SYNTHETIC BIOLOGY

Designer cells tackle diabetes

Diabetes is associated with pathologically high blood-glucose levels (hyperglycaemia), which can result from either a complete deficiency of insulin (type 1 diabetes (T1D)) or a reduced sensitivity of cells to insulin in combination with pancreatic β-cell dysfunction (T2D). In studies published in *Science* and *Nature Biomedical Engineering*, Fussenegger and colleagues report on two independent designer cell systems that hold potential for correcting these defects.

> “these synthetic circuits demonstrate great potential for improving glucose homeostasis”

Xie *et al.* focused on designing a transcriptional circuit that is responsive to high glucose levels, similarly to β-cells, in which glucose metabolism is associated with the activation of the voltage-gated calcium channel $Ca_V1.3$ and calcium signalling. The authors engineered human embryonic kidney 293 (HEK293) cells to constitutively express $Ca_V1.3$, together with a construct driving transgene expression from a promoter that is recognized by calcium-responsive transcription factors. When exposed to high concentrations of glucose, these engineered cells responded with robust transgene expression (assessed using a secreted embryonic alkaline phosphatase (SEAP) assay). This response was specific to glucose, and transgene expression was reversible and scaled with glucose levels. Importantly, hyperglycaemia-induced expression of SEAP was also observed *in vivo*, when engineered HEK293 cells were implanted into diabetic mice.

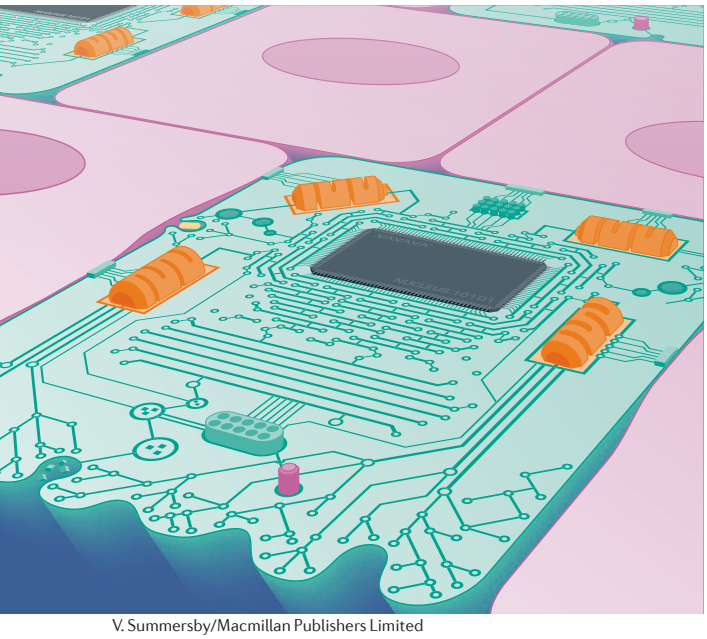
Next, the authors explored the usefulness of this engineered expression system for the therapeutic delivery of insulin. They introduced an insulin transgene into the circuit and implanted these HEK293 cells into T1D mice. This rescued insulin deficiency in the mice, resulting in both glucose and insulin levels reaching those of control mice within 3 days after implantation. Stable glucose levels were maintained during a 3-week follow-up period, indicating that the system is efficient and self-regulating. In addition, the system was used to express glucagon-like peptide 1 in T2D mice, resulting in improved insulin secretion and postprandial glucose metabolism.

Ye *et al.* focused on designing a system that improves insulin sensitivity and prevents the onset of T2D. This system combines the expression of the insulin receptor (conferring an insulin response) with a transcriptional module comprising the chimeric transcription factor TetR-ELK1 and a construct that drives transgene expression from a TetR-specific promoter. TetR-ELK1 is phosphorylated in response to insulin signalling and only then can activate gene expression, thereby linking insulin sensing to gene regulation. As the interaction of TetR-ELK1 with the promoter is negatively regulated by doxycycline, transgene expression can be further regulated by the addition of this antibiotic. Insulin-stimulated HEK293 cells ectopically expressing this gene circuit induced robust transgene expression, which was precisely correlated with insulin dosage and could be readily switched on or off, depending on the availability of insulin. As expected, transgene expression was negatively and reversibly modulated by doxycycline. The functionality of this circuit was also confirmed *in vivo* by implanting engineered HEK293 cells into insulin-resistant mice and observing robust transgene expression.

To evaluate its therapeutic potential, the system was used to express adiponectin — a protein with insulin-sensitizing properties — in insulin-resistant mice. Implantation of engineered HEK293 cells into these mice readily increased adiponectin levels, and significantly improved glucose homeostasis and decreased insulin resistance. When HEK293 cells were engineered to stably express the components of the circuit, long-term beneficial effects of cell implantation on blood glucose levels, as well as fat and insulin homeostasis, were documented.

Collectively, these synthetic circuits demonstrate great potential for improving glucose homeostasis in both T1D and T2D, as well as other metabolic disorders.

Paulina Strzyz



V. Summersby/Macmillan Publishers Limited

ORIGINAL ARTICLES Xie, M. *et al.* β-cell-mimetic designer cells provide closed-loop glycemic control. *Science* **354**, 1296–1301 (2016) | Ye, H. *et al.* Self-adjusting synthetic gene circuit for correcting insulin resistance. *Nat. Biomed. Eng.* http://dx.doi.org/10.1038/s41551-016-0005 (2016)