Macroutophagy (hereafter referred as “autophagy”) is a process where cellular components are sequestered into a vesicle (autophagosome) and are then degraded by lysosomal enzymes through formation of a fused vesicle (autolysosome). “Constitutive” autophagy was recently shown to have a role in maintaining mass and function of pancreatic islet β-cells. Additionally, dysregulated autophagy in β-cells was observed to contribute to the development of type 2 diabetes. However, the role of “inductive” autophagy has not been clearly elucidated in the function of β-cells.

Autophagy is induced by various physiological and pathological conditions. A representative condition is starvation. During nutrient deprivation, cells induce autophagy, supplying catabolites to use for themselves, and maintaining energy homeostasis. However, β-cells should consider not only their own energy homeostasis, but also that of the whole body, because it is the responsibility of insulin-secreting β-cells. If β-cells induce autophagy on starvation, resultant catabolism of nutrients could trigger insulin secretion, which should not occur for the balance of the whole-body energy status and for maintaining blood glucose levels. Recently, Goginashvili et al. dissected the acute response of β-cells to nutrient deprivation in terms of autophagy. They showed that deprivation of serum and either glucose or amino acids suppressed formation of autophagosomes in INS1 cells (a rat insulinoma cell line). Such a phenomenon appeared approximately 20 min after fasting, and was maintained for at least 6 h. Four-hour fasting of mice also inhibited in vivo formation of autophagosomes in β-cells. Such a response to starvation was explained by starvation-induced nascent granule degradation (SINGD). On starvation, secretory granules were found co-localized with lysosomes, and granule-containing lysosomes (GCLs) increased in INS1 cells on electron microscopy. Further starvation for 6 h decreased proinsulin levels, a marker for nascent secretory granules. Co-localization of (pro)insulin and lysosomes was also observed in β-cells of fasted mice, but that of (pro)insulin and autophagosomes was not observed. Therefore, starvation acutely induced lysosomal degradation of (pro)insulin in the nascent secretory granules, although autophagy was depressed. Then, could there be a relationship between the two phenomena? Lysosome-derived amino acids had been reported to induce translocation of the mechanistic target of rapamycin complex 1 (mTORC1) to lysosomal membranes, and mTORC1 activation is the last step of the series in the insulin secretory process, and the nascent granules are preferentially secreted, degradation of nascent insulin granules shortly after starvation would be most effective in the defense against hypoglycemia. In addition, such SINGD suppressed autophagy, and it prevented autophagy-induced insulin secretion. β-Cells appear to use a distinct mechanism to overcome a shortage of nutrients, but it might be different in the case of prolonged starvation. After...
the completion of the mission as a primary defender against hypoglycemia and passing it to following defenders, such as α-cells and sympathoadrenal signals, β-cells might induce autophagy just like other cells to maintain cellular homeostasis and survival. The depletion of secretory granules and suspension of SINGD would contribute to this conversion (Figure 1). Indeed, there are observations that overnight fasting was insufficient for in vivo induction of autophagy in mice β-cells, but 24 h-fasting was sufficient\(^2\text{,}^5\).

In conclusion, according to the study by Goginashvili et al.\(^4\), fasted β-cells acutely induced inactivation of PKD and lysosomal degradation of nascent secretory granules, and subsequently activated mTOR through co-localization with lysosomes. mTOR activation suppressed so-called “inductive” autophagy in the starved β-cells. As compulsory induction of autophagy in the β-cells enhanced insulin secretion ex vivo despite low-glucose condition, this strategy of starved β-cells seems appropriate to cope with hypoglycemia in a nutrient-deficient environment. The role of “inductive” autophagy on not only the suppression of insulin secretion but also its stimulation would be further elucidated.

DISCLOSURE
The author declares no conflict of interest.

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