Commentary

MTOR and Beta Cell Adaptation in T2D

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Abbreviations: IFG, impaired fasting glucose MTOR, mechanistic target of rapamycin; ND, nondiabetic; T2D, type 2 diabetes.

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Beta cells are exquisite sensors of the organism’s nutritional status, and a key metabolic regulator via insulin secretion. Systemic insulin requirements vary during the day, but also through life in response to pathophysiological circumstances such as pregnancy or the insulin resistance associated with obesity. These changes impose a burden on beta cells, which must adapt to conditions of higher metabolic load by increasing insulin synthesis and secretion. This adaptation can be achieved by increases in beta cell mass (hyperplasia and hypertrophy), as well as enhanced function per unit of mass.

The key molecular machinery that allows beta cell flexibility is the mechanistic target of rapamycin (MTOR). MTOR, an evolutionarily conserved serine/threonine kinase, exists in 1 of 2 complexes defined by regulatory and targeting subunits Raptor (defining MTORC1) or Rictor (MTORC2). Of these, MTORC1 has emerged as a key sensor of the energetic and nutritional status of the cell, integrating hormonal and metabolic cues. This balance provides regulation of both anabolic and catabolic processes, such as protein synthesis and degradation, and decision trees involved in cell growth and proliferation (1). Specifically, MTORC1 and its upstream signaling regulators are necessary and sufficient to induce beta cell mass adaptation to stress in rodent models (2, 3). These findings had a translational counterpoint in the known toxic effect of MTORC1 inhibition, commonly used in immunosuppressant regimens following solid organ transplantation, on human islets. MTORC1 inhibition is likely causal to delayed post-transplantation diabetes (4), and may complicate interpretations of success of islet transplantation following the Edmonton Protocol (5).

Whether these compelling rodent and pharmacologic data, showing MTORC1 effects on beta cell biology, are also seen in progression of human type 2 diabetes (T2D) was unknown. To address this important question, in this issue of the Journal of Clinical Endocrinology & Metabolism, Ni and colleagues perform histological characterization of MTORC1 activity in beta cells in patients undergoing partial pancreatectomy, presumably for evaluation of a suspicious pancreatic mass (6). After exclusion of patients with a diagnosis of a malignant tumor, the authors enrolled body mass index–matched subjects who were nondiabetic (ND), had impaired fasting glucose (IFG), or had a clinical history of T2D. Although higher than ND subjects, glycated hemoglobin levels were similar and not statistically different in IFG (6.1%) and T2D (6.4%) groups, suggesting the T2D patients were very well controlled. By staining paraffin-fixed sections of pancreatic tissue with an antibody corresponding to a downstream readout of MTORC1 activity (phosphorylation of ribosomal protein S6), the authors determined that beta cell MTORC1 activity positively correlated with fasting blood glucose in ND subjects, but not subjects with IFG or T2D. Intriguingly, beta cell MTORC1 activity was significantly increased in patients with IFG (but not T2D) when compared with ND. A stratification of the IFG cases according to their MTORC1 activity found that IFG patients with higher MTORC1 activity showed greater retention of markers of beta cell functional maturity, such as UCN3 and GLUT2, as compared to patients with lower MTORC1 activity. Overall, these results suggest...
that MTORC1 may act as a compensatory mechanism to
insulin resistance, preserving glucose homeostasis, perhaps
by increasing beta cell functional maturity. These data are
consistent with loss of beta cell maturity in mice lacking
MTORC1 activity by means of Raptor deletion (7). By cor-
ollary, in the absence of MTORC1 activation, inadequate
beta cell compensation may provoke progression to T2D.

This study offers important insight into T2D patho-
physiology, and provides an important example of the
translational work necessary to confirm mechanistic studies
in rodent models. There are also some hidden nuggets of
very interesting data, including the authors finding of large
interislet variability in MTORC1 activity even in the same
person, suggesting cellular heterogeneity that would be
worth investigation in future work, using different meth-
odology (ie, single-cell RNA sequencing). The use of sur-
gical pancreatic specimens is an additional strength, as
rapid fixation may “freeze” labile islet signaling pathways
in time; this avoids potential artifacts induced by laborious
and time-consuming islet isolations that may impose cel-
lar stress. There are also several important limitations of
this study worth acknowledging. For example, it is unclear
which (if any) medications the T2D subjects were taking,
and what influence these may have on islet MTORC1
signaling. Another limitation is in the cross-sectional nature
of the study, which offers us a single view in the progres-
sion of the T2D disease process and prevents firm conclu-
sions about beta cell compensatory mechanisms. Beta cell
compensation and hyperinsulinemia delays T2D progres-
sion; thus, there is great variability and length, and not a
clean demarcation in the beta cell response to insulin resis-
tance. Longitudinal studies are not currently feasible, given
need for multiple biopsies. There is, however, hope on the
horizon, as techniques for non-invasive imaging of pan-
creas continue to improve.

Looking at the bigger picture, although MTORC1 is
clearly important for beta cell compensation, MTORC1
inhibitors extend lifespan in mice and other model organ-
isms. So while chronic MTORC1 activation may lead to
increased beta cell mass, it may also be contributory to beta
cell demise. How might that be? In the face of chronic in-
sulin resistance, a progressive increase in beta cell work-
load may lead to oxidative and endoplasmic reticulum
stress. The cellular defense to this chronic stress is to in-
crease autophagy, which is fundamental for the recycling of
damaged proteins and organelles. Several decades of work
have shown that MTORC1 is a key negative regulator of
autophagy, across tissues and species. Consistently, consti-
tutive MTORC1 activity in beta cells impairs autophagy,
leading to accumulation of dysfunctional mitochondria
and beta cell death (3, 8). Combining these data with those
from Ni et al, increase in beta cell MTORC1 activity may
be necessary for beta cell compensation in the insulin-
resistant state, but if excessive, may be contributory to beta
cell failure and T2D. Further research is needed to disen-
tangle these dichotomous roles of MTORC1 on human
beta cell pathophysiology, to understand the role of this
critical signaling component in T2D progression, and per-
haps, therapy.

Additional Information

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