Altered metabolism with excess provision of lipid substrates may be a major pathogenetic factor linking diabetes with cardiovascular disease—lipoprotein lipase (LPL) being one facilitator of such a process (1,2). Hyperlipidemia, by itself, plays a major role in lipid-provoked cardiovascular pathologies, largely mediated through LPL (3). Under physiological state, due to their presence on the endothelial cell surface, LPLs break down triglyceride lipoproteins in the circulation and provide tissues, like heart and skeletal muscle, with the required fatty acid substrates to derive ATP (3,4). A large volume of data, using genetically manipulated animal models and clinical studies, has found that LPL homeostasis is required for normal cardiac metabolism and function (5,6). In diabetes, increased metabolic demand of the heart is met by the breakdown of fatty acids by coronary LPL. LPL is produced by cardiomyocytes, which need endothelial-derived heparanase for LPL production. In this issue, Wang et al. (7) demonstrated that endothelial heparanase is taken up by the cardiomyocytes through caveolae and is converted to an active form in the lysosomal compartments of these cells. Endothelium-derived heparanase is instrumental for cleaving and releasing LPL from the heparan sulfate proteoglycans on the cardiomyocyte cell surface. Activated heparanase further translocates in the nucleus, increases histone acetylation, and augments matrix metalloproteinase-9 (MMP-9) production. Although this is an adaptive mechanism, increased MMP-9 may act as a mediator of lipotoxicity in chronic diabetes. To this extent, the authors show that MMP-9 degrades the myocyte surface proteoglycan, syndecan-1. This is a key finding that explains how a vicious cycle of events is stimulated following endothelial exposure to hyperglycemia and thus turning on an endothelial—cardiomyocyte cross talk through the mediation of heparanase.

Earlier studies in this area were focused on the transcription of LPL gene and regulation of this protein in the cardiac tissue in metabolic stress (8). Only in the past decade has interest grown in the mechanism of LPL shuttling from cardiomyocytes to the endothelial barrier surface, where it performs triglyceride breakdown. The same group has previously shown that there was an increased occupancy of LPL on the capillary endothelial cells in streptozotocin-induced diabetic animals (2). However, the exact signaling mechanism, which pushes LPL from cardiomyocyte to the membrane surface of endothelial cells, was not evident. Earlier studies from this group further showed that activation of AMPK-p38 MAP kinase leading to heat-shock protein 25 (Hsp25) phosphorylation and F-actin polymerization plays a role in recruiting LPL from cardiomyocyte inner side to the membrane surface (9). They further demonstrated the process of vesicular fission from the Golgi bodies, where the mature enzyme is emitted (10). A common target for both the processes was found to be Hsp25 (9,10). Phosphorylation of Hsp25 detaches it from protein kinase Cδ (PKCδ); the dissociated PKCδ activates downstream molecule protein kinase D, with subsequent stimulation of vesicular fission of LPL and transport to the membrane surface (10).

Although information on how a cardiomyocyte surface LPL could reach the endothelial surface remained a mystery, several consequences of heparanase release were identified. Wang et al. (11) previously showed that the active form of heparanase, derived from the endothelial cells, helps in cleaving and releasing LPL from the heparan sulfate proteoglycans on cardiomyocyte cell surface, whereas the inactive form serves in bringing the intracellular LPL pool to the membrane surface following RhoA activation. Active heparanase also was found to release vascular endothelial growth factor (VEGF) from the same proteoglycan holder (12). The released VEGF may stimulate an autocrine signaling by signaling through VEGF receptors present on the cardiomyocyte cell surface, turning on the
AMPK-p38 MAP kinase pathway and rearranging cytoskeleton to propagate the LPL vesicles from inside of cardiomyocytes to the outer membrane (12). Wang et al. (7) showed that heparanase augments cellular transcriptional machinery through increased histone acetyl transferase (HAT) activity (Fig. 1). However, the exact mechanism of how such a process stimulates HAT activity needs further characterization. This study further suggests that endoglycosidase heparanase could be a potential therapeutic target in diabetes-induced cardiovascular diseases. Interestingly, the heparanase inhibitor, PI-88, in NOD mice (a model of type 1 diabetes) prevents reactive oxygen species generation and destruction of islet heparan sulfate (13).

The majority, if not all, of chronic diabetes complications is triggered by glucose-induced damage to the endothelial cells (14). However, the effects of hyperglycemia-mediated endothelial abnormalities causing cellular changes may be organ-specific, possibly dictated by cellular constituents and functions peculiar to the specific organ. Wang et al. (7) explain how a cycle of events is initiated by hyperglycemia and turns on an endothelial–cardiomyocyte cross talk. The authors have raised additional interesting scientific questions; e.g., Are similar mechanisms important in long-term diabetes? Is this mechanism also important in type 2 diabetes? We need additional carefully designed studies to answer these questions. Nevertheless, data from this study suggest that targeting endothelial cells may be a rational approach for the development of adjuvant therapy for diabetic cardiovascular complications.

Amid these advancements in knowledge we still face some challenges as cardiomyocytes are also neighbored by cells like vascular smooth muscle cells, fibroblasts, monocytes, and even adipose tissue. It would be really tough to differentiate and compartmentalize the contributions of these cell types as they are also known to secrete growth factors, reactive oxygen/nitrogen species, cytokines, and proteinases. A better understanding of how these different

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**Figure 1** — A diagrammatic outline of the mechanism of endothelial-derived heparanase-mediated regulation of cardiomyocyte lipid uptake and toxicity. Metabolic defect in hyperglycemia starts cross talk between neighboring endothelial cells and cardiomyocytes through the release of an endoglycosidase called heparanase. Heparanase cleaves the cardiomyocyte surface inhabiting heparan sulfate proteoglycans (HSPG), thus releasing LPL and VEGF. This released VEGF turns on VEGF receptor signaling, and through the mediation of p38MAP kinase-Hsp25 and cytoskeletal rearrangement, it stimulates the membrane translocation of LPL. Latent heparanase gets inside the cardiomyocytes and gets activated to active form by a lysosomal-mediated pathway. This active heparanase enters the nucleus and increases transcription of other matrix proteinases, like MMP-9, through augmented HAT activity. MMP-9 cleaves (dashed line) the cell surface matrix component, perhaps allowing syndecan-1 to alter the structural integrity. It is also possible that other cells, e.g., fibroblasts, vascular smooth muscle cells, also may contribute to such cell-to-cell communication. A-HS, active heparanase; L-HS, latent heparanase; VEGFR, VEGF receptor.
cell types communicate in normal physiology and various pathologies would help us in repairing the miscommunication and developing specific treatments for chronic diabetes complications.

Acknowledgments. The author thanks Dr. P. Puthanveetil, Pathology Department, Western University, for help with preparing the manuscript.

Funding. This work was partially funded by Heart and Stroke Foundation of Canada (grant G-13-0003041).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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