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Review

Low Density Lipoprotein Receptor Related Protein 1 and Abdominal Aortic Aneurysms

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WHAT THIS PAPER ADDS

- A recent genome wide association study has demonstrated a highly significant association between abdominal aortic aneurysm (AAA) and the LRP1 (low density lipoprotein receptor related protein 1) gene. This review outlines how this cell surface transport molecule may influence the establishment and propagation of aneurysmal disease, essentially introducing LRP1 as a new potential candidate gene for AAA.

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ABSTRACT

Objectives: A recent GWAS demonstrated an association between low density lipoprotein receptor related protein 1 (LRP1) and Abdominal Aortic Aneurysm (AAA). This review aims to identify how LRP1 may be involved in the pathogenesis of abdominal aortic aneurysm.
Design and materials: A systematic review of the English language literature was undertaken in order to determine whether LRP1 and associated pathways were plausible candidates for contributing to the development and/or progression of AAA.
Methods and results: A comprehensive literature search of MEDLINE (since 1948), Embase (since 1980) and Health and Psychological Instruments (since 1985) was conducted in January 2012 identified 50 relevant articles. These studies demonstrate that LRP1 has a diverse range of biological functions and is a plausible candidate for playing a central role in aneurysmogenesis. Importantly, LRP1 downregulates MMP (matrix metalloproteinase) activity in vascular smooth muscle cells and regulates other key pathways involved in extracellular matrix remodelling and vascular smooth muscle migration and proliferation. Crucially animal studies have shown that LRP1 depletion leads to progressive destruction of the vascular architecture and aneurysm formation.
Conclusions: Published evidence suggests that LRP1 may play a key role in the development of AAA.

Introduction

A recent genome wide association study (GWAS) has demonstrated a genetic association between LRP1 (Low density lipoprotein receptor related protein 1) and abdominal aortic aneurysm (AAA).[1] This association between LRP1 and AAA was independent of risk factors for generalized cardiovascular disease, suggesting that the association is specific for AAA. The lead SNP (single nucleotide polymorphism) at the LRP1 locus was associated with altered LRP1 expression in aortic adventitial tissues.

LRP1 has multiple ligands (Fig. 1)[2,3] with a wide variety of biological activity, which include diverse processes previously implicated in AAA disease. Although the pathological process that leads to AAA is not fully understood, several key hallmarks have been identified such as extracellular matrix degradation and vascular smooth muscle cell (VSMC) depletion.[4,5] LRP1 is implicated in VSMC migration and proliferation via the binding of specific growth factors,[6] and LRP1 also binds matrix metalloproteinase 9 (MMP9),[2,3] a protease capable of degrading collagen. Finally, compelling evidence that LRP1 is involved in AAA arises from

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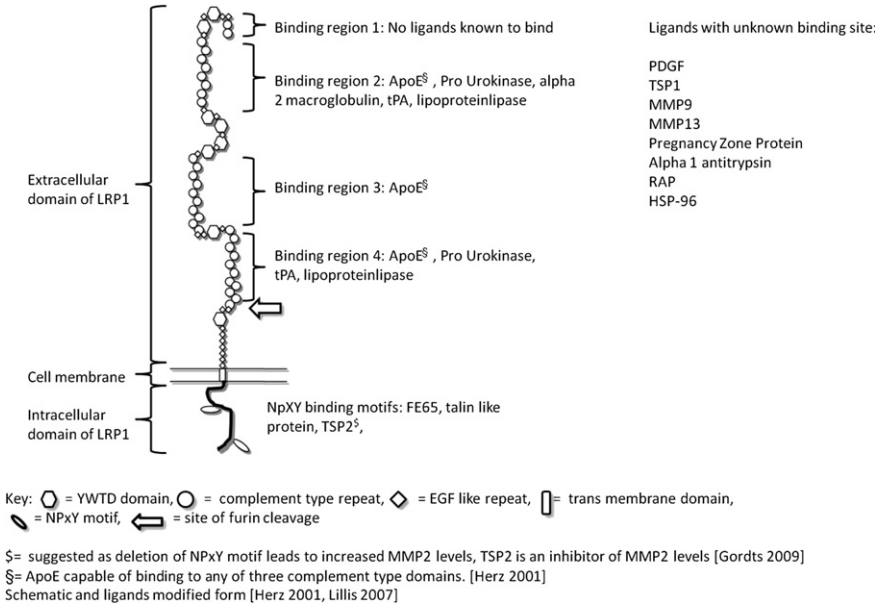

Figure 1. Schematic of LRP1 and annotated sites of ligand binding. Where site of ligand binding is not known, inferred locations are displayed, or else they are listed on the right hand side of the diagram.

animal knockout studies, where mice with VSMC specific LRP1 knockout had a diversely altered vascular histology and ultimately developed AAA.[6] This evidence highlights LRP1s involvement in AAA.

