Editorial

Some Things Just Have to Be Done In Vivo
GPIHBP1, Caloric Delivery, and the Generation of Remnant Lipoproteins

Kevin Jon Williams

Abstract—The recent discovery of a dysfunctional mutation of GPIHBP1 in a man with chylomicronemia implicates this protein in human physiology. GPIHBP1 can be placed in the larger context of other molecular participants in chylomicron docking and hydrolysis on microvascular endothelium, caloric delivery, and remnant lipoprotein generation. Critical questions include the regulation—and dysregulation—of these processes in states of overnutrition, underexertion, obesity, insulin resistance, and diabetes.

For decades, we were convinced that heparan sulfate proteoglycans (HSPGs) on the microvascular endothelium of adipose tissue and striated muscle served as the docking site for chylomicrons (CMs) during their lipolysis by lipoprotein lipase (LpL). A serendipitous observation of docking site for chylomicrons (CMs) during their lipolysis by um of adipose tissue and striated muscle served as the regulation. Regarding location, hydrolysis of CM triglyceride molecular participants share crucial features of location and documented only in vitro.

The Figure presents a recent attempt to place GPIHBP1 in the larger context of other molecular participants in CM docking, hydrolysis, caloric delivery, and remnant lipoprotein generation. Some of these molecules, such as caveolin-113,14 and CD36,15,16 have been implicated in mice and humans in vivo. But some processes, such as HSPG-mediated endocytosis and destruction of LpL by adipocytes17,18 and transendothelial transport of LpL by HSPGs and the VLDL receptor. As noted above, cell-culture data implicate HSPGs and the VLDL receptor,19 have been documented only in vitro.

Nevertheless, the available evidence suggests that key molecular participants share crucial features of location and regulation. Regarding location, hydrolysis of CM triglyceride and then tissue uptake of nonesterified fatty acids (NEFAs) may be facilitated by being concentrated within cholesterol-rich membrane microdomains, also known as rafts.12 The major HSPGs of endothelial cells include the transmembrane syndecans and the GPI-anchored glypicans. Syndecan HSPGs move laterally into rafts on clustering,20,21 and binding a dimer of LpL, the enzymatically active form, appears to be a sufficient trigger.20 GPI-anchored molecules also move into rafts on clustering.22 Thus, syndecans, glypicans, and GPI-HBP1 should come into close proximity within rafts after the transendothelial transport of dimeric LpL, thereby facilitating the transfer of this enzyme from HSPGs onto higher-affinity binding sites on GPIHBP1. Likewise, the CD36 fatty acid translocase also localizes to rafts,23 which could facilitate its ability to accept NEFAs from LpL-GPIHBP1-CM complexes during triglyceride hydrolysis (Figure). Consistent with this model, knock-out of caveolin-1, a scaffolding molecule required for the formation of certain types of cholesterol-rich microdomains, impairs lipolysis of postprandial lipoproteins and the importation of NEFAs into adipose tissue.13 Similar effects have been associated with a nonsense mutation of human caveolin-1.14

To complete this picture, we need to address several additional questions. What molecules mediate transendothelial transport of LpL in vivo? Endothelium does not make LpL, but must acquire it from underlying adipocytes and myocytes. As noted above, cell-culture data implicate HSPGs and the VLDL receptor. The VLDL receptor was reported to affect LpL regulation in vivo, possibly related to transendothelial transport.24 If HSPGs are involved in vivo, which ones? Syndecans-1, -2, and -4 and glypican-1 would be attractive candidates, owing to their expression by cultured endothelial cells25,26 and their ability to directly mediate ligand internalization.20,21,27–29 Syndecans bind LpL in vitro20,27 and mediate endocytosis via rafts.20,30 Glypican-1 undergoes caveolar-associated recycling,28 and digestion of cultured adipocytes and myocytes with phosphatidylinositol-specific phospholipase-C releases HSPG-bound LpL,31–33 although digestion of cultured endothelial cells did not.10 Thus, under some circumstances, syndecans and glypicans function as LpL receptors in vitro, but their role in LpL trafficking across the endothelium in vivo remains unknown.

