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Publication

# Argonaute2 Mediates Compensatory Expansion of the Pancreatic $\beta$ Cell

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Pancreatic $\beta$ cells adapt to compensate for increased metabolic demand during insulin resistance. Although the microRNA pathway has an essential role in $\beta$ cell proliferation, the extent of its contribution is unclear. Here, we report that miR-184 is silenced in the pancreatic islets of insulin-resistant mouse models and type 2 diabetic human subjects. Reduction of miR-184 promotes the expression of its target Argonaute2 (Ago2), a component of the microRNA-induced silencing complex. Moreover, restoration of miR-184 in leptin-deficient ob/ob mice decreased Ago2 and prevented compensatory $\beta$ cell expansion. Loss of Ago2 during insulin resistance blocked $\beta$ cell growth and relieved the regulation of miR-375-targeted genes, including the growth suppressor Cadm1. Lastly, administration of a ketogenic diet to ob/ob mice rescued insulin sensitivity and miR-184 expression and restored Ago2 and $\beta$ cell mass. This study identifies the targeting of Ago2 by miR-184 as an essential component of the compensatory response to regulate proliferation according to insulin sensitivity.

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