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INVITED REVIEW

Lipoprotein receptor signalling in atherosclerosis

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Abstract

The founding member of the lipoprotein receptor family, low-density lipoprotein receptor (LDLR) plays a major role in the atherogenesis through the receptor-mediated endocytosis of LDL particles and regulation of cholesterol homeostasis. Since the discovery of the LDLR, many other structurally and functionally related receptors have been identified, which include low-density lipoprotein receptor-related protein (LRP)1, LRP5, LRP6, very low-density lipoprotein receptor, and apolipoprotein E receptor 2. The scavenger receptor family members, on the other hand, constitute a family of pattern recognition proteins that are structurally diverse and recognize a wide array of ligands, including oxidized LDL. Among these are cluster of differentiation 36, scavenger receptor class B type I and lectin-like oxidized low-density lipoprotein receptor-1. In addition to the initially assigned role as a mediator of the uptake of macromolecules into the cell, a large number of studies in cultured cells and in *in vivo* animal models have revealed that these lipoprotein receptors participate in signal transduction to modulate cellular functions. This review highlights the signalling pathways by which these receptors influence the process of atherosclerosis development, focusing on their roles in the vascular cells, such as macrophages, endothelial cells, smooth muscle cells, and platelets. Human genetics of the receptors is also discussed to further provide the relevance to cardiovascular disease risks in humans. Further knowledge of the vascular biology of the lipoprotein receptors and their ligands will potentially enhance our ability to harness the mechanism to develop novel prophylactic and therapeutic strategies against cardiovascular diseases.

Keywords Atherosclerosis • Cardiovascular disease • Lipoprotein • LDL receptors • Scavenger receptors • Endothelium • Vascular smooth muscle cells • Macrophages • Platelets

1. Introduction

Atherosclerosis is the underlying process of cardiovascular and cerebrovascular diseases, which are leading causes of mortality and morbidity worldwide.[1] It is a chronic vascular disorder of large and medium-sized arteries that progresses from fatty streaks in the early stage to advanced lesions with complicated and unstable plaques prone to rupture resulting in athero-thrombotic events.[2–4] Researches encompassing several decades have established that circulating lipoproteins and their receptors play a major role in atherogenesis. The Nobel Prize winning work by Goldstein and Brown revealed for the first time that the low-density lipoprotein (LDL) receptor regulates cholesterol homeostasis by the receptor-mediated endocytosis of LDL particles, and that the mutations in the LDL receptor gene cause elevated serum LDL cholesterol and coronary atherosclerosis in familial hypercholesterolaemia patients.[5] Subsequent success of cholesterol-lowering statins and a discovery of the scavenger receptors that bind to modified LDL and contribute to foam cell formation in the atheroma further expanded the critical importance of lipoproteins and their receptors in atherogenesis.[5,6] Although elevations of circulating cholesterol carrying lipoproteins, stemming from excessive dietary lipid intake and inadequate removal of cholesterol in the liver, play a key causal role in atherosclerosis, it has become increasingly apparent that dysfunction of vascular cells also contributes to atherogenesis. These cells include monocytes/macrophages, platelets, blood and lymphatic endothelium, and vascular smooth muscle cells (SMCs).[2] During the decades-long process, diverse events occur in the vascular wall, including endothelial dysfunction, leucocyte/monocyte adhesion and infiltration, lipid-laden foam cell formation, abnormal vascular SMC growth, and platelet activation.[2,7] Manifestation of endothelial dysfunction is a relatively early occurrence that precedes clinical complications of atherosclerosis.[8,9] Following activation of the innate immunity response by proinflammatory cytokines and oxidized lipids, endothelial cells upregulate adhesion molecules, provoking leucocyte-endothelial cell adhesion, and recruitment of inflammatory cells into the lesions.[10,11] Upon infiltration into the arterial wall, these inflammatory monocytes/macrophages in turn generate oxidative stress and accumulate lipids,

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contributing to perpetuation of proinflammatory processes and foam cell formation.[12] In addition, there is an increasing recognition for a complex role of vascular SMCs. Aberrant SMC proliferation, infiltration, and transition to non-contractile phenotypes likely contribute to plaque progression.[2,13] In the later stage, SMCs produce the extracellular matrix which provides a stable fibrous cap, preventing a rupture of plaques.[13] The plaque rupture further leads to exposure of prothrombotic factors to activate platelets and thrombus formation, causing major cardiovascular episodes such as myocardial infarction (MI) and stroke.

Since the early discovery of the LDL receptor, many other related receptors that bind to native or modified lipoproteins have been identified. In addition to the initially assigned role as cholesterol transporters, these LDL receptor-related proteins have a wide range of additional functions that influence diverse physiological and pathological processes, including embryonic development, inflammation, haemodynamics, thrombosis, neointima hyperplasia, and atherosclerosis.[14–18] This review will focus on the LDL-receptor family members, low-density lipoprotein receptor-related protein (LRP)1, LRP5, LRP6, apolipoprotein E receptor 2 (ApoER2 or LRP8), very-low density lipoprotein receptor (VLDLR), and the scavenger receptor family members, cluster of differentiation 36 (CD36), scavenger receptor class B type I (SR-BI), and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1). It will provide a concise view on how these lipoprotein receptors influence atherosclerosis progression through a network of signal transduction pathways in the vascular cells. There are multiple additional receptors and binding proteins for lipoproteins and lipids that also play key roles in atherosclerosis and cardiovascular diseases. The scavenger receptor-A (SR-A), also known as the macrophage scavenger receptor or CD204, has major functions in lipid metabolism and atherogenesis through its interaction with a diverse array of ligands, including oxidized LDL and advanced glycation end-product modified proteins.[5,6,19–21] Various proteoglycans also bind to LDL, and they are abundantly expressed in human atherosclerotic lesions.[22,23] Both chondroitin sulfate proteoglycans and heparin sulfate proteoglycans, including versican and perlecan, have been shown to contribute to development of atherosclerosis in hyperlipidaemic mouse models.[24–26] A group of receptors that binds to lipid molecules such as sphingosines and ceramides also mediates cellular signalling to influence the process of atherogenesis and other vascular disorders.[27–30] A number of excellent reviews provide the updates on functions of these molecules related to atherosclerosis.

2. Low-density lipoprotein receptor family members

The LDL receptor family consists of multiple structurally related transmembrane proteins that participate in a wide range of biological processes, including lipid metabolism, brain development, nutrients delivery, thrombosis, and atherogenesis. These receptors share common structural features, with a large extracellular domain with ligand-binding motifs, a single transmembrane domain, and a cytoplasmic tail with multiple adaptor-binding sites[16] (*Figure 1*, *Table 1*). Whereas the role of the LDL receptors is likely limited to lipid metabolism, growing evidence indicates that the other members of the family have additional functions as signal transducing receptors.

2.1 Lipoprotein receptor-related protein 1

The low-density lipoprotein receptor-related protein 1 (LRP1) consists of a 515 kDa heavy chain containing four clusters of ligand binding domains and a non-covalently associated 85 kDa light chain containing EGF-like repeats, YWTD β-propeller domains, a transmembrane, and intracellular cytoplasmic domain (ICD)[16,71] (*Figure 1*). LRP1 was initially cloned as a protein with multiple LDL receptor type A repeats, which mediates chylomicron remnant uptake.[72,73] It was also identified as a receptor in the liver responsible for catabolism of α2-macroglobulin-proteinase complexes.[74,75] To date, LRP1 is known to bind to more than 40 distinct ligands that are structurally unrelated.

LRP1 is expressed in multiple cell types including hepatocytes, vascular SMCs, neurons, macrophages, fibroblasts, and endothelial cells.[71] LRP1 in the liver cooperates with the LDL receptor in the endocytosis and clearance of cholesterol-rich chylomicron remnants from the circulation. However, the large number and functionally diverse ligands for LRP1 and the embryonic lethality in global LRP1$^{-/-}$ mice suggest that LRP1 is essential in various physiological and pathological processes in addition to lipid metabolism.[31–34,46,47,76–83] First, LRP1 acts as an endocytic receptor for extracellular ligands, which escorts the ligands to lysosomes for degradation. Several extracellular molecules involved in signalling pathways have been identified to bind to LRP1, and LRP1 modulates these pathways by facilitating the removal of the ligand from cell surface. Second, in some cell types, upon binding to a ligand LRP1 initiates a signal transduction through the recruitment of adaptor proteins to its ICD of the receptor. For example, tissue-type plasminogen activator stimulates the N-methyl-D-aspartate receptor cascade via an LRP1-mediated interaction with the adaptor protein postsynaptic density protein 95.[84] Third, LRP1 is known to undergo a regulated intramembrane proteolysis in which shedding of the LRP1 generates a substrate for γ-secretase-mediated cleavage, releasing the ICD of LRP1. The ICD domain then translocates to the nucleus to modulate gene expression.[85,86] Furthermore, genome-wide association studies (GWAS) in humans have revealed that LRP1 gene represents a susceptibility locus for elevated plasma lipid, coronary heart disease, and abdominal aortic aneurysms.[87–89]

2.1.1 SMC LRP1

Under pathological conditions, SMCs are induced to proliferate and migrate, contributing to the development of atherosclerosis and restenosis.[2,13] Platelet-derived growth factor (PDGF) is a potent mitogen for SMCs and numerous studies have revealed a critical role for this pathway in atherosclerosis and neointima formation.[90–93] PDGF binding to PDGF receptor β (PDGFRβ), a tyrosine kinase receptor, initiates a signalling pathway that promotes SMC growth and migration, and LRP1 has been shown to potently suppress the process.[31–33,35–37] This was initially demonstrated by Boucher *et al.* using mice with SMC-specific deletion of LRP1 (smLRP1$^{-/-}$) on hypercholesterolaemic LDLR$^{-/-}$ background.[31] The study found that smLRP1$^{-/-}$;LDLR$^{-/-}$ mice were more susceptible to atherosclerosis compare to LDLR$^{-/-}$ mice, and that these mice showed upregulation of PDGFRβ expression and the downstream signalling, leading to excessive proliferation of vascular SMCs and markedly enlarged aortas. These effects were inhibited by a treatment of the mice with Gleevec (Imatinib Mesylate), an inhibitor of tyrosine kinases including the PDGFRβ. These studies revealed that LRP1 in SMCs plays a major role in protecting the integrity of the vascular wall and reducing atherosclerosis by suppressing PDGFRβ activation. Mechanistically, LRP1 modulates PDGF signalling through recruitment of various adaptor molecules to its ICD. Upon activation of PDGFRβ, LRP1 is tyrosine phosphorylated at NPxY motif within the ICD, which creates a docking site for phosphotyrosine-binding domain and Src homology 2 domain

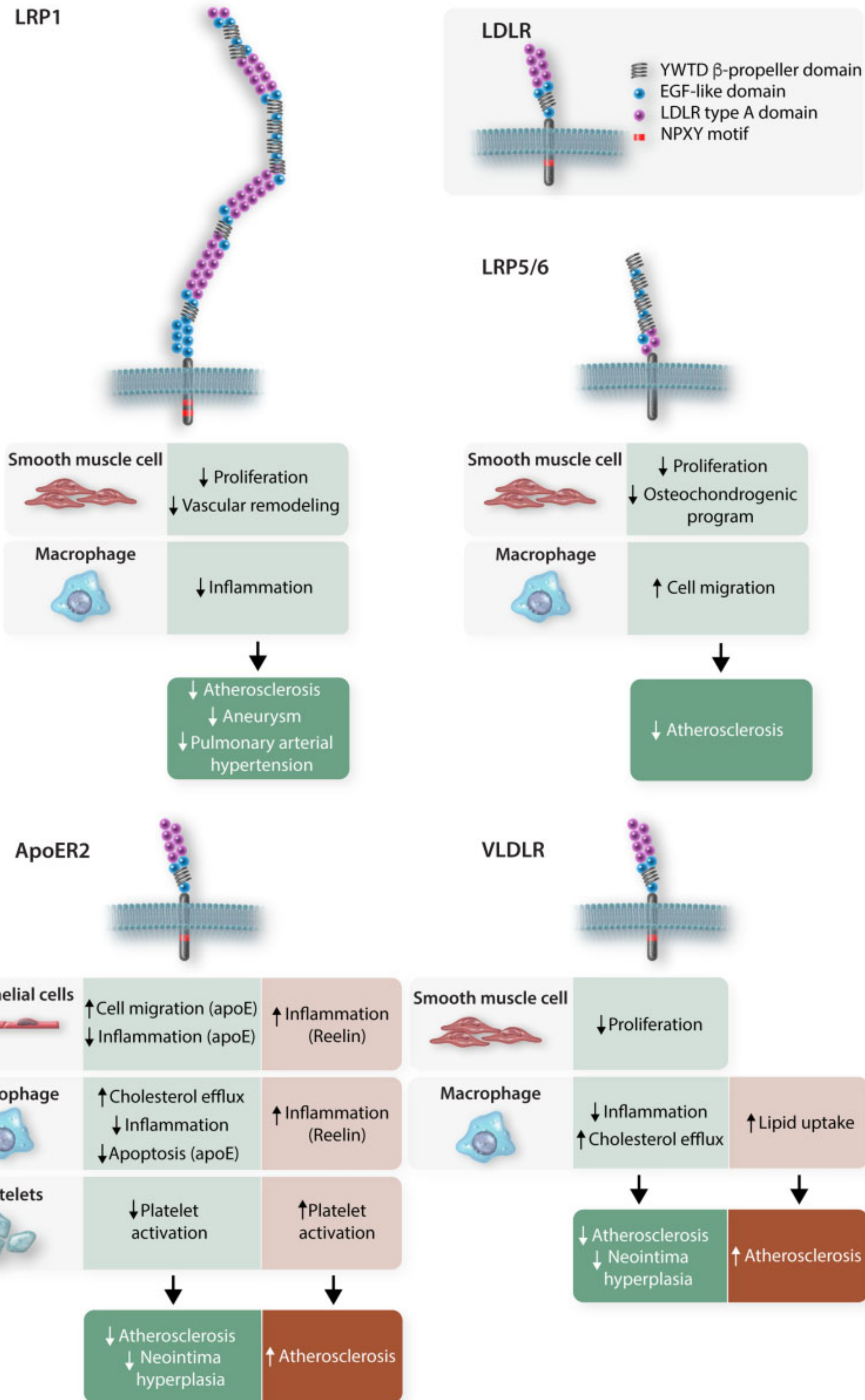

Figure 1 Structure and function of LDL receptor family members, LRP1, LRP5/6, ApoER2, and VLDLR in atherosclerosis. LRP1, LRP5/6, ApoER2, and VLDLR belong to the LDL receptor family that shares common structural features, with a large extracellular domain with ligand-binding motifs, EGF-like repeats, and YWTD β-propeller domains, a single transmembrane domain, and a cytoplasmic tail with multiple adaptor-binding sites. LRP1 in vascular smooth muscle cells and macrophages shows a potent protective role against atherosclerosis. LRP5 and LRP6, the coreceptors for the Wnts signalling receptor Frizzled, also exert anti-atherogenic actions in smooth muscle cells and macrophages. ApoER2 and VLDLR, which does not play a major role in systemic lipid homeostasis, have both anti-and pro-atherosclerotic actions. ApoE binding to ApoER2 in vascular cells leads to decreased inflammation and platelet activation, whereas reelin binding to the receptor causes opposite effects.

Table 1 **Anti- and proatherogenic functions of the LDL receptor family members**

	Lipoprotein receptor	Antiatherogenic functions			Proatherogenic functions			References
		Cell type	Cellular function	Mechanism	Cell type	Cellular function	Mechanism	
LDLR family members	LRP1	SMC	Proliferation↓	SHP-2-PDGF signalling↓	SMC			31–45
				TGFβ signalling ↓				
			Phenotype Switching↓	Protenases ↓				
				Connective tissue growth factor ↓				
		Macrophages	Inflammation ↓	Inflammatory genes ↓	Macrophages			46–49
	LRP6	SMC	Proliferation ↓	PDGF-ERK1/2-JAK1/STAT1 ↓	SMC			50–52
				PDGFR degradation ↑				
			Osteochondrogenic program ↓	Non canonical Wnt signalling↓				
	LRP5	Macrophages	Cell migration ↑	Wnt signalling ↑	Macrophages			53,54
	ApoER2	Endothelial cells	Inflammation ↓	eNOS activity (apoE) ↑	Endothelial cells	Inflammation ↑	eNOS activity (Reelin) ↓	55,56
			Cell migration↑					
		Macrophages	Apoptosis ↓	Akt ↑, p53 ↓	Macrophages			57–59
			Cholesterol efflux↑	PI3 kinase/PKC/Sp1-ABCA1 ↑				
			Inflammation ↓	Src/p38 MAPK ↑, NF-kB ↓				
		Platelets	Activation ↓	Agonist actions ↓	Platelets	Activation ↑	Inhibitory ApoE3 actions ↓	60–64
	VLDLR	SMC	Proliferation/migration ↓?		SMC			65–69
		Macrophages	Cholesterol efflux↑	ABCA1 ↑	Macrophages	Lipid uptake ↑?		58,65,69,70
			Inflammation ↓	Src/p38 MAPK ↑, NF-kB ↓				

containing adaptor proteins.[36,38,39] One such protein is SHP-2, a tyrosine phosphatase that is required for activation of the extracellular signal-regulated kinase (ERK) pathway by PDGFR.[94] SHP-2 binds with high affinity to the phosphorylated form of the LRP1-ICD and its association with LRP1 seems to attenuate PDGF-mediated signalling events.[39] Another study found that LRP1-ICD can associate with c-Cbl, a ubiquitin E3-ligase that regulates turnover of receptor tyrosine kinases such as PDGFRβ, and that LRP1 deficiency in mouse fibroblasts results in an accelerated turnover of PDGFRβ, suggesting a role of LRP1 as an anchor protein that controls the traffic of PDGFRβ from the cell surface to intracellular compartments.[40] However, whether or how these molecular mechanisms contribute to the anti-atheroprotective action of LRP1 *in vivo* is yet to be elucidated.

In addition to atherogenesis, studies in mice with genetic modifications revealed that LRP1 expressed in SMCs plays a protective role against aneurysm formation.[31,33–35] In healthy arteries, SMCs maintain a contractile phenotype, which allows them to contract in response to changes in vascular pulse pressure. Disruptions of SMC contractile function, which switch the cells to a synthetic phenotype, are known to predispose the aorta to aneurysms.[95,96] SmLRP1$^{-/-}$ mice have exaggerated aortic dilatation that is attributed to extensive disruption of elastic lamina with numerous breaks.[31,34] Histological analyses of the aortic vessel wall demonstrated that SMCs from smLRP1$^{-/-}$ mice have appearance of a synthetic phenotype, containing more synthetic organelles and fewer focal adhesions, compared to those from control mice.[34] This effect is unlikely to arise from excessive PDGF signalling, as the PDGF signalling pathway is not upregulated in smLRP1$^{-/-}$ mice in the absence of LDLR deficiency.[34] Multiple potential mechanisms by which LRP1 regulates SMC phenotype-switching are proposed. First, the extensive disruption of the elastic lamina in smLRP1$^{-/-}$ mice seems to be resulted from excessive expression of several proteases. One of these proteases, high-temperature requirement factor A1 (HtrA1), is an LRP1 ligand and it was detected in excess in the aortic wall of smLRP1$^{-/-}$ mice.[34] In addition to HtrA1, increased expression of metalloproteinases, including MMP-9, MMP-2 and membrane associated type 1-matrix metalloproteinase, was also found in the vessel wall of smLRP1$^{-/-}$ mice.[41,42] Degradation of extracellular matrix proteins and elastic fibres by these proteases may contribute to the development of aneurysms in the mouse model. Secondly, an increased matrix deposition in the vessel walls observed in smLRP1$^{-/-}$ mice may be due to excessive connective tissue growth factor accumulation.[31,32,34] Connective tissue growth factor is a secreted matricellular protein that is a key mediator of fibrosis and plays an important role in vascular development.[43] Together, these studies highlight the important role for LRP1 in vascular homeostasis, in which it protects the integrity and function of elastic lamina by regulating protease activity, as well as the pathways involved in vascular extracellular matrix deposition. A small study conducted on human tissues revealed that LRP1 expression was significantly attenuated in abdominal aortic tissues with aneurysms, compared with normal aortic tissue.[44,71]

In addition to atherogenesis and aneurysm, LRP1 in SMCs is also implicated in development of pulmonary arterial hypertension (PAH) through modulation of TGFβ signalling that is known to regulate vascular remodelling.[97–99] PAH is characterized by remodelling of pulmonary arterioles, leading to increased vascular resistance, right ventricular hypertrophy, and heart failure. SMC proliferation, deposition of extracellular matrix, and vascular remodelling are hallmarks of PAH. A recent study by Calvier *et al.* has demonstrated that smLRP1$^{-/-}$ mice display exaggerated TGFβ1 signalling in SMCs and that these mice develop spontaneous PAH.[45] Earlier studies *in vivo* and in cultured cells showed that LRP1 directly interacts with TGFβ, and that the lipoprotein receptor is required for growth inhibition by TGFβ.[33,81,100] Furthermore, in pulmonary artery SMCs derived from PAH patients LRP1 protein expression was downregulated, which was associated with enhanced TGFβ1 signalling.[45]

2.1.2 Macrophage LRP1

Lipoprotein receptors in macrophages are generally implicated in promotion of foam cell formation and vascular inflammation.[2,10] However, macrophage LRP1 has been shown to exert atheroprotective effects. Hu *et al.*[46] reported that mice with selective deletion of LRP1 in macrophages (macLRP1$^{-/-}$) on apoE$^{-/-}$ and LDLR$^{-/-}$ background display an increase in total atherosclerotic lesion area with a higher prevalence of advanced lesions. Another study also found that LDLR$^{-/-}$ mice receiving bone marrow transplantation from macLRP1$^{-/-}$ mice fed on high-fat diet have an increased lipid deposition and macrophage infiltration in the aorta compared to those receiving control bone marrow.[47,48] Macrophages from macLRP1$^{-/-}$ mice showed an elevated production of proinflammatory markers, such as macrophage chemoattractant protein-1 (MCP1) and tumour necrosis factor α (TNFα).[47,48] Increased production of TNFα by lipopolysaccharides (LPS) treatment was also observed in macrophages isolated from mice carrying a knock-in mutation in the LRP1-ICD, revealing that interaction with adaptor molecules via LRP1-ICD may be important for this activity.[49] A potential mechanism in macrophages by which LRP1 influences the inflammatory response may be through transcriptional regulation of inflammatory genes. In cultured macrophages, it has been shown that inflammatory mediators, such as LPS and interferon-γ, can induce the LRP1 shedding and release of LRP1-ICD from the plasma membrane, which translocates to the nucleus where it suppresses activation of the genes responsive to inflammatory stimuli.[85,86]

These studies in cultured cells and in genetically modified mice collectively point to a strong protective role of LRP1 in SMCs and macrophages against development of multiple vascular disorders.

