

Pancreatic beta cells play a critical role in maintaining glucose homeostasis by precisely sensing nutrients and regulating insulin production. Among the key regulators of the adaptive response to environmental cues, Transcription Factor EB (TFEB) and its homolog TFE3 have emerged as crucial players in controlling cell metabolism. This study explores the role of TFEB and TFE3 in regulating beta-cell function and insulin gene expression in response to variations in nutrient availability. The research reveals that nutrient deprivation in beta cells activates TFEB/TFE3, leading to the suppression of insulin gene expression. Notably, TFEB overexpression alone is sufficient to inhibit insulin transcription. Depletion of both TFEB and TFE3 in beta cells prevents the suppression of insulin gene expression in response to amino acid deprivation. ChIP-seq analysis uncovers the binding of TFEB to super-enhancer regions that regulate insulin transcription. In vivo experiments involving conditional, beta-cell-specific Tfeb-overexpressing mice and Tfeb/Tfe3 double-knockout mice demonstrate severe alterations in insulin transcription, secretion, and glucose tolerance. These findings underscore the physiological importance of TFEB and TFE3 as key mediators of pancreatic function. In summary, this study unravels a nutrient-controlled transcriptional mechanism orchestrated by TFEB and TFE3, shedding light on their pivotal role in regulating insulin production. The identified mechanism operates at both cellular and organismal levels, significantly contributing to our understanding of glucose homeostasis.