



HDL and pancreatic β cells: a SMO-king gun?¹

Liam R. Brunham

Departments of Medicine and Medical Genetics, Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada

ORCID ID: 0000-0002-3686-3807

Levels of HDL cholesterol (HDL-C) are inversely correlated with risk of diabetes mellitus (1), and administration of reconstituted HDL to patients with diabetes mellitus enhances β -cell function (2). HDL protects β cells from apoptosis and inhibits the pro-apoptotic effects of LDL on islets (3). How HDL exerts these beneficial effects on β cell survival and function is unknown, but it has been hypothesized that these effects are mediated by ATP transporters, known to be critical for β -cell function (4, 5), or, alternatively, via an effect of HDL on the subcellular distribution of cholesterol and its metabolites and their interactions with various cellular receptors. In this issue of the *Journal of Lipid Research*, Yalcinkaya and colleagues provide new evidence in support of an important role of oxysterols and hedgehog signaling in mediating the effect of HDL on β -cell survival.

Using the immortalized rat β -cell line INS-1e and HDL isolated from human plasma, the authors report on an elegant series of experiments in which they used siRNA or pharmacological agents to inhibit various steps involved in cholesterol transport, metabolism, and signaling. They demonstrate that treating INS-1e cells with either HDL or CSL-111, a form of artificially reconstituted HDL and the precursor to the molecule CSL-112 currently being tested in clinical trials (6), can prevent ER stress-dependent cell death induced by the sarco/ER Ca^{2+} ATPase inhibitor thapsigargin. Silencing of either *ABCA1* or *ABCG1* abrogated the ability of HDL or CSL-111 to prevent thapsigargin-induced cell death, indicating that the sterol efflux mediated by these transporters is essential for the anti-apoptotic effect of HDL. Incubation of INS-1e cells with HDL or CSL-111 resulted in efflux of specific sterols, namely 7α -hydroxycholesterol, 7β -hydroxycholesterol, and 24- and 25-hydroxycholesterol. Interestingly, supplementing HDL with either 24- or 25-hydroxycholesterol enhanced the anti-apoptotic effects of HDL. Consistent with this observation, silencing of *CYP46A1*, which produces 24-hydroxycholesterol from cholesterol, entirely abrogated the anti-apoptotic effects of HDL on β cells. This effect could be rescued, to some extent, by supplementation with 24- or 25-hydroxycholesterol, indicating that the presence of these specific oxysterols is necessary for the anti-apoptotic effects of HDL.

Because oxysterols are known to regulate the activity of the hedgehog signaling molecule Smoothed (SMO), the authors next investigated whether SMO is required for the pro-survival effects of HDL on β cells. siRNA-mediated or pharmacological inhibition of SMO blunted the anti-apoptotic effects of HDL. Treatment of INS-1e cells with thapsigargin decreased the nuclear abundance of GLI family zinc finger 1, a transcription factor downstream of SMO, an effect that was blocked by treatment with HDL.

Collectively, these results provide detailed new insight into the mechanisms by which HDL particles exert their beneficial, anti-apoptotic effects on β cells. By demonstrating that the anti-apoptotic effects of HDL are dependent on specific oxysterols, this work also deepens our understanding of the mechanisms of lipotoxicity and its role as an important component of β cell failure in the progression of diabetes. These results also highlight the exquisite importance of cellular homeostatic regulation of not only cholesterol but also of other sterols as well as for β cell function. Finally, these results hint at a potential benefit that HDL-based therapies may have on β cells. In this regard, it is worthwhile noting that CSL-112, a derivative of the CSL-111 molecule used in this study, is currently being evaluated in the Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome (AEGIS-II) (<https://clinicaltrials.gov/ct2/show/NCT03473223>). The estimated completion date of this trial is 2022, and it is fascinating to speculate on what effects this molecule may have on glycemic parameters in humans.

Nonetheless, many caveats remain. The experiments in the present study were conducted in immortalized rat β cells. Validating the relevance of these findings in primary islets, including human cells, and in vivo will be important. In addition, although substantial preclinical and mechanistic data now link HDL with islet function, the importance of these findings for human physiology remains uncertain, and Mendelian randomization has indicated that genetically determined HDL cholesterol levels are not causally related to the risk for diabetes (7). Regardless, the results of the study by Yalcinkaya and colleagues provide intriguing insights into the cellular effects of HDL on β cells and

should reinforce our view of the multiple important physiological functions of HDL beyond atherosclerosis.^{6,7}

REFERENCES

1. von Eckardstein, A., H. Schulte, and G. Assmann. 2000. Risk for diabetes mellitus in middle-aged Caucasian male participants of the PROCAM study: implications for the definition of impaired fasting glucose by the American Diabetes Association. Prospective Cardiovascular Münster. *J. Clin. Endocrinol. Metab.* **85**: 3101–3108.
2. Drew, B. G., S. J. Duffy, M. F. Formosa, A. K. Natoli, D. C. Henstridge, S. A. Penfold, W. G. Thomas, N. Mukhamedova, B. de Courten, J. M. Forbes et al. 2009. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. *Circulation.* **119**: 2103–2111.
3. Roehrich, M. E., V. Mooser, V. Lenain, J. Herz, J. Nimpf, S. Azhar, M. Bideau, A. Capponi, P. Nicod, J. A. Haefliger, and G. Waeber. 2003. Insulin-secreting beta-cell dysfunction induced by human lipoproteins. *J. Biol. Chem.* **278**: 18368–18375.
4. Brunham, L. R., J. K. Kruit, T. D. Pape, J. M. Timmins, A. Q. Reuwer, Z. Vasanthi, B. J. Marsh, B. Rodrigues, J. D. Johnson, J. S. Parks, et al. 2007. Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. *Nat. Med.* **13**: 340–347.
5. Hou, L., S. Tang, B. J. Wu, K. L. Ong, M. Westerterp, P. J. Barter, B. J. Cochran, F. Tabet, and K. A. Rye. 2019. Apolipoprotein A-I improves pancreatic beta-cell function independent of the ATP-binding cassette transporters ABCA1 and ABCG1. *FASEB J.* **33**: 8479–8489.
6. Diditchenko, S., A. Gille, I. Pragst, D. Stadler, M. Waelchli, R. Hamilton, A. Leis, and S. D. Wright. 2013. Novel formulation of a reconstituted high-density lipoprotein (CSL112) dramatically enhances ABCA1-dependent cholesterol efflux. *Arterioscler. Thromb. Vasc. Biol.* **33**: 2202–2211.
7. Haase, C. L., A. Tybjaerg-Hansen, B. G. Nordestgaard, and R. Frikke-Schmidt. 2015. HDL cholesterol and risk of type 2 diabetes: a Mendelian randomization study. *Diabetes.* **64**: 3328–3333.