Editorial

Regulation of Postnatal β Cell Mass

Pancreatic β cells are responsible for producing all of the insulin required by an organism to maintain glucose homeostasis. Defects in the development, maintenance, or expansion of β cell mass can result in diabetes. Current treatments for diabetes primarily focus on replacing insulin (Types 1 and 2 diabetes) and improving β cell function (Type 2 diabetes only). However, increasing a patient's own β cell mass or preventing β cell loss could improve or cure their condition. Currently, efforts are ongoing in several laboratories to differentiate β cells from precursor populations and to expand β cells *in vitro* to generate an unlimited supply for transplantation. Theoretically, the same could be done *in vivo* to regenerate and/or expand a patient's existing β cell population. Thus, it is important to understand the molecular regulation of β cell mass development, survival, and expansion.

β cell mass is increased by β cell neogenesis (differentiation from precursor cells), β cell proliferation, and β cell hypertrophy (increased cell size), while β cell mass is decreased by β cell death and atrophy (decreased cell size). Although it was once thought that β cell number did not expand after birth, prevailing evidence now shows that new β cells can form throughout life in both rodent models and humans. The primary mechanism by which new β cells form during adulthood in the mouse is via proliferation rather than neogenesis, although this is less clear in humans. A reduced β cell population at birth may result in fewer β cells available to enter the cell cycle later in life, and therefore a reduction in adult β cell mass expansion leading to diabetes with age. Under normal circumstances during adulthood, β cells are a slowly-renewing population, with steady low levels of proliferation and apoptosis, although β cell proliferation normally declines with age. In addition to maintaining β cell mass under normal circumstances, an organism must also be able to alter its β cell mass in accordance with its requirements for insulin. In states of insulin resistance, such as pregnancy and obesity, β cell mass is known to increase, and when compensatory β cell mass expansion is inadequate, diabetes ensues. Inherent defects that render β cells more susceptible to apoptosis, would also result in a negative balance in β cell mass, and could contribute to diabetes risk.

This special issue of *The Open Endocrinology Journal* focuses on our current understanding of the genetics and signaling pathways that augment β cell mass and enhance β cell survival postnatally. Each of the articles in this issue provides an in-depth review of a different facet of β cell mass regulation, and in addition provides new, previously unpublished data highlighting the ongoing work in the field. Soundarapandian *et al*. compare and contrast the regulation of β cell mass homeostasis in rodents versus humans, and among different human populations. In addition, the authors discuss the genetic basis for the difference between closely related mouse strains in their susceptibility to diabetes. This review indicates the value of the mouse as a model amenable to testing gene function via genetic manipulations, but clearly points out the limitations of this species as a model for β cell mass regulation in humans. From this starting point, the issue then discusses in some detail, intracellular signaling pathways that have been shown to play a major role in regulating β cell mass. Zeng *et al*. review the evidence that modulation of PTEN (phosphatase and tensin homologue deleted in chromosome 10), a negative regulator of cell growth, represents an attractive candidate for enhancing β cell mass *in vivo*. Cras-Meneur *et al*. review the regulation of β cell mass by the Tuberous Sclerosis Complex, focusing on gene inactivation in mice, while Rohatgi *et al*. provide a comprehensive review on mTOR, GSK-3, and β-catenin signaling, particularly in human β cells. These reviews nicely highlight the multiple parallel and intersecting pathways that culminate in increased β cell replication and β cell mass.

In addition, to second messenger pathways acting downstream of growth factors, this issue reviews metabolic alterations that can increase β cell replication and mass. In most overweight individuals, β cell mass increases to compensate for increased insulin resistance, and diabetes does not ensue. Two reviews discuss nutrients that likely contribute to the expansion of β cell mass that normally accompanies weight gain. The review from Garcia-Ocana and Alonso summarizes the existing *in vitro* and *in vivo* evidence that glucose stimulates β cell replication. The article from Golson *et al*. explores the impact of high fat diet on

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insulin responsive tissues and how this may result in altered β cell replication and function. While much of the issue stresses mechanisms for promoting β cell replication as a means for augmenting β cell mass, the issue ends with an article by Kondegowda *et al*. that summarizes the factors that promote survival of existing β cells as a means of maintaining β cell mass. A combination of increased β cell replication and enhanced β cell survival in the face of aging, increased DNA damage and oxidative stress, likely represents the best strategy for preventing the decline in β cell mass that can precipitate Type 2 diabetes.

In understanding how β cell mass is established, maintained, and altered, new therapeutic targets will be identified for the treatment of diabetes. Ultimately, the processes of β cell neogenesis, replication, and survival will likely be controlled *in vivo* as a means to reverse or prevent diabetes.

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