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COMMENTARY

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Imeglimin is a novel, first-in-class small molecule tetrahydrotriazine that ameliorates hyperglycemia in preclinical studies and clinical trials in patients with type 2 diabetes mellitus. It received its first approval for clinical use as an oral anti-diabetic agent in Japan in 2021. Although it has a chemical structure similar to metformin, imeglimin acts on the pancreas as well as the liver and muscle[1]. Previous studies on human and animal models show that imeglimin enhances glucose-induced insulin secretion (GIIS), reduces hepatic glucose production, and improves glucose uptake by muscle[1,2]. Despite its promising properties to improve glycemic control in type 2 diabetes mellitus, little is known regarding the mechanisms by which imeglimin exerts its favorable effects on pancreatic β-cells. Recently, several preclinical reports have shed light on the underlying mechanism of imeglimin action on pancreatic β-cells (Figure 1): while the drug optimizes glucose-induced insulin secretion and insulin production, it also attenuates the loss of β-cell mass (BCM) by improving their mitochondrial structure and function in a type 2 diabetes mouse models[3,4]. The preservation of β-cell mass may be mainly due to inhibition of β-cell apoptosis by modulation of endoplasmic reticulum (ER) stress-related and mitochondria-mediated pathways[4,5].

Enhancement of glucose-induced insulin secretion by imeglimin has been found in studies using both rodent and human islets[6,7]. Batch-incubation studies demonstrated that imeglimin amplified glucose-induced insulin secretion in isolated islets of Goto-Kakizaki rats, C57BL/6J mice, and db/db mice[3,6,7] by enhancing a salvage pathway and increasing glucose-induced production of intracellular nicotinamide adenine dinucleotide (NAD^+) *via* nicotinamide phosphoribosyltransferase (NAMPT)[6,7]. NAD^+ metabolism *via* adenosine diphosphate (ADP) ribosyl cyclase/cyclic ADP ribose (cADPR) hydrolase (CD38) generates second messengers such as cADPR and/or NAADP[6,7], which are involved in Ca^{2+} release from the ER and insulin granule exocytosis. This pathway is distinct from that of earlier anti-diabetic agents such as G protein-coupled receptor 40 agonist, which activate a phospholipase C pathway to enhance glucose-induced insulin secretion. In addition, Funazaki *et al.*[7] reported that imeglimin might well activate the transient receptor melastatin 2 (TRPM2) channel, a non-selective cation channel (NSCC), to increase the NSCC current and thus enhance glucose-induced insulin secretion in pancreatic β-cells. Imeglimin increased NSCC currents in isolated islets of C57BL/6J mice, but the currents were abolished, and enhanced glucose-induced insulin secretion by imeglimin did not occur in islets from TRPM2-KO mice. As cADPR is a potent opener and/or promoter of TRPM2, and cADPR can bind and activate TRPM2 channels, the cADPR-TRPM2 pathway may well be partly responsible in the amplification of glucose-induced insulin secretion by imeglimin. Consistent with preclinical indications of imeglimin-induced enhancement of glucose-induced insulin secretion, 7 day administration of imeglimin was found to increase glucose-induced insulin secretion in patients with type 2 diabetes mellitus[2]. It was reported that treatment with imeglimin reduced the ratio of proinsulin/insulin and improved the amelioration of β-cell dysfunction in a clinical setting[2].

Evidence of the action and effects of imeglimin on the mitochondria of pancreatic β-cells has accumulated recently; for example, several studies have demonstrated imeglimin preservation of mitochondrial function and morphology in pancreatic β-cells of type 2 diabetes mellitus model mice[3,4]. In db/db mice, a 1 week *in vivo* administration of imeglimin restored the mitochondrial membrane potential (MMP) level in islets while vehicle administration did not[4]. Interestingly, *in vivo* imeglimin administration resulted in a higher MMP level in islets than that by insulin glargine; db/db mice receiving insulin glargine showed a comparable blood glucose level to those receiving imeglimin, while insulin glargine also restored islet MMP level compared with that by vehicle administration. This is consistent with *ex vivo* observations; a significant decrease of MMP in islets incubated in 33.0 mM glucose compared with those incubated in 11.1 mM glucose was found. Even so, addition of imeglimin to 33.0 mM glucose was found to partly restore MMP in islets[4]. These findings suggest that imeglimin may restore the mitochondrial functions of islets against the progression of diabetes in db/db mice and that imeglimin's effect on islet mitochondria may be, at least partially, independent of the glucose level[4].

