[Frontiers in Bioscience 6, d406-d416, March 1, 2001]

MEMBERS OF THE LOW DENSITY LIPOPROTEIN RECEPTOR FAMILY CONTROL DIVERSE PHYSIOLOGICAL PROCESSES

W. Scott Argraves

Department of Cell Biology and Anatomy, Medical University of South Carolina, Charleston, SC 29425

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Current Knowledge
3.1. LDLR family members cooperate with other cell surface proteins to mediate ligand endocytosis
3.2. Roles of LDLR family members in mediating biosynthetic processing of other proteins
3.3. LDLR family members function in reproduction
3.4. Roles of LDLR family members in development
3.5. LDLR family members in renal absorption and homeostatic regulation
4. Perspective
5. Acknowledgements
6. References

1. ABSTRACT

The low density lipoprotein receptor (LDLR) family is a group of receptors that mediate endocytosis leading to lysosomal degradation of an enormous repertoire of ligands. To date, over 50 distinct macromolecules have been shown to bind members of the family. This wide spectrum of ligand recognition is the basis for an immense diversity in physiological processes in which these receptors participate. In this article, the physiological roles of the LDLR family members are briefly reviewed and a comprehensive list of the ligands with which the receptors interact is presented.

2. INTRODUCTION

The low density lipoprotein receptor (LDLR) family presently contains at least eight mammalian members: LDLR, LDLR-related protein (LRP), megalin (LRP-2), VLDLR, SORLA-1, LRP-3, ApoER2 and LR3 (Table 1). Various orthologs of these receptors have also been identified in the round worm, fruit fly, frog and chicken. Members of the LDLR family have modular structures similar to that of the prototypic family member, LDLR (for review see (1, 2)). The modular elements of these receptors include cysteine-rich complement-type repeats, EGF precursor-like repeats separated by YWTD tetrapeptide-containing spacer regions, a hydrophobic transmembrane domain, and a cytoplasmic domain containing at least one coated-pit internalization signal (FXNPXY). Members of this family function as receptors that mediate endocytosis and lysosomal targeting of a diverse array of macromolecules including lipoproteins (e.g., chylomicrons, LDL, Lp(a) and high density lipoproteins (HDL)), proteinases (e.g., urinary-type plasminogen activator (uPA)), complexes of proteinases and proteinase inhibitors (e.g., uPA-plasminogen activator inhibitor-1), hormones (e.g., parathyroid hormone, insulin, prolactin and thyroglobulin), vitamins (e.g., B_{12}, D, retinol and riboflavin) and extracellular matrix proteins (e.g., thrombospondin-1 and 2 and reelin) (Table 2) (1-3). The function of these receptors in catabolism makes them essential to homeostatic regulation of the level and activity of macromolecules in biological fluids and interstitial spaces. As a result, receptors of this family impact directly or indirectly most, if not all, physiological processes including reproduction, development and nutrition and many pathophysiological processes including atherosclerosis, cytotoxicity and infection. This article is a brief review of the current knowledge pertaining to physiological functions of the LDLR family.

3. CURRENT KNOWLEDGE

3.1. LDLR family members cooperate with other cell surface proteins to mediate ligand endocytosis

While LDLR family members can function independently to mediate binding and endocytosis of various ligands, it is also evident that LDLR family members function in concert with other cell surface proteins. Prototypic of this phenomenon is the process by which the glycolipid-anchored urokinase receptor (uPAR) and LRP function together to mediate endocytosis of pro-urokinase (pro-uPA) or complexes of uPA and plasminogen activator inhibitor-1 (PAI-1) or complexes of uPA and protease nexin-1 (4-6). In these cases, the ligands first interact with uPAR and are then internalized by the action of LRP. VLDLR and megalin have also been shown to mediate uptake of pro-uPA and uPA-PAI-1 complex by such a two-step process involving initial binding to uPAR

Table 1. Mammalian Members of the LDLR Family

	LDLR	LRP	Megalin	VLDLR	SORLA-1	LRP-3	ApoER2	LR3
Synonymous names	Classical LDLR	Low density lipoprotein receptor - related protein (LRP), LRP-1	LRP-2, gp330, gp600, brushin	LR8	Sortilin-related receptor, L(DLR class) A repeat-containing, mosaic protein LR11	LDL receptor related protein 105	LR7, LR8B, LRP-8	LRP-5
Human chromosome location	19p13.3	12q13-q14	2q24-q31	9p24	11q23.2-q24.4	19q12-q13	1p34	11q13.4
Database accession no. (Human)	P01130	X13916	U33837	I59603	CAA69325	AB009462	BAA09328	AF064548
Phenotype of knockout mouse	Increased total plasma cholesterol due to increased IDL and LDL levels (64)	Death at embryonic day 10 (45)	Perinatal death within 2-3 h of birth, craniofacial defects, holo-prosencephalic syndrome, lung and kidney abnormalities (46)	Grossly normal, slight decrease in whole body and adipose tissue mass (41)			Grossly normal (44)	

Table 2. Ligand Specificity of LDLR Family Members

Ligand	Ligand Function	Physiological Category	LDLR	LRP (LRP-1)	Megalin (LRP-2, gp330)	VLDLR (LR8)	SORLA-1 (mosaic protein LR11)	ApoER2 (LR7, LR8B, LRP-8)
RAP	Biosynthetic Chaperon	Receptor Biosynthesis	yes (65)	yes (66)	yes (67-69)	yes (70, 71)	yes (31, 72)	
Apolipoprotein E	Uptake of triglyceride-rich lipoproteins	Lipoprotein Metabolism	yes (73, 74)	yes (75)	yes (76)	yes (77)	yes (72)	yes (30)
Apolipoprotein B	Structural component of chylomicrons, VLDL, IDL and LDL	Lipoprotein Metabolism	yes (73, 74)		yes (78)			
Apolipoprotein J/clusterin	Adaptor	Lipoprotein Metabolism		no (79)	yes (79)	yes (37)		
Apolipoprotein J-amyloid beta					yes (61)			
Lipoprotein(a)	Atherogenic lipoprotein	Lipoprotein Metabolism			yes (80)	yes (81)		
Lipoprotein Lipase	Hydrolysis of lipoprotein phospholipids and triglycerides	Lipoprotein Metabolism	yes (82)	yes (12)	yes (13)	yes (8)		yes (83)
Hepatic Lipase	Hydrolysis of lipoprotein phospholipids and triglycerides	Lipoprotein Metabolism		yes (14)				
Cubilin	Receptor for intrinsic factor-B12 and HDL	Lipoprotein Metabolism			yes (10)			
$alpha_2$-Macroglobulin-Protease Complexes	Regulation of extracellular proteinase activity	Proteinase Homeostasis		yes (84, 85)	no (13)			
Pro-Urokinase	Thrombolysis	Proteinase Homeostasis		yes (5)	yes (7)	yes (8)		
Two-chain active uPA (tc-uPA)	Thrombolysis and cell motility	Proteinase Homeostasis		yes (5)				
Plasminogen Activator Inhibitor-1 (PAI-1)	Serine Proteinase inhibitor	Proteinase Homeostasis		yes (86)	yes (7, 76, 87)			
uPA-PAI-1	Regulation of cell surface plasminogen activator activity	Proteinase Homeostasis		yes (4, 45)	yes (7)	yes (8, 9)		
uPA-Protease Nexin-1	Regulation of cell surface plasminogen activator activity	Proteinase Homeostasis		yes (6)		yes (88)		
Tissue-Type Urokinase (tPA)	Thrombolysis	Proteinase Homeostasis		yes (89)				
tPA-PAI-1	Thrombolysis	Proteinase Homeostasis		yes (90)	yes (76)			

