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STATE-OF-THE-ART REVIEW

Interplay of Low-Density Lipoprotein Receptors, LRPs, and Lipoproteins in Pulmonary Hypertension

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HIGHLIGHTS

- **LDLR regulates oxidized LDL level, which is increased in lung and blood from PAH patients.**
- **LRP1 preserving vascular homeostasis is decreased in PAH patients.**
- **LRP5/6 regulating Wnt signaling is upregulated in PH.**
- **The LRP8 (aka ApoER2) ligand ApoE protects from PAH.**

SUMMARY

The low-density lipoprotein receptor (LDLR) gene family includes LDLR, very LDLR, and LDL receptor–related proteins (LRPs) such as LRP1, LRP1b (aka LRP-DIT), LRP2 (aka megalin), LRP4, and LRP5/6, and LRP8 (aka ApoER2). LDLR family members constitute a class of closely related multifunctional, transmembrane receptors, with diverse functions, from embryonic development to cancer, lipid metabolism, and cardiovascular homeostasis. While LDLR family members have been studied extensively in the systemic circulation in the context of atherosclerosis, their roles in pulmonary arterial hypertension (PAH) are understudied and largely unknown. Endothelial dysfunction, tissue infiltration of monocytes, and proliferation of pulmonary artery smooth muscle cells are hallmarks of PAH, leading to vascular remodeling, obliteration, increased pulmonary vascular resistance, heart failure, and death. LDLR family members are entangled with the aforementioned detrimental processes by controlling many pathways that are dysregulated in PAH; these include lipid metabolism and oxidation, but also platelet-derived growth factor, transforming growth factor β1, Wnt, apolipoprotein E, bone morpohogenetic proteins, and peroxisome proliferator-activated receptor gamma. In this paper, we discuss the current knowledge on LDLR family members in PAH. We also review mechanisms and drugs discovered in biological contexts and diseases other than PAH that are likely very relevant in the hypertensive pulmonary vasculature and the future care of patients with PAH or other chronic, progressive, debilitating cardiovascular diseases.
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Initially thought to control only lipid metabolism, the low-density lipoprotein receptor (LDLR) gene family is an ancient class of cell surface receptors for which new functions in many diseases have been continuously reported. Emerging research has outlined important roles for LDLR family members and oxidized LDL in the pathobiology of pulmonary arterial hypertension (PAH). Here, we review how the aforementioned important players interact with major pathways that are dysregulated in pulmonary vascular disease. We also discuss innovative drugs modulating LDLR family signaling and potential future preclinical investigations in PAH research based on LDLR family's mechanisms already delineated in other diseases.

The LDLR gene family consists of multifunctional, transmembrane receptors that reside on the cell surface. These receptors share structural and functional properties, interact with a diverse group of ligands, and are engaged in numerous biological functions. LDLR core family members share 7 characteristic features (**Figure 1**): cell-surface expression; an extracellular ligand binding domain consisting of complement-type repeats; requirement of Ca^{2+} for ligand binding; recognition of receptor-associated protein and apolipoprotein E (ApoE); epidermal growth factor precursor homology domain containing YWTD repeats; single membrane-spanning region; and receptor-mediated endocytosis of various ligands (1,2). The complement-type repeats constitute a ligand binding domain rich in cysteines. The epidermal growth factor precursor homology domain is necessary for the dissociation of ligands from the receptor in endosomes. The O-linked glycosylation domains, rich in serine and threonine residues, are not involved in ligand binding but serve to keep the ligand binding domains away from the cell surface and as a shield against shedding proteases (3). Finally, as opposed to signaling receptors that contain large intracellular domains, LDLR family members have relatively short cytoplasmic tails. On this tail, the NPxY [Asn-Pro-any amino acid (x)-Tyr] sequence controls both endocytosis and signaling by interacting with a range of cytoplasmic adaptor and scaffolding proteins such as phosphotyrosine binding domain-containing proteins (for example, disabled-1) (1,2). Differences in position and number of each domain create the diversity in LDLR family members.

Throughout evolution from nematodes to mammals, the extracellular domains of LDLR family members have been conserved, but their cytoplasmic domains share little sequence similarity, with the exception of the NPxY motif (4). About 50 years ago, the pioneering work of Brown and Goldstein led to the identification and characterization of the first member, the LDLR, during their search for the molecular basis of familial hypercholesterolemia (5-7). The LDLR has been extensively studied for its prominent role in cholesterol homeostasis and the removal of LDLs from the circulation. For this historical reason, the biological function initially attributed to all members of this evolutionarily ancient gene family was a role in lipid metabolism. However, since the initial discovery, many other functions have been unraveled for this family, including transport and activation of steroid hormones, regulation of Ca^{2+} homeostasis, and pivotal roles in intercellular signaling during embryonic development and adult life (2,8).

Owing to their roles in lipid metabolism, many LDLR gene family members have been investigated in the context of atherosclerosis, unraveling further functions in the related vascular pathobiology. Atherosclerosis is a chronic vascular inflammatory disease associated with endothelial dysfunction, leukocytes or monocytes adhesion and infiltration, aberrant vascular smooth muscle cells (VSMCs) switch from contractile to synthetic phenotype promoting proliferation, extracellular matrix synthesis, and eventually neointimal hyperplasia (9). Interestingly, these mechanisms are also observed in PAH, a fatal heart-lung (10) and even systemic (11) disease that is characterized by obliterative remodeling of pulmonary arterioles (10,12) and increasing pulmonary vascular resistance, resulting in heart failure (13,14). Perivascular hypoxia, inflammation and remodeling (10,15,16), endothelial dysfunction, endothelial-mesenchymal transition (17), hypoxia-triggered microRNA dysregulation (18,19), aberrant glucose and lipid metabolism (20-22), and pulmonary artery smooth muscle cell (PASMC) proliferation (20) are hallmarks of PAH. PAH has an underestimated occurrence, especially in at-risk groups. It is rather highly prevalent on a global scale (23), and despite advances toward effective therapies, it remains an aggressive condition with a mortality of 25% to 50% within 5 years of diagnosis (13,24-26). Therefore, understanding novel mechanisms of PAH pathobiology, including beneficial and detrimental regulators, will open the path to new reverse-remodeling therapies, which is a top priority for the global PAH research community.

ABBREVIATIONS AND ACRONYMS

ApoE = apolipoprotein E

BMPR = bone morphogenetic protein receptor

COPD = chronic obstructive pulmonary disease

CTGF = connective tissue growth factor

HDL = high-density lipoprotein

KO = knockout

LDL = low-density lipoprotein

LDLR = low-density lipoprotein receptor

LRP = low-density lipoprotein receptor-related protein

Mesd = mesoderm development

mRNA = messenger RNA

PH = pulmonary hypertension

PAH = pulmonary arterial hypertension

PASMC = pulmonary artery smooth muscle cell

PDGFR-β = platelet-derived growth factor receptor-β

PPARγ = peroxisome proliferator-activated receptor gamma

RV = right ventricle/ventricular

RVSP = right ventricular systolic pressure

TGF-β1 = transforming growth factor β1

TGFBR = transforming growth factor β1 receptor

TNF = tumor necrosis factor receptor

VLDLR = very low density lipoprotein receptor

VSMC = vascular smooth muscle cell

FIGURE 1 The LDLR Family

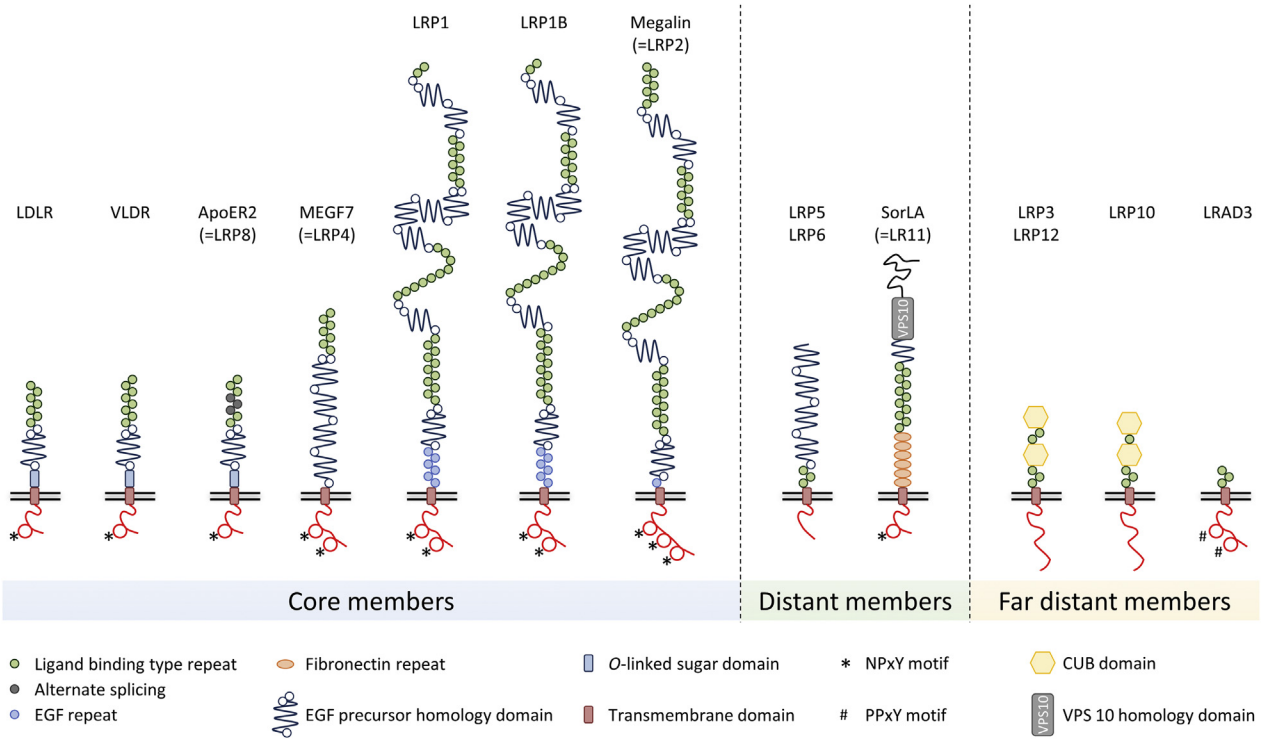


Illustration showing the domain structure of the low-density lipoprotein receptor (LDLR) family members for vertebrates organized as core, distant and far distant. The N-terminal part is on the **top side** (extracellular domain) and the C-terminal part is on the **bottom side** (intracellular domain). Members of the core are characterized by the presence of NPxY-motif, N-terminal ligand binding domain, and epidermal growth factor (EGF) precursor homology domain composed of EGF repeats and YWTD/b-propeller domain. LDLR, very LDLR (VLDLR), and ApoER2 express an additional extracellular O-linked sugar domain adjacent to the transmembrane segment. Distant members are the LDLR-related protein 5 (LRP5) and LRP6 lacking NPxY-motif as well as SorLA (or SORL1, SORLA1, LR11) with additional fibronectin repeats and VPS 10 motif. The 4 far distant members only harbor ligand binding-type repeats with the CUB domain (binding complement C1r/C1s, Uegf, and Bmp1) for LRP3, LRP12, and LRP10. Adapted with permission from Herz (8) and Pohlkamp et al (125).

In 2007 to 2009, the first 2 studies reported a link between abnormal glucose metabolism (insulin resistance) and PAH in mice (27) and humans (28). Since then, abnormalities of many intersecting metabolic pathways (glucose, lipid, glutamine, and others) in the right ventricle (RV), pulmonary vessels, and skeletal muscle have been discovered to be crucial in preclinical and clinical PAH (20-22,29-31). In pulmonary hypertensive vascular disease, a growing body of evidence points toward a crucial role for LDLR family members (**Table 1, Central Illustration**).

