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β Cell Dysfunction in Type 2 Diabetes: Drained of Energy?

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Type 2 diabetes is a progressive disorder, but exactly how the progression occurs remains unknown. In this issue of *Cell Metabolism*, Zhang et al. (2019) present evidence that diabetes, via hyperglycemia, leads to aberrant insertion of a mitochondrial ion channel in the plasma membrane, rendering it leaky to key intracellular signaling molecules with resultant suppression of insulin secretion.

The β cells of the pancreatic islets play a central role in systemic metabolism by secreting insulin, the body's only hormone lowering plasma glucose. Systemic glucose homeostasis reflects the balance between β cell insulin secretion and insulin sensitivity of glucose-storing organs. Type 2 diabetes results from a mismatch of the β cells' capacity to secrete insulin and an increasing systemic requirement for this hormone. Initially, the β cells are capable of increasing insulin output in the face of insulin resistance, but ultimately hyperglycemia results, moderate to begin with but then more severe as β cell function and mass decline (Weir and Bonner-Weir, 2004).

The mechanisms underlying the progressive deterioration of β cell function in type 2 diabetes remain to be established. The decline has been attributed to a variety of external factors such as low-grade inflammation (Imai et al., 2013) and increased pancreatic fat (Taylor et al., 2018). However, recent evidence implicates hyperglycemia as a crucial factor, but the precise molecular mechanism remains enigmatic (Ashcroft et al., 2017).

Zhang et al. now report, in a tour de force study involving islets from >30 human islet preparations (15 with type 2 diabetes), that type 2 diabetes is associated with increased expression of the mitochondrial voltage-dependent anion channel (VDAC1) in β cells. They elegantly demonstrate that there is a positive correlation between long-term plasma glucose (HbA1C) and the expression of VDAC1, finding that some of these channels erroneously end up in the plasma membrane, which culminates in (1) impaired oxidative glucose metabolism with (2) consequential loss of glucose-induced insulin secretion (GIIS) and (3) increased cell death.

From the data presented, it appears that there may be a single, as unexpected as elegant, explanation to these diverse disturbances (Figure 1).

VDAC1 is the most abundant protein in the outer mitochondrial membrane, where its main purpose is to shuttle adenine nucleotides between the mitochondria and cytosol (Colombini, 2012). Mitochondrial ATP production plays a key role in β cell stimulus-secretion coupling: an increase in the cytoplasmic ATP/ADP ratio stimulates electrical activity and insulin secretion by closing ATP-regulated K^+ (K_{ATP}) channels (Rorsman and Ashcroft, 2018).

Zhang et al. now demonstrate that diabetic β cells "leak" ATP and that this is mediated by plasmalemmal VDAC1. In quantitative terms, the amounts of ATP released via VDAC1 are impressive: >100,000 molecules of ATP released per cell every second! A similarly high figure can be estimated from electrophysiological measurements, which also provides the important observation that VDAC1 is normally absent from the plasma membrane. Clearly, loss of ATP at this rate is unsustainable and the resultant depletion of cytoplasmic ATP will be associated with opening of the K_{ATP} channels and suppression of GIIS.

However, VDAC1 is not only permeable to adenine nucleotides; it is also highly permeable to the glucose metabolite pyruvate and Krebs cycle intermediates such as succinate and citrate (Colombini, 2012). Loss of these compounds via plasmalemmal VDAC1 channels provides a simple explanation for the reduction of oxidative metabolism the authors observe, an effect further exacerbated by the tonic leakage of ATP through the membrane.

VDAC1-mediated loss of the Krebs cycle intermediates will ultimately require their replenishment by deamination of amino acids obtained by breakdown of proteins, which may compromise cell survival and explain the increased cell death. This is consistent with the reduction of insulin content in islets from donors with type 2 diabetes (Rosengren et al., 2012). This scenario resolves a paradox: overexpression of VDAC1 only increases cell death when the cells are cultured at high glucose (20 mM), but not under normoglycemic conditions (5 mM), although the rates of ATP release are not so different. This is because glucose metabolism in the β cell is much slower at low glucose concentrations, thus limiting the requirement of anaplerotic replenishment of the Krebs cycle intermediates.