Table 2. continued

Ligand	Ligand Function	Physiological Category	LDLR	LRP (LRP-1)	Megalin (LRP-2, gp330)	VLDLR (LR8)	SORLA-1 (mosaic protein LR11)	ApoER2 (LR7, LR8B, LRP-8)
Thrombin-PAI-1	Blood coagulation	Proteinase Homeostasis		yes (91)				
Thrombin-protease nexin 1		Proteinase Homeostasis		yes (92)				
Thrombin-Antithrombin III		Proteinase Homeostasis		yes (93)				
Thrombin -Heparin cofactor II		Proteinase Homeostasis		yes (93)				
Trypsin-alpha1-antitrypsin		Proteinase Homeostasis		yes (93)				
Coagulation Factor VIII	Blood coagulation	Proteinase Homeostasis		yes (94)				
Coagulation factor Xa-Tissue Factor Pathway Inhibitor Complex	Regulation of blood coagulation	Proteinase Homeostasis		yes (95)				
Tissue Factor Pathway Inhibitor	Coagulation factor Xa inhibitor Regulation of TF-initiated blood coagulation	Proteinase Homeostasis		yes (96)				
Aprotinin	Antifibrinolytic polypeptide	Proteinase Homeostasis			yes (97)			
Cathepsin G-alpha$_1$ antichymotrypsin		Proteinase Homeostasis		no (98)	yes (98)			
Elastase-alpha$_1$ antitrypsin	Regulation of elastin containing ECM degradation	Proteinase Homeostasis		yes (98)	yes			
Receptor for collagenase-3 (MMP-13)	Extracellular matrix remodeling	Proteinase Homeostasis		yes (11)				
Thrombospondin-1	ECM protein effector of vascular cell growth and motility			yes (16, 17)	yes (17)	yes (99)		
Thrombospondin-2	ECM protein			yes (18)				
Reelin	Extracellular protein that directs neuronal migration					yes (42, 43)		yes (42)
Alzheimer's Precursor Protein				yes (100)				
Beta$_2$-Glycoprotein, apolipoprotein H	Anionic phospholipid-binding protein				yes (57)			
Transcobalamin-Vitamin B12	Vitamin transport	Vitamin Metabolism			yes (101)			
Vitamin D-Binding Protein	Vitamin transport, regulation of calcium metabolism	Vitamin Metabolism			yes (56)			
Retinol-Binding Protein	Vitamin transport	Vitamin Metabolism			yes (54)			
Thyroglobulin	Thyroid hormone precursor	Hormone Metabolism			yes (102)			
Parathyroid hormone	Regulates blood calcium and phosphate	Hormone Metabolism			yes (103)			
Insulin	Regulation of blood glucose, lipid storage	Hormone Metabolism			yes (60)			
Prolactin	Mammary gland development and milk production	Hormone Metabolism			yes (60)			
Midkine	Growth factor with migration- and survival-promoting activities			yes (104)				
Epidermal growth factor	Regulation of cellular differentiation and proliferation				yes (60)			
Albumin	Carrier protein (fatty acid) , colloid osmotic pressure regulation				yes (105)			

Table 2. continued

Ligand	Ligand Function	Physiological Category	LDLR	LRP (LRP-1)	Megalin (LRP-2, gp330)	VLDLR (LR8)	SORLA-1 (mosaic protein LR11)	ApoER2 (LR7, LR8B, LRP-8)
Beta(2)-microglobulin	Control of beta2-microglobulin amyloidosis in bone and joint structures				yes (60)			
Alpha(1)-microglobulin	Odorant-binding protein				yes (55)			
Complement component 3 (C3)	Ag-IgG elimination	Innate Immunity		yes (106)				
Lysozyme	Lysis of microorganisms	Innate Immunity			yes (60)			
Lactoferrin	Anti-inflammatory, antimicrobial glycoprotein	Innate Immunity		yes (76)	yes (76)			
Pseudomonas Exotoxin A	ADP-ribosylation of translational elongation factor 2, inactivation of protein synthesis	Cytotoxicity		yes (21)	no (13)			
Ricin A	Type I ribosome-inactivating protein	Cytotoxicity		yes (107)				
Saporin	Type I ribosome-inactivating protein	Cytotoxicity		yes (107)				
Trichosanthin	Type I ribosome-inactivating protein	Cytotoxicity		yes (108)	yes (108)			
Saposin	Activator of degradation of glycosphingolipids by acidic hydrolases			yes (20)				
Circumsporozoite protein	Major surface protein of the malaria sporozoite	Infection		yes (15)				
Minor Group Rhinovirus	Virus	Infection		yes (109)				
Aminoglycosides, gentamicin and polymyxcin B	Antibiotics			yes (97)	yes (97)			
Seminal Vesicle Secretory Protein II	Seminal coagulum protein involved in fertilization	Reproduction			yes (24)			
Disabled protein 2 (Dab2)	Cytosolic adaptor protein	Intracelluar Signaling			yes (110)			
NHE3 (NHE3 kinase A regulatory protein)	Nayes/Hyes exchanger	Acid-base balance and NaCl homeostasis			(19)			
Cytochrome c	Oxidative phosphorylation	Bioenergetics			yes (60)			
Totals			5	36	36	10	2	2

Yes indicates that binding has been formally demonstrated. No indicates that no binding was observed when tested.

(7-9). Similarly, the endocytosis of HDL/apolipoprotein A-I (apoA-I) involves megalin acting in concert with cubilin, a recently described receptor for HDL, apoA-1 and intrinsic factor-vitamin B_{12} (10). Further, the endocytosis of the matrix metalloproteinase collagenase-3 has been shown to involve primary interaction with a 170-kDa cell surface receptor followed by internalization via LRP (11). It is not yet known whether LRP mediates uptake of the entire collagenase-3-receptor complex or whether the enzyme dissociates from its receptor and binds to LRP. Finally, several proteins are endocytosed by sequential receptor binding involving cell surface proteoglycans and members of the LDLR family. For example, the uptake of lipoprotein lipase (8, 12, 13), hepatic lipase (14), circumsporozoite protein (15) and thrombospondins 1 and 2 (16-18) are dependent on primary binding to cell surface heparan sulfate proteoglycans followed by endocytosis by LRP, megalin or VLDLR. Since the internalization of these ligands is completely inhibited by RAP, the ligand binding proteoglycans are themselves unable to mediate ligand endocytosis. This inability to independently mediate endocytosis also seems to be the case with uPAR and cubilin. Therefore, the endocytic action of members of the LDLR family are essential to the process by which many receptor-bound ligands are internalized by cells.

Recently, megalin has been shown to exist in complex with the renal brush border Na^+/H^+ exchanger NHE3 (19). The significance of megalin's association with NHE3 is not yet known, but megalin-mediated endocytosis may serve to regulate plasma membrane levels of the transporter and thereby control its activity.