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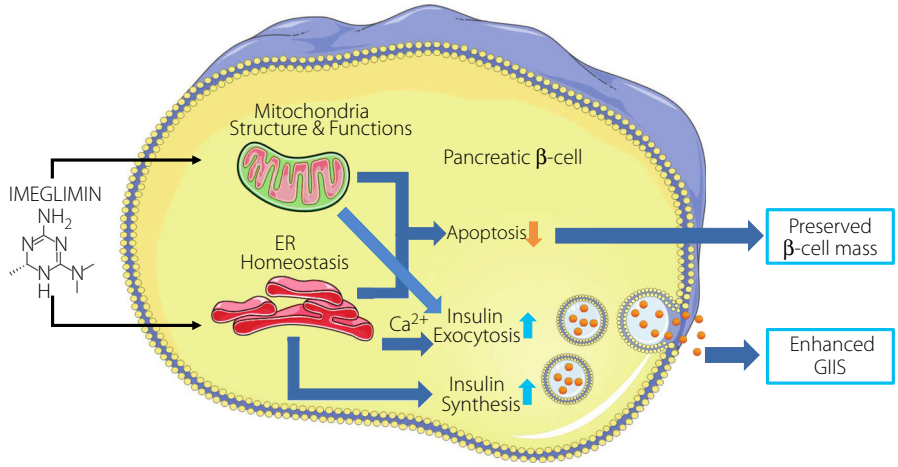

Figure 1 | Multifaceted actions of imeglimin on pancreatic β-cells. Imeglimin improves the mitochondrial function and structural integrity and restores homeostasis of the endoplasmic reticulum (ER). These actions might lead to preservation of β-cell mass as well as enhancement of glucose-induced insulin secretion (GIIS).

Maintenance of β-cell mitochondrial membrane structure has been noted using transmission electron microscopy (TEM)[3,4]. In db/db[3,4] and KK-Ay[3] mice, swollen mitochondria with disarrayed cristae were seen less frequently in pancreatic β-cells under imeglimin administration compared with control. The ratio of abnormal mitochondria to total mitochondria per β-cell was restored in 5 week imeglimin-treated db/db mice to the ratio in prediabetic mice[4]. These findings indicate that imeglimin may contribute to functional and structural integrity of β-cell mitochondria[4].

Imeglimin-induced improvement of the mitochondria may well contribute to the preservation of β-cell mass (BCM) as well as to glucose-induced insulin secretion in type 2 diabetes mellitus. The preservation of functional β-cell mass is a key strategy for promising diabetes treatment. In the recent preclinical studies, imeglimin was found to preserve β-cell mass or, at least, attenuate β-cell mass loss in Zucker diabetic fatty (ZDF) rats[8], db/db mice[4], and Akita[5] mice. The preservation of β-cell mass by imeglimin could be due to inhibition of apoptosis of pancreatic β-cells[4]. In imeglimin-treated ZDF rats, a significantly lower proportion of caspase-3/insulin co-positive cells within islets was found compared with controls[8]. Consistently, imeglimin-treated db/db mice had a drastically reduced ratio of TUNEL/insulin/DAPI co-positive cells to total insulin-positive cells compared with that of vehicle-treated db/db mice[4]. Furthermore, a reduced the apoptosis rate of pancreatic β-cells in imeglimin-treated mice might be inferred from the inhibition of pro-apoptotic cytochrome c release from the mitochondria[4]; the release of cytochrome c into cytosol triggers apoptosome formation and activates pro-apoptotic enzymes in the mitochondrial-mediated apoptosis cascade. Interestingly, in imeglimin-treated db/db mice, the released cytosolic cytochrome c level in islets was significantly lower compared with that of vehicle- and insulin glargine-treated db/db mice, although blood glucose levels were comparable between imeglimin- and insulin glargine-treated groups[4]. Thus, imeglimin might suppress mitochondria-mediated apoptosis in β-cells in both a glucose-dependent and -independent manner to contribute to the preservation of β-cell mass[4]. Furthermore, Li *et al.*[5] has provided insight into the mechanism of inhibition of β-cell apoptosis by noting an unfolded protein response against ER stress. Gene expression microarray analysis in C57BL/6J mouse islets under a high-glucose condition revealed an increase of ER stress-related genes such as C/EBP homologous protein (*Chop*), growth arrest deoxyribonucleic acid, and damage protein 34 (*Gadd34*) and activating transcription factor 3 under imeglimin treatment. Mouse and human islets incubated with thapsigargin, an ER stress inducer, showed a further increase of *Chop* and *Gadd34* messenger ribonucleic acid expressions under imeglimin treatment compared with thapsigargin alone, by which phosphorylation of eukaryotic initiation factor 2α (eIF2α), a modulator of integrated stress response, in mouse islets was decreased under imeglimin treatment. In addition, imeglimin restored global protein synthesis in thapsigargin-treated MIN6 cells[5]. This might partly explain the increased number of insulin granules in the pancreatic β-cells of db/db mice under chronic administration of imeglimin[3]. Since GADD34 and eIF2α are downstream molecules of CHOP, and GADD34 regulates protein phosphatase 1 (PP1) to dephosphorylate eIF2α, imeglimin could facilitate CHOP/GADD34/PP1 signaling to promote dephosphorylation of eIF2α and thus avoid β-cell apoptosis.

In summary, recent preclinical studies have provided insight on imeglimin's action on pancreatic β-cells and the

mechanisms underlying its clinical benefits. Imeglimin may enhance glucose-induced insulin secretion and inhibit apoptosis of pancreatic β-cells leading to a preserved β-cell mass by maintaining or restoring the functional and structural integrity of the mitochondria and the ER homeostasis in pancreatic β-cells (Figure 1). Further investigations to elaborate the comprehensive mechanisms of imeglimin actions in type 2 diabetes mellitus are anticipated.

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