FEATURE

Stem Cells Can Treat and Cure Diabetes

Written by Maria Vinall

Douglas A. Melton, PhD, Howard Hughes Medical Institute, Cambridge, Massachusetts, USA presented the State-of-the-Art Lecture during the Opening Plenary session. The subject was making pancreatic β cells for tissue repair and regeneration in diabetic therapy.

The injection of insulin with the intent of keeping blood sugar levels in the "normal range" has been the only viable option for insulin-dependent diabetics since the 1920s. However, insulin injections do not cure diabetes and frequently result in costly complications, such as heart failure and peripheral neuropathy. Stem cell therapy has the potential to replace dysfunctional pancreatic insulin-producing β cells and cure type 1 diabetes, which is the result of autoimmune destruction of β cells in the pancreatic islet. Two programs have attempted to make pancreatic β cells: direct reprogramming, which has only partially worked, and directed differentiation of stem cells (embryonic or induced pluripotent stem cells). Using the first approach, researchers attempt to reprogram the cell. In mice, the adult exocrine cells can be directly reprogrammed into insulin-producing cells by the expression of 3 transcription factors: Pdx1, Ngn3, and MafA. These developmental regulators reprogram differentiated pancreatic exocrine cells into cells that closely resemble endogenous islet β cells that could provide insulin in response to a glucose challenge. Dr Melton has spent decades attempting to advance this technique without much success. He no longer believes that transdifferentiation is the best way to make new functional β cells. Instead, he believes a better approach is to make pancreatic β cells from embryonic (ES) or induced pluripotent stem cells through 4 stages of development.

Several investigators had been successful with using normal embryogenesis growth factors in differentiating human embryonic and pluripotent stem cells into cells that have features characteristic of kidney lineage cells [Lam AQ et al. *J Am Soc Nephrol*. 2014; Takasato M et al. *Nat Cell Biol*. 2014; Xia Y et al. *Nat Cell Biol*. 2013]. However, many challenges remain to achieve the goal of creating cells that can actually secrete insulin after glucose stimulation.

The idea is to recapitulate the normal stepwise progression from embryonic pluripotent cells to definitive endoderm (DE), exocrine, pancreatic progenitors, and finally fully differentiated β cells. DE and pancreatic progenitors can be differentiated a lot easier than other parts of the process. However, it has proven extremely difficult to move to the last stage, the development of fully differentiated β cells. Dr Melton and his team developed a scalable differentiation protocol that can generate hundreds of millions of glucose-responsive β cells in a relatively short period of time.

The strategy entails sequential modulation of multiple signaling pathways in a three-dimensional cell culture system. Through a trial-and-error process, varying culture conditions, the application of growth factors, and the use of small molecules as signaling inducers, many combinations of signaling pathways and chemical modulators were tested to determine which chemicals modulate signals. This was performed without any transgenes or genetic modifications.

The new differentiation process generated β cells from human embryonic and pluripotent stem cells in a culture of hedgehog inhibitor SANT1, KFG, and a low concentration of retinoic acid to generate high levels of NKX6-1 + PDX1 + coexpressing pancreatic progenitor clusters. One of the tests of functioning β cells is the cells' ability to secrete insulin when challenged by glucose (glucose-stimulated insulin secretion [GSIS]). Using this new process, the generated β cells respond to multiple sequential glucose challenges similar to primary adult cadaveric islets (1^0 β cells) and superior to polyhormonal (PH) cells. PH cells are in vitro differentiated human pluripotent stem cells that have immature or abnormal phenotypes, and they resemble human fetal but not adult β cells. PH cells show neither GSIS nor other key properties of

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functioning β cells. After sequential low- and high-glucose challenges, cells were depolarized with 30 mM KCl. Membrane depolarization causes an influx of calcium ions, which triggers insulin exocytosis [Mohammed JS et al. *Lab Chip*. 2009]

Stem cell–derived β (SC-β) and 1^0 β cells respond to glucose challenges by increasing intracellular calcium more than PH cells. The new differentiation strategy creates SC-β cells that can package and crystallize insulin protein into granules similar to 1^0 β cells. The human SC-β cells, when transplanted into the kidney capsule of a diabetic mouse, were secreting insulin into the bloodstream in a glucose-regulated manner similar to that of human islet cells.

In the diabetic mice receiving ES-β cells, blood sugars were normalized, whereas animals receiving control cells showed progressively worsening hyperglycemia [Pagliuca FW et al. *Cell*. 2014]. The mice maintained human insulin secretion up to 18 weeks after transplantation and lived longer.

The screening of new drugs for diabetes is currently hindered by the supply of islets. A large consistent number of SC-β cells would aid in the drug discovery process and would be useful for disease modeling of diabetes. The next challenge will be blocking the immune response for type 1 diabetes and transplantation of ES-β cells into diabetic humans.

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