The aim of this systematic review of the literature was therefore to determine if the known functions and interactions of LRP1 form a plausible basis for its involvement in the initiation and progression of AAA.

Methods

This review was conducted according to established guidelines[7] (Fig. 2). Initially an electronic search of MEDLINE (since 1948), Embase (since 1980) and Health and Psychological Instruments (since 1985) was conducted using OVID Online (2000–2012 Ovid Technologies, Inc. New York, USA). The search terms used were the synonyms for LRP1 (http://www.genecards.org/), 'LRP1', 'Low density lipoprotein receptor related protein 1', 'LRP', 'Alpha-2-macroglobulin receptor', 'A2MR', 'CD91', 'apolipoprotein E receptor', 'APOER', 'type V tgf-beta receptor' and also 'vascular' and 'aneurysm'. Additional articles were identified from reference lists. Following combination of the database and reference list cohorts of articles, duplicates were removed. Articles were included if they related to LRP1 and its involvement in vascular biology, arterial wall structure or atherosclerosis. Two reviewers (JBW, PWS) independently selected appropriate studies based on abstract content. Studies that met the inclusion criteria were reviewed in full text, along with those for which it was unclear whether inclusion was warranted. Research methodology was also scrutinized as an assessment of article quality. Discrepancies between reviewers' opinions were resolved by discussion.

LRP1 Structure

The structure of LRP1 permits the binding of a wide variety of ligands (Fig. 1). It is through structural similarities with the LDL (low density lipoprotein) receptor that LRP1 was classified as a member of the LDL receptor family. In 1988 Herz and colleagues first described a 500 kDa liver cell surface protein whose sequence closely resembled LDL receptor and epidermal growth factor (EGF).[8] They proposed this protein, LDL-receptor related protein (LRP) functioned not only as a lipoprotein receptor but also had possible functions in modulating cell growth. LRP was located at the cell surface, had high levels of tissue expression in liver, lung and brain and significant levels in intestine and muscle. LRP1, as LRP is now known, is initially synthesised as a 600 kDa precursor that then undergoes furin cleavage within the golgi apparatus, resulting in the 85 kDa intracellular and intramembrane fragment and the 515 kDa extracellular fragment.[9,10] These two fragments form a non covalently bonded heterodimer spanning the cell membrane; with both domains featuring structural motifs capable of binding a diverse range of over 40 ligands.[2,3] LRP1 is a member of a gene family of low density lipoprotein receptors, including LRP1B, LRP5, LRP6, low density lipoprotein receptor (LDLR), very low density lipoprotein receptor (VLDLR) and megalin.[11] Structural homology exists between the different members of the family; however LRP1, LRP1B and megalin are the 3 largest members. All members of the LRP protein family have at least one NPxY motif (asparagine-proline-x-tyrosine, where x can be any amino acid) in their intracellular tail. LRP1 has 2 NPxY motifs within its intracellular region, and a variety of ligands are known to bind specifically to these motifs.[12] The extracellular domain contains a variety of binding sites, cysteine-rich complement type binding domains, EGF receptor like cysteine repeats and YWTD (Tyrosine-Tryptofan-Threonine-Aspartic acid) domains. LRP1 acts as a membrane receptor for a wide variety of ligands thanks to the 4 cysteine-rich complement binding domains. As it is capable of binding such a wide variety of ligands LRP1 is involved in multiple processes and several of these have potential to affect the arterial wall. For example, the proteases MMP2, MMP9 and the growth factor PDGF can all bind to the extracellular portion of LRP1.[2,3] LRP1 is essential for embryonic implantation and LRP1 knockout in mice is an early embryonic lethal variant, demonstrating its importance.[13] In summary, LRP1 has structural similarity to other members of the lipoprotein receptor family and several distinct binding regions that facilitate adhesion to multiple ligands, some of which have potential to affect the arterial wall and lead to aneurysm formation.

