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Impaired cholesterol and LDL uptake pathways in the development of oncological and cardiovascular diseases

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ABSTRACT

Dietary lipids play a critical role in the development of cardiovascular disease and cancer by influencing key cellular processes. Lipoprotein and fatty acid receptors activate intracellular signaling pathways that promote tumor growth and vascular remodeling. A key event in both cancer and vascular diseases is the retention of low-density lipoproteins (LDL) and other lipoprotein particles by proteoglycans in the extracellular matrix (ECM) of atherosclerotic plaques and the tumor stroma. This retention facilitates lipoprotein modification processes. Dysregulated uptake of modified lipoproteins—particularly through receptors that are not downregulated by intracellular cholesterol levels—leads to excessive lipid accumulation within lipid droplets (LDs) and other intracellular organelles. The lipid and protein content of LDs and mitochondria determine the biophysical and functional characteristics of the crucial interactions between these suborgalles. In particular, lipid-derived mediators such as prostaglandins, leukotrienes, ceramides, oxidized fatty acids, and cholesterol can disrupt LD biogenesis and dynamics, impair mitochondrial function, and alter the expression, activity, and subcellular localization of proteins that regulate LD-mitochondria interactions. Dysfunctional communication between LDs and mitochondria contributes to the onset and progression of cancer and cardiovascular disease by disturbing cellular metabolism and energy homeostasis. Common LDL-related mechanisms in atherosclerosis and cancer have been summarized in Figure 1.

Abbreviations: ACC, Acetyl-Coenzyme A Carboxylase; AKT, protein kinase B; AgLDL, Aggregated LDL; ApoB100, Apolipoprotein B100; ApoE, Apolipoprotein E; ATP, Adenosine Triphosphate; ASCVD, AtheroSclerotic CardioVascular Disease; CE, Cholesteryl Esters; CRC, ColonoRectal Cancer; CVD, Cardiovascular Disease; ECM, ExtraCellular Matrix; EMT, Epitelial-Mesenchymal Transition; ERK, Extracellular signal-Regulated Kinase; FA, Fatty Acids; FAS, Fatty Acid Synthase; FATP4, Fatty Acid Transport Protein 4; FH, Familial Hypercholesterolemia; HCC, HepatoCelular Carcinoma; HDL, High Density Lipoproteins; IL, Interleukin; IRAK-1, Interleukin-1 Receptor-Associated Kinase 1; LD, Lipid Droplet; LDL, Low-Density Lipoproteins; LDL-C, LDL cholesterol; LDLR, Low-Density Lipoprotein Receptor; LOX-1, Lectin-like Oxidized low-density lipoprotein receptor-1; LRP1, Low-density lipoprotein Receptor-related Protein 1; MIGA, MItochondria-associated GAurdian; MUFA, MonoUnsaturated Fatty Acids; NAFLD, Non-Alcoholic Fatty Liver Disease; NF-kB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; Ox-LDL, Oxidized LDL; PDAC, Pancreatic Ductal Carcinoma; PDGF-B, Platelet Derived Growth Factor B; PG, ProteoGlycans; PI3, PhosphoInositide-3-kinase/protein kinase B; PLIN, Perilipin; PUFA, Poliunsaturated Fatty Acids; ROS, Reactive Oxigen Species; TG, triglycerides; TGF-B, Transforming Growth Factor Beta; SLRP1, soluble low-density lipoprotein receptor-related protein 1; SM, Sphingomyelin; T-PA, Tissue Plasminogen Activator; TNF-α, Tumor necrosis factor alpha; TNFR1, Tumor Necrosis Factor Receptor 1; UPF-, ultra processed foods; VAMP, Vesicle-Associated Membrane Protein; VAP, VAMP-associated proteins; VEFG-C, Vascular endothelial growth factor C; VLDL, Very Low-Density Lipoproteins; VSMC, Vascular Smooth Muscle Cells.

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1. Dietary fatty acids as modulators of lipoprotein cholesterol content

An increasing body of evidence suggests that specific characteristics of lipoproteins—such as their lipid composition, particle size, and associated molecular components—serve as valuable indicators of an individual's overall health status, rather than acting solely as direct determinants of cardiovascular disease risk [1,2]. In the present narrative, we explore how diet modulates the structural and functional properties of lipoproteins, with a particular focus on low-density lipoproteins (LDL), which play a central role in cholesterol metabolism. This relationship is not only relevant to cardiovascular health, but also to the development and progression of oncologic diseases.

Dietary composition plays a pivotal role in modulating the lipid content and structural properties of lipoproteins in both serum and peripheral tissues. The distribution of cholesterol and fatty acids among different lipoprotein classes, and their subsequent delivery to target tissues, is significantly influenced by the type of dietary fat consumed. Specifically, the chain length and degree of saturation of fatty acids determine their efficiency of intestinal absorption and subsequent incorporation into circulating lipoproteins such as chylomicrons, LDL, and high-density lipoproteins (HDL) [3,4].

These diet-dependent alterations in lipoprotein composition have important implications for systemic lipid homeostasis and disease pathophysiology. Experimental studies in animal models have demonstrated that short- and medium-chain saturated fatty acids (SFAs), primarily derived from plant sources such as coconut and palm oil, are preferentially metabolized in the liver. This hepatic metabolism limits their incorporation into circulating lipoproteins. Conversely, polyunsaturated fatty acids (PUFAs), which are abundant in animal-derived foods and fatty fish, are more readily incorporated into tissue lipids and plasma lipoproteins [5,6]. These findings underscore the role of fatty acid structure in determining lipid fate and lipoprotein composition.

Monounsaturated (MUFA) and PUFA, abundantly present in nuts such as walnuts and almonds, as well as in olive oil, have been consistently associated with improved lipid profiles, particularly through the reduction of circulating low-density lipoprotein cholesterol (LDL-C). The underlying mechanisms proposed for these effects include: (1) increased hepatic catabolisme of cholesterol [7,8], and protection of LDL particles from oxidative modification and aggregation [9,10]. Furthermore, plant-derived sterols and stanols—naturally occurring in various vegetables—have been shown to inhibit intestinal cholesterol absorption, thereby contributing to lower plasma cholesterol levels [11,12].

