and disease. *Annu Rev Pathol* 17: 459–483
- Katzeff JS, Bright F, Lo K, Kril JJ, Connolly A, Crossett B, Ittner LM, Kassiou M, Loy CT, Hodges JR, Piguet O, Kiernan MC, Halliday GM, Kim WS (2020) Altered serum protein levels in frontotemporal dementia and amyotrophic lateral sclerosis indicate calcium and immunity dysregulation. *Sci Rep* 10(1): 13741. <https://doi.org/10.1038/s41598-020-70687-7>
- Kawase Ishihara K, Kokubo Y, Yokota C, Hida E, Miyata T, Toyoda K, Matsumoto M, Minematsu K, Miyamoto Y (2015) Effect of plasma fibrinogen, high-sensitive c-reactive protein, and cigarette smoking on carotid atherosclerosis: the Suita study. *J Stroke Cerebrovasc Dis* 24(10): 2385–2389
- Khoonsari PE, Häggmark A, Lönnberg M, Mikus M, Kilander L, Lannfelt L, Bergquist J, Ingelsson M, Nilsson P, Kulthra K, Shevchenko G (2016) Analysis of the cerebrospinal fluid proteome in Alzheimer's disease. *PLoS One* 11(3): e0150672. <https://doi.org/10.1371/journal.pone.0150672>
- Ko Y-A, Billheimer JT, Lyssenko NN, Kueider-Paisley A, Wolk DA, Arnold SE, Leung YY, Shaw LM, Trojanowski JQ, Kaddurah-Daouk RF, Kling MA, Rader DJ (2022) ApoJ/Clusterin concentrations are determinants of cerebrospinal fluid cholesterol efflux capacity and reduced levels are associated with Alzheimer's disease. *Alzheimers Res Ther* 14(1): 194. <https://doi.org/10.1186/s13195-022-01119-z>
- Kobayashi T, Kurano M, Nanya M, Shimizu T, Ohkawa R, Tozuka M, Yatomi Y (2021) Glycation of HDL polymerizes apolipoprotein m and attenuates its capacity to bind to sphingosine 1-phosphate. *J Atheroscler Thromb* 28(7): 730–741
- Koga S, Miyata Y, Funakoshi A, Ibayashi H (1985) Plasma apolipoprotein A-IV levels decrease in patients with chronic pancreatitis and malabsorption syndrome. *Digestion* 32(1): 19–24
- Kronenberg F, Kuen E, Ritz E, König P, Kraatz G, Lhotta K, Mann JFE, Müller GA, Neyer U, Riegel W, Riegler P, Schwenger V, von Eckardstein A (2002) Apolipoprotein A-IV serum concentrations are elevated in patients with mild and moderate renal failure. *J Am Soc Nephrol* 13(2): 461–469
- Kuiperij HB, Hondius DC, Kersten I, Versleijen AAM, Rozemuller AJM, Greenberg SM, Schreuder FHBM, Klijn CJM, Verbeek MM (2020) Apolipoprotein D: a potential biomarker for cerebral amyloid angiopathy. *Neuropathol Appl Neurobiol* 46(5): 431–440
- Kumaraswamy SB, Linder A, Åkesson P, Dahlbäck B (2012) Decreased plasma concentrations of apolipoprotein M in sepsis and systemic inflammatory response syndromes. *Crit Care* 16(2): R60. <https://doi.org/10.1186/cc11305>
- Kurano M, Tsukamoto K, Ohkawa R, Hara M, Iino J, Kageyama Y, Ikeda H, Yatomi Y (2013) Liver involvement in sphingosine 1-phosphate dynamism revealed by adenoviral hepatic overexpression of apolipoprotein M. *Atherosclerosis* 229(1): 102–109
- Kurano M, Hara M, Tsuneyama K, Sakoda H, Shimizu T, Tsukamoto K, Ikeda H, Yatomi Y (2014) Induction of insulin secretion by apolipoprotein M, a carrier for sphingosine 1-phosphate. *Biochim Biophys Acta* 1841(9): 1217–1226
