The triglyceride lipase gene subfamily plays a central role in lipid and lipoprotein metabolism. There are three members of this subfamily: lipoprotein lipase (LPL), hepatic lipase (HL), and endothelial lipase (EL).

LPL, in general, is considered to be inversely associated with atherosclerosis; however, in several in vitro analysis using cultured cells, this enzyme has been found to increase monocyte adhesion to aortic endothelial cells, function as a monocyte adhesion protein \(^1\), and promote foam cell formation \(^2\).

In experiments using animal models, mice overexpression of human LPL \(^3\) or rabbit expressing human LPL \(^4\) caused reductions in aortic atherosclerotic lesions.

In a clinical point of view, LPL deficiency might be the best model for predicting the relation of LPL to the development of cardiovascular disease. But the atherogenicity of this rare genetic disease is still controversial \(^5\). In a cross-sectional study, Japanese investigators have reported that males with coronary atherosclerosis had significantly lower serum LPL mass than those without coronary atherosclerosis or who are healthy \(^6\).

The contribution of HL to the development of atherosclerosis is less clear than LPL. In a study with animal model, Mezdour et al., in their study using mice lacking both HL and apoE, have suggested that HL deficiency may be associated with increases in plasma cholesterol but reduced susceptibility to atherosclerosis \(^8\).

In humans, HL deficiency might be a good model for understanding how this enzyme affects the development of atherosclerosis, but the prevalence of this disease in the general population might be even lesser than that of LPL deficiency. The available message from the reported HL deficiency is that unlike LPL deficiency, most of the reported HL deficiency is pro-atherogenic \(^9\). This suggests that HL is an anti-atherogenic molecule. However, there is no prospective study investigating whether this lipolytic enzyme is atherogenic. Recently we established a new ELISA method for measuring serum human HL proteins \(^10\), which would enable us to measure HL protein mass in large number of samples.

EL was identified by Hirata et al. in 1999 \(^11\), mainly contributing to HDL catabolism. Since then, numerous investigators have studied on the association of this lipase with the development of atherosclerosis. A number of studies have suggested that EL can predict the development of atherosclerotic disease in humans \(^12\)-\(^15\), whereas a prospective case-control study nested in the EPIC-Norfolk cohort (1138 CAD cases, 2237 matched controls) has denied the association between common genetic variants in LIPG and CAD risk \(^16\).

To the best of our knowledge, there are no previous reports directly comparing the atherogenicity of these three enzymes. In this issue of JAT, Yu et al. \(^17\) have compared the atherogenicity of these three enzymes in 86 patients with CAD and 65 healthy controls and found that serum EL and HL concentrations were significantly increased in patients with CAD or in-stent restenosis, whereas serum LPL concentration was significantly reduced in patients with CAD. Their multivariate logistic regression analysis indicated that the three lipases were simultaneous independent risk factors for CAD but only serum EL concentration was considered an independent risk factor for in-stent restenosis. In our univariate analysis on the associations of carotid artery intima-media thickness (IMT) with the

---

**Which is the Best Predictor for the Development of Atherosclerosis Among Circulating Lipoprotein Lipase, Hepatic Lipase, and Endothelial Lipase?**

Junji Kobayashi

Kanazawa Medical University General Internal Medicine, Kanazawa, Japan
three triglyceride lipases in Japanese subjects with het-
erozygous familial hypercholesterolemia (n = 16; mean age, 63 years)\textsuperscript{18}, we found that among the three lipases, only serum EL concentrations had a statistically sig-
nificant association with right carotid artery IMT (EL, \(r = 0.59\) \(p = 0.017\); HL, \(r = 0.074\) \(p = 0.79\); LPL, \(r = 0.32\) \(p = 0.22\)) and left carotid artery IMT (EL, \(r = 0.51\) \(p = 0.044\); HL, \(r = 0.25\) \(p = 0.35\); LPL, \(r = 0.29\) \(p = 0.28\)). This observation combined with the above mentioned find-
ing by Yu et al.\textsuperscript{17} showed that EL may be the strongest determi-
nant of atheronenicity among the three triglyc-
eride lipases. Additional studies, with much larger sam-
ple size for long term follow-up, are needed to confirm the current findings on the effects of these three tri-
glyceride lipases on the development of atherosclerotic disease.

Conflict of Interest (COI)

I have no COI to declare regarding this manu-
script.

