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TARGET IDENTIFICATION

Stopping β-cell death in diabetes

Apoptotic death of pancreatic β-cells, which is a characteristic of both type 1 and type 2 diabetes, is induced by inflammatory and oxidative insults but the triggering mechanisms are not fully understood. A recent paper published in *Nature Medicine* has identified a new regulator of β-cell apoptosis, mammalian STE20–like protein kinase 1 (MST1), which could be a new target for the treatment of diabetes.

The serine/threonine kinase MST1 is a target and activator of caspases and mediates several apoptotic signalling pathways, which led the authors to hypothesize that it could initiate apoptotic signalling in β-cells. They first showed that MST1 was activated during diabetic conditions, such as in islets from individuals with type 2 diabetes and in islets from mouse models of diabetes (*db/db* mice and mice with diet-induced obesity). The activation of MST1 in islets correlated with levels of β-cell apoptosis.

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Further investigation of MST1-induced β-cell apoptosis, using overexpression of MST1 in human islets and a rat β-cell line, showed that apoptosis occurred via the mitochondria-dependent pathway. Namely, MST1 activated the BCL-2-interacting mediator of cell death (BIM), and this apoptotic pathway was controlled by upstream AKT and JUN N-terminal kinase (JNK) signalling.

Because results from studies in islets suggested that a reduction in glucose-stimulated insulin secretion following MST1 overexpression could not be accounted for solely by the induction of apoptosis, the authors hypothesized that MST1 activation could also alter β-cell-specific gene transcription. The β-cell transcription factor PDX1 (pancreas/duodenum homeobox protein 1), which is mislocalized in diabetes, was their chosen target. Indeed, they showed that MST1 downregulated the expression of target genes (including those encoding insulin, the glucose transporter GLUT2 and glucokinase) and promoted the phosphorylation of PDX1 at a site located within its transactivational domain. This led to the ubiquitylation and subsequent degradation of PDX1, which then impaired β-cell function.

Next, the authors studied the effects of MST1 deficiency. Genetic knockdown of MST1 in human or mouse islets, or in a rat β-cell line, improved β-cell survival and function. Mice with type 2 diabetes (induced by streptozotocin injections or a high-fat diet) that lacked MST1 had improved hyperglycaemia, glucose tolerance, insulin secretion and a lower rate of β-cell apoptosis compared to wild-type mice with type 2 diabetes. Moreover, mice that lacked MST1 had a greater β-cell mass, which occurred as a result of enhanced β-cell survival and proliferation.

So this study showed that MST1 modulates β-cell survival by inducing apoptosis and modifying the action of the transcription factor PDX1. Therefore, further work to identify inhibitors of this target is warranted, as these could protect β-cells against the effects of autoimmune attack in type 1 diabetes and preserve β-cell mass and function in type 2 diabetes.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Ardestani, A. *et al.* MST1 is a key regulator of beta cell apoptosis and dysfunction in diabetes. *Nature Med.* http://dx.doi.org/10.1038/nm.3482 (2014)
FURTHER READING Vetere, A. *et al.* Targeting the pancreatic β-cell to treat diabetes. *Nature Rev. Drug Discov.* **13**, 278–289 (2014)