- Kurano M, Tsukamoto K, Kamitsuji S, Kamatani N, Hara M, Ishikawa T, Kim B-J, Moon S, Kim YJ, Teramoto T (2016) Genome-wide association study of serum lipids confirms previously reported associations as well as new associations of common SNPs within PCSK7 gene with triglyceride. *J Hum Genet* 61(5): 427–433

- Kurano M, Hara M, Ikeda H, Tsukamoto K, Yatomi Y (2017) Involvement of CETP (cholesteryl ester transfer protein) in the shift of sphingosine-1-phosphate among lipoproteins and in the modulation of its functions. *Arterioscler Thromb Vasc Biol* 37(3): 506–514
- Kurano M, Yatomi Y (2018) Sphingosine 1-phosphate and atherosclerosis. *J Atheroscler Thromb* 25(1): 16–26
- Kurano M, Ikeda H, Iso-O N, Hara M, Tsukamoto K, Yatomi Y (2018a) Regulation of the metabolism of apolipoprotein M and sphingosine 1-phosphate by hepatic PPAR γ activity. *Biochem J* 475(12): 2009–2024
- Kurano M, Tsuneyama K, Morimoto Y, Shimizu T, Jona M, Kassai H, Nakao K, Aiba A, Yatomi Y (2018b) Apolipoprotein M protects lipopolysaccharide-treated mice from death and organ injury. *Thromb Haemost* 118(6): 1021–1035
- Kurano M, Kano K, Hara M, Tsukamoto K, Aoki J, Yatomi Y (2019a) Regulation of plasma glycerol-lysophospholipid levels by lipoprotein metabolism. *Biochem J* 476(23): 3565–3581
- Kurano M, Tsuneyama K, Morimoto Y, Nishikawa M, Yatomi Y (2019b) Apolipoprotein M suppresses the phenotypes of IgA nephropathy in hyper-IgA mice. *FASEB J* 33(4): 5181–5195
- Kurano M, Yasukawa K, Ikeda H, Aoki J, Yatomi Y (2019c) Redox state of albumin affects its lipid mediator binding characteristics. *Free Radic Res* 53(8): 892–900
- Kurano M, Tsukamoto K, Shimizu T, Kassai H, Nakao K, Aiba A, Hara M, Yatomi Y (2020) Protection against insulin resistance by apolipoprotein m/sphingosine-1-phosphate. *Diabetes* 69(5): 867–881
- Kurano M, Tsukamoto K, Kamitsui S, Kamatani N, Hasegawa K, Hara M, Ishikawa T, Yatomi Y, Teramoto T (2023a) Apolipoprotein D modulates lipid mediators and osteopontin in an anti-inflammatory direction. *Inflamm Res* 72(2): 263–280
- Kurano M, Tsukamoto K, Shimizu T, Hara M, Yatomi Y (2023b) Apolipoprotein M/sphingosine 1-phosphate protects against diabetic nephropathy. *Transl Res* 258: 16–34
- Kurano M, Uranbileg B, Yatomi Y (2023c) Apolipoprotein M bound sphingosine 1-phosphate suppresses NETosis through activating S1P1 and S1P4. *Biomed Pharmacother* 166: 115400. <https://doi.org/10.1016/j.biopha.2023.115400>
- Kurano M, Tsukamoto K, Isago H, Hara M, Yatomi Y (2025a) C-reactive protein modulates lipid mediators in a pro-inflammatory direction. *J Inflamm (Lond)* 22(1): 32. <https://doi.org/10.1186/s12950-025-00459-5>
- Kurano M, Uranbileg B, Yatomi Y (2025b) Hepatic apolipoprotein m suppresses hepatocyte secretion of prothrombin by upregulating Arid5B. *Thromb Haemost*. <https://doi.org/10.1055/a-2664-8170>
- Lamant M, Smih F, Harmancey R, Philip-Couderc P, Pathak A, Roncalli J, Galinier M, Collet X, Massabuau P, Senard J-M, Rouet P (2006) ApoO, a novel apolipoprotein, is an original glycoprotein up-regulated by diabetes in human heart. *J Biol Chem* 281(47): 36289–36302
