commentary

Stabilizing lipoprotein lipase[1]

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Evidence from several prospective observational studies points toward the independent predictive value of plasma triglycerides in assessing cardiovascular risk (1). Hence, plasma triglycerides are increasingly targeted as a specific cardiovascular treatment outcome. To effectively lower triglycerides, detailed understanding of the molecular mechanisms that govern plasma triglyceride levels is required. Plasma triglycerides originate from the small intestine and liver and enter the bloodstream in the form of chylomicrons or very low density lipoproteins, respectively. Once they enter into the circulation, triglycerides are rapidly cleared via lipolysis catalyzed by the enzyme lipoprotein lipase (LPL), which is attached to the capillary endothelium in heart, skeletal muscle, and adipose tissue. Additionally, hepatic lipase expressed in liver impacts plasma triglycerides by promoting the conversion of intermediate density lipoproteins to low density lipoproteins. The physical positioning of LPL on the vascular endothelium occurs via binding to cell surface heparan sulfate proteoglycans (HSPGs) and to the newly described glycoprotein glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP-1) (2). In adipose tissue, activity of LPL is highest after a meal, consistent with the anabolic function of adipose tissue, whereas skeletal muscle LPL activity is increased by fasting and exercise training. The total activity of LPL is regulated via changes in gene transcription as well as via modulation of its enzymatic activity (3). Known modulators of LPL activity include apolipoproteins APOC2 and APOA5, which stimulate in vivo LPL activity, and APOC3, which inhibits LPL activity (4).

Since its discovery in 1955, much has been learned about the function of LPL and its importance for human lipid metabolism (5). However, several aspects of LPL-dependent lipolysis have remained elusive. Several years ago, angiopoietin-like proteins 3 and 4 (ANGPTL3, ANGPTL4) were uncovered as novel inhibitors of LPL activity (6, 7). Using mutant mouse models, ANGPTL3, which was initially discovered as a novel angiopoietin-related protein expressed specifically in liver, and ANGPTL4, which emerged in screenings for target genes of peroxisome proliferator-activated receptor (PPAR)α and PPARγ, were shown to markedly raise plasma triglyceride levels (6, 8–10). The proteins share a similar modular structure, are proteolytically cleaved subsequent to secretion, and are able to self-associate. In vitro and in vivo, ANGPTL3 and ANGPTL4 are able to inhibit LPL-dependent lipolysis with ANGPTL4 being particularly potent (11). The inhibitory effect of ANGPTL4 on LPL activity is at least partially explained by the conversion of active LPL-dimers into catalytically inactive LPL monomers (12, 13).

More recently, another major discovery was made pertaining to the molecular mechanism of in vivo LPL-mediated lipolysis. It was found that mice lacking the GPIHBP-1 gene exhibited severe hypertriglyceridemia related to defective clearance of triglyceride-rich lipoproteins (2). The GPIHBP-1 gene encodes a protein of 28 kDa that is anchored in the vascular endothelium via its GPI anchor and is thus positioned adjacent to HSPG. It has been shown to be able to bind both LPL and chylomicrons (2). According to the current model, GPIHBP-1 deletion may lead to the loss of a high affinity binding site for attachment of LPL to the endothelium, which may function in concert to the low affinity binding of LPL to HSPG (14).

Although so far explored independently, a recent study suggests that the functions of GPIHBP-1 and ANGPTL4 may actually intersect. The research by Sonnenburg et al. (15) was aimed at investigating how GPIHBP-1 may affect in vivo LPL activity and to study the potential modulating influence of ANGPTL3 and ANGPTL4. Their data show that GPIHBP-1 not only binds LPL but actually stabilizes it without affecting activity. The most important finding of the paper was that ANGPTL4 was capable of inhibiting soluble LPL and heparin-bound LPL but not LPL that was associated to GPIHBP-1, demonstrating that GPIHBP-1 protects LPL from inhibition by ANGPTL4. Similarly, ANGPTL3 inhibited soluble LPL and, to a lesser extent, heparin-bound LPL but not GPIHBP-1 associated LPL. These in vitro findings were supported by in vivo data showing that deletion of ANGPTL4 in hypertriglyceridemic GPIHBP-1 knockout mice drastically reduced the

Abbreviations: ANGPTL, angiopoietin-like protein; GPIHBP, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; HSPG, heparan sulfate proteoglycan.

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hypertriglyceridemia, resulting in plasma triglyceride levels approaching those of wild-type littermates. In contrast, serum triglycerides in mice with a double knockout of ANGPTL3 and GPIHBP-1 were only slightly decreased compared with GPIHBP-1 knockout mice. These novel data raise the interesting possibility that in addition to serving as a platform for LPL and its substrates, GPIHBP-1 may be a major factor in regulating LPL activity on the endothelium by shielding LPL from the inhibitory effects of ANGPTL4 and ANGPTL3.

These results also suggest that ANGPTL3 and ANGPTL4 are not completely alike in their interaction with LPL and GPIHBP-1, which is in agreement with in vitro results showing that ANGPTL4 is a much more potent inhibitor of LPL than ANGPTL3. Consistent with this notion, there is evidence suggesting that ANGPTL3 and ANGPTL4 inhibit LPL via different mechanisms (11).

The paper by Sonnenburg et al. (15) provides very useful new insights into the possible functional role of GPIHBP-1 in LPL-mediated clearance. Together with already published data, it suggests that LPL is present on the endothelium associated with either GPIHBP-1 or HSPG, yet HSPG-bound LPL may be largely inactive due to the action of ANGPTL4. According to this scenario, LPL activity on the endothelium is dependent on the number of LPL molecules bound to GPIHBP-1 versus HSPG, the local concentration of ANGPTL3 and ANGPTL4, and the relative affinities of ANGPTL3 and ANGPTL4 for the two pools of LPL. The study also raises a number of important questions. Importantly, does GPIHBP-1 stabilize LPL and suppress ANGPTL4-mediated LPL inhibition by stabilizing the catalytically active LPL dimers? One could speculate that GPIHBP-1 selectively interacts with LPL dimers but not monomers. Another interesting question is whether GPIHBP-1 and ANGPTL4 may compete for interaction with LPL, possibly by associating with the same domain on LPL. LPL has been shown to bind GPIHBP-1 via its positively charged heparin binding domain (16). Whether the same domain is targeted by ANGPTL4 remains to be determined. Finally, an issue that needs to be resolved is why transcription of ANGPTL4 is extremely sensitive to external cues, including fatty acids, if ANGPTL4 is largely ineffective toward LPL when GPIHBP-1 is present. It has been shown that modest overexpression of ANGPTL4 gives rise to hypertriglyceridemia even in the presence of GPIHBP-1 (9). Assuming that GPIHBP-1-stabilized LPL is indeed refractory to inhibition by ANGPTL4, the effect of ANGPTL4 on plasma triglycerides in vivo must then be explained by predominant targeting of HSPG-bound LPL by ANGPTL4.

Overall, the recent studies on ANGPTL3, ANGPTL4, and GPIHBP-1 and their convergent role in governing LPL activity attest to the multiple layers of regulation of plasma triglyceride clearance. These and other studies have put LPL at the center of the complex network of complementary pathways that feed back between the cell and the plasma compartment to adjust plasma triglyceride breakdown to the specific cellular requirements for fatty acid substrate.

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