In contrast, high intake of saturated fatty acids (SFA) has been associated with increased LDL-C levels and substitution of saturated fats with unsaturated fats—particularly n-6 PUFAs—has been shown to effectively reduce LDL-C concentrations, with greater efficacy observed for n-6 PUFAs compared to MUFAs [13]. Notably, the dietary fatty acid composition appears to exert a more significant influence on serum LDL-C and total cholesterol levels than dietary cholesterol intake *per se* [14,15].

In the context of cancer, dietary intake of MUFA and PUFA has been shown to limit the availability of pro-inflammatory lipid mediators that may promote tumor initiation and progression [16]. Notably, extra virgin olive oil (EVOO), which is particularly rich in bioactive MUFAs and phenolic compounds, has demonstrated superior anti-tumoral effects compared to other vegetable oils in preclinical models of breast cancer. Experimental studies have shown that EVOO not only attenuates tumor growth but also modulates gene expression profiles in the mammary gland in a manner that may reduce cancer susceptibility [17–19]. These effects are thought to be mediated through the combined action of EVOO lipid composition and minor compounds, which influence inflammatory signaling pathways, oxidative stress, and cell proliferation.

In contrast to the protective effects associated with diets rich in unsaturated fatty acids, the consumption of ultra-processed foods (UPF)—typically high in saturated and trans fats—has been linked to adverse lipid profiles, including increased LDL cholesterol levels and enhanced lipid peroxidation, both of which are established risk factors for carcinogenesis. Emerging evidence from systematic reviews and meta-analyses suggests a strong association between high consumption of UPF and increased cancer risk, highlighting the importance of dietary quality not only in cardiovascular but also in oncologic health [20]. Beyond their fat content, ultra-processed foods often contain additional components that may further contribute to cancer risk. These include high concentrations of simple sugars such as glucose and fructose, artificial flavor enhancers, additives that impair satiety regulation, and various chemical preservatives. Evidence from the PREDIMED study demonstrated that higher consumption of simple sugars, especially in liquid form, is significantly associated with increased cancer incidence and mortality [21]. Moreover, a meta-analysis of prospective cohort studies identified a positive relationship between fructose intake and pancreatic cancer risk, suggesting a direct involvement of this monosaccharide in carcinogenesis [22].

2. Influence of diet in the individual susceptibility of LDL to aggregation

LDL particles are retained in the vascular wall becoming aggregated, mainly due to the actions of lipolytic enzymes present in the arterial intima [23,24]. The susceptibility of LDL to aggregation is increased in patients with coronary and peripheral atherosclerosis and is a predictor of future adverse cardiovascular events [25,26].

In addition to local factors within the arterial intima, diet composition plays a significant role in the individual variation for LDL aggregation susceptibility, with fat type—particularly saturated fats—being a key dietary factor [27]. Higher consumption of vegetable oils and spreads enriched with plant stanols can reduce LDL aggregation by altering the surface phospholipids of LDL particles [25]. Oils like Camelina sativa oil enriched in alpha-linolenic acid, decrease LDL susceptibility to aggregation by shifting the balance between saturated and monounsaturated cholesteryl ester (CE) species in LDL and replacing them with polyunsaturated triglycerides (TGs) [28]. These studies suggest that dietary n-3 PUFA are incorporated into both the phospholipids and neutral lipids of LDL, increasing the degree of unsaturation in both the core and surface of the particles, which, in turn, affects LDL's tendency to aggregate. Notably, LDL aggregation appears to be inversely related to specific unsaturated PC species and directly correlated with unsaturated SM species. Thus, LDL aggregation susceptibility varies depending on the specific phospholipid species incorporated and their degree of unsaturation.

In individuals with obesity, the hepatic lipid profile influences the lipid composition of LDL particles, contributing to an increased susceptibility to LDL aggregation [29]. Lahelma et al. were the first to demonstrate that the distribution of double bonds and acyl carbon numbers in TGs, SMs, and phosphatidylcholines of LDL particles closely mirrors that of the liver. Additionally, qualitative sphingolipid changes were observed on the surface of LDL particles and in the liver of individuals with increased susceptibility to LDL aggregation. Elevated levels of dihydroceramide and ceramide in the liver were also associated with SM-rich LDL particles prone to aggregation. Together, these findings highlight the important role that dietary-induced changes in LDL lipid composition play in influencing LDL aggregation susceptibility in humans.

Individual with familial hipercholesterolemia (FH) have increased susceptibility to LDL aggregation [30,31]. In adult patients with FH, the increased susceptibility of LDL to aggregation is closely linked to a hightened and stabilized cholesteryl ester core that reduces LDL size and promotes a loss of a specific flexible α-helix component in ApoB100 [31].While LDL aggregation has been consistently shown to have prognostic value in cardiovascular disease, no studies have yet evaluated the prognostic significance of this variable in the context of cancer.

3. Lipoproteins as biomarkers of cancer progression

Mendelian randomization studies and randomized trials involving over 2 million participants, with more than 20 million person-years of follow-up and over 150,000 cardiovascular events, have demonstrated that exposure of the vasculature to LDLc mechanistically causes atherosclerosis, and that this effect intensifies with longer durations of exposure to LDL [32]. However, less known is the potential relation of LDL with oncological processes, and sometimes controversial results have been reported.

Diet-induced alterations in LDL cholesterol composition may contribute to the development of several cancer types, including pancreatic [33], lung [34], esophageal [35], breast [36], prostate [37,38], and colorectal cancers [39]. In addition, there is a consistent and significant association between intake of UPF and the risk of overall and several cancers, including colorectal-, breast- and pancreatic cancer [20]. Recent evidence also suggests that qualitative changes in LDL particles may also promote cancer progression in various models, including liver, breast, and prostate cancer [40,41].

In line with these results, it has been recently postulated that LDL-C may serve as a useful biomarker for tracking cancer progression. Early assessment of LDL-C levels could help stratify patients into low- and high-risk groups [42]. Dense VLDL and large, buoyant LDL contribute to develop early diagnosis strategies for individuals at high risk of nasopharyngeal carcinoma [43], and patients with colorectal cancer tend to exhibit smaller LDL and HDL particles [44].