2.2 LRP5 and LRP6

LRP5 and LRP6 are closely related type I membrane proteins, and their extracellular domains are comprised of LDLR type A repeats, EGF-like domain, and YWTD-type β-propeller domain[101,102] (*Figure 1*). These receptors act as coreceptors for the frizzled, the seven-transmembrane receptors for Wnts.[103,104] The Wnt signalling pathway is a ubiquitous signalling cascade that regulates a wide range of physiologic processes, and aberrant Wnt signalling has been implicated in cancer, developmental disorders, pulmonary diseases, renal disorders, and cardiovascular diseases in humans.[105–107] In the canonical Wnt pathway, Wnt ligands bind to the frizzled receptor and LRP5/6 coreceptors, resulting in formation of multiprotein complexes in the plasma membrane which contain axin and GSK3β.[108–111] The complex formation promotes stabilization of β-catenin and its translocation into the nucleus, where it regulates transcription of various genes.[53,109,110,112,113]

2.2.1 Lipoprotein receptor-related protein 6

LRP6 gene maps to human chromosome 12p11-p13, which translates to the transmembrane protein containing 1613 amino acid residues.[101] Importance of LRP6 in atherogenesis came to light by a discovery of a missense mutation in LRP6 gene in humans.[114] The index patient presented with MI at 48 years of age with a history of hypertension, hyperlipidaemia, and diabetes without obesity. The mutation resulted in

substitution of cysteine for arginine at the amino acid 611 in the second EGF-like domain (LRP6-R611C), and it cosegregated with the metabolic phenotypes. The crystal structure of LRP6 revealed that this substitution disrupts a salt bridge between arginine at 611 and glutamate at 477 in the E2 propeller domain, altering the relative orientation between YWTD and the EGF domains.[115] Through screening of individuals with early onset familial coronary artery disease and metabolic syndrome, three additional mutations in LRP6 gene were identified, which cosegregated with the metabolic traits in the kindred of the affected subjects.[116] All three mutations reside in the second propeller domain responsible for ligand binding. Patients with the LRP6-R611C mutation had extremely high levels of plasma cholesterol,[114] and common variants in LRP6 gene have also been linked to a mild increase of plasma LDL cholesterol in the general population.[117] Thus the function of LRP6 in LDL clearance was investigated in cells expressing wild-type LRP6 or LRP6-R611C mutant.[118] Overexpression of the mutant receptor resulted in lower LDL uptake, compared to the wild-type receptor. Similarly LDL uptake in lymphocytes isolated from heterozygote R611C mutation carriers was significantly lower compared to those from unaffected family members.[118] In cells expressing wild-type LRP6, the receptor was mainly localized at the cell surface and early endocytic compartments. In contrast, LRP6-R611C mutant cells had reduced cell surface expression with marked accumulation of the receptor in late endocytic compartments.[118] Further examinations also revealed a lower rate of LDL/apoB dissociation from LRP6-R611C at an acidic pH, compared to wild-type receptor. These studies suggest that LRP6 may serve as a receptor for LDL endocytosis for LDL clearance in the liver.

In addition to its role in the lipid metabolism, an athero-protective function of LRP6 has been demonstrated in SMCs through suppression of PDGF signalling. In human atherosclerotic coronary arteries, colocalization of LRP6 expression with PDGFRβ was detected in the subintimal layers.[50] In cultured SMCs, the antiproliferative effect of LRP6 was associated with decrease in PDGF-induced activation of ERK1/2 and JAK1/STAT1 pathway, and these inhibitory effects on PDGF signalling were not observed in SMCs expressing LRP6-R611C mutant.[50] *In vivo* studies in the knock-in mice harbouring LRP6-R611C mutation showed that the mutant mice have medial hyperplasia, and that the effect was further augmented by an arterial injury, resulting in partial to total vascular obstruction.[51] Furthermore, LRP6-R611C mice on LDLR$^{-/-}$ background fed high-cholesterol diet displayed markedly increased arterial neointima formation and an accelerated atherosclerosis. Enhanced expressions of PDGFR and PDGF ligands were detected in the aortic media and in SMCs in the knock-in mice, compared with wild-type controls. Mechanistically, excessive PDGF signalling in LRP-R611C mice has been linked to activation of non-canonical Wnt signalling and upregulation of Sp1, a transcription factor known to target PDGF and PDGFRβ gene expression.[51] Another mechanism has been also proposed in cultured SMCs that LRP6 suppresses PDGF-induced SMC proliferation through promotion of lysosome degradation of PDGFRβ.[50] These findings suggest that LRP6 serves as a negative regulator of PDGF-dependent SMC proliferation and that a loss of the function may contribute to development of atherosclerosis in humans with the LRP6 mutation. A specific role of SMC LRP6 in atherogenesis was further investigated in a study using mice lacking LRP6 selectively in SMCs.[52] Compared to control LRP6$^{fl/fl}$ mice on LDLR$^{-/-}$ background, mice lacking LRP6 selectively in vascular SMCs (LRP6$^{fl/fl}$; SM22-Cre; LDLR$^{-/-}$, designated LRP6-VKO) on atherogenic diet exhibited increased osteochondrogenic calcification and arterial stiffening without affecting plasma lipid profiles. Vascular calcification paralleled upregulation of aortic osteochondrogenic programs and circulating osteopontin, a matricellular regulator of arteriosclerosis. In LRP6-VKO mice multiple canonical and non-canonical Wnt ligands along with Frizzled 10, a receptor for non-canonical Wnt signalling, were upregulated in aortas. Mechanistically, the study proposed that LRP6 suppresses non-canonical Wnt signalling that drives vascular SMC osteochondrogenic programs through a pathway involving upstream stimulatory factor 1 and protein arginine methylation. In summary, the strong proatherogenic phenotypes in humans with the LRP6 gene variation and in the genetic loss-of-function mouse models indicate that LRP6 provides a key protection against dyslipidaemia and atherosclerosis.

2.2.2 Lipoprotein receptor-related protein 5

LRP5 gene is located on chromosome 11q12-13, and it encodes 1615 amino acid protein, which is 71% homologous to LRP6.[119] Polymorphisms of LRP5 gene have been associated with a variety of human diseases, including osteoporosis, obesity, and diabetes.[119–123] LRP5 is widely expressed in multiple tissues, including the liver, where the receptor is implicated in LDL and chylomicron clearance.[54,124] In human atherosclerotic lesions, LRP5 has been detected in endothelial cells, vascular SMC, monocytes, and macrophages.[53] Studies in cultured human macrophages showed that treatment with aggregated LDL, a mimic of modified LDL, increases LRP5 expression, resulting in upregulation of Wnt pathway proteins, including β-catenin and its downstream targets, and that silencing LRP5 by siRNA attenuates macrophage migration.[53] Involvement of LRP5 in atherosclerosis has been further demonstrated in mice deficient in LRP5 globally (LRP5$^{-/-}$).[54] These mice fed high-cholesterol diet displayed downregulation of β-catenin in the aorta compared to wild-type mice, indicating that LRP5 is required for Wnt signalling activation in the vascular wall. Compare to control mice on high-cholesterol diet, LRP5$^{-/-}$ mice displayed increased plasma cholesterol levels and enhanced formation of atherosclerotic lesions, with elevated levels of circulating inflammatory cytokines and macrophage infiltration in the aorta. In sum, LRP5 deficiency and resulting downregulation of Wnt pathway contributes to exaggeration atherosclerosis, likely due to hypercholesterolaemia, systemic, or local inflammation and macrophage migration in the arterial wall.

2.3 ApoER2 and VLDLR

ApoER2, also known as LRP8, and its closely related receptor VLDLR belong to LDL receptor family, and they share common structural features with other members, with a large extracellular domain containing ligand-binding motifs, a single transmembrane domain, and a cytoplasmic tail with multiple adaptor-binding sites[16] (*Figure 1*). However, unlike other members of the family, which play a major role in maintaining lipid homeostasis by mediating internalization of lipoproteins, ApoER2 or VLDLR does not contribute to the lipid metabolism. Global deletion of ApoER2 or VLDLR gene in mice did not result in alterations of plasma lipid profiles.[55,125] Instead, earlier works established the receptors as a signalling receptor for reelin, and they showed that the ligand–receptor complex is critically involved in neuronal migration during brain development.[126–128] In the neuronal cells, reelin binding to ApoER2 or VLDLR initiates recruitment of its adaptor Disabled-1 (Dab-1) to the cytoplasmic NPxY motif, which in turn activates a series of kinases to regulate cellular function required for normal brain development.[126–128] Subsequently it has become apparent that ApoER2 is abundantly expressed in cells in the circulation and in the vascular walls, including platelets, monocytes/macrophages, endothelial cells, and SMCs.[55,57,60,129–132] Similar to the other members of the LDLR, ApoER2

binds to discreet sets of ligands, including reelin, apolipoprotein E (apo E), activated protein C, and β2 glycoprotein I.[55,56,126,131,132] Studies in both cultured cells and in mouse models have revealed that ApoER2 in the vascular cells has critical functions in regulation of coagulation, neointima hyperplasia, and atherosclerosis. In humans, GWAS have linked polymorphisms of ApoER2 gene to premature coronary artery disease and MI.[133–136] In particular, homozygous carriers of the ApoER2-R952Q variant have a two-fold increased risk of these conditions.[133,135,136]

2.3.1 Endothelial cell ApoER2

Reelin is an extracellular matrix glycoprotein that was originally found in the developing brain where it is secreted by Cajal–Retzius neurons, and reelin binding to ApoER2 and VLDLR in the neuron is required for normal brain development and neuronal survival in the adult brain.[137] Further studies found that reelin is also abundantly present in the circulation and in the hepatic stellate cells.[138] Extraneuronal actions of reelin have been initially reported, which include promotion of platelet spreading, thrombin generation, and clot formation.[139] A proatherogenic function of reelin-ApoER2 tandem has been recently revealed.[56] Using hyperlipidaemic $LDLR^{-/-}$ mice with inducible deletion of reelin either ubiquitously or selectively in the liver, the study demonstrated that these mice lacking circulating reelin have attenuated atherosclerosis progression. In the atherosclerotic lesion, reelin deficient mice showed reduced macrophage infiltration and endothelial inflammation, with lower expression of adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Analysis by intravital microscopy further confirmed decreased leucocyte-endothelial interaction in the reelin-deficient mice *in vivo*. Mechanistically, the study in cultured human endothelial cells showed that reelin treatment increases expression of ICAM-1, VCAM-1, and E-selectin by suppressing endothelial nitric oxide synthase (eNOS) activity and increasing NF-kB activity in an ApoER2-dependent manner.

ApoER2 in endothelial cells also binds to apolipoprotein E (apoE), and in contrast to reelin, interaction with apoE3, a common apoE allele in humans, with the receptor has been shown to result in anti-atherogenic actions.[55] In humans, cardiovascular disease risk is modified by genetic variants of apoE. Compared with the most common allele apoE3, individuals with apoE4 allele have an increased risk of atherosclerosis and coronary heart disease.[140,141] An ApoER2 variant ApoER2-R952Q, which is associated with early onset of MI, also has an additive effect with apoE4, with the combined genotype R952Q/E4 showing a 3.9-fold greater susceptibility to cardiovascular disease.[133] Ulrich *et al.*[55] demonstrated that in endothelial cells apoE3 binding to ApoER2 stimulates eNOS and endothelial cell migration, and that it also attenuates monocyte-endothelial cell interaction. Interestingly, apoE4 did not alter eNOS activation, endothelial migration or monocyte-endothelial interaction; instead it antagonized apoE3-ApoER2 actions. Reconstitution experiments in culture further revealed that ApoER2-R952Q is incapable of mediating apoE3 actions, and *in vivo* studies further indicated that endothelial repair followed by arterial injury is attenuated by deletion of ApoER2 or overexpression of apoE4. Furthermore, in a model of neointima formation invoked by carotid artery endothelial denudation, $ApoER2^{-/-}$ mice displayed exaggerated neointima hyperplasia.[55] Thus, the apoE3-ApoER2 tandem promotes endothelial NO production, endothelial repair, and endothelial anti-inflammatory properties, and it prevents neointima formation. These findings collectively indicate that ApoER2 in endothelium exerts ligand-dependent signalling that influences the processes related to atherogenesis.

2.3.2 Macrophage ApoER2

A role of macrophage ApoER2 in atherosclerosis development has been implicated in a study using mice with global ApoER2 deficiency.[57] $ApoER2^{-/-}$ mice on hypercholesterolaemic $LDLR^{-/-}$ background showed accelerated atherosclerosis with more complex lesions and extensive necrosis cores compared to single $LDLR^{-/-}$ mice. The atherosclerotic plaques of the double knockout mice contained higher numbers of macrophages expressing the pro-apoptotic phospho-p53. *In vitro* studies using cultured mouse primary macrophages or cell lines showed that oxidized LDL (oxLDL) treatment induces more lipid accumulation and cell death in ApoER2-deficient cells, compared with control cells.[57] Furthermore, ApoER2-null macrophages displayed attenuated Akt activation, increased levels of the phospho-p53 and increased activation of peroxisome proliferator-activated receptor γ (PPARγ). Additional anti-atherogenic mechanisms of macrophage ApoER2 have been found in studies using cultured macrophages.[58] One study showed that treatment with reelin or human apoE3 upregulates ABCA1 mRNA and protein levels, which was associated with increased apoAI-mediated cholesterol efflux. It further demonstrated that the upregulation of ABCA1 requires ApoER2 and Dab-1, and that pharmacological or genetic inhibitions of PI3 kinase, Protein Kinase Cζ and Sp1 DNA binding abrogates the effect on ABCA1.[58] Another study using cultured mouse macrophages overexpressing human ApoER2 demonstrated that apoE treatment promotes conversion into anti-inflammatory M2 phenotypes with reduced NFkB activation, cell motility and proinflammatory cytokine production.[59] These effects of apoE on macrophage polarization were inhibited by inhibitors of Src family kinases or p38 MAP kinase. These studies suggest an anti-atherogenic function of ApoER2 in macrophages, likely through promotion of cholesterol efflux, prevention of apoptosis, and/or conversion to anti-inflammatory phenotypes.

2.3.3 Platelet ApoER2

Three splice variants of ApoER2 are expressed in platelets,[61,62] and in isolated human platelets, lipidated apoE has been shown to attenuate agonist-induced platelet activation by stimulating intracellular NOS and cGMP likely through ApoER2.[60–63] Studies by Robertson *et al.*[64] also showed that platelets isolated from $ApoER2^{+/-}$ or $ApoER2^{-/-}$ mice had reduced activation in response to ADP or thrombin, compared to those from wild-type mice. *Ex vivo* treatment of the isolated wild-type mouse platelets with lipidated apoE inhibited the platelet activation and this effect was markedly attenuated in $ApoER2^{-/-}$ mouse platelets. *In vivo*, both $ApoER2^{+/-}$ and $ApoER2^{-/-}$ mice demonstrated increased time for vessel occlusion in response to vascular injury; however, significantly smaller increase in occlusion time was observed in homozygous $ApoER2^{-/-}$ mice compared to $ApoER2^{+/-}$. These *in vivo* and *ex vivo* studies suggest that platelet ApoER2 may play two conflicting functions, one as a receptor that augments platelet activation by agonists and the other as a mediator for inhibitory actions of apoE3 on platelets.

2.3.4 Very-low density lipoprotein receptor

As mentioned above, global deletion of the VLDLR gene in mice did not alter the plasma lipoprotein profiles, indicating VLDLR has a minimum contribution to regulation of systemic lipid metabolism.[125] However, when crossed with $LDLR^{-/-}$ mice, lack of the VLDLR resulted in an increase in serum triglyceride levels on a high-fat diet or after prolonged fasting, suggesting that the VLDLR may be involved in peripheral triglyceride uptake.[142,143] Furthermore, $VLDLR^{-/-}$ mice fed a high-fat diet or placed on ob/ob background showed decreased weight gain, possibly

due to a reduction in whole-body free fatty acid uptake.[144] These studies suggest that VLDLR may contribute to delivery of triglyceride or free fatty acid to peripheral cells.

A role of VLDLR in atherosclerotic process is yet to be clarified. Abundant VLDLR expression was observed in endothelial cells on capillaries and small arteries as well as in coronary arteries, but it was minimally detected in aortic endothelium.[145] The receptor was also expressed in neointimal SMCs and macrophage-derived foam cells in the lesion.[65–68] When placed on LDLR$^{-/-}$ background, VLDLR deficiency alone or in combination with selective overexpression of VLDLR in endothelium had minimum impact on atherosclerotic development compared to LDLR$^{-/-}$ mice.[69] In contrast, VLDLR$^{-/-}$ mice displayed increased intimal thickening induced by vascular injury, indicating that VLDLR in SMC likely has a protective role against neointima hyperplasia.[69] In macrophages, both pro- and anti-atherogenic roles of VLDLR have been reported. Transplantation of VLDLR$^{+/+}$ macrophages into VLDLR$^{-/-}$ mice accelerated the development of atherosclerotic lesions, suggesting a pro-atherogenic role of macrophage VLDLR.[70] In contrast, studies in cultured macrophages have demonstrated that activation of VLDLR by reelin or ApoE3 increases ABCA1 transporter expression to promote macrophage cholesterol efflux.[58] In addition, the suppression of anti-inflammatory M2 phenotype was observed in bone marrow macrophages derived from VLDLR$^{-/-}$ mice but not wild-type or LDLR$^{-/-}$ mice, and treatment with ApoE promoted conversion of cultured macrophages from pro-inflammatory M1 to M2 phenotype through a process dependent on p38MAPK and Src family kinase.[59] Collectively, these observations in the experimental models suggest that the proatherogenic effect of VLDLR arising from the lipid uptake function may be counter-balanced by their antiatherogenic effects, such as elevation of ABCA1 transporter and conversion into an anti-inflammatory phenotype.