3.2. Roles of LDLR family members in mediating biosynthetic processing of other proteins

Several studies have revealed the importance of LRP-mediated endoctyosis to the biosynthetic processing of various proteins. The secreted precursor of sphingolipid activator protein is proteolytically processed following lysosomal delivery via LRP-mediated endocytosis (20). LRP-mediated protein delivery to lysosomal vesicles has also been shown to be the pathway for proteolytic processing of *Pseudomonas* exotoxin A. Such cleavage of the exotoxin is required to generate the enzymatically active fragment which can translocate to the cytosol and inhibit protein synthesis (21). Similarly, the process of LRP-mediated internalization of beta-amyloid precursor protein (APP) from the cell surface has been implicated in proteolytic processing of APP and production of beta-amyloid peptide (22). Finally, megalin has been implicated as having a chaperon-like function in yolk sac endoderm cells, mediating efficient post-translational trafficking of nascent cubilin to the plasma membrane (10).

3.3. LDLR family members function in reproduction

Megalin is highly expressed in the male reproductive tract by epithelial cells of the efferent duct, epididymis and seminal vesicle (23, 24). Indeed, many megalin ligands are found in the epididymis, seminal vesicle (24) and seminal plasma. The ligands include apolipoprotein J/clusterin, apolipoprotein B, apolipoprotein E, tissue type plasminogen activator, uPA and PAI-1 and each has been speculated to be involved in sperm maturation and fertilization (23). It is therefore hypothesized that megalin-mediated catabolism of these proteins may be a contributing factor to spermatozoa maturation (23). Megalin is also expressed in the female reproductive tract by epithelial cells lining the uterus (25) and by oviduct epithelial cells (Dr. Carlos Morales, personal communication).

LRP is expressed in Sertoli cells of the testis and has been shown to be present in the endocytic compartment of these cells (26). This subcellular localization is consistent with the receptor functioning in the clearance of proteinase/proteinease-inhibitor complexes involved in seminiferous tubule remodeling and/or the uptake of cholesterol-containing lipoproteins necessary for the biosynthesis of testosterone (26). Furthermore, LRP on the surface of spermatozoa is thought to bind to complexes of $alpha_2$-macroglobulin and prostate-specific antigen (PSA), a member of the kallikrein family and the major proteinase in seminal fluid (27). In the female reproductive tract, LRP is expressed in the stroma of secretory and proliferative endometrium, perhaps indicating a role in endometrial remodeling (28). LRP is also expressed by follicular cells of the ovary (25).

In mammals, very little is known about the role of other members of the LDLR family in the male and female reproductive tracts. VLDLR expression has been detected in testis, ovary and uterus (29). ApoER2 is highly expressed in the testis and to a lesser extent in ovary (30). SORLA-1 has also been shown to be expressed in testis (31).

The accumulation of vitellogenins (yolk proteins that function as lipid-, phosphate-, ion- and vitamin-carriers) into membrane-bound vesicles in oocytes of worms, insects and vertebrates is mediated by receptors of the LDLR family. Structurally related vitellogenin receptors have been described in the fruit fly, frog and chicken (32-34). The chicken vitellogenin receptor has been shown to import VLDL, riboflavin-binding protein, and $alpha_2$-macroglobulin into growing oocytes (35, 36). Indeed, mutations that abrogate expression of the chicken vitellogenin receptor result in non-egg laying hens. Megalin and two oocyte-specific members of the LDLR gene family, LR8 and LDLR-related protein (LRP-380) also mediate oocyte uptake and yolk deposition of granulosa cell-derived clusterin (37). In *Drosophila melanogaster*, the vitellogenin receptor is encoded by the gene yolkless (*yl*) (38). Female sterility occurs in insects having genetic deficiency of *yl* gene expression (38). Analysis of oocytes produced by $yl^{-/-}$ females shows drastic reduction in the numbers of coated pits and coated vesicles and very little proteinaceous yolk (39). In *Caenorhabditis elegans*, RME-2 is a recently described vitellogenin receptor also structurally related to the LDLR (40).

3.4. Roles of LDLR family members in development

While mutations that abrogate expression of functional LDLR in mice and humans have adverse consequences on adult physiology (e.g., hypercholesterolemia and coronary heart disease), such mutations do not appear to affect the process of embryonic development. Similarly, mutations that abolish the expression of the VLDLR in transgenic mice do not affect development (41). However, transgenic mice that lack both VLDLR and apolipoprotein E receptor 2 (ApoER2) have cortical and cerebellar morphological abnormalities that mimic the phenotype of mice lacking reelin, a common ligand for both receptors (42-44). Murine models of deficiency of LRP and megalin expression reveal the vital roles that each of these receptors also play in embryonic development. For example, mice deficient in the ability to express functional LRP die at embryonic day 10, although the mechanisms underlying lethality are not understood (45). Megalin gene knockout mice display abnormal morphogenesis of tissues of the central nervous system as well as lung and kidney abnormalities (46). While the basis for the developmental effects observed in the $megalin^{-/-}$ mice is not yet known, embryonic insufficiency in maternally-derived nutrients (e.g., lipids and vitamins) that associate with megalin ligands is speculated to be a contributing factor (47, 48). Consistent with the essential role of megalin in mouse development, null mutations in the *Caenorhabditis elegans* ortholog of megalin reveal that this receptor is also essential for nematode growth and development (49).

Megalin is expressed on the apical surfaces of the visceral yolk sac endoderm, where it presumably mediates uptake of maternal lipoprotein particles (e.g., HDL and LDL) carrying cholesterol, lipid-soluble vitamins, phospholipids and triglycerides. While the importance of maternally derived lipoprotein-associated cholesterol to embryogenesis is uncertain, maternal lipid-soluble vitamins

such as vitamin A (retinol) are critical to embryogenesis. Evidence for this comes from the consequences of maternal vitamin A deficiency on embryogenesis (50). For example, vitamin A-deficient quail embryos have brain and cardiovascular abnormalities (51). Vitamin A-deficient mammalian embryos have a similar spectrum of malformations that include brain, cardiovascular, ocular, lung, limb and urogenital defects (52). Mouse embryos accumulate maternally-derived vitamin A in the visceral yolk sac endoderm, the major site of embryonic retinol-binding protein (RBP) synthesis. Inhibition of yolk-sac RBP synthesis by antisense oligonucleotide treatment results in developmental abnormalities that include neural tube, ocular and vitelline vessel malformations (53). These RBP-antisense oligonucleotide-induced malformations could be prevented by addition of exogenous retinoic acid (53). The spectrum of observed retinol/RBP deficiency-related developmental abnormalities are consistent with those seen in the megalin knockout mouse embryos and with the role of megalin as an endocytic receptor for retinol-RBP complexes (54). As of yet, natural or engineered monogenic mutations of the other LDLR family members have not been shown to impact mammalian embryogenesis.

3.5. LDLR family members in renal absorption and homeostatic regulation

Mice genetically deficient in the ability to express megalin exhibit urinary wastage of a number of macromolecules including vitamin D-binding protein, retinol-binding protein (and their associated lipophilic vitamins), beta2-glycoprotein-I, alpha(1)-microglobulin and albumin (54-58). Since megalin is expressed on the apical surfaces of proximal convoluted tubule cells, the proteinuria observed in the megalin$^{-/-}$ mice indicates the role of megalin in the absorption of the aforementioned proteins from the glomerular filtrate. Another protein that is thought to be absorbed by renal proximal tubule cells via the action of megalin is apoA-I (10). Although verification of apoA-I wastage in megalin$^{-/-}$ mice has not yet been reported, urinary wastage of apoA-I has been described in humans and dogs deficient in the expression of cubilin, the apoA-I-binding cell surface protein that mediates renal uptake of apoA-I in conjunction with megalin (59). A number of other low molecular weight, megalin-binding serum proteins including insulin, prolactin and beta2-microglobulin are also presumed to be absorbed from the glomerular filtrate through the action of megalin (60).