LDLR REGULATES OXIDIZED LDL LEVEL

LDLR is the oldest known member of the LDLR family identified because its defect causes familial hypercholesterolemia and atherosclerosis (6). While multiple studies have investigated the role of LDLR in atherosclerosis, very few are focused on the pulmonary vasculature. In 2007, a study reported the presence of advanced atherosclerotic lesions in the pulmonary artery of *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$ double knockout (KO) mice under Western diet feeding (32), while only rarely such lesions were found in 3-month-old *ApoE*$^{-/-}$ mice on a high-fat diet (27). The first extensive and dedicated study on LDLR protection against experimental pulmonary hypertension (PH) was published in 2013 by Douglas et al (33), which was confirmed and extended in a recent paper from Umar et al in 2020 (34).

***LDLR* KO MICE HAVE INCREASED OXIDIZED LDL AND DEVELOP PAH.** In *Ldlr*$^{-/-}$ mice fed a high-fat diet for 16 weeks, atherosclerosis in the aorta was similar in mice under intermittent hypoxia and hypercapnia versus normoxia control mice (33). This was

TABLE 1 Preclinical PAH Studies on LDLR Family Members

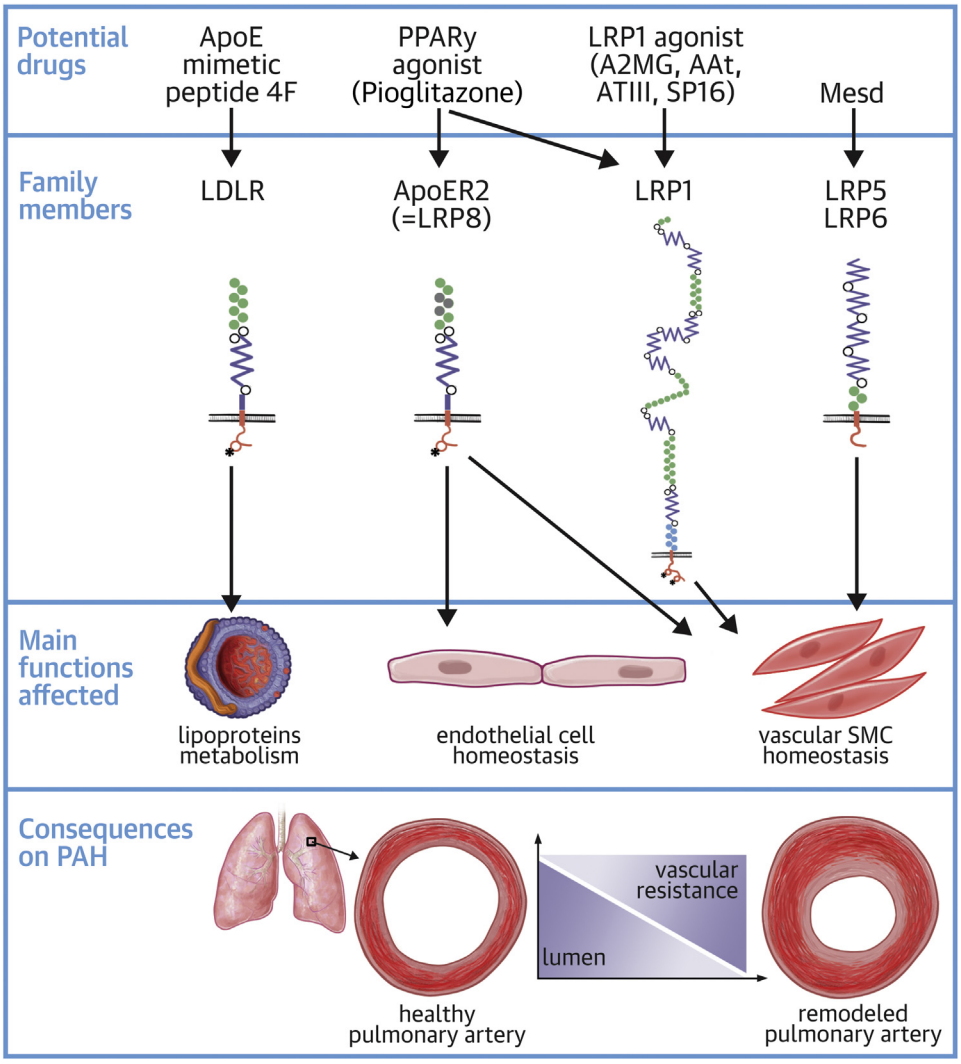
Receptor	Reference (#)	Models	Main Conclusions	Treatment
LDLR	Langheinrich et al, *Atherosclerosis*. 2007 (32)	ApoE-/-/Ldlr-/- double KO mice under Western diet	Presence of advanced atherosclerotic lesions in the pulmonary artery	
	Douglas et al, *J Appl Physiol*. 2013 (33)	*Ldlr-/-* mice exposed to intermittent hypoxia/hypercapnia with a high-fat diet	Exposure of Western diet-fed *Ldlr-/-* mice to intermittent hypoxia/hypercapnia led to PAH and exaggerated development of atherosclerotic lesions in the pulmonary artery with elevated oxidized lipids	Apolipoprotein A-1 mimetic (HDL mimetic) peptide 4F
	Umar et al, *J Am Heart Assoc*. 2020 (34)	*Ldlr-/-* mice with a high-fat diet	Western diet in Ldlr-/- mice induces PAH preceding the development of LV dysfunction, elevated oxidized lipids,	
		Monocrotaline-induced PAH in rats and Sugen-hypoxia-induced PAH in rats	Increased oxidized lipids associated with PAH	
		HPASMC culture	Knockdown of *Ldlr* or oxidized LDL treatment resulted in cell proliferation	
LRP1	Calvier et al, *Circ Res*. 2019 (55)	*SM22-Cre*$^{+/-}$; *LRP1*$^{flox/flox}$; *LDLR*$^{-/-}$ mice	Mice spontaneously develop moderate PAH (increased RVSP, RV hypertrophy, and muscularization of distal pulmonary arteries)	Pioglitazone (a PPARγ agonist)
		HPASMC culture and PAH patients	LRP1 expression is decreased in pulmonary arteries and explanted PASMC of PAH patients.	
	Zucker et al, *Biochim Biophys Acta Mol Basis Dis*. 2019 (70)	HPASMC culture	Controversial in vitro study reporting that LRP1 is detrimental and promotes synthetic phenotype in PASMC	
LRP5/6	Alapati et al, *Pediatr Res*. 2013 (88)	Neonatal rats exposed to hyperoxia (bronchopulmonary dysplasia model with PAH)	LRP5/6 inhibition by Mesd blocked hyperoxia-induced Wnt/β-catenin, attenuated chronic hyperoxia-induced RVSP, RV hypertrophy, pulmonary vascular thickening, and PASMC proliferation.	Mesd (LRP5/6 chaperone)
LRP8	Bertero et al, *Cell Rep*. 2015 (111)	Pulmonary artery adventitial fibroblasts, PASMCs, and PAEC cultures	In primary human pulmonary cells, a miR-130/301-PPARγ-ApoE-LRP8 axis regulating extracellular matrix deposition has been identified	

HDL = high-density lipoprotein; HPASMC = human pulmonary artery smooth muscle cell; KO = knockout; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; LRP = low-density lipoprotein receptor-related protein; PAEC = pulmonary artery endothelial cell; PAH = pulmonary arterial hypertension; PASMC = pulmonary artery smooth muscle cell; PPARγ = peroxisome proliferator-activated receptor gamma; RV = right ventricular; RVSP = right ventricular systolic pressure

remarkable because mice exposed to intermittent hypoxia and hypercapnia had lower weight gain, lower plasma cholesterol, and lower triglyceride levels than normoxic control mice. However, in intermittent hypoxia and hypercapnia mice, atherosclerosis was markedly increased in the trunk and proximal branches of the pulmonary artery. Hemodynamic analysis revealed that the RV systolic pressure (RVSP) and isovolumic relaxation constant were significantly increased in mice exposed to intermittent hypoxia and hypercapnia, and left ventricular percentage fractional shortening was reduced. Increased atherosclerotic lesions were marked by increased lipid accumulation, intimal lesions, collagen deposition, media thickness, foam cells, and necrotic areas, all typical hallmarks of advanced atherosclerotic lesions. This study suggested that exposure of Western diet-fed *Ldlr*$^{-/-}$ mice to intermittent hypoxia and hypercapnia led to PH and exaggerated development of atherosclerotic lesions in the pulmonary artery trunk and proximal branches, compared with normoxia (33). All these adverse effects were prevented by treatment with apolipoprotein A-1 mimetic (high-density lipoprotein [HDL] mimetic) peptide 4F, which inhibited the formation and accumulation of inflammatory LDL-derived oxidized phospholipids.

The conclusions of this first study were later confirmed by a second study using *Ldlr*$^{-/-}$ mice fed with Western diet for 12 weeks or regular chow under normoxia (34). Only the Western diet group developed PH, characterized by RV hypertrophy and dysfunction (increased RVSP), followed by left ventricular dysfunction. In the group of mice developing PH, histology showed accumulation of oxidized lipids, especially in the pulmonary vasculature, perivascular regions, and infiltrated macrophages. Increased oxidized lipids in the lungs were also

CENTRAL ILLUSTRATION **Main LDLR Family Members Involved in PAH**



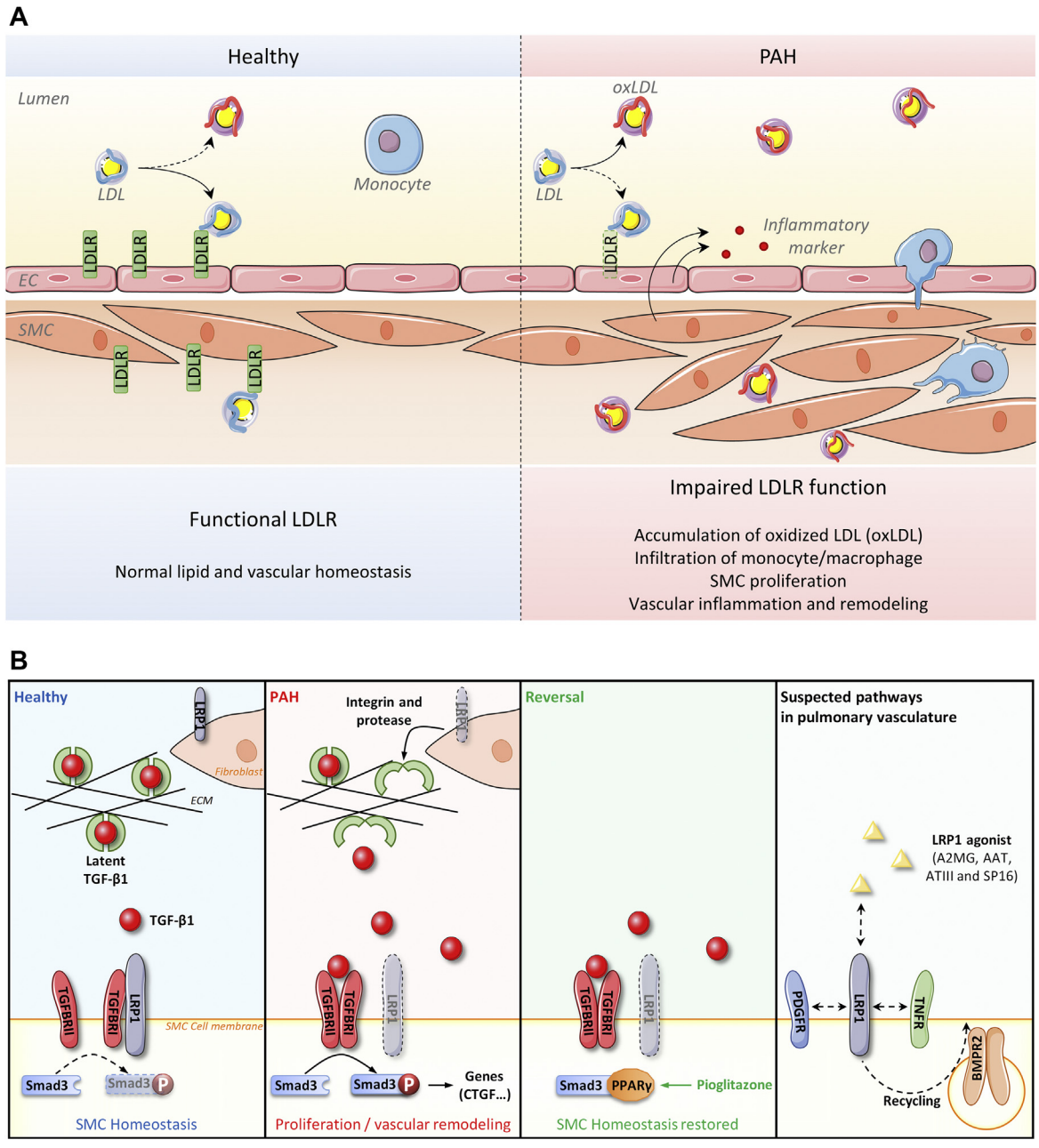
Calvier, L. et al. J Am Coll Cardiol Basic Trans Science. 2022;7(2):164–180.

