**Supplementary Methods:**

**Immunohistochemical Detection of Ki67**

To test the pharmacological effect of verapamil on MIN6 cell proliferation, immunohistochemical (IHC) analysis of Ki67 was investigated (Hu, Wang, & Sun, 2021). Cells were seeded on number 1.5 coverslips, 12 mm in diameter, in either low or high glucose media supplemented with 2% bovine serum albumin free fatty acid (BSA FFA) (Cat# 820024, Sigma, USA) for 24 hours. The cells were then either treated with verapamil (50 μM) for another 24 hours or were left untreated. After this culturing period, cells were washed twice with PBS. Then, cells were fixed with 4% paraformaldehyde for 15 minutes at room temperature (RT; 21-23 oC). Fixed cells were immediately washed twice with PBS and permeabilized in 0.5% saponin for 15 minutes at RT. Next, cells were blocked in blocking solution (5% FBS; 0.1% Tween-20 in PBS) for 40 minutes at RT. Cells were then incubated for 2 hours with rabbit Anti-Mouse Ki67 primary antibodies (Cat# 15580, Abcam, Waltham, MA, USA), diluted 1:1000 in blocking solution, at RT. Next, the cells were washed 3 times, with intervals of 5 minutes, with PBS-Tween (0.1% Tween-20 in PBS), followed by incubation with secondary goat Anti-Rabbit antibody (Alexa Fluor® 488, cat# ab150077, AbCam, Waltham, MA, USA), diluted 1:1000 in blocking solution, and incubated at RT for 1 hour. Then, the cells were also incubated with the Phalloidin-iFluor 594 reagent (Cat#: ab176757, Abcam, Waltham, MA, USA) to visualize their actin filaments. After incubation, the cells were washed 3 times, with 5-minute intervals, with PBS and mounted on the slide with Mounting Medium with DAPI – Aqueous, Fluoroshield (Cat#: ab104139, Abcam, Waltham, MA, USA) to visualize their nuclei. Confocal images were obtained by using inverted Zeiss LSM710 spectral confocal microscope (Carl Zeiss, Gottingen, Germany). All samples were analyzed using the same parameters and the resulting color markup of the analysis was confirmed for each sample. The correlated total cell fluorescence (CTCF) was calculated from 10 different fields of each number (n) *via* ImageJ, using the following equation:

CTCF = Integrated Density - (Area of selected cell × Mean fluorescence of background readings) (El-Sharkawey, 2016).

**Western Blotting**

Protein extraction and Western Blotting were performed, as previously described (Al Madhoun et al., 2021; Al Madhoun et al., 2020). Cells were seeded in 6-well plates (Costar, High Wycombe, UK) in either low or high glucose media supplemented with 2% BSA FFA (Cat# 820024, Sigma, USA) for 24 hours. Then, the cells were either treated with verapamil (50 μM) for another 24 hours or were left untreated. After this culturing period, cells were washed with PBS, harvested, and incubated for 30 minutes with lysis buffer (Tris 62.5 mM, 1% Triton X-100, 10% glycerol, pH: 7.5). The lysates were then centrifuged at 14000 × g for 10 minutes, following which, the supernatant was collected. The concentration of protein in lysates was measured using the Quickstart Bradford Dye Reagent, 1x Protein Assay kit (Bio-Rad Laboratories, Inc, CA, USA). Protein samples (20 or 30 µg) were mixed with sample loading buffer, heated for 5 minutes at 95 °C, and resolved by 12% sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Cellular proteins were transferred to nitrocellulose membrane (Bio-Rad Laboratories, USA) by electroblotting. The membranes were then blocked with 5% non-fat milk in PBS for 1 hour, followed by incubation with primary antibodies Anti-Histone H3 (D1H2) XP® Rabbit mAb #4499 and Anti-β-Actin (8H10D10) Mouse mAb #3700. Both antibodies were purchased from Cell Signaling Technology, Inc, USA, and CCK (PA5-103116, Abcam, Waltham, MA, USA). The blots were then washed 3 times with TBST and incubated for 2 hours with goat Anti-Rabbit IgG H&L (IRDye® 680RD) (Cat#: ab216777, Abcam, Waltham, MA, USA), goat Anti-Mouse IgG H&L (IRDye® 800RD) (Cat#: ab216772, Abcam, Waltham, MA, USA), or horseradish peroxidase-linked conjugated secondary antibodies. Immunofluorescence or chemiluminescence bands were visualized by Molecular Imager ® ChemiDocTM MP Imaging Systems (Bio-Rad Laboratories, Hercules, CA, USA).

