Triglyceride Rich Lipoprotein-LPL-VLDL Receptor and Lp(a)-VLDL Receptor Pathways for Macrophage Foam Cell Formation

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Very low-density lipoprotein (VLDL) receptor is a member of the low-density lipoprotein (LDL) receptor family. It binds triglyceride rich lipoprotein (TGRL) but not LDL, because it recognizes apolipoprotein (apo)E only but not apoB. The VLDL receptor functions as a peripheral lipoprotein receptor in concert with lipoprotein lipase (LPL) in heart, muscle, adipose tissue and macrophages. In contrast to the LDL receptor, VLDL receptor binds apoE2/2 VLDL and apoE3/3 VLDL particles, and its expression is not down-regulated by intracellular lipoproteins. It has been reported that both LDL-cholesterol (LDL-C) and postprandial triglyceride (chryomicron and VLDL remnants) are risk factors for human atherosclerotic cardiovascular disease (ASCVD). True ligands such as lipoprotein particles of the VLDL receptor are chyromicron remnant (CMR) and VLDL remnant (postprandial hyperlipidemia). Although the oxidized LDL (oxLDL)-scavenger receptors pathway is considered to be the main mechanism for macrophage foam cell formation, it seems that the TGRL-LPL-VLDL receptor pathway is also involved. Since Lp(a) is one of the ligands for the VLDL receptor, the Lp(a)-VLDL receptor pathway is another potential alternative. The expression of VLDL receptor protein in mouse macrophages is modest compared to that in rabbit and human macrophages, both in vitro and in vivo. Therefore, we need to elucidate the mechanism of human ASCVD not by using the mouse model and scavenger receptors pathway but instead using the rabbit model and VLDL receptor pathway, respectively.

Key words: VLDL receptor, Lipoprotein lipase, Lp(a), Atherosclerosis, Macrophage foam cell formation

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there remains some uncertainty regarding the direct causal role of TGRL in ASCVD. True ligands such as lipoprotein particles of the VLDL receptor are CMR, VLDL remnant, and Lp(a). In addition macrophages express both VLDL receptor and LPL. In this review, I want to advocate the importance of TGRL-LPL-VLDL receptor and Lp(a)-VLDL receptor pathways for macrophage foam cell formation.

**Difference between VLDL and LDL Receptors**

We first cloned and characterized the VLDL receptor and found structural domains that were similar to those of the LDL receptor, including: (i) an aminoterminal ligand binding domain composed of multiple cysteine-rich repeats, (ii) an epidermal growth factor (EGF) precursor homology domain, (iii) an O-linked sugar domain with clustered serine and threonine, (iv) a single transmembrane domain, and (v) a cytoplasmic domain with an FDNPVY sequence described in rabbit and human VLDL receptor cDNA.  

The exon-intron organization of the VLDL receptor gene is almost identical to that of the LDL receptor gene, except for an extra exon that encodes an additional repeat in the ligand binding domain (LDL receptor contains a 7-fold repeat while the VLDL receptor has an 8-fold repeat) (Fig. 1). The two genes are located on different chromosomes; the VLDL receptor gene on chromosome 9 (9p24) and the LDL receptor gene on chromosome 19 (19p13.2). Subsequent studies indicated that LDL receptor mutation causes familial hypercholesterolemia (FH)9). In 2005, a human VLDL receptor mutant was discovered and homozygous deletion of the VLDL receptor gene was found to be the cause of autosomal recessive cerebellar hypoplasia with cerebral gyral simplification13). Table 1.  

VLDL receptor cDNA overexpressing ldlA-7 (LDL receptor-deficient CHO) cells bound apoE-containing lipoproteins, including VLDL, intermediate-density lipoprotein (IDL) from Watanabe heritable hyperlipidemic (WHHL) rabbits, and β-VLDL (β-migrating VLDL) from cholesterol-fed rabbits, but did not bind LDL from WHHL rabbits. On the other hand, ldlA-7 cells transfected with the LDL receptor cDNA bound both apoB- and apoE-containing lipoproteins, including VLDL, IDL, LDL from WHHL rabbits, and β-VLDL from cholesterol-fed rabbits. Notably, VLDL from fasted normal human subjects bound with lower affinity compared to VLDL prepared from WHHL rabbits. The VLDL from WHHL rabbits was recognized by VLDL receptor cDNA overexpress-
qualitatively. On the other hand, the low affinity binding of fasting human VLDL to the VLDL receptor could be overcome by enriching VLDL with either apoE or LPL\cite{14}. Niemeier et al.\cite{15} reported that the same mechanism was the case for chylomicron particles. The VLDL receptor mediated the uptake of CMR, and this uptake was further increased by the addition of apoE and inactivated LPL. Argraves et al.\cite{16} found that LPL itself bound with high affinity to purified VLDL receptor.\cite{14}

