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Deoxysphingolipids: β-Cell, Beware of These New Kids on the Block

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Recent estimates by the International Diabetes Federation suggest that the incidence of diabetes soared to an all-time high of 382 million in 2013, compared with 371 million in 2012. The federation predicts that by 2035 the number of individuals afflicted with this disease will increase to 592 million. Furthermore, an alarmingly high number of individuals (~175 million) is as yet undiagnosed (1). Therefore, efforts to understand the pathophysiology of diabetes are critical for forward movement toward development of novel therapeutic strategies for this disease. Against this backdrop, original investigations by Unger and colleagues (2,3) suggested that chronic exposure and stimulation of the islet β-cell to glucose (glucotoxicity) or free fatty acids (FFAs) (lipotoxicity) result in β-cell dysfunction. Numerous studies using both in vitro and in vivo models have implicated ceramide, a sphingolipid derived from palmitate, in islet dysfunction and death (4–6). Sphingolipids have also been implicated in the metabolic dysfunction of cells and tissues that are also associated with hypertension and atherosclerosis (7,8).

Recently, Othman et al. (9) reported significantly higher plasma levels of deoxysphingolipids (1-deoxySLs) in patients with metabolic syndrome, suggesting that these atypical sphingolipids might serve as biomarkers for diagnosis and treatment of these patients. It has been shown that mutations in genes encoding specific subunits of serine palmitoyl transferase (SPT), which mediates the de novo biosynthesis of ceramide from palmitoyl CoA and serine, lead to alterations in the amino acid specificity of SPT from serine to alanine (9). From a cellular standpoint, 1-deoxySLs do not undergo the canonical sphingolipid degradation pathway; rather, they accumulate intracellularly and adversely affect cellular metabolism and function (9,10). It has been demonstrated that 1-deoxySLs are cytotoxic in various model systems, and more important, they are implicated in the pathology of neuronal functional impairment in hereditary sensory and autonomic neuropathy in patients with type 1 diabetes (HSAN1) (10).

In this issue, Zuellig et al. (11) provide the first direct evidence implicating 1-deoxySLs in induction of metabolic dysfunction of insulin-secreting Ins-1 cells and primary rodent islets. They report that exposing these cells to 1-deoxysphinganine (dSA) induced significant defects in glucose-stimulated insulin secretion (GSIS), cellular dysfunction, and cell death. dSA also promoted activation of Rac1, a small G-protein, and caused alterations in cytoskeletal makeup, including intracellular accumulation of F-actin, and activation of stress kinases. Evidence is also presented that indicates upregulation of ceramide synthase 5 activity in dSA-treated cells resulted in its conversion to 1-deoxydihydroceramide. Pharmacological inhibition of intracellular trafficking of sphingolipids partially restored the cytotoxic effects of dSA. Together, these findings demonstrate that dSA and its metabolic intermediate 1-deoxydihydroceramide exert deleterious effects on islet β-cell function, including inhibition of GSIS and induction of loss in metabolic cell viability. These observations are both novel and timely. It is noteworthy that the cytotoxic effects of dSA are demonstrable at much lower concentrations (1–5 μmol/L) compared with known cellular effects of cell permeable analogs of ceramide (10–50 μmol/L) and FFAs (0.1–0.5 mmol/L). Based on their longer half-lives (due to limited intracellular degradation), 1-deoxySLs indeed represent a novel class of biolipids that induce metabolic stress and defects in the islet β-cell. Interestingly, cellular effects of 1-deoxySLs, ceramides, and FFAs appear to involve activation of overlapping signaling pathways including activation of Rac1, stress kinases, and caspase-3 culminating in cell death (Fig. 1).

Taken together, the observations by Zuellig et al. (11) offer significant advances in the area of sphingolipid-induced metabolic dysregulation and demise of the islet β-cell. Future

