Role of GIP receptor signaling in β -cell survival

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Abbreviations

EGFRE	Epidermal growth factor receptor
PI3K	Phosphoinositide 3-kinase
cAMP	Cyclic adenosine 3',5'-monophosphate
Epac2	Exchange protein directly activated by cAMP 2
PKB	Protein kinase B
PKA	Protein kinase A
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-xL
Bax	Bcl-2-like protein 4
PDX-1	Pancreatic duodenal homeobox 1
TCF1	T-cell factor 1

Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are two major incretin hormones secreted by enteroendocrine K cells and L cells into the circulation after meal ingestion. Nutrients such as glucose, fat, and protein induce incretin secretion. In β cells, GIP and GLP-1 bind to their respective class B G-protein-coupled receptor (GPCR), namely the GIP receptor (GIPR) and the GLP-1 receptor (GLP-1R), respectively, to potentiate glucose-dependent insulin secretion through cyclic adenosine 3',5'-monophosphate (cAMP) protein kinase A (PKA) and

exchange protein (directly activated by cAMP 2 (Epac2) signaling) (Fig. 1). Systemic incretin receptor-knockout and incretin peptide-knockout mice exhibit impaired glucose tolerance due to a lack of incretin-induced insulin secretion [1–3]. Thus, the insulinotropic actions of GIP and GLP-1 play an important role in postprandial insulin secretion.

GLP-1 mediates extra-insulinotropic functions in the β cell [4] (Fig. 1). GLP-1 activates protein kinase B (PKB/Akt)—which is downstream of phosphoinositide 3-kinase (PI3K)—via epidermal growth factor receptor (EGFR) activation, and increases the expression levels of anti-apoptotic gene B-cell lymphoma (Bcl)-2 and Bcl-xL, resulting in a reduction in the proapoptotic gene Bax (Bcl-2-like protein 4) expression in β cells. GLP-1 is associated with β -cell maturation and differentiation through the transcriptional factor pancreatic duodenal homeobox 1 (PDX-1), which is increased by the PKA-cAMP response element-binding protein (CREB) pathway. In addition, GLP-1 signaling reduces endoplasmic reticulum (ER) stress by PKB/Akt and CREB activation. Thus, GLP-1 plays an important role in β -cell proliferation and protection from β -cell apoptosis, resulting in the preservation of β -cell mass.

GIP also has anti-apoptotic functions that are mostly mediated by the activation of CREB and the suppression of p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) [5, 6]. In addition, GIP also protects β cells from ER stress [7]. However, the importance of GIPR in β -cell survival remains relatively unclear. Campbell et al. generated β -cell-specific GIPR-knockout (*GIPR*^{-/- β Cell}) mice using floxed GIPR and mouse insulin promoter-tamoxifen inducible Cre (*MIP-CreERT*) mice, and showed the role of GIPR in insulin secretion and β -cell survival in vivo [8]. *GIPR*^{-/- β Cell} mice exhibited similar

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Fig. 1 Molecular mechanism of GIP- and GLP-1-induced insulin secretion and β -cell survival. GIP and GLP-1 potentiate glucose-dependent insulin secretion through PKA and Epac2 (black arrows). GLP-1 is well known to be associated with β -cell survival (as it exerts an antiapoptotic effect), reduction of ER stress, and β -cell maturation and differentiation (blue arrows). Campbell et al. have shown a new pathway for GIP-induced β -cell survival (red arrows)

levels of insulin secretion in response to glucose compared to the MIP-CreERT control mice. However, streptozotocin (STZ)-induced apoptotic β cells were increased in $GIPR^{-/-\beta Cell}$ mice compared to MIP-CreERT mice.

Transcription factor 7-like 2 (*TCF7L2*) is a member of the TCF family that regulates β -cell function and survival [9]. *TCF7L2* levels are reported to be negatively correlated with GIPR and GLP-1R expression in human β cells [10]. Campbell et al. investigated the mRNA expression of TCF family members such as *TCF7L1*, *TCF7L2*, *TCF4*, and *TCF7*, and showed that only *TCF7* mRNA expression is suppressed in islets of $GIPR^{-/-\beta Cell}$ mice. The T-cell factor 1 (TCF1) protein encoded by *TCF7* is a transcriptional activator which plays an important role in lymphocyte differentiation in T cells [11], but its functional role in β cells has not been reported. The authors of [11] were able to show that the TCF1 protein may be involved in β -cell survival and that GIPR signaling may be one of the key mediators (Fig. 1). *TCF7* was expressed in β cells, and GIP directly induced *TCF7* mRNA expression through cAMP and extracellular signal-regulated kinase (ERK) signaling in rat pancreatic β -cell line INS-1. In addition, *TCF7*-knockout (*TCF7*^{-/-}) mice were found to have lower insulin secretion in response to glucose ingestion, which resulted in postprandial hyperglycemia. Finally, GIP reduced STZ-induced TUNEL-positive cells in the islets of wild-type mice, but not in the islets of *TCF7*^{-/-} mice. Accordingly, it is likely that TCF1 plays an important role

