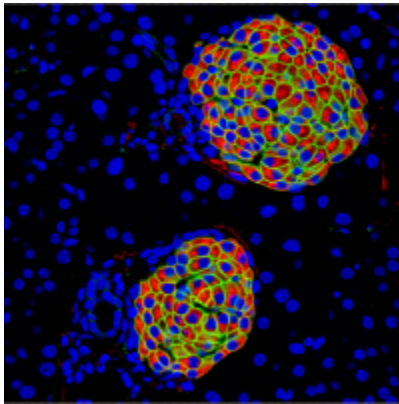


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Pancreatic beta-cell boost in mice paves way for future diabetes treatments



A cross-section of islets of Langerhans, a cluster of cells within the pancreas that are responsible for the production and release of hormones that regulate glucose levels. Insulin in beta cells is stained red, Glut 2 in endocrine cells is stained in green and cell nuclei are stained in blue. Credit: Miguel Angel Maestro/CRG

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A research team has uncovered the role of a gene that is critical to boosting the number of insulin-producing cells during the early development of the pancreas. The findings could bolster diabetes research efforts and eventually lead to new replacement therapies for the disease. The findings are published in the journal [Genes and Development](#).

Researchers at the Centre for Genomic Regulation (CRG), the Bellvitge Biomedical Research Institute (IDIBELL) and the University of Barcelona studied the RE1 Silencing Transcription Factor gene, also known as REST, in mouse and zebrafish models as well as in human pancreatic organoids. Researchers have previously suspected a role for this gene in pancreas development, though studies so far have been inconclusive.

They found that REST is expressed in embryonic pancreatic cells which are yet to differentiate, also known as progenitor cells, as well as in adult cells which form the pancreatic duct. The researchers did not detect REST activity in adult beta-cells that produce insulin.

Experiments with mouse models revealed that knocking the REST gene out at the early embryonic stage, before the pancreas is formed, resulted in doubling the number of insulin-

producing cells. The cells were maintained into adulthood, with all mice showing normal weight. Further experiments using zebrafish models found similar boosts to beta-cell formation.

Inactivating REST was not able to boost beta cell formation after the pancreas has already formed. Mice with inactivated rest soon after birth exhibited a short-lived boost to endocrine cell formation, but this was not sustained through adulthood. Inactivating REST in human pancreatic organoids did not lead to beta-cell formation, though researchers did detect increased activity of endocrine genes.

“Though important for the development of the pancreas, we have shown that REST is not the sole guardian of endocrine differentiation. However, if one day we come up with a future cocktail of drugs to boost insulin-producing cells in the pancreas, I suspect that REST inhibitors would be part of the recipe. We are now testing whether REST inhibitors can be used to artificially boost the formation of beta cells in a dish,” says **Jorge Ferrer**, senior author of the study and Group Leader of the Regulatory Genomics and Diabetes at the CRG.

New therapies and treatments that can boost or replace the number of insulin-producing beta cells in the pancreas would transform the treatment of diabetes, which affects over 400 million people worldwide. For people with type-1 diabetes, the only alternative treatment to daily insulin shots are transplantations, requiring potential side effects through taking immunosuppressant medication and hampered by a shortage of organ donors. Being able to boost existing numbers directly in the pancreas would circumvent many of these hurdles.

“REST joins a very short list of dominant suppressors of endocrine differentiation during pancreas development,” says **Meritxell Rovira**, co-author of the study and researcher with joint affiliation with IDIBELL and the University of Barcelona. “REST modulators will most likely play an important role for future manipulations to promote endocrinogenesis in experimental model systems or replacement therapies for diabetes.”