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TRANSLATIONAL MEDICINE

β cells from stomach-derived organoids

Pyloric cells from the antral stomach can be induced to form insulin-secreting organoids that ameliorate hyperglycaemia in diabetic mice, according to results of a new study published in *Cell Stem Cell*. Such organoids might be a future source of functional β cells for transplantation and consequently glycaemic control in humans.

The investigators used cells from the antral region of the mouse stomach, which can be induced to form small organoids in culture. These cells are derived from the same endodermal precursors as the pancreas, and express many of the same transcription factors as β cells during their development, making them ideal candidates for reprogramming into insulin-secreting cells.

The team first showed that three transcription factors (Neurogenin-3, Pancreas/duodenum homeobox protein 1 and transcription factor MafA, which are collectively known as the NPM factors) are sufficient to induce insulin-secreting cells in these organoids. "A significant finding is the identification that pylorus tissue of the stomach is a highly amenable adult tissue source to derive functional insulin-positive cells," says Qiao Zhou, from Harvard University, Massachusetts, USA, who led the study.

The investigators then created a transgenic mouse line (the NRT mouse) in which they were able to induce expression of the NPM factors specifically in enteroendocine cells of the gastrointestinal tract using doxycycline. Using this NRT mouse line, Zhou and colleagues first ablated pancreatic β cells with streptozotocin to cause hyperglycaemia, and then induced cells in the gastrointestinal tract to secrete insulin using doxycycline. After doxycycline treatment, the hyperglycaemia in NRT mice was reversed and, remarkably, they remained normoglycaemic for up to 6 months.

Unfortunately, inducing insulin-secreting cells in the gastrointestinal tract is not a viable therapeutic option owing to important physiological processes occurring in pyloric tissues. Consequently, the team investigated the functionality of insulin-secreting organoids derived from the antral stomach of NRT mice. Tissue from the antral stomach was used as its cells are most efficiently reprogrammed into insulin-secreting cells. The team transplanted organoids derived from NRT mice into wild-type mice. These transplanted mice were then treated with streptozotocin to cause hyperglycaemia, before being treated with doxycycline to induce insulin-secreting cells in the organoids.

Of 22 mice, five had sustained decreases in blood glucose levels, which was reversed when the organoids were removed. Importantly, these organoids were subsequently found to have many insulin-secreting cells. Conversely, organoids removed from the 17 mice that were still hyperglycaemic had little evidence of insulin-producing cells.

The team now hope to translate these findings into a treatment for patients with diabetes mellitus. "We are using two approaches to generate insulin-secreting cells from human gastric tissues: one approach is to use cultured human gastric stem cells, the other approach is to use human stomach mini-organs derived from human embryonic stem cells," explains Zhou. "Our goal is to derive transplantable, patient-specific insulin-secreting cells or mini-organs as therapeutics."

Tim Geach

ORIGINAL ARTICLE Ariyachet, C. *et al.* Reprogrammed stomach tissue as a renewable source of functional β cells for blood glucose regulation. *Cell Stem Cell* http://dx.doi.org/10.1016/j.stem.2016.01.003 (2016)

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