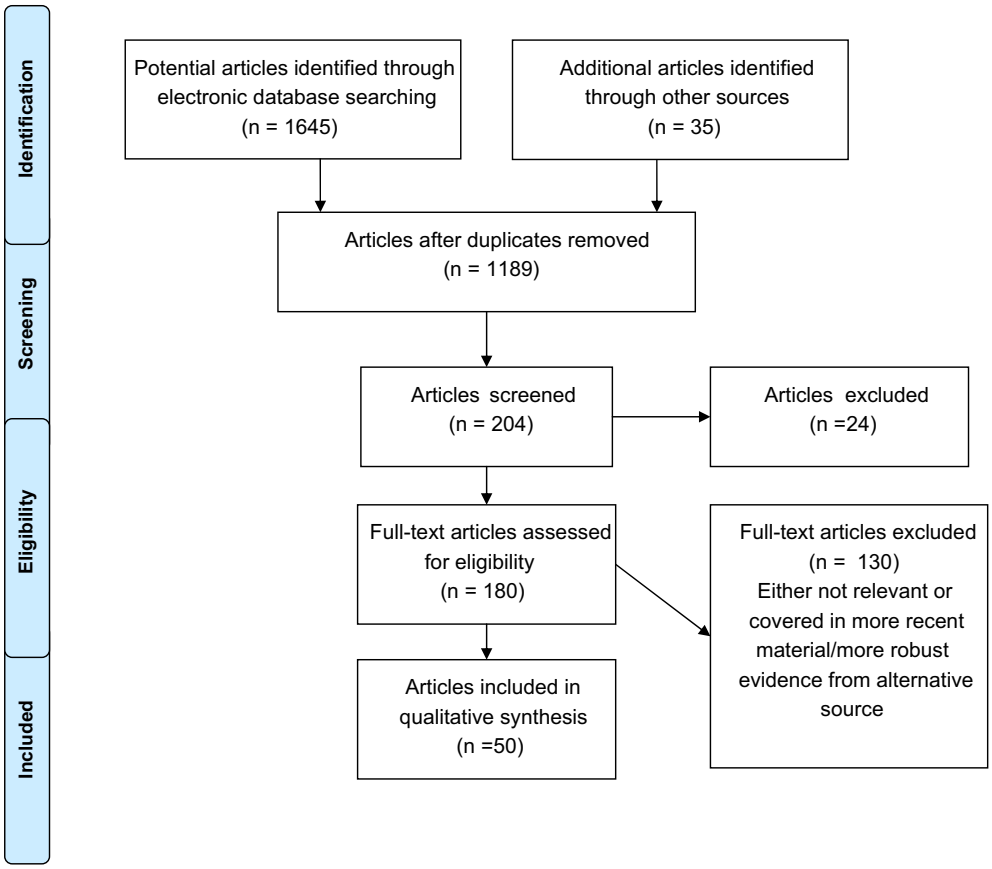

Figure 2. Literature Search Flow diagram according to the PRISMA guidelines [Moher 2009]. *n* = number of articles.

LRP1 and extracellular matrix degradation

The regulation of proteases by LRP1 may impact on aneurysmal development, via degradation of the extracellular matrix (ECM), a key feature of aneurysm development.[4] MMP9 is a member of the matrix metalloproteinase family, a group of proteinases that have been widely implicated in AAA. MMP9 was localized to within macrophages of the wall of AAA[14] and found to be elevated in the plasma of patients with AAA.[15] Subsequently MMP9 gene polymorphisms were significantly associated with AAA in a meta-analysis.[16] MMP9 has been shown to directly bind to LRP1 with high specificity, with LRP1 depleted cell lines having reduced capacity to internalize and degrade MMP9, proving LRP1 is a regulator of active MMP9 levels.[17] This experimental evidence was achieved in a cell line of mouse embryonic fibroblasts, where LRP1 activity was depleted by addition of the receptor associated protein, a ligand antagonist, to culture media. LRP1 is essential for MMP9 upregulation, as LRP1 depleted microglial cells have upregulated MMP9 in response to ischaemia; however a further study showed that both LRP1 and MMP9 were upregulated in response to hypoxia in renal cells.[18,19] This conflicting evidence may be due to the interaction between LRP1 and MMP9 being cell dependent or due to a lack of knowledge of the underlying mechanism of LRP1's interaction with MMP9. This interaction may be through transport of MMP9 through the cell membrane via LRP1 or through its interaction with other matrix proteins that regulate MMP9 activity. Despite the relationship between LRP1 and MMPs not being clear, crucial data from aortic tissue and animal models demonstrate LRP1 loss increases levels of MMP and ultimately leads to AAA formation.[6,20]

LRP1 may also regulate ECM degradation and AAA propagation via thrombospondins, TSP1 and TSP2 which both bind to LRP1.[21,22] TSPs 1 and 2 inhibit the gelatinases MMPs 2 and 9 by preventing the conversion of inactive precursor into the active form of the molecule. LRP1 is responsible for the endocytosis that leads to degradation of TSPs.[23] If a cell had reduced levels of LRP1 then TSP levels would be increased, decreasing the levels of active MMP2 and 9. TSP2 polymorphisms have previously been associated with thoracic aortic aneurysms (TAA) in hypertensive patients, but not AAA.[24] The NPxY motif within the intracytoplasmic region of LRP1 has been shown to be essential in the regulation in MMP2 levels, with knock out of this region leading to increased MMP2 activity of up to 3 times the normal level in mouse aortic tissue, implicating this motif as a potential binding region for TSP or another MMP regulatory protein.[20] In addition TSP2 knockout mice demonstrate increased blood vessel density, highlighting a regulatory role for TSP2 in angiogenesis, which may also impact on AAA.[25] Therefore LRP1 depletion may act both directly and indirectly on the activity of MMPs.