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Could GPIHBP1 be involved in transendothelial transport of LpL? It seems unlikely, given its apparently exclusive expression on the luminal surface. But why, then, is the amount of LpL released into postheparin plasma affected by a deficiency of functional GPIHBP1, even though tissue stores of the enzyme remain normal? Plasma levels of LpL were low at early, but not later, time points after a heparin injection into GPIHBP1-deficient mice, and LpL was low in a single sample of postheparin plasma from the individual with the dysfunctional missense mutation. In addition, GPIHBP1 deficiency blocked the release of LpL into plasma at all time points tested after an injection of artificial triglyceride emulsion particles.

There may be two pools of LpL, one displayed on luminal GPIHBP1 and one deep within adipose tissue and striated muscle. Both pools might be eventually accessible to heparin, which has been reported to readily pass through arterial endothelium, but only the pool adherent to GPIHBP1 would be accessible to emulsions and able to hydrolyze lipoprotein triglyceride. On the other hand, because heparin inhibits transendothelial transport of LpL in vitro, heparin that reaches the tissue pool of LpL might strand it there, rather than facilitating its release into plasma. Moreover, delayed release of nonluminal depots of LpL has been documented from hearts perfused with heparin, but the mechanism implicated in that study was the gradual transport of this enzyme to the endothelial surface, after...
which it was nearly immediately released by heparin in the perfusate.\textsuperscript{36}

Alternatively, if transfer of LpL from endothelial HSPGs and VLDL receptors onto GPIHBP1 does in fact occur, it could prevent HSPG- or VLDL-receptor-mediated endocytosis or transcytosis back into the subendothelial space, particularly if those molecules continuously recycle. Evidence in vivo indirectly supports the existence of a pool of LpL molecules that recirculate between the luminal surface of the endothelium and extravascular sites in adipose tissue.\textsuperscript{37} Cultured endothelial cells also internalize LpL and then recycle it back to the cell surface intact.\textsuperscript{17,33,38} Here, the model presumes that LpL cycling back and forth across the luminal endothelial membrane remains inaccessible to triglyceride-rich lipoproteins and emulsion particles in the bloodstream, unless the enzyme can move onto GPIHBP1. As a speculative example, LpL bound to the heparan sulfate side-chains of glypicans would sit close to the plasma membrane (Figure), where very large particles might not be able to approach.\textsuperscript{39}

Does GPIHBP1 affect the enzymatic activity of LpL? It has long been known that heparin-induced release of LpL from its binding sites on the luminal surface of endothelium quickly accelerates the hydrolysis of triglyceride-rich lipoproteins in plasma in vivo.\textsuperscript{1,34,40,41} It could simply be a matter of better access to substrate when the enzyme is in solution than when it is confined to a surface, but it is also possible that the conformation of LpL is altered by its association with GPIHBP1. If the latter, the conformational changes could be regulated.

What physical determinants allow remnant lipoproteins and artificial emulsions to acquire LpL from the luminal surface of the endothelium? In normal physiology, the shift in apoprotein composition before CM docking (apoB\textsubscript{48}, apoA-V, apoC-II, apoE) versus after remnant release (apoB\textsubscript{48}, LpL, apoE) sets the stage for rapid hepatic uptake via the unusual, highly charged HSPGs that are displayed on the basal surface of healthy hepatocytes\textsuperscript{12,27,42–44} (Figure). Post-prandial apoB\textsubscript{48}-containing lipoproteins that contain LpL are cleared from human plasma much faster than particles without this important molecule,\textsuperscript{45} consistent with the earlier suggestion that LpL should be regarded as an apoprotein whose function is recognition by hepatic HSPGs.\textsuperscript{27,42} Do changes in particle size and composition during lipolysis enhance adsorption of LpL? A role for apoB\textsubscript{48} seems unlikely, because artificial triglyceride emulsions acquire LpL in vivo in wild-type animals,\textsuperscript{46} consistent with well-established physical properties of the enzyme.\textsuperscript{1,47} Do GPIHBP1 or other proteins alter their conformations to handle--and mishandle--dietary lipids?

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