Lipoprotein(a), or Lp(a), is a type of cholesterol particle similar to LDL but with an added protein called apolipoprotein a. High levels of Lp(a) are genetically determined and are associated with an increased risk of cardiovascular diseases [45]. Controversial results about the prognostic value of Lp(a) in cancer have been reported. While some studies reported a inverse association between circulating levels of Lp(a) and cancer risk [46], others proposed that due to its pro-inflammatory effects, Lp(a) contributes to cardiovascular and cancer risk [47,48].

Further research is warranted—particularly large-scale studies using Mendelian randomization approaches—to clarify the prognostic value of lipoproteins in cancer.

4. Lipoprotein retention in the extracellular matrix (ECM) of the arterial intima and the stroma

LDL retention in the extracellular matrix (ECM) of the arterial intima and stroma plays a crucial role in the pathogenesis of atherosclerosis [49] and has emerging implications in tumor biology. Proteoglycans (PGs), major components of the ECM, electrostatically bind apolipoprotein B100 (ApoB100), the principal protein of LDL, facilitating LDL retention in these tissues [50]. The differential composition and structural organization of ECM in the stroma likely influences the degree and nature of LDL retention in tumors. In the arterial intima, PGs interact with specific amino acid residues of ApoB100, leading to LDL aggregation and subsequent atherogenic modification, initiating a cascade of inflammatory responses that contribute to plaque formation and progression [50]. The stroma of tumors exhibits a distinct ECM remodeling characterized by increased acidity and hypoxia, which alters PG reactivity and LDL behavior [51,52]. ECM promotes the retention of modified LDL forms, including oxidized LDL (oxLDL), which acts not only as a pro-atherogenic factor but also modulates cancer cell behavior and the tumor microenvironment [53,54].

5. Apolipoprotein B100 structural conformation as a key determinant of cholesterol metabolism

Apolipoprotein B100 (apoB100) is the primary structural protein of LDL and serves as the main ligand for the LDL receptor (LDLR). Genetic mutations in either the APOB gene or the LDLR gene result in FH, characterized by markedly elevated levels of LDL-C and a significantly increased risk of cardiovascular disease. The ultrastructure of ApoB100 on LDL bound to LDLR has been recently elucidated through cryo-electron microscopy [55].

From a biophysical perspective, both an increased cholesterol content in LDL particles and a reduction in LDL size may contribute to alterations in ApoB100 conformation and missfolding [31,56]. In turn, apoB100 misfolding plays a critical role in the dysregulation of cholesterol metabolism. The structural conformation of apoB100 is essential for maintaining physiological homeostasis through at least two key mechanisms. First, it ensures the structural integrity of LDL particles, thereby preventing their pathological accumulation in the arterial intima [53] and within the tumor stroma [52,54]. Second, proper apoB100 folding is required for effective binding to the classical LDL receptor (LDLR), facilitating the physiological uptake and metabolism of LDL cholesterol by target cells [56].

Structural alterations or misfolding of apoB100 impair its affinity for LDLR, redirecting LDL particles toward alternative clearance pathways mediated by non-regulated scavenger receptors. These include CD36 in macrophages [57], the low-density lipoprotein receptor-related protein 1 (LRP1) in vascular smooth muscle cells [58] and cardiomyocytes [59], as well as lectin-like oxidized LDL receptor-1 (LOX-1) [60,61].

These alternative pathways have been implicated in both cardiovascular and oncologic pathophysiology. Aberrant cholesterol uptake via these non-regulated receptors is strongly associated with a pro-inflammatory microenvironment in vascular tissues and tumors. In addition, LDL-driven tumorigenesis has been linked to several mechanisms, including increased intracellular reactive oxygen species (ROS) production, activation of oncogenic signaling pathways, and provision of metabolic substrates necessary for tumor growth and metastasis.

6. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) levels and signaling in atherosclerosis and cancer

OxLDL exerts its effects primarily through binding to the lectin-like oxidized LDL receptor-1 (LOX-1) (encoded by *OLR1*), which is upregulated in endothelial cells, macrophages, and tumor cells. In atherosclerosis, LOX-1 mediates oxLDL uptake, foam cell formation, and endothelial dysfunction [60,61]. In tumors, LOX-1 activation promotes epithelial-mesenchymal transition, lymphangiogenesis, and metastatic niche formation via pathways involving Vascular Endothelial Growth Factor C (VEGF-C) and chemokine signaling [62–65].

The overexpression of LOX-1 is a hallmark of various pathological conditions, notably atherosclerosis and cancer. In cardiovascular disease, stimuli such as oxidative stress, inflammatory cytokines, and hyperlipidemia induce LOX-1 upregulation, which amplifies ox-LDL uptake, promotes endothelial dysfunction, and triggers a feed-forward loop of ROS production and activation of NF-κB signaling pathways, exacerbating vascular inflammation and plaque instability [66,67]. Moreover, LOX-1 overexpression in vascular smooth muscle cells fosters phenotypic switching toward a pro-inflammatory and proliferative state, contributing to neointimal hyperplasia and atherogenesis [68].

In the arterial intima. beyond its involvement in foam cell formation, LOX-1 is implicated in several pro-atherosclerotic mechanisms, including the generation of reactive oxygen species (ROS), collagen degradation, and thrombus formation [61]. LOX-1 also plays a pathological role in cardiac remodeling following myocardial infarction, as demonstrated in an experimental murine model [69]. In line, the soluble form of LOX-1 is considered a potential biomarker for myocardial ischemia in humans [70].

In oncology, LOX-1 overexpression has been increasingly recognized as a driver of tumor progression. It is associated with enhanced neoangiogenesis, epithelial–mesenchymal transition (EMT), and immune evasion, mediated through pro-inflammatory and pro-angiogenic signaling pathways such as NF-κB and VEGF [65]. For example, in colorectal cancer, LOX-1 overexpression correlates with increased invasiveness and metastatic potential through ox-LDL-induced EMT and

angiogenesis [71]. Similarly, in prostate and breast cancers, LOX-1 activation supports tumor cell survival, migration, and dissemination by enhancing oxidative stress-dependent signaling cascades [72]. These results point to LOX-1 as a promising target for therapeutic intervention. Experimental studies have shown that inhibition or genetic silencing of LOX-1 can reduce atherosclerotic lesion formation and tumor growth in vivo, emphasizing its translational potential in cardiovascular and cancer therapy [73].