**Proteome Sample Preparation**

Proteome sample preparation was conducted based on the standard protocol as previously described (Abu-Farha et al., 2008). Frozen cell pellets were lysed according to the Biognosys sample preparation kit protocol (Ki-3013). Cell pellets were lysed with 80 µl of denaturing buffer for 30 minutes at room temperature. A total of 100 µg of total cell lysates were reduced in reduction buffer at 37 °C, by gently shaking for 30 minutes. Samples were then alkylated by adding 16 µL of alkylation solution to each well after cooling, and were incubated at room temperature in the dark for 30 minutes. Samples were then digested by adding 0.4 µg of trypsin at 37°C overnight. Samples were then acidified by adding 20 µl of 10% (v/v) TFA and cleaned-up by using C-18 MACROSpin plates provided by the kit as per protocol. The digested peptides were eluted in 340 µl/well of C18 Elution solution (0.1% (v/v) TFA in 50% Acetonitrile). The samples were then dried down and constituted to a concentration of 1µg/µl and analyzed on the liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) system.

Samples were analyzed on Q-Exactive HF LC-ESI-MS/MS system from Thermo Fisher Scientific coupled with an EASY-nLC™ 1200 nano-LC System through an EASY-Spray Ion Source (Thermo Fisher Scientific). Mobile phase A was 0.1% formic acid in water and mobile phase B was 80% acetonitrile plus 0.1% FA in water. LC separation was performed with a trap-elute configuration including a trapping column (Acclaim PepMap100 75 μm x 2 cm) (Thermo Fisher Scientific) and an analytical column (ES801A PepMap RSLC C18, 2um, 100A, 50um x 15cm) (Thermo Fisher Scientific). The trapping column was loaded by an injection of 5 μg of digested peptide with the mobile phase A delivered at a flow rate of 5 μl/min for 3 minutes to trap and clean peptides, and then the samples were applied onto the column at a flow rate of 300 nl/min. The nano flow column was maintained at 40°C. Peptides were eluted and separated with a 170-minute run. The eluent was ionized using an Easy Spray nano ESI source operating in positive ion mode. Ionization voltage was 2.3 kV and the capillary temperature was 230°C. The Q Exactive HF instrument was operated in the data-dependent acquisition (DDA) mode to automatically switch between full scan MS and MS/MS acquisition. MS1 full scans were acquired for 350-2000 m/z at 120,000 resolution, 60ms maximum IT, 3e6 AGC target. The top 10 multiply charged ions were selected from each scan for MS/MS analysis and then fragmented by higher-energy collisional dissociation (HCD) with a normalized collision energy setting of 27 eV, at 30,000 resolution, 20 ms maximum IT, 1e5 AGC target, and an isolation window of 2.0 m/z.