- Li L-Y, Chen S, Wang Y-X, Ji R, Ding F-H, Wang X-Q, Chen Q-J, Lu L, Dai Y (2022) Serum apolipoprotein A-IV levels are associated with flow-mediated dilation in patients with type 2 diabetes mellitus. *BMC Cardiovasc Disord* 22(1): 446. <https://doi.org/10.1186/s12872-022-02898-x>
- Li M, Yang X, Sun L, Qing Y, Hu X, Jiang J, Wang D, Cui G, Gao Y, Zhang E, Zhang J, Yang Y, Wan C (2021) Decreased serum apolipoprotein A4 as a potential peripheral biomarker for patients with schizophrenia. *J Psychiatr Res* 137: 14–21
- Liu L, Mo Z, Qin N, Pi J, Mao L, Deng G, Qian M, Huang Q, Duan S (2025) Hepatocyte apolipoprotein j accelerates injury-induced liver fibrosis by activation signal transducer and activator of transcription 3 through ranbp2 mediated-SUMOylation. *Cell Mol Gastroenterol Hepatol* 19(10): 101556. <https://doi.org/10.1016/j.jcmgh.2025.101556>
- Liu W, Lan T, Xie X, Huang K, Peng J, Huang J, Shen X, Liu P, Huang H (2012) S1P2 receptor mediates sphingosine-1-phosphate-induced fibronectin expression via MAPK signaling pathway in mesangial cells under high glucose condition. *Exp Cell Res* 318(8): 936–943
- Liu Y, Morton RE (2020) Apolipoprotein F: a natural inhibitor of cholesteryl ester transfer protein and a key regulator of lipoprotein metabolism. *Curr Opin Lipidol* 31(4): 194–199
- Liu Y, Xiong Z, Zhou W, Chen Y, Huang Q, Wu Y (2022) Role of apolipoprotein O in autophagy via the p38 mitogen-activated protein kinase signaling pathway in myocardial infarction. *Clinics (Sao Paulo)* 77: 100046. <https://doi.org/10.1016/j.clinsp.2022.100046>
- Liu Y, Wu Y, Jiang X, Chen B, Lu J, Cai Z, Fu B, Zheng W, Wu R, Chen G, Tian S, Ren J (2023) Apolipoprotein H induces sex-specific steatohepatitis and gut dysbiosis during chronic hepatitis B infection. *iScience* 26(3): 106100. <https://doi.org/10.1016/j.isci.2023.106100>
- Liu Y, Wu Z, Zhao Y, Zhen M, Wang Y, Liu Q (2024a) Apolipoprotein H-based prognostic risk correlates with liver lipid metabolism disorder in patients with HBV-related hepatocellular carcinoma. *Heliyon* 10(10): e31412. <https://doi.org/10.1016/j.heliyon.2024.e31412>
- Liu Y, Zhao Y, Liu Q, Li B, Daniel PV, Chen B, Wu Z (2024b) Effects of apolipoprotein H downregulation on lipid metabolism, fatty liver disease, and gut microbiota dysbiosis. *J Lipid Res* 65(1): 100483. <https://doi.org/10.1016/j.jlcr.2023.100483>
- Loosen SH, Kostev K, Luedde M, Luedde T, Roderburg C (2022) Low blood levels of high-density lipoprotein (HDL) cholesterol are positively associated with cancer. *J Cancer Res Clin Oncol* 148(11): 3039–3046
- Lu H, Wang B, Liu Y, Wang D, Fields L, Zhang H, Li M, Shi X, Zetterberg H, Li L (2023) DiLeu isobaric labeling coupled with limited proteolysis mass spectrometry for high-throughput profiling of protein structural changes in Alzheimer's disease. *Anal Chem* 95(26): 9746–9753
- Luo G, Hurtig M, Zhang X, Nilsson-Ehle P, Xu N (2005) Leptin inhibits apolipoprotein M transcription and secretion in human hepatoma cell line, HepG2 cells. *Biochim Biophys Acta* 1734(2): 198–202