The physiological significance of megalin-mediated uptake of macromolecules from the glomerular filtrate is not completely understood at the present time. However, at least one known consequence of the impairment of this uptake process is that the megalin$^{-/-}$ mice develop vitamin D deficiency and defective bone mineralization (56). This process is also expected to impact calcium homeostasis since megalin endocytosis of retinol is required to provide the renal cells with the steroid precursor for generation of 1,25-(OH)2 vitamin D3, a regulator of calcium metabolism (56). Analysis of megalin$^{-/-}$ mice has also revealed an absence of retinol-binding protein in proximal tubules of these mice as compared to normal mice, thus indicating a critical role for this receptor in vitamin A homeostasis (54). The renal action of megalin may also be protective against pathological accumulation of certain macromolecules. For example, beta2-microglobulin-associated amyloidosis in joints and bones is a major complication in patients on nontransplant modes of renal therapy. The fact that this amyloidosis does not occur in patients with a functioning renal transplant or, if already present, does not progress any further, suggests that normal renal clearance of beta2-microglobulin might function to prevent the pathological accumulation of beta2-microglobulin fibrils. Such a role is similar to that ascribed to megalin in preventing pathological accumulation in the central nervous system of another fibril forming protein, beta-amyloid peptide (61).

The recent discovery that megalin associates with the Na^+/H^+ exchanger NHE3 (19) suggests that megalin might play a role in exchange of Na^+ and H^+ across renal proximal tubule plasma membranes and contribute to the maintenance of acid-base balance and NaCl homeostasis. Similarly, megalin has been demonstrated to function as a calcium-sensing receptor on parathyroid cells (62). Megalin binding of external calcium inversely regulates release of parathyroid hormone (PTH) (63). In this way, megalin participates in the regulation of systemic calcium homeostasis by the parathyroid gland.

4. PERSPECTIVE

In slightly more than a decade of research, the LDLR family has been revealed and great progress made in our understanding of the functions of several of its prominent members. Based on what we have learned, receptors of this family represent specialized scavengers whose catabolic functions are central to the homeostasis of many macromolecules of diverse function. The large size of the LDLR family combined with the sheer number and functional diversity of its ligands creates major challenges for understanding the full impact that these receptors have on physiological and pathological processes. To meet this challenge, systematic development of animal models of genetic deficiencies of each LDLR family member using both non-conditional and conditional gene inactivation strategies will need to be pursued. As for additional avenues of discovery in the field of LDLR family biology, recent findings that LRP and megalin interact with cytoplasmic adaptors highlight receptor-mediated signal transduction as an exciting new frontier for future research.

5. ACKNOWLEDGEMENTS

The author acknowledges support from the National Institutes of Health (HL61873) and the American Heart Association, National (9950344N).

6. REFERENCES

1. Gliemann, J.: Receptors of the low density lipoprotein (LDL) receptor family in man. Multiple functions of the large family members via interaction with complex ligands. *J Biol Chem* 379(8-9), 951-64 (1998)

2. Hussain, M.M., D.K. Strickland, and A. Bakillah: The mammalian low-density lipoprotein receptor family. *Annu Rev Nutr* 19, 141-72 (1999)

3. Strickland, D.K., M.Z. Kounnas, and W.S. Argraves: LDL receptor-related protein: a multiligand receptor for lipoprotein and proteinase catabolism. *Faseb J* 9(10), 890-8 (1995)

4. Nykjaer, A., C.M. Petersen, B. Moller, P.H. Jensen, S.K. Moestrup, T.L. Holtet, M. Etzerodt, H.C. Thogersen, M. Munch,and P.A. Andreasen: Purified alpha 2-macroglobulin receptor/LDL receptor-related protein binds urokinase plasminogen activator inhibitor type-1 complex. Evidence that the alpha 2-macroglobulin receptor mediates cellular degradation of urokinase receptor-bound complexes. *J Biol Chem* 267(21), 14543-6 (1992)

5. Kounnas, M.Z., J. Henkin, W.S. Argraves, and D.K. Strickland: Low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor mediates cellular uptake of pro-urokinase. *J Biol Chem* 268(29), 21862-7 (1993)

6. Conese, M., D. Olson, and F. Blasi: Protease nexin-1-urokinase complexes are internalized and degraded through a mechanism that requires both urokinase receptor and alpha 2-macroglobulin receptor. *J Biol Chem* 269(27), 17886-92 (1994)

7. Stefansson, S., M.Z. Kounnas, J. Henkin, R.K. Mallampalli, D.A. Chappell, D.K. Strickland, and W.S. Argraves: gp330 on type II pneumocytes mediates endocytosis leading to degradation of pro-urokinase, plasminogen activator inhibitor-1 and urokinase-plasminogen activator inhibitor-1 complex. *J Cell Sci* 108(Pt 6), 2361-8 (1995)

8. Argraves, K.M., F.D. Battey, C.D. MacCalman, K.R. McCrae, M. Gafvels, K.F. Kozarsky, D.A. Chappell, J.F. Strauss, and D.K. Strickland: The very low density lipoprotein receptor mediates the cellular catabolism of lipoprotein lipase and urokinase-plasminogen activator inhibitor type I complexes. *J Biol Chem* 270(44), 26550-7 (1995)

9. Heegaard, C.W., A.C. Simonsen, K. Oka, L. Kjoller, A. Christensen, B. Madsen, L. Ellgaard, L. Chan, and P.A. Andreasen: Very low density lipoprotein receptor binds and mediates endocytosis of urokinase-type plasminogen activator-type-1 plasminogen activator inhibitor complex. *J Biol Chem* 270(35), 20855-61 (1995)

10. Hammad, S.M., J.L. Barth, C. Knaak, and W.S. Argraves: Megalin Acts in Concert with Cubilin to Mediate Endocytosis of High Density Lipoproteins. *J Biol Chem* 275(16), 12003-12008 (2000)

11. Barmina, O.Y., H.W. Walling, G.J. Fiacco, J.M. Freije, C. Lopez-Otin, J.J. Jeffrey, and N.C. Partridge: Collagenase-3 binds to a specific receptor and requires the low density lipoprotein receptor-related protein for internalization. *J Biol Chem* 274(42), 30087-93 (1999)

12. Chappell, D.A., G.L. Fry, M.A. Waknitz, P.H. Iverius, S.E. Williams, and D.K. Strickland: The low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor binds and mediates catabolism of bovine milk lipoprotein lipase. *J Biol Chem* 267(36), 25764-7 (1992)

13. Kounnas, M.Z., D.A. Chappell, D.K. Strickland, and W.S. Argraves: Glycoprotein 330, a member of the low density lipoprotein receptor family, binds lipoprotein lipase in vitro. *J Biol Chem* 268(19), 14176-81 (1993)

