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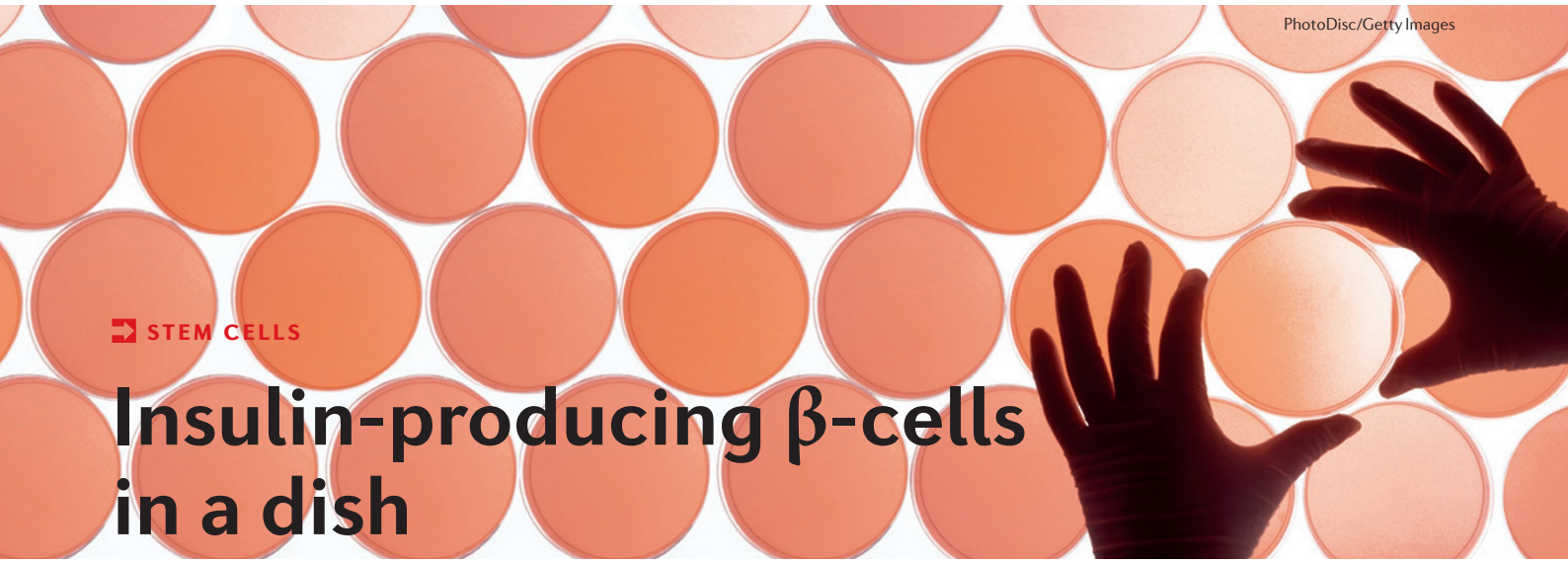

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STEM CELLS

Insulin-producing β-cells in a dish

Human pluripotent stem cells can potentially generate cells and tissues that could be used for the treatment of several diseases. Melton and colleagues at the Harvard Stem Cell Institute, Massachusetts, USA, have developed a protocol for the efficient large-scale differentiation of human stem cells into functional β-cells that behave similarly to adult pancreatic β-cells and might be effective for treating type 1 diabetes.

Diabetes affects over 380 million people worldwide, and this figure is likely to increase according to the International Diabetes Federation. Type 1 diabetes is caused by the autoimmune-mediated destruction of pancreatic β-cells, and although it affects a much smaller proportion (approximately 10%) of the population than type 2 diabetes (which results from β-cell dysfunction and peripheral tissue insulin resistance), it is the most common type of childhood diabetes. Professor Elaine Fuchs at Rockefeller University, New York, USA, commented: "For decades, researchers have tried to generate human pancreatic beta cells that could be cultured and passaged long term under conditions where they produce insulin. Melton and his colleagues have now overcome this hurdle and opened the door for drug discovery and transplantation therapy in diabetes". (*The Guardian*, 10 Oct 2014).

To be able to obtain large amounts of β-cells, the authors used a scalable suspension-based culture system that can generate more than 108 human pluripotent stem cells, and later, differentiated cell types. They used one human embryonic cell line and two human induced pluripotent stem cell (iPSC) lines, which were induced into definite endoderm and subsequently pancreatic progenitors. These progenitors were then used as the starting material to test over 150 combinations of sequential culture steps involving more than 70 compounds that regulate signalling pathways initiated by ligands such as WNT, activin, Hedgehog, epidermal growth factor, transforming growth factor-β, tyroid hormone and retinoic acid, and inhibit γ-secretase. The developed protocol to convert progenitor cells to β-cells takes 4–5 weeks.

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Importantly, Melton and colleagues found that the human β-cells obtained with their protocol responded to multiple sequential glucose challenges *in vitro*, which is a key functional feature of β-cells, and that the amount of insulin secreted per cell was similar to that secreted by primary adult β-cells from cadavers. Ca^{2+} influx in response to increased amounts of glucose, which is the trigger for insulin secretion, also occurred similarly in generated and primary adult β-cells. Moreover, ultrastructural analysis showed that stem-cell-derived β-cells package insulin into developing and mature granules like primary β-cells. Transcriptional analysis also revealed that the stem-cell-derived β-cells expressed key β-cell markers, including the transcription factor pancreas and duodenum homeobox protein 1, indicating that they are very similar (although not identical) to cadaveric β-cells.

Lastly, the authors tested the functionality of these cells *in vivo* by transplanting them in mice. In contrast to transplanted pancreatic progenitors, of which only a small proportion differentiate into mature insulin-secreting cells after 3–4 months, stem-cell-derived β-cells could secrete insulin into the host bloodstream in response to glucose challenge in as little as 2 weeks after transplantation. Furthermore, transplanted cells ameliorated progressive hyperglycaemia rapidly in a diabetic mouse model.

This work describes a method for the large-scale generation of differentiated human β-cells that mimic their normal *in vivo* counterpart. This is an important step towards the treatment of type 1 diabetes. Moreover, this progress could be useful for the treatment of the small proportion of patients with type 2 diabetes who are dependent on insulin shots. "We are now just one preclinical step away from the finish line", said Melton (*The Guardian*, 10 Oct 2014)

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ORIGINAL RESEARCH PAPER Pagliuca, F. W., Millman, J. R., Gürtler, M. *et al.* Generation of functional human pancreatic β cells *In vitro*. *Cell* **159**, 428–439 (2014)