DIABETES

A Kit for increasing β -cell function

Mice in which the mast/stem cell growth factor receptor Kit is overexpressed specifically in β cells are protected against diabetes mellitus, show Rennian Wang and colleagues in a study published in *Diabetologia*.

Kit (also known as c-Kit) is a tyrosine kinase that plays a part in β -cell development. Previous studies in a mouse model with a loss-of-function *Kit* mutation (*c-Kit^{Wv}* mice) have also indicated a relationship between Kit and β -cell function, as glucose homeostasis is impaired in these mice leading to early-onset diabetes mellitus. However, “those were global mutants,” comments Michael Welsh (Uppsala University, Sweden), who was not involved in the study, “making it hard to exclude indirect effects”.

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To elucidate the mechanisms by which Kit acts on β -cell proliferation, function and survival *in vivo*, Wang and colleagues developed a transgenic mouse model in which the human *KIT* cDNA is overexpressed exclusively in β cells under the control of the rat insulin promoter. “The major surprise of the study is that β -cell function was improved

so much in this transgenic mouse,” says Welsh. In addition to improvements in β -cell function and insulin secretion, the researchers observed increased β -cell mass and β -cell proliferation in transgenic mice consuming a diabetes-mellitus-inducing high-fat diet, in comparison with wild-type mice consuming the same diet. By crossbreeding the transgenic mice with the *c-Kit^{Wv}* mice, the investigators also showed that the diabetes mellitus phenotype typical of *c-Kit^{Wv}* mice could be rescued by overexpression of *KIT* in β cells.

The researchers then explored the downstream mechanisms of action of Kit in β cells by analysing islets isolated from transgenic animals. Overexpression of *KIT* upregulated the Akt/Gsk3 β pathway, which could underlie promotion of β -cell function and insulin secretion. “The hypothesis is very attractive and has some experimental support, but there might be twists to the story that are not yet apparent, so I’m still a bit cautious,” comments Welsh. “It is now important that we determine, at the cellular and molecular level, how Kit interacts with other factors and receptors to mediate downstream mechanisms in the developing pancreas and in β cells,” Wang agrees.

“Kit is a potential therapeutic target to influence β -cell function and proliferation,” says Wang, who is also interested in identifying molecules that cooperate with Kit in mediating β -cell survival and function, which could be additional targets for managing diabetes mellitus.

Welsh observes that, upon starvation, blood glucose levels dropped faster in transgenic animals than in controls; therefore, a therapeutic approach built on the basis of Kit activation might carry a risk of severe hypoglycemic episodes in treated patients. In addition, he points out that mouse β cells have a much higher proliferative capacity than adult human β cells, so future research should be aimed at investigating whether “the strategy of overexpressing growth factor receptors, particularly Kit, has the same dramatic effect on human β cells or if these cells have some major block in replication that prevents substantial proliferation”. In line with Wang’s opinion, Welsh comments that detailed elucidation of the signalling responsible for the effects of Kit might reveal a druggable β -cell-specific target that could reproduce the results of the study. “Clinical implications of the findings relate to the success of these future endeavours,” he concludes.

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