The observation that VDAC1-mediated ATP release is associated with inhibition of insulin secretion might seemingly be in contradiction to previous reports that ATP stimulates insulin secretion (Khan et al., 2014). However, there are important differences between the effects of physiological ATP release during insulin granule exocytosis and the pathological ATP leakage now reported. In the former case, ATP is released when the K_{ATP} channels are largely closed and the small depolarizing currents, due to activation of P2X and/or P2Y receptors, stimulate electrical activity. This does not happen when intracellular ATP is low, due to leakage of ATP out of the β cells. Under these conditions, high K_{ATP} channel activity will clamp the membrane potential at −80 mV (the

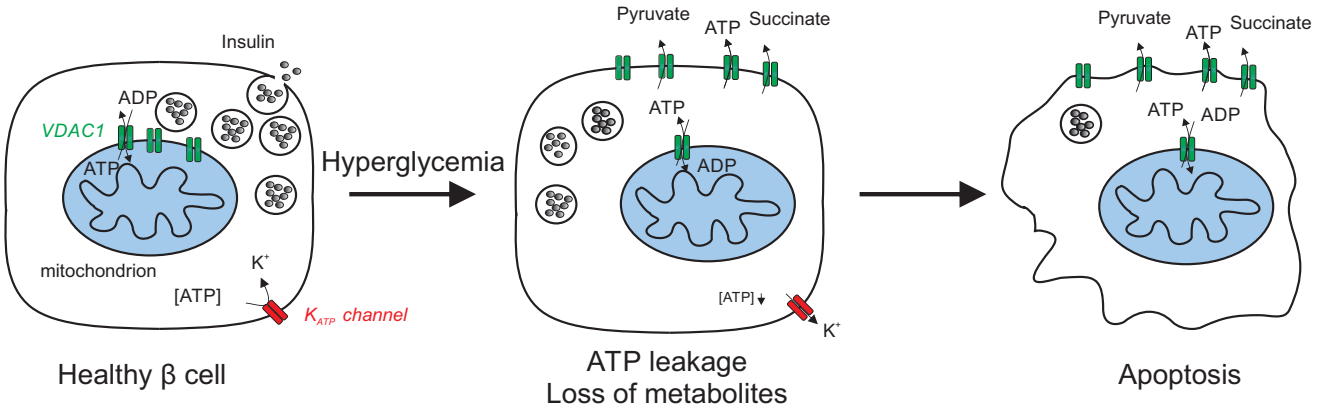

Figure 1. VDAC1 and the Progression of β Cell Dysfunction in Type 2 Diabetes

Under normoglycemic conditions (left), expression of voltage-gated anion channel 1 (VDAC1; green) in β cells is restricted to the outer mitochondrial membrane. When hyperglycemia develops (middle), β cells upregulate the expression of VDAC1. Some of the VDAC1s become mistargeted to the plasma membrane, leading to the exit of adenine nucleotides, pyruvate, Krebs cycle intermediates (such as succinate), and other low-molecular-weight glucose metabolites. This interferes with glucose metabolism and oxidative ATP production, effects compounded by loss of ATP via VDAC1. The fall in intracellular [ATP] leads to the opening of ATP-regulated K^+ channels (K_{ATP}), membrane repolarization, and inhibition of insulin secretion. VDAC1-mediated loss of Krebs cycle intermediates activates anaplerotic processes, ultimately requiring protein breakdown, culminating in apoptosis (and before that, a progressive reduction of insulin content; illustrated by fewer insulin granules; right).

K^+ equilibrium potential), which is too negative for electrical activity and secretion to occur, and ATP-induced depolarizing membrane currents will be ineffective.