The low-density lipoprotein receptor (LDLR) family constitutes a class of closely related multifunctional receptors, with diverse functions, especially in cardiovascular homeostasis. However, their roles in pulmonary hypertension are understudied; here, we review emerging pulmonary hypertension publications on LDLR family members. PAH = pulmonary arterial hypertension.

associated with PH in 2 well-established experimental models of PH in rats (monocrotaline-induced PH and Sugen-hypoxia-induced PH) (34). Therefore, it has been suggested that elevated oxidized lipid levels in the lungs, owing to the combination of Ldlr KO and Western diet, led to lung inflammation (with infiltration of macrophages) and PASMC proliferation. Indeed, oxidized lipids are known to induce vascular inflammation, and in vitro using human PASMCs, they demonstrated that knockdown of *Ldlr* by siRNA or oxidized LDL treatment resulted in cell proliferation, which is a hallmark of the pulmonary vascular disease (34).

LIPOTOXICITY OWING TO INCREASED OXIDIZED LDL IN LUNG AND PLASMA CONCENTRATION IN HUMAN PAH. Atherosclerosis has a high prevalence in many cardiovascular diseases and is an important cause of morbidity and mortality. However, it is unclear why pulmonary arterial atherosclerosis is not a common feature in PAH, as far as we know. Humans

FIGURE 2 **LDLR Regulates Oxidized LDL Level and LRP1 Preserves Vascular Homeostasis**



(A) Illustration outlining the publications to date on LDLR functions in pulmonary arterial hypertension (PAH). In PAH, LDLR expression is reduced, affecting the LDL homeostasis and leading to accumulation of oxidized LDL (oxLDL) in the circulation and lungs. The impaired LDLR pathway and oxLDL induce the release of proinflammatory markers by endothelial cells (ECs) and smooth muscle cells (SMCs) followed by monocyte infiltration and differentiation into macrophages as well as SMC proliferation. Altogether, this creates an inflammatory environment and vascular remodeling. **(B)** Illustration outlining the publications to date on LRP1 function in pulmonary artery SMCs during PAH and pathways suspected to occur in pulmonary vasculature. Under normal conditions, LRP1 dampens the transforming growth factor (TGF)-β1 pathway by direct interaction with TGF-β receptor 1 (TGFBRI) in pulmonary artery SMCs and inhibits the differentiation of lung fibroblasts to a contractile phenotype. In PAH, LRP1 expression is reduced, disturbing the TGF-β1 balance and thus promoting proinflammatory and profibrotic genes such as connective tissue growth factor (CTGF). In fibroblasts, loss of LRP1 results in acquisition of a contractile phenotype and integrin- and protease-dependent release of active transforming growth factor TGF-β1 from the extracellular matrix (ECM) stores. Pioglitazone treatment (a peroxisome proliferator-activated receptor gamma [PPARγ] agonist) in *smLRP1*$^{-/-}$ mice reverses PAH caused by LRP1 deficiency, restoring an inhibition on TGF-β1 signaling. Other pathways known in non-PAH context remain to be investigated in the pulmonary vasculature, such as LRP1 interaction with platelet-derived growth factor receptor (PDGFR), tumor necrosis factor receptor (TNFR), or bone morphogenetic protein receptor (BMPR). Abbreviations as in Figure 1.

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FEBRUARY 2022:164–180

with LDLR loss-of-function mutations (ie, familial hypercholesterolemia) do not typically develop PAH. Nonetheless, pulmonary arterial atherosclerosis has been observed in adult patients with chronic obstructive pulmonary disease (COPD) or chronic thromboembolic PH (35-38). Both LDL and HDL were reported to be dysfunctional in PAH (39). HDL cholesterol levels are significantly depressed in patients with PAH, which is associated with worse clinical outcomes (28,40). In addition, expression of LDLR and fatty acid transporter CD36 are reduced in human lungs, while oxidized LDL is increased in both whole lung and plasma (34). CD36 is highly relevant in PAH as it is also a bone morphogenetic protein receptor 2 (BMPR2) and peroxisome proliferator activated receptor gamma (PPARγ) target (41), 2 vasoprotective partners dysregulated in PAH. Increased lipid deposition and lipotoxicity have also been reported in the RV of PAH patients (22,29,42,43).

Lung histology has shown increased lipid deposition, inflammation (monocyte/macrophage infiltration), and oxidized LDL in PAH patients compared with healthy donors (34). These clinical observations highlight the critical importance of lipids, particularly oxidized lipids (39,44-47), in the pathogenesis of PAH. Based on the previous literature we can postulate that, in the pulmonary arteries, the decrease in LDL-metabolizing machinery alters the cholesterol transport, resulting in elevated oxidized LDL levels in plasma and lungs. This lipotoxicity promotes oxidative stress and inflammation, resulting in pulmonary vascular remodeling. Undoubtedly, oxidized lipids mediate the development of atherosclerosis, directly contributing to pulmonary vascular inflammation and PASMC proliferation (**Figure 2A**). Importantly in the heart, RV dysfunction in PAH is strongly associated with insulin resistance, maladaptive fatty acid metabolism (decreased or blocked fatty acid oxidation), and intraventricular lipid accumulation, resulting in RV lipotoxicity and RV dysfunction (18,22,28,29). This hypothesis is corroborated in different PAH animal models, not only in *Ldlr* KO mice, but also in the dominant negative BMPR2 mice harboring RV lipid deposition, which was exacerbated in the presence of Western diet (43).

Together, those studies would suggest that lipid-lowering therapies might be beneficial in PAH. However, the effect of statins in PAH is controversial, especially in humans: results of a meta-analysis of earlier small clinical studies did not show any statistically significant effect of statin therapy in the improvement of the distance walked in 6 minutes, pulmonary arterial pressure, right atrial pressure, cardiac index, and pulmonary vascular resistance (48). This lack of benefits might appear counterintuitive because statins have pleiotropic effects, such as lipid-lowering, antiproliferative, antioxidant, anti-inflammatory, and endothelial cell function-maintaining properties (49), which may be helpful in attenuating the progression of PAH. More recently, in 2019, another meta-analysis focused on clinical subgroup analysis: PAH and PH due to COPD (50). It suggests that statins can efficiently and safely reduce pulmonary arterial pressure in PH, especially in PH associated with COPD (50). Therefore, the effect of lipid-lowering therapies remains controversial, but it appears that their effect varies between PH subtypes and further randomized controlled trials are needed to focus on the efficacy and safety of statin therapy in different subtypes.

LRP1 PRESERVES VASCULAR HOMEOSTASIS

LRP1 was the first LRP discovered by Herz et al, in 1988 (51). It is ubiquitously expressed, with high protein levels found in the liver (hepatocytes), brain (neurons), and lung (SMCs) (52). LRP1 is a multifunctional receptor involved in various biological processes including lipoprotein metabolism, degradation of proteases, activation of lysosomal enzymes, cellular entry of bacterial toxins and viruses, integrin maturation and recycling, regulation of vascular tone and permeability, inflammation, cell adhesion (via integrins), growth, migration and apoptosis (52-54). Deletion of the LRP1 gene is lethal in mice, owing to vascular formation defects and extensive hemorrhage, indicating a critical role in development. Three important properties of LRP1 dictate its diverse role in systemic physiology: 1) its ability to recognize more than 100 ligands such as lipoproteins, extracellular matrix glycoproteins (fibronectin, heparan sulfate proteoglycans, amyloid β), cytokines (tissue plasminogen activator, leptin), and growth factors (including transforming growth factor [TGF] β1, plasminogen activator inhibitor-1, and connective tissue growth factor [CTGF]); 2) its ability to bind a large number of cytoplasmic adaptor proteins; and 3) its ability to associate with and modulate the activity of other transmembrane receptors such as integrins, receptor tyrosine kinases, BMPR, and TGF-β1 receptors (TGFBRs) (52-55).

LRP1 has important functions in metabolic regulation, especially in hepatocytes, adipocytes, and muscle cells, with implications for circulating glucose and lipids (56). For example, LRP1 regulates the insulin receptor and GLUT4 to protect against insulin resistance (56), which is a risk factor or disease modifier for human PAH (28). Moreover,

single nucleotide polymorphisms are associated with carbohydrate metabolism, and LRP1 mediates ApoE uptake and recycling, and can bind some modified LDLs (56). In endothelial cells, hypoxia promotes LRP1 activation by PARP-1 and LRP1 protein complex dissociation, allowing PARP-1-dependent activation of cyclin-dependent kinase 2, cell cycle progression, and angiogenesis (57). Hypoxia stimulates LRP1 expression via hypoxia-inducible factor-1α in SMCs (58,59). The latter has implication for SMC metabolism because hypoxia-inducible factor-1 can promote the endocytosis of lipoproteins, by up-regulating the expression of LRP1, the receptor that internalizes LDL in VSMCs. Interestingly, uptake of extracellular fatty acid and triacylglycerol synthesis are also promoted under hypoxia by the transcription factor PPARγ, the gene expression of which is directly activated by hypoxia-inducible factor-1 (59,60). The presence of the peroxisome proliferator response element on the LRP1 promoter suggests that it is regulated by PPARγ as well. This interaction is particularly relevant for PAH because PPARγ is antimitogenic, anti-inflammatory, and a major cardioprotective regulator of glucose and lipid metabolism. Targeted deletion of PPARγ in SMCs (61) or endothelial cells (62) leads to PAH in mice, and targeted deletion of PPARγ in cardiomyocytes results in biventricular dysfunction in the absence of PAH (22).

Thus, PPARγ agonist pioglitazone underwent a recent revival for clinical use in cardiovascular diseases (63), including PAH (64). In the pulmonary artery, PPARγ activation protects from vascular remodeling, stiffening, and elevation of pulmonary arterial pressure (20,55,65). In the RV, PPARγ activation in cardiomyocytes can normalize lipid metabolism and mitochondrial morphology or function in the failing RV, restoring physiologic fatty acid oxidation instead of a pathologic glycolytic switch (14,22).

