Apolipoprotein M and Sphingosine-1-Phosphate: A Potentially Antidiabetic Tandem Carried by HDL

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The frequent finding of low HDL cholesterol in patients with type 2 diabetes (T2D) or at increased risk for T2D has been traditionally interpreted as the consequence of hypertriglyceridemia and hyperacylemia, which are caused by insulin resistance and hyperinsulinemia (1). However, several observations also point to antidiabetic actions of HDL (1,2). Post hoc analyses of randomized controlled trials showed that inhibitors of cholesteryl ester transfer protein, which increase HDL cholesterol by 25 to 100%, improve the glycemic control of subjects with diabetes and lower the incidence of diabetes in patients who are treated with statins (3). Infusion of artificial reconstituted HDL led to acute decreases in glucose levels and improved insulin sensitivity in subjects with diabetes (4). Mendelian randomization studies generated controversial data, with one study supporting and another disproving genetic causality of HDL for T2D (5,6). Data from genetic mouse models indicate that HDL secures both insulin production in pancreatic β-cells and insulin action in the periphery (2). The clinical exploitation of HDL in the prevention and management of diabetes—for example, the development of drugs that stimulate or mimic the antidiabetic effects of HDL or biomarkers that improve risk prediction—is hampered by the presence of hundreds of different proteins and lipid species in HDL, several of which show antidiabetic properties (7).

In this issue of *Diabetes*, Kurano et al. (8) provide evidence that at least a part of HDL's antidiabetic action involves apolipoprotein M (apoM) and its lipid ligand sphingosine-1-phosphate (S1P), two quantitatively minor components of HDL. S1P is the agonist of five G-protein–coupled receptors named S1P1, S1P2, S1P3, S1P4, and S1P5 (9). The presence of apoM is mandatory for the activation of S1P1 by S1P in endothelial cells (9) (Fig. 1). *APOM* is one of the most responsive target genes of the transcription factor HNF1α, whose gene is mutated in patients with maturity onset diabetes of the young type 3 (MODY3) (10).

In *Apom* knockout mice fed with a high-fat diet (HFD), Kurano et al. (8) found plasma levels of S1P decreased and insulin resistance of liver, muscle, and adipose tissue increased. Conversely, HFD-fed mice overexpressing human APOM showed increased plasma levels of S1P, lower blood glucose levels, and less insulin resistance. The glucose-lowering effect of the *APOM* transgene was abrogated by the treatment with an inhibitor of S1P and S1P3 but not with an inhibitor of S1P2. In liver and skeletal muscle, the phosphorylation of Akt and AMPK, i.e., two well-known downstream targets of S1P1 and S1P3 as well as insulin, was decreased in *Apom* knockout mice but increased in *APOM* transgenic mice. Concomitantly, the expression of glucose-metabolizing enzymes was oppositely altered in *Apom* knockout mice and APOM transgenic mice. Oxygen consumption and the expression of mitochondrial proteins such as Ucp2 were decreased in livers of *Apom* knockout mice but increased in livers of *APOM* transgenic mice. Cell culture experiments provided evidence that the activation of S1P1 by apoM/S1P inhibits the degradation of sirtuin 1, which is regulated by AMPK and promotes mitochondrial function (8).

Previous studies have indicated antidiabetic effects of S1P (Fig. 1). *Apom* knockout mice showed hepatic steatosis (11). Overexpression of the S1P-generating enzyme sphingosine kinase 1 (*SPHK1*) reduced muscle insulin resistance in HFD-fed mice (12). Kurano et al. (8) did not find any effect of apoM/S1P on β-cell function. However, in a previous study by the same authors, adenovirus-mediated overexpression of *APOM* in mice enhanced insulin secretion (13). Conversely, reduced S1P production by either pharmacological inhibition of SPHK or knockout of *Sphk1* led to decreases in β-cell mass and insulin secretion (14,15). Intraperitoneal S1P administration induced islet β-cell proliferation and abrogated β-cell apoptosis in mice with streptozotocin-induced diabetes (16). Ex vivo, S1P protects β-cells in isolated murine and human islets from IL-1β and glucose-induced apoptosis (17). ApoM and S1P