14. Kounnas, M.Z., D.A. Chappell, H. Wong, W.S. Argraves, and D.K. Strickland: The cellular internalization and degradation of hepatic lipase is mediated by low density lipoprotein receptor-related protein and requires cell surface proteoglycans. *J Biol Chem* 270(16), 9307-12 (1995)

15. Shakibaei, M., and U. Frevert: Dual interaction of the malaria circumsporozoite protein with the low density lipoprotein receptor-related protein (LRP) and heparan sulfate proteoglycans. *J Exp Med* 184(5), 1699-711 (1996)

16. Mikhailenko, I., M.Z. Kounnas, and D.K. Strickland: Low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor mediates the cellular internalization and degradation of thrombospondin. A process facilitated by cell-surface proteoglycans. *J Biol Chem* 270(16), 9543-9 (1995)

17. Godyna, S., G. Liau, I. Popa, S. Stefansson, and W.S. Argraves: Identification of the low density lipoprotein receptor-related protein (LRP) as an endocytic receptor for thrombospondin-1. *J Cell Biol* 129(5), 1403-10 (1995)

18. Chen, H., D.K. Strickland, and D.F. Mosher: Metabolism of thrombospondin 2. Binding and degradation by 3t3 cells and glycosaminoglycan-variant Chinese hamster ovary cells. *J Biol Chem* 271(27), 15993-9 (1996)

19. Biemesderfer, D., T. Nagy, B. DeGray, and P.S. Aronson: Specific association of megalin and the Na+/H+ exchanger isoform NHE3 in the proximal tubule. *J Biol Chem* 274(25), 17518-24 (1999)

20. Hiesberger, T., S. Huttler, A. Rohlmann, W. Schneider, K. Sandhoff, and J. Herz: Cellular uptake of saposin (SAP) precursor and lysosomal delivery by the low density lipoprotein receptor-related protein (LRP) *Embo J* 17(16), 4617-25 (1998)

21. Kounnas, M.Z., R.E. Morris, M.R. Thompson, D.J. FitzGerald., D.K. Strickland, and C.B. Saelinger: The alpha 2-macroglobulin receptor/low density lipoprotein receptor-related protein binds and internalizes Pseudomonas exotoxin A. *J Biol Chem* 267(18), 12420-3 (1992)

22. Ulery, P.G., J. Beers, I. Mikhailenko, R.E. Tanzi, G.W. Rebeck, B.T. Hyman, and D.K. Strickland: Modulation of beta-amyloid precursor protein processing by the low density lipoprotein receptor-related protein (LRP) Evidence that LRP contributes to the pathogenesis of Alzheimer's disease. *J Biol Chem* 275(10), 7410-5 (2000)

23. Morales, C.R., S.A. Igdoura, U.A. Wosu, J. Boman, and W.S. Argraves: Low density lipoprotein receptor-related protein-2 expression in efferent duct and epididymal epithelia: evidence in rats for its in vivo role in endocytosis of apolipoprotein J/clusterin. *Biol Reprod* 55(3), 676-83 (1996)

24. Ranganathan, S., C. Knaak, C.R. Morales, and W.S. Argraves: Identification of low density lipoprotein receptor-related protein- 2/megalin as an endocytic receptor for seminal vesicle secretory protein II. *J Biol Chem* 274(9), 5557-63 (1999)

25. Zheng, G., D.R. Bachinsky, I. Stamenkovic, D.K. Strickland, D. Brown, G. Andres, and R.T. McCluskey: Organ distribution in rats of two members of the low-density lipoprotein receptor gene family, gp330 and LRP/alpa 2MR, and the receptor-associated protein (RAP) *J Histochem Cytochem* 42(4), 531-42 (1994)

26. Igdoura, S.A., W.S. Argraves, and C.R. Morales: Low density lipoprotein receptor-related protein-1 expression in the testis: regulated expression in Sertoli cells. *J Androl* 18(4), 400-10 (1997)

27. Birkenmeier, G., E. Usbeck, A. Schafer, A. Otto, and H.J. Glander: Prostate-specific antigen triggers transformation of seminal alpha2-macroglobulin (alpha2-M) and its binding to alpha2-macroglobulin receptor/low-density lipoprotein receptor-related protein (alpha2-M-R/LRP) on human spermatozoa. *Prostate* 36(4), 219-25 (1998)

28. Sayegh, R.A., X.I. Tao, and K.B. Isaacson: Immunohistochemical localization of alpha-2 macroglobulin receptor/low-density lipoprotein receptor-related protein, receptor-associated protein, and Gp330 in the human endometrium. *J Soc Gynecol Investig* 2(6), 748-53 (1995)

29. Iijima, H., M. Miyazawa, J. Sakai, K. Magoori, M.R. Ito, H. Suzuki, M. Nose, Y. Kawarabayasi, and T.T. Yamamoto: Expression and characterization of a very low density lipoprotein receptor variant lacking the O-linked sugar region generated by alternative splicing. *J Biochem* 124(4), 747-55 (1998)

30. Kim, D.H., H. Iijima, K. Goto, J. Sakai, H. Ishii, H.J. Kim, H. Suzuki, H. Kondo, S. Saeki, and T. Yamamoto: Human apolipoprotein E receptor 2. A novel lipoprotein receptor of the low density lipoprotein receptor family predominantly expressed in brain. *J Biol Chem* 271(14), 8373-80 (1996)

31. Jacobsen, L., P. Madsen, S.K. Moestrup, A.H. Lund, N. Tommerup, A. Nykjaer, L. Sottrup-Jensen, J. Gliemann, and C.M. Petersen: Molecular characterization of a novel human hybrid-type receptor that binds the alpha2-macroglobulin receptor-associated protein. *J Biol Chem* 271(49), 31379-83 protein. (1996)

32. Stifani, S., J. Nimpf, and W.J. Schneider: Vitellogenesis in Xenopus laevis and chicken: cognate ligands and oocyte receptors. The binding site for vitellogenin is located on lipovitellin I. *J Biol Chem* 265(2), 882-8 (1990)

33. Schneider, W.J.: Vitellogenin receptors: oocyte-specific members of the low-density lipoprotein receptor supergene family. *Int Rev Cytol* 166, 103-37 (1996)

34. Sappington, T.W., and A.S. Raikhel: Molecular characteristics of insect vitellogenins and vitellogenin receptors. *Insect Biochem Mol Biol* 28(5-6), 277-300 (1998)

35. Stifani, S., D.L. Barber, J. Nimpf, and W.J. Schneider: A single chicken oocyte plasma membrane protein mediates uptake of very low density lipoprotein and vitellogenin. *Proc Natl Acad Sci USA* 87(5), 1955-9 (1990)

36. Mac Lachlan, I., J. Nimpf, and W.J. Schneider: Avian riboflavin binding protein binds to lipoprotein receptors in association with vitellogenin. *J Biol Chem* 269(39), 24127-32 (1994)

37. Mahon, M.G., K.A. Lindstedt, M. Hermann, J. Nimpf, and W.J. Schneider: Multiple involvement of clusterin in chicken ovarian follicle development. Binding to two oocyte-specific members of the low density lipoprotein receptor gene family. *J Biol Chem* 274(7), 4036-44 (1999)