In vivo, VLDL receptor KO mice have reduced LPL activity\cite{17}. Taking into account that the VLDL receptor and LPL are expressed in the same tissues (heart, muscle, adipose tissue, and macrophages), these findings suggest that CMR and VLDL remnant are true ligands for the VLDL receptor in concert with LPL. In contrast to the LDL receptor, VLDL receptor bound apoE2/2 VLDL and apoE3/3 VLDL identically\cite{18}. Further adenovirus-mediated VLDL receptor expression in the liver of apoE2/2 and apoE3-Leiden transgenic mice resulted in lowering plasma cholesterol levels, indicating that the VLDL receptor recognized apoE2/2 and apoE3-Leiden. The reduction in plasma cholesterol was mainly due to a reduction in VLDL levels\cite{19}. Ruiz et al.\cite{20} showed that the VLDL receptor recognizes all apoE isoforms (apoE2, apoE3, and apoE4) and avidly binds lipid-free apoE.

It is controversial that whether LDL receptor binds Lp(a). It seems that Lp(a) is recognized by LDL receptor in vitro, but most of the in vivo data including human have shown that LDL receptor does not involved in the catabolism of Lp(a).

| Table 1. Differences between VLDL receptor and LDL receptor |
|-------------------------------------------------------------|
| **Gene location**     | 9p24 | 19p13.2 |
| **Phenotype of human mutant** | Cerebellar hypoplasia with cerebral gyral simplification | Familial hypercholesterolemia (FH) |
| **Ligands**            | ApoE, LPL, Lp(a), RAP, PCSK9, Reelin, Thrombospondin-1, uPA/ plasminogen activator inhibitor-1 complex, Serine protease-serpin complex, Tissue factor pathway inhibitor (TFPI), Fibrin, Hepatitis C virus | ApoE, ApoB, RAP, PCSK9, Hepatitis C virus |
| **Main expression sites** | Heart, Muscle, Adipose tissue, Macrophages, Endothelial cells, Brain | Liver, Adrenal gland |
| **Binding capacity of apoE2/2** | Equal to apoE3/3 | Less than 1% |
| **Sterol regulation**  | None | Negative feedback |
| **Alternative splicing** | + | – |

Apo: apolipoprotein, LPL: lipoprotein lipase, RAP: receptor-associated-protein, PCSK9: proprotein convertase subtilisin/kexin type 9, uPA: urokinase plasminogen activator

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The VLDL receptor mRNAs produce mainly two kinds of VLDL receptor proteins by alternative splicing; type 1 VLDL receptor and type 2 VLDL receptor that lacks O-linked sugar domain encoded by exon 16.\(^\text{(12)}\)

**Multiple Ligands for VLDL and LDL Receptors**

In addition to apoE and LPL, the VLDL receptor binds Lp(a)\(^\text{(24)}\), receptor-associated protein (RAP)\(^\text{(25)}\), proprotein convertase subtilisin/kexin type 9 (PCSK9)\(^\text{(26-28)}\), reelin\(^\text{(29)}\), thrombospondin-1\(^\text{(30-32)}\), urokinase plasminogen activator (uPA)/plasminogen activator inhibitor-1 complex\(^\text{(16, 33-36)}\), serine protease-serpin complex\(^\text{(37)}\), and tissue factor pathway inhibitor (TFPI)\(^\text{(36)}\). It seems that ECs are important sites for the action of the VLDL receptor because the movement of active LPL across
ECs involves both heparan sulfate proteoglycan and the VLDL receptor. In addition, it is intriguing that fibrin is one of the ligands for the VLDL receptor. Interaction of fibrin with the VLDL receptor promotes transendothelial migration of leukocyte as in the case for LPL and thereby enhances inflammation. Anti-VLDL receptor antibodies inhibit fibrin-VLDL receptor interaction and significantly reduce myocardial injury induced by ischemia-perfusion. The common ligands of the VLDL and LDL receptors are apoE, RAP, PCSK9 and hepatitis C virus. Because anti-PCSK9 monoclonal antibody (evolocumab and alirocumab) increases the protein expression of both VLDL and LDL receptors, patients with hepatitis C treated with anti-PCSK9 monoclonal antibody should be watched carefully (Table 1, Fig. 1).