In humans, a few genetic variants of VLDLR have been reported that are associated with lipid traits and cardiovascular disease risk.[146–148] One variant (rs1454626) located in the 5' flanking region of VLDLR was associated with coronary artery disease, BMI, and levels of LDL-associated apolipoprotein B.[147] The study also identified receptor–ligand genetic interactions between the common VLDLR SNP and an apoE genotype for predicting coronary artery disease case status. More recently, another association signal was located in the intron of VLDLR; minor A allele of rs3780181 was associated with increased plasma total cholesterol and LDL-associated cholesterol.[146,148] Using a functional genetic approach, the study demonstrated that deletion of the intronic enhancer domain containing the risk allele affects VLDLR expression, potentially influencing the circulating levels of total cholesterol.[148]

3. Scavenger receptor family members

The scavenger receptors belong to a large family of pattern recognition receptors, which show capacity to interact with a wide range of ligands, and they are expressed in many cell types related to lipid metabolism and atherogenesis, including hepatocytes, macrophages, endothelial cells, SMCs, and platelets.[149,150] Interacting with the circulating native or modified lipoproteins, such as oxLDL, these receptors modulate vascular inflammation, lipid accumulation, and plaque formation (*Figure 2*, *Table 2*).

3.1 Cluster of differentiation 36

CD36 (also referred as SR-B2) belongs to the class B scavenger receptor family, and it is highly expressed in vascular and hematopoietic cells, including vascular SMCs, endothelial cells, macrophages, and platelets.[166,167,214] CD36 has two short N- and C-terminal cytoplasmic tails, two transmembrane domains, and a large extracellular domain that is heavily glycosylated[166,214] (*Figure 2*). A homology modelling based on published extracellular structure of the related protein Lysosomal Integral Membrane Protein II (LIMP-II) indicates that there are distinct hydrophobic pockets potentially responsible for lipid recognition and fatty acid trafficking.[215] Through discrete sites on the extracellular loop, CD36 interacts with multiple ligands, including oxidized phospholipid ($oxPC_{CD36}$),[216] free fatty acids,[217] the matricellular protein thrombospondins (TSP),[160] and proteins containing the thrombospondin type 1 repeat (TSR) domain[218] and cell-derived microparticles.[219] CD36 has at least three well-established, cell-type specific functions. First, it serves as a membrane receptor for TSP in endothelium to modify cellular functions, such as angiogenesis.[160] Second, CD36 facilitates translocation of free fatty acids from the extracellular milieu into the cytoplasm, mainly in adipocytes and myocardium.[217,220] Third, it functions as a scavenger receptor that recognizes and internalizes specific exogenous and endogenous danger signals, including modified LDL and HDL.[166,167,214] This function plays a pivotal role in the pathogenesis of atherosclerosis, by promoting endothelial dysfunction, macrophage foam cell formation, vascular inflammation, and atherothrombosis.

3.1.1 Macrophage CD36

Under hyperlipidaemic condition, cholesterol derived from LDL particles accumulates in the subendothelial space in the vascular wall and triggers inflammation, leading to foam cell formation.[2,12] Numerous studies in cultured cells and in mouse models have shown that CD36 plays a major part in the process through multiple mechanisms. First, in response to oxLDL CD36 promoted lipid accumulation in cultured macrophages, and CD36 deficiency in mice (CD36$^{-/-}$) was associated with attenuated foam cell formation and protection from atherosclerosis.[151,152] However, the *in vivo* consequence of CD36 deletion in foam cell formation and atherogenesis in mice has been disputed by another study, which did not find significant reduction in foam cell formation or atherosclerosis.[153] Secondly, CD36 has been shown to promote a pro-inflammatory process in macrophages by oxLDL internalization and subsequent conversion into cholesterol crystals, potent inducers of the NLRP3 inflammasome, and production of proinflammatory cytokine Interleukin 1β (IL-1β).[154] Third, CD36 promotes macrophage dysfunction by initiating a signalling pathway in macrophages in response to oxLDL. Park *et al.*[155] revealed that CD36 mediates oxLDL-induced inhibition of macrophage spreading and migration via sustained activation of focal adhesion kinase and inactivation of Src homology 2-containing phosphotyrosine phosphatase (SHP-2), leading to disruption of actin cytoskeletal rearrangements. Another study showed that oxLDL-CD36 signalling leads to a loss of macrophage cellular polarity due to dysregulation of Rac and non-muscle myosin II, key determinants of cellular symmetry and lamellipodia formation.[156] Additionally, a mechanism in macrophages has been reported that involves CD36-mediated activation of Vav family guanine nucleotide exchange factors.[157,158] Vav is highly regulated by Src-mediated tyrosine phosphorylation and it acts as a central signalling hub to several signalling pathways,[159] and CD36 has been shown to activate Vav via Src family kinases, which in turn promotes uptake of oxLDL.[157,158] *In vivo*, analysis of aortas from hyperlipidaemic mice

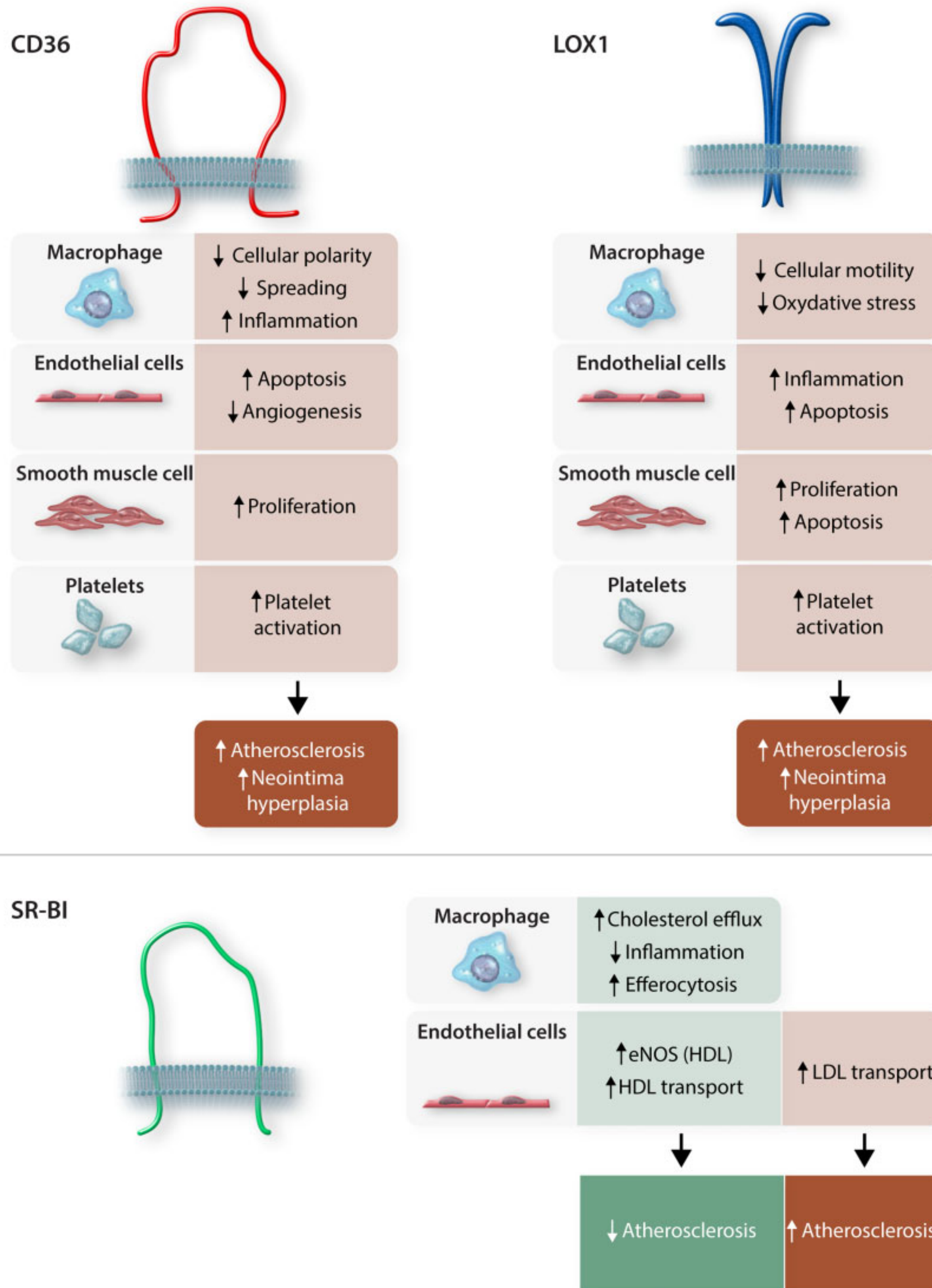

Figure 2 Structure and function of scavenger receptor family members, CD36, SR-BI, and LOX-1 in atherosclerosis. The scavenger receptors belong to a large family of pattern recognition receptors, which can interact with a wide range of ligands. Interacting with the circulating native or modified lipoproteins, such as oxLDL, these receptors modulate vascular inflammation, lipid accumulation, and plaque formation. Both CD36 and SR-BI have two short N- and C-terminal cytoplasmic tails, two transmembrane domains, and a large extracellular domain that binds to the ligands. CD36, through binding to modified lipoproteins and lipids, plays a major role in atherogenesis, by promoting endothelial dysfunction, macrophage foam cell formation, vascular inflammation, and atherothrombosis. Hepatic SR-BI protects against atherosclerosis by facilitating the reverse cholesterol transport and maintaining anti-atherogenic characteristics of HDL in the vascular cells; however, recent findings indicate that the receptor has a key pro-atherogenic function in endothelium by mediating transport of LDL into the artery wall. LOX-1 contains a short N-terminal cytoplasmic domain, a single transmembrane domain, a NECK or stalk domain, and a C-terminal extracellular domain that binds to oxLDL. In a variety of vascular cells, LOX-1 mediates a majority of pro-atherogenic actions of oxLDL, contributing inflammation, smooth muscle cell proliferation, and platelet activation.

Table 2 Anti- and proatherogenic functions of the scavenger receptor family members

	Lipoprotein receptor	Antiatherogenic functions			Proatherogenic functions			References
		Cell type	Cellular function	Mechanism	Cell type	Cellular function	Mechanism	
Scavenger receptors	CD36	Macrophages			Macrophages	Inflammation ↑	NLRP3 inflammasome ↑	151–159
						Spreading ↓	FAK, SHP-2 ↓	
						Cellular polarity ↓	Rac, non-muslce myosin II ↓	
						oxLDL uptake ↑	Vav ↑	
		Endothelial cells			Endothelial cells	Apoptosis ↑	TSP-Fyn-p38 ↑	160–165
						Cell migration/tube formation ↓	TSP-VEGFR signalling ↓	
							Fyn-NADPH oxydase-ROS ↑	
		SMC			SMC	Proliferation ↑		
		Platelets			Platelets	Activation ↑	Fyn-PKC-NADPH oxidase-ROS ↑	166–173
							JNK/ERK5 ↑	
							NO-cGMP ↓	
	SR-BI	Macrophages	Cholesterol efflux ↑		Macrophages			174–185
			Inflammation ↓	NF-kB, p38, JNK ↓				
			Cholesterol hydrolysis ↑					
			Efferocytosis ↑	Src, PI3 kinase Rac1 ↑				
		Endothelial cells	eNOS activity ↑	Src, Akt ↑	Endothelial cells	LDL transcytosis ↑	DOCK4-Rac1 ↑	186–196
				Sphingosine-1-phosphate receptor signalling ↑				
			HDL transport ↑					
	LOX1	Endothelial cells			Endothelial cells	Inflammation ↑	MCP1 ↑	197–201
						Apoptosis ↑	Caspase ↑	
							Anti-apoptotic proteins ↓	
						eNOS activity ↓	RhoA-ROCK-arginase II ↑	
							Dysfuncitonal HDL action ↑	
		SMC			SMC	Proliferation ↑		202–205
						Apoptosis ↑		
		Macrophages			Macrophages	Oxidative stress ↑		206–209
						Cell migration ↓		
		Platelets			Platelets	Aggregation/activation ↑		210–213

indicated that Vav proteins are activated in a CD36-dependent manner. In sum, CD36 mediates pro-inflammatory and proatherogenic actions of oxLDL in macrophages.

3.1.2 Endothelial cell and smooth muscle cell CD36

Several studies have linked CD36 to endothelial dysfunction, which plays a key role in the initial stage of cardiovascular diseases.[2,8] CD36 in endothelium has been shown to interact with to the TSR domain in TSP1 and TSP2.[160] A study showed that the interaction between TSP1 and endothelial CD36 increases phosphorylation of Src family kinase Fyn, followed by activation of p38 MAPK, leading to enhanced apoptosis.[161] Another study found that TSP1-CD36 interaction promotes dephosphorylation of pro-angiogenic vascular endothelial growth factor receptors (VEGFR), resulting in reduction of endothelial cell migration and formation of tube-like structures.[162] CD36 on microvascular endothelial cells also binds to anionic phosphatidylserine on the surface of extracellular vesicles, leading to inhibition of cell migration.[163] This is mediated by a pathway that involves activation of Fyn and NADPH oxidase and generation of reactive oxygen species (ROS). Recent studies found that mice lacking CD36 selectively in endothelial cells have reduced uptake of fatty acids in the heart, skeletal muscle, and brown adipose tissue and that these mice are resistant to high-fat diet-induced insulin resistance.[164]

CD36 has also been shown to contribute to development of neointima hyperplasia through enhancement of SMC proliferation.[165] Yue *et al.* found that CD36 is highly expressed in human vessels with intimal hyperplasia and luminal occlusion, and that mice lacking CD36 globally or selectively in SMCs on hyperlipidaemic background have reduction in carotid artery injury-induced neointima thickening. In primary vascular SMCs in culture, the study further demonstrated that CD36 is required for induction of cell proliferation and cell cycle progression by serum or a TSR peptide. These observations indicate that CD36 in the endothelium or SMCs exerts various proatherogenic functions; however, an effect of tissue-specific CD36 deletion on atherogenesis is yet to be tested.

3.1.3 Platelet CD36

Studies in mice and in isolated platelets have demonstrated a critical role of platelet CD36 in linking dyslipidaemia and oxidative stress with prothrombotic phenotypes. $CD36^{-/-}$ mice on the hyperlipidaemic $apoE^{-/-}$ background exhibited reduced thrombus formation induced by vascular injury.[167] In isolated human platelets, inhibition of CD36 actions by the blocking antibody or the competing lipid ligand attenuated platelet activation by oxidized lipids without affecting basal platelet functions. In response to oxLDL, platelet CD36 has been shown to activate Src family kinase Fyn, which leads to increased ROS production via NADPH oxidase 2 (NOX2).[166,168] Activation of Fyn upregulated another tyrosine kinase Syk and PLCγ2, linking the CD36 signalling to PKC, which in turn promotes phosphorylation of the p47 subunit of NOX2 to induce NOX complex formation to generate ROS.[166,168] Platelets express a number of redox-sensitive effectors for ROS, including MAP kinase family members JNK and ERK5.[169–172] Inhibition of JNK activity prevented platelet activation by oxLDL, and an activated form of JNK was detected within growing thrombi in wild-type mice, but not in $CD36^{-/-}$ mice.[169] For ERK5, in isolated platelets activation of the kinase by oxLDL was observed, and platelets isolated from mice exposed to hyperlipidaemia showed elevated activation of ERK5.[170] *In vivo*, $apoE^{-/-}$ mice harboring ERK5 deficient platelets displayed attenuated thrombus formation compared to those expressing the kinase in platelets.[170] Intervention studies in mice confirmed that oxLDL induction of ERK5 requires CD36, Src family kinases, and NOX. Platelet CD36-ERK5 has been also implicated in a coagulation pathway.[173] The study reported that CD36 activation of ERK5 upregulates the caspases, resulting in externalization of phosphatidylserine that promotes a formation of coagulation enzyme complexes, and that inhibition of CD36 or ERK5 prevents accelerated fibrin formation.[173] In addition to the direct activation of platelets or the coagulation pathway, ROS generated by the CD36-NOX pathway has also been shown to suppress an inhibitory pathway in platelets that is mediated by nitric oxide-cGMP signalling.[221] Collectively, CD36 promotes platelet activation and coagulation by oxLDL, contributing to prothrombotic phenotypes under hyperlipidaemia.

3.1.4 Human genetics of CD36

The human CD36 gene is located on chromosome 7q11.2, and it has 15 exons encoding a 471 amino acid protein.[222,223] CD36 deficiency has been reported to occur in 3–10% of Asian and African populations.[224–226] Two types of CD36 deficiency have been described; type I lacks CD36 both in monocytes and platelets, and type II lacks the receptor expression in platelets but not monocytes.[227] Type I CD36 deficiency has been associated with insulin resistance, postprandial hypertriglyceridaemia and hypertension in Japanese populations.[228–231] In addition to CD36 deficiency, a number of common genetic variants have been discovered that are associated with metabolic syndrome, hypertension, coronary artery diseases, and ischaemic stroke in multiple populations.[226,232–238] Ghosh *et al.* demonstrated that platelet CD36 expression levels vary among individuals and that specific polymorphisms in the CD36 gene are associated with platelet surface expression levels of the receptor and with responsiveness to its ligand oxLDL.[233] In agreement with the proinflammatory and proatherogenic functions of the receptor shown in the experimental models, SNPs associated with higher CD36 in platelets were linked to obesity, metabolic syndrome, and dyslipidemia.[233] However, the basis for the contrasting effects of complete vs. a partial loss of CD36 on the metabolic and cardiovascular complications is not yet fully understood.

3.2 Scavenger receptor class B type I

The scavenger receptor Class B type I (SR-BI, SR-B1, or SCARB1) was first identified as a protein with a sequence closely related to CD36 and LIMP-II, and the gene was initially named CLA1, subsequently termed SCARB1[239,240] (*Figure 2*). The work by Acton *et al.* identified SR-BI as the high-affinity HDL receptor, which mediates the selective uptake of HDL-associated cholesterol ester (CE) into the liver.[239] SR-BI also facilitates the bidirectional flux of free cholesterol (FC) between cells and HDL.[241,242] A major role of SR-BI in lipoprotein metabolism and atherogenesis was initially established in mice lacking the receptor globally ($SR\text{-}BI^{-/-}$). $SR\text{-}BI^{-/-}$ mice on hyperlipidaemic backgrounds displayed accelerated atherosclerosis resulting in coronary artery occlusion, MI, and decreased survival rate.[174,243,244] These mice have severe hypercholesterolaemia with abnormally enlarged HDL particles compared to control mice. Subsequent investigations revealed that the accelerated atherosclerosis observed in $SR\text{-}BI^{-/-}$ mice is due primarily to a loss of hepatic SR-BI. Liver-specific SR-BI deficiency in mice resulted in increased atherosclerosis, mimicking the phenotype in global SR-BI knockout mice,[186,245] and overexpression of hepatic SR-BI reduced atherosclerosis in $LDLR^{-/-}$ mice.[246] Multiple mechanisms by which hepatic SR-BI provides atheroprotection have been proposed. First, SR-BI in the liver plays a

critical role in the reverse cholesterol transport, in which peripheral cholesterol is delivered to the liver for excretion in both mice and humans.[14,17] In humans, although majority of plasma cholesterol in LDL is internalized by hepatic LDL receptors, it has been estimated that hepatic SR-BI is responsible for at least 33% of HDL CE uptake.[247] Consistent with a role for SR-BI in hepatic uptake of HDL in humans, subjects carrying a loss of CE transport function variant in the SR-BI (SCARB1) gene (P297S) have elevated HDL cholesterol in the form of enlarged, apoE-enriched particles, parallel to those observed in SR-BI$^{-/-}$ mice.[248,249] Additionally, the HDL particles isolated from SR-BI$^{-/-}$ mice showed altered lipid and protein compositions with increased FC and decreased antioxidative molecules, likely contributing to reduced cholesterol efflux capacity.[243,250,251] Secondly, hepatic SR-BI has been implicated in clearance of proatherogenic lipoproteins VLDL and Lp(a),[252,253] suggesting that impaired removal of these molecules may also contribute to the exaggerated atherogenesis in SR-BI$^{-/-}$ mice. Third, hepatic SR-BI may also provide atheroprotection by attenuating thrombosis.[254–256] SR-BI$^{-/-}$ mice displayed increased susceptibility to arterial thrombosis.[254,255] Bone marrow transplantation experiments demonstrated that hyperlipidaemia and resulting platelet FC overload due to loss of hepatic SR-BI, not SR-BI deficiency in platelets, are likely responsible for the prothrombotic phenotype observed in SR-BI$^{-/-}$ mice.[254,255] Studies in humans also found that platelets isolated from subjects carrying the SR-BI variant P297S are enriched in FC and that they are prothrombotic compared with control platelets.[248,249] Taking together, hepatic SR-BI protects against atherosclerosis by facilitating the reverse cholesterol transport and maintaining anti-atherogenic characteristics of HDL.