The interaction between LRP1 and MMPs illustrates the diversity of LRP1 function, with LRP1 affecting levels of MMPs via different pathways in different tissue types. As it has already been shown that members of the MMP family play a role in the development of AAA, the fact that their level of activity is regulated by LRP1 indicates this may be the avenue by which LRP1 modulates aneurysmogenesis.

LRP1 and vascular smooth muscle cell depletion

Depletion of VSMCs is a hallmark of AAA.[26] Boucher et al demonstrated that LRP1 regulates smooth muscle cell migration and proliferation via interaction with PDGFRβ (platelet derived growth factor receptor beta).[6] A strain of mice was created that

were LDLR knockout with smooth muscle depletion of LRP1 (smLRP1$^-$). The LDLR$^-$smLRP1$^-$ mice had a significantly altered vascular phenotype, although they appeared superficially normal. Macroscopically the mice had aortas that were consistently distended and dilated, a feature that worsened with increasing age, together with progressive thickening of the aorta due to VSMC proliferation and eventually suprarenal aneurysm formation. Microscopically there was gross disruption of the elastic laminae of the aorta. These animals, whether fed a raised cholesterol diet or normal chow, did not have increased serum triglycerides or cholesterol, however there was an increase in the activity of MMPs 2 and 9 in the smLRP1$^-$ animals suggesting that LRP1 has an overall negative regulatory affect on MMPs. Furthermore smLRP1$^-$ arterial smooth muscle cells were α actin depleted when compared to wild type cells of the same nature, reducing the ability of the vessels to contract.[27] Boucher postulates that the mechanism by which LRP1 regulates smooth muscle cell proliferation and migration is via PDGF dependant phosphorylation of the LRP1 tail leading to Shc binding and activation of the Ras pathway. Tyrosine kinase inhibitors (TKI) not only suppress LRP1 and PDGFRβ (PDGF receptor β) phosphorylation in bovine smooth muscle cells but also reduce aortic thickness and improve elastic layer stability in LDLR$^-$smLRP1$^-$ mice. PDGFRβ co-precipitates with LRP1 and comparison of LRP1 deficient and LRP1 expressing mouse aortas demonstrated that LRP1$^+$ mice have decreased levels of PDGFRβ, with PDGFRβ signalling known to precede atherosclerotic lesion formation. This demonstrates that LRP1 can suppress pro-atherosclerotic PDGFRβ activation. As TKIs can rescue the LRP1 knockout to a degree, reducing aortic thickness and improving elastic layer stability, this may have potential as a future therapeutic strategy in AAA. These key experiments demonstrate that LRP1 depletion is a stage in AAA development. This work, and subsequent experiments, produced invaluable insight in to the importance of LRP1 to arterial wall structure, however the mainstay of these publications all arise from the same group of researchers.[6,27,28] LRP1 knockout not only raised MMP levels but impaired smooth muscle cell proliferation and migration. Finally it is apparent that the deleterious effects of LRP1 depletion can be improved with the addition of a tyrosine kinase inhibitor, which may prove to be a future treatment for AAA.

If medications are going to be used to stabilise the expansion of small AAA, then utilising medications that are already in use for the treatment of other diseases will be desirable in order to reduce time and developmental costs. Aside from TKI treated LRP1 knockout mice demonstrating a reduction in arterial wall destruction, the addition of rosiglitazone to smLRP1$^-$, one of the thiazolidinedione class of insulin sensitizers, reduced atherosclerosis and features such as elastic layer disruption and smooth muscle proliferation.[28] With partial correction of effects of LRP1 knockout, rosiglitazone may also have clinical potential in modulating AAA progression. Rosiglitazone has been withdrawn due to negative effects seen in patients with heart failure, acute coronary syndrome, ischaemic heart disease and peripheral vascular disease; however another thiazolidinedione, pioglitazone, has not been withdrawn. Therefore the use of drugs from the thiazolidinedione class may be of use in reducing the impact of LRP1 loss on arterial structure. This experiment also demonstrated the potential importance of TGFβ (transforming growth factor beta) in AAA pathogenesis.[28] TGFβ is a cytokine and an LRP1 ligand, it has also been implicated in AAA pathogenesis, the *TGFβR2* (TGFβ receptor 2) gene is found to have significant deletions in AAA wall biopsies with a proposed reduction of the antiproliferative effect of TGFβ.[29]

Data from LRP1 smooth muscle knockout mouse experiments suggest that loss of normal LRP1 results in destruction of the arterial wall associated with increased MMP levels which may have been responsible for the tissue damage. The use of tyrosine kinase inhibitors and an insulin sensitizer, rosiglitazone, were able to ameliorate some of the negative feature of LRP1 depletion and may prove to have potential for treatment.