LRP1 IS PROTECTIVE IN THE SYSTEMIC VASCULATURE. In the vasculature, most studies have been focused on the protective LRP1 role in atherosclerosis. Despite early in vitro studies suggested that direct binding of ligands to LRP1 may promote VSMC proliferation, the targeted deletion of LRP1 in mouse VSMCs enhanced atherogenesis, demonstrating the dominant activity of LRP1 in VSMCs in vivo is antiatherogenic, by limiting proinflammatory and profibrotic activation of platelet-derived growth factor receptor (PDGFR)-β and TGF-β1 signaling (54,66,67). In macrophages, LRP1 also inhibits atherogenesis, mainly but not exclusively by modulating inflammatory mediators such as monocyte chemoattractant protein-1/chemokine ligand-2, reduction of local matrix metalloproteinase-9 activity, moderation of TGF-β1, tumor necrosis factor receptor-1 as well as nuclear factor kappa B pathways, and downregulation of extracellular matrix deposition (54).

LRP1 SMC KO MICE SPONTANEOUSLY DEVELOP PAH. In PAH, the first 2 studies focused on LRP1 have been recently published in 2019. Calvier et al unraveled spontaneous PAH and pulmonary arterial remodeling in the mouse with targeted deletion of LRP1 in SMC, highlighting the vasoprotective role of LRP1 in the pulmonary vasculature (**Figure 2B**) (55). Comparison of $LRP1^{flox/flox}$; $LDLR^{-/-}$ (or LRP1 WT) with $SM22\text{-}Cre^{+/-}$; $LRP1^{flox/flox}$; $LDLR^{-/-}$ (or $smLRP1^{-/-}$) mice showed that $smLRP1^{-/-}$ mice spontaneously develop PAH characterized by increased RVSP, RV hypertrophy, and hypermuscularization of distal pulmonary arteries, in the absence of systolic or diastolic LV dysfunction. Mechanistically, LRP1 is known to interact with the TGF-β1 pathway in VSMCs (66). In PASMCs, LRP1 binds to TGFBR1, dampening both TGF-β1 signaling and expression of downstream targets as CTGF or NOX4 in vitro and in vivo (55). Interestingly, PPARγ inhibits overactivation of the TGF-β1 pathway in PAH by binding to Smad3 (20,64,65,68), and pioglitazone treatment (a PPARγ agonist) in $smLRP1^{-/-}$ mice reverses PAH caused by LRP1 deficiency, restoring inhibition of TGF-β1 signaling. The authors could translate their findings in human disease by demonstrating decreased expression of LRP1 in pulmonary arteries and cultured PASMCs from PAH patients (55). In addition to this mechanism, loss of LRP1 overactivates the JNK1/2-c-Jun-Fra-2 signaling pathway, leading to the induction of α-smooth muscle actin and periostin expression in human lung fibroblasts (69). These changes are important because they are accompanied by increased cell contractility, leading to integrin- and protease-dependent release of active TGF-β1 from the extracellular matrix stores (69). Paracrine liberation of active TGF-β1 from the extracellular matrix by fibroblasts may also further stimulate its own pathway in PASMCs and exacerbate vascular remodeling. Controversially, an in vitro study reports that LRP1 is detrimental and promotes the synthetic phenotype in PASMCs (70). As described previously for atherosclerosis, it is not surprising to face now in PAH research also contradictory results in cultured SMCs versus in vivo. One can argue that the use of $smLRP1^{-/-}$ mice might be more representative than LRP1 deletion in PASMC culture, but further investigations are clearly needed to unravel other

FIGURE 3 **LRP5/6-Wnt and LRP8-ApoE Roles in PAH**

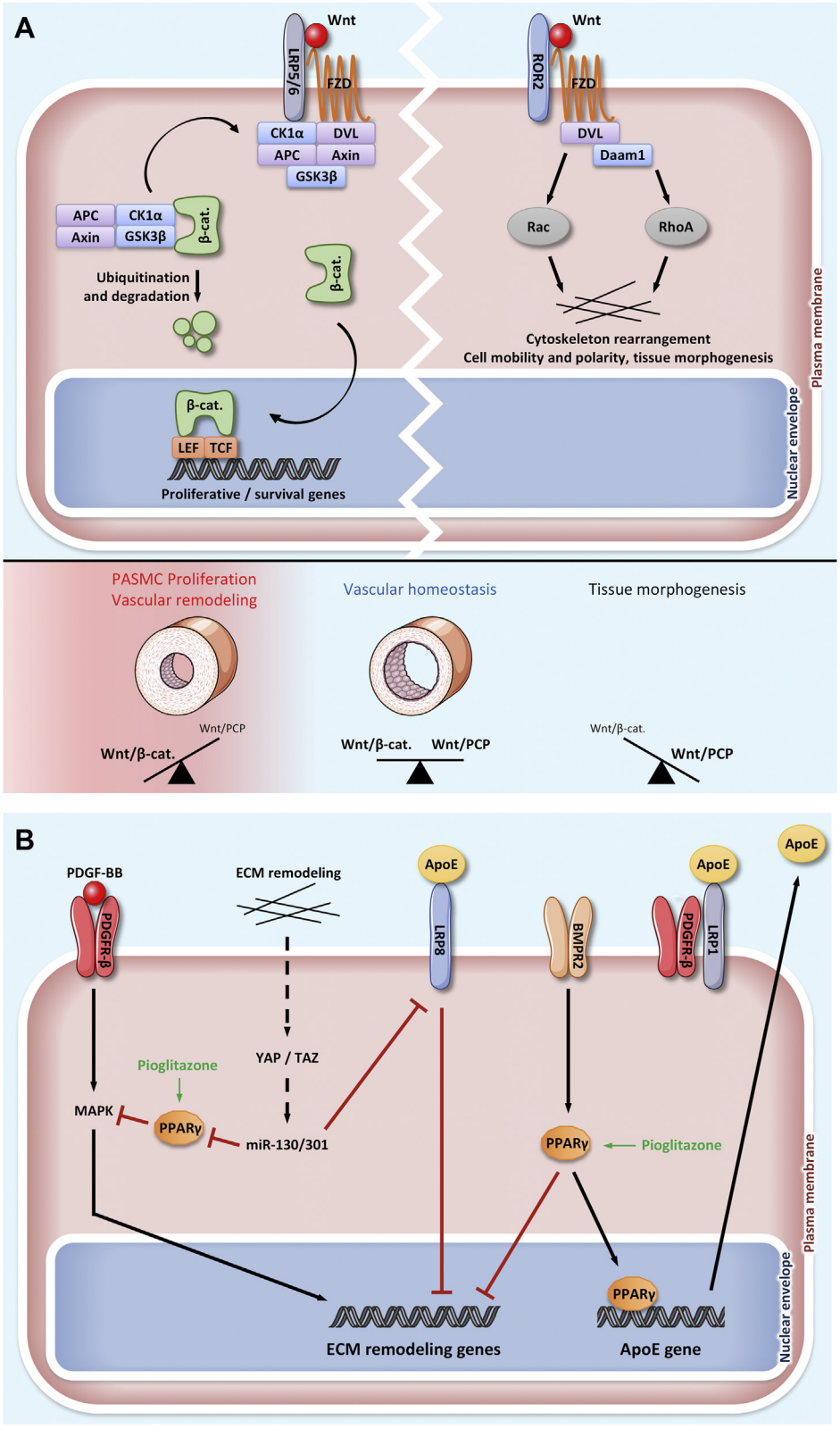

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FIGURE 4 VLDLR, LRP2, LRP4, and LRP1B Pathways Not Linked to PAH Yet

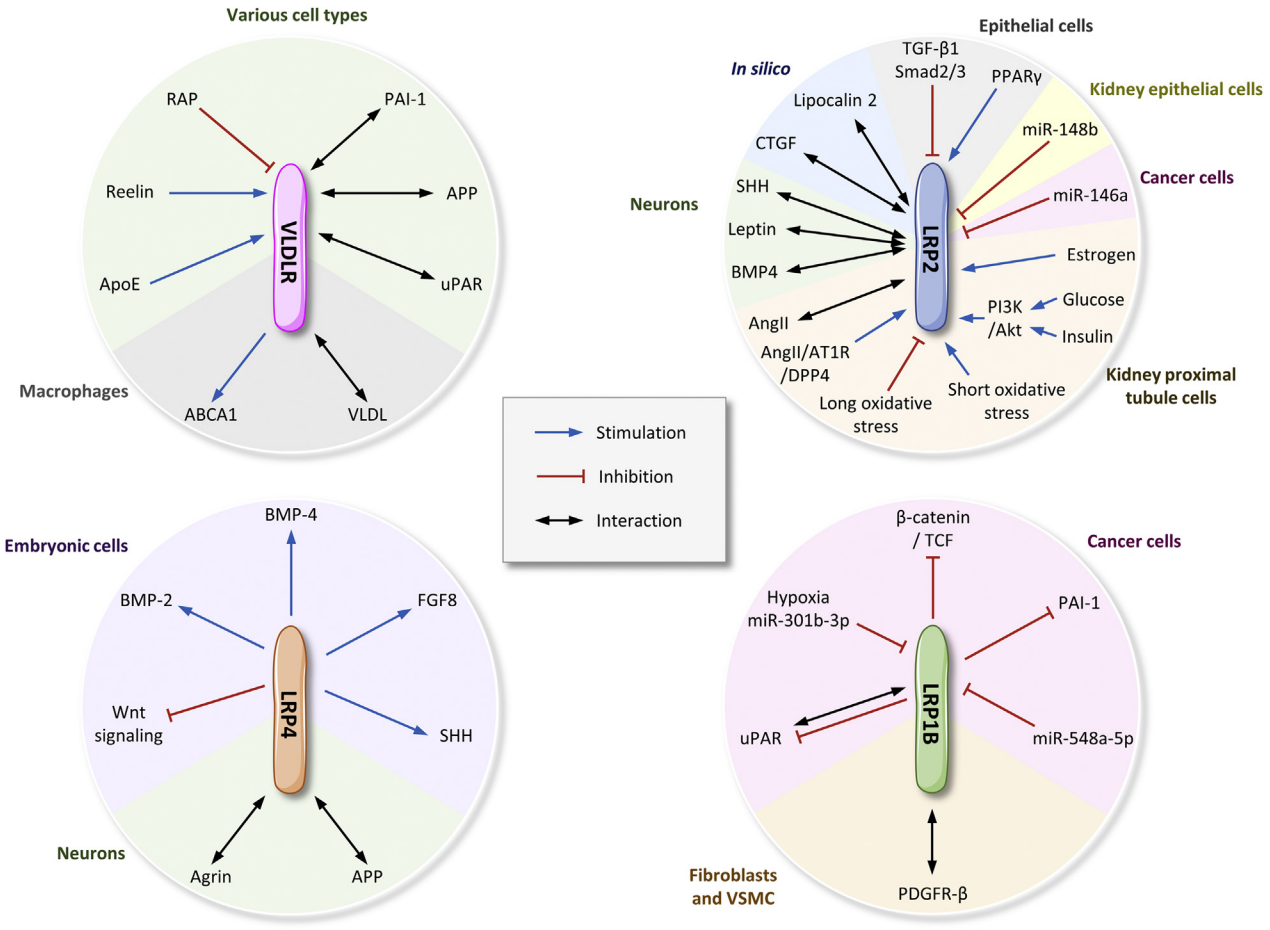

Illustration outlining the publications to date on VLDLR, LRP2, LRP4, and LRP1B pathways in different cell types not yet linked to PAH but potentially relevant for the disease. Details on these interactions are documented in the Supplemental Appendix. APP = amyloid precursor protein; PAI = plasminogen activator inhibitor; RAP = receptor-associated protein; uPAR = urokinase receptor; VSMC = vascular smooth muscle cell; other abbreviations as in Figures 1 to 3.

potential pathways regulated by LRP1 in PAH, such as PDGFR, tumor necrosis factor receptor, or BMPs (BMP-2, -4, -9, -10).