In addition to the liver, SR-BI is abundantly expressed in macrophages and endothelial cells, and accumulating evidence indicates that the receptor has extrahepatic functions to influence the progress of atherosclerosis.[175–179,186,245,257]

3.2.1 Macrophage SR-BI

Bone marrow transplantation studies have established that SR-BI in monocyte or macrophages provides atheroprotection. ApoE$^{-/-}$ or LDLR$^{-/-}$ mice receiving transplantation of SR-BI deficient bone marrow cells developed accelerated atherosclerosis, compared those receiving control bone marrow cells.[175–178] No differences were observed in plasma cholesterol or lipoprotein profiles, indicating that proatherogenic effect of monocyte/macrophage SR-BI deficiency is not likely due to abnormal lipoproteins. Likewise, transplantation of SR-BI$^{-/-}$ mice on apoE hypomorphic background with SR-BI$^{+/+}$ bone marrow cells markedly reduced coronary atherosclerosis and MI.[179] Multiple mechanisms have been proposed by which macrophage SR-BI affords atheroprotection. One mechanism is through mediating removal of cholesterol from macrophages. Several studies in culture have shown that SR-BI, along with ABCA1, is responsible for cholesterol efflux to HDL from cholesterol-laden monocyte-derived macrophages.[180–182] Macrophage SR-BI has been also implicated in suppression of proinflammatory aspects associated with atherosclerosis. Studies have found that hyperlipidaemic mice receiving SR-BI$^{-/-}$ bone marrow showed increased serum levels of proinflammatory cytokines including IL-1β, IL-6, and TNF-α, compared to those receiving control bone marrow.[175] Furthermore, both *in vitro* and *in vivo* models indicate that SR-BI deficiency promotes macrophage conversion to the pro-inflammatory phenotype likely through activation NF-kB, p38, and JNK signalling pathway.[174,183] Another mechanism by which macrophage SR-BI could reduce atherosclerosis is by targeting cytoplasmic CE via autophagosome for lysosomal hydrolysis.[184] Studies in cultured macrophages demonstrated that autophagic process is impaired in SR-BI-deficient macrophages in the setting of infection. An additional mechanism for macrophage SR-BI in efferocytosis has also been proposed, in which haematopoietic SR-BI deficiency results in severely defective efferocytosis in mouse atherosclerotic lesions.[175,185] The studies further found that efferocytosis of apoptotic cells was reduced in SR-BI$^{-/-}$ vs. wild-type macrophages and that SR-BI interaction with cell surface phosphatidylserine of the apoptotic cells triggers efferocytosis process via activation of Src, PI3 kinase, and Rac1.[175] Defective efferocytosis in macrophages thus may play a role in exaggerated atherosclerotic phenotypes in SR-BI$^{-/-}$ mice. Collectively, a number of studies both *in vitro* and *in vivo* strongly support atheroprotective functions of macrophage SR-BI.

3.2.2 Endothelial cell SR-BI

Disruption of vascular endothelial function is a key initial step in atherosclerotic lesion progression, facilitating monocyte infiltration into the arterial intima.[2,8] A series of studies have established that SR-BI interaction with HDL prevents endothelial dysfunction by stimulating eNOS activity and increasing bioavailable NO.[187,188] NO is a key signalling molecule for the maintenance of normal vascular function, through regulation of vascular tone, prevention of endothelial inflammation and platelet activation, and reduction of SMC growth.[258,259] Studies in cultured endothelial cells indicate that HDL-SR-BI activation of eNOS requires recruitment of the adaptor molecule PDZK1 to C-terminal cytoplasmic domain of the receptor, which in turn activates Akt kinase, resulting in the phosphorylation of eNOS at Ser1177.[188,189] *In vivo*, mice lacking SR-BI or PDZK1 show attenuated endothelial repair.[189,190] Furthermore, both *in vivo* and *in vitro* studies revealed that anti-inflammatory and atheroprotective effects of HDL-associated sphingosine 1-phosphate (S1P) are mediated by endothelial SR-BI along with S1P receptors.[191,192] *In vivo* overexpression of SR-BI selectively in endothelial cell has been shown to decrease atherosclerosis in wild-type, apoE$^{-/-}$ or SR-BI$^{-/-}$ mice on atherogenic diet.[193] Although the atheroprotective phenotype in these mice is likely in part due to decreased plasma cholesterol and increased HDL cholesterol, endothelial SR-BI may also contribute to the reduced atherosclerosis by facilitating HDL transport between circulation and arterial wall to promote cholesterol efflux from macrophages.[193,194] An additional atheroprotective mechanism has been proposed by which lymphatic endothelial SR-BI mediates the transport of HDL in lymphatic vessels to effectively remove cholesterol from peripheral tissue.[195,196]

In contrast to these atheroprotective roles of endothelial SR-BI described above, a strong proatherogenic function of endothelial SR-BI has been recently revealed.[186,260] In cultured endothelia cells and in isolated mouse aortas *ex vivo*, Armstrong *et al.*[260] first demonstrated using total internal reflection fluorescence microscopy that LDL is transported across endothelial cells, and that the LDL transport is mediate by SR-BI, but not LDL receptor. More recently, using mice lacking SR-BI selectively in endothelial cells, Huang *et al.*[186] have demonstrated *in vivo* that endothelial SR-BI promotes atherosclerosis by facilitating delivery of LDL into arteries and its accumulation in macrophages. The study discovered that internalization of LDL-SR-BI requires recruitment of the guanine nucleotide exchange factor dedicator of cytokinesis 4 (DOCK4) to the C-terminal domain of SR-BI and subsequent activation of Rac1. It further revealed that the expressions of SR-BI and DOCK4 transcripts are elevated in human atherosclerotic arteries, compared with normal arteries. In summary, current evidence indicates a dichotomous role of endothelial SR-BI in atherogenesis. The receptor mediates anti-inflammatory effects of HDL, contributing to increased bioavailable NO and

protection against atherosclerosis. On the other hand, in conditions of high plasma LDL, SR-BI facilitates LDL transport across the endothelial layer into the artery wall, which leads to foam cell formation and progression of atherosclerosis.

3.2.3 Human genetics of SR-BI

The discovery of SR-BI encoded by SCARB1 gene as the high affinity HDL receptor triggered numerous studies to identify human variants at the locus for their relationship with plasma lipid phenotypes and cardiovascular diseases.[261,262] Earlier works using targeted resequencing and genotyping discovered several coding polymorphisms that are associated with high plasma levels of HDL or low levels of LDL cholesterol.[261,262] Some of the studies found the variants that are associated with increased risk for vascular diseases, including MI, peripheral arterial disease, common carotid intimal–medial artery thickness and coronary heart disease.[263–265] GWAS further identified SCARB1 SNPs that are associated with HDL cholesterol levels and cardiovascular disease risks.[88,266,267] More recently, rare nonsynonymous variants in SCARB1 gene have been reported, further indicating the association of SR-BI, HDL metabolism, and risk for cardiovascular diseases. Through targeted sequencing of participants with extremely high HDL cholesterol levels, Vergeer *et al.* identified a carrier of a novel P297S variant in SCARB1 gene.[248] Compared to non-carrier family members, P297S carriers exhibited higher HDL cholesterol levels, and HDL isolated from the carriers displayed reduced cholesterol efflux capacity to macrophages, compared to non-carriers. However, the variant was not associated with differences in carotid intimal-medial thickness. Subsequently, a second non-synonymous coding variant in SCARB1 (P376L) was reported.[249] The variant was also identified through targeted sequencing in individuals with high HDL cholesterol levels. The P376L homozygous subject exhibited extremely high levels of circulating HDL cholesterol and a carotid intimal medial thickness that was higher than 75th percentile for age and gender. Genotyping of the P376L variant in multiple cohorts revealed a significant association of the P376L variant with increased coronary heart disease. Biochemical analysis demonstrated that HDL particles in P376L carriers are larger in size with increased apoA-I content, and that the selective HDL cholesterol uptake function is absent in hepatocyte-like cells derived from induced pluripotent stem cells (iPSC) from the homozygous subject. Collectively, these studies in humans offered a strong support for a key role of SR-BI in HDL metabolism and atherosclerosis.

3.3 Lectin-like oxidized low-density lipoprotein receptor-1

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1, also known as OLR1, SR-E1) is a 50 kDa transmembrane glycoprotein that belongs to the C-type lectin family.[268,269] LOX-1 contains a short N-terminal cytoplasmic domain, a single transmembrane domain, a NECK or stalk domain, and a C-terminal extracellular domain that binds to oxLDL (*Figure 2*). In human atherosclerotic lesions, LOX-1 mRNA and proteins were detected in endothelial layers, intimal SMCs and macrophages, whereas they were undetectable in normal human aortas.[270] Furthermore, elevations in circulating indicators of LOX-1 expression or activation in humans have been associated with a higher risk for coronary heart diseases.[271,272] A causal role of LOX-1 for atherogenesis was revealed by Mehta *et al.* using mice lacking LOX-1 globally (LOX-1$^{-/-}$).[273] These mice displayed attenuated oxLDL binding to aortic endothelial cells, and on hyperlipidaemic LDLR$^{-/-}$ background, LOX-1$^{-/-}$ mice showed a marked reduction in atherosclerotic lesion and intima thickness, compared to LDLR$^{-/-}$ mice. The study further found that LOX-1$^{-/-}$ mice have decreased expression of proinflammatory markers NF-κB, CD68, and the phosphorylated p38 MAPK in the vascular wall. In agreement with the proatherogenic role of LOX-1, the receptor is also implicated in pathogenesis of myocardial ischaemia in mice. Using a rat model of coronary artery ischaemia–reperfusion, a study showed that treatment with an anti-LOX-1 neutralizing antibody, which blocks LOX-1-mediated cellular uptake of oxLDL, results in reduction in infarct size.[274] In this rat model, expression of LOX-1 mRNA and protein was upregulated in the ischaemic heart, which was associated with elevations of markers of inflammation, oxidative stress, and apoptosis.[274] Studies in LOX-1$^{-/-}$ vs. wild-type mice confirmed the role of LOX-1 in ischaemia, showing that LOX-1 deficiency improved survival and reduced collagen deposition and cardiomyocyte hypertrophy.[275]

LOX-1 was originally identified in cultured aortic endothelial cells as a major receptor responsible for binding, internalization, and degradation of oxLDL.[268] LOX-1 was subsequently detected in other cell types, including macrophages, platelets, SMCs, and cardiomyocytes.[202,206,207,210,276,277] The cellular expression of LOX-1 at basal state is normally low, but it is known to be rapidly upregulated by oxidative and proinflammatory stimuli.[210,269,276]

3.3.1 Endothelial cell and smooth muscle cell LOX-1

A number of studies in culture and *in vivo* models demonstrated that activation of LOX-1 promotes endothelial dysfunction through multiple mechanisms. First, in cultured human endothelial cells, oxLDL was shown to increase MCP1 production and monocyte adhesion in an LOX-1 dependent manner.[197] In a rat model of low-dose endotoxin-induced uveitis, the LOX-1 blocking antibody suppressed leucocyte infiltration *in vivo* and it reduced leucocyte interaction with retinal veins *in situ*.[198] Second, LOX-1 has been shown to mediate oxLDL-induced endothelial cell apoptosis in human coronary artery endothelial cells through increased activation of the caspases and reduced expression of anti-apoptotic proteins.[199] Third, oxLDL-LOX-1 also contributes to endothelial dysfunction through upregulation of arginase II, which inhibits NOS activity by competing for the substrate L-arginine.[200] In cultured endothelial cells, arginase II activation by oxLDL was attenuated by pre-incubation with the LOX-1 blocking antibody, and in aortas from wild-type mice fed high-cholesterol diet showed increased arginase II activity and reduced NO production, whereas LOX-1$^{-/-}$ mice were protected from the adverse effects of the atherogenic diet. Mechanistically, the effect of oxLDL-LOX-1 on arginase II activation was shown to be mediated by RhoA and ROCK signalling. In addition to its role as a mediator of proatherogenic actions of oxLDL, LOX-1 has been implicated in the actions of dysfunctional HDL in endothelial cells. Studies by Besler *et al.* showed that disease-modified dysfunctional HDL engages LOX-1 instead of SR-BI, resulting in endothelial dysfunction and elevated inflammatory responses.[201] In contrast to HDL from normal subjects that promotes endothelial NO release in cultured human endothelial cells, HDL from patients with acute coronary syndromes or stable coronary artery diseases failed to induce endothelial NO release. Treatment of the cells with the LOX-1 blocking antibody reversed the defect.[201]

Involvement of LOX-1 in SMCs has been shown in neointima hyperplasia. In balloon-injury animal models, expression of LOX-1 mRNA and protein was upregulated in medial and neointimal SMCs in response to injury, and administration of the LOX-1 blocking antibody suppressed injury-induced neointima hyperplasia, along with ROS formation and leucocyte infiltration in the vascular wall.[202] LOX-1 expression was also

detected in proliferating SMCs in human restenotic lesions after balloon-angioplasty.[203] In addition to neointima formation, LOX-1 in SMC has been implicated in destabilization and rupture of atherosclerotic plaques.[204,205] In cultured SMCs, the studies showed that oxLDL treatment enhances SMC apoptosis through LOX-1 and that the neutralizing LOX-1 antibody prevents the oxLDL-induced apoptosis.[204,205] Furthermore, LOX-1 expression was colocalized with apoptosis proteins in the rupture-prone regions of human atherosclerotic plaques. Collectively, these findings indicate that LOX-1 in endothelial cells and SMCs mediate potent atherogenic effects of oxLDL during various phases of atherogenesis.

3.3.2 Macrophage and platelet LOX-1

In addition to endothelial cells and SMCs, LOX-1 also facilitates binding and uptake of oxLDL in monocytes and macrophages.[206,207] Studies in cultured macrophages have shown that oxLDL treatment increases oxidative stress in an LOX-1 dependent manner, and that oxLDL suppresses cell motility in macrophages isolated from wild-type mice, but not from LOX-1$^{-/-}$ mice.[208,209]

In activated human platelets, LOX-1 expression is upregulated and the receptor mediates the binding and internalization of oxLDL, similar to other cell types.[210,211] A study in isolated human platelets showed that ADP-induced platelet aggregation was inhibited by the LOX-1 blocking antibody through suppression of the inside-out integrin signalling-dependent activation of glycoprotein IIb/IIIa.[211] Additionally, human electronegative LDL (L5) isolated from patients with MI, which is known to serve as a ligand for LOX-1,[212] induced platelet activation and aggregation.[213] *In vivo*, injection of the L5 into wild-type mice resulted in platelet activation and shortening of tail bleeding time, whereas the effect of L5 was attenuated in LOX-1$^{-/-}$ mice. In sum, there is evidence suggesting that LOX-1 mediates oxLDL actions in macrophages and in platelets that promote oxidative stress, inflammation, and thrombosis.

3.3.3 Human genetics of LOX-1

Human LOX-1 is encoded by the oxidized low density lipoprotein receptor 1 (OLR1) gene located in the p12.3-p13.2 region of human chromosome 12.[268,278] Genetic studies have identified SNPs in the OLR1 gene that are associated with myocardial ischemia and coronary artery diseases. One of the SNPs is G501C variant in the coding region, resulting in a missense mutation substituting lysine (K) for asparagine (N) at amino acid location 167 (K167N). Amino acid residue 167 is located on the surface of the C-terminal domain of LOX-1, suggesting that the mutation may affect its interactions with ligands. In cross-sectional studies, this variation was associated with an increased incidence of MI, as well as with increased carotid intima-media thickness.[279–281] A meta-analysis of seven case–control studies indicated that the C allele is significantly associated with ischemic stroke.[282] However, an *in vitro* study showed that 167N LOX-1, corresponding to C allele, binds to oxLDL less efficiently than 167K (G allele), which likely confers protection against atherosclerosis.[283] This disparity in the biochemical and human genetic association studies needs further clarification.

When SNPs at distinct locations of the genome are more highly associated than expected, they are in the linkage disequilibrium (LD). An LD block comprises six such SNPs (GGAAGC haplotype vs. CTGGTT) has been found within introns 4 and 5, as well as the 3' untranslated region (3'-UTR) of the OLR1. Studies found an association between the SNPs within the LD block and the risk for MI or atherosclerotic cerebral infarction in some cohorts.[284,285] *In vitro* and *in vivo* studies have shown that LD block SNPs regulate the production of an alternatively spliced version of the LOX-1 mRNA by modulating retention of the LOX-1 mRNA exon 5.[286] Exclusion of exon 5 results in the production of a LOX-1 isoform, termed LOXIN, which lacks a part of the C-terminal lectin-like domain involved in ligand binding. Studies in isolated peripheral blood monocytes from risk (GGAAGC) vs. non-risk (CTGGTT) carriers of the LD SNPs showed that the non-risk SNPs correlate with higher expression of LOXIN, which results in a significant reduction of apoptosis induced by oxLDL treatment.[286] The splice variant may have a functional role on plaque instability and pathogenesis of MI.[286,287] In summary, studies in human genetics provide supportive evidence that implicates LOX-1 as an important mediator of proatherogenic functions of oxLDL.

4. Conclusions

The lipoprotein receptors are expressed in multiple types of vascular cells, and they mediate actions of a broad range of ligands to accelerate or block atherogenesis. It is of pivotal importance that we harness these functions of the lipoprotein receptors to develop therapeutic modalities that can prevent or lessen atherosclerosis. To achieve the goal, more comprehensive understanding of the complex process will be needed, likely through employment of innovative strategies. *In vitro* cell culture models, using either established cell lines or primary human or mouse cells, have allowed us to identify the players in particular signal transduction pathways; however, there are well acknowledged limitations in the approach, stemming from inevitable changes in signature characteristics or a partial loss of cellular identity in cells transferred to culture. Although still in an early stage, human iPSC-derived vascular cells may provide an *in vitro* modelling of human atherosclerosis or vascular disorders.[288] Animal models, especially genetically modified mice on hyperlipidaemia background, have made loss- and gain-of-function studies possible. However, because these receptors regulate diverse aspects of the disease process, it has become apparent that a more temporal and cell-type specific manipulation is necessary to distinguish the direct effects from less specific consequences of compensatory or indirect mechanisms. Lastly, an approach of using human genetics to search for variants that show associations with human conditions has yielded a wealth of information, connecting data from experimental models with human diseases. However, due to involvement of multiple biological pathways and cell types, clear associations with cardiovascular disease may not be readily apparent, especially for more common variants. Recent advancement in the area of transcriptome analysis, including a single cell sequencing of normal and diseased human tissues, indicates that such approach will provide much-needed information regarding the processes which occur in unique sets of vascular cells during atherosclerosis development in humans.[289]