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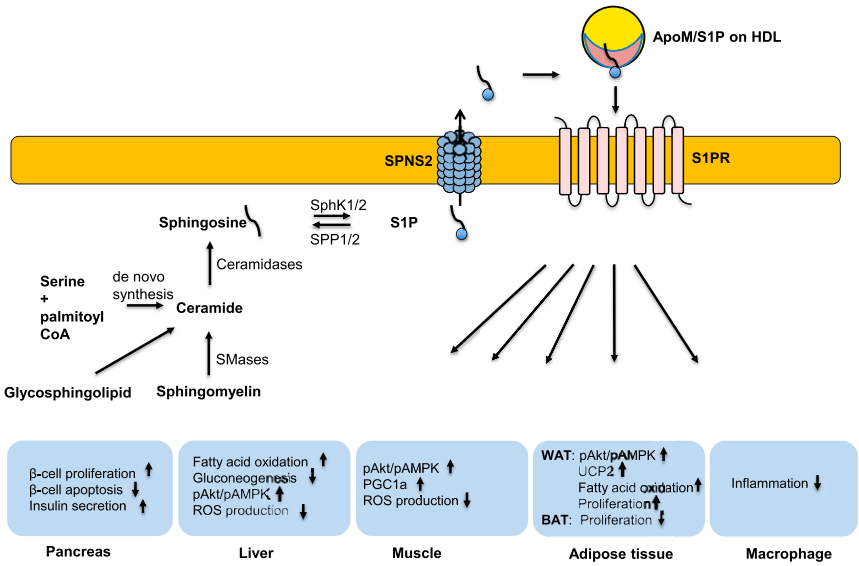

Figure 1— Biogenesis of S1P and potential role of ApoM and S1P in diabetes, obesity, and insulin resistance. Ceramides are formed either by de novo synthesis or by degradation of sphingomyelins and glycosphingolipids. Hydrolysis of the *O*-linked fatty acid by ceramidases yields sphingosine, which is phosphorylated into sphingosine S1P by sphingosine kinases 1 or 2 (SphK1/2). This phosphorylation can be reverted by S1P phosphatases 1 and 2 (SPP1/2). The intracellular S1P is effluxed by spinster homolog 2 (SPNS2). S1P-bound ApoM interacts with S1P receptors (S1PRs) to regulate various cellular functions. With respect to the regulation of glucose metabolism and insulin resistance, these functions include the promotion of pancreatic β-cell survival and insulin secretion, inhibition of glucose production in the liver, enhancement of fatty acid oxidation in liver, muscle, and adipose tissue, and inhibition of reactive oxygen species (ROS) production in hepatocytes and myocytes. Indirectly, S1P improves insulin sensitivity by suppressing inflammatory actions of macrophages. BAT, brown adipose tissue; pAkt, phosphorylated Akt; pAMPK, phosphorylated AMP-activated protein kinase; PGC1a, peroxisome proliferator–activated receptor γ coactivator 1-α; SMase, sphingomyelinase; UCP2, mitochondrial uncoupled protein 2; WAT, white adipose tissue.

can also exert additional indirect antidiabetic effects by inhibiting inflammatory actions of immune cells (9). However, some data contradict the antidiabetic actions of S1P and apoM. Compared with wild-type mice, *Apom* knockout mice are characterized by larger brown adipose tissue mass, accelerated normalization of postprandial hypertriglyceridemia, and protection from HFD-induced obesity (18). The treatment of mice with fingolimod, which inhibits all five S1P receptors and is in clinical use for the treatment of multiple sclerosis, improved both secretion and peripheral action of insulin as well as HFD-induced hepatosteatosis (19–21). Likewise, genetic interference with *S1p2* and *Sphk2* in mice resulted in improved β-cell function and insulin resistance (22,23).

When testing the relevance of their findings in humans, Kurano et al. (8) found significantly decreased plasma levels of apoM in patients with diabetes as compared with euglycemic control subjects. However, these differences were rather small. Likewise, correlations between apoM plasma levels and indices of insulin resistance were weak but statistically significant (8). Similar weak associations and correlations of apoM and S1P with T2D and measures of insulin resistance, respectively, were found in some but not all previous studies (9,24). They cannot be interpreted as any indication of causality, as both apoM and S1P levels correlate with plasma levels of HDL cholesterol and apoA-I (25) so that the decrease in HDL particle number in T2D may secondarily cause a decrease in apoM and S1P. In agreement with this, Kurano et al. (8) observed increased rather than decreased plasma levels of apoA-I, apoM, and S1P in mice with diet-induced obesity. However, the decrease of apoM levels in MODY3 patients (10) or the association of single nucleotide polymorphisms of APOM with diabetes (26) may be interpreted as initial hints to causality. Genes contributing to the metabolism, transport, and action of S1P must be tested more comprehensively for their association with diabetes to understand the role of apoM and S1P in human T2D and hence their utility as targets for the management of diabetes. Because S1P plays an important role for the function and survival of many cell types including those of the cardiovascular system and the kidney (9), it will also be interesting to test these genes for their associations with the chronic complications of diabetes.