7. Low-density lipoprotein receptor-related protein 1 (LRP1) levels and/or signaling in atherosclerosis and cancer

The clinical relevance of Low density lipoprotein receptor-related protein 1 (LRP1) in the dysregulated uptake of cholesterol from LDL particles, as well as the upregulating effect of LDL-derived cholesterol on LRP1 expression and its contribution to atherosclerosis progression, has been firmly established. However, the specific mechanisms of LDL uptake by LRP1 and the dysregulation of LRP1 signaling in response to lipid uptake have been less extensively studied in cancer. There are not direct evidences linking LDL binding to LRP1 signaling in cancer.

LRP1 is a large endocytic receptor belonging to the family of LDLR that is composed of two chains, the α-chain**,** mostly extracellular that is responsible for ligand binding, linked to the shorter β-chain, a transmembrane chain that contains the cytoplasmic domain and that is involved in intracellular signaling and endocytosis.

The alpha chain binds to a wide variety of ligands involved in different pathologies (Table 1), including aggregated LDL (agLDL) [74,75].

LRP1 is upregulated by hypercholesterolemia, hypertension, and hypoxia in vascular cells in *in vitro* and *in vivo* models [76–78]. These results suggest that LRP1 function is crucial in the manangement of cardiovascular diseases.

From the traslational point of view, it is fundamental to consider the critical role of LRP1 β-chain as a signaling mediator critically involved in cytoprotection and anti-inflammatory funcions. The LRP1 β-chain is phosphorylated by PDGF-BB signaling, regulating VSMC proliferation limiting apoptosis and inflammation [79–82]. LRP1 complete disruption leads to lipid accumulation and impaired apoptotic cell clearance, accelerating atherosclerosis [80]. LRP1 also plays a key role in vascular function by mediating Wnt5a induction induced by TGF-β [83], Akt and ERK1/2 phosphorylation exerting cytoprotective effects [84,85], and ApoE-IRAK-1 signaling that modulates NF-κB inflammation [86], (summarized in Figs. 1 and 2, left panel). Controversially, LRP1 contributes to the activation of TNFR1/NF-κB axis in the vasculature of hypercholesterolemic rabbits driving vascular inflammation and atherosclerosis progression [87]. Significant efforts have been invested in the identification of the aminoacidic sequences of cluster II involved in the interaction with agLDL. AgLDL binds to LRP1 through the CR9 domain, and specifically by the P3 sequence (amino acids Gly1127–Cys1140) that interact with the sequence Ile3227-Lys3226 of ApoB100 [58,88]. Targeting the P3 region using anti-P3 antibodies has been shown to be an efficient therapeutic strategy to reduce atherosclerosis and cardiac metabolic dysrgulation remodeling induced by high fat diets [89,90].

The soluble form of LRP1 (sLRP1) is nowadays considered a biomarker of subclinical atherosclerosis in different populations of patients and has predictive value for acute myocardial infarction and recurrent stroke [91–93]. Recently, a specific ApoER2 mutation (apoER2 R952Q) has been shown to promote LRP1 release, contributing to increased hypercholesterolemia and accelerated atherosclerosis [94].

In the cancer scenario multiple studies have demonstrated that LRP1 expression is dysregulated across various cancer types, with its role varying depending on the tumor context. Reduced LRP1 expression has been linked to more aggressive phenotypes in melanoma [95], whereas overexpression is associated EphA2 glioblastoma invasion [96]. In prostate cancer, LRP1 expression is predominantly found in high Gleason grade tumors, which are the most aggressive [97], while in hepatocellular carcinoma, loss of LRP1 correlates with tumor progression [98]. In bladder cancer, LRP1 serves as an independent prognostic factor for overall survival, where high expression levels are associated with reduced therapeutic efficacy [99]. In pancreatic ductal adenocarcinomas (PDAC), LRP1 overexpression appears stage-dependent and correlates with poorer survival outcomes [100].

In *in vitro* studies performed in the tumor cell line PANC-1, aggregated LDL causes aberrant intracellular cholesteryl ester accumulation which is associated with an upregulation of cell proliferation rate. Interestingly, anti-LDL aggregation peptides, such as DP3, efficiently inhibit the formation of intracellular lipid droplets and cell proliferation [101].Intriguingly, in a subcutaneous PanO2 pancreatic cancer isograft model, deficiency of LRP1 in macrophages enhances macrophage infiltration into tumors, increases proinflammatory chemokine expression, and promotes tumor angiogenesis, suggesting a complex role for LRP1 in the pancreatic tumor microenvironment [102].

Functionally, LRP1 binding to certain ligands such as serpins and nexins supports epithelial-to-mesenchymal transition (EMT) and metastatic dissemination in breast tumor cells through autocrine signaling pathways that increase the expression of matrix metalloproteinases [103,104]. In this context, LRP1-mediated activation of FAK, ERK1/2, and Akt signaling pathways are involved in tumor cell proliferation, migration, and invasion [105,106] (summarized in Fig. 2, right panel). Together, these findings highlight the multifaceted role of LRP1 in cancer biology, influencing tumor growth, metastasis, and interaction with the microenvironment in a context-dependent manner.

Table 1
LRP1 – associated diseases and key ligands.