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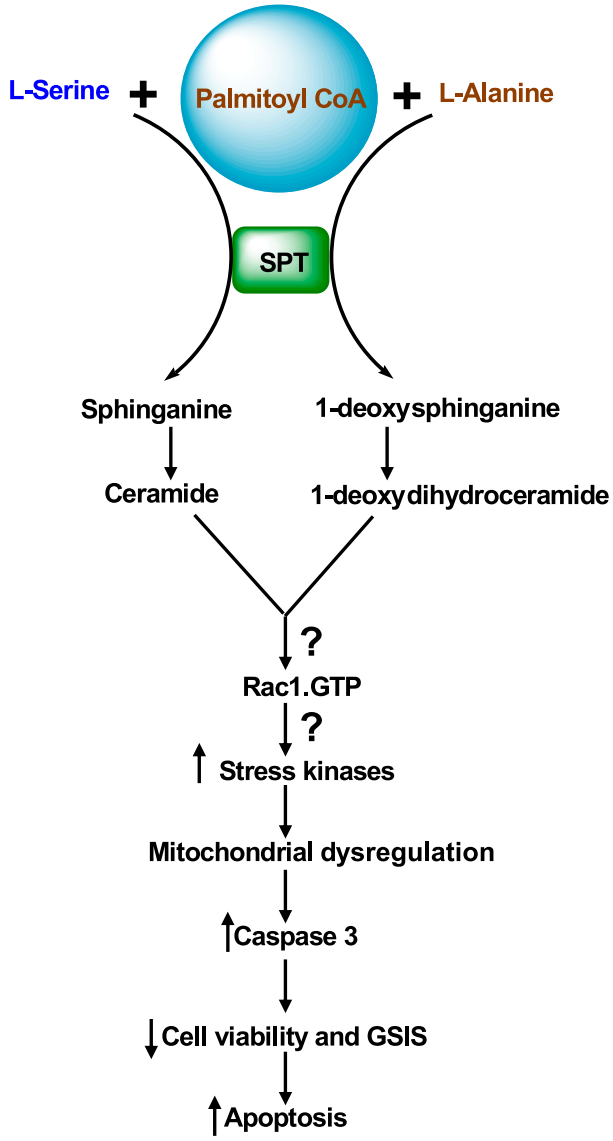

Figure 1—Current findings of Zuellig et al. (11) lend further support to the long-held hypothesis that sphingolipids play key regulatory roles in the pathology of type 1 and type 2 diabetes and associated complications in target tissues. Their findings identify novel signaling mechanisms involved in dSA-induced metabolic dysfunction of the islet β-cell. 1-DeoxySLs (1–5 μmol/L) elicit significant deleterious effects on β-cell function and survival. Interestingly, Rac1 activation appears to be a common signaling step in FFAs, ceramides, and 1-deoxySL–mediated effects. This schematic provides an overview of signaling steps involved in the effects of these biolipids. Additional studies, including in human islets, are needed to further validate this model. Also, not shown here, are additional as-yet-unknown signals derived from high glucose treatment conditions that appear to augment the cytotoxic effects of 1-deoxySLs as shown by Zuellig et al. (11). Rac1.GTP, active form of Rac1.

studies will undoubtedly validate this model and the significance of the findings. Ideally, these findings will need to be reproduced in human islets to demonstrate their translational significance. It is hoped that future studies will decipher the intermediate signaling steps that couple the Rac1-p38 MAP kinase-Caspase-3 cascade in the onset of β-cell metabolic dysfunction under conditions of dSA-induced stress. One attractive candidate is phagocyte-like NADPH oxidase that is activated in islet β-cells following exposure to high glucose, FFAs, ceramides, and proinflammatory cytokines (12–15). Moreover, high glucose, FFAs, cytokines, and ceramides have been shown to activate Rac1 (13,14,16–19), a member of the NADPH oxidase holoenzyme complex. These points need to be addressed further. As appropriately pointed out by the authors, elevated levels of 1-deoxySLs in patients with HSAN1 and metabolic syndrome do not result in overt diabetes. This suggests that additional metabolic signals, presumably derived from established chronic hyperglycemia (glucotoxicity), may be necessary to elicit maximal damaging effects of 1-deoxySLs on the islet β-cell. From a therapeutic standpoint, recent findings by Garofalo et al. (20) demonstrated a significant reduction in the production of neurotoxic 1-deoxySLs in mice and humans with HSAN1 following oral supplementation of L-serine. This intervention improved motor and sensory performance indices in mice, suggesting that channeling the sphingolipid biosynthetic pathway away from 1-deoxySLs via serine supplementation might prove to be beneficial. Similar approaches can be tested in the model systems used by Zuellig et al. (11) to further validate this model in the context of 1-deoxySL–induced metabolic dysfunction. It should be noted that although these studies are focused on the islet β-cell, it is likely that this class of cytotoxic sphingolipids might exert unfavorable effects and induce metabolic dysfunction in other cell types and target tissues, a consideration that has potential implications for conditions other than diabetes. In conclusion, the findings reported in the study by Zuellig et al. (11) will likely serve as stepping stones for immediate investigations in this area. Pursuit of this line of investigation will not only promote further understanding of underlying metabolic signaling cascades, but it will also aid in identification of novel drug targets to halt β-cell dysfunction and the onset of diabetes and associated complications.

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