The role of triglyceride-rich lipoproteins (chylomicrons and very low-density lipoproteins [VLDL]) in promoting cardiovascular disease (CVD) has been an area of debate over many years. Epidemiological and genetic evidence supports the idea of raised triglycerides, or triglyceride-rich lipoproteins (TRLs) and their remnants, as a pathogenesis of CVD. However, human intervention trials have failed to show conclusive effects, perhaps because other risk factors are often associated with elevated triglycerides, such as insulin resistance and diabetes mellitus, or because plasma triglycerides might be a marker of CVD rather than an independent risk factor. Both fasting and nonfasting plasma triglyceride levels vary widely, with concentrations of 2 to 10 mmol/L (177–885 mg/dL) conferring an association with increased risk of CVD and concentrations >10 mmol/L conferring increased risk of acute pancreatitis. Large-scale clinical trials on well-defined subject populations are needed to shed light onto the role of triglycerides in CVD risk.

Triglyceride-rich chylomicrons are generated in the postprandial state by intestinal enterocytes, secreted into the intestinal lymph, and then released into circulation through the thoracic duct. After reaching the bloodstream, the triglycerides within chylomicrons and VLDL are hydrolyzed by lipoprotein lipase (LpL) along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue. This process allows release of fatty acids that can be used as an energy source or stored for safekeeping to be used in times of energy deprivation. However, recent studies in mice have demonstrated that adipocyte-derived LpL plays a smaller role in adipose tissue triglyceride accumulation than previously thought. Two hypotheses, which are not mutually exclusive, have been put forward to explain how the smaller fraction of LpL bound to the luminal endothelium in larger arteries, as compared with the majority bound to the capillary endothelium, might promote atherosclerosis. The remnant hypothesis states that LpL hydrolyzes TRLs into smaller remnants, which are then able to traverse the endothelium and enter the artery wall, where they are engulfed by macrophages. The lipolytic toxin hypothesis states that LpL-mediated hydrolysis of TRLs results in release lipids, such as fatty acids and oxidized lipids, which in turn promote proatherosclerotic changes in endothelial cells. The dogma in the field held that LpL was tethered to endothelial cells only through the interaction of its positively charged heparin-binding domains via negatively charged heparan sulfate glycosaminoglycans on the surface of endothelial cells. LpL, however, is not synthesized by endothelial cells, but rather by myocytes and adipocytes. How LpL transverses the capillary endothelium and details on its subsequent tethering to the luminal side have only recently begun to be illuminated.

In 2007, the Young laboratory demonstrated that mice deficient in glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) exhibited a striking accumulation of chylomicrons in the plasma and had plasma triglyceride levels in excess of 1000 mg/dL (11 mmol/L) without altered LpL expression in adipocytes and myocytes. Furthermore, the vast majority of the plasma triglycerides were located in the large lipoprotein fraction, suggesting a defect in lipolytic processing of chylomicrons. Further studies revealed that GPIHBP1 expression in capillary endothelial cells is critical for the transportation of LpL from the basolateral to the capillary apical surface, as shown in Figure A. Moreover, through a series of elegant experiments, this group has demonstrated that the heparan sulfate glycosaminoglycans are neither required nor sufficient to mediate LpL hydrolysis of triglycerides on the apical surface and recently that LpL-binding to GPIHBP1, rather than LpL-binding to heparan sulfate glycosaminoglycans, is the main determinant of TRL margination in heart capillaries. Interestingly, GPIHBP1 is expressed in capillary endothelium, but not in large vessel endothelium or brain capillaries. Therefore, LpL tethering to the luminal surface of large arteries susceptible to atherosclerosis is presumably more dependent on heparan sulfate glycosaminoglycans.

