Title: Genetics and molecular biology: HDL-endoplasmic reticulum connection and cholesterol sensor.
Authors: Widmann C
Journal: Current opinion in lipidology
Year: 2013 Feb
Volume: 24
Issue: 1
Pages: 103-4
DOI: 10.1097/MOL.0b013e32835c7b49

Genetics and molecular biology: HDL-ER connection and cholesterol sensor

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Word counts: 555

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There is accumulating evidence indicating that HDLs improve the functionality of pancreatic beta cells and the insulin sensitivity of peripheral tissues (e.g. skeletal muscle, liver). A very recent review [1] discusses the data supporting a protective role of HDLs in these tissues and the consequence that this may have on diabetes development. Oddly, this review does not mention the now amply demonstrated anti-apoptotic function exerted by HDLs on pancreatic beta cells [2;3]. Since beta cell apoptosis contributes to the development of type 2 diabetes [4], understanding the pro-survival function of HDLs in beta cells is of particular importance. A study published a few months ago uncovered a link between HDL and the functionality of the endoplasmic reticulum (ER) in beta cells. This work shows that HDLs prevent beta cell death induced by various ER stressors, such as palmitate, ER overload, or the sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitor thapsigargin, by maintaining the functionality of the ER in terms of protein folding and protein trafficking [●●5]. This is of interest because ER stress is a likely important contributor to the development of type 2 diabetes [6]. The beneficial role of HDLs on pancreatic beta cells can therefore be multiple. Firstly, by favoring their insulin secretory capacity, possibly via a concerted, still ill-defined, action on specific cholesterol transporters [7]. Secondly by decreasing the cholesterol load in beta cells, although it should not be forgotten that cholesterol levels need to be adequately maintained in the ER for proper insulin export in beta cells [8]. Thirdly by preserving the functionality of the ER [5]. This last effect, as mentioned above, appears to be required for the anti-apoptotic activity of HDLs against some ER stressors (e.g. palmitate) but should also help the beta cell synthesize and secrete insulin more efficiently. Most of the studies allowing these conclusions to be drawn do not provide mechanistic insights as to how this proceeds. The challenge in the field is now to

identify the molecular players that mediate the beneficial effects of HDLs in beta cells.

In beta cells, HDLs exert their protective functions independently of scavenger receptor class B, type I (SR-BI) [5;9]. In endothelial cells, in contrast, SR-BI mediates HDL signaling leading to Akt activation and eNOS stimulation [10;10], which is thought to mediate the beneficial effects of HDLs in these cells [11;12]. How HDLs mediate these signaling events had been unclear for many years. A logical possibility was that HDLs or HDL components directly activated SR-BI to stimulate its signaling activity. A series of elegant experiments using a point mutant of SR-BI that cannot interact with cholesterol in the plasma membrane [●●13] now indicate that this assumption was incorrect. What activates SR-BI signaling is a reduction in plasma membrane cholesterol levels. Hence, the ability of HDLs to activate SR-BI comes from their capacity to promote cholesterol efflux from the plasma membrane. Cholesterol efflux can be mediated when HDLs dock to SR-BI leading to SR-BI activation but it is not the docking per se that is involved in the stimulation of the receptor but rather the decrease in cholesterol in the vicinity of SR-BI [●●13]. The physiological function of the cholesterol sensing capacity of SR-BI will now need to be addressed and, in this context, generation of KI mice expressing the SR-BI receptor mutant that cannot sense plasma membrane cholesterol is eagerly awaited!

Acknowledgements

I thank Nicholas Broskey for critical reading of the manuscript. C.W. is supported by grants from the Swiss National Science Foundation (n°31003A_141242/1) and the Swiss Cancer League (n° KFS-02543-02-2010).

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The mechanisms by which HDLs protect beta cells are obscure. The molecules and proteins involved in this protection still await characterization. The merit of this study is that it defines the connection of HDLs with an important cellular function of beta cells, namely protein folding and trafficking in the endoplasmic reticulum. HDLs have the capacity to maintain the functionality of the ER, despite the presence of various stresses, and this appears to be required for the HDL-mediated protective functions in beta cells, at least in response to some pro-diabetogenic stresses such as palmitate. Based on these findings, it may be worth investigating in the future whether HDLs have the capacity to modulate the activity of the proteins and molecules that mediate or control the functionality of the ER.

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This work shows that the carboxy-terminal transmembrane segment of SR-BI, which has a cholesterol-binding capacity, is required for SR-BI's ability to signal in response to HDLs (e.g. activation of eNOS in endothelial cells and stimulation of the p38 MAPK pathway in enterocytes). What this study convincingly demonstrates is that HDLs are not direct activators of SR-BI. They do stimulate the receptor though by inducing a local decrease in plasma membrane cholesterol that is then sensed by the carboxy-terminal transmembrane domain of SR-BI. This sensing leads to the stimulation of the receptor's signaling activity. Hence, this work provides key structural information on the signaling property of SR-BI and clarifies the role played by HDLs in this process. The new paradigm that this study establishes is that SR-BI monitors the extent of cholesterol depletion resulting, for example, from HDL-mediated efflux. Once the decrease in plasma membrane cholesterol reaches a certain threshold, SR-BI activates a series of signaling events that regulate various cell type-specific functions and, presumably, that also contribute to cellular cholesterol homeostasis.

Further recommended reading

Belalcazar LM, Lang W, Haffner SM, Hoogeveen RC, Pi-Sunyer FX, Schwenke DC, Balasubramanyam A, Tracy RP, Kriska AP, Ballantyne CM: **Adiponectin and the mediation of HDL cholesterol change with improved lifestyle: The Look AHEAD Study**. *J.Lipid.Res.* 2012.

Adiponectin is a hormone secreted by the adipose tissues that favors insulin sensitivity. The study by Belalcazar and colleagues now shows that adiponectin levels are significantly associated with HDL-C levels in individuals who are improving their lifestyle by decreasing caloric intake and by increasing physical activity (Look AHEAD study; see https://www.lookaheadtrial.org). Therefore, it appears that adiponectin levels are correlated with HDL levels in humans, confirming earlier data obtained in mice. The authors suggest that this association results from the capacity of adiponectin to increase the expression of proteins involved in HDL formation (e.g. ApoAI and ABCA1). With this interpretation, changes in HDL levels would be secondary to a rise in adiponectin levels. However, the reverse may just be as correct, i.e. increase in HDL levels leads to higher circulating adiponectin levels. This latter interpretation derives from the observation that increasing HDL levels by ApoAI infusion in mice led to an augmentation in circulating levels of adiponectin (Atherosclerosis 2010, 210:438-444). If this is what really happens, it would give HDLs another recognized means of exerting their beneficial action in humans: increasing circulating levels of adiponectin to favor insulin sensitivity. Whatever the reasons for the association of HDL and adiponectin levels in the blood, the study of Belalcazar and colleagues provides yet another good argument that lifestyle improvement brings tractable benefits to individuals.