LRP1 and inflammation

The role of LRP1 in inflammation is unknown with evidence demonstrating pleiotropic effects. The association between AAA and local chronic inflammation is well established, with transmural infiltration of the arterial wall in AAA by macrophages and lymphocytes a prominent histological feature,[30] additionally mast cells, regulators of inflammation, are key to AAA development with mast cell deficient mice resistant to AAA formation.[31] Mast cells contain granules that store a wide variety of proteases, cytokines and growth factors including PDGF and TGFβ, known LRP1 ligands.[32] Macrophages are known to express LRP1 and after adipocytes, monocytes show the highest level of expression.[33] Experimental work from a rat microglial cell model has demonstrated that LRP1 functions as a pro-inflammatory molecule. 2′-hydroxycinnamaldehyde is an anti-angiogenic, anti-proliferative and pro-apoptotic compound that binds to LRP1. When LRP1 is bound to 2′-hydroxycinnamaldehyde it induces an anti-inflammatory state in microglial cells, by the inhibition of cell signalling pathways suggesting LRP1 is pro-inflammatory.[34] This study utilised novel and established cell lines and defined protein level and activity under a variety of experimental conditions to from a robust argument for their findings. However, LRP1 depletion has been shown to increase the levels of MMP9 and tissue necrosis factor α, INOS (inducible nitric oxide synthase), activated complement proteases and IL-6 (interleukin-6), indicating that LRP1 may have innate anti-inflammatory properties.[35,36] The article from Overtan et al. utilised a mouse model with LRP1 depleted macrophages.[35] Through Western blotting, real time PCR and gel electrophoresis they demonstrated that MMP activity was increased.[36] However Gaultier et al. utilised an LRP1 deficient mouse fibroblast cell line and similar experimental techniques to prove increased expression of several inflammatory mediators takes place when LRP1 is absent. Therefore it has been shown that LRP1 can exhibit both pro and anti-inflammatory behaviour, however with greater understanding of the specific ligand binding regions of the molecule it may be possible to inhibit the pro-inflammatory effects whilst maintaining the anti-inflammatory potential of LRP1.

LRP1 Regulation

In understanding the mechanisms regulating LRP1 function it may be possible to identify potential therapeutic targets for LRP1 that could be used to slow the progression of small AAA. LRP1 is regulated by several factors; one of these is angiotensin II (AngII). It is well characterised that continuous infusion of AngII leads to the development of aneurysms in apolipoprotein-E deficient mice.[37] AngII induces overexpression of LRP1 in the arterial wall and also increased its activity, resulting in increased uptake of aggregated LDL in cultured human VSMC.[38] These effects can be negated with administration of the angiotensin receptor blocker, losartan. Additionally in mouse models of TAA, the thoracic aorta of mice treated with losartan were found to have improved structural integrity and elastic fibre organisation and reduced levels of MMP 2 and 9 activation when compared to untreated mice.[39] These data suggests that reduction of LRP1 expression is beneficial in aneurysms, which conflicts with the other data we have presented. The exact mechanisms are still unclear but from these data, it is likely that AngII related development of aneurysms is LRP1 independent

or any aneurysmogenic effects of AngII induction override the protection achieved from increased LRP1 expression.

Implications for the treatment of small AAA

Aside from inducing LRP1 expression with known medications in order to halt small AAA progression it may be possible to modulate AAA growth via novel methods involving the LRP1 pathways. LRP1 is regulated by systemic lipoprotein levels; in response to aggregated LDL (agLDL) in VSMC LRP1 is upregulated. This upregulation is coexistent with downregulation of SREBP (sterol regulatory binding protein).[40] Experimental silencing of SREBP isoforms increased LRP1 levels whereas SREBP overexpression reduced LRP1 expression. Furthermore, agLDL prevent the SREBP-2 isoform from efficiently binding to the promoter region of LRP1 gene. This demonstrates that silencing of specific SREBP isoforms may be utilised to increase LRP1 expression in AAA patients, without having to increase systemic lipoprotein levels which would be associated with other deleterious effects. Recent hepatocyte cell culture experimental evidence indicates that LRP1 is upregulated in the presence of the cholesterol lowering medication, hydroxymethylglutaryl-coenzyme A (HMG co-A) reductase inhibitor, Atorvastatin.[41] This is coupled with data that the aortic diameter of AAA patients treated with a HMG co-A reductase inhibitor expand at a reduced rate when compared to patients not receiving this group of medications.[42]

Possible methods of regulating LRP1 at the level of transcription is via miR-205, a microRNA, which down-regulates the expression of LRP1 mRNA, therefore miR-205 blockade may increase LRP1 activity.[43] Similarly a short interfering RNA has been shown as an effective silencer of LRP1 expression in smooth muscle cells leading to inhibition of VSMC migration.[44] Modulation of LRP1 expression may be achieved by the selective inhibition of both these negative regulatory elements; however this form of molecular medicine is a long way from mainstream practice. If high LRP1 levels reduce AAA growth then this may form the basis of small AAA treatment. Modulation of LRP1 expression may be achievable in a laboratory setting, however these examples show that although theoretically possible the systemic administration of an agent that would interfere with one of these regulatory elements would need rigorous investigation in order to determine safety before a treatment could be utilised.