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References

1. Mozaffarian D, Stroke Statistics Subcommittee, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P,

Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;**133**:e38–360.
2. Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, Doran AC, Vickers KC. The role of lipids and lipoproteins in atherosclerosis. In Feingold KR, Anawalt B, Boyce A *et al.* (eds). Endotext. South Dartmouth (MA): MDText.com, Inc., 2000. https://www.ncbi.nlm.nih.gov/books/NBK343489/.
3. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res* 2014;**114**:1852–1866.
4. Yahagi K, Kolodgie FD, Otsuka F, Finn AV, Davis HR, Joner M, Virmani R. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. *Nat Rev Cardiol* 2016;**13**:79–98.
5. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* 2015;**161**:161–172.
6. Brown MS, Goldstein JL. Lipoprotein metabolism in the macrophage: implications for cholesterol deposition in atherosclerosis. *Annu Rev Biochem* 1983;**52**:223–261.
7. Pant S, Deshmukh A, GuruMurthy GS, Pothineni NV, Watts TE, Romeo F, Mehta JL. Inflammation and atherosclerosis—revisited. *J Cardiovasc Pharmacol Ther* 2014;**19**: 170–178.
8. Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* 2016;**118**:620–636.
9. Rao RM, Yang L, Garcia-Cardena G, Luscinskas FW. Endothelial-dependent mechanisms of leukocyte recruitment to the vascular wall. *Circ Res* 2007;**101**:234–247.
10. Yan ZQ, Hansson GK. Innate immunity, macrophage activation, and atherosclerosis. *Immunol Rev* 2007;**219**:187–203.
11. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. *Nat Rev Immunol* 2006;**6**:508–519.
12. Weber C, Zernecke A, Libby P. The multifaceted contributions of leukocyte subsets to atherosclerosis: lessons from mouse models. *Nat Rev Immunol* 2008;**8**: 802–815.
13. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res* 2016;**118**:692–702.
14. Linton MF, Tao H, Linton EF, Yancey PG. SR-BI: a multifunctional receptor in cholesterol homeostasis and atherosclerosis. *Trends Endocrinol Metab* 2017;**28**:461–472.
15. Silverstein RL, Febbraio M. CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior. *Sci Signal* 2009;**2**:re3–re3.
16. Dieckmann M, Dietrich MF, Herz J. Lipoprotein receptors–an evolutionarily ancient multifunctional receptor family. *Biol Chem* 2010;**391**:1341–1363.
17. Krieger M, Herz J. Structures and functions of multiligand lipoprotein receptors: macrophage scavenger receptors and LDL receptor-related protein (LRP). *Annu Rev Biochem* 1994;**63**:601–637.
18. Kattoor AJ, Goel A, Mehta JL. LOX-1: regulation, signaling and its role in atherosclerosis. *Antioxidants (Basel)* 2019;**8**:218.
19. Babaev VR, Runner RP, Fan D, Ding L, Zhang Y, Tao H, Erbay E, Görgün CZ, Fazio S, Hotamisligil GS, Linton MF. Macrophage Mal1 deficiency suppresses atherosclerosis in low-density lipoprotein receptor-null mice by activating peroxisome proliferator-activated receptor-gamma-regulated genes. *Arterioscler Thromb Vasc Biol* 2011;**31**:1283–1290.
20. Kelley JL, Ozment TR, Li C, Schweitzer JB, Williams DL. Scavenger receptor-A (CD204): a two-edged sword in health and disease. *Crit Rev Immunol* 2014;**34**: 241–261.
21. Suzuki H, Kurihara Y, Takeya M, Kamada N, Kataoka M, Jishage K, Ueda O, Sakaguchi H, Higashi T, Suzuki T, Takashima Y, Kawabe Y, Cynshi O, Wada Y, Honda M, Kurihara H, Aburatani H, Doi T, Matsumoto A, Azuma S, Noda T, Toyoda Y, Itakura H, Yazaki Y, Horiuchi S, Takahashi K, Kruijt JK, van Berkel TJC, Steinbrecher UP, Ishibashi S, Maeda N, Gordon S, Kodama T. A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. *Nature* 1997;**386**:292–296.
22. Theocharis AD. Versican in health and disease. *Connect Tissue Res* 2008;**49**:230–234.
23. Wight TN, Merrilees MJ. Proteoglycans in atherosclerosis and restenosis: key roles for versican. *Circ Res* 2004;**94**:1158–1167.
24. Tran-Lundmark K, Tran PK, Paulsson-Berne G, Friden V, Soininen R, Tryggvason K. Heparan sulfate in perlecan promotes mouse atherosclerosis: roles in lipid permeability, lipid retention, and smooth muscle cell proliferation. *Circ Res* 2008;**103**: 43–52.
25. Vikramadithyan RK, Kako Y, Chen G, Hu Y, Arikawa-Hirasawa E, Yamada Y, Goldberg IJ. Atherosclerosis in perlecan heterozygous mice. *J Lipid Res* 2004;**45**: 1806–1812.
26. Wight TN. A role for proteoglycans in vascular disease. *Matrix Biol* 2018;**71-72**: 396–420.
27. Kurano M, Yatomi Y. Sphingosine 1-phosphate and atherosclerosis. *J Atheroscler Thromb* 2018;**25**:16–26.
28. Mihanfar A, Nejabati HR, Fattahi A, Latifi Z, Pezeshkian M, Afrasiabi A, Safaie N, Jodati AR, Nouri M. The role of sphingosine 1 phosphate in coronary artery disease and ischemia reperfusion injury. *J Cell Physiol* 2019;**234**:2083–2094.
29. Poti F, Simoni M, Nofer JR. Atheroprotective role of high-density lipoprotein (HDL)-associated sphingosine-1-phosphate (S1P). *Cardiovasc Res* 2014;**103**:395–404.
30. Weigert A, Olesch C, Brune B. Sphingosine-1-phosphate and macrophage biology-how the sphinx tames the big eater. *Front Immunol* 2019;**10**:1706.
31. Boucher P, Gotthardt M, Li WP, Anderson RG, Herz J. LRP: role in vascular wall integrity and protection from atherosclerosis. *Science* 2003;**300**:329–332.
32. Basford JE, Moore ZW, Zhou L, Herz J, Hui DY. Smooth muscle LDL receptor-related protein-1 inactivation reduces vascular reactivity and promotes injury-induced neointima formation. *Arterioscler Thromb Vasc Biol* 2009;**29**:1772–1778.
33. Boucher P, Li W-P, Matz RL, Takayama Y, Auwerx J, Anderson RGW, Herz J. LRP1 functions as an atheroprotective integrator of TGFbeta and PDFG signals in the vascular wall: implications for Marfan syndrome. *PLoS One* 2007;**2**:e448.
34. Muratoglu SC, Belgrave S, Hampton B, Migliorini M, Coksaygan T, Chen L, Mikhailenko I, Strickland DK. LRP1 protects the vasculature by regulating levels of connective tissue growth factor and HtrA1. *Arterioscler Thromb Vasc Biol* 2013;**33**: 2137–2146.
35. Zhou L, Takayama Y, Boucher P, Tallquist MD, Herz J. LRP1 regulates architecture of the vascular wall by controlling PDGFRbeta-dependent phosphatidylinositol 3-kinase activation. *PLoS One* 2009;**4**:e6922.
36. Newton CS, Loukinova E, Mikhailenko I, Ranganathan S, Gao Y, Haudenschild C, Strickland DK. Platelet-derived growth factor receptor-beta (PDGFR-beta) activation promotes its association with the low density lipoprotein receptor-related protein (LRP). Evidence for co-receptor function. *J Biol Chem* 2005;**280**:27872–27878.
37. Muratoglu SC, Mikhailenko I, Newton C, Migliorini M, Strickland DK. Low density lipoprotein receptor-related protein 1 (LRP1) forms a signaling complex with platelet-derived growth factor receptor-beta in endosomes and regulates activation of the MAPK pathway. *J Biol Chem* 2010;**285**:14308–14317.
38. Loukinova E, Ranganathan S, Kuznetsov S, Gorlatova N, Migliorini MM, Loukinov D, Ulery PG, Mikhailenko I, Lawrence DA, Strickland DK. Platelet-derived growth factor (PDGF)-induced tyrosine phosphorylation of the low density lipoprotein receptor-related protein (LRP). Evidence for integrated co-receptor function betwenn LRP and the PDGF. *J Biol Chem* 2002;**277**:15499–15506.
39. Craig J, Mikhailenko I, Noyes N, Migliorini M, Strickland DK. The LDL receptor-related protein 1 (LRP1) regulates the PDGF signaling pathway by binding the protein phosphatase SHP-2 and modulating SHP-2- mediated PDGF signaling events. *PLoS One* 2013;**8**:e70432.
40. Takayama Y, May P, Anderson RG, Herz J. Low density lipoprotein receptor-related protein 1 (LRP1) controls endocytosis and c-CBL-mediated ubiquitination of the platelet-derived growth factor receptor beta (PDGFR beta). *J Biol Chem* 2005;**280**: 18504–18510.
41. Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, Baxter BT. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. *J Clin Invest* 2002; **110**:625–632.
42. Xiong W, Knispel R, MacTaggart J, Greiner TC, Weiss SJ, Baxter BT. Membrane-type 1 matrix metalloproteinase regulates macrophage-dependent elastolytic activity and aneurysm formation in vivo. *J Biol Chem* 2009;**284**:1765–1771.
43. Phanish MK, Winn SK, Dockrell ME. Connective tissue growth factor-(CTGF, CCN2)—a marker, mediator and therapeutic target for renal fibrosis. *Nephron Exp Nephrol* 2010;**114**:e83–e92.
44. Chan CY, Chan YC, Cheuk BL, Cheng SW. A pilot study on low-density lipoprotein receptor-related protein-1 in Chinese patients with abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2013;**46**:549–556.
45. Calvier L, Boucher P, Herz J, Hansmann G. LRP1 deficiency in vascULAR SMC leads to pulmonary arterial hypertension that is reversed by PPARgamma activation. *Circ Res* 2019;**124**:1778–1785.
46. Hu L, Boesten LSM, May P, Herz J, Bovenschen N, Huisman MV, Berbée JFP, Havekes LM, van Vlijmen BJM, Tamsma JT. Macrophage low-density lipoprotein receptor-related protein deficiency enhances atherosclerosis in ApoE/LDLR double knockout mice. *Arterioscler Thromb Vasc Biol* 2006;**26**:2710–2715.
47. Overton CD, Yancey PG, Major AS, Linton MF, Fazio S. Deletion of macrophage LDL receptor-related protein increases atherogenesis in the mouse. *Circ Res* 2007; **100**:670–677.
48. Yancey PG, Blakemore J, Ding L, Fan D, Overton CD, Zhang Y, Linton MF, Fazio S. Macrophage LRP-1 controls plaque cellularity by regulating efferocytosis and Akt activation. *Arterioscler Thromb Vasc Biol* 2010;**30**:787–795.
49. Gordts PL, Reekmans S, Lauwers A, Van DA, Verbeek L, Roebroek AJ. Inactivation of the LRP1 intracellular NPxYxxL motif in LDLR-deficient mice enhances postprandial dyslipidemia and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2009;**29**: 1258–1264.
50. Keramati AR, Singh R, Lin A, Faramarzi S, Ye Z-J, Mane S, Tellides G, Lifton RP, Mani A. Wild-type LRP6 inhibits, whereas atherosclerosis-linked LRP6R611C increases PDGF-dependent vascular smooth muscle cell proliferation. *Proc Natl Acad Sci USA* 2011;**108**:1914–1918.
51. Srivastava R, Zhang J, Go GW, Narayanan A, Nottoli TP, Mani A. Impaired LRP6-TCF7L2 activity enhances smooth muscle cell plasticity and causes coronary artery disease. *Cell Rep* 2015;**13**:746–759.
52. Cheng S-L, Ramachandran B, Behrmann A, Shao J-S, Mead M, Smith C, Krchma K, Bello Arredondo Y, Kovacs A, Kapoor K, Brill LM, Perera R, Williams BO, Towler DA. Vascular smooth muscle LRP6 limits arteriosclerotic calcification in diabetic LDLR-/- mice by restraining noncanonical Wnt signals. *Circ Res* 2015;**117**:142–156.

53. Borrell-Pages M, Romero JC, Juan-Babot O, Badimon L. Wnt pathway activation, cell migration, and lipid uptake is regulated by low-density lipoprotein receptor-related protein 5 in human macrophages. *Eur Heart J* 2011;**32**:2841–2850.
54. Borrell-Pages M, Romero JC, Badimon L. LRP5 deficiency down-regulates Wnt signalling and promotes aortic lipid infiltration in hypercholesterolaemic mice. *J Cell Mol Med* 2015;**19**:770–777.
55. Ulrich V, Konaniah ES, Herz J, Gerard RD, Jung E, Yuhanna IS, Ahmed M, Hui DY, Mineo C, Shaul PW. Genetic variants of ApoE and ApoER2 differentially modulate endothelial function. *Proc Natl Acad Sci USA* 2014;**111**:13493–13498.
56. Ding Y, Huang L, Xian X, Yuhanna IS, Wasser CR, Frotscher M, Mineo C, Shaul PW, Herz J. Loss of Reelin protects against atherosclerosis by reducing leukocyte-endothelial cell adhesion and lesion macrophage accumulation. *Sci Signal* 2016;**9**: ra29–ra29.
57. Waltmann MD, Basford JE, Konaniah ES, Weintraub NL, Hui DY. Apolipoprotein E receptor-2 deficiency enhances macrophage susceptibility to lipid accumulation and cell death to augment atherosclerotic plaque progression and necrosis. *Biochim Biophys Acta* 2014;**1842**:1395–1405.
58. Chen X, Guo Z, Okoro EU, Zhang H, Zhou L, Lin X, Rollins AT, Yang H. Up-regulation of ATP binding cassette transporter A1 expression by very low density lipoprotein receptor and apolipoprotein E receptor 2. *J Biol Chem* 2012;**287**: 3751–3759.
59. Baitsch D, Bock HH, Engel T, Telgmann R, Müller-Tidow C, Varga G, Bot M, Herz J, Robenek H, von Eckardstein A, Nofer J-R. Apolipoprotein E induces antiinflammatory phenotype in macrophages. *Arterioscler Thromb Vasc Biol* 2011;**31**:1160–1168.
60. Riddell DR, Vinogradov DV, Stannard AK, Chadwick N, Owen JS. Identification and characterization of LRP8 (apoER2) in human blood platelets. *J Lipid Res* 1999;**40**: 1925–1930.
61. Korporaal SJA, Relou IAM, van Eck M, Strasser V, Bezemer M, Gorter G, van Berkel TJC, Nimpf J, Akkerman J-WN, Lenting PJ. Binding of low density lipoprotein to platelet apolipoprotein E receptor 2' results in phosphorylation of p38MAPK. *J Biol Chem* 2004;**279**:52526–52534.
62. Pennings MT, Derksen RH, Urbanus RT, Tekelenburg WL, Hemrika W, de Groot PG. Platelets express three different splice variants of ApoER2 that are all involved in signaling. *J Thromb Haemost* 2007;**5**:1538–1544.
63. Riddell DR, Graham A, Owen JS. Apolipoprotein E inhibits platelet aggregation through the L-arginine: nitric oxide pathway. Implications for vascular disease. *J Biol Chem* 1997;**272**:89–95.
64. Robertson JO, Li W, Silverstein RL, Topol EJ, Smith JD. Deficiency of LRP8 in mice is associated with altered platelet function and prolonged time for in vivo thrombosis. *Thromb Res* 2009;**123**:644–652.
65. Hiltunen TP, Luoma JS, Nikkari T, Yla-Herttuala S. Expression of LDL receptor, VLDL receptor, LDL receptor-related protein, and scavenger receptor in rabbit atherosclerotic lesions: marked induction of scavenger receptor and VLDL receptor expression during lesion development. *Circulation* 1998;**97**:1079–1086.
66. Multhaupt HA, Gåfvels ME, Kariko K, Jin H, Arenas-Elliot C, Goldman BI, Strauss JF, Angelin B, Warhol MJ, McCrae KR. Expression of very low density lipoprotein receptor in the vascular wall. Analysis of human tissues by in situ hybridization and immunohistochemistry. *Am J Pathol* 1996;**148**:1985–1997.
67. Argraves KM, Kozarsky KF, Fallon JT, Harpel PC, Strickland DK. The atherogenic lipoprotein Lp(a) is internalized and degraded in a process mediated by the VLDL receptor. *J Clin Invest* 1997;**100**:2170–2181.
68. Nakazato K, Ishibashi T, Shindo J, Shiomi M, Maruyama Y. Expression of very low density lipoprotein receptor mRNA in rabbit atherosclerotic lesions. *Am J Pathol* 1996;**149**:1831–1838.
69. Tacken PJ, Delsing DJM, Gijbels MJJ, Quax PHA, Havekes LM, Hofker MH, van Dijk KW. VLDL receptor deficiency enhances intimal thickening after vascular injury but does not affect atherosclerotic lesion area. *Atherosclerosis* 2002;**162**:103–110.
70. Eck M, Oost J, Goudriaan J, Hoekstra M, Hildebrand R, Bos I, Vandijk K, Vanberkel T. Role of the macrophage very-low-density lipoprotein receptor in atherosclerotic lesion development. *Atherosclerosis* 2005;**183**:230–237.
71. Strickland DK, Au DT, Cunfer P, Muratoglu SC. Low-density lipoprotein receptor-related protein-1: role in the regulation of vascular integrity. *Arterioscler Thromb Vasc Biol* 2014;**34**:487–498.
72. Kowal RC, Herz J, Goldstein JL, Esser V, Brown MS. Low density lipoprotein receptor-related protein mediates uptake of cholesteryl esters derived from apoprotein E-enriched lipoproteins. *Proc Natl Acad Sci USA* 1989;**86**:5810–5814.
73. Rohlmann A, Gotthardt M, Hammer RE, Herz J. Inducible inactivation of hepatic LRP gene by cre-mediated recombination confirms role of LRP in clearance of chylomicron remnants. *J Clin Invest* 1998;**101**:689–695.
74. Kristensen T, Moestrup SK, Gliemann J, Bendtsen L, Sand O, Sottrup-Jensen L. Evidence that the newly cloned low-density-lipoprotein receptor related protein (LRP) is the alpha 2-macroglobulin receptor. *FEBS Lett* 1990;**276**:151–155.
75. Strickland DK, Ashcom JD, Williams S, Burgess WH, Migliorini M, Argraves WS. Sequence identity between the alpha 2-macroglobulin receptor and low density lipoprotein receptor-related protein suggests that this molecule is a multifunctional receptor. *J Biol Chem* 1990;**265**:17401–17404.
76. Gonias SL, Campana WM. LDL receptor-related protein-1: a regulator of inflammation in atherosclerosis, cancer, and injury to the nervous system. *Am J Pathol* 2014; **184**:18–27.
77. Polavarapu R, Gongora MC, Yi H, Ranganthan S, Lawrence DA, Strickland D, Yepes M. Tissue-type plasminogen activator-mediated shedding of astrocytic low-density lipoprotein receptor-related protein increases the permeability of the neurovascular unit. *Blood* 2007;**109**:3270–3278.
78. Su EJ, Fredriksson L, Geyer M, Folestad E, Cale J, Andrae J, Gao Y, Pietras K, Mann K, Yepes M, Strickland DK, Betsholtz C, Eriksson U, Lawrence DA. Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. *Nat Med* 2008;**14**:731–737.
79. Yepes M, Sandkvist M, Moore EG, Bugge TH, Strickland DK, Lawrence DA. Tissue-type plasminogen activator induces opening of the blood-brain barrier via the LDL receptor-related protein. *J Clin Invest* 2003;**112**:1533–1540.
80. Cao C, Lawrence DA, Li Y, Von Arnim CAF, Herz J, Su EJ, Makarova A, Hyman BT, Strickland DK, Zhang L. Endocytic receptor LRP together with tPA and PAI-1 coordinates Mac-1-dependent macrophage migration. *EMBO J* 2006;**25**:1860–1870.
81. Muratoglu SC, Belgrave S, Lillis AP, Migliorini M, Robinson S, Smith E, Zhang L, Strickland DK. Macrophage LRP1 suppresses neo-intima formation during vascular remodeling by modulating the TGF-beta signaling pathway. *PLoS One* 2011;**6**: e28846.
82. Herz J, Clouthier DE, Hammer RE. LDL receptor-related protein internalizes and degrades uPA-PAI-1 complexes and is essential for embryo implantation. *Cell* 1992; **71**:411–421.
83. Ranganathan S, Cao C, Catania J, Migliorini M, Zhang L, Strickland DK. Molecular basis for the interaction of low density lipoprotein receptor-related protein 1 (LRP1) with integrin alphaMbeta2: identification of binding sites within alphaMbeta2 for LRP1. *J Biol Chem* 2011;**286**:30535–30541.
84. Martin AM, Kuhlmann C, Trossbach S, Jaeger S, Waldron E, Roebroek A, Luhmann HJ, Laatsch A, Weggen S, Lessmann V, Pietrzik CU. The functional role of the second NPXY motif of the LRP1 beta-chain in tissue-type plasminogen activator-mediated activation of N-methyl-D-aspartate receptors. *J Biol Chem* 2008;**283**: 12004–12013.
85. Zurhove K, Nakajima C, Herz J, Bock HH, May P. Gamma-secretase limits the inflammatory response through the processing of LRP1. *Sci Signal* 2008;**1**:ra15.
86. Gorovoy M, Gaultier A, Campana WM, Firestein GS, Gonias SL. Inflammatory mediators promote production of shed LRP1/CD91, which regulates cell signaling and cytokine expression by macrophages. *J Leukoc Biol* 2010;**88**:769–778.
87. Bown MJ, Jones GT, Harrison SC, Wright BJ, Bumpstead S, Baas AF, Gretarsdottir S, Badger SA, Bradley DT, Burnand K, Child AH, Clough RE, Cockerill G, Hafez H, Scott DJA, Futers S, Johnson A, Sohrabi S, Smith A, Thompson MM, van Bockxmeer FM, Waltham M, Matthiasson SE, Thorleifsson G, Thorsteinsdottir U, Blankensteijn JD, Teijink JAW, Wijmenga C, de Graaf J, Kiemeney LA, Assimes TL, McPherson R, Folkersen L, Franco-Cereceda A, Palmen J, Smith AJ, Sylvius N, Wild JB, Refstrup M, Edkins S, Gwilliam R, Hunt SE, Potter S, Lindholt JS, Frikke-Schmidt R, Tybjærg-Hansen A, Hughes AE, Golledge J, Norman PE, van Rij A, Powell JT, Eriksson P, Stefansson K, Thompson JR, Humphries SE, Sayers RD, Deloukas P, Samani NJ. Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. *Am J Hum Genet* 2011;**89**:619–627.
88. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee J-Y, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RYL, Wright AF, Witteman JCM, Wilson JF, Willemsen G, Wichmann H-E, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJG, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BWJH, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PKE, Lucas G, Luben R, Loos RJF, Lokki M-L, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw K-T, Kaprio J, Kaplan LM, Johansson Å, Jarvelin M-R, Cecile J. W. Janssens A, Ingelsson E, Igl W, Kees Hovingh G, Hottenga J-J, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJC, de Faire U, Crawford G, Collins FS, Chen Y-D. I, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai E-S, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJP, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S.

Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010; **466**:707–713.

89. McCarthy JJ, Parker A, Salem R, Moliterno DJ, Wang Q, Plow EF, et al. Large scale association analysis for identification of genes underlying premature coronary heart disease: cumulative perspective from analysis of 111 candidate genes. *J Med Genet* 2004;**41**:334–341.
90. Ross R. Platelet-derived growth factor. *Annu Rev Med* 1987;**38**:71–79.
91. Caglayan E, Vantler M, Leppänen O, Gerhardt F, Mustafov L, ten Freyhaus H, Kappert K, Odenthal M, Zimmermann WH, Tallquist MD, Rosenkranz S. Disruption of platelet-derived growth factor-dependent phosphatidylinositol 3-kinase and phospholipase Cgamma 1 activity abolishes vascular smooth muscle cell proliferation and migration and attenuates neointima formation in vivo. *J Am Coll Cardiol* 2011;**57**:2527–2538.
92. Ferns GA, Raines EW, Sprugel KH, Motani AS, Reidy MA, Ross R. Inhibition of neointimal smooth muscle accumulation after angioplasty by an antibody to PDGF. *Science* 1991;**253**:1129–1132.
93. Yamasaki Y, Miyoshi K, Oda N, Watanabe M, Miyake H, Chan J, Wang X, Sun L, Tang C, McMahon G, Lipson KE. Weekly dosing with the platelet-derived growth factor receptor tyrosine kinase inhibitor SU9518 significantly inhibits arterial stenosis. *Circ Res* 2001;**88**:630–636.
94. Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem Sci* 2003;**28**:284–293.
95. Gillis E, Van LL, Loeys BL. Genetics of thoracic aortic aneurysm: at the crossroad of transforming growth factor-beta signaling and vascular smooth muscle cell contractility. *Circ Res* 2013;**113**:327–340.
96. Guo D-C, Papke CL, Tran-Fadulu V, Regalado ES, Avidan N, Johnson RJ, Kim DH, Pannu H, Willing MC, Sparks E, Pyeritz RE, Singh MN, Dalman RL, Grotta JC, Marian AJ, Boerwinkle EA, Frazier LQ, LeMaire SA, Coselli JS, Estrera AL, Safi HJ, Veeraraghavan S, Muzny DM, Wheeler DA, Willerson JT, Yu RK, Shete SS, Scherer SE, Raman CS, Buja LM, Milewicz DM. Mutations in smooth muscle alpha-actin (ACTA2) cause coronary artery disease, stroke, and Moyamoya disease, along with thoracic aortic disease. *Am J Hum Genet* 2009;**84**:617–627.
97. Nabel EG, Shum L, Pompili VJ, Yang ZY, San H, Shu HB, Liptay S, Gold L, Gordon D, Derynck R. Direct transfer of transforming growth factor beta 1 gene into arteries stimulates fibrocellular hyperplasia. *Proc Natl Acad Sci USA* 1993;**90**: 10759–10763.
98. Yamamoto K, Morishita R, Tomita N, Shimozato T, Nakagami H, Kikuchi A, Aoki M, Higaki J, Kaneda Y, Ogihara T. Ribozyme oligonucleotides against transforming growth factor-beta inhibited neointimal formation after vascular injury in rat model: potential application of ribozyme strategy to treat cardiovascular disease. *Circulation* 2000;**102**:1308–1314.
99. Smith JD, Bryant SR, Couper LL, Vary CPH, Gotwals PJ, Koteliansky VE, Lindner V. Soluble transforming growth factor-beta type II receptor inhibits negative remodeling, fibroblast transdifferentiation, and intimal lesion formation but not endothelial growth. *Circ Res* 1999;**84**:1212–1222.
100. Huang SS, Ling T-Y, Tseng W-F, Huang Y-H, Tang F-M, Leal SM, Huang JS. Cellular growth inhibition by IGFBP-3 and TGF-beta1 requires LRP-1. *FASEB J* 2003;**17**: 2068–2081.
101. Brown SD, Twells RCJ, Hey PJ, Cox RD, Levy ER, Soderman AR, Metzker ML, Caskey CT, Todd JA, Hess JF. Isolation and characterization of LRP6, a novel member of the low density lipoprotein receptor gene family. *Biochem Biophys Res Commun* 1998;**248**:879–888.
102. Hey PJ, Twells RC, Phillips MS, Yusuke N, Brown SD, Kawaguchi Y, et al. Cloning of a novel member of the low-density lipoprotein receptor family. *Gene* 1998;**216**: 103–111.
103. Abou Ziki MD, Mani A. The interplay of canonical and noncanonical Wnt signaling in metabolic syndrome. *Nutr Res* 2019;**70**:18–25.
104. Mi K, Johnson GV. Role of the intracellular domains of LRP5 and LRP6 in activating the Wnt canonical pathway. *J Cell Biochem* 2005;**95**:328–338.
105. Clevers H. Wnt/beta-catenin signaling in development and disease. *Cell* 2006;;**127**: 469–480.
106. Edeling M, Ragi G, Huang S, Pavenstadt H, Susztak K. Developmental signalling pathways in renal fibrosis: the roles of Notch, Wnt and Hedgehog. *Nat Rev Nephrol* 2016;**12**:426–439.
107. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol* 2004;**20**:781–810.
108. Mao J, Wang J, Liu B, Pan W, Farr GH, Flynn C, Yuan H, Takada S, Kimelman D, Li L, Wu D. Low-density lipoprotein receptor-related protein-5 binds to Axin and regulates the canonical Wnt signaling pathway. *Mol Cell* 2001;**7**:801–809.
109. Pinson KI, Brennan J, Monkley S, Avery BJ, Skarnes WC. An LDL-receptor-related protein mediates Wnt signalling in mice. *Nature* 2000;**407**:535–538.
110. Tamai K, Semenov M, Kato Y, Spokony R, Liu C, Katsuyama Y, Hess F, Saint-Jeannet J-P, He X. LDL-receptor-related proteins in Wnt signal transduction. *Nature* 2000; **407**:530–535.
111. Wehrli M, Dougan ST, Caldwell K, O'Keefe L, Schwartz S, Vaizel-Ohayon D, Schejter E, Tomlinson A, DiNardo S. Arrow encodes an LDL-receptor-related protein essential for Wingless signalling. *Nature* 2000;**407**:527–530.
112. Johnson ML, Harnish K, Nusse R, Van HW. LRP5 and Wnt signaling: a union made for bone. *J Bone Miner Res* 2004;**19**:1749–1757.
113. Komiya Y, Habas R. Wnt signal transduction pathways. *Organogenesis* 2008;**4**:68–75.
114. Mani A, Radhakrishnan J, Wang H, Mani A, Mani M-A, Nelson-Williams C, Carew KS, Mane S, Najmabadi H, Wu D, Lifton RP. LRP6 mutation in a family with early coronary disease and metabolic risk factors. *Science* 2007;**315**:1278–1282.
115. Cheng Z, Biechele T, Wei Z, Morrone S, Moon RT, Wang L, Xu W. Crystal structures of the extracellular domain of LRP6 and its complex with DKK1. *Nat Struct Mol Biol* 2011;**18**:1204–1210.
116. Singh R, Smith E, Fathzadeh M, Liu W, Go G-W, Subrahmanyan L, Faramarzi S, McKenna W, Mani A. Rare nonconservative LRP6 mutations are associated with metabolic syndrome. *Hum Mutat* 2013;**34**:1221–1225.
117. Tomaszewski M, Charchar FJ, Barnes T, Gawron-Kiszka M, Sedkowska A, Podolecka E, Kowalczyk J, Rathbone W, Kalarus Z, Grzeszczak W, Goodall AH, Samani NJ, Zukowska-Szczechowska E. A common variant in low-density lipoprotein receptor-related protein 6 gene (LRP6) is associated with LDL-cholesterol. *Arterioscler Thromb Vasc Biol* 2009;**29**:1316–1321.
118. Liu W, Mani S, Davis NR, Sarrafzadegan N, Kavathas PB, Mani A. Mutation in EGFP domain of LDL receptor-related protein 6 impairs cellular LDL clearance. *Circ Res* 2008;**103**:1280–1288.
119. Joiner DM, Ke J, Zhong Z, Xu HE, Williams BO. LRP5 and LRP6 in development and disease. *Trends Endocrinol Metab* 2013;**24**:31–39.
120. Ashouri E, Meimandi EM, Saki F, Dabbaghmanesh MH, Omrani GR, Bakhshayeshkaram M. The impact of LRP5 polymorphism (rs556442) on calcium homeostasis, bone mineral density, and body composition in Iranian children. *J Bone Miner Metab* 2015;**33**:651–657.
121. Chubachi S, the Keio COPD Comorbidity Research (K-CCR) Group, Nakamura H, Sasaki M, Haraguchi M, Miyazaki M, Takahashi S, Tanaka K, Funatsu Y, Asano K, Betsuyaku T. Polymorphism of LRP5 gene and emphysema severity are associated with osteoporosis in Japanese patients with or at risk for COPD. *Respirology* 2015; **20**:286–295.
122. Mendez JP, Rojano-Mejia D, Coral-Vazquez RM, Coronel A, Pedraza J, Casas MJ, et al. Impact of genetic variants of IL-6, IL6R, LRP5, ESR1 and SP7 genes on bone mineral density in postmenopausal Mexican-Mestizo women with obesity. *Gene* 2013;**528**:216–220.
123. Xuan M, Wang Y, Wang W, Yang J, Li Y, Zhang X. Association of LRP5 gene polymorphism with type 2 diabetes mellitus and osteoporosis in postmenopausal women. *Int J Clin Exp Med* 2014;**7**:247–254.
124. Fujino T, Asaba H, Kang M-J, Ikeda Y, Sone H, Takada S, Kim D-H, Ioka RX, Ono M, Tomoyori H, Okubo M, Murase T, Kamataki A, Yamamoto J, Magoori K, Takahashi S, Miyamoto Y, Oishi H, Nose M, Okazaki M, Usui S, Imaizumi K, Yanagisawa M, Sakai J, Yamamoto TT. Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion. *Proc Natl Acad Sci USA* 2003;**100**:229–234.
125. Frykman PK, Brown MS, Yamamoto T, Goldstein JL, Herz J. Normal plasma lipoproteins and fertility in gene-targeted mice homozygous for a disruption in the gene encoding very low density lipoprotein receptor. *Proc Natl Acad Sci USA* 1995;**92**: 8453–8457.
126. Herz J. Apolipoprotein E receptors in the nervous system. *Curr Opin Lipidol* 2009;**20**: 190–196.
127. Hiesberger T, Trommsdorff M, Howell BW, Goffinet A, Mumby MC, Cooper JA, Herz J. Direct binding of Reelin to VLDL receptor and ApoE receptor 2 induces tyrosine phosphorylation of disabled-1 and modulates tau phosphorylation. *Neuron* 1999;**24**:481–489.
128. Trommsdorff M, Gotthardt M, Hiesberger T, Shelton J, Stockinger W, Nimpf J, Hammer RE, Richardson JA, Herz J. Reeler/disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell* 1999;**97**:689–701.
129. Pennings MTT, Derksen RHWM, VAN Lummel M, Adelmeijer J, Vanhoorelbeke K, Urbanus RT, Lisman T, DE Groot PG. Platelet adhesion to dimeric beta-glycoprotein I under conditions of flow is mediated by at least two receptors: glycoprotein Ibalpha and apolipoprotein E receptor. *J Thromb Haemost* 2007;**5**:369–377.
130. Swertfeger DK, Hui DY. Apolipoprotein E receptor binding versus heparan sulfate proteoglycan binding in its regulation of smooth muscle cell migration and proliferation. *J Biol Chem* 2001;**276**:25043–25048.
131. Yang XV, Banerjee Y, Fernandez JA, Deguchi H, Xu X, Mosnier LO, Urbanus RT, de Groot PG, White-Adams TC, McCarty OJT, Griffin JH. Activated protein C ligation of ApoER2 (LRP8) causes Dab1-dependent signaling in U937 cells. *Proc Natl Acad Sci USA* 2009;**106**:274–279.
132. Sacharidou A, Shaul PW, Mineo C. New insights in the pathophysiology of antiphospholipid syndrome. *Semin Thromb Hemost* 2018;**44**:475–482.
133. Martinelli N, Olivieri O, Shen G-Q, Trabetti E, Pizzolo F, Busti F, Friso S, Bassi A, Li L, Hu Y, Pignatti PF, Corrocher R, Wang QK, Girelli D. Additive effect of LRP8/ APOER2 R952Q variant to APOE epsilon2/epsilon3/epsilon4 genotype in modulating apolipoprotein E concentration and the risk of myocardial infarction: a case-control study. *BMC Med Genet* 2009;**10**:41.
134. Shen G-Q, Girelli D, Li L, Rao S, Archacki S, Olivieri O, Martinelli N, Park JE, Chen Q, Topol EJ, Wang QK. A novel molecular diagnostic marker for familial and early-onset coronary artery disease and myocardial infarction in the LRP8 gene. *Circ Cardiovasc Genet* 2014;**7**:514–520.

135. Shen G-Q, Li L, Girelli D, Seidelmann SB, Rao S, Fan C, Park JE, Xi Q, Li J, Hu Y, Olivieri O, Marchant K, Barnard J, Corrocher R, Elston R, Cassano J, Henderson S, Hazen SL, Plow EF, Topol EJ, Wang QK. An LRP8 variant is associated with familial and premature coronary artery disease and myocardial infarction. *Am J Hum Genet* 2007;**81**:780–791.
136. Wang Q, Rao S, Shen G-Q, Li L, Moliterno DJ, Newby LK, Rogers WJ, Cannata R, Zirzow E, Elston RC, Topol EJ. Premature myocardial infarction novel susceptibility locus on chromosome 1P34-36 identified by genomewide linkage analysis. *Am J Hum Genet* 2004;**74**:262–271.
137. Herz J, Chen Y. Reelin, lipoprotein receptors and synaptic plasticity. *Nat Rev Neurosci* 2006;**7**:850–859.
138. Smalheiser NR, Costa E, Guidotti A, Impagnatiello F, Auta J, Lacor P, Kriho V, Pappas GD. Expression of reelin in adult mammalian blood, liver, pituitary pars intermedia, and adrenal chromaffin cells. *Proc Natl Acad Sci USA* 2000;**97**:1281–1286.
139. Tseng W-L, Chen T-H, Huang C-C, Huang Y-H, Yeh C-F, Tsai H-J, Lee H-Y, Kao C-Y, Lin S-W, Liao H-R, Cheng J-C, Tseng C-P. Impaired thrombin generation in Reelin-deficient mice: a potential role of plasma Reelin in hemostasis. *J Thromb Haemost* 2014;**12**:2054–2064.
140. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *J Lipid Res* 2009;**50** Suppl:S183–S188.
141. Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med* 2004;**141**:137–147.
142. Ishibashi S, Brown MS, Goldstein JL, Gerard RD, Hammer RE, Herz J. Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. *J Clin Invest* 1993;**92**:883–893.
143. Tacken PJ, Teusink B, Jong MC, Harats D, Havekes LM, van Dijk KW, Hofker MH. LDL receptor deficiency unmasks altered VLDL triglyceride metabolism in VLDL receptor transgenic and knockout mice. *J Lipid Res* 2000;**41**:2055–2062.
144. Goudriaan JR, Tacken PJ, Dahlmans VEH, Gijbels MJJ, van Dijk KW, Havekes LM, Jong MC. Protection from obesity in mice lacking the VLDL receptor. *Arterioscler Thromb Vasc Biol* 2001;**21**:1488–1493.
145. Wyne KL, Pathak K, Seabra MC, Hobbs HH. Expression of the VLDL receptor in endothelial cells. *Arterioscler Thromb Vasc Biol* 1996;**16**:407–415.
146. Willer CJ, Global Lipids Genetics Consortium, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang H-Y, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson Å, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen L-P, Magnusson PKE, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen A-K, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney ASF, Döring A, Elliott P, Epstein SE, Ingi Eyjolfsson G, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen A-L, Hayward C, Hernandez D, Hicks AA, Holm H, Hung Y-J, Illig T, Jones MR, Kaleebu P, Kastelein JJP, Khaw K-T, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin S-Y, Lindström J, Loos RJF, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TVM, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen Y-DI, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin M-R, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PEH, Sheu WH-H, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BHR, Ordovas JM, Boerwinkle E, Palmer CNA, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E, Abecasis GR. Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013;**45**:1274–1283.
147. Crawford DC, Nord AS, Badzioch MD, Ranchalis J, McKinstry LA, Ahearn M, Bertucci C, Shephard C, Wong M, Rieder MJ, Schellenberg GD, Nickerson DA, Heagerty PJ, Wijsman EM, Jarvik GP. A common VLDLR polymorphism interacts with APOE genotype in the prediction of carotid artery disease risk. *J Lipid Res* 2008;**49**:588–596.
148. Davis JP, Vadlamudi S, Roman TS, Zeynalzadeh M, Iyengar AK, Mohlke KL. Enhancer deletion and allelic effects define a regulatory molecular mechanism at the VLDLR cholesterol GWAS locus. *Hum Mol Genet* 2019;**28**:888–895.
149. Yamada Y, Doi T, Hamakubo T, Kodama T. Scavenger receptor family proteins: roles for atherosclerosis, host defence and disorders of the central nervous system. *Cell Mol Life Sci* 1998;**54**:628–640.
150. PrabhuDas MR, Baldwin CL, Bollyky PL, Bowdish DME, Drickamer K, Febbraio M, Herz J, Kobzik L, Krieger M, Loike J, McVicker B, Means TK, Moestrup SK, Post SR, Sawamura T, Silverstein S, Speth RC, Telfer JC, Thiele GM, Wang X-Y, Wright SD, El Khoury J. A consensus definitive classification of scavenger receptors and their roles in health and disease. *J Immunol* 2017;**198**:3775–3789.
151. Nozaki S, Kashiwagi H, Yamashita S, Nakagawa T, Kostner B, Tomiyama Y, Nakata A, Ishigami M, Miyagawa J, Kameda-Takemura K. Reduced uptake of oxidized low density lipoproteins in monocyte-derived macrophages from CD36-deficient subjects. *J Clin Invest* 1995;**96**:1859–1865.
152. Febbraio M, Podrez EA, Smith JD, Hajjar DP, Hazen SL, Hoff HF, Sharma K, Silverstein RL. Targeted disruption of the class B scavenger receptor CD36 protects against atherosclerotic lesion development in mice. *J Clin Invest* 2000;**105**: 1049–1056.
153. Manning-Tobin JJ, Moore KJ, Seimon TA, Bell SA, Sharuk M, Alvarez-Leite JI, de Winther MPJ, Tabas I, Freeman MW. Loss of SR-A and CD36 activity reduces atherosclerotic lesion complexity without abrogating foam cell formation in hyperlipidemic mice. *Arterioscler Thromb Vasc Biol* 2009;**29**:19–26.
154. Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhelawon B, Carpenter SB, Becker CE, Ediriweera HN, Mullick AE, Golenbock DT, Stuart LM, Latz E, Fitzgerald KA, Moore KJ. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nat Immunol* 2013;**14**:812–820.
155. Park YM, Febbraio M, Silverstein RL. CD36 modulates migration of mouse and human macrophages in response to oxidized LDL and may contribute to macrophage trapping in the arterial intima. *J Clin Invest* 2009;**119**:136–145.
156. Park YM, Drazba JA, Vasanji A, Egelhoff T, Febbraio M, Silverstein RL. Oxidized LDL/CD36 interaction induces loss of cell polarity and inhibits macrophage locomotion. *Mol Biol Cell* 2012;**23**:3057–3068.
157. Rahaman SO, Li W, Silverstein RL. Vav Guanine nucleotide exchange factors regulate atherosclerotic lesion development in mice. *Arterioscler Thromb Vasc Biol* 2013; **33**:2053–2057.
158. Rahaman SO, Zhou G, Silverstein RL. Vav protein guanine nucleotide exchange factor regulates CD36 protein-mediated macrophage foam cell formation via calcium and dynamin-dependent processes. *J Biol Chem* 2011;**286**:36011–36019.
159. Bustelo XR. Vav family exchange factors: an integrated regulatory and functional view. *Small GTPases* 2014;**5**:9.
160. Klenotic PA, Page RC, Li W, Amick J, Misra S, Silverstein RL. Molecular basis of antiangiogenic thrombospondin-1 type 1 repeat domain interactions with CD36. *Arterioscler Thromb Vasc Biol* 2013;**33**:1655–1662.
161. Jimenez B, Volpert OV, Crawford SE, Febbraio M, Silverstein RL, Bouck N. Signals leading to apoptosis-dependent inhibition of neovascularization by thrombospondin-1. *Nat Med* 2000;**6**:41–48.
162. Chu LY, Ramakrishnan DP, Silverstein RL. Thrombospondin-1 modulates VEGF signaling via CD36 by recruiting SHP-1 to VEGFR2 complex in microvascular endothelial cells. *Blood* 2013;**122**:1822–1832.
163. Ramakrishnan DP, Hajj-Ali RA, Chen Y, Silverstein RL. Extracellular vesicles activate a CD36-dependent signaling pathway to inhibit microvascular endothelial cell migration and tube formation. *Arterioscler Thromb Vasc Biol* 2016;**36**:534–544.
164. Son N-H, Basu D, Samovski D, Pietka TA, Peche VS, Willecke F, Fang X, Yu S-Q, Scerbo D, Chang HR, Sun F, Bagdasarov S, Drosatos K, Yeh ST, Mullick AE, Shoghi KI, Gumaste N, Kim K, Huggins L-A, Lhakhang T, Abumrad NA, Goldberg IJ. Endothelial cell CD36 optimizes tissue fatty acid uptake. *J Clin Invest* 2018;**128**: 4329–4342.
165. Yue H, Febbraio M, Klenotic PA, Kennedy DJ, Wu Y, Chen S, Gohara AF, Li O, Belcher A, Kuang B, McIntyre TM, Silverstein RL, Li W. CD36 enhances vascular smooth muscle cell proliferation and development of neointimal hyperplasia. *Arterioscler Thromb Vasc Biol* 2019;**39**:263–275.
166. Yang M, Silverstein RL. CD36 signaling in vascular redox stress. *Free Radic Biol Med* 2019;**136**:159–171.
167. Podrez EA, Byzova TV, Febbraio M, Salomon RG, Ma Y, Valiyaveettil M, Poliakov E, Sun M, Finton PJ, Curtis BR, Chen J, Zhang R, Silverstein RL, Hazen SL. Platelet CD36 links hyperlipidemia, oxidant stress and a prothrombotic phenotype. *Nat Med* 2007;**13**:1086–1095.
168. Qiao J, Arthur JF, Gardiner EE, Andrews RK, Zeng L, Xu K. Regulation of platelet activation and thrombus formation by reactive oxygen species. *Redox Biol* 2018;**14**: 126–130.
169. Chen K, Febbraio M, Li W, Silverstein RL. A specific CD36-dependent signaling pathway is required for platelet activation by oxidized low-density lipoprotein. *Circ Res* 2008;**102**:1512–1519.