Pathology	Role of LRP1	Key Ligands Involved
Atherosclerosis	Mediates uptake of aggregated/modified lipoproteins; regulates inflammation, VSMC proliferation	Aggregated LDL, apoE, HSPs, MMPs, PDGF, TGF-β
Alzheimer's Disease	Regulates Aβ clearance across blood–brain barrier (BBB); influences neuroinflammation	Amyloid-β peptide, α2-macroglobulin, apoE, tPA
Cancer (various types)	Modulates cell migration, invasion, angiogenesis; interacts with ECM-degrading enzymes	uPA–uPAR, MMPs, PAI−1, tPA, α2-macroglobulin
Thrombosis / Coagulation disorders	Regulates fibrinolysis and clot degradation	tPA, uPA, PAI−1, α2-macroglobulin
Obesity and Insulin Resistance	Impacts adipocyte metabolism, insulin signaling, and inflammation	ApoE, serpins, TGF-β, integrins
Neuroinflammation / Multiple Sclerosis	Modulates immune cell migration across BBB; involved in remyelination	α2-macroglobulin, apoE, HSPs, proteases
Liver diseases (e.g., NAFLD/NASH)	Involved in lipid uptake and inflammation in hepatocytes	ApoE, lipoprotein remnants, serpins
Pulmonary Hypertension	Regulates vascular remodeling and cell proliferation	PDGF, TGF-β, integrins
Fibrosis (lung, liver, kidney)	Modulates TGF-β signaling, ECM turnover, and fibroblast activation	TGF-β, fibronectin, MMPs

8. Classical low-density lipoprotein receptor (LDLR) in cancer

In the context of cancer, not only are scavenger receptors—which are not downregulated by cholesterol—relevant, but the classical LDL receptor, which is typically downregulated in response to elevated cholesterol levels, also plays a significant role. Many cancer cells—including HER2-positive and triple-negative breast cancer cells—overexpress LDLR and elevated levels of circulating LDL have been associated with increased cholesterol uptake, which promotes cell

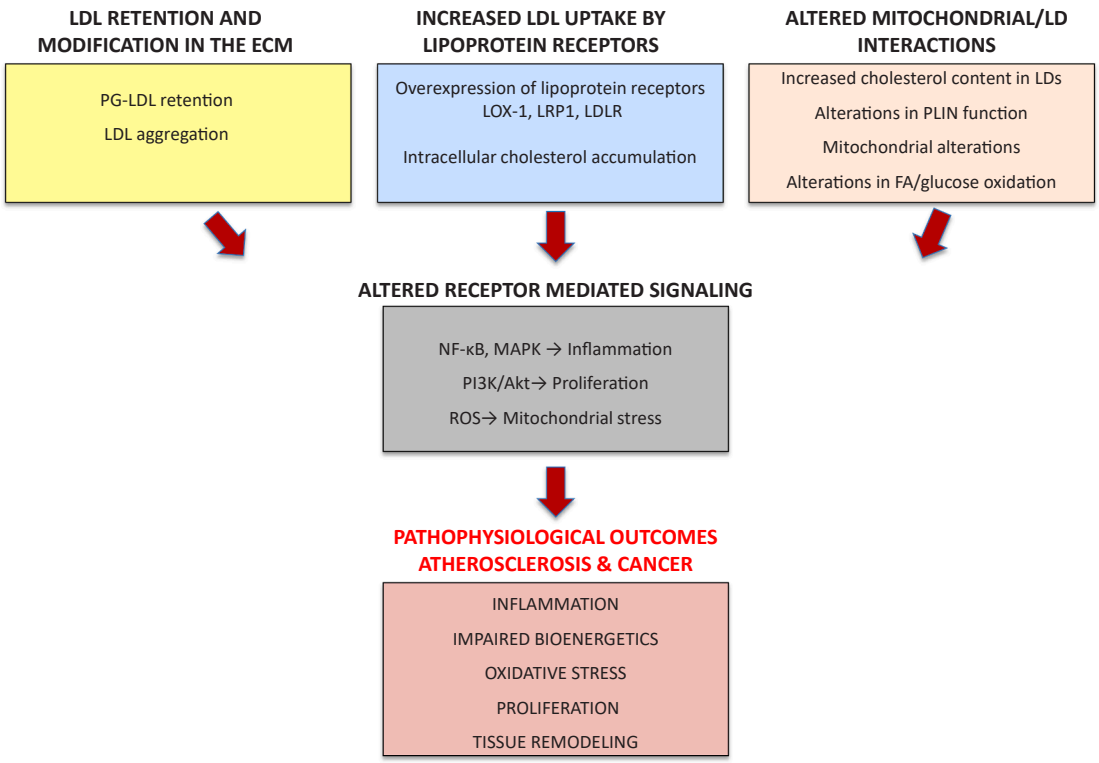

Fig. 1. Common LDL-related mechanisms in atherosclerosis and cancer. FA, fatty acids; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LOX-1, lectin-like oxidized low-density lipoprotein receptor 1; LRP1, low-density lipoprotein receptor-related protein 1; MAPK, mitogen activated protein kinase; NF-kB, nuclear factor kappa-light chain enhancer of activated B cells; PI3/AkT, phosphoinositide-3-kinase/protein kinase B; PG, proteoglicans; PLIN, perilipin; ROS, reactive oxygen species.

proliferation and tumor survival [107]. In addition to serving as a cholesterol source, LDL activates key proliferative signaling pathways, such as PI3K/Akt/mTOR and MAPK/p38, thereby enhancing proliferation, stress resistance, and metastatic potential [108,109].In colorectal cancer, LDL has been shown to induce oxidative stress through the generation of reactive oxygen species (ROS), which in turn activates the MAPK pathway, promoting hepatic migration and metastasis [110].

Following endocytosis via LDLR, LDL-derived cholesterol is trafficked through endosomes and lysosomes, a process regulated by NPC1 and NPC2 proteins. This cholesterol is then distributed to cellular membranes, signaling platforms, and organelles, supporting tumor growth and contributing to drug resistance [111].

9. Lipid droplet (LD)/mitochondria interactions are crucially involved in atherosclerosis and cancer progression

It is well known the crucial role of certain proteins in protein/lipid physical connections that crucially modulate LD/mitochondrial interactions. Key regulatory proteins involved include perilipins (PLIN), mitochondrial outer membrane proteins (MIGA) and VAMP-associated proteins (VAPs), and OSBP-related proteins (ORP) [112–115]. In particular, perilipins are a family of LD-associated proteins that regulate lipid storage and mobilization in cells. They coat the surface of LDs, controlling access of lipases to stored lipids. Among them, PLIN5 is highly expressed in oxidative tissues (like heart and muscle) and regulates lipid metabolism and mitochondrial function. PLIN3, also known as TIP47, is more ubiquitously expressed and involved in early LD formation, trafficking, and lipolysis.These proteins facilitate the attachment of LDs to the mitochondrial membrane, creating an optimal environment for lipid exchange, and adaptation to various nutritional conditions.