- Luo G, Shi Y, Zhang J, Mu Q, Qin L, Zheng L, Feng Y, Berggren-Söderlund M, Nilsson-Ehle P, Zhang X, Xu N (2014) Palmitic acid suppresses apolipoprotein M gene expression via the pathway of PPAR β/δ in HepG2 cells. *Biochem Biophys Res Commun* 445(1): 203–207
- Mahadik SP, Khan MM, Evans DR, Parikh VV (2002) Elevated plasma level of apolipoprotein D in schizophrenia and its treatment and outcome. *Schizophr Res* 58(1): 55–62
- Makide K, Uwamizu A, Shinjo Y, Ishiguro J, Okutani M, Inoue A, Aoki J (2014) Novel lysophospholipid receptors: their structure and function. *J Lipid Res* 55(10): 1986–1995
- Makino Y, Noguchi E, Takahashi N, Matsumoto Y, Kubo S, Yamada T, Imoto Y, Ito Y, Osawa Y, Shibasaki M, Uchida K, Meno K, Suzuki H, Okubo K, Arinami T, Fujieda S (2010) Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 126(6): 1163–1169. e5
- Marfia G, Navone S, Guarnaccia L, Campanella R, Mondoni M, Locatelli M, Barassi A, Fontana L, Palumbo F, Garzia E, Ciniglio Appiani G, Chiumello D, Miozzo M, Centanni S, Riboni L (2021) Decreased serum level of sphingosine-1-phosphate: a novel predictor of clinical severity in COVID-19. *EMBO Mol Med* 13(1): e13424. <https://doi.org/10.15252/emmm.202013424>
- Martinelli N, Consoli L, Girelli D, Grison E, Corrocher R, Olivieri O

- (2013) Paraoxonases: ancient substrate hunters and their evolving role in ischemic heart disease. *Adv Clin Chem* 59: 65–100
- Matsubara E, Frangione B, Ghiso J (1995) Characterization of apolipoprotein J-Alzheimer's A β interaction. *J Biol Chem* 270(13): 7563–7567
- Matsuo S, Moriyama Y, Ushida T, Imai K, Tano S, Miki R, Yoshida K, Yokoi A, Kajiyama H, Kotani T (2024) Elevated levels of apolipoprotein A4 in umbilical cord serum from the maternal major depressive disorder. *J Obstet Gynaecol Res* 50(11): 2038–2045
- Men J, Zhao C, Xiang C, Zhu G, Yu Z, Wang P, Wu S, Zhang Y, Li Y, Wang L, Gong X, Yang X, Zou S, Ma J, Cui C, Li H, Ma X, Wu W, Wang Y (2025) Effects of high-intensity interval training on physical morphology, cardiopulmonary function, and metabolic indicators in older adults: a PRISMA-based systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 16: 1526991. <https://doi.org/10.3389/fendo.2025.1526991>
- Mu Q, Luo G, Wei J, Zheng L, Wang H, Yu M, Xu N (2021) Apolipoprotein M promotes growth and inhibits apoptosis of colorectal cancer cells through upregulation of ribosomal protein S27a. *EXCLI J* 20: 145–159
- Mughal SA, Park R, Nowak N, Gloyn AL, Karpe F, Matile H, Malecki MT, McCarthy MI, Stoffel M, Owen KR (2013) Apolipoprotein M can discriminate HNF1A-MODY from Type 1 diabetes. *Diabet Med* 30(2): 246–250
- Nojiri T, Kurano M, Tokuhara Y, Ohkubo S, Hara M, Ikeda H, Tsukamoto K, Yatomi Y (2014) Modulation of sphingosine-1-phosphate and apolipoprotein M levels in the plasma, liver and kidneys in streptozotocin-induced diabetic mice. *J Diabetes Investig* 5(6): 639–648
- Obinata H, Kuo A, Wada Y, Swendeman S, Liu CH, Blaho VA, Nagumo R, Satoh K, Izumi T, Hla T (2019) Identification of ApoA4 as a sphingosine 1-phosphate chaperone in ApoM- and albumin-deficient mice. *J Lipid Res* 60(11): 1912–1921
