

# Maintenance of $\beta$ Cell Mass Requires Foxm1b

Hongjie Zhang, David E. Lowe, Amanda M. Ackermann, Xue Feng, Usa G. Kopsombut, Robert H. Costa, and Maureen Gannon

Medicine/Diabetes and Endocrinology,  
Vanderbilt University Medical Center, Nashville,  
TN

---

$\beta$  cell mass changes throughout life in response to metabolic demands. Increases in  $\beta$  cell mass are thought to occur via replication of existing  $\beta$  cells and  $\beta$  cell neogenesis from progenitor cells. Since diabetes results from an absolute or relative inadequate functional  $\beta$  cell mass, genes involved in maintaining or altering  $\beta$  cell mass are candidates for being affected in diabetic individuals. The Foxm1b transcription factor is expressed in proliferating cells and activates cell cycle genes. We found that Foxm1b is strongly expressed in embryonic and neonatal endocrine cells when these cells are highly proliferative but decreases dramatically after weaning. Using a Cre-lox strategy, we generated mice with a pancreas-specific inactivation of Foxm1b. Foxm1b <sup>$\Delta$ panc</sup> male mice were glucose intolerant at 6 weeks of age and diabetic by 9 weeks of age, suggesting a role for Foxm1b in normal  $\beta$  cell function. Examination of mutant pancreata revealed a gradual loss of  $\beta$  cell mass between 4 and 9 weeks of age, associated with reduced  $\beta$  cell proliferation,  $\beta$  cell necrosis, and reduced pancreatic insulin content. The  $\beta$  cell phenotype is manifested after birth, despite Foxm1b inactivation occurring early in development. Our findings suggest that the factors responsible for regulating  $\beta$  cell mass during embryogenesis differ from those that function during adulthood and concur with previous studies in which other cell cycle proteins were found to be specifically required by postnatal  $\beta$  cells for proper proliferation and maintenance of  $\beta$  cell mass. Because both  $\beta$  cell neogenesis and proliferation are thought to contribute to expansion of  $\beta$  cell mass during embryogenesis, and proliferation alone is thought to be the primary contributor to  $\beta$  cell turnover during adulthood, it is possible that these processes are differentially regulated. In summary, our studies show that Foxm1b is required for proper postnatal  $\beta$  cell proliferation and maintenance of  $\beta$  cell mass in adult mice. A thorough understanding of Foxm1b regulation of  $\beta$  cell mass may lead to strategies for maintaining  $\beta$  cell mass and enhancing  $\beta$  cell proliferation in diabetics.