

# Lysosomal function in $\beta$ -cell survival during glucolipototoxicity

Ana Batista-Gonzalez<sup>1,2</sup>, Rajat Singh<sup>1,2,3,4</sup>

<sup>1</sup>Department of Medicine, <sup>2</sup>Department of Molecular Pharmacology, <sup>3</sup>Institute for Aging Research, <sup>4</sup>Diabetes Research Center, Albert Einstein College of Medicine, Bronx, NY, USA

*Correspondence to:* Rajat Singh, MD, MBBS. Department of Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Forchheimer 505D Bronx, NY 10461, USA. Email: rajat.singh@einstein.yu.edu.

*Provenance:* This is a Guest Editorial commissioned by Section Editor Qi-Nan Wu, MD, PhD (Associate Professor of Endocrinology Department, Southwest Hospital, Third Military Medical University, Diabetic Foot Diagnosis & Treatment Medical Center of Chongqing, Chongqing, China).

*Comment on:* Zummo FP, Cullen KS, Honkanen-Scott M, *et al.* Glucagon-Like Peptide 1 Protects Pancreatic  $\beta$ -Cells From Death by Increasing Autophagic Flux and Restoring Lysosomal Function. *Diabetes* 2017;66:1272-85.

Submitted Sep 10, 2017. Accepted for publication Sep 15, 2017.

doi: 10.21037/atm.2017.09.20

**View this article at:** <http://dx.doi.org/10.21037/atm.2017.09.20>

Type 2 diabetes (T2D) is an increasingly prevalent disease worldwide the incidence of which correlates in many cases with development of obesity. Elevated circulating free fatty acids (FFA) are thought to trigger key steps in development of insulin resistance and T2D (1). An early response to reduced insulin action in peripheral tissues is increased production and secretion of insulin by pancreatic  $\beta$ -cells, however, progressive  $\beta$ -cell loss and reduced insulin secretion lead to hyperglycemia and the complications associated with T2D (1). A factor contributing to loss of  $\beta$ -cells in T2D patients is increased apoptosis (2), which is thought to occur from chronic exposure to increased circulating glucose and FFA levels.

Macroautophagy (hereafter referred to as autophagy) is a lysosomal degradative pathway that recycles damaged organelles, proteins, and fat droplets to maintain quality control and generate an alternative source of energy during stress and starvation (3). Autophagy has been the subject of intense research in biological processes ranging from cellular metabolism to aging (4,5), and impaired autophagy has been linked to progression and pathogenesis of several diseases including T2D (4). Briefly, during autophagy, phagophores give rise to double-membrane autophagosomes that are labelled by lipidated light chain 3 (LC3), the only reliable marker to follow autophagy activity or flux (3). Autophagosomes encapsulate cytoplasmic contents that are destined for degradation in lysosomes. The formation of autophagosomes is tightly regulated by greater than 35 autophagy-related genes (*Atg*) that orchestrate membrane

formation with donor membranes originating from plasma membrane, endoplasmic reticulum (ER), and Golgi to drive autophagosome biogenesis (3). Fusion of autophagosomes with lysosomes is a critical step in cargo degradation (3), and is influenced by lipid composition of their membranes as well as by SNARE protein syntaxin 17 (6). Recent *in vitro* and *in vivo* work have suggested that exposure to increasing lipid concentrations disrupts autophagosome-lysosome fusion leading to autophagy failure (7).

Despite being a well-characterized process, the physiological roles of autophagy in diverse tissue systems remain unclear. Several studies have shown key roles of autophagy in regulation of lipid and energy metabolism (4,8). In this regard, studies have shown the requirement of autophagy in proper functioning of  $\beta$ -cells with reported increases in autophagy in  $\beta$ -cells exposed to fatty acids. In addition,  $\beta$ -cell-specific loss of the critical autophagy gene *Atg7* leads to accumulation of protein aggregates that associates with impaired insulin secretion and glucose intolerance (9). Furthermore, when fed HFD,  $\beta$ -cell-specific *Atg7* knockout mice develop severe glucose intolerance due to increased  $\beta$ -cell apoptosis that decreases  $\beta$ -cells mass (10). By contrast, surprisingly, studies have also shown that increased autophagy in  $\beta$ -cells associates with increased cell death, and inhibition of autophagy—a pathway typically known to confer protection—increases cell survival (11). Hence the pathophysiological links between autophagy and  $\beta$ -cell function remain unclear.