Label-free quantitation was performed using Thermo Scientific™ Proteome Discoverer™ 2.4 software using SEQUEST® HT search engine with a precursor mass tolerance of 10 ppm and fragment mass tolerance of 0.02 Da. Enzyme name was set to trypsin, with a maximum missed cleavages value of 2. Carbamidomethylation (+57.021 Da) of cysteine was considered a fixed modification, while oxidation (+15.995 Da) of methionine was considered a dynamic peptide modification. Data were searched against a Mus musculus fastafile with a 1% false discovery rate (FDR) using Percolator. The area of the precursor ion from the identified peptides was calculated using the Feature Mapper and Precursor Ions Quantifier nodes in the Consensus Step and Minora Feature Detector node in the Processing Step with default settings. Further processing was performed using the new Rt-Aligner and Feature Mapper nodes also created for the untargeted label-free quantification workflow in the software. The false discovery rate (FDR) for proteins, peptides and peptide spectral matches (PSMs) were kept at 1%. All results were filtered by a q- value of <0.01 (equals an FDR of 1% on peptide level and a filter of minimum 2 unique peptides.) Each experiment was performed in technical triplicates.

**Glucose-Stimulated Insulin Secretion (GSIS) Assay**

GSIS assay was performed using the static incubation method (Marafie, Al-Shawaf, Abubaker, & Arefanian, 2019). Briefly 1 × 105 cells were grown per well, in 24-well plates (Costar, High Wycombe, UK), as a monolayer. After 24 hours, the cells were pretreated with 50 μM verapamil for another 24 hours. The following day, the medium was removed, and cells were washed twice with PBS. Next, for equilibration, the cells were incubated for 1 hour with 500 μl of 2.8 mM glucose, supplemented in Krebs–Ringer HEPES buffer (basal media, pH-adjusted to 7.4 with 1 mol/l NaOH), containing 135 mM NaCl, 3.6 mM KCl, 5 mM NaHCO3, 0.5 mM MgCl2, 1.5 mM CaCl2, 10 mM HEPES, and 0.1% BSA). After equilibration, 500 μl of glucose-containing stimulation media, Krebs–Ringer HEPES buffer supplemented with 2.8, 5.6, 8.4, 11.2, or 16.8 mM glucose, was added to each well and incubated for 2 hours at 37 °C. Following which, the GSIS assay was terminated by placing the plate on ice. Conditioned medium (500 μl) was removed from each well, centrifuged at 1400 rpm at 4 °C for 5 minutes, was transferred to an ice-cold Eppendorf tube, and was then kept in -20 °C to detect the level of secreted insulin.

To measure the total insulin content of the cells, each well was washed with PBS, after which, 500 μl of cold acidified ethanol (1.5% HCl in 70% EtOH) was added to each tube and kept overnight at -80 °C. The following day, freeze/thaw cycles (-20 °C /4 °C) were performed thrice. The cells were removed by scraping and were transferred to a labeled tube. The tubes were centrifuged for 15 min at 15000 × g at 4 °C. The supernatants were transferred to new labeled tubes, acid-ethanol extracts were neutralized with same volume of 1M Tris pH 7.5, and were kept in -20 °C for insulin measurements using ELISA. The levels of total insulin content and secreted insulin were normalized by the level of total protein measured by Bradford assay against a standard curve.

**Protection Assays**

In this study, MIN6 cells were stressed by one of three stressors, as follows:

1. Streptozotocin (STZ): STZ stock solution (0.3 M) was prepared by dissolving STZ in cold citrate buffer and was used immediately. The final concentration of STZ was 3 mM (Gao, Parker, & Hart, 2000).
2. T1D-cytomix: A T1D-cytomix was prepared using a combination of TNF-α, IL-1β, and INF-γ (Final concentration: 50, 50, and 100 ng/ml, respectively)(Damame, Rooge, Patil, & Arvindekar, 2020; Wang, Guan, & Yang, 2010).
3. T2D-cytomix: A combination of TNF-α, IL-1β, and palmitic acid (Final concentration: 50 ng/ml, 50 ng/ml, and 500 µM, respectively) was used to prepare the T2D-cytomix (Damame et al., 2020).

For the protection assays, the concentrations of verapamil used were 1, 5, 10, or 50 μM, and the protection assays were conducted in the following conditions, as indicated.

