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DIABETES

β-cell heterogeneity — key to unlocking islet regeneration

New research has identified a subpopulation of immature adult β cells that is proliferative and can also be differentiated into mature insulin-producing β cells. The findings published in *Nature* by researchers from the Helmholtz Centre, Munich, Germany, represent a step towards replacing dysfunctional or lost β cells in patients with diabetes mellitus.

"Although different subpopulations of β cells have been known to exist for over 50 years, the mechanisms underlying this heterogeneity have remained unknown due to a lack of molecular markers capable of distinguishing between the different subpopulations," explains lead investigator Heiko Lickert. "We, therefore, screened for markers that could subdivide insulin-producing β-cell populations and identified *Fltp* (encoding the protein Flattop), a Wnt/planar cell polarity (PCP) effector and reporter gene involved in the acquisition of tissue polarity and 3D architecture."

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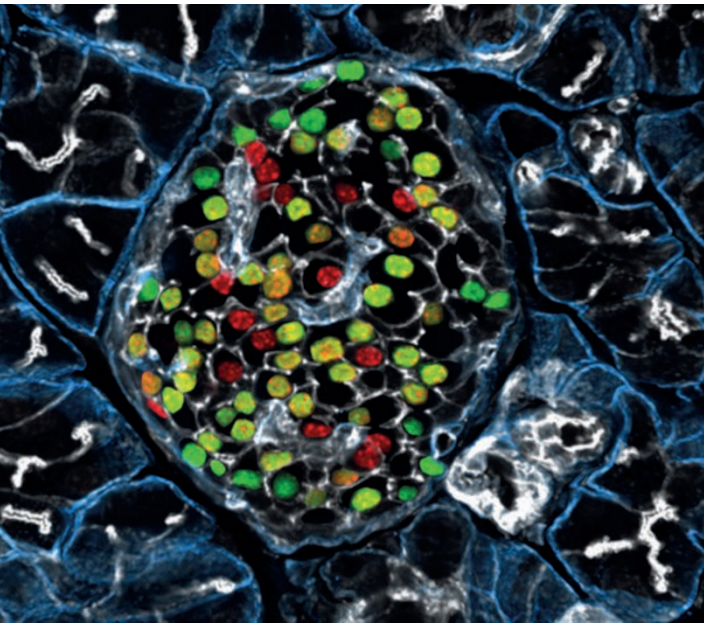

Helmholtz Zentrum München/Heiko Lickert/Erik Bader

To distinguish between β cells expressing *Fltp* from those not expressing the gene, the investigators generated a knockin/knockout mouse ($Fltp^{ZV}$), in which the open-reading frame of *Fltp* was replaced by a cassette encoding a fluorescent reporter protein designated FVR, such that cells normally expressing *Fltp* (FVR^+) fluoresced. In heterozygous $Fltp^{ZV}$ mice, two β-cell populations were identified — FVR^+ and FVR^-. The percentage of FVR^+ cells in islets increased from 50% at postnatal day (P) 1 to 80% at 12 weeks (adult mice). The biological significance of the two β-cell populations was demonstrated by measuring their rates of proliferation at gestational day 15.5, P1, P11 and 12 weeks. At all time points, proliferation was markedly increased in FVR^- cells compared with FVR^+ cells, which suggests that *Fltp* expression correlates with β-cell proliferative capacity and subdivides β cells into either proliferative or mature cells.

To test this hypothesis, the team purified the two β-cell populations and performed genome-wide mRNA profiling, identifying 997 genes differentially expressed by >1.5-fold between FVR^- and FVR^+ cells. Noticeably, the FVR^- population was enriched in genes associated with G-protein-coupled receptor, Wnt and MAPK signalling pathways (which mediate responses to environmental cues), whereas the FVR^+ population was enriched in genes involved in mature β-cell function (including Wnt/PCP genes), further supporting the notion that FVR^+ (*Fltp* expressing) cells are mature β cells and linking planar polarity with β-cell maturation. As the gene expression analysis suggested the two populations of β cells react differently to environmental changes, the investigators performed *in vitro* single-cell tracking to follow the fate of cells over time. Remarkably, *Fltp*-lineage negative cells became *Fltp*-lineage positive cells, which indicates that FVR^- cells differentiate into FVR^+ mature β cells. Finally, by treating reaggregated β cells and pseudo-islets of Min6 insulinoma cells with the Wnt/PCP ligand Wnt5a, the team showed that 3D architecture and Wnt/PCP ligands are sufficient to initiate β-cell maturation.

"Activating the receptors and pathways that associate with the two β-cell populations might enable us to target β-cell proliferation and maturation for islet-regeneration therapy," speculates Lickert. "Moreover, as stem-cell-derived β-like cells can be differentiated *in vitro* but are not functionally mature, our finding of a novel marker of the transition and the pathway involved provides a way to improve differentiation protocols for cell-replacement therapy."

David Holmes

ORIGINAL ARTICLE Bader, E. *et al.* Identification of proliferative and mature β-cells in the islets of Langerhans. *Nature* http://dx.doi.org/10.1038/nature18624 (2016)
FURTHER READING Wang, P. *et al.* Diabetes mellitus — advances and challenges in human β-cell proliferation. *Nat. Rev. Endocrinol.* **11**, 201–212 (2015)