38. Schonbaum, C.P., S. Lee, and A.P. Mahowald: The Drosophila yolkless gene encodes a vitellogenin receptor belonging to the low density lipoprotein receptor superfamily. *Proc Natl Acad Sci USA* 92(5), 1485-9 (1995)

39. DiMario, P.J., and A.P. Mahowald: Female sterile (1) yolkless: a recessive female sterile mutation in Drosophila melanogaster with depressed numbers of coated pits and coated vesicles within the developing oocytes. *J Cell Biol* 105(1), 199-206 (1987)

40. Grant, B., and D. Hirsh: Receptor-mediated endocytosis in the Caenorhabditis elegans oocyte. *Mol Biol Cell* 10(12), 4311-26 (1999)

41. Frykman, P.K., M.S. Brown, T. Yamamoto, J.L. Goldstein, and J. Herz: Normal plasma lipoproteins and fertility in gene-targeted mice homozygous for a disruption in the gene encoding very low density lipoprotein receptor. *Proc Natl Acad Sci USA* 92(18), 8453-7 (1995)

42. D'Arcangelo, G., R. Homayouni, L. Keshvara, D.S. Rice, M. Sheldon, and T. Curran: Reelin is a ligand for lipoprotein receptors. *Neuron* 24(2), 471-9 (1999)

43. Hiesberger, T., M. Trommsdorff, B.W. Howell, A. Goffinet, M.C. Mumby, J.A. Cooper, and J. Herz: Direct binding of Reelin to VLDL receptor and ApoE receptor 2 induces tyrosine phosphorylation of disabled-1 and modulates tau phosphorylation. *Neuron* 24(2), 481-9 (1999)

44. Trommsdorff, M., M. Gotthardt, T. Hiesberger, J. Shelton, W. Stockinger, J. Nimpf, R.E. Hammer, J.A.

Richardson, and J. Herz: Reeler/Disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell* 97(6), 689-701 (1999)

45. Herz, J., D.E. Clouthier, and R.E. Hammer: LDL receptor-related protein internalizes and degrades uPA-PAI-1 complexes and is essential for embryo implantation [published erratum. *Cell* 71(3), 411-21 (1992)

46. Willnow, T.E., J. Hilpert, S.A. Armstrong, A. Rohlmann, R.E. Hammer, D.K. Burns, and J. Herz: Defective forebrain development in mice lacking gp330/megalin. *Proc Natl Acad Sci USA* 93(16), 8460-4 (1996)

47. Herz, J., and R.V. Farese, Jr.: The LDL receptor gene family, apolipoprotein B and cholesterol in embryonic development. *J Nutr* 129(2S Suppl), 473S-475S (1999)

48. Hammad, S.M., S. Stefansson, W.O.Twal, C.J. Drake, P. Fleming, A. Remaley, H.B. Brewer, Jr., and W.S. Argraves: Cubilin, the endocytic receptor for intrinsic factor-vitamin B(12) complex, mediates high-density lipoprotein holoparticle endocytosis. *Proc Natl Acad Sci USA* 96(18), 10158-10163 (1999)

49. Yochem, J., S. Tuck, I. Greenwald, and M. Han: A gp330/megalin-related protein is required in the major epidermis of Caenorhabditis elegans for completion of molting. *Development* 126(3), 597-606 (1999)

50. Thompson, J.N.: The fat soluble vitamins. Eds: DeLuca, H.F., and Suttie, J.W., The University of Wisconsin Press, Madison, WI, 267-281 (1969)

51. Maden, M., E. Gale, I. Kostetskii, and M. Zile: Vitamin A-deficient quail embryos have half a hindbrain and other neural defects. *Curr Biol* 6(4), 417-26 (1996)

52. Morriss-Kay, G.M., and N. Sokolova: Embryonic development and pattern formation. *Faseb J* 10(9), 961-8 (1996)

53. Bavik, C., S.J. Ward, and P. Chambon: Developmental abnormalities in cultured mouse embryos deprived of retinoic by inhibition of yolk-sac retinol binding protein synthesis. *Proc Natl Acad Sci USA* 93(7), 3110-4 (1996)

54. Christensen, E.I., J.O. Moskaug, H. Vorum, C. Jacobsen, T.E. Gundersen, A. Nykjaer, R. Blomhoff, T.E. Willnow, and S.K. Moestrup: Evidence for an essential role of megalin in transepithelial transport of retinol. *J Am Soc Nephrol* 10(4), 685-95 (1999)

55. Leheste, J.R., B. Rolinski, H. Vorum, J. Hilpert, A. Nykjaer, C. Jacobsen, P. Aucouturier, J.O. Moskaug, A. Otto, E.I. Christensen, and T.E. Willnow: Megalin knockout mice as an animal model of low molecular weight proteinuria. *Am J Pathol* 155(4), 1361-70 (1999)

56. Nykjaer, A., D. Dragun, D. Walther, H. Vorum, C. Jacobsen, J. Herz, F. Melsen, E.I. Christensen, and T.E. Willnow: An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. *Cell* 96(4), 507-15 (1999)

57. Moestrup, S.K., I. Schousboe, C. Jacobsen, J.R. Leheste, E.I. Christensen, and T.E. Willnow: beta2-glycoprotein-I (apolipoprotein H) and beta2-glycoprotein-I-phospholipid complex harbor a recognition site for the endocytic receptor megalin. *J Clin Invest* 102(5), 902-9 (1998)

58. Birn, H., J.C. Fyfe, C. Jacobsen, F. Mounier, P.J. Verroust, H. Orskov, T.E. Willnow, S.K. Moestrup, and E.I. Christensen: Cubilin is an albumin binding protein important for renal tubular albumin reabsorption. *J Clin Invest* 105(10), 1353-1361 (2000)

59. Kozyraki, R., J. Fyfe, M. Kristiansen, C. Gerdes, C. Jacobsen, S. Cui, E.I. Christensen, M. Aminoff, A. de la Chapelle, R. Krahe, P.J. Verroust, and S.K. Moestrup: The intrinsic factor-vitamin B12 receptor, cubilin, is a high-affinity apolipoprotein A-I receptor facilitating endocytosis of high-density lipoprotein. *Nat Med* 5(6), 656-61 (1999)

60. Orlando, R.A., K. Rader, F. Authier, H. Yamazaki, B.I. Posner, J.J. Bergeron, and M.G. Farquhar: Megalin is an endocytic receptor for insulin. *J Am Soc Nephrol* 9(10), 1759-66 (1998)

61. Hammad, S.M., S. Ranganathan, E. Loukinova, W.O. Twal, and W.S. Argraves: Interaction of apolipoprotein J-amyloid beta-peptide complex with low density lipoprotein receptor-related protein-2/megalin. A mechanism to prevent pathological accumulation of amyloid beta-peptide. *J Biol Chem* 272(30), 18644-9 (1997)

62. Lundgren, S., G. Hjalm, P. Hellman, B. Ek, C. Juhlin, J. Rastad, L. Klareskog, G. Akerstrom, and L. Rask: A protein involved in calcium sensing of the human parathyroid and placental cytotrophoblast cells belongs to the LDL-receptor protein superfamily. *Exp Cell Res* 212(2), 344-50 (1994)

63. Hellman, P., T. Carling, L. Rask, and G. Akerstrom: Pathophysiology of primary hyperparathyroidism. [In Process Citation], *Histol Histopathol* 15(2), 619-27 (2000)