TGRL-LPL-VLDL Receptor and Lp(a)-VLDL Receptor Pathways for Macrophage Foam Cell Formation

The expression of VLDL receptor primarily in macrophages has been confirmed in human and rabbit atherosclerotic lesions. In vitro, we reported that IFN-γ inhibited VLDL receptor expression and foam cell formation in three types of human macrophages (PMA-induced THP-1, PMA-induced HL-60, and human monocyte-derived macrophages) by β-VLDL, a representative lipoprotein in the metabolic syndrome and type III hyperlipoproteinemia. These results suggest that the VLDL receptor could be a macrophage β-VLDL receptor, which is one of the receptors involved in macrophage foam cell formation. However, controversial in vivo findings using a mouse model were reported. Atherosclerotic lesions were not different between HuB (human apoB) transgenic mice and VLDL receptor-deficient HuB transgenic mice fed atherogenic diet for 4 months. Tacken et al. also showed that both VLDL receptor deficiency and endothelial VLDL receptor overexpression did not affect the size of atherosclerotic lesions. Interestingly, they indicated that deficiency of the VLDL receptor profoundly increased intimal thickening after vascular injury. We also compared the area of atherosclerotic lesions in double KO and LDL receptor KO mice, but found no difference in the area even though we...
showed clear difference in lipoprotein profile (Fig. 2). Fortunately, we were able to obtain rabbit polyclonal anti-VLDL receptor antibody that recognized human, rabbit, rat, and mouse VLDL receptors. A synthetic peptide, CASVGHYPALSYVSTDDDL, which corresponds to the carboxy-terminus of the human, rabbit, rat, and mouse VLDL receptors, was synthesized and injected into Japanese White rabbits to obtain polyclonal antibody (named VR2). VR2 reacted only with human VLDL receptor, but not with human LDL receptor or human ApoER2 cDNA transfected ldlA-7 cells. Furthermore, VR2 specifically recognized the human and wild-type mouse heart VLDL receptor while it did not detect VLDL receptor bands in hearts of VLDL receptor KO mice. Western blots showed that although VLDL receptor protein was detected in PMA-treated THP-1 human macrophages and wild- type mouse heart, it was not detected in cell lines derived from mouse macrophages (Raw264.7 and J774.2) and also mouse peritoneal macrophages. The VR2 antibody detected rabbit VLDL receptor protein in heart but not in liver by immunohistochemistry. VLDL receptor proteins were clearly detected in some of the RAM11-positive macrophages in the thoracic aorta of WHHLMI rabbits, which are indicative of atherosclerotic lesion. In contrast to the atherosclerotic lesions in WHHLMI rabbit thoracic aorta, no VLDL receptor protein was observed in BM8-positive mouse macrophages in aortic atherosclerotic lesions in chow-fed apoE KO mice and LDL receptor KO mice whose diet had been supplemented with 1.25% cholesterol for 12 weeks. We detected abundant amounts of VLDL receptor protein in human atherosclerotic coronary arteries but not in non-atherosclerotic coronary arteries, using the same VR2 antibody (data not shown). Argraves et al. have already detected the VLDL receptor protein in human atherosclerotic plaque and the VLDL receptor protein was co-located with plaque KP-1-positive macrophages and foam cells. TGRL has also been isolated from human artery segments. Recently Matsuo et al. reported that serum remnant lipoprotein levels were positively correlated with the necrotic components of the coronary plaques and negatively correlated with the fibrotic components evaluated by intravascular ultrasound (IVUS) in patients with stable angina and it is known that both LDL-C and TGRL are independent risk factors for human ASCVD. Therefore, I consider that the mechanisms of macrophage foam cell formation are somewhat different between mice and humans or rabbits. Finally, I want to call up the TGRL-LPL-VLDL receptor pathway for macrophage foam cell formation, especially in rabbit and human. Since Lp(a) is one of the ligands for the VLDL receptor, the Lp(a)-VLDL receptor pathway may be considered as another alternative pathway (Fig. 3). Since both rabbit and human macrophages express VLDL receptor protein, studies on the importance of VLDL receptor signaling for TGRL should focus on these species rather than on the mouse systems (mouse peritoneal macrophages, apoE KO mice, and LDL receptor KO mice).

Conclusions

The VLDL receptor could be a so-called macrophage β-VLDL receptor which is involved in macrophage foam cell formation. Notably researchers in atherosclerosis should be known that macrophage VLDL receptor protein expression is different among species. I want to see more detailed researches about TGRL-LPL-VLDL receptor pathways for macrophage foam cell formation in the future.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgments

I thank Akihisa Kamataki (Hirosaki University Graduate School of Medicine), Tokuo Yamamoto (Tohoku University), and Takaumi Ishida (Fukushima Medical University) for collaboration. I also appreciate Jinya Suzuki (University of Fukui) for preparation of the manuscript.

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