



**Supplementary Fig. 3.** An illustration depicting the effects of PDZ domain-containing 8 (PDZD8) on mitochondria-associated endoplasmic reticulum (ER) membrane (MAM) formation and mitochondria-related death of diabetic pancreatic  $\beta$ -cells. PDZD8 can promote mitochondrial dysfunction by promoting MAM formation, increase the flow of  $\text{Ca}^{2+}$  into the mitochondria, and cause mitochondrial-related cell death of pancreatic  $\beta$ -cells, ultimately contributing to diabetes mellitus progression. HFD, high-fat diet; STZ, streptozotocin; mPTP, mitochondrial permeability transition pore; Cypd, cyclophilin D; IP3R1, inositol 1,4,5-triphosphate receptor type 1; VDAC, voltage-dependent anion-selective channel.