The dysregulation of LD/mitochondria interactions lead to mitochondrial dysfunction and metabolic disorders, most of them associated to increased lipotoxicity [116]. LD/mitochondria interactions are essential for the transport of fatty acids to mitochondria, where they undergo β-oxidation to produce ATP, crucial for maintaining cellular energy balance and overall homeostasis. Moreover, it plays an important role in regulating other physiological processes, such as lipid metabolism and redox balance [117,118]. In terms of lipid metabolism, disruptions in the LD-mitochondria connection can affect the synthesis, degradation, and storage of fatty acids, phospholipids, and cholesterol among other processes. Such impairments are linked to several diseases, including diabetes, cardiovascular diseases, obesity, and non-alcoholic fatty liver disease (NAFLD) [119–121].

In the cardiovascular arena, PLINs are key protein regulators of LD metabolism, especially in adipocytes [122]. Their expression and isoforms are associated with metabolic disorders such as obesity and diabetes. [123,124]. PLIN1 primarily controls lipolysis and lipid storage, while PLIN5 anchors LDs to mitochondria, enabling efficient transfer of fatty acids for oxidation [125]. Drevinge et al. explored PLIN5's role in cardiac lipid metabolism and its influence on cardiac function. In PLIN5-/- mice, cardiac TG content was drastically reduced, though this was compensated by increased glucose uptake, leading to enhanced glucose oxidation, greater ROS production, and decreased cardiac function with age [126]. These results demonstrated that PLIN5 is critical for maintaining LDs in the heart, preventing excessive fatty acid oxidation and reducing oxidative stress. Coherently, PLIN5 deficiency in the myocardium led to severe reductions in cardiac function and increased mortality. In humans, a SNP (rs884164) that results in reduced PLIN5 levels is associated with diminished cardiac function following myocardial ischemia [125]. However, PLIN5 overexpression has been linked to cardiac steatosis and a greater propensity for cardiac hypertrophy [127,128]. Acetyl-CoA synthetase FATP4, identified in murine and human cells, serves as the primary transport channel for fatty acids from LDs to mitochondria for oxidation through its interaction with PLIN5 [129].

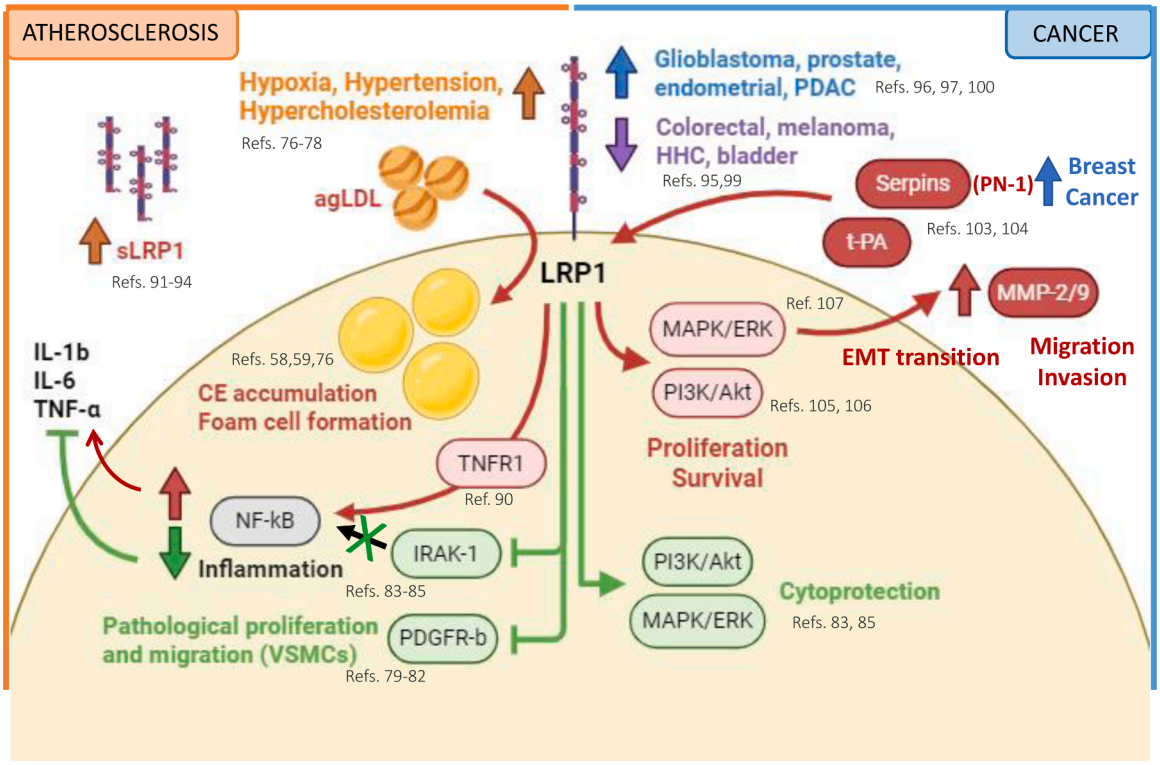

Fig. 2. Comparative diagram summarizing LRP1 signaling pathways involved in cardiovascular and cancer-related pathologies. agLDL, aggregated LDL; CE, cholesteryl esters; EMT, epitelial-mesenchimal transition; ERK, extracellular signal-regulated kinase; HCC, hepatocellular carcinoma; IL, interleukin; IRAK-1, interleukin-1 receptor associated kinase 1; LRP1, low-density lipoprotein receptor-related protein 1; MAPK, mitogen activated protein kinase; MMP, metaloproteinase; NF-kB, nuclear factor kappa-light chain enhancer of activated B cells; PDGFR, platelet derived growth factor receptor; PDAC, pancreatic ductal adenocarcinoma; PI3/AkT, phosphoinositide-3-kinase/protein kinase B; sLRP1, soluble low-density lipoprotein receptor-related 1; TNFR1, transforming necrosis factor receptor 1; t-PA, tissue plasminogen activator; VSMC, vascular smooth muscle cells.