These data are of immediate therapeutic significance. The authors show that both GIIS and intracellular ATP content are corrected *in vitro* when islets from donors with type 2 diabetes are treated with inhibitors of VDAC1. They also find that treatment of diabetes-prone *db*/*db* mice with an agent inhibiting VDAC1 activity prevented diabetes but that hyperglycemia quickly developed once treatment was discontinued.

Intriguingly, the authors also show that plasmalemmal VDAC1 channels are blocked by metformin, an antidiabetic medication used since the 1950s but whose mechanism of action has only partially been resolved. Metformin has been proposed to act by inhibition of AMP-dependent protein kinase (AMPK), but it is clear that not all effects are AMPK dependent (Rena et al., 2017). The observation that metformin, by blocking VDAC1, exerts a direct effect on the β cell function rather than insulin action is in fact supported by a recent clinical study (Retnakaran et al., 2018). It is perhaps surprising that this effect has escaped detection for so long, but if these observations can be confirmed, it clearly opens exciting therapeutic opportunities.

Finally, it deserves pointing out that diabetes and hyperglycemia ultimately affect every cell of the body. It remains to be determined whether this effect is confined to the β cells or if similar mechanisms contribute to the wide spectrum of diabetes complications (Zheng et al., 2018).

REFERENCES

Ashcroft, F.M., Rohm, M., Clark, A., and Brereton, M.F. (2017). Is type 2 diabetes a glycogen storage disease of pancreatic β cells? Cell Metab. *26*, 17–23.

Colombini, M. (2012). VDAC structure, selectivity, and dynamics. Biochim. Biophys. Acta *1818*, 1457–1465.

Imai, Y., Dobrian, A.D., Morris, M.A., and Nadler, J.L. (2013). Islet inflammation: a unifying target for diabetes treatment? Trends Endocrinol. Metab. *24*, 351–360.

Khan, S., Yan-Do, R., Duong, E., Wu, X., Bautista, A., Cheley, S., MacDonald, P.E., and Braun, M. (2014). Autocrine activation of P2Y1 receptors couples Ca (2+) influx to Ca (2+) release in human pancreatic beta cells. Diabetologia *57*, 2535–2545.

Rena, G., Hardie, D.G., and Pearson, E.R. (2017). The mechanisms of action of metformin. Diabetologia *60*, 1577–1585.

Retnakaran, R., Choi, H., Ye, C., Kramer, C.K., and Zinman, B. (2018). Two-year trial of intermittent insulin therapy vs metformin for the preservation of β-cell function after initial short-term intensive insulin induction in early type 2 diabetes. Diabetes Obes. Metab. *20*, 1399–1407.

Rorsman, P., and Ashcroft, F.M. (2018). Pancreatic β-cell electrical activity and insulin secretion: of mice and men. Physiol. Rev. *98*, 117–214.

Rosengren, A.H., Braun, M., Mahdi, T., Andersson, S.A., Travers, M.E., Shigeto, M., Zhang, E., Almgren, P., Ladenvall, C., Axelsson, A.S., et al. (2012). Reduced insulin exocytosis in human pancreatic β-cells with gene variants linked to type 2 diabetes. Diabetes *61*, 1726–1733.

Taylor, R., Al-Mrabeh, A., Zhyzhneuskaya, S., Peters, C., Barnes, A.C., Aribisala, B.S., Hollingsworth, K.G., Mathers, J.C., Sattar, N., and Lean, M.E.J. (2018). Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. Cell Metab. *28*, 667.

Weir, G.C., and Bonner-Weir, S. (2004). Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes *53* (*Suppl 3*), S16–S21.

Zhang, E., Mohammed Al-Amily, I., Mohammed, S., Luan, C., Asplund, O., Ahmed, M., Ye, Y., Ben-Hail, D., Soni, A., Vishnu, N., et al. (2019). Preserving insulin secretion in diabetes by inhibiting VDAC1 overexpression and surface translocation in β cells. Cell Metab. *29*, this issue, 64–77.

Zheng, Y., Ley, S.H., and Hu, F.B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. *14*, 88–98.