in β -cell survival through GIPR signaling. GIPR-TCF1 signaling may have potential as a therapeutic target in the treatment of β -cell mass loss under diabetic conditions.

References

- Scrocchi LA, Brown TJ, McClusky N, Brubaker PL, Auerbach AB, Joyner AL, Drucker DJ. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. *Nat Med*. 1996;2(11):1254–8.
- Miyawaki K, Yamada Y, Yano H, Niwa H, Ban N, Ihara Y, Kubota A, Fujimoto S, Kajikawa M, Kuroe A, Tsuda K, Hashimoto H, Yamashita T, Jomori T, Tashiro F, Miyazaki J, Seino Y. Glucose intolerance caused by a defect in the entero-insular axis: a study in gastric inhibitory polypeptide receptor knockout mice. *Nat Med*. 2002;8(7):738–42.
- Nasteska D, Harada N, Suzuki K, Yamane S, Hamasaki A, Joo E, Iwasaki K, Shibue K, Harada T, Inagaki N. Chronic reduction of GIP secretion alleviates obesity and insulin resistance under high-fat diet conditions. *Diabetes*. 2014;63(7):2332–43.
- Yabe D, Seino Y. Two incretin hormones GLP-1 and GIP: comparison of their actions in insulin secretion and β cell preservation. *Prog Biophys Mol Biol*. 2011;107(2):248–56.
- Kim SJ, Nian C, Widenmaier S, McIntosh CH. Glucose-dependent insulinotropic polypeptide-mediated up-regulation of beta-cell antiapoptotic Bcl-2 gene expression is coordinated by cyclic AMP (cAMP) response element binding protein (CREB) and cAMP-responsive CREB coactivator 2. *Mol Cell Biol*. 2008;28(5):1644–56.
- Ehses JA, Casilla VR, Doty T, Pospisilik JA, Winter KD, Demuth HU, Pederson RA, McIntosh CH. Glucose-dependent insulinotropic polypeptide promotes beta-(INS-1) cell survival via cyclic adenosine monophosphate-mediated caspase-3 inhibition and regulation of p38 mitogen-activated protein kinase. *Endocrinology*. 2003;144(10):4433–45.
- Widenmaier SB, Ao Z, Kim SJ, Warnock G, McIntosh CH. Suppression of p38 MAPK and JNK via Akt-mediated inhibition of apoptosis signal-regulating kinase 1 constitutes a core component of the beta-cell pro-survival effects of glucose-dependent insulinotropic polypeptide. *J Biol Chem*. 2009;284(44):30372–82.
- Campbell JE, Ussher JR, Mulvihill EE, Kolic J, Baggio LL, Cao X, Liu Y, Lamont BJ, Morii T, Streutker CJ, Tamarina N, Philipson LH, Wrana JL, MacDonald PE, Drucker DJ. TCF1 links GIPR signaling to the control of beta cell function and survival. *Nat Med*. 2016;22(1):84–90.
- Shu L, Matveyenko AV, Kerr-Conte J, Cho JH, McIntosh CH, Maedler K. Decreased TCF7L2 protein levels in type 2 diabetes mellitus correlate with downregulation of GIP- and GLP-1 receptors and impaired beta-cell function. *Hum Mol Genet*. 2009;18(13):2388–99.
- Shu L, Sauter NS, Schulthess FT, Matveyenko AV, Oberholzer J, Maedler K. Transcription factor 7-like 2 regulates beta-cell survival and function in human pancreatic islets. *Diabetes*. 2008;57(3):645–53.
- Yu Q, Sharma A, Sen JM. TCF1 and beta-catenin regulate T cell development and function. *Immunol Res*. 2010;47(1–3):45–55.