LRP1 AS A NOVEL THERAPEUTIC TARGET FOR HUMAN PAH. Fifteen percent of PAH patients have a familial form of the disease, and among those, 70% carry an autosomal dominant mutation causing haploinsufficiency or loss of function of BMPR2, and this mutation is also present in 20% of sporadic cases of idiopathic PAH (71). BMP2 and TGFβ1 are functional

FIGURE 3 Continued

(A) Illustration outlining the publications to date on LRP5/6 function in pulmonary artery SMCs (PASMCs) during PAH. Under normal conditions, Both Wnt/β-catenin **(left)** and Wnt/planar cell polarity **(right)** signaling pathways are suspected to be necessary for preservation of pulmonary vascular homeostasis and vascular regeneration in response to injury. However, loss of this balance and overactivation of the Wnt/β-catenin axis may lead to excessive PASMC growth, vessel obstruction, and PAH. **(B)** Illustration outlining the publications to date on LRP8 and apolipoprotein E (ApoE) functions in pulmonary artery endothelial cells and PASMCs during PAH. The PDGFR-β and YAP/TAZ pathways are profibrotic, while LRP8, LRP1, and BMPR2 preserve vascular homeostasis. Under BMP-2 or PPARγ activation, ApoE is expressed and binds on the one hand to PDGFR-β, blocking its signaling, and on the second hand to LRP8. miR-130/301 binds directly to LRP8 and PPARγ messenger RNA, blocking their expression. Abbreviations as in Figures 1 and 2.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 2, 2022
FEBRUARY 2022:164–180

antagonists of pathological remodeling in the arteries, and Calvier et al. recently demonstrated PPARγ as the major link between BMP2 and TGF-β1 pathways in human PASMCs (20,64,65,72). Furthermore, it is suspected that LRP1 regulates BMPR2, recycling the BMP ligand-receptor complex back to the cell surface (73,74).

Finally, LRP1 expression is decreased in human pulmonary arteries and cultured PASMCs from PAH patients (55). With its numerous ligands, LRP1 represents an obvious therapeutic target to sustain vascular homeostasis and quench inflammatory signals in several complex diseases. Different LRP1 agonists have been identified, such as the natural α2-macroglobulin, α1-antitrypsin, antithrombin III, and the synthetic SP16. Moreover, several LRP1 agonists have already been successfully evaluated in preclinical models of ischemia-reperfusion, and 2 of them (α1-antitrypsin and SP16) are being tested in clinical trials for acute myocardial infraction (75). Therefore, translating the use of these LRP1 agonists to PAH in order to restore its vasoprotective function could open groundbreaking therapeutic avenues for this fatal disease.

LRP5 AND LRP6 MEDIATE Wnt SIGNALING

Discovered in 1981, the Wnt pathway is involved in many mechanisms, and therefore mutations leading to abnormal Wnt signaling have been linked to many clinical diseases, including developmental anomalies (eg, spina bifida) (76), degenerative conditions (eg, Alzheimer's disease) (77), malignancies (eg, colon cancer) (78) and chronic diseases (eg, atherosclerosis) (79). Both LRP6 and its close homolog LRP5 (80) are essential Wnt co-receptors, bind to Wnt ligands, and activate downstream Wnt signaling (81-84). The main Wnt signaling goes through the co-receptors LRP5/6 and a member of the frizzled family; together, they recruit and inactivate a protein complex including the glycogen synthase kinase 3b that would otherwise target β-catenin for subsequent ubiquitination and proteasomal degradation (**Figure 3A**) (83). Upon Wnt activation, β-catenin is released from the degradation complex and translocates to the nucleus, where it binds to lymphoid-enhancing factor and T cell factor to form a transcriptional complex regulating genes involved in cell fate, proliferation, survival, and differentiation (83). Besides β-catenin, Wnt can also activate the planar cell polarity signaling pathway. Both Wnt/β-catenin and Wnt/planar cell polarity signaling pathways are suspected to be necessary for preservation of pulmonary vascular homeostasis and vascular regeneration in response to injury. However, loss of this balance and overactivation of the Wnt/β-catenin axis may lead to excessive PASMC growth, vessel obstruction, and PAH (85).

LRP5/6 AND WNT SIGNALING ARE UPREGULATED IN PH. Wnt signaling is upregulated in the lungs of adult patients with PAH (86). In human PAH, LRP6 and its target Wnt-induced signaling protein-1 messenger RNA (mRNA) are also induced in pulmonary mesenchymal progenitor cells that are known to mediate vascular homeostasis, vessel loss, or muscularization (87). The role and inhibition of LRP5/6 was studied in neonatal rat model of bronchopulmonary dysplasia with PH: rats were exposed to normoxia or hyperoxia (90% O_2) for 2 weeks and treated with recombinant mesoderm development (Mesd) protein (88), which functions as a specific chaperone for LRP5/6 and is essential for specification of embryonic polarity and mesoderm induction (89,90). LRP5/6 inhibition by Mesd blocked hyperoxia-induced Wnt/β-catenin signaling and expression of the downstream targets cyclin D1 and Wnt-induced signaling protein-1 in the rat lung (88). Mesd treatment also attenuated chronic hyperoxia-induced RVSP, RV hypertrophy, pulmonary vascular remodeling (media wall thickness), and PASMC proliferation (88). Therefore, this study suggested a role for LRP5/6 in PH and proposed it as a therapeutic target to alleviate PH in neonates with severe bronchopulmonary dysplasia (88). More studies on LRP5/6 in several adult models of PH are needed to reliably conclude on the positive or negative role of this receptor on the pulmonary vasculature.

LRP8 RELAYS APOE SIGNAL

LRP8 (syn.: ApoE receptor 2, ApoER2) has several ligands but mainly ApoE and reelin. Unlike its synonymous name (ApoER2) suggests, LRP8 is hardly known to play a role in lipid regulation. Expressed in neurons, LRP8 is essential for neuronal migration and positioning in the developing brain (91-93). In the adult brain this receptor modulates synaptic plasticity (94,95), migration of neuroblasts (96), as well as dendrite (97) and dendritic spine (98) formation. Outside of the central nervous system, global deletion of the LRP8 in mice has no effect on the plasma lipoprotein profile, suggesting a minimal or redundant contribution in plasma lipid regulation (99). It is expressed on endothelial cells, VSMC, monocytes and macrophages (99-101). In humans, genome-wide association studies have linked polymorphisms of the LRP8 gene to premature coronary artery disease and myocardial infarction (102-105). In particular, homozygous carriers of the ApoER2-R952Q variant

have a 2-fold increased risk of these conditions (102,104,105). In macrophages, studies suggest that LRP8 is antiatherogenic, likely through the promotion of cholesterol efflux (via ABCA1) (106), preventing lipotoxicity and favoring an anti-inflammatory phenotype (9). In endothelial cells, ApoE-LRP8 interaction has been studied in atherosclerosis. In humans, cardiovascular disease risk is modified by genetic variants of ApoE: the risk of developing atherosclerosis and coronary heart disease is increased with the presence of the ApoE4 allele compared with ApoE3 (most prevalent with 75% of the population) (107). ApoE3-LRP8 signaling promotes nitric oxide production, repair and anti-inflammatory events in the endothelium, and prevents neointima formation, suggesting a vasoprotective role for this tandem (9). These aforementioned effects of ApoE3 are antagonized by ApoE4 (99).

THE LRP8 LIGAND ApoE PROTECTS FROM PAH. LRP8 has not been investigated in PAH yet. However, deficiency of ApoE, the major ligand of LRP8 (ApoER2), has been associated with PAH (**Figure 3B**) and validated by several research groups. In 2007, Hansmann et al (27) reported that *ApoE*$^{-/-}$ mice on a high-fat diet develop PAH as judged by elevated RVSP, RV hypertrophy, and peripheral pulmonary artery muscularization. These conclusions were confirmed later by other groups (108,109). Male (but not female) *ApoE*$^{-/-}$ mice on a high-fat diet become insulin resistant, and PPARγ agonist treatment improves insulin sensitivity and reverses PAH. Interestingly, ApoE is a target gene for the transcription factor PPARγ (PPRE in the ApoE promotor), downstream of BMP-2/BMPRII in human PASMCs (61). Both BMP-2 or PPARγ agonists induce ApoE secretion in human PASMCs. Such PPARγ activation prevents PDGF-induced proliferation of PASMCs (61), as ApoE binds to LRP1 initiating the endocytosis and degradation of the LRP1/PDGFR-β/PDGF complex (67,110).

Importantly, subsequent papers report on and are consistent with a similar role for LRP8 in other cell types or disease context. In primary human pulmonary vascular cells (pulmonary artery adventitial fibroblasts, PASMCs, pulmonary artery endothelial cells), Bertero et al (111,112) identified an miR-130/301-PPARγ-ApoE-LRP8 axis regulating extracellular matrix deposition. The profibrotic miR-130/301 blocked PPARγ and LRP8 expression by binding to their mRNA, and consequently, diminished their mRNA and protein expression and increased collagen expression and lysyl oxidase activity, an enzyme that crosslinks extracellular matrix proteins. Therefore, the authors proposed a negative feedback loop, in which extracellular matrix remodeling stimulates miR-130/301 expression (via YAP/TAZ activation), thus reducing PPARγ-ApoE-LRP8 signaling, and consequently promoting collagen deposition, so that matrix remodeling and arterial stiffening worsen. An impaired PPARγ-ApoE-LRP8 axis has been confirmed in preclinical PH models in vivo: mouse hypoxia; mice treated with SU5416 (SUGEN), a vascular endothelial growth factor receptor 2 kinase inhibitor; and rats treated with monocrotaline (111).

REELIN, ANOTHER LRP8 LIGAND, AND VASOPROTECTIVE ApoE MAY HAVE OPPOSITE EFFECTS. Although not yet investigated in PAH, reelin besides ApoE, is the other major LRP8 ligand. In the systemic circulation, reelin-LRP8 is known to regulate leukocyte-endothelial cell adhesion, including E-selectin, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (113-117). Importantly, *Lrp8* deletion in mice reduces leukocyte-endothelial cell adhesion in response to antiphospholipid antibodies (115,118). In the endothelium, reelin-LRP8 signaling activates the nuclear factor kappa B pathway to promote adhesion molecule expression on the endothelium such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1. Consequently, it increases monocyte rolling, adhesion, and diapedesis, allowing monocytes to infiltrate the subendothelial space and propagate inflammation (113,114,116,117). Therefore, reelin-LRP8 appears to promote leukocyte adhesion to the endothelium, the first step toward leukocyte infiltration, which would confer a deleterious role, unlike the protective antiproliferative and anti-inflammatory ApoE-LRP8 mechanisms in PAH. We can postulate that LRP8 function depends on its ligand, either protective with ApoE or deleterious with reelin. Therefore, important LRP8 functions in the pulmonary vasculature remain yet to be determined.

OTHER LDLR FAMILY MEMBERS NOT YET LINKED TO PAH

Only 5 of 12 receptors in the LDLR family have been linked to PH. For LRP2 and LRP4, human monogenic disorders are not associated with PAH, suggesting a limited role in PAH for those 2 receptors. For instance, LRP2 gene mutations causes Donnai-Barrow syndrome characterized by multiple congenital malformation, including defective renal reabsorption (119). A LRP4 mutation is responsible for Cenani-Lenz syndrome, a congenital skeletal malformation syndrome involving both upper and lower extremities (120-122).