170. Yang M, Cooley BC, Li W, Chen Y, Vasquez-Vivar J, Scoggins NO, Cameron SJ, Morrell CN, Silverstein RL. Platelet CD36 promotes thrombosis by activating redox sensor ERK5 in hyperlipidemic conditions. *Blood* 2017;**129**:2917–2927.
171. Cameron SJ, Ture SK, Mickelsen D, Chakrabarti E, Modjeski KL, McNitt S, Seaberry M, Field DJ, Le N-T, Abe J-I, Morrell CN. Platelet extracellular regulated protein kinase 5 is a redox switch and triggers maladaptive platelet responses and myocardial infarct expansion. *Circulation* 2015;**132**:47–58.
172. Kamata H, Honda S, Maeda S, Chang L, Hirata H, Karin M. Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. *Cell* 2005;**120**:649–661.
173. Yang M, Kholmukhamedov A, Schulte ML, Cooley BC, Scoggins NO, Wood JP, Cameron SJ, Morrell CN, Jobe SM, Silverstein RL. Platelet CD36 signaling through ERK5 promotes caspase-dependent procoagulant activity and fibrin deposition in vivo. *Blood Adv* 2018;**2**:2848–2861.
174. Fuller M, Dadoo O, Serkis V, Abutouk D, MacDonald M, Dhingani N, Macri J, Igdoura SA, Trigatti BL. The effects of diet on occlusive coronary artery atherosclerosis and myocardial infarction in scavenger receptor class B, type 1/low-density lipoprotein receptor double knockout mice. *Arterioscler Thromb Vasc Biol* 2014;**34**: 2394–2403.
175. Tao H, Yancey PG, Babaev VR, Blakemore JL, Zhang Y, Ding L, Fazio S, Linton MF. Macrophage SR-BI mediates efferocytosis via Src/PI3K/Rac1 signaling and reduces atherosclerotic lesion necrosis. *J Lipid Res* 2015;**56**:1449–1460.
176. Covey SD, Krieger M, Wang W, Penman M, Trigatti BL. Scavenger receptor class B type I-mediated protection against atherosclerosis in LDL receptor-negative mice involves its expression in bone marrow-derived cells. *Arterioscler Thromb Vasc Biol* 2003;**23**:1589–1594.
177. Zhang W, Yancey PG, Su YR, Babaev VR, Zhang Y, Fazio S, Linton MF. Inactivation of macrophage scavenger receptor class B type I promotes atherosclerotic lesion development in apolipoprotein E-deficient mice. *Circulation* 2003;**108**:2258–2263.
178. Van EM, Bos IS, Hildebrand RB, Van Rij BT, van Berkel TJ. Dual role for scavenger receptor class B, type I on bone marrow-derived cells in atherosclerotic lesion development. *Am J Pathol* 2004;**165**:785–794.
179. Pei Y, Chen X, Aboutouk D, Fuller MT, Dadoo O, Yu P, White EJ, Igdoura SA, Trigatti BL. SR-BI in bone marrow derived cells protects mice from diet induced coronary artery atherosclerosis and myocardial infarction. *PLoS One* 2013;**8**:e72492.
180. Larrede S, Quinn CM, Jessup W, Frisdal E, Olivier M, Hsieh V, et al. Stimulation of cholesterol efflux by LXR agonists in cholesterol-loaded human macrophages is ABCA1-dependent but ABCG1-independent. *Arterioscler Thromb Vasc Biol* 2009;**29**: 1930–1936.
181. Langer C, Gansz B, Goepfert C, Engel T, Uehara Y, von Dehn G, Jansen H, Assmann G, von Eckardstein A. Testosterone up-regulates scavenger receptor BI and stimulates cholesterol efflux from macrophages. *Biochem Biophys Res Commun* 2002;**296**:1051–1057.
182. Badeau RM, Metso J, Wahala K, Tikkanen MJ, Jauhiainen M. Human macrophage cholesterol efflux potential is enhanced by HDL-associated 17beta-estradiol fatty acyl esters. *J Steroid Biochem Mol Biol* 2009;**116**:44–49.
183. Cai L, Wang Z, Meyer JM, Ji A, van der Westhuyzen DR. Macrophage SR-BI regulates LPS-induced pro-inflammatory signaling in mice and isolated macrophages. *J Lipid Res* 2012;**53**:1472–1481.
184. Pfeiler S, Khandagale AB, Magenau A, Nichols M, Heijnen HFG, Rinninger F, Ziegler T, Seveau S, Schubert S, Zahler S, Verschoor A, Latz E, Massberg S, Gaus K, Engelmann B. Distinct surveillance pathway for immunopathology during acute infection via autophagy and SR-BI. *Sci Rep* 2016;**6**:34440.
185. Linton MF, Babaev VR, Huang J, Linton EF, Tao H, Yancey PG. Macrophage apoptosis and efferocytosis in the pathogenesis of atherosclerosis. *Circ J* 2016;**80**: 2259–2268.
186. Huang L, Chambliss KL, Gao X, Yuhanna IS, Behling-Kelly E, Bergaya S, Ahmed M, Michaely P, Luby-Phelps K, Darehshouri A, Xu L, Fisher EA, Ge W-P, Mineo C, Shaul PW. SR-B1 drives endothelial cell LDL transcytosis via DOCK4 to promote atherosclerosis. *Nature* 2019;**569**:565–569.
187. Shaul PW. Regulation of endothelial nitric oxide synthase: location, location, location. *Annu Rev Physiol* 2002;**64**:749–774.
188. Mineo C, Shaul PW. Functions of scavenger receptor class B, type I in atherosclerosis. *Curr Opin Lipidol* 2012;**23**:487–493.
189. Zhu W, Saddar S, Seetharam D, Chambliss KL, Longoria C, Silver DL, Yuhanna IS, Shaul PW, Mineo C. The scavenger receptor class B type I adaptor protein PDZK1 maintains endothelial monolayer integrity. *Circ Res* 2008;**102**:480–487.
190. Seetharam D, Mineo C, Gormley AK, Gibson LL, Vongpatanasin W, Chambliss KL, Hahner LD, Cummings ML, Kitchens RL, Marcel YL, Rader DJ, Shaul PW. High-density lipoprotein promotes endothelial cell migration and reendothelialization via scavenger receptor-B type I. *Circ Res* 2006;**98**:63–72.
191. Nofer JR, Assmann G. Atheroprotective effects of high-density lipoprotein-associated lysosphingolipids. *Trends Cardiovasc Med* 2005;**15**:265–271.
192. Lee M-H, Appleton KM, El-Shewy HM, Sorci-Thomas MG, Thomas MJ, Lopes-Virella MF, Luttrell LM, Hammad SM, Klein RL. S1P in HDL promotes interaction between SR-BI and S1PR1 and activates S1PR1-mediated biological functions: calcium flux and S1PR1 internalization. *J Lipid Res* 2017;**58**:325–338.
193. Vaisman BL, Vishnyakova TG, Freeman LA, Amar MJ, Demosky SJ, Liu C, Stonik JA, Sampson ML, Pryor M, Bocharov AV, Eggerman TL, Patterson AP, Remaley AT. Endothelial expression of scavenger receptor class B, type I protects against development of atherosclerosis in mice. *Biomed Res Int* 2015;**2015**:1–13.
194. Rohrer L, Ohnsorg PM, Lehner M, Landolt F, Rinninger F, von EA. High-density lipoprotein transport through aortic endothelial cells involves scavenger receptor BI and ATP-binding cassette transporter G1. *Circ Res* 2009;**104**:1142–1150.
195. Lim HY, Thiam CH, Yeo KP, Bisoendial R, Hii CS, McGrath KCY, Tan KW, Heather A, Alexander JSJ, Angeli V. Lymphatic vessels are essential for the removal of cholesterol from peripheral tissues by SR-BI-mediated transport of HDL. *Cell Metab* 2013;**17**:671–684.
196. Martel C, Li W, Fulp B, Platt AM, Gautier EL, Westerterp M, Bittman R, Tall AR, Chen S-H, Thomas MJ, Kreisel D, Swartz MA, Sorci-Thomas MG, Randolph GJ. Lymphatic vasculature mediates macrophage reverse cholesterol transport in mice. *J Clin Invest* 2013;**123**:1571–1579.
197. Li D, Mehta JL. Antisense to LOX-1 inhibits oxidized LDL-mediated upregulation of monocyte chemoattractant protein-1 and monocyte adhesion to human coronary artery endothelial cells. *Circulation* 2000;**101**:2889–2895.
198. Honjo M, Nakamura K, Yamashiro K, Kiryu J, Tanihara H, McEvoy LM, Honda Y, Butcher EC, Masaki T, Sawamura T. Lectin-like oxidized LDL receptor-1 is a cell-adhesion molecule involved in endotoxin-induced inflammation. *Proc Natl Acad Sci USA* 2003;**100**:1274–1279.
199. Chen J, Mehta JL, Haider N, Zhang X, Narula J, Li D. Role of caspases in Ox-LDL-induced apoptotic cascade in human coronary artery endothelial cells. *Circ Res* 2004;**94**:370–376.
200. Ryoo S, Bhunia A, Chang F, Shoukas A, Berkowitz DE, Romer LH. OxLDL-dependent activation of arginase II is dependent on the LOX-1 receptor and downstream RhoA signaling. *Atherosclerosis* 2011;**214**:279–287.
201. Besler C, Heinrich K, Rohrer L, Doerries C, Riwanto M, Shih DM, Chroni A, Yonekawa K, Stein S, Schaefer N, Mueller M, Akhmedov A, Daniil G, Manes C, Templin C, Wyss C, Maier W, Tanner FC, Matter CM, Corti R, Furlong C, Lusis AJ, von Eckardstein A, Fogelman AM, Lüscher TF, Landmesser U. Mechanisms underlying adverse effects of HDL on eNOS-activating pathways in patients with coronary artery disease. *J Clin Invest* 2011;**121**:2693–2708.
202. Hinagata J, Kakutani M, Fujii T, Naruko T, Inoue N, Fujita Y, Mehta J, Ueda M, Sawamura T. Oxidized LDL receptor LOX-1 is involved in neointimal hyperplasia after balloon arterial injury in a rat model. *Cardiovasc Res* 2006;**69**:263–271.
203. Eto H, Miyata M, Kume N, Minami M, Itabe H, Orihara K, Hamasaki S, Biro S, Otsuji Y, Kita T, Tei C. Expression of lectin-like oxidized LDL receptor-1 in smooth muscle cells after vascular injury. *Biochem Biophys Res Commun* 2006;**341**:591–598.
204. Kataoka H, Kume N, Miyamoto S, Minami M, Morimoto M, Hayashida K, Hashimoto N, Kita T. Oxidized LDL modulates Bax/Bcl-2 through the lectinlike Ox-LDL receptor-1 in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2001;**21**: 955–960.
205. Kume N, Kita T. Apoptosis of vascular cells by oxidized LDL: involvement of caspases and LOX-1 and its implication in atherosclerotic plaque rupture. *Circ Res* 2004;**94**:269–270.
206. Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and atherosclerosis. *Mediators Inflamm* 2013;**2013**:1–12.
207. Schaeffer DF, Riazy M, Parhar KS, Chen JH, Duronio V, Sawamura T, Steinbrecher UP. LOX-1 augments oxLDL uptake by lysoPC-stimulated murine macrophages but is not required for oxLDL clearance from plasma. *J Lipid Res* 2009;**50**:1676–1684.
208. Yang H-Y, Bian Y-F, Zhang H-P, Gao FEN, Xiao C-S, Liang BIN, Li JIN, Zhang N-N, Yang Z-M. LOX1 is implicated in oxidized lowdensity lipoproteininduced oxidative stress of macrophages in atherosclerosis. *Mol Med Rep* 2015;**12**:5335–5341.
209. Wang X, Ding Z, Lin J, Guo Z, Mehta JL. LOX-1 in macrophage migration in response to ox-LDL and the involvement of calpains. *Biochem Biophys Res Commun* 2015;**467**:135–139.
210. Chen M, Kakutani M, Naruko T, Ueda M, Narumiya S, Masaki T, Sawamura T. Activation-dependent surface expression of LOX-1 in human platelets. *Biochem Biophys Res Commun* 2001;**282**:153–158.
211. Marwali MR, Hu C-P, Mohandas B, Dandapat A, Deonikar P, Chen J, Cawich I, Sawamura T, Kavdia M, Mehta JL. Modulation of ADP-induced platelet activation by aspirin and pravastatin: role of lectin-like oxidized low-density lipoprotein receptor-1, nitric oxide, oxidative stress, and inside-out integrin signaling. *J Pharmacol Exp Ther* 2007;**322**:1324–1332.
212. Lu J, Yang J-H, Burns AR, Chen H-H, Tang D, Walterscheid JP, Suzuki S, Yang C-Y, Sawamura T, Chen C-H. Mediation of electronegative low-density lipoprotein signaling by LOX-1: a possible mechanism of endothelial apoptosis. *Circ Res* 2009;**104**: 619–627.
213. Chan H-C, Ke L-Y, Chu C-S, Lee A-S, Shen M-Y, Cruz MA, Hsu J-F, Cheng K-H, Chan H-CB, Lu J, Lai W-T, Sawamura T, Sheu S-H, Yen J-H, Chen C-H. Highly electronegative LDL from patients with ST-elevation myocardial infarction triggers platelet activation and aggregation. *Blood* 2013;**122**:3632–3641.
214. Park YM. CD36, a scavenger receptor implicated in atherosclerosis. *Exp Mol Med* 2014;**46**:e99.
215. Neculai D, Schwake M, Ravichandran M, Zunke F, Collins RF, Peters J, Neculai M, Plumb J, Loppnau P, Pizarro JC, Seitova A, Trimble WS, Saftig P, Grinstein S, Dhe-Paganon S. Structure of LIMP-2 provides functional insights with implications for SR-BI and CD36. *Nature* 2013;**504**:172–176.