- Okajima F (2002) Plasma lipoproteins behave as carriers of extracellular sphingosine 1-phosphate: is this an atherogenic mediator or an anti-atherogenic mediator? *Biochim Biophys Acta* 1582(1–3): 132–137
- Omori M, Watanabe M, Matsumoto K, Honda H, Hattori H, Akizawa T (2010) Impact of serum apolipoprotein A-IV as a marker of cardiovascular disease in maintenance hemodialysis patients. *Ther Apher Dial* 14(3): 341–348
- Palmieri C, Bonsignore A, Augsburg M (2015) Measurement of apolipoprotein M in sepsis-related deaths. *Clin Chem Lab Med* 53(4): e93–e96
- Park WH (2026) Eicosanoids and Inflammation: a delicate balance of Pro-Inflammatory and Pro-Resolving mediators. *Biochem Pharmacol* 245: 117662. <https://doi.org/10.1016/j.bcp.2025.117662>
- Paslawski W, Svenningsson P (2023) Elevated ApoE, ApoJ and lipoprotein-bound α -synuclein levels in cerebrospinal fluid from Parkinson's disease patients - Validation in the BioFIND cohort. *Parkinsonism Relat Disord* 116: 105765. <https://doi.org/10.1016/j.parkreldis.2023.105765>
- Pays E, Radwanska M, Magez S (2023) The pathogenesis of African trypanosomiasis. *Annu Rev Pathol* 18: 19–45
- Pays E (2024) Apolipoprotein-I functions in membrane remodeling. *Cells* 13(24): 2115. <https://doi.org/10.3390/cells13242115>
- Polz E, Kostner GM (1979) The binding of β_2 -glycoprotein-I to human serum lipoproteins: distribution among density fractions. *FEBS Lett* 102(1): 183–186
- Qiang E, Xu H (2024) PGE₂ synthesis and signaling in the liver physiology and pathophysiology: an update. *Prostaglandins Other Lipid Mediat* 174: 106875. <https://doi.org/10.1016/j.prostaglandins.2024.106875>
- Rader DJ, Hovingh GK (2014) HDL and cardiovascular disease. *Lancet* 384(9943): 618–625
- Rasic-Milutinovic Z, Popovic T, Perunicic-Pekovic G, Arsic A, Borozan S, Glibetic M (2012) Lower serum paraoxonase-1 activity is related to linoleic and docosahexanoic fatty acids in type 2 diabetic patients. *Arch Med Res* 43(1): 75–82
- Reindl M, Knipping G, Wicher I, Dilitz E, Egg R, Deisenhammer F, Berger T (2001) Increased intrathecal production of apolipoprotein D in multiple sclerosis. *J Neuroimmunol* 119(2): 327–332
- Richter S, Shih DQ, Pearson ER, Wolfrum C, Fajans SS, Hattersley AT, Stoffel M (2003) Regulation of apolipoprotein M gene expression by MODY3 gene hepatocyte nuclear factor-1 α : haploinsufficiency is associated with reduced serum apolipoprotein M levels. *Diabetes* 52(12): 2989–2995
- Romagnoli T, Ortolani B, Sanz JM, Trentini A, Seripa D, Nora ED, Capatti E, Cervellati C, Passaro A, Zuliani G, Brombo G (2021) Serum Apo J as a potential marker of conversion from mild cognitive impairment to dementia. *J Neurol Sci* 427: 117537. <https://doi.org/10.1016/j.jns.2021.117537>
- Rosales C, Davidson WS, Gillard BK, Gotto Jr AM, Pownall HJ (2016) Speciated high-density lipoprotein biogenesis and functionality. *Curr Atheroscler Rep* 18(5): 25. <https://doi.org/10.1007/s11883-016-0572-7>