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 2, 2022
FEBRUARY 2022:164–180

Although never studied in the pulmonary vasculature yet, very LDLR (VLDLR) and LRP1B roles have been investigated in VSMCs. The structure of VLDLR is similar to that of LRP8 (50% homology) and thus they have similar functions (123). Like LRP8, VLDLR is expressed in endothelial cells, VSMCs, and macrophages (9). VLDLR binds many ligands such as VLDL, ApoE, receptor-associated protein, reelin (although not in endothelial cells) (114), or plasminogen activator inhibitor-1 and interacts with amyloid precursor protein and urokinase receptor (124,125). Global deletion of the VLDLR in mice has no effect on plasma lipoprotein profile, suggesting a minimal or redundant contribution in plasma lipid regulation (126). In the cardiovascular system, VLDLR KO mice displayed increased intimal thickening induced by vascular injury, indicating a protective role in VSMC against neointima hyperplasia (127). Controversial studies have observed both proatherogenic and antiatherogenic effects for this receptor. One interpretation of these data is that the proatherogenic effect of VLDLR arising from the lipid uptake function may be counterbalanced by its antiatherogenic effects, such as elevation of ABCA1 transporter and conversion into an anti-inflammatory cellular phenotype (9). Interestingly, one human VLDLR variant appears to be associated with coronary artery disease, body mass index, and LDL-associated ApoB (128).

LRP1B, originally named LRP-DIT (deleted in tumors), was first described in 2000 as a gene that is frequently inactivated in non-small cell lung cancer (129). LRP1B was subsequently shown to be mutated in tumors affecting different tissues (130-135), and LRP1B deletion suggests a role as a tumor suppressor, but the exact mechanism remains elusive. LRP1 and LRP1B share 86% mRNA and 52% amino acid identity, and therefore not surprisingly some functions are shared by both receptors, for example, the regulation of urokinase receptor and PDGFR-β trafficking at the membrane level (136,137). Although not yet studied in PAH, in VSMC LRP1B interacts with PDGFR-β, resulting in a decrease in ERK1/2 signaling and dampened cell migration (138,139). Decreased cell migration and proliferation by LRP1B was further explored and confirmed in cancer cells (non-small cell lung cancer, renal cancer, and prostate cancer) (140-142).

Although none of these last LDLR family members have been linked to PAH as of yet, they are linked to pathways that have key roles in pulmonary vascular remodeling (**Figure 4**) and may incite dedicated studies in the pulmonary vasculature. Last, little is known on other distant members like the sortilin-related receptor (SorLA or LR11), LRP3/12, LRP10, and LRAD3. More dedicated studies are needed to explore their functions and potential implications in PAH.

LRPs AND LDLRs IN PH: AREAS OF UNCERTAINTY

PH animal models do not completely recapitulate all the histological and hemodynamic features observed in human PH (143), and consequently, divergent results have been observed in PH patients while translating treatments from animal models to clinic care, as it was demonstrated for statins or beta blockers for example (48,50,144,145). Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications commonly used as hyperlipidemia treatment to lower cholesterol level. Furthermore, they have additional properties like antiproliferative and anti-inflammatory effects, beneficial in cardiovascular diseases (48,50,146-148). Interestingly, several studies with statins in vitro and in experimental models have demonstrated both attenuation in the development and regression of experimental PH by restoring endothelial function and inhibiting SMC proliferation (146,148). However, recent published clinical trials and systematic reviews assessing the potential of statins in PH patients are controversial (48,50,144,149) and statins as an effective treatment in PH is still under debate. Nevertheless, additional studies like randomized control trials in different PH subcategories are needed to test the safety and efficacy of these drugs.

The contribution of the pulmonary vascular remodeling and rarefication, along with evolving both systolic and diastolic RV dysfunction, to the clinical progression of PH is complex. It is commonly believed that PH and associated shear stress and inflammation can trigger a series of events, including elevated vasomotor tone and a proproliferative state, ultimately leading to peripheral pulmonary arterial obliteration, increased pulmonary vascular resistance, RV dysfunction, and heart failure (150,151). We and others have identified metabolic aberrations as crucial components of the disease process in both pulmonary arteries and RV (20,22,151), and many LDLR family members are involved in these mechanisms as detailed in this review. The aforementioned processes render the RV adaptive to PH by developing RV hypertrophy without dilation and sustained systolic RV function. However, if PH persists, then RV systolic dysfunction and failure evolves, accompanied or caused by RV ischemia, alterations in substrate and mitochondrial energy metabolism, increased free oxygen radicals, inflammation, and fibrosis (150,151). Most PH therapies do not address

RV contractility or RV dilation directly, but may improve both by lowering pulmonary vascular resistance. Consequently, targeting RV dysfunction separately from dysregulation of pulmonary vascular remodeling, if used in combination with classical therapeutic approaches, can become a successful strategy to manage PH, especially as we learn more about the transition from adaptive RV remodeling to maladaptive RV failure in the future (150,151). The role of LRP1 and its downstream targets in PAH-associated RV dysfunction is still unknown.

CONCLUSIONS

LDLR family members are involved at different levels in PAH mechanisms, not only by regulating lipid metabolism, but also by interacting with other ligands or receptors. Most of them are vasoprotective, and a better understanding of their functions opens new treatment options for PAH. Indeed, many drugs have been described to modulate the activity of those receptors, especially LDLR, LRP1, LRP5/6, and LRP8, with some drugs being tested in clinical trials for cardiovascular diseases but not yet for PAH. In addition, this review reports how these LDLR family members interact with pathways in different diseases and tissues but relevant for PAH, paving future research especially on VLDLR, LRP2, LRP4 and LRP1B.

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REFERENCES

1. Beffert U, Stolt PC, Herz J. Functions of lipoprotein receptors in neurons. *J Lipid Res*. 2004;45:403–409.

2. Hussain MM, Strickland DK, Bakillah A. The mammalian low-density lipoprotein receptor family. *Annu Rev Nutr*. 1999;19:141–172.

3. Wasser CR, Masiulis I, Durakoglugil MS, et al. Differential splicing and glycosylation of Apoer2 alters synaptic plasticity and fear learning. *Sci Signal*. 2014;7:ra113.

4. Willnow TE, Christ A, Hammes A. Endocytic receptor-mediated control of morphogen signaling. *Development*. 2012;139:4311–4319.

5. Brown MS, Goldstein JL. Familial hypercholesterolemia: defective binding of lipoproteins to cultured fibroblasts associated with impaired regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. *Proc Natl Acad Sci U S A*. 1974;71:788–792.

6. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science*. 1986;232:34–47.

7. Goldstein JL, Brown MS. Familial hypercholesterolemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. *Proc Natl Acad Sci U S A*. 1973;70:2804–2808.

8. Herz J. The LDL receptor gene family: (un)expected signal transducers in the brain. *Neuron*. 2001;29:571–581.

9. Mineo C. Lipoprotein receptor signaling in atherosclerosis. *Cardiovasc Res*. 2020;116:1254–1274.

10. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019;53:1801887.

11. Rosenkranz S, Howard LS, Gomberg-Maitland M, Hoeper MM. Systemic consequences of pulmonary hypertension and right-sided heart failure. *Circulation*. 2020;141:678–693.

12. Sheikh AQ, Lighthouse JK, Greif DM. Recapitulation of developing artery muscularization in pulmonary hypertension. *Cell Rep*. 2014;6:809–817.

13. Hansmann G. Pulmonary hypertension in infants, children, and young adults. *J Am Coll Cardiol*. 2017;69:2551–2569.

14. Zelt JGE, Chaudhary KR, Cadete VJ, Mielniczuk LM, Stewart DJ. Medical therapy for heart failure associated with pulmonary hypertension. *Circ Res*. 2019;124:1551–1567.

15. Pullamsetti SS, Schermuly R, Ghofrani A, Weissmann N, Grimminger F, Seeger W. Novel and emerging therapies for pulmonary hypertension. *Am J Respir Crit Care Med*. 2014;189:394–400.

16. Pullamsetti SS, Mamazhakypov A, Weissmann N, Seeger W, Savai R. Hypoxia-inducible factor signaling in pulmonary hypertension. *J Clin Invest*. 2020;130:5638–5651.

17. Ranchoux B, Antigny F, Rucker-Martin C, et al. Endothelial-to-mesenchymal transition in pulmonary hypertension. *Circulation*. 2015;131:1006–1018.

18. Chouvarine P, Giera M, Kastenmüller G, et al. Trans-right ventricle and transpulmonary metabolite gradients in human pulmonary arterial hypertension. *Heart*. 2020;106:1332–1341.

19. Zhao J, Florentin J, Tai Y-Y, et al. Long range endocrine delivery of circulating miR-210 to endothelium promotes pulmonary hypertension. *Circ Res*. 2020;127:677–692.

20. Calvier L, Chouvarine P, Legchenko E, et al. PPARγ links BMP2 and TGFβ1 pathways in vascular smooth muscle cells, regulating cell proliferation and glucose metabolism. *Cell Metab*. 2017;25:1118–1134.e7.

21. Culley MK, Chan SY. Mitochondrial metabolism in pulmonary hypertension: beyond mountains there are mountains. *J Clin Invest*. 2018;128:3704–3715.

22. Legchenko E, Chouvarine P, Borchert P, et al. PPARγ agonist pioglitazone reverses pulmonary hypertension and prevents right heart failure via fatty acid oxidation. *Sci Transl Med*. 2018;10:eaao0303.

23. Hasan B, Hansmann G, Budts W, et al. Challenges and special aspects of pulmonary hypertension in middle- to low-income regions: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;75:2463–2477.

24. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119.

25. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019;53:1801889.

26. Hansmann G, Koestenberger M, Alastalo T-P, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant*. 2019;38:879–901.

27. Hansmann G, Wagner RA, Schellong S, et al. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. *Circulation*. 2007;115:1275–1284.

28. Zamanian RT, Hansmann G, Snook S, et al. Insulin resistance in pulmonary arterial hypertension. *Eur Respir J*. 2009;33:318–324.

29. Hemnes AR, Luther JM, Rhodes CJ, et al. Human PAH is characterized by a pattern of lipid-related insulin resistance. *JCI Insight*. 2019;4:e123611.

30. Prins KW, Thenappan T, Weir EK, Kalra R, Pritzker M, Archer SL. Repurposing medications for treatment of pulmonary arterial hypertension: what's old is new again. *J Am Heart Assoc*. 2019;8:e011343.

31. Tian L, Wu D, Dasgupta A, et al. Epigenetic metabolic reprogramming of right ventricular fibroblasts in pulmonary arterial hypertension: a pyruvate dehydrogenase kinase-dependent shift in mitochondrial metabolism promotes right ventricular fibrosis. *Circ Res*. 2020;126:1723–1745.

32. Langheinrich AC, Michniewicz A, Bohle RM, Ritman EL. Vasa vasorum neovascularization and lesion distribution among different vascular beds in ApoE–/–/LDL–/– double knockout mice. *Atherosclerosis*. 2007;191:73–81.

33. Douglas RM, Bowden K, Pattison J, et al. Intermittent hypoxia and hypercapnia induce pulmonary artery atherosclerosis and ventricular dysfunction in low density lipoprotein receptor deficient mice. *J Appl Physiol*. 2013;115:1694–1704.

34. Umar S, Ruffenach G, Moazeni S, et al. Involvement of low-density lipoprotein receptor in the pathogenesis of pulmonary hypertension. *J Am Heart Assoc*. 2020;9:e012063.

35. Nascimento D, Nunes L, Oliveira F, Vencio E, Teixeira V, Reis M. Pulmonary atherosclerosis associated with an atrial septal defect in old age: case report of an elderly autopsied patient. *Pathol Res Pract*. 2009;205:137–141.

36. Russo A, De Luca M, Vigna C, et al. Central pulmonary artery lesions in chronic obstructive pulmonary disease: a transesophageal echocardiography study. *Circulation*. 1999;100:1808–1815.

37. Blauwet LA, Edwards WD, Tazelaar HD, McGregor CGA. Surgical pathology of pulmonary thromboendarterectomy: a study of 54 cases from 1990 to 2001. *Hum Pathol*. 2003;34:1290–1298.

38. Kivrak T, Ata Bolayir H, Gönenc Kanar B, et al. Prevelance of pulmonary atherosclerosis in patients with chronic thromboembolic pulmonary hypertension. *Am J Cardiovasc Thorac Surg*. 2017;2:1–4.