Recent studies highlight the crucial role of neutral lipid composition of LD, an in particular of cholesteryl esters (CEs), as potential regulator of mitochondria/LD interactions. A recent study using a rabbit model of hypercholesterolemia reported for the first time that LDs with a high CE content exhibit reduced interaction with mitochondria, as indicated by a smaller portion of the mitochondrial perimeter being involved in LD–mitochondria contacts [130]. Moreover, this study shows that CEs carried by lipoproteins reach the mitochondria and drive mitochondrial CE accumulation. The CE loading of both LD and mitochondria could be involved in the reduction of CII/CIV ratio of the electron transport chain in the heart of this rabbit model [130]. These findings highlighting the crucial role of CE uptake from CE-enriched lipoproteins as a potential underlying mechanism for cardiac dysfunction. Treatment of rabbits with anti-P3 (based on CR9 domain of cluster II in LRP1) Abs reduces CE accumulation in LDs, restores mitochondrial architecture, and enhances bioenergetically efficient interactions between mitochondria and LDs, improving mitochondrial respiration in the heart [130]. Anti-P3 Abs also promote the morphologic expansion of LDs mainly composed by TGs, inducing lateral LD-mitochondria interactions, bioenergetically efficient, in the heart (Fig. 3). These interactions are characteristic of peridroplet mitochondria (PDM) contacts, and have been previously reported to be bioenergetically favorable in adipose and hepatic tissues [131–133]. These results hightlight the potential of new therapies that inhibit mitochondrial CE accumulation to improve the management of cardiac dysfunction.

A pioneering and outstanding study described how vesicles containing LDL and LDLR fuse with the outer mitochondrial membrane (OMM), facilitating the entry of LDL-cholesterol into the mitochondria through a process mediated by the LDLR. Two proteins located at the OMM—phospholipase D6 and CDGSH iron-sulfur domain-containing protein 2—are essential for the fusion of LDL particles with mitochondria. CDGSH iron-sulfur domain-containing protein 2 binds to the cytosolic tail of LDLR and connects LDLR-containing vesicles to the mitochondria, while phospholipase D6 hydrolyzes cardiolipin from the OMM into phosphatidic acid, a process that facilitates the degradation of LDLR [134]. The study by Zhou *et al.* combined with other previously described pathways—such as cholesterol transport from HDLs to the ER via the plasma membrane Aster-B pathway and subsequently to the mitochondria [135]—support the idea that cholesteryl esters can accumulate in mitochondria under certain conditions.

Alterations in the expression and function of perilipins underlie profound changes in the interactions between LDs and mitochondria in tumor cells, leading to severe metabolic abnormalities characteristic of cancer [136,137]. In prostate cancer, low levels of PLIN3 promote resistance to docetaxel through the activation of autophagy [138]. PLIN3 overexpression has also been associated with increased LD accumulation, immunosuppression, and metastatic potential in oral squamous cell carcinoma [139]. In ovarian tumor cells, demethylation of PLIN5 inhibits proliferation, migration, and invasion of ovarian cancer cells while promoting apoptosis [140].

Investigations into PLIN1 and PLIN5 polymorphisms have provided insights into the specific contributions of these perilipins to cancer progression, as well as to certain pathologies associated with or resulting from cancer. Mutations in PLIN5 were found to be significantly and independently associated with overall survival in patients with gastric cancer. Specifically, patients with PLIN5 mutations showed a better prognosis [141]. The single nucleotide polymorphism (SNP) 13041 A>G has shown promise as a molecular predictor for malnutrition, particularly related to severe fat mass loss, in patients with head and neck cancer (HNC). Compared to traditional subjective assessment tools like the Subjective Global Assessment (SGA) and Nutritional Risk Screening 2002 (NRS-2002), evaluating this SNP may provide greater