- Roula D, Theiler A, Luschnig P, Sturm GJ, Tomazic PV, Marsche G, Heinemann A, Sturm EM (2020) Apolipoprotein A-IV acts as an endogenous anti-inflammatory protein and is reduced in treatment-naive allergic patients and allergen-challenged mice. *Allergy* 75(2): 392–402
- Russo GT, De Cosmo S, Viazzi F, Pacilli A, Ceriello A, Genovese S, Guida P, Giorda C, Cucinotta D, Pontremoli R, Fioretto P, AMD-Annals Study Group (2016) Plasma triglycerides and HDL-C levels predict the development of diabetic kidney disease in subjects with type 2 diabetes: the AMD annals initiative. *Diabetes Care* 39(12): 2278–2287
- Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, Folsom AR, Chambless LE, Atherosclerosis Risk in Communities Investigators (2005) Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 28(8): 2013–2018
- Schwarzenbacher R, Zeth K, Diederichs K, Gries A, Kostner GM, Laggner P, Prassl R (1999) Crystal structure of human β_2 -glycoprotein I: implications for phospholipid binding and the antiphospholipid syndrome. *EMBO J* 18(22): 6228–6239
- Seo JA, Kang M-C, Yang W-M, Hwang WM, Kim SS, Hong SH, Heo J-I, Vijayakumar A, Pereira de Moura L, Uner A, Huang H, Lee SH, Lima IS, Park KS, Kim MS, Dagon Y, Willnow TE, Aroda V, Ciaraldi TP, Henry RR, Kim Y-B (2020) Apolipoprotein J is a hepatokine regulating muscle glucose metabolism and insulin sensitivity. *Nat Commun* 11(1): 2024. <https://doi.org/10.1038/s41467-020-15963-w>
- Shimura T, Isago H, Morita Y, Ohkawa R, Yoshikawa N, Ono Y, Kurano M (2025) Modulating lysophospholipids with Paraoxonase-1: exploring its impact on inflammatory responses and immune reactions. *Biochem Biophys Res Commun* 746: 151234. <https://doi.org/10.1016/j.bbrc.2024.151234>
- Souza Junior DR, Silva ARM, Rosa-Fernandes L, Reis LR, Alexandria G, Bhosale SD, de Rose Ghilardi F, Dalcoquio TF, Bertolin AJ, Nicolau JC, Marinho CRF, Wrenger C, Larsen MR, Siciliano RF, Di Mascio P, Palmisano G, Ronsein GE (2021) HDL proteome remodeling associates with COVID-19 severity. *J Clin Lipidol* 15(6): 796–804

- Stangl S, Kollerits B, Lamina C, Meisinger C, Huth C, Stöckl A, Dähnhardt D, Böger CA, Krämer BK, Peters A, Kronenberg F (2015) Association between apolipoprotein A-IV concentrations and chronic kidney disease in two large population-based cohorts: results from the KORA studies. *J Intern Med* 278(4): 410–423
- Svarrer EMM, Andersen HØ, Helvind M, Slagman MCJ, Navis G, Dullaart RPF, Dahlbäck B, Nielsen LB (2016) Urinary apolipoprotein M as a biomarker of acute kidney injury in children undergoing heart surgery. *Biomark Med* 10(1): 81–93
- Swendeman SL, Xiong Y, Cantalupo A, Yuan H, Burg N, Hisano Y, Cartier A, Liu CH, Engelbrecht E, Blaho V, Zhang Y, Yanagida K, Galvani S, Obinata H, Salmon JE, Sanchez T, Di Lorenzo A, Hla T (2017) An engineered S1P chaperone attenuates hypertension and ischemic injury. *Sci Signal* 10(492): eaal2722. <https://doi.org/10.1126/scisignal.aal2722>
