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Safety in numbers: Identifying multiple targets for beta cell proliferation

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Abstract

Combined inhibition of DYRK1A and TGF- β pathways synergistically enhances proliferation and differentiation of human pancreatic beta cells.

The adult pancreatic beta cell is highly evolved to efficiently control glucose homeostasis, and loss of beta cell function leads to diabetes mellitus. The replicative capacity of beta cells, however, diminishes with age, with an inverse correlation between proliferation and functional maturation. In the last decade, in order to expand the pools of insulin-producing beta cells, numerous efforts have been directed toward identifying factors that can trigger beta cell replication. Such efforts have underscored the characteristic resistance of adult pancreatic beta cells to replication.

Wang and colleagues demonstrated that combining two different strategies, namely the inhibition of the enzyme dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and the inhibition of the transforming growth factor- β superfamily (TGF- β SF), induces a synergistic increase in proliferation and differentiation of mature human beta cells. The same group of researchers had previously revealed using genomic and transcriptomic analyses that both DYRK1A and TGF- β SF signaling pathways were markedly activated in human insulinoma. In the present work, the authors used a straightforward flow cytometric method to assess human beta cell numbers. The rates of proliferation they observed, in the 5 to 8% range, are unprecedented and even exceed the proliferation rate commonly detected in the first year of life (the only stage of human development at which an appreciable beta cell proliferation occurs). Moreover, the authors were able to translate the efficacy of such combined inhibition from in vitro systems to different, physiologically relevant in vivo models, including the partial (60%) pancreatectomy murine model and human islets transplanted in the NOD-SCID mouse. Mechanistically, the authors showed that inhibiting DYRK1A stimulated cell-cycle activators such as cyclins and cyclin-dependent kinases, whereas the TGF- β SF inhibitors preferentially repressed cell-cycle inhibitors.

Comment on:

P. Wang, E. Karakose, H. Liu, E. Swartz, C. Ackeifi, V. Zlatanic, J. Wilson, B. J. González, A. Bender, K. K. Takane, L. Ye, G. Harb, F. Pagliuca, D. Homann, D. Egli, C. Argmann, D. K. Scott, A. Garcia-Ocaña, A. F. Stewart, Combined inhibition of DYRK1A, SMAD, and Trithorax pathways synergizes to induce robust replication in adult human beta cells.

The present findings demonstrate for a dual therapeutic approach that acts in a synergistic manner to boost adult beta cell proliferation and differentiation. This finding could make a treatment to restore beta cell deficiency and function in both type 1 and 2 diabetes more feasible in the future.

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