64. Ishibashi, S., M.S. Brown, J.L. Goldstein, R.D. Gerard, R.E. Hammer, and J. Herz: Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. *J Clin Invest* 92(2), 883-93 (1993)

65. Medh, J.D., G.L. Fry, S.L. Bowen, M.W. Pladet, D.K. Strickland, and D.A. Chappell: The 39-kDa receptor-associated protein modulates lipoprotein catabolism by binding to LDL receptors. *J Biol Chem* 270(2), 536-40 (1995)

66. Herz, J., J.L. Goldstein, D.K. Strickland, Y.K. Ho, and M.S. Brown: 39-kDa protein modulates binding of ligands to low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor. *J Biol Chem* 266(31), 21232-8 (1991)

67. Kounnas, M.Z., W.S. Argraves, and D.K. Strickland: The 39-kDa receptor-associated protein interacts with two members of the low density lipoprotein receptor family, alpha 2-macroglobulin receptor and glycoprotein 330. *J Biol Chem* 267(29), 21162-6 (1992)

68. Orlando, R.A., D. Kerjaschki, H. Kurihara, D. Biemesderfer, and M.G. Farquhar: gp330 associates with a 44-kDa protein in the rat kidney to form the Heymann nephritis

antigenic complex. *Proc Natl Acad Sci USA* 89(15), 6698-702 (1992)

69. Christensen, E.I., J. Gliemann, and S.K. Moestrup: Renal tubule gp330is a calcium binding receptor for endocytic uptake of protein. *J Histochem Cytochem* 40(10), 1481-90 (1992)

70. Battey, F.D., M.E. Gafvels, D.J. Fitz Gerald, W.S. Argraves, D.A. Chappell, J.F.R. Strauss, and D.K. Strickland: The 39-kDa receptor-associated protein regulates ligand binding by the very low density lipoprotein receptor. *J Biol Chem* 269(37), 23268-73 (1994)

71. Simonsen, A.C., C.W. Heegaard, L.K. Rasmussen, L. Ellgaard, L. Kjoller, A. Christensen, M. Etzerodt, and P.A. Andreasen: Very low density lipoprotein receptor from mammary gland and mammary epithelial cell lines binds and mediates endocytosis of M(r) 40,000 receptor associated protein. *FEBS Lett* 354(3), 279-83 (1994)

72. Yamazaki, H., H. Bujo, J. Kusunoki, K. Seimiya, T. Kanaki, N. Morisaki, W.J. Schneider, and Y. Saito: Elements of neural adhesion molecules and a yeast vacuolar protein sorting receptor are present in a novel mammalian low density lipoprotein receptor family member. *J Biol Chem* 271(40), 24761-8 (1996)

73. Esser, V., L. E. Limbird, M.S. Brown, J.L. Goldstein, and D.W. Russell: Mutational analysis of the ligand binding domain of the low density lipoprotein receptor. *J Biol Chem* 263(26), 13282-90 (1988)

74. Russell, D.W., M.S. Brown, and J.L. Goldstein: Different combinations of cysteine-rich repeats mediate binding of low density lipoprotein receptor to two different proteins. *J Biol Chem* 264(36), 21682-8 (1989)

75. Beisiegel, U., W. Weber, G. Ihrke, J. Herz, and K.K. Stanley: The LDL-receptor-related protein, LRP, is an apolipoprotein E-binding protein. *Nature* 341(6238), 162-4 (1989)

76. Willnow, T.E., J.L. Goldstein, K. Orth, M.S. Brown, and J. Herz: Low density lipoprotein receptor-related protein and gp330 bind similar ligands, including plasminogen activator-inhibitor complexes and lactoferrin, an inhibitor of chylomicron remnant clearance. *J Biol Chem* 267(36), 26172-80 (1992)

77. Takahashi, S., K. Oida, M. Ookubo, J. Suzuki, M. Kohno, T. Murase, T. Yamamoto, and T. Nakai: Very low density lipoprotein receptor binds apolipoprotein E2/2 as well as apolipoprotein E3/3. *FEBS Lett* 386(2-3), 197-200 (1996)

78. Stefansson, S., D.A. Chappell, K. M. Argraves, D.K. Strickland, and W.S. Argraves: Glycoprotein 330/low density lipoprotein receptor-related protein-2 mediates endocytosis of low density lipoproteins via interaction with apolipoprotein B100. *J Biol Chem* 270(33), 19417-21 (1995)

79. Kounnas, M.Z., E.B. Loukinova, S. Stefansson, J.A. Harmony, B.H. Brewer, D.K. Strickland, and W.S. Argraves: Identification of glycoprotein 330 as an endocytic receptor for apolipoprotein J/clusterin. *J Biol Chem* 270(22), 13070-5 (1995)

80. Niemeier, A., T. Willnow, H. Dieplinger, C. Jacobsen, N. Meyer, J. Hilpert, and U. Beisiegel: Identification of megalin/gp330 as a receptor for lipoprotein(a) in vitro. *Arterioscler Thromb Vasc Biol* 19(3), 552-61 (1999)

81. Argraves, K.M., K. F. Kozarsky, J.T. Fallon, P.C. Harpel, and D.K. Strickland: The atherogenic lipoprotein Lp(a) is internalized and degraded in a process mediated by the VLDL receptor. *J Clin Invest* 100, 2170-2181 (1997)

82. Medh, J.D., S.L. Bowen, G.L. Fry, S. Ruben, M. Andracki, I. Inoue, J.M. Lalouel, D.K. Strickland, and D.A. Chappell: Lipoprotein lipase binds to low density lipoprotein receptors and induces receptor-mediated catabolism of very low density lipoproteins in vitro. *J Biol Chem* 271(29), 17073-80 (1996)

83. Tacken, P.J., F.D. Beer, L.C. Vark, L.M. Havekes, M.H. Hofker, and K. Willems Van Dijk: Very-low-density lipoprotein binding to the apolipoprotein E receptor 2 is enhanced by lipoprotein lipase, and does not require apolipoprotein E. *Biochem J* 347(Pt 2), 357-361 (2000)

84. Strickland, D.K., J. D. Ashcom, S. Williams, W.H. Burgess, M. Migliorini, and W.S. Argraves: Sequence identity between the alpha 2-macroglobulin receptor and low density lipoprotein receptor-related protein suggests that this molecule is a multifunctional receptor. *J Biol Chem* 265(29), 17401-4 (1990)

85. Moestrup, S.K., and J. Gliemann: Purification of the rat hepatic alpha 2-macroglobulin receptor as an approximately 440-kDa single chain protein. *J Biol Chem* 264(26), 15574-7 (1989)

86. Stefansson, S., S. Muhammad, X.F. Cheng, F.D. Battey, D.K. Strickland, and D.A. Lawrence: Plasminogen activator inhibitor-1 contains a cryptic high affinity binding site for the low density lipoprotein receptor-related protein. *J Biol Chem* 273(11), 6358-66 (1998)

87. Moestrup, S.K., S. Nielsen, P. Andreasen, K.E. Jorgensen, A. Nykjaer, H. Roigaard, J. Gliemann, and E.I. Christensen: Epithelial glycoprotein-330 mediates endocytosis of plasminogen activator-plasminogen activator inhibitor type-1 complexes. *J Biol Chem* 268(22), 16564-70 (1993)