39. Ross DJ, Hough G, Hama S, et al. Proinflammatory high-density lipoprotein results from oxidized lipid mediators in the pathogenesis of both idiopathic and associated types of pulmonary arterial hypertension. *Pulm Circ*. 2015;5:640–648.

40. Heresi GA, Aytekin M, Newman J, DiDonato J, Dweik RA. Plasma levels of high-density lipoprotein cholesterol and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;182:661–668.

41. Chen X, Austin ED, Talati M, et al. Oestrogen inhibition reverses pulmonary arterial hypertension and associated metabolic defects. *Eur Respir J*. 2017;50:1602337.

42. Brittain EL, Talati M, Fessel JP, et al. Fatty acid metabolic defects and right ventricular lipotoxicity in human pulmonary arterial hypertension. *Circulation*. 2016;133:1936–1944.

43. Talati M, Hemnes A. Fatty acid metabolism in pulmonary arterial hypertension: role in right ventricular dysfunction and hypertrophy. *Pulm Circ*. 2015;5:269–278.

44. Sharma S, Umar S, Potus F, et al. Apolipoprotein A-I mimetic peptide 4F rescues pulmonary hypertension by inducing microRNA-193-3p. *Circulation*. 2014;130:776–785.

45. Al-Husseini A, Wijesinghe DS, Farkas L, et al. Increased eicosanoid levels in the Sugen/chronic hypoxia model of severe pulmonary hypertension. *PLoS One*. 2015;10:e0120157.

46. Al-Naamani N, Sagliani KD, Dolnikowski GG, et al. Plasma 12- and 15-hydroxyeicosanoids are predictors of survival in pulmonary arterial hypertension. *Pulm Circ*. 2016;6:224–233.

47. Bowers R, Cool C, Murphy RC, et al. Oxidative stress in severe pulmonary hypertension. *Am J Respir Crit Care Med*. 2004;169:764–769.

48. Rysz-Górzynska M, Gluba-Brzózka A, Sahebkar A, et al. Efficacy of statin therapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Sci Rep*. 2016;6:30060.

49. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circ Res*. 2017;120:229–243.

50. Chen F, Yang M, Wan C, Liu L, Chen L. Efficacy and safety of statin therapy in pulmonary hypertension: a systematic review and meta-analysis. *Ann Transl Med*. 2019;7:786.

51. Herz J, Hamann U, Rogne S, Myklebost O, Gausepohl H, Stanley KK. Surface location and high affinity for calcium of a 500-kd liver membrane protein closely related to the LDL-receptor suggest a physiological role as lipoprotein receptor. *EMBO J*. 1988;7:4119–4127.

52. Lillis AP, Van Duyn LB, Murphy-Ullrich JE, Strickland DK. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. *Physiol Rev*. 2008;88:887–918.

53. Wujak L, Schnieder J, Schaefer L, Wygrecka M. LRP1: a chameleon receptor of lung inflammation and repair. *Matrix Biol*. 2018;68-69:366–381.

54. 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.

55. Calvier L, Boucher P, Herz J, Hansmann G. LRP1 deficiency in vascular SMC leads to pulmonary arterial hypertension that is reversed by PPARγ activation. *Circ Res*. 2019;124:1778–1785.

56. Actis Dato V, Chiabrando GA. The role of low-density lipoprotein receptor-related protein 1 in lipid metabolism, glucose homeostasis and inflammation. *Int J Mol Sci*. 2018;19:1780.

57. Mao H, Xie L, Pi X. Low-density lipoprotein receptor-related protein-1 signaling in angiogenesis. *Front Cardiovasc Med*. 2017;4:34.

58. Castellano J, Aledo R, Sendra J, et al. Hypoxia stimulates low-density lipoprotein receptor-related protein-1 expression through hypoxia-inducible factor-1α in human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2011;31:1411–1420.

59. Mylonis I, Simos G, Paraskeva E. Hypoxia-inducible factors and the regulation of lipid metabolism. *Cells*. 2019;8:E214.

60. Krishnan J, Suter M, Windak R, et al. Activation of a HIF1alpha-PPARgamma axis underlies the integration of glycolytic and lipid anabolic pathways in pathologic cardiac hypertrophy. *Cell Metab*. 2009;9:512–524.

61. Hansmann G, de Jesus Perez VA, Alastalo T-P, et al. An antiproliferative BMP-2/PPARgamma/apoE axis in human and murine SMCs and its role in pulmonary hypertension. *J Clin Invest*. 2008;118:1846–1857.

62. Guignabert C, Alvira CM, Alastalo T-P, et al. Tie2-mediated loss of peroxisome proliferator-activated receptor-gamma in mice causes PDGF receptor-beta-dependent pulmonary arterial muscularization. *Am J Physiol Lung Cell Mol Physiol*. 2009;297:L1082–L1090.

63. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374:1321–1331.

64. Hansmann G, Calvier L, Risbano MG, Chan SY. Activation of the metabolic master regulator PPARγ: A Potential PIOneering Therapy for Pulmonary Arterial Hypertension. *Am J Respir Cell Mol Biol*. 2020;62:143–156.

65. Kökény G, Calvier L, Legchenko E, Chouvarine P, Mózes MM, Hansmann G. PPARγ is a gatekeeper for extracellular matrix and vascular cell homeostasis: beneficial role in pulmonary hypertension and renal/cardiac/pulmonary fibrosis. *Curr Opin Nephrol Hypertens*. 2020;29:171–179.

66. Boucher P, Li W-P, Matz RL, et al. LRP1 functions as an atheroprotective integrator of TGFbeta and PDFG signals in the vascular wall: implications for Marfan syndrome. *PLoS One*. 2007;2:e448.

67. Boucher P, Gotthardt M, Li W-P, Anderson RGW, Herz J. LRP: role in vascular wall

integrity and protection from atherosclerosis. *Science*. 2003;300:329–332.

68. Calvier L, Chouvarine P, Legchenko E, Kokeny G, Mozes MM, Hansmann G. Chronic TGF-β1 signaling in pulmonary arterial hypertension induces sustained canonical Smad3 pathways in vascular smooth muscle cells. *Am J Respir Cell Mol Biol*. 2019;61:121–123.

69. Schnieder J, Mamazhakypov A, Birnhuber A, et al. Loss of LRP1 promotes acquisition of contractile-myofibroblast phenotype and release of active TGF-β1 from ECM stores. *Matrix Biol*. 2020;88:69–88.

70. Zucker MM, Wujak L, Gungl A, et al. LRP1 promotes synthetic phenotype of pulmonary artery smooth muscle cells in pulmonary hypertension. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865:1604–1616.

71. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J*. 2019;53:1801899.

72. Calvier L, Chouvarine P, Legchenko E, Hansmann G. Transforming growth factor β1- and bone morphogenetic protein 2/PPARγ-regulated MicroRNAs in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2017;196:1227–1228.

73. Pi X, Schmitt CE, Xie L, et al. LRP1-dependent endocytic mechanism governs the signaling output of the bmp system in endothelial cells and in angiogenesis. *Circ Res*. 2012;111:564–574.

74. Gu M, Shao N-Y, Sa S, et al. Patient-specific iPSC-derived endothelial cells uncover pathways that protect against pulmonary hypertension in BMPR2 mutation carriers. *Cell Stem Cell*. 2017;20:490–504.e5.

75. Potere N, Del Buono MG, Niccoli G, Crea F, Toldo S, Abbate A. Developing LRP1 agonists into a therapeutic strategy in acute myocardial infarction. *Int J Mol Sci*. 2019;20:544.

76. Ueno N, Greene NDE. Planar cell polarity genes and neural tube closure. *Birth Defects Res C Embryo Today*. 2003;69:318–324.

77. De Ferrari GV, Inestrosa NC. Wnt signaling function in Alzheimer's disease. *Brain Res Brain Res Rev*. 2000;33:1–12.

78. Burgess AW, Faux MC, Layton MJ, Ramsay RG. Wnt signaling and colon tumorigenesis–a view from the periphery. *Exp Cell Res*. 2011;317:2748–2758.

79. Marinou K, Christodoulides C, Antoniades C, Koutsilieris M. Wnt signaling in cardiovascular physiology. *Trends Endocrinol Metab*. 2012;23:628–636.

80. Hey PJ, Twells RC, Phillips MS, et al. Cloning of a novel member of the low-density lipoprotein receptor family. *Gene*. 1998;216:103–111.

81. Mao B, Wu W, Li Y, et al. LDL-receptor-related protein 6 is a receptor for Dickkopf proteins. *Nature*. 2001;411:321–325.

82. 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.

83. Steinhart Z, Angers S. Wnt signaling in development and tissue homeostasis. *Development*. 2018;145:dev146589.

84. Tamai K, Semenov M, Kato Y, et al. LDL-receptor-related proteins in Wnt signal transduction. *Nature*. 2000;407:530–535.

85. de Jesus Perez V, Yuan K, Alastalo T-P, Spiekerkoetter E, Rabinovitch M. Targeting the Wnt signaling pathways in pulmonary arterial hypertension. *Drug Discov Today*. 2014;19:1270–1276.

86. Cohen ED, Ihida-Stansbury K, Lu MM, Panettieri RA, Jones PL, Morrisey EE. Wnt signaling regulates smooth muscle precursor development in the mouse lung via a tenascin C/PDGFR pathway. *J Clin Invest*. 2009;119:2538–2549.

87. Gaskill C, Marriott S, Pratap S, et al. Shared gene expression patterns in mesenchymal progenitors derived from lung and epidermis in pulmonary arterial hypertension: identifying key pathways in pulmonary vascular disease. *Pulm Circ*. 2016;6:483–497.

88. Alapati D, Rong M, Chen S, Lin C, Li Y, Wu S. Inhibition of LRP5/6-mediated Wnt/β-catenin signaling by Mesd attenuates hyperoxia-induced pulmonary hypertension in neonatal rats. *Pediatr Res*. 2013;73:719–725.

89. Hsieh J-C, Lee L, Zhang L, et al. Mesd encodes an LRP5/6 chaperone essential for specification of mouse embryonic polarity. *Cell*. 2003;112:355–367.

90. Lu W, Liu C-C, Thottassery JV, Bu G, Li Y. Mesd is a universal inhibitor of Wnt coreceptors LRP5 and LRP6 and blocks Wnt/beta-catenin signaling in cancer cells. *Biochemistry*. 2010;49:4635–4643.

91. Trommsdorff M, Gotthardt M, Hiesberger T, et al. Reeler/disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell*. 1999;97:689–701.

92. Tissir F, Goffinet AM. Reelin and brain development. *Nat Rev Neurosci*. 2003;4:496–505.

93. Herz J, Reelin Chen Y. lipoprotein receptors and synaptic plasticity. *Nat Rev Neurosci*. 2006;7:850–859.

94. Weeber EJ, Beffert U, Jones C, et al. Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. *J Biol Chem*. 2002;277:39944–39952.

95. Beffert U, Weeber EJ, Durudas A, et al. Modulation of synaptic plasticity and memory by Reelin involves differential splicing of the lipoprotein receptor Apoer2. *Neuron*. 2005;47:567–579.

96. Gong C, Wang T-W, Huang HS, Parent JM. Reelin regulates neuronal progenitor migration in intact and epileptic hippocampus. *J Neurosci*. 2007;27:1803–1811.

97. Niu S, Renfro A, Quattrocchi CC, Sheldon M, D'Arcangelo G. Reelin promotes hippocampal dendrite development through the VLDLR/ApoER2-Dab1 pathway. *Neuron*. 2004;41:71–84.

98. Niu S, Yabut O, D'Arcangelo G. The Reelin signaling pathway promotes dendritic spine development in hippocampal neurons. *J Neurosci*. 2008;28:10339–10348.

