ERRgamma Is Required for the Metabolic Maturation of Therapeutically Functional Glucose-Responsive beta Cells.

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Public Summary:
Pancreatic beta cells undergo postnatal maturation to achieve maximal glucose-responsive insulin secretion, an energy intensive process. We identify estrogen-related receptor gamma (ERRgamma) expression as a hallmark of adult, but not neonatal beta cells. Postnatal induction of ERRgamma drives a transcriptional network activating mitochondrial oxidative phosphorylation, the electron transport chain, and ATP production needed to drive glucose-responsive insulin secretion. Mice deficient in beta cell-specific ERRgamma expression are glucose intolerant and fail to secrete insulin in response to a glucose challenge. Notably, forced expression of ERRgamma in iPSC-derived beta-like cells enables glucose-responsive secretion of human insulin in vitro, obviating in vivo maturation to achieve functionality. Moreover, these cells rapidly rescue diabetes when transplanted into beta cell-deficient mice. These results identify a key role for ERRgamma in beta cell metabolic maturation, and offer a reproducible, quantifiable, and scalable approach for in vitro generation of functional human beta cell therapeutics.

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