Bengt-Frederik Belgardt[1] and Eckhard Lammert[1,2]

DYRK1A: A Promising Drug Target for Islet Transplant–Based Diabetes Therapies

Diabetes 2016;65:1496–1498 | DOI: 10.2337/dbi16-0013

COMMENTARY

A hallmark of all forms of diabetes, including type 2, is abnormal insulin release by pancreatic islets. This occurs either through impaired β-cell function and/or a reduction in β-cell number resulting from apoptosis or dedifferentiation (1). Currently available drugs only temporally ameliorate these processes, and many patients need insulin injections to reduce hyperglycemia 10–15 years after diagnosis (2). Mass transplantation of islets is not feasible due to the low availability of donor islets and side effects caused by immunosuppression. Further, although notable progress in targeted differentiation of stem cells into functional β-cells has been made (3), this approach has not yet advanced into routine clinical practice. An obvious therapeutic approach to improve islet transplantation would be to pharmacologically stimulate the proliferation of β-cells (Fig. 1) (4). These pharmacological agents could be used either to treat human islets before transplantation or to supplement protocols that transform stem cells into transplantable human islets. Alternatively, they could be used as oral medication to enhance β-cell proliferation once safety concerns are fully addressed.

β-Cell proliferation is rare in both adults who are healthy and adults who have diabetes, and the molecular underpinnings of the natural resistance of β-cells to undergo mitosis are complex (5), difficult to study (6), and species dependent (7). Nonetheless, several small molecules have been reported to induce human β-cell proliferation (8–10), among them the adenosine kinase inhibitor 5-iodotubercidin (5-IT) (11). The latter compound was previously identified to promote β-cell and δ-cell proliferation in murine (and porcine) islets (12).

In this issue of *Diabetes*, Dirice et al. (8) convincingly demonstrate that 5-IT also stimulates human β-cell proliferation in vitro, as well as upon transplantation of human islets into mice in vivo. Notably, the authors report that this effect appears to be specific to endocrine pancreatic cells, in particular the β-cells (Fig. 1), and they did not find any increase in cell proliferation in several nonpancreatic tissues (8). Of significance, long-term treatment of islets with 5-IT improved glucose-stimulated insulin secretion (8). The authors also present gene expression analyses showing that 5-IT enhanced expression of genes involved in proliferation (such as cyclins necessary for mitosis) and secretory function (such as glucose transporter 2) (8).

When the authors tested another adenosine kinase inhibitor, they surprisingly failed to observe increased proliferation rates (8). As most chemical compounds, especially kinase inhibitors, never exhibit exclusive specificity for only one target (13), the authors reasoned that 5-IT targets another enzyme to induce β-cell proliferation in the human setting. They consequently screened for kinases affected by 5-IT treatment and found that this treatment inhibited the dual-specificity tyrosine phosphorylation–regulated kinase DYRK1A and several other related kinases with high affinity (8). This is a crucial finding, as recent, independent reports demonstrated that the inhibition of DYRK1A by structurally unrelated compounds, including the plant-derived alkaloid harmine (9), switches on NFATc (nuclear factor of activated T-cells, cytoplasmic), a Ca^{2+}-dependent transcription factor, in order to trigger human β-cell proliferation (8–10). The crucial role of NFATc in β-cell proliferation and insulin secretion has been previously established (14). Dirice et al. (8) went on to show that the effect of 5-IT on β-cell proliferation can be inhibited by concomitantly blocking NFATc activation.

Previous studies using genetically modified mice showed that partial ablation of DYRK1A inhibits β-cell growth and causes diabetes (15). In turn, genetic overexpression is beneficial in the context of diabetes (16). However, these

[1]Institute for Beta Cell Biology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research, and German Center for Diabetes Research (DZD e.V.), Düsseldorf, Germany
[2]Institute for Metabolic Physiology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
Corresponding author: Eckhard Lammert, lammert@hhu.de.