- Takagi Y, Nishikado S, Omi J, Aoki J (2022) The many roles of lysophospholipid mediators and Japanese contributions to this field. *Biol Pharm Bull* 45(8): 1008–1021
- Takuwa Y, Okamoto Y, Yoshioka K, Takuwa N (2012) Sphingosine-1-phosphate signaling in physiology and diseases. *Biofactors* 38(5): 329–337
- Tang X, Li S, Yang X, Tang Q, Zhang Y, Zeng S, Li M, Jiang K, Guo L, Huang P (2021) Novel proteins associated with chronic intermittent hypoxia and obstructive sleep apnea: From rat model to clinical evidence. *PLoS One* 16(6): e0253943. <https://doi.org/10.1371/journal.pone.0253943>
- The Emerging Risk Factors Collaboration (2012) C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 367(14): 1310–1320
- Thomas EA, Dean B, Pavay G, Sutcliffe JG (2001) Increased CNS levels of apolipoprotein D in schizophrenic and bipolar subjects: implications for the pathophysiology of psychiatric disorders. *Proc Natl Acad Sci USA* 98(7): 4066–4071
- Tsai M-H, Peng Y-S, Chen Y-C, Lien J-M, Tian Y-C, Fang J-T, Weng H-H, Chen P-C, Yang C-W, Wu C-S (2009) Low serum concentration of apolipoprotein A-I is an indicator of poor prognosis in cirrhotic patients with severe sepsis. *J Hepatol* 50(5): 906–915
- Tu S-T, Chang S-J, Chen J-F, Tien K-J, Hsiao J-Y, Chen H-C, Hsieh M-C (2010) Prevention of diabetic nephropathy by tight target control in an Asian population with type 2 diabetes mellitus: a 4-year prospective analysis. *Arch Intern Med* 170(2): 155–161
- Turkieh A, Caubère C, Barutaut M, Desmoulin F, Harmancey R, Galinier M, Berry M, Dambrin C, Polidori C, Casteilla L, Koukoui F, Rouet P, Smih F (2014) Apolipoprotein O is mitochondrial and promotes lipotoxicity in heart. *J Clin Invest* 124(5): 2277–2286
- Tydén H, Lood C, Jönsen A, Gullstrand B, Kahn R, Linge P, Kumaraswamy SB, Dahlbäck B, Bengtsson AA (2019) Low plasma concentrations of apolipoprotein M are associated with disease activity and endothelial dysfunction in systemic lupus erythematosus. *Arthritis Res Ther* 21(1): 110. <https://doi.org/10.1186/s13075-019-1890-2>
- Uzureau S, Lecordier L, Uzureau P, Hennig D, Graversen JH, Homblé F, Mfutu PE, Oliveira Arcolino F, Ramos AR, La Rovere RM, Luyten T, Vermeersch M, Tebabi P, Dieu M, Cuypers B, Deborggrave S, Rabant M, Legendre C, Moestrup SK, Levchenko E, Bultynck G, Erneux C, Pérez-Morga D, Pays E (2020) APOL1 C-terminal variants may trigger kidney disease through interference with APOL3 control of actomyosin. *Cell Rep* 30(11): 3821–3836. e13
- Valesini G, Shoenfeld Y (1992) A new player in the antiphospholipid syndrome: the β_2 glycoprotein I cofactor. *Autoimmunity* 14(2): 105–110
- Wan G, Zhaorigetu S, Liu Z, Kaini R, Jiang Z, Hu C-A (2008) Apolipoprotein L1, a novel Bcl-2 homology domain 3-only lipid-binding protein, induces autophagic cell death. *J Biol Chem* 283(31): 21540–21549
- Wang M, Luo G-H, Liu H, Zhang Y-P, Wang B, Di D-M, Zhan X-H, Yu Y, Yao S, Zhang X-Y, Xu N (2019) Apolipoprotein M induces inhibition of inflammatory responses via the S1PR1 and DHCR24 pathways. *Mol Med Rep* 19(2): 1272–1283