References

1) Saxena, U., Kulkarni, N.M., Ferguson, E., and Newton, R.S. Lipoprotein lipase-mediated lipolysis of very low den-
sity lipoproteins increases monocyte adhesion to aortic endothelial cells. Biochem. Biophys. Res. Commun. 1992; 189: 1653-1658
2) Babaev VR, Fazio S, Gleaves LA, Carter KJ, Semenkovich CF, Linton MF. Macrophage lipoprotein lipase promotes foam cell formation and atherosclerosis in vivo. J Clin Invest. 1999; 103: 1697-1705
3) Shimada M, Ishibashi S, Inaba T, Yagyu H, Harada K, Osuga JI, Ohashi K, Yazaki Y, Yamada N. Suppression of diet-induced atherosclerosis in low density lipoprotein receptor knockout mice overexpressing lipoprotein lipase. Proc Natl Acad Sci USA 1996; 93: 7242-7246
4) Fan J, Unoki H, Kojima N, Sun H, Shimoyamada H, Deng H, Okazaki M, Shikama H, Yamada N, Watanabe T. Overexpression of lipoprotein lipase in transgenic rabbits inhibits diet-induced hypercholesterolemia and atherosclerosis. J Biol Chem 2001; 276: 40071-40079
5) Kobayashi J, Mabuchi H. Lipoprotein lipase and athero-
sclerosis. Ann Clin Biochem. 2015; 52: 632-637
6) Hitsumoto T, Ohsawa H, Uchi T, Noike H, Kanai M, Yoshinuma M, Miyashita Y, Watanabe H, Shirai K. Pre-
heparin serum lipoprotein lipase mass is negatively related to coronary atherosclerosis. Atherosclerosis 2000; 153: 391-396
7) Rip J, Nierman MC, Wareham NJ, Luben R, Bingham SA, Day NE, Miert JNIV, Hutten BA, Kastelein JJP, Kuivenhoven JA, Khaw KT, Boekholdt SM. Serum lipoprotein lipase concentration and risk for future coronary artery disease: the EPIC-Norfolk prospective population study. Arterioscler Thromb Vasc Biol 2006; 26: 637-642
8) Mezdour H, Jones R, Dengremont C, Castro G, and Maeda N: Hepatic lipase deficiency increases plasma cho-
esterol but reduces susceptibility to atherosclerosis in apo-
lipoprotein E-deficient mice. J Biol Chem, 1997; 272: 13570-13575
9) Kobayashi J, Miyashita K, Nakajima K, Mabuchi H. Hepatic Lipase: a Comprehensive View of its Role on Plasma Lipid and Lipoprotein Metabolism. J Atheroscler Thromb. 2015; 22: 1001-1011
10) Miyashita K, Nakajima K, Fukamachi I, Muraba Y, Koga T, Shimomura Y, Machida T, Murakami M, Kobayashi J. A new enzyme-linked immunosorbent assay system for human serum hepatic triglyceride lipase. J Lipid Res. 2017; 58: 1591-1597
11) Hirata K, Dichek HL, Gioffi JA, Choi SY, Leeper NJ, Quintana L, Kronmal GS, Cooper AD and Quertermous T: Cloning of a unique lipase from endothelial cells extends the lipase gene family. J Biol Chem, 1999; 274: 14170-14175
12) Sun L, Ishida T, Miyashita K, Kinoshita N, Mori K, Yas-
uda T, Toh R, Nakajima K, Imamura S, Hirata K. Plasma activity of endothelial lipase impacts high-density lipopro-
tein metabolism and coronary risk factors in humans. J Atheroscler Thromb. 2014; 21: 313-321
13) Singaraja RR, Sivapalaratnam S, Hovingh KG, Dubé MP, Castro-Perez J, Collins HL, Adelman SJ, Riwanto M, Manz J, Hubbard B, Tietjen I, Wong K, Mitnall LJ, van Heek M, Lin L, Roddy TA, McEwen J, Dallinge-Thie G, van Vark-van der Zee L, Verwoert G, Winther M, van Duijn C, Hofman A, Trip MD, Marias AD, Asztalos B, Landmesser U, Sijbrands E, Kastelein JJ, Hayden MR. The impact of partial and complete loss-of-function muta-
tions in endothelial lipase on high-density lipoprotein lev-
els and functionality in humans. Circ Cardiovasc Genet. 2013; 6: 54-62
14) Xie Y, Sun Y, Tong Y, Liu Y, Deng Y Association of endo-
thelial lipase gene-384A/C with coronary artery disease in Han Chinese people. BMJ Open. 2015; 5: e007621
15) Badellino KO, Wolfe ML, Reilly MP, Rader DJ. Endo-
theelial lipase concentrations are increased in metabolic syn-
drome and associated with coronary atherosclerosis. PLoS Med. 2006; 3: e22
16) Vergeer M, Cohn DM, Boekholdt SM, Sandhu MS, Prins HM, Ricketts SL, Wareham NJ, Kastelein JJ, Khaw KT, Kamphuisen PW, Dallinga-Thie GM. Lack of association between common genetic variation in endothelial lipase (LIPG) and the risk for CAD and DVT. Atherosclerosis. 2010; 211: 558-564
17) Yu X, Lu J, Li J, Guan W, Deng S, Deng Q, Ye H, Han W, Yu Y, Zhang R Serum triglyceride lipase concentration is an independent risk factor for coronary artery disease and in-stent restenosis. J Atheroscler Thromb. 2019; 26: 762-774
18) Tada H, Kobayashi J, Kawashiri MA, Miyashita K, Nohara A, Inazu A, Nakajima K, Mabuchi H, Yamagishi M. Changes in lipoprotein lipase and endothelial lipase mass in familial hypercholesterolemia during three-drug lipid-
lowering combination therapy. Lipids Health Dis. 2016; 15: 66