1. Pretreatment condition: Cells were pretreated with 1, 5, 10, or 50 μM of verapamil for 24 hours. The next day, the medium was removed, the cells were washed with PBS, and the cells were then exposed to one of the mentioned stressors, as indicated, for another 24 hours. Following which, the MTT assay was performed to measure cell survival.
2. Cotreatment condition: Cells were cotreated with a combination of a stressor and verapamil (1, 5, 10, or 50 μM) for 24 hours, after which, the MTT assay was conducted to measure cell survival.
3. Pretreatment 🡪 cotreatment condition: Cells were pretreated with verapamil, as detailed in the “pretreatment” condition, for 24 hours. On the following day, the medium was removed, cells were washed with PBS, and then the “cotreatment” condition, with the indicated stressor, and used verapamil concentration was applied for another 24 hours, and then MTT assay was conducted to measure cell survival.

The MTT assay (Trevigen, USA) was conducted according to the manufacturer’s instructions. The plates were analyzed using the Synergy H4 Hybrid Microplate Reader (BioTek, USA), and data analysis was performed using the Gen5 software.

**References:**

Abu-Farha, M., Lambert, J. P., Al-Madhoun, A. S., Elisma, F., Skerjanc, I. S., & Figeys, D. (2008). The tale of two domains: proteomics and genomics analysis of SMYD2, a new histone methyltransferase. *Mol Cell Proteomics, 7*(3), 560-572. doi:10.1074/mcp.M700271-MCP200

Al Madhoun, A., Haddad, D., Al Tarrah, M., Jacob, S., Al-Ali, W., Nizam, R., . . . Al-Mulla, F. (2021). Microarray analysis reveals ONC201 mediated differential mechanisms of CHOP gene regulation in metastatic and nonmetastatic colorectal cancer cells. *Sci Rep, 11*(1), 11893. doi:10.1038/s41598-021-91092-8

Al Madhoun, A., Marafie, S. K., Haddad, D., Melhem, M., Abu-Farha, M., Ali, H., . . . Al-Mulla, F. (2020). Comparative Proteomic Analysis Identifies EphA2 as a Specific Cell Surface Marker for Wharton's Jelly-Derived Mesenchymal Stem Cells. *Int J Mol Sci, 21*(17). doi:10.3390/ijms21176437

Damame, H. H., Rooge, S. B., Patil, R. S., & Arvindekar, A. U. (2020). In vitro model using cytokine cocktail to evaluate apoptosis in Min6 pancreatic beta cells. *J Pharmacol Toxicol Methods, 106*, 106914. doi:10.1016/j.vascn.2020.106914

El-Sharkawey, A. (2016). *Calculate the Corrected Total Cell Fluorescence (CTCF)*.

Gao, Y., Parker, G. J., & Hart, G. W. (2000). Streptozotocin-induced beta-cell death is independent of its inhibition of O-GlcNAcase in pancreatic Min6 cells. *Arch Biochem Biophys, 383*(2), 296-302. doi:10.1006/abbi.2000.2094

Hu, W., Wang, R., & Sun, B. (2021). Meteorin-Like Ameliorates β Cell Function by Inhibiting β Cell Apoptosis of and Promoting β Cell Proliferation via Activating the WNT/β-Catenin Pathway. *Front Pharmacol, 12*, 627147. doi:10.3389/fphar.2021.627147

Marafie, S. K., Al-Shawaf, E. M., Abubaker, J., & Arefanian, H. (2019). Palmitic acid-induced lipotoxicity promotes a novel interplay between Akt-mTOR, IRS-1, and FFAR1 signaling in pancreatic β-cells. *Biol Res, 52*(1), 44. doi:10.1186/s40659-019-0253-4

Wang, C., Guan, Y., & Yang, J. (2010). Cytokines in the Progression of Pancreatic β-Cell Dysfunction. *Int J Endocrinol, 2010*, 515136. doi:10.1155/2010/515136