DIABETES

Preventing β -cell apoptosis and T2DM with microRNAs—a role for miR-200?

In vitro evidence suggests that members of the microRNA-200 (miR-200) family are involved in pancreatic β -cell apoptosis. In a new study, investigators provide the first *in vivo* evidence that miR-200 family members initiate β -cell apoptosis during metabolic stress; furthermore, removal of these miRs ameliorates type 2 diabetes mellitus (T2DM) in mice and apoptosis in human islets.

The team first confirmed that miR-200 is highly expressed in the endocrine pancreas; and in *db/db* mice on the C57BLKS/J background, which develop uncontrolled T2DM, miR-200 levels were significantly increased. The team then created a transgenic line in which *miR-141* and *miR-200c* were specifically overexpressed in β cells. These mice developed a T2DM-like phenotype and, importantly, had more islet-cell apoptosis than wild types littermates.

To test if an overall reduction in miR-200 levels could protect against β -cell apoptosis,

the investigators generated a mouse line, in which all five miR-200 family members were genetically ablated. Complete loss of miR-200 did not affect β -cell function or glucose tolerance in unstressed conditions; however, these mice had higher plasma insulin levels and β -cell mass than wild type mice when treated with streptozotocin, which induces β -cell apoptosis and a T2DM phenotype. These findings were replicated in other mouse models of T2DM, such as diet-induced obese mice and the Akita line, which have a mutation in *Ins2*.

Expression of *Dnajc3*, *Jazf1*, *Rps6kb1* and *Xiap* (which encode anti-apoptotic proteins), and *Dusp26* (which encodes a prosurvival signalling protein) were reduced in the islets of miR-200 knockout mice, suggesting that these miRs promote β -cell survival. The team also identified that the tumour suppressor, Trp53, is regulated by miR-200, and ablation of *Trp53* or its downstream target, *Bax*,

prevents miR-200-induced apoptosis of β cells and the resultant T2DM phenotype.

Importantly, inhibiting *miR-200c* in primary human islet cells prevented the expression of pro-apoptotic genes that are induced by cytokines associated with T2DM. The investigators believe that inhibiting miR-200 activity might one day be used as a therapeutic strategy against this disease.

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