Conclusion

LRP1 and its associated pathways are biologically plausible candidates that may have a role in the development of AAA. These effects go beyond the ability of LRP1 to bind a wide variety of ligands that interact with the arterial wall such as the matrix metalloproteinases. LRP1 knockout studies in mice implicate the importance of the regulatory relationship between LRP1 and PDGFRβ, with loss of LRP1 leading to a pro atherosclerotic state, extracellular matrix disruption and even aneurysmal formation.

LRP1 has already been implicated in several diverse diseases, notably Alzheimer's disease[45] obesity.[46] myocardial infarction,[47] bicuspid aortic valve[48] and in cancers such as medulloblastoma,[49] although modulation of LRP1 activity is yet to be utilised as a therapeutic target in clinical practice.

This review was prepared using a systematic approach; however despite the literature search utilising a recognised framework it is very difficult to apply a quality assessment to basic scientific studies. We acknowledge that the majority of the evidence presented arises from animal studies; however the methodology utilised appears to be scientifically appropriate.

This review highlights the current knowledge on LRP1 and its potential role in AAA pathophysiology, further investigation is required to fully elucidate the LRP1 pathway and the exact mechanism by which it plays a role in the pathogenesis of AAA. LRP1 mutation is likely to part of a collaboration of genetic and environmental factors. The most significant environmental factor is smoking[50] and it is likely that the damage to the cellular structure from cigarette smoking will interact with several underlying genetic aberrations, such as LRP1 mutation, allowing an aneurysm to form. LRP1 and its associated pathways appear to be a potential candidate target for the treatment of AAA, but further work is required to define the specific role of LRP1 in aneurysmogenesis.

Conflict of Interest

None.

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References

1 Bown MJ, Jones GT, Harrison SC, Wright BJ, Bumpstead S, Baas AF, et al, CARDIoGRAM Consortium; Global BPgen Consortium; DIAGRAM Consortium; VRCNZ Consortium. Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. *Am J Hum Genet* 2011;**89**(5):619–27.
2 Herz J, Strickland DK. LRP: a multifunctional scavenger and signaling receptor. *J Clin Invest* 2001;**108**(6):779–84.
3 Lillis AP, Van Duyk LB, Murphy-Ullrich JE, Strickland DK. LDL receptor related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. *Physiol Rev* 2007;**88**:887–918.
4 Thompson RW, Parks WC. Role of matrix metalloproteinases in abdominal aortic aneurysms. *Ann N Y Acad Sci* 1996;**800**:157–74.
5 Lopez-Candales A, Holmes DR, Liao S, Scott MJ, Wickline SA, Thompson RW. Decreased vascular smooth muscle cell density in medial degeneration of human abdominal aortic aneurysms. *Am J Pathol* 1997;**150**(3):993–1007.
6 Boucher P, Gotthardt M, Li WP, Anderson RGW, Herz J. LRP: role in vascular wall integrity and protection from atherosclerosis. *Science* 2003;**300**(5617):329–32.
7 Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
8 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 associated to the LDL-receptor suggests a physiological role as lipoprotein receptor. *EMBO J* 1988;**7**(13):4119–27.
9 Herz J, Kowal RC, Goldstein JL, Brown MS. Proteolytic processing of the 600 kD low density lipoprotein receptor related protein (LRP) occurs in a trans-Golgi compartment. *EMBO J* 1990;**9**(6):1769–76.
10 Van der Geer P. Phosphorylation of LRP1: regulation of transport and signal transduction. *Trends Cardiovasc Med* 2002;**12**(4):160–5.
11 Boucher P, Gotthardt M. LRP and PDGF signalling: a pathway to atherosclerosis. *Trends Cardiovasc Med* 2004;**14**(2):55–60.
12 Trommsdorff M, Borg JP, Margolis B, Herz J. Interaction of cytosolic adaptor proteins with neuronal apolipoprotein E receptors and the myloid precursor protein. *J Biol Chem* 1998;**273**:33556–60.
13 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**(3):411–21.
14 Newman KM, Jean-Claude J, Li H, Scholes JV, Ogata Y, Nagase H, et al. Cellular localization of matrix metalloproteinases in the abdominal aortic aneurysm wall. *J Vasc Surg* 1994;**20**(5):814–20.
15 Hovsepian DM, Ziporin SJ, Sakurai MK, Lee JK, Curci JA, Thompson RW. Elevated plasma levels of matrix metalloproteinase-9 in patients with abdominal aortic aneurysms: a circulating marker of degenerative aneurysm disease. *J Vasc Interv Radiol* 2000;**11**(10):1345–52.
16 Thompson AR, Drenos F, Hafez H, Humphries SE. Candidate gene association studies in abdominal aortic aneurysm disease: a review and meta-analysis. *Eur J Vasc Endovasc Surg* 2008;**35**(1):19–30.
17 Hahn-Dantona E, Ruiz JF, Bornstein P, Strickland DK. The low density lipoprotein receptor-related protein modulates levels of matrix Metalloproteinase 9