88. Kasza, A., H.H. Petersen, C.W. Heegaard, K. Oka, A. Christensen, A. Dubin, L. Chan, and P.A. Andreasen: Specificity of serine proteinase/serpin complex binding to very-low-density lipoprotein receptor and alpha2-macroglobulin receptor/low-density-lipoprotein-receptor-related protein. *Eur J Biochem* 248(2), 270-81 (1997)

89. Bu, G., S. Williams, D.K. Strickland, and A.L. Schwartz: Low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor is an hepatic receptor for tissue-type plasminogen activator. *Proc Natl Acad Sci USA* 89(16), 7427-31 (1992)

90. Orth, K., T. Willnow, J. Herz, M.J. Gething, and J. Sambrook: Low density lipoprotein receptor-related protein is necessary for the internalization of both tissue-type

plasminogen activator-inhibitor complexes and free tissue-type plasminogen activator. *J Biol Chem* 269(33), 21117-22 (1994)

91. Stefansson, S., D.A. Lawrence, and W.S. Argraves: Plasminogen activator inhibitor-1 and vitronectin promote the cellular clearance of thrombin by low density lipoprotein receptor-related proteins 1 and 2. *J Biol Chem* 271(14), 8215-20 (1996)

92. Knauer, M.F., S.J.Kridel, S.B. Hawley, and D.J. Knauer: The efficient catabolism of thrombin-protease nexin 1 complexes is a synergistic mechanism that requires both the LDL receptor-related protein and cell surface heparins. *J Biol Chem* 272(46), 29039-45 (1997)

93. Kounnas, M.Z., F.C. Church, W.S. Argraves, and D.K. Strickand: Cellular internalization and degradtion of antithrombin III-thrombin, heparin cofactor II-thrombin, and alpha1-antitrypsin-trypsin complexes is mediated by the low density lipoprotein receptor-related protein. *J Biol Chem* 271(11), 6523-9 (1996)

94. Saenko, E.L., A.V. Yakhyaev, I. Mikhailenko, D.K. Strickland, and A.G. Sarafanov: Role of the low density lipoprotein-related protein receptor in mediation of factor VIII catabolism. *J Biol Chem* 274(53), 37685-92 (1999)

95. Ho, G., J.R. Toomey, G.J. Broze, Jr., and A.L. Schwartz: Receptor-mediated endocytosis of coagulation factor Xa requires cell surface-bound tissue factor pathway inhibitor. *J Biol Chem* 271(16), 9497-502 (1996)

96. Warshawsky, I., G.J. Broze, Jr., and A.L. Schwartz: The low density lipoprotein receptor-related protein mediates the cellular degradation of tissue factor pathway inhibitor. *Proc Natl Acad Sci USA* 91(14), 6664-8 (1994)

97. Moestrup, S.K., S. Cui, H. Vorum, C. Bregengard, S.E. Bjorn, K. Norris, J. Gliemann, and E.I. Christensen: Evidence that epithelial glycoprotein 330/megalin mediates uptake of polybasic drugs. *J Clin Invest* 96(3), 1404-13 (1995)

98. Poller, W., T.E. Willnow, J. Hilpert, and J. Herz: Differential recognition of alpha 1-antitrypsin-elastase and alpha 1-antichymotrypsin-cathepsin G complexes by the low density lipoprotein receptor-related protein. *J Biol Chem* 270(6), 2841-5 (1995)

99. Mikhailenko, I., D. Krylov, K.M. Argraves, D.D. Roberts, G. Liau, and D.K. Strickland: Cellular internalization and degradation of thrombospondin-1 is mediated by the amino-terminal heparin binding domain (HBD) High affinity interaction of dimeric HBD with the low density lipoprotein receptor-related protein. *J Biol Chem* 272(10), 6784-91 (1997)

100. Kounnas, M.Z., R.D. Moir, G.W. Rebeck, A.I. Bush, W.S. Argraves, R.E. Tanzi, B.T. Hyman, and D.K. Strickland: LDL receptor-related protein, a multifunctional ApoE receptor, binds secreted beta-amyloid precursor protein and mediates its degradation. *Cell* 82(2), 331-40 (1995)

101. Moestrup, S.K., H. Birn, P.B. Fischer, C.M. Petersen, P.J. Verroust, R.B. Sim, E.I. Christensen, and E. Nexo: Megalin-mediated endocytosis of transcobalamin-vitamin-B12 complexes suggests a role of the receptor in vitamin-B12 homeostasis. *Proc Natl Acad Sci USA* 93(16), 8612-7 (1996)

102. Zheng, G., M. Marino, J. Zhao, and R.T. McCluskey: Megalin (gp330): a putative endocytic receptor for thyroglobulin (Tg) *Endocrinology* 139(3), 1462-5 (1998)

103. Hilpert, J., A. Nykjaer, C. Jacobsen, G. Wallukat, R. Nielsen, S.K. Moestrup, H. Haller, F.C. Luft, E.I. Christensen, and T.E. Willnow: Megalin antagonizes activation of the parathyroid hormone receptor. *J Biol Chem* 274(9), 5620-5 (1999)

104. Muramatsu, H., K. Zou, N. Sakaguchi, S. Ikematsu, S. Sakuma, and T. Muramatsu: LDL Receptor-Related Protein as a Component of the Midkine Receptor. *Biochem Biophys Res Commun* 270(3), 936-941 (2000)

105. Cui, S., P.J. Verroust, S.K. Moestrup, and E.I. Christensen: Megalin/gp330 mediates uptake of albumin in renal proximal tubule. *Am J Physiol* 271(4 Pt 2), F900-7 (1996)

106. Meilinger, M., C. Gschwentner, I. Burger, M. Haumer, M. Wahrmann, L. Szollar, J. Nimpf, and M. Huettinger: Metabolism of activated complement component C3 is mediated by the low density lipoprotein receptor-related protein/alpha(2)-macroglobulin receptor. *J Biol Chem* 274(53), 38091-6 (1999)

107. Cavallaro, U., A. Nykjaer, M. Nielsen, and M.R. Soria: Alpha 2-macroglobulin receptor mediates binding and cytotoxicity of plant ribosome-inactivating proteins. *Eur J Biochem* 232(1), 165-71 (1995)

108. Chan, W.L., P.C. Shaw, S.C. Tam, C. Jacobsen, J. Gliemann, and M.S. Nielsen: Trichosanthin Interacts with and Enters Cells via LDL Receptor Family Members. *Biochem Biophys Res Commun* 270(2), 453-457 (2000)

109. Hofer, F., M. Gruenberger, H. Kowalski, H. Machat, M. Huettinger, E. Kuechler, and D. Blass: Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. *Proc Natl Acad Sci USA* 91(5), 1839-42 (1994)

110. Oleinikov, A.V., J. Zhao, and S.P. Makker: Cytosolic adaptor protein Dab2 is an intracellular ligand of endocytic receptor gp600/megalin. *Biochem J* 347(Pt 3), 613-621 (2000)

Key words: LDL receptor, LRP, megalin, LRP-2, VLDLR, ApoER2, Review

Send correspondence to: W. Scott Argraves, Ph.D., Medical University of South Carolina, Department of Cell Biology and Anatomy, 171 Ashley Avenue, Charleston, SC 29425, Tel.: 843-792-5482, Fax: 843-792-0664, E-mail: argraves@musc.edu