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References

1. Vollenweider P, von Eckardstein A, Widmann C. HDLs, diabetes, and metabolic syndrome. Handb Exp Pharmacol 2015;224:405–421
2. Manandhar B, Cochran BJ, Rye KA. Role of high-density lipoproteins in cholesterol homeostasis and glycemic control. J Am Heart Assoc 2020;9:e013531

3. Masson W, Lobo M, Siniawski D, et al. Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk. Diabetes Metab 2018;44:508–513
4. Drew BG, Duffy SJ, Formosa MF, et al. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. Circulation 2009;119:2103–2111
5. Haase CL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. HDL cholesterol and risk of type 2 diabetes: a Mendelian randomization study. Diabetes 2015;64:3328–3333
6. White J, Swerdlow DI, Preiss D, et al. Association of lipid fractions with risks for coronary artery disease and diabetes. JAMA Cardiol 2016;1:692–699
7. Cardner M, Yalcinkaya M, Goetze S, et al. Structure-function relationships of HDL in diabetes and coronary heart disease. JCI Insight 2020;5:131491
8. Kurano M, Tsukamoto K, Shimizu T, et al. Protection against insulin resistance by apolipoprotein M/sphingosine-1-phosphate. Diabetes 2020;69:867–881
9. Bisgaard LS, Christoffersen C. Apolipoprotein M/sphingosine-1-phosphate: novel effects on lipids, inflammation and kidney biology. Curr Opin Lipidol 2019; 30:212–217
10. Richter S, Shih DQ, Pearson ER, et al. Regulation of apolipoprotein M gene expression by MODY3 gene hepatocyte nuclear factor-1alpha: haploinsufficiency is associated with reduced serum apolipoprotein M levels. Diabetes 2003;52:2989–2995
11. Zhang X, Zhang P, Gao J, Huang Q. Autophagy dysregulation caused by ApoM deficiency plays an important role in liver lipid metabolic disorder. Biochem Biophys Res Commun 2018;495:2643–2648
12. Bruce CR, Risis S, Babb JR, et al. Overexpression of sphingosine kinase 1 prevents ceramide accumulation and ameliorates muscle insulin resistance in high-fat diet-fed mice. Diabetes 2012;61:3148–3155
13. Kurano M, Hara M, Tsuneyama K, et al. Induction of insulin secretion by apolipoprotein M, a carrier for sphingosine 1-phosphate. Biochim Biophys Acta 2014;1841:1217–1226
14. Cantrell Stanford J, Morris AJ, Sunkara M, Popa GJ, Larson KL, Özcan S. Sphingosine 1-phosphate (S1P) regulates glucose-stimulated insulin secretion in pancreatic beta cells. J Biol Chem 2012;287:13457–13464
15. Qi Y, Chen J, Lay A, Don A, Vadas M, Xia P. Loss of sphingosine kinase 1 predisposes to the onset of diabetes via promoting pancreatic β-cell death in diet-induced obese mice. FASEB J 2013;27:4294–4304
16. He Y, Shi B, Zhao X, Sui J. Sphingosine-1-phosphate induces islet β-cell proliferation and decreases cell apoptosis in high-fat diet/streptozotocin diabetic mice. Exp Ther Med 2019;18:3415–3424
17. Rütti S, Ehses JA, Sibler RA, et al. Low- and high-density lipoproteins modulate function, apoptosis, and proliferation of primary human and murine pancreatic beta-cells. Endocrinology 2009;150:4521–4530
18. Christoffersen C, Federspiel CK, Borup A, et al. The apolipoprotein M/S1P axis controls triglyceride metabolism and brown fat activity. Cell Reports 2018;22:175–188
19. Bruce CR, Risis S, Babb JR, et al. The sphingosine-1-phosphate analog FTY720 reduces muscle ceramide content and improves glucose tolerance in high fat-fed male mice. Endocrinology 2013;154:65–76
20. Zhao Z, Choi J, Zhao C, Ma ZA. FTY720 normalizes hyperglycemia by stimulating β-cell in vivo regeneration in db/db mice through regulation of cyclin D3 and p57(KIP2). J Biol Chem 2012;287:5562–5573
21. Ravichandran S, Finlin BS, Kern PA, Özcan S. *Sphk2*$^{-/-}$ mice are protected from obesity and insulin resistance. Biochim Biophys Acta Mol Basis Dis 2019; 1865:570–576
22. Rohrbach TD, Asgharpour A, Maczis MA, et al. FTY720/fingolimod decreases hepatic steatosis and expression of fatty acid synthase in diet-induced non-alcoholic fatty liver disease in mice. J Lipid Res 2019;60:1311–1322
23. Japtok L, Schmitz EI, Fayyaz S, Krämer S, Hsu LJ, Kleuser B. Sphingosine 1-phosphate counteracts insulin signaling in pancreatic β-cells via the sphingosine 1-phosphate receptor subtype 2. FASEB J 2015;29:3357–3369
24. Memon AA, Bennet L, Zöller B, et al. The association between apolipoprotein M and insulin resistance varies with country of birth. Nutr Metab Cardiovasc Dis 2014;24:1174–1180
25. Karuna R, Park R, Othman A, et al. Plasma levels of sphingosine-1-phosphate and apolipoprotein M in patients with monogenic disorders of HDL metabolism. Atherosclerosis 2011;219:855–863
26. Niu N, Zhu X, Liu Y, et al. Single nucleotide polymorphisms in the proximal promoter region of apolipoprotein M gene (apoM) confer the susceptibility to development of type 2 diabetes in Han Chinese. Diabetes Metab Res Rev 2007;23: 21–25