In the manuscript entitled, “*Glucagon-like peptide-1 protects*

*pancreatic beta-cells from death by increasing autophagic flux and restoring lysosomal function*”, the authors Zummo *et al.* reveal the role of autophagy in protection conferred by exendin-4, a glucagon-like peptide-1 (GLP-1) receptor agonist, against glucolipotoxicity (GLT) in INS-1E pancreatic  $\beta$ -cells. GLP-1 receptor activation mediates a series of events leading to increased  $\beta$ -cell mass and increased insulin biosynthesis and secretion (12). In fact, GLP-1 receptor agonists have been shown to improve insulin sensitivity in patients with T2D (12). In this work, the authors show that GLT leads to increased lipidated LC3-II levels reflecting an increase in the number of autophagosomes in pancreatic  $\beta$ -cells. However, accumulation of autophagosomes occurs from impaired autophagic flux, which is a consequence of decreased autophagosome-lysosome fusion. One of the characteristics of islets from T2D subjects is reduced  $\beta$ -cell mass (12), and the authors of the present study support this notion by showing a correlation between impaired autophagy activity/flux and increased cell death during GLT, which likely results in decreased  $\beta$ -cell mass *in vivo*. Consistent with this observation, the authors found accumulation of p62/SQSTM1, an autophagy cargo adapter protein, in islets from T2D patients. These data suggest that inducing autophagy flux/activity protects pancreatic  $\beta$ -cells from the noxious effects of elevated concentrations of glucose and FFA, which support previous studies showing the induction of autophagy in high fat diet-fed mice. The authors go on to show that treatment with the GLP-1 receptor agonist exendin-4 partially restores autophagic flux and decreases GLT-induced cell death in INS-1E cells. These results point to the pathogenic role of impaired autophagic flux in  $\beta$ -cell death in the setting of nutrient excess, and suggest that exendin-4 protects by restoring autophagy. It is worth pointing out here that GLP-1 receptor agonists have been shown to protect  $\beta$ -cells from lipotoxicity providing evidence for the use of GLP-1 receptor agonists in treatment of T2D (13).

While attempting to understand how exendin-4 restores autophagic flux, the authors found that GLT increases lysosomal membrane permeabilization and leakage of lysosomal enzymes into the cytosol, which is thought to promote cell death (14). Paradoxically, GLT also enhanced lysosomal biogenesis through increased nuclear translocation of transcription factor EB (TFEB), a master regulator of lysosome biogenesis. Nuclear translocation of TFEB is likely a compensatory event aimed to restore autophagy activity in stressed  $\beta$ -cells although the effect of inhibiting TFEB translocation

on cell viability was not tested in this study. However, interestingly, despite the increase in expression of TFEB targets, GLT blocked autophagosome-lysosome fusion, which likely led to reduced cellular quality control. The authors further noted that exendin-4 reversed, in part, this block in autophagosome-lysosome fusion. In addition, exendin-4 increased GLT-induced lysosome biogenesis and prevented the release of lysosomal enzyme cathepsin D into the cytosol. Loss of cathepsin D was also confirmed in tissue samples from T2D patients supporting the notion that altered lysosome membrane integrity and impaired autophagy each contributes to  $\beta$ -cell death in T2D subjects. It is worthwhile to ask here how exendin-4 promotes autophagosome-lysosome fusion—could fusion events be restored via correction of membrane lipid compositions of autophagic structures?

ER stress is a key event causing  $\beta$ -cell dysfunction during diabetes (15), and in this context, ER stress is known to occur in pancreatic cells exposed to FFA and high glucose concentration and when the ER faces high protein-folding burden (16). In this study, from a functional perspective, ER stress was identified as an upstream inhibitor of autophagy flux. Blocking ER stress with tauroursodeoxycholic acid (TUDCA) prevented, in part, some of the lysosomal defects and reduced GLT-induced cell death, although whether the beneficial effect of TUDCA occurred through reactivation of autophagy flux was not tested. More importantly, exendin-4 treatment attenuated ER stress, which could be the underlying cause of improved autophagic flux and increased viability in response to exendin-4.