- Wang P-W, Hung Y-C, Wu T-H, Chen M-H, Yeh C-T, Pan T-L (2017) Proteome-based identification of apolipoprotein A-IV as an early diagnostic biomarker in liver fibrosis. *Oncotarget* 8(51): 88951–88964
- Wang T, Wang Y, Wang Y, Wang X, Cheng X, Tan Q, Zhu T, Teng X, Huang H, Shen Z (2024) Identification of serum biomarkers and therapeutic targets for aortic diseases in obesity through multi-omics analysis. *J Thorac Dis* 16(12): 8435–8449
- Wilson PWF, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino Sr RB (2007) Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med* 167(10): 1068–1074
- Wu X, Yan T, Wang Z, Dong X, Yu W, Zheng Y, Hu W, Wang K, Du Q (2022) Role of plasma Apo-J as a biomarker of severity and outcome after intracerebral hemorrhage: a prospective and cohort study. *Clin Chim Acta* 533: 148–155
- Xie Z, Harris-White ME, Wals PA, Frautschy SA, Finch CE, Morgan TE (2005) Apolipoprotein J (clusterin) activates rodent microglia *in vivo* and *in vitro*. *J Neurochem* 93(4): 1038–1046
- Xiong Y, Hla T (2014) S1P control of endothelial integrity. In: Oldstone MBA, Rosen H (eds.) Sphingosine-1-phosphate signaling in immunology and infectious diseases. Cham: Springer, pp 85–105
- Xu N, Dahlbäck B (1999) A novel human apolipoprotein (apoM). *J Biol Chem* 274(44): 31286–31290
- Yaginuma S, Omi J, Uwamizu A, Aoki J (2023) Emerging roles of lysophosphatidylserine as an immune modulator. *Immunol Rev* 317(1): 20–29
- Yanai H, Adachi H, Hakoshima M, Katsuyama H (2022) Atherogenic lipoproteins for the statin residual cardiovascular disease risk. *Int J Mol Sci* 23(21): 13499. <https://doi.org/10.3390/ijms232113499>
- Yatomi Y, Kurano M, Ikeda H, Igarashi K, Kano K, Aoki J (2018) Lysophospholipids in laboratory medicine. *Proc Jpn Acad Ser B Phys Biol Sci* 94(10): 373–389
- Yokomizo T, Shimizu T (2023) The leukotriene B₄ receptors BLT1 and BLT2 as potential therapeutic targets. *Immunol Rev* 317(1): 30–41
- Yu B-L, Wu C-L, Zhao S-P (2012) Plasma apolipoprotein O level increased in the patients with acute coronary syndrome. *J Lipid Res* 53(9): 1952–1957
- Yu Y, Zhang J, Yao S, Pan L, Luo G, Xu N (2020) Apolipoprotein M overexpression through adeno-associated virus gene transfer improves insulin secretion and insulin sensitivity in Goto-Kakizaki rats. *J Diabetes Investig* 11(5): 1150–1158
- Yu Z, Xiao C, Liu R, Pi D, Jin B, Zou Z, Xu F (2024) The protective effect of apolipoprotein H in paediatric sepsis. *Crit Care* 28(1): 36. <https://doi.org/10.1186/s13054-024-04809-2>
- Zhang X, Yu W, Cao X, Wang Y, Zhu C, Guan J (2022) Identification of serum biomarkers in patients with Alzheimer's disease by 2D-DIGE proteomics. *Gerontology* 68(6): 686–698
- Zhou Y, Yao S, Yu M, Wei J, Fang Q, Xu N, Luo G (2022) The effects and possible mechanism of action of apolipoprotein M on the growth of breast cancer cells. *Mol Biol Rep* 49(2): 1171–1179
- Zhu B, Luo G-H, Feng Y-H, Yu M-M, Zhang J, Wei J, Yang C, Xu N, Zhang X-Y (2018) Apolipoprotein M protects against lipopolysaccharide-induced acute lung injury via sphingosine-1-phosphate signaling. *Inflammation* 41(2): 643–653