216. Podrez EA, Poliakov E, Shen Z, Zhang R, Deng Y, Sun M, Finton PJ, Shan L, Febbraio M, Hajjar DP, Silverstein RL, Hoff HF, Salomon RG, Hazen SL. A novel family of atherogenic oxidized phospholipids promotes macrophage foam cell formation via the scavenger receptor CD36 and is enriched in atherosclerotic lesions. *J Biol Chem* 2002;**277**:38517–38523.
217. Coburn CT, Knapp FF Jr, Febbraio M, Beets AL, Silverstein RL, Abumrad NA. Defective uptake and utilization of long chain fatty acids in muscle and adipose tissues of CD36 knockout mice. *J Biol Chem* 2000;**275**:32523–32529.
218. Asch AS, Barnwell J, Silverstein RL, Nachman RL. Isolation of the thrombospondin membrane receptor. *J Clin Invest* 1987;**79**:1054–1061.
219. Ghosh A, Li W, Febbraio M, Espinola RG, McCrae KR, Cockrell E, Silverstein RL. Platelet CD36 mediates interactions with endothelial cell-derived microparticles and contributes to thrombosis in mice. *J Clin Invest* 2008;**118**:1934–1943.
220. Nakatani K, Masuda D, Kobayashi T, Sairyo M, Zhu Y, Okada T, Naito AT, Ohama T, Koseki M, Oka T, Akazawa H, Nishida M, Komuro I, Sakata Y, Yamashita S. Pressure overload impairs cardiac function in long-chain fatty acid transporter CD36-knockout mice. *Int Heart J* 2019;**60**:159–167.
221. Magwenzi S, Woodward C, Wraith KS, Aburima A, Raslan Z, Jones H, McNeil C, Wheatcroft S, Yuldasheva N, Febbriao M, Kearney M, Naseem KM. Oxidized LDL activates blood platelets through CD36/NOX2-mediated inhibition of the cGMP/protein kinase G signaling cascade. *Blood* 2015;**125**:2693–2703.
222. Fernández-Ruiz E, Armesilla AL, Sánchez-Madrid F, Vega MA. Gene encoding the collagen type I and thrombospondin receptor CD36 is located on chromosome 7q11.2. *Genomics* 1993;**17**:759–761.
223. Armesilla AL, Vega MA. Structural organization of the gene for human CD36 glycoprotein. *J Biol Chem* 1994;**269**:18985–18991.
224. Aitman TJ, Cooper LD, Norsworthy PJ, Wahid FN, Gray JK, Curtis BR, McKeigue PM, Kwiatkowski D, Greenwood BM, Snow RW, Hill AV, Scott J. Malaria susceptibility and CD36 mutation. *Nature* 2000;**405**:1015–1016.
225. Yanai H, Chiba H, Fujiwara H, Morimoto M, Abe K, Yoshida S, Takahashi Y, Fuda H, Hui S-P, Akita H, Kobayashi K, Matsuno K. Phenotype-genotype correlation in CD36 deficiency types I and II. *Thromb Haemost* 2000;**84**:436–441.
226. Love-Gregory L, Abumrad NA. CD36 genetics and the metabolic complications of obesity. *Curr Opin Clin Nutr Metab Care* 2011;**14**:527–534.
227. Yamamoto N, Akamatsu N, Sakuraba H, Yamazaki H, Tanoue K. Platelet glycoprotein IV (CD36) deficiency is associated with the absence (type I) or the presence (type II) of glycoprotein IV on monocytes. *Blood* 1994;**83**:392–397.
228. Hirano K, Kuwasako T, Nakagawa-Toyama Y, Janabi M, Yamashita S, Matsuzawa Y. Pathophysiology of human genetic CD36 deficiency. *Trends Cardiovasc Med* 2003;**13**: 136–141.
229. Kuwasako T, Hirano K-I, Sakai N, Ishigami M, Hiraoka H, Yakub MJ, Yamauchi-Takihara K, Yamashita S, Matsuzawa Y. Lipoprotein abnormalities in human genetic CD36 deficiency associated with insulin resistance and abnormal fatty acid metabolism. *Diabetes Care* 2003;**26**:1647–1648.
230. Miyaoka K, Kuwasako T, Hirano K, Nozaki S, Yamashita S, Matsuzawa Y. CD36 deficiency associated with insulin resistance. *Lancet* 2001;**357**:686–687.
231. Yamashita S, Hirano K-I, Kuwasako T, Janabi M, Toyama Y, Ishigami M, Sakai N. Physiological and pathological roles of a multi-ligand receptor CD36 in atherogenesis; insights from CD36-deficient patients. *Mol Cell Biochem* 2007;**299**:19–22.
232. Love-Gregory L, Sherva R, Schappe T, Qi J-S, McCrea J, Klein S, Connelly MA, Abumrad NA. Common CD36 SNPs reduce protein expression and may contribute to a protective atherogenic profile. *Hum Mol Genet* 2011;**20**:193–201.
233. Ghosh A, Murugesan G, Chen K, Zhang L, Wang Q, Febbraio M, Anselmo RM, Marchant K, Barnard J, Silverstein RL. Platelet CD36 surface expression levels affect functional responses to oxidized LDL and are associated with inheritance of specific genetic polymorphisms. *Blood* 2011;**117**:6355–6366.
234. Ma X, Bacci S, Mlynarski W, Gottardo L, Soccio T, Menzaghi C. A common haplotype at the CD36 locus is associated with high free fatty acid levels and increased cardiovascular risk in Caucasians. *Hum Mol Genet* 2004;**13**:2197–2205.
235. Momeni-Moghaddam MA, Asadikaram G, Akbari H, Abolhassani M, Masoumi M, Nadimy Z, Khaksari M. CD36 gene polymorphism rs1761667 (G > A) is associated with hypertension and coronary artery disease in an Iranian population. *BMC Cardiovasc Disord* 2019;**19**:140.
236. Zhang Y, Zang J, Wang B, Li B, Yao X, Zhao H, Li W. CD36 genotype associated with ischemic stroke in Chinese Han. *Int J Clin Exp Med* 2015;**8**:16149–16157.
237. Fujii R, Hishida A, Suzuki K, Imaeda N, Goto C, Hamajima N, Wakai K, Kondo T. Cluster of differentiation 36 gene polymorphism (rs1761667) is associated with dietary MUFA intake and hypertension in a Japanese population. *Br J Nutr* 2019;**121**: 1215–1222.
238. Zhang Y, Ling ZY, Deng SB, Du HA, Yin YH, Yuan J, She Q, Chen YQ. Associations between CD36 gene polymorphisms and susceptibility to coronary artery heart disease. *Braz J Med Biol Res* 2014;**47**:895–903.
239. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* 1996;**271**: 518–520.
240. Calvo D, Vega MA. Identification, primary structure, and distribution of CLA-1, a novel member of the CD36/LIMPII gene family. *J Biol Chem* 1993;**268**:18929–18935.
241. Yancey PG, de la Llera-Moya M, Swarnakar S, Monzo P, Klein SM, Connelly MA, Johnson WJ, Williams DL, Rothblat GH. High density lipoprotein phospholipid composition is a major determinant of the bi-directional flux and net movement of cellular free cholesterol mediated by scavenger receptor BI. *J Biol Chem* 2000;**275**: 36596–36604.
242. Kellner-Weibel G, de la Llera-Moya M, Connelly MA, Stoudt G, Christian AE, Haynes MP, Williams DL, Rothblat GH. Expression of scavenger receptor BI in COS-7 cells alters cholesterol content and distribution. *Biochemistry (Mosc)* 2000;**39**: 221–229.
243. Trigatti B, Rayburn H, Vinals M, Braun A, Miettinen H, Penman M, Hertz M, Schrenzel M, Amigo L, Rigotti A, Krieger M. Influence of the high density lipoprotein receptor SR-BI on reproductive and cardiovascular pathophysiology. *Proc Natl Acad Sci USA* 1999;**96**:9322–9327.
244. Braun A, Trigatti BL, Post MJ, Sato K, Simons M, Edelberg JM, Rosenberg RD, Schrenzel M, Krieger M. Loss of SR-BI expression leads to the early onset of occlusive atherosclerotic coronary artery disease, spontaneous myocardial infarctions, severe cardiac dysfunction, and premature death in apolipoprotein E-deficient mice. *Circ Res* 2002;**90**:270–276.
245. Huby T, Doucet C, Dachet C, Ouzilleau B, Ueda Y, Afzal V, Rubin E, Chapman MJ, Lesnik P. Knockdown expression and hepatic deficiency reveal an atheroprotective role for SR-BI in liver and peripheral tissues. *J Clin Invest* 2006;**116**:2767–2776.
246. Kozarsky KF, Donahee MH, Glick JM, Krieger M, Rader DJ. Gene transfer and hepatic overexpression of the HDL receptor SR-BI reduces atherosclerosis in the cholesterol-fed LDL receptor-deficient mouse. *Arterioscler Thromb Vasc Biol* 2000;**20**: 721–727.
247. Fielding CJ, Fielding PE. Reverse cholesterol transport—new roles for preb1-HDL and lecithin: cholesterol acyltransferase. In Fielding CJ (ed.) High-density Lipoproteins: From Basic Biology to Clinical Aspects. Weinheim: Wiley, 2007. pp. 143–162.
248. Vergeer M, Korporaal SJA, Franssen R, Meurs I, Out R, Hovingh GK, Hoekstra M, Sierts JA, Dallinga-Thie GM, Motazacker MM, Holleboom AG, Van Berkel TJC, Kastelein JJP, Van Eck M, Kuivenhoven JA. Genetic variant of the scavenger receptor BI in humans. *N Engl J Med* 2011;**364**:136–145.
249. Zanoni P, CHD Exome+ Consortium, Khetarpal SA, Larach DB, Hancock-Cerutti WF, Millar JS, Cuchel M, DerOhannessian S, Kontush A, Surendran P, Saleheen D, Trompet S, Jukema JW, De Craen A, Deloukas P, Sattar N, Ford I, Packard C, Majumder A. A S, Alam DS, Di Angelantonio E, Abecasis G, Chowdhury R, Erdmann J, Nordestgaard BG, Nielsen SF, Tybjærg-Hansen A, Schmidt RF, Kuulasmaa K, Liu DJ, Perola M, Blankenberg S, Salomaa V, Männistö S, Amouyel P, Arveiler D, Ferrieres J, Müller-Nurasyid M, Ferrario M, Kee F, Willer CJ, Samani N, Schunkert H, Butterworth AS, Howson JMM, Peloso GM, Stitziel NO, Danesh J, Kathiresan S, Rader DJ. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science* 2016;**351**:1166–1171.
250. Yancey PG, Kawashiri MA, Moore R, Glick JM, Williams DL, Connelly MA. In vivo modulation of HDL phospholipid has opposing effects on SR-BI- and ABCA1-mediated cholesterol efflux. *J Lipid Res* 2004;**45**:337–346.
251. Lee J-Y, Badeau RM, Mulya A, Boudyguina E, Gebre AK, Smith TL, Parks JS. Functional LCAT deficiency in human apolipoprotein A-I transgenic, SR-BI knockout mice. *J Lipid Res* 2007;**48**:1052–1061.
252. Van EM, Hoekstra M, Out R, Bos IS, Kruijt JK, Hildebrand RB, et al. Scavenger receptor BI facilitates the metabolism of VLDL lipoproteins in vivo. *J Lipid Res* 2008; **49**:136–146.
253. Yang X-P, Amar MJ, Vaisman B, Bocharov AV, Vishnyakova TG, Freeman LA, Kurlander RJ, Patterson AP, Becker LC, Remaley AT. Scavenger receptor-BI is a receptor for lipoprotein(a). *J Lipid Res* 2013;**54**:2450–2457.
254. Korporaal SJA, Meurs I, Hauer AD, Hildebrand RB, Hoekstra M, Cate HT, Praticò D, Akkerman J-WN, Van Berkel TJC, Kuiper J, Van Eck M. Deletion of the high-density lipoprotein receptor scavenger receptor BI in mice modulates thrombosis susceptibility and indirectly affects platelet function by elevation of plasma free cholesterol. *Arterioscler Thromb Vasc Biol* 2011;**31**:34–42.
255. Ma Y, Ashraf MZ, Podrez EA. Scavenger receptor BI modulates platelet reactivity and thrombosis in dyslipidemia. *Blood* 2010;**116**:1932–1941.
256. Dole VS, Matuskova J, Vasile E, Yesilaltay A, Bergmeier W, Bernimoulin M, Wagner DD, Krieger M. Thrombocytopenia and platelet abnormalities in high-density lipoprotein receptor-deficient mice. *Arterioscler Thromb Vasc Biol* 2008;**28**:1111–1116.
257. Saddar S, Mineo C, Shaul PW. Signaling by the high-affinity HDL receptor scavenger receptor B type I.*Arterioscler Thromb Vasc Biol* 2010;**30**:144–150.
258. Forstermann U, Munzel T. Endothelial nitric oxide synthase in vascular disease: from marvel to menace. *Circulation* 2006;**113**:1708–1714.
259. Moncada S. Nitric oxide in the vasculature: physiology and pathophysiology. *Ann NY Acad Sci* 1997;**811**:60–67.
260. Armstrong SM, Sugiyama MG, Fung KYY, Gao Y, Wang C, Levy AS, Azizi P, Roufaiel M, Zhu S-N, Neculai D, Yin C, Bolz S-S, Seidah NG, Cybulsky MI, Heit B, Lee WL. A novel assay uncovers an unexpected role for SR-BI in LDL transcytosis. *Cardiovasc Res* 2015;**108**:268–277.
261. Chadwick AC, Sahoo D. Functional genomics of the human high-density lipoprotein receptor scavenger receptor BI: an old dog with new tricks. *Curr Opin Endocrinol Diabetes Obes* 2013;**20**:124–131.
262. Vitali C, Khetarpal SA, Rader DJ. HDL cholesterol metabolism and the risk of CHD: new insights from human genetics. *Curr Cardiol Rep* 2017;**19**:132.

263. Manichaikul A, Naj AC, Herrington D, Post W, Rich SS, Rodriguez A. Association of SCARB1 variants with subclinical atherosclerosis and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;**32**: 1991–1999.
264. Manichaikul A, Wang X-Q, Musani SK, Herrington DM, Post WS, Wilson JG, Rich SS, Rodriguez A. Association of the lipoprotein receptor SCARB1 common missense variant rs4238001 with incident coronary heart disease. *PLoS One* 2015;**10**: e0125497.
265. Naj AC, West M, Rich SS, Post W, Kao WHL, Wasserman BA, Herrington DM, Rodriguez A. Association of scavenger receptor class B type I polymorphisms with subclinical atherosclerosis: the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Genet* 2010;**3**:47–52.
266. Webb TR, Erdmann J, Stirrups KE, Stitziel NO, Masca NGD, Jansen H, Kanoni S, Nelson CP, Ferrario PG, König IR, Eicher JD, Johnson AD, Hamby SE, Betsholtz C, Ruusalepp A, Franzén O, Schadt EE, Björkegren JLM, Weeke PE, Auer PL, Schick UM, Lu Y, Zhang H, Dube M-P, Goel A, Farrall M, Peloso GM, Won H-H, Do R, van Iperen E, Kruppa J, Mahajan A, Scott RA, Willenborg C, Braund PS, van Capelleveen JC, Doney ASF, Donnelly LA, Asselta R, Merlini PA, Duga S, Marziliano N, Denny JC, Shaffer C, El-Mokhtari NE, Franke A, Heilmann S, Hengstenberg C, Hoffmann P, Holmen OL, Hveem K, Jansson J-H, Jöckel K-H, Kessler T, Kriebel J, Laugwitz KL, Marouli E, Martinelli N, McCarthy MI, Van Zuydam NR, Meisinger C, Esko T, Mihailov E, Escher SA, Alver M, Moebus S, Morris AD, Virtamo J, Nikpay M, Olivieri O, Provost S, AlQarawi A, Robertson NR, Akinsansya KO, Reilly DF, Vogt TF, Yin W, Asselbergs FW, Kooperberg C, Jackson RD, Stahl E, Müller-Nurasyid M, Strauch K, Varga TV, Waldenberger M, Zeng L, Chowdhury R, Salomaa V, Ford I, Jukema JW, Amouyel P, Kontto J, Nordestgaard BG, Ferrières J, Saleheen D, Sattar N, Surendran P, Wagner A, Young R, Howson JMM, Butterworth AS, Danesh J, Ardissino D, Bottinger EP, Erbel R, Franks PW, Girelli D, Hall AS, Hovingh GK, Kastrati A, Lieb W, Meitinger T, Kraus WE, Shah SH, McPherson R, Orho-Melander M, Melander O, Metspalu A, Palmer CNA, Peters A, Rader DJ, Reilly MP, Loos RJF, Reiner AP, Roden DM, Tardif J-C, Thompson JR, Wareham NJ, Watkins H, Willer CJ, Samani NJ, Schunkert H, Deloukas P, Kathiresan S. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. *J Am Coll Cardiol* 2017;**69**:823–836.
267. Howson JMM, CARDIoGRAMplusC4D, Zhao W, Barnes DR, Ho W-K, Young R, Paul DS, Waite LL, Freitag DF, Fauman EB, Salfati EL, Sun BB, Eicher JD, Johnson AD, Sheu WHH, Nielsen SF, Lin W-Y, Surendran P, Malarstig A, Wilk JB, Tybjærg-Hansen A, Rasmussen KL, Kamstrup PR, Deloukas P, Erdmann J, Kathiresan S, Samani NJ, Schunkert H, Watkins H, Do R, Rader DJ, Johnson JA, Hazen SL, Quyyumi AA, Spertus JA, Pepine CJ, Franceschini N, Justice A, Reiner AP, Buyske S, Hindorff LA, Carty CL, North KE, Kooperberg C, Boerwinkle E, Young K, Graff M, Peters U, Absher D, Hsiung CA, Lee W-J, Taylor KD, Chen Y-H, Lee I-T, Guo X, Chung R-H, Hung Y-J, Rotter JI, Juang J-MJ, Quertermous T, Wang T-D, Rasheed A, Frossard P, Alam DS, Majumder A. A S, Di Angelantonio E, Chowdhury R, Chen Y-DI, Nordestgaard BG, Assimes TL, Danesh J, Butterworth AS, Saleheen D. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. *Nat Genet* 2017;**49**:1113–1119.
268. Sawamura T, Kume N, Aoyama T, Moriwaki H, Hoshikawa H, Aiba Y, Tanaka T, Miwa S, Katsura Y, Kita T, Masaki T. An endothelial receptor for oxidized low-density lipoprotein. *Nature* 1997;**386**:73–77.
269. Pothineni NVK, Karathanasis SK, Ding Z, Arulandu A, Varughese KI, Mehta JL. LOX-1 in atherosclerosis and myocardial ischemia: biology, genetics, and modulation. *J Am Coll Cardiol* 2017;**69**:2759–2768.
270. Kataoka H, Kume N, Miyamoto S, Minami M, Moriwaki H, Murase T, Sawamura T, Masaki T, Hashimoto N, Kita T. Expression of lectinlike oxidized low-density lipoprotein receptor-1 in human atherosclerotic lesions. *Circulation* 1999;**99**:3110–3117.
271. Hayashida K, Kume N, Murase T, Minami M, Nakagawa D, Inada T, Tanaka M, Ueda A, Kominami G, Kambara H, Kimura T, Kita T. Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are elevated in acute coronary syndrome: a novel marker for early diagnosis. *Circulation* 2005;**112**:812–818.
272. Xu S, Ogura S, Chen J, Little PJ, Moss J, Liu P. LOX-1 in atherosclerosis: biological functions and pharmacological modifiers. *Cell Mol Life Sci* 2013;**70**:2859–2872.
273. Mehta JL, Sanada N, Hu CP, Chen J, Dandapat A, Sugawara F, Satoh H, Inoue K, Kawase Y, Jishage K-I, Suzuki H, Takeya M, Schnackenberg L, Beger R, Hermonat PL, Thomas M, Sawamura T. Deletion of LOX-1 reduces atherogenesis in LDLR knockout mice fed high cholesterol diet. *Circ Res* 2007;**100**:1634–1642.
274. Li D, Williams V, Liu L, Chen H, Sawamura T, Romeo F, Mehta JL. Expression of lectin-like oxidized low-density lipoprotein receptors during ischemia-reperfusion and its role in determination of apoptosis and left ventricular dysfunction. *J Am Coll Cardiol* 2003;**41**:1048–1055.
275. Lu J, Wang X, Wang W, Muniyappa H, Hu C, Mitra S, Long B, Das K, Mehta JL. LOX-1 abrogation reduces cardiac hypertrophy and collagen accumulation following chronic ischemia in the mouse. *Gene Ther* 2012;**19**:522–531.
276. Aoyama T, Chen M, Fujiwara H, Masaki T, Sawamura T. LOX-1 mediates lysophosphatidylcholine-induced oxidized LDL uptake in smooth muscle cells. *FEBS Lett* 2000;**467**:217–220.
277. Mehta JL, Chen J, Hermonat PL, Romeo F, Novelli G. Lectin-like, oxidized low-density lipoprotein receptor-1 (LOX-1): a critical player in the development of atherosclerosis and related disorders. *Cardiovasc Res* 2006;**69**:36–45.
278. Nagase M, Abe J, Takahashi K, Ando J, Hirose S, Fujita T. Genomic organization and regulation of expression of the lectin-like oxidized low-density lipoprotein receptor (LOX-1) gene. *J Biol Chem* 1998;**273**:33702–33707.
279. Predazzi IM, Norata GD, Vecchione L, Garlaschelli K, Amati F, Grigore L, Cutuli L, Pirillo A, Tramontana S, Romeo F, Novelli G, Catapano AL. Association between OLR1 K167N SNP and intima media thickness of the common carotid artery in the general population. *PLoS One* 2012;**7**:e31086.
280. Tatsuguchi M, Furutani M, Hinagata J-I, Tanaka T, Furutani Y, Imamura S-I, Kawana M, Masaki T, Kasanuki H, Sawamura T, Matsuoka R. Oxidized LDL receptor gene (OLR1) is associated with the risk of myocardial infarction. *Biochem Biophys Res Commun* 2003;**303**:247–250.
281. Trabetti E, Biscuola M, Cavallari U, Malerba G, Girelli D, Olivieri O, Martinelli N, Corrocher R, Pignatti PF. On the association of the oxidised LDL receptor 1 (OLR1) gene in patients with acute myocardial infarction or coronary artery disease. *Eur J Hum Genet* 2006;**14**:127–130.
282. Au A, Griffiths LR, Cheng KK, Wee KC, Irene L, Keat WL. The influence of OLR1 and PCSK9 gene polymorphisms on ischemic stroke: evidence from a meta-analysis. *Sci Rep* 2015;**5**:18224.
283. Biocca S, Falconi M, Filesi I, Baldini F, Vecchione L, Mango R, Romeo F, Federici G, Desideri A, Novelli G. Functional analysis and molecular dynamics simulation of LOX-1 K167N polymorphism reveal alteration of receptor activity. *PLoS One* 2009; **4**:e4648.
284. Mango R, Clementi F, Borgiani P, Forleo GB, Federici M, Contino G, et al. Association of single nucleotide polymorphisms in the oxidised LDL receptor 1 (OLR1) gene in patients with acute myocardial infarction. *J Med Genet* 2003;**40**:933–936.
285. Guo X, Xiang Y, Yang H, Yu L, Peng X, Guo R. Association of the LOX-1 rs1050283 polymorphism with risk for atherosclerotic cerebral infarction and its effect on sLOX-1 and LOX-1 expression in a Chinese population. *J Atheroscler Thromb* 2017;**24**:572–582.
286. Mango R, Predazzi IM, Romeo F, Novelli G. LOX-1/LOXIN: the yin/yang of atheroscleorosis. *Cardiovasc Drugs Ther* 2011;**25**:489–494.
287. Mango R, Biocca S, del Vecchio F, Clementi F, Sangiuolo F, Amati F, Filareto A, Grelli S, Spitalieri P, Filesi I, Favalli C, Lauro R, Mehta JL, Romeo F, Novelli G. In vivo and in vitro studies support that a new splicing isoform of OLR1 gene is protective against acute myocardial infarction. *Circ Res* 2005;**97**:152–158.
288. Jang S, Collin de l'Hortet A, Soto-Gutierrez A. Induced pluripotent stem cell-derived endothelial cells: overview, current advances, applications, and future directions. *Am J Pathol* 2019;**189**:502–512.
289. Van KK, Kuppe C, Betsholtz C, Vanlandewijck M, Kramann R, Sluimer JC. Heterogeneity and plasticity in healthy and atherosclerotic vasculature explored by single cell sequencing. *Cardiovasc Res* 2019;**115**:1705–1715.