See accompanying article, p. 1660.

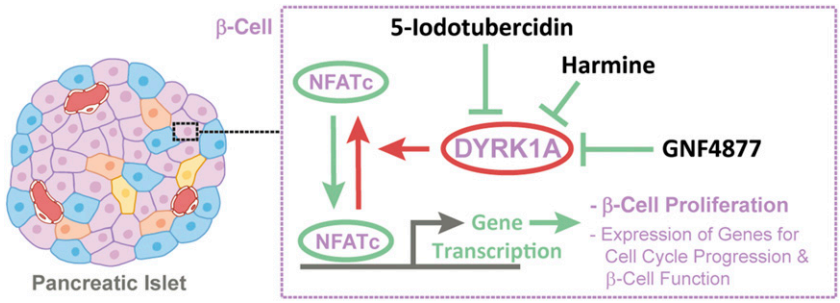

Figure 1—Pancreatic islets are composed of different endocrine cells, in particular insulin-secreting β-cells (shown in pink). These cells secrete insulin into a dense microvascular network for distribution to peripheral tissues. Several structurally unrelated inhibitors of DYRK1A (e.g., 5-IT, harmine, and GNF4877) have been recently identified to promote NFATc-dependent β-cell proliferation in human pancreatic islets (8–10). Notably, these inhibitors promote cell cycle progression and expression of genes required for β-cell function. Green, factors stimulating β-cell proliferation; red, factors inhibiting β-cell proliferation.

findings are opposed to the effects observed when DYRK1A is pharmacologically inhibited (8–10). It is noteworthy that in genetic loss- and gain-of-function experiments (15,16), DYRK1A expression is apparently altered in all tissues from early embryonic development to adulthood. A distinctive role of DYRK1A in embryonic tissues (vs. adult) might thus explain these opposing results. Furthermore, gene deletion has full penetrance in the entire organism, whereas the compounds used to target DYRK1A might not reach all tissues relevant to glucose homeostasis. Finally, inconsistencies between mouse and human β-cell proliferation might further contribute to the contradictory results (7).

Multiple other kinases related to DYRK1A exist, which are also inhibited by 5-IT as described by Dirice et al. (8). It will be interesting to investigate if these related kinases are expressed at the protein level in β-cells and if they are involved in the observed mitogenic effects of 5-IT. Further, DYRK1A has been linked to numerous other biological functions, including neurological processes, especially in the context of Down syndrome (17). Of relevance, a recent report using conditional ablation of DYRK1A in mice showed that DYRK1A controls lymphocyte differentiation (18). For application as an antidiabetes drug, the compound requires further optimization followed by studies to comprehensively address drug safety. However, the current findings already warrant testing DYRK1A inhibitors in islet transplant–based diabetes therapies. For example, 5-IT could be applied in vitro to human islets to stimulate β-cell proliferation and improve functionality imminently after their transplantation. These inhibitors could also be added to increase β-cell density and functionality in islets derived from stem cells with the ultimate goal of improving the success of subsequent islet transplantations.

In conclusion, Dirice et al. (8) used advanced molecular tools to demonstrate that 5-IT inhibits DYRK1A with high affinity and induces β-cell proliferation in human islets in vitro and in vivo after transplantation. This study also prompts additional research on how DYRK1A activity is endogenously inhibited to facilitate β-cell proliferation (for example, during pregnancy and obesity) to help prevent diabetes.

Acknowledgments. The authors thank Molly Kelly-Goss of the Peirce-Cottler Laboratory at the University of Virginia (Charlottesville, VA) for proofreading the manuscript and Yousun Koh, Koh Scientific Illustration, for the islet artwork.
Funding. The research of B.-F.B. and E.L. has been funded by the German Center for Diabetes Research (DZD e.V.), the Federal Ministry of Health, and the Ministry for Innovation, Science and Research of North Rhine-Westphalia.
Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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