(MMP9) by mediating its cellular catabolism. *J Biol Chem* 2001;**276**(28):15498–503.
18 Zhang C, An J, Haile WB, Echeverry R, Strickland DK, Yepes M. Microglial low-density lipoprotein receptor-related protein 1 mediates the effect of tissue-type plasminogen activator on matrix matelloproeinases-9 activity in the ischemic brain. *J Cereb Blood Flow Metab* 2009;**29**(12):1946–54.
19 Caron A, Desrosiers RR, Beliveau R. Ischemia injury alters endothelial cell properties of kidney cortex: stimulation of MMP-9. *Exp Cell Research* 2005;**310**(1):105–16.
20 Gordts PLSM, Reekmans S, Lauwers A, Dongen AV, Verbeek L, Roebroek AJM. Inactivation of the LRP1 intracellular NPxYxxL motif in LDLR-deficient mice enhances postprandial dyslipidemia and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2009;**29**(9):1258–64.
21 Bein K, Simons M. Thrombospondin type 1 repeats interact with matrix metalloproteinase 2. Regulation of metalloproteinase activity. *J Biol Chem* 2000;**275**:32167–73.
22 Bornstein P, Kyriades TR, Yang Z, Armstrong LC, Birk DE. Thrombospondin 2 modulates collagen fibrillogenesis and angiogenesis. *J Investig Dermatol Symp Proc* 2000;**5**(1):61–6.
23 Godyna S, Liau G, Popa I, Stefansson S, Argraves WS. Identification of the low density lipoprotein receptor-related protein (LRP) as an endocytic receptor for thrombospondin-1. *J Cell Biol* 1995 Jun;**129**(5):1403–10.
24 Kato K, Oguri M, Kato N, Hibino T, Yajima K, Yoshida T, et al. Assessment of genetic risk factors for thoracic aortic aneurysm in hypertensive patients. *Am J Hypertens* 2008;**21**(9):1023–7.
25 Kyriakides TR, Zhu YH, Smith LT, Bain SD, Yang Z, Lin MT, et al. Mice that lack thrombospondin 2 display connective tissue abnormalities that are associated with disordered collagen fibrillogenesis, an increased vascular density, and a bleeding diathesis. *J Cell Biol* 1998 Jan 26;**140**(2):419–30.
26 Dai J, Michineau S, Franck G, Desgranges P, Becquemin JP, Gervais M, et al. Long term stabilization of expanding aortic aneurysms by a short course of cyclosporine a through transforming growth factor-beta induction. *PLoS One* 2011;**6**(12). e28903.
27 Basford JE, Moore ZWQ, Zhou L, Herz J, Hui DY. Smooth muscle LDL receptor-related protein-1 inactivation reduces vascular reactivity and promotes injury-induced neointima formation. *Arteriosclerosis, Thromb Vasc Biol* 2009;**29**(11):1772–8.
28 Boucher P, Li WP, Matz RL, Takayama Y, Auwerx J, Anderson RG, 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**(5). e448.
29 Biros E, Walker PJ, Nataatmadja M, West M, Golledge J. Downregulation of transforming growth factor beta receptor 2 and Notch signalling pathway in human abdominal aortic aneurysm. *Atherosclerosis* 2012;**221**(2):383–6.
30 Ailawadi G, Eliason JL, Upchurch Jr GR. Current concepts in the pathogenesis of abdominal aortic aneurysm. *J Vasc Surg* 2003;**38**(3):584–8.
31 Sun J, Sukhova GK, Yang M, Wolters PJ, MacFarlane LA, Libby P, et al. Mast cells modulate the pathogenesis of elastase-induced abdominal aortic aneurysms in mice. *J Clin Invest* 2007;**117**:3359–68.
32 Krishnaswamy G, Ajitawi O, Chi DS. The human mast cell: an overview. *Methods Mol Biol* 2006;**315**:13–34.
33 Su AI, Wiltshire T, Batalov S, Lapp H, Ching KA, Block D, et al. A gene atlas of the mouse and human protein-encoding transcriptomes. *Proc Natl Acad Sci U.S.A* 2004;**101**(16):6062–7.
34 Hwang H, Jeon H, Ock J, Hong S, Han Y, Kwon B, et al. 2'-Hydroxycinnamaldehyde targets low-density lipoprotein receptor-related protein-1 to inhibit lipopolysaccharide-induced microglial activation. *J Neuroimmunol* 2011 Jan;**230**(1–2):52–64.