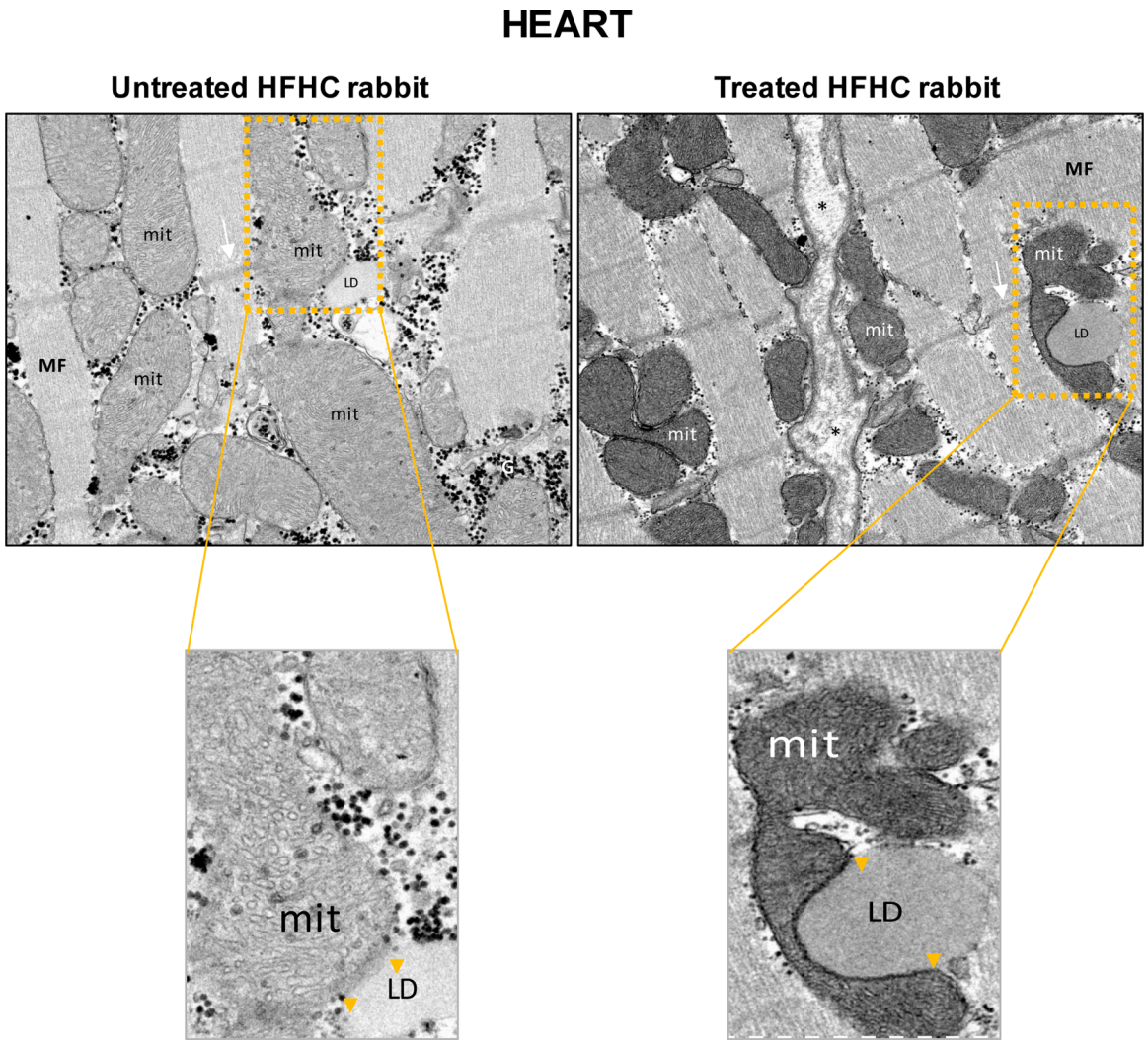

Fig. 3. Anti-P3 antibody treatment enhances lateral mitochondria–lipid droplet (LD) interactions in cardiomyocytes of hypercholesterolemic (HFHC) rabbits. Representative transmission electron microscopy (TEM) images of cardiomyocyte ultrastructure from the hearts of untreated (left panels) and anti-P3–treated (right panel) HFHC rabbits. Inset images highlight clear differences in the electrodensity and morphology of both mitochondria (mit) and lipid droplets (LDs) between the two groups. Treated rabbits exhibited increased electrodensity in both mitochondria and LDs compared to untreated controls. Moreover, the untreated group displayed greater mitochondrial vacuolization and smaller LDs. These morphological and biophysical changes reflect the reduced cholesteryl ester (CE) content observed in the LDs and mitochondria of treated animals. Orange dotted rectangles indicate examples of enhanced lateral and extended mitochondria–LD contacts in treated hearts, in contrast to the shorter, apical contacts seen in untreated hearts.

accuracy in identifying patients at risk. Notably, men with the AA genotype of SNP 13041 A>G prior to radiotherapy (RTH) are more likely to experience significant fat mass loss, suggesting that early nutritional intervention and supportive care targeted at preserving body and fat mass could improve treatment outcomes. Incorporating genetic screening for this SNP could therefore enhance personalized nutritional management in HNC patients [142].

Since reprogrammed lipid metabolism is a recognized hallmark of cancer and obesity is a known risk factor for cancer and other comorbidities, the modulation of perilipins (PLINs) presents promising opportunities to improve current treatments or develop new therapeutic strategies. Although PLINs have not yet been directly targeted by pharmacological interventions, several existing drugs can influence their activity. In breast cancer, genetic alterations in PLIN genes are rare, with amplification being the most frequent change. Expression patterns vary among PLIN family members and breast cancer subtypes: PLIN3 is generally upregulated, especially in luminal A and B subtypes along with PLIN1, PLIN4, and PLIN5, while PLIN2 is elevated in HER2-positive and basal-like subgroups. Importantly, high PLIN1 expression correlates with better overall survival, whereas PLIN2 overexpression predicts poorer outcomes. This evidence highlights the involvement of PLINs in diseases related to lipid metabolism dysregulation and supports their potential as therapeutic targets in cancer and obesity [143,144].

LDs play a multifaceted role in tumor development and progression, contributing to key cancer hallmarks such as altered energy metabolism and increased pro-inflammatory signaling by enhancing PGE2 synthesis [145]. Arachidonic acid, stored in esterified form within lipid bodies, serves as a precursor for prostaglandins and leukotrienes, making lipid bodies functionally active organelles that compartmentalize eicosanoid-forming enzymes and generate lipid mediators like PGE2. Additionally, the alteration of oncogenic signaling pathways such as PI3K/Akt, along with enzymes like FAS or ACC, leads to increased lipogenesis in cancer cells. The Inhibition of these enzymes reduces tumor cell proliferation and induce apoptosis [146]. In the early stages of carcinogenesis, increased lipogenesis leads to the progression of tumor and pre-tumor lesions. The increased lipid synthesis, accompanied by alterations in lipid-related signaling pathways, helps cancer cells meet their energy needs, maintain structural integrity, and resist oxidative stress [147]. Enhanced lipid metabolism promotes cancer progression and survival by increasing FA synthesis and LD

accumulation, either through improved transport or de novo lipogenesis (DNL), to meet energy demands and combat ROS [148]. A study revealed that DNL is important in colorectal cancer cells, where drug-tolerant (DTP) cells show increased lipogenesis, leading to LD accumulation. LD accumulation is a characteristic feature of many tumor types and correlates with tumor aggressiveness, clinical stage, and tissue differentiation [149].

CRediT authorship contribution statement

Àngels Solanelles Curcó (A.S-C.): Conceptualization, Writing – original draft, Writing – review & editing. **Eduardo Garcia (EG):** Conceptualization, Writing – original draft, Writing – review & editing. **Anna Polishchuk (AP):** Conceptualization, Writing – original draft, Writing – review & editing. **Maria Teresa La Chica Lhoëst (MTLL):** Writing – original draft, Figure preparation. **Vicenta Llorente Cortés (VLl-C):** Writing– review.

Declaration of Competing Interest

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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