99. Ulrich V, Konaniah ES, Herz J, et al. Genetic variants of ApoE and ApoER2 differentially modulate endothelial function. *Proc Natl Acad Sci U S A*. 2014;111:13493–13498.

100. Komaravolu RK, Waltmann MD, Konaniah E, Jaeschke A, Hui DY. ApoER2 (apolipoprotein E receptor-2) deficiency accelerates smooth muscle cell senescence via cytokinesis impairment and promotes fibrotic neointima after vascular injury. *Arterioscler Thromb Vasc Biol*. 2019;39:2132–2144.

101. 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.

102. Martinelli N, Olivieri O, Shen G-Q, et al. 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.

103. Shen G-Q, Girelli D, Li L, et al. 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.

104. Shen G-Q, Li L, Girelli D, et al. An LRP8 variant is associated with familial and premature coronary artery disease and myocardial infarction. *Am J Hum Genet*. 2007;81:780–791.

105. Wang Q, Rao S, Shen G-Q, et al. Premature myocardial infarction novel susceptibility locus on chromosome 1P34-36 identified by genomewide linkage analysis. *Am J Hum Genet*. 2004;74:262–271.

106. Chen X, Guo Z, Okoro EU, et al. 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.

107. Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med*. 2004;141:137–147.

108. Lawrie A, Hameed AG, Chamberlain J, et al. Paigen diet-fed apolipoprotein E knockout mice develop severe pulmonary hypertension in an interleukin-1-dependent manner. *Am J Pathol*. 2011;179:1693–1705.

109. Umar S, Partow-Navid R, Ruffenach G, Iorga A, Moazeni S, Eghbali M. Severe pulmonary hypertension in aging female apolipoprotein E-deficient mice is rescued by estrogen replacement therapy. *Biol Sex Differ*. 2017;8:9.

110. Strickland MR, Holtzman DM. Dr. Jekyll and Mr. Hyde: ApoE explains opposing effects of neuronal LRP1. *J Clin Invest*. 2019;129:969–971.

111. Bertero T, Cottrill KA, Lu Y, et al. Matrix remodeling promotes pulmonary hypertension through feedback mechanoactivation of the YAP/TAZ-miR-130/301 circuit. *Cell Rep*. 2015;13:1016–1032.

112. Bertero T, Handen AL, Chan SY. Factors associated with heritable pulmonary arterial hypertension exert convergent actions on the miR-

130/301-vascular matrix feedback loop. *Int J Mol Sci*. 2018;19:2289.

113. Calvier L, Demuth G, Manouchehri N, et al. Reelin depletion protects against autoimmune encephalomyelitis by decreasing vascular adhesion of leukocytes. *Sci Transl Med*. 2020;12:eaay7675.

114. Ding Y, Huang L, Xian X, et al. Loss of Reelin protects against atherosclerosis by reducing leukocyte-endothelial cell adhesion and lesion macrophage accumulation. *Sci Signal*. 2016;9:ra29.

115. Ramesh S, Morrell CN, Tarango C, et al. Antiphospholipid antibodies promote leukocyte-endothelial cell adhesion and thrombosis in mice by antagonizing eNOS via β2GPI and apoER2. *J Clin Invest*. 2011;121:120–131.

116. Calvier L, Manouchehri N, Sacharidou A, et al. Apolipoprotein E receptor 2 deficiency decreases endothelial adhesion of monocytes and protects against autoimmune encephalomyelitis. *Sci Immunol*. 2021;6:eabd0931.

117. Calvier L, Xian X, Lee RG, et al. Reelin depletion protects against atherosclerosis by decreasing vascular adhesion of leukocytes. *Arterioscler Thromb Vasc Biol*. 2021;41:1309–1318.

118. Romay-Penabad Z, Aguilar-Valenzuela R, Urbanus RT, et al. Apolipoprotein E receptor 2 is involved in the thrombotic complications in a murine model of the antiphospholipid syndrome. *Blood*. 2011;117:1408–1414.

119. Longoni M, Kantarci S, Donnai D, Pober BR. Donnai-Barrow syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed August 25, 2020. http://www.ncbi.nlm.nih.gov/books/NBK1878/

120. Johnson EB, Hammer RE, Herz J. Abnormal development of the apical ectodermal ridge and polysyndactyly in Megf7-deficient mice. *Hum Mol Genet*. 2005;14:3523–3538.

121. Johnson EB, Steffen DJ, Lynch KW, Herz J. Defective splicing of Megf7/Lrp4, a regulator of distal limb development, in autosomal recessive mulefoot disease. *Genomics*. 2006;88:600–609.

122. Al-Qattan MM, Alkuraya FS. Cenani-Lenz syndrome and other related syndactyly disorders due to variants in LRP4, GREM1/FMN1, and APC: insight into the pathogenesis and the relationship to polyposis through the WNT and BMP antagonistic pathways. *Am J Med Genet A*. 2019;179:266–279.

123. Kim DH, Iijima H, Goto K, et al. Human apolipoprotein E receptor 2. A novel lipoprotein receptor of the low density lipoprotein receptor family predominantly expressed in brain. *J Biol Chem*. 1996;271:8373–8380.

124. Webb DJ, Nguyen DH, Sankovic M, Gonias SL. The very low density lipoprotein receptor regulates urokinase receptor catabolism and breast cancer cell motility in vitro. *J Biol Chem*. 1999;274:7412–7420.

125. Pohlkamp T, Wasser CR, Herz J. Functional roles of the interaction of APP and lipoprotein receptors. *Front Mol Neurosci*. 2017;10:54.

126. 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 U S A*. 1995;92:8453–8457.

127. Tacken PJ, Delsing DJM, Gijbels MJJ, et al. VLDL receptor deficiency enhances intimal thickening after vascular injury but does not affect atherosclerotic lesion area. *Atherosclerosis*. 2002;162:103–110.

128. Crawford DC, Nord AS, Badzioch MD, et al. A common VLDLR polymorphism interacts with APOE genotype in the prediction of carotid artery disease risk. *J Lipid Res*. 2008;49:588–596.

129. Liu CX, Musco S, Lisitsina NM, Forgacs E, Minna JD, Lisitsyn NA. LRP-DIT, a putative endocytic receptor gene, is frequently inactivated in non-small cell lung cancer cell lines. *Cancer Res*. 2000;60:1961–1967.

130. Cengiz B, Gunduz M, Nagatsuka H, et al. Fine deletion mapping of chromosome 2q21-37 shows three preferentially deleted regions in oral cancer. *Oral Oncol*. 2007;43:241–247.

131. Langbein S, Szakacs O, Wilhelm M, et al. Alteration of the LRP1B gene region is associated with high grade of urothelial cancer. *Lab Invest*. 2002;82:639–643.

132. Li B, Liu C, Cheng G, et al. LRP1B polymorphisms are associated with multiple myeloma risk in a Chinese Han population. *J Cancer*. 2019;10:577–582.

133. Nakagawa T, Pimkhaokham A, Suzuki E, Omura K, Inazawa J, Imoto I. Genetic or epigenetic silencing of low density lipoprotein receptor-related protein 1B expression in oral squamous cell carcinoma. *Cancer Sci*. 2006;97:1070–1074.

134. Rahmatpanah FB, Carstens S, Guo J, et al. Differential DNA methylation patterns of small B-cell lymphoma subclasses with different clinical behavior. *Leukemia*. 2006;20:1855–1862.

135. Sonoda I, Imoto I, Inoue J, et al. Frequent silencing of low density lipoprotein receptor-related protein 1B (LRP1B) expression by genetic and epigenetic mechanisms in esophageal squamous cell carcinoma. *Cancer Res*. 2004;64:3741–3747.

136. Boucher P, Liu P, Gotthardt M, Hiesberger T, Anderson RGW, Herz J. Platelet-derived growth factor mediates tyrosine phosphorylation of the cytoplasmic domain of the low Density lipoprotein receptor-related protein in caveolae. *J Biol Chem*. 2002;277:15507–15513.

137. Loukinova E, Ranganathan S, Kuznetsov S, et al. Platelet-derived growth factor (PDGF)-induced tyrosine phosphorylation of the low density lipoprotein receptor-related protein (LRP). Evidence for integrated co-receptor function between LRP and the PDGF. *J Biol Chem*. 2002;277:15499–15506.

138. Tanaga K, Bujo H, Zhu Y, et al. LRP1B attenuates the migration of smooth muscle cells by reducing membrane localization of urokinase and PDGF receptors. *Arterioscler Thromb Vasc Biol*. 2004;24:1422–1428.

139. Seki N, Bujo H, Jiang M, et al. LRP1B is a negative modulator of increased migration activity of intimal smooth muscle cells from rabbit aortic plaques. *Biochem Biophys Res Commun*. 2005;331:964–970.

140. Beer AG, Zenzmaier C, Schreinlechner M, et al. Expression of a recombinant full-length LRP1B receptor in human non-small cell lung cancer cells confirms the postulated growth-suppressing function of this large LDL receptor family member. *Oncotarget*. 2016;7:68721–68733.

141. Ni S, Hu J, Duan Y, et al. Down expression of LRP1B promotes cell migration via RhoA/Cdc42 pathway and actin cytoskeleton remodeling in renal cell cancer. *Cancer Sci*. 2013;104:817–825.

142. Zheng H, Bai L. Hypoxia induced microRNA-301b-3p overexpression promotes proliferation, migration and invasion of prostate cancer cells by targeting LRP1B. *Exp Mol Pathol*. 2019;111:104301.

143. Maarman G, Lecour S, Butrous G, Thienemann F, Sliwa K. A comprehensive review: the evolution of animal models in pulmonary hypertension research; are we there yet? *Pulm Circ*. 2013;3:739–756.

144. Zhang Y, Zeng W, Cheng S, et al. Efficacy and safety of statins for pulmonary hypertension: a meta-analysis of randomised controlled trials. *Heart Lung Circ*. 2017;26:425–432.

145. Perros F, de Man FS, Bogaard HJ, et al. Use of β-blockers in pulmonary hypertension. *Circ Heart Fail*. 2017;10:e003703.

146. Wang L, Yang T, Wang C. Are statins beneficial for the treatment of pulmonary hypertension? *Chronic Dis Transl Med*. 2017;3:213–220.

147. Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. *Eur Respir Rev*. 2009;18:222–232.

148. Zhang M-Z, Qian D-H, Xu J-C, Yao W, Fan Y, Wang C-Z. Statins may be beneficial for patients with pulmonary hypertension secondary to lung diseases. *J Thorac Dis*. 2017;9:2437–2446.

149. Reed RM, Iacono A, DeFilippis A, et al. Statin therapy is associated with decreased pulmonary vascular pressures in severe COPD. *COPD*. 2011;8:96–102.

150. Ren X, Johns RA, Gao WD. EXPRESS: right heart in pulmonary hypertension: from adaptation to failure. *Pulm Circ*. 2019;9:2045894019845611.

151. Chan SY, Rubin LJ. Metabolic dysfunction in pulmonary hypertension: from basic science to clinical practice. *Eur Respir Rev*. 2017;26:170094.

KEY WORDS β-catenin, Apoer2, apolipoprotein E receptor 2, BMP, BMPR2, endothelial cell, gp330, LDL receptor related protein, LDLR, low-density lipoprotein receptor, LRP, LRP1, LRP1B, LRP2, LRP4, megalin, MEgf7, monocyte, multiple epidermal growth factor-like domains 7, LRP5, LRP6, LRP8, PAH, PDGF, PPARγ, pulmonary arterial hypertension, pulmonary vascular disease, PVD, right ventricle heart failure, RVHF, smooth muscle cell, TGF-β1, very low density lipoprotein receptor, VLDLR, Wnt

APPENDIX For expanded Methods and References sections, please see the online version of this paper.