Taken together, the results by Zummo *et al.* suggest that GLT causes  $\beta$ -cell death by increasing the autophagosome load and the failure of these vesicles to fuse with lysosomes likely from GLT—induced defects in lysosomes. The key question remains—is  $\beta$ -cell death a direct consequence of reduced quality control? It is likely that  $\beta$ -cells—a highly specialized cell that is programmed to produce, package, and release insulin in secretory vesicles in response to circulating glucose levels, requires a sophisticated quality control system that clears excessively produced insulin granules. Indeed, studies have shown that crinophagy helps maintain  $\beta$ -cells “clean” through lysosomal degradation of insulin granules (17). Whether failure of autophagic quality control in the setting of GLT is the prime reason for  $\beta$ -cell death remains to be tested. The precise mechanism of reduced autophagosome-lysosome fusion in the setting of nutrient excess also remains unknown. An important observation here is the ability of exendin-4 to enhance autophagic flux

by improving autophagosome-lysosome fusion and hence promoting cell survival. These results open possibilities of interventions at the level of  $\beta$ -cell autophagy in treatment of T2DM. Although drugs such as rapamycin are potent autophagy inducers, the side-effects of rapamycin and its ability to impair glucose homeostasis prevent its use in diabetic clinics. Moreover, therapies targeting GLP-1 receptor have increased in recent years, and recent studies have shown their effectiveness in improving glycemic control in patients with T2D (18), although additional studies will be required to determine the mechanism behind restoration of autophagy and prevention of  $\beta$ -cell death by exendin-4.

### Acknowledgements

*Funding:* This work was supported by R01 AG043517 and R21 AG056754 (R Singh), P30 DK020541 (Einstein Diabetes Research Center), and P01 AG031782 (R Singh). A Batista-Gonzalez is supported by T32 AG023475.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

### References

- Wilding JP. The importance of free fatty acids in the development of Type 2 diabetes. *Diabet Med* 2007;24:934-45.
- Chandra J, Zhivotovsky B, Zaitsev S, et al. Role of apoptosis in pancreatic beta-cell death in diabetes. *Diabetes* 2001;50 Suppl 1:S44-7.
- He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. *Annu Rev Genet* 2009;43:67-93.
- Singh R, Cuervo AM. Autophagy in the cellular energetic balance. *Cell Metab* 2011;13:495-504.
- Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. *Cell* 2011;146:682-95.
- Itakura E, Kishi-Itakura C, Mizushima N. The hairpin-type tail-anchored SNARE syntaxin 17 targets to autophagosomes for fusion with endosomes/lysosomes. *Cell* 2012;151:1256-69.
- Koga H, Kaushik S, Cuervo AM. Altered lipid content inhibits autophagic vesicular fusion. *FASEB J* 2010;24:3052-65.
- Singh R, Kaushik S, Wang Y, et al. Autophagy regulates lipid metabolism. *Nature* 2009;458:1131-5.
- Jung HS, Chung KW, Won Kim J, et al. Loss of autophagy diminishes pancreatic beta cell mass and function with resultant hyperglycemia. *Cell Metab* 2008;8:318-24.
- Ebato C, Uchida T, Arakawa M, et al. Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. *Cell Metab* 2008;8:325-32.
- Fujimoto K, Hanson PT, Tran H, et al. Autophagy regulates pancreatic beta cell death in response to Pdx1 deficiency and nutrient deprivation. *J Biol Chem* 2009;284:27664-73.
- Stoffers DA. The development of beta-cell mass: recent progress and potential role of GLP-1. *Horm Metab Res* 2004;36:811-21.
- Jing Yin J, Bo Li Y, Ming Cao M, et al. Liraglutide Improves the Survival of INS-1 Cells by Promoting Macroautophagy. *Int J Endocrinol Metab* 2013;11:184-90.
- Aits S, Jäättelä M. Lysosomal cell death at a glance. *J Cell Sci* 2013;126:1905-12.
- Bachar-Wikstrom E, Wikstrom JD, Ariav Y, et al. Stimulation of autophagy improves endoplasmic reticulum stress-induced diabetes. *Diabetes* 2013;62:1227-37.
- Zhang N, Cao MM, Liu H, et al. Autophagy regulates insulin resistance following endoplasmic reticulum stress in diabetes. *J Physiol Biochem* 2015;71:319-27.
- Marsh BJ, Soden C, Alarcón C, et al. Regulated autophagy controls hormone content in secretory-deficient pancreatic endocrine beta-cells. *Mol Endocrinol* 2007;21:2255-69.
- Lee S, Lee DY. Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes. *Ann Pediatr Endocrinol Metab* 2017;22:15-26.

**Cite this article as:** Batista-Gonzalez A, Singh R. Lysosomal function in  $\beta$ -cell survival during glucolipototoxicity. *Ann Transl Med* 2017;5(23):471. doi: 10.21037/atm.2017.09.20