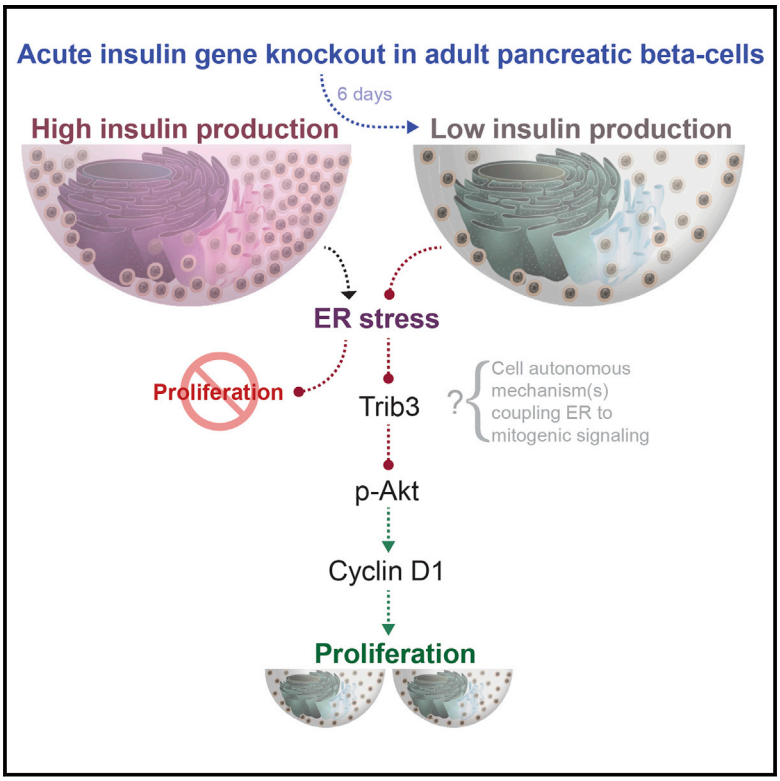
Article

Cell Metabolism

Reduced Insulin Production Relieves Endoplasmic Reticulum Stress and Induces β Cell Proliferation

Graphical Abstract



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In Brief

Szabat et al. show that the normally high rate of insulin production acts as a brake on adult β cell proliferation in mice. Reducing this burden via acute deletion of the insulin gene relieves baseline ER stress, increases mitogenic signaling, and promotes cell-cycle progression in a cell-autonomous manner.

Highlights

- Acute reduction of insulin production reverses baseline ER stress
- Loss of insulin production reduces Trib3 and hyper-activates Akt
- Reduced insulin production increases β cell proliferation cell autonomously
- Insulin knockout induces glucagon mis-expression via hyperglycemia

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Reduced Insulin Production Relieves Endoplasmic Reticulum Stress and Induces β Cell Proliferation

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SUMMARY

Pancreatic β cells are mostly post-mitotic, but it is unclear what locks them in this state. Perturbations including uncontrolled hyperglycemia can drive β cells into more pliable states with reduced cellular insulin levels, increased β cell proliferation, and hormone mis-expression, but it is unknown whether reduced insulin production itself plays a role. Here, we define the effects of ~50% reduced insulin production in *Ins1*$^{-/-}$:*Ins2*$^{f/f}$:*Pdx1*Cre^{ERT}:mTmG mice prior to robust hyperglycemia. Transcriptome, proteome, and network analysis revealed alleviation of chronic endoplasmic reticulum (ER) stress, indicated by reduced *Ddit3*, *Trib3*, and *Atf4* expression; reduced *Xbp1* splicing; and reduced phospho-eIF2α. This state was associated with hyper-phosphorylation of Akt, which is negatively regulated by Trib3, and with cyclinD1 upregulation. Remarkably, β cell proliferation was increased 2-fold after reduced insulin production independently of hyperglycemia. Eventually, recombined cells mis-expressed glucagon in the hyperglycemic state. We conclude that the normally high rate of insulin production suppresses β cell proliferation in a cell-autonomous manner.

INTRODUCTION

Pancreatic β cells are long-lived specialized secretory cells tasked with the production of all circulating insulin, which is essential for healthy long-term survival (Mezza and Kulkarni, 2014). When stressed, β cells can exit their mature differentiated state into states of dysfunction and dedifferentiation, including conditions wherein β cells have little to no insulin protein (Szabat et al., 2012; Weir et al., 2013). Dedifferentiation has been proposed as an important mechanism of β cell dysfunction in diabetes (Akirav et al., 2008; Brereton et al., 2014; Guo et al., 2013; Talchai et al., 2012; Wang et al., 2014; Weir et al., 2013) but remains poorly understood. For example, it is not clear whether the loss of insulin production in adult β cells is causally linked to proliferation, dedifferentiation, or transdifferentiation (Szabat et al., 2012). The inverse relationship between differentiation and proliferation is illustrated by the demonstration that halting proliferation in a human β cell line dramatically increased insulin content (Scharfmann et al., 2014), but it is not known whether inhibiting insulin production alone might be sufficient to increase adult β cell proliferation. Germ-line disruption of both insulin genes in mice caused severe diabetes and neonatal death, precluding analysis of adult β cells in that model (Duvillié et al., 2002). In post-natal mice, near complete β cell ablation increases β cell proliferation (Nir et al., 2007) and plasticity of other islet cell types (Chera et al., 2014; Thorel et al., 2010), but it is not clear to what extent the effects in these acute injury models are due to the loss of insulin, rather than the loss of β cells. To address the question of whether the burden of producing large quantities of insulin normally suppresses proliferation in a cell-autonomous manner, one must acutely reduce insulin in adult β cells. Such an animal model would provide, for the first time, an opportunity to study the fates of cells that had lost their ability to produce their primary secreted protein.

In the present study, we use transcriptomics, proteomics, and metabolomics to define systems-wide changes that accompany the acute loss of insulin production in adult mouse β cells following deletion of two floxed *Ins2* alleles in mice already lacking both *Ins1* alleles. This unbiased survey identified a reversal of baseline ER stress in cells with reduced insulin production. We observed a significant increase in proliferation prior to the inevitable robust hyperglycemia in this model and