35 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**:670–7.
36 Gaultier A, Arandjelovic S, Niessen S, Overton CD, Linton MF, Fazio S, et al. Regulation of tumor necrosis factor receptor-1 and the IKK-NF-kappaB pathway by LDL receptor-related protein explains the anti-inflammatory activity of this receptor. *Blood* 2008;**111**:5316–25.
37 Daugherty A, Manning MW, Cassis LA. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. *J Clin Invest* 2000 Jun;**105**(11):1605–12.
38 Sendra J, Llorente-Cortes V, Costales P, Huesca-Gomez C, Badimon L. Angiotensin II upregulates LDL receptor-related protein (LRP1) expression in the vascular wall: a new pro-atherogenic mechanism of hypertension. *Cardiovasc Res* 2008;**78**(3):581–9.
39 Yang HHC, Kim JM, van Breeman C, Hung AWY. Long-term effects of losartan on structure and function of the thoracic aorta in a mouse model of Marfan syndrome. *Br J Pharmacol* 2009;**158**(6):1503–12.
40 Costales P, Aledo R, Vernia S, Das A, Shah VH, Casado M, et al. Selective role of sterol regulatory element binding protein isoforms in aggregated LDL-induced vascular low density lipoprotein receptor-related protein-1 expression. *Atherosclerosis* 2010;**213**(2):458–68.
41 Moon JH, Kang SB, Park JS, Lee BW, Kang EK, Ahn CW, et al. Up-regulation of hepatic low-density lipoprotein receptor-related protein1: a possible novel mechanism of antiatherogenic activity of hydroxymethylglutaryl-coenzyme A reductase inhibitor atorvastatin and hepatic LRP1 expression. *Metabolism* 2011;**60**:930–40.
42 Karrowni W, Dughman S, Hajj GP, Miller Jr FJ. Statin therapy reduces growth of abdominal aortic aneurysms. *J Investig Med* 2011 Dec;**59**(8):1239–43.
43 Song H, Bu G. MicroRNA-205 inhibits tumor cell migration through down-regulating the expression of the LDL receptor-related protein 1. *Biochem Biophys Res Commun* 2009;**388**(2):400–5.
44 Li Y, Lu W, Bu G. Essential role of the low density lipoprotein receptor – related protein in vascular smooth muscle migration. *FEBS Lett* 2003;**555**:346–50.
45 Bates KA, Verdile G, Li QX, Ames D, Hudson P, Masters CL, et al. Clearance mechanisms of Alzheimer's amyloid-[beta] peptide: implications for therapeutic design and diagnostic tests. *Mol Psychiatry* 2009;**14**(5):469–86.
46 Hofmann SM, Zhou L, Perez tilve D, Greer T, Grant E, Wancata L, et al. Adipocyte LDL receptor-related protein-1 expression modulates postprandial lipid transport and glucose homeostasis in mice. *J Clin Invest* 2007;**117**(11):3271–82.
47 Gonzalez P, Alvarez R, Reguero JR, Batalla A, Alvarez V, Cortina A, et al. Variation in the lipoprotein receptor-related protein, [alpha]2-macroglobulin and lipoprotein receptor-associated protein genes in relation to plasma lipid levels and risk of early myocardial infarction. *Coron Artery Dis* 2002;**13**(5):251–4.
48 Folkersen L, Wagsater D, Paloschi V, Jackson V, Petrini J, Kurtovic S, et al. Unravelling divergent gene expression profiles in bicuspid and tricuspid aortic valve patients with thoracic aortic dilatation: the ASAP study. *Mol Med* 2011;**17**(11):1365–73.
49 Annabi B, Doumit J, Plouffe K, LaFlamme C, Lorddufour S, Beliveau R. Members of the low-density lipoprotein receptor-related proteins provide a differential molecular signature between parental and CD133(+) daoy medulloblastoma cells. *Mol Carcinog* 2010;**49**(7):710–7.
50 Svensjö S, Björck M, Gürtelschmid M, Djavani Gidlund K, Hellberg A, Wanhainen A. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease. *Circulation* 2011 Sep 6;**124**(10):1118–23 [Epub 2011 Aug 15].