Mature human GPIHBP1 contains a signal peptide, an acidic/negatively charged amino-terminal domain, a short linker domain, a highly conserved lymphocyte antigen 6 motif (residues 65–136), and a hydrophobic carboxyl-terminal that triggers the addition of a glycosylphosphatidylinositol (GPI) anchor. The aspartic and glutamic acid–enriched acidic domain is involved in the binding of LpL. The acidic domain also mediates apolipoprotein A-V interaction with GPIHBP1. The lymphocyte antigen 6 domain is characterized by 10 conserved cysteine residues that have a defined disulfide-bonding pattern. These cysteine residues generate a 3-fingered structural motif. The lymphocyte antigen 6 motif also contains a N-linked glycosylation site (Asn-78 in human and, Asn-76 in mouse) that is critical for trafficking of GPIHBP1 to the cell surface and for binding LpL. GPIHBP1 is tethered to the surface of the plasma membrane by its GPI anchor, which can be cleaved by a phosphatidylinositol–specific phospholipase C.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Mature human GPIHBP1 contains a signal peptide, an acidic/negatively charged amino-terminal domain, a short linker domain, a highly conserved lymphocyte antigen 6 motif (residues 65–136), and a hydrophobic carboxyl-terminal that triggers the addition of a glycosylphosphatidylinositol (GPI) anchor. The aspartic and glutamic acid–enriched acidic domain is involved in the binding of LpL. The acidic domain also mediates apolipoprotein A-V interaction with GPIHBP1. The lymphocyte antigen 6 domain is characterized by 10 conserved cysteine residues that have a defined disulfide-bonding pattern. These cysteine residues generate a 3-fingered structural motif. The lymphocyte antigen 6 motif also contains a N-linked glycosylation site (Asn-78 in human and, Asn-76 in mouse) that is critical for trafficking of GPIHBP1 to the cell surface and for binding LpL. GPIHBP1 is tethered to the surface of the plasma membrane by its GPI anchor, which can be cleaved by a phosphatidylinositol–specific phospholipase C.
To date, >10 different rare mutations/deletions in the GPIHBP1 gene resulting in changes in the GPIHBP1 protein in patients with severe hypertriglyceridemia have been reported. One patient with total loss of GPIHBP1 had extremely high serum triglycerides (>280 mmol/L; 25 000 mg/dL) at the age of 2 months. Another family had a deletion of exons 3 and 4 in 4 adult individuals with serum triglycerides ranging between <2000 and 9000 mg/dL (23–102 mmol/L). Whether there was some partial function of the remaining exons 1 and 2 was not determined, but deletion of exons 3 and 4 eliminates the GPI-membrane anchor as well as the Ly6 motif. The most common mutations in GPIHBP1-associated chylomicronemia are missense mutations in one of the conserved cysteines or other amino acids in the LpL-binding Ly6 motif, such as the mutations C65S, C65Y, C68G, C68Y, C89F, and Q115P. It was first hypothesized that mutations of the cysteine residues would result in misfolding and accumulation of GPIHBP1 in the ER; however, work by Beigneux and colleagues revealed that many, but not all, mutations in GPIHBP1 associated with hypertriglyceridemia cause dimerization or multimerization of GPIHBP1, thereby preventing LpL binding. The study by Beigneux et al reveals that many, but not all, mutations in GPIHBP1 associated with hypertriglyceridemia cause dimerization or multimerization of GPIHBP1, thereby preventing LpL binding.

In binding LpL, suggesting that this highly conserved residue may directly interact with LpL. Further studies with crystallography or nuclear magnetic resonance will be needed to determine the specific details of the interaction. Furthermore, because these studies are based on in vitro overexpression systems, analysis of GPIHBP1 dimerization and multimerization in animal models and humans would be a logical and interesting next step.

It is hard not to draw similarity between the current article and that of Plengpanich et al by the same group. In that article, the serine to cysteine S107C mutation discovered in a Thai family was found to not affect trafficking of GPIHBP1 to the cell surface, but to result in GPIHBP1 multimerisation. Furthermore, the authors demonstrated in that study that LpL greatly prefers to bind monomeric GPIHBP1 (wild-type GPIHBP1 also forms multimers); moreover, they attributed the lack of LpL binding of 2 previously identified GPIHBP1 mutants (S107C and C68G) to the reduction of monomers. In the current study by Beigneux et al., the authors studied >15 different mutations in the Ly6 domain with special emphasis on the cysteines. Together, both manuscripts strongly suggest that the majority of GPIHBP1 mutations associated with chylomicronemia are correlated with multimerization of the protein and loss of LpL-binding capacity. The possibility that GPIHBP1 multimerization can offer a therapeutic strategy for hypertriglyceridemia.

Recently, a polymorphism (rs72691625) was identified in the GPIHBP1 gene promoter. Carriers of this g.-469G>A polymorphism have a significantly higher risk of elevated triglycerides (2.0 mmol/L; 177 mg/dL) than noncarriers. However, whether this polymorphism affects gene expression was not determined. Nonetheless, it suggests that modulation of GPIHBP1 expression or activity could offer a therapeutic treatment strategy for hypertriglyceridemia.

Finally, it is interesting to ponder the potential role of GPIHBP1 in CVD in humans. The Gpihbp1−/− mouse, which develops severe chylomicronemia even on a low-fat diet,
exhibits small macrophage-rich fatty streak lesions of atherosclerosis in the aortic sinus and coronary arteries at 11 to 12 months of age and larger aortic sinus lesions at 22 months of age. These proatherosclerotic effects of GPIHBP1-deficiency are probably caused by the markedly elevated levels of chylomicrons/VLDL, which might exacerbate atherosclerosis through increased remnant formation in large arteries or through increased generation of proatherogenic lipid products. It is clear, however, that the effect of GPIHBP1-deficiency on atherosclerosis is weak compared with that of LDL receptor-deficiency or ApoE-deficiency in mouse models, which develop large and complex advanced lesions when fed low-fat diets at the ages studied in the Gpihbp1−/− mice.

The studies by Beigneux and colleagues43 have undoubtedly advanced our understanding of how GPIHBP1 mediates LpL transport and the likely effect of GPIHBP1 point mutations in humans with hypertriglyceridemia. Further understanding of the role of GPIHBP1 and TRLs in the development of CVD in humans is urgently needed.

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Disclosures

None.

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