Re-engineering gut cells to produce insulin for treating type I diabetes

Published date: April 19, 2016

Technology description

Summary

Type I diabetes is an autoimmune disorder that is characterized by the destruction of insulin-producing beta cells in the pancreas. Patients with type I diabetes require regular doses of insulin to manage their glucose levels. Currently, the primary treatment options for these patients involve injections of insulin and/or automated insulin pumps, but these are crude approximations of glucose-responsive insulin release when compared to that of native pancreatic beta cells. Alternative treatments in development include the use of stem cell therapies to generate insulin-producing cells that could then be used to replace or replenish a patient's pancreatic beta cells. However, the production of glucose-responsive, insulin-producing cells remains a challenge. This technology is a method to reprogram gut stem cells into insulin-producing enteroendocrine cells. The technology manipulates native gut stem cells by eliminating expression of a single gene, which allows these cells to differentiate into insulin-producing cells that are glucose-responsive and express markers of pancreatic beta cells. As such, the technology provides a sustainable, cellular alternative to insulin injections as a treatment for type I diabetes and for instances of type II diabetes when insulin is needed.

Single gene inhibition for reprogramming patient-specific gut stem cells into sustainable glucose-responsive, insulin-producing enteroendocrine cells

This technology re-engineers intestinal stem cells by eliminating expression of a single transcription factor, FoxO1, which causes the intestinal stem cells to differentiate into glucose-responsive, insulin-producing cells. Unlike pancreatic beta cells, gut cells have a relatively rapid turnover rate (~4 days), thereby creating a sustainable system in which the intestinal stem cells can be continuously differentiated into insulin-producing cells. Since the technology does not require the use of either embryonic stem (ES) cells or induced pluripotent stem (iPS) cells, there is a much lower risk of creating cancerous cells. Moreover, unlike ES or iPS cells, reprogramming native gut cells would eliminate the need for transplantation of these insulin-producing cells into the patient. This technology can potentially be delivered by injection or oral administration of an agent that inhibits either Foxo1 gene

expression (via bacteria encoding Foxo1 siRNA or Foxo1 antisense oligonucleotide) or FoxO1 transcriptional activity (via small molecule inhibitors of FoxO1) in intestinal stem cells. Thus, this technology provides a means to treat patients with type I diabetes (and certain cases of type II diabetes where insulin is required) that would circumvent the need for insulin injections without requiring organ or cellular transplants.

This technology has been shown produce glucose-responsive, insulin-producing enteroendocrine cells in mouse models, as well as in human gut organoids.

Publications

Talchai C, Xuan, S, Kitamura T, DePinho RA, Accili D. "Generation of functional insulin-producing cells in the gut by Foxo1 ablation" Nat Genet. 2012. Mar 11;44(4):406-12.

Bouchi R, Foo KS, Hua H, Tsuchiya K, Ohmura Y, Sandoval PR, Ratner LE, Egli D, Leibel RL, Accili D "FOXO1 inhibition yields functional insulin-producing cells in human gut organoid cultures" Nat Commun. 2014. Jun 30;5:4242

Application area

Treatment of type I diabetes

Treatment of type II diabetes in cases where insulin is required

Method to produce insulin-producing gut cells for cellular and biochemical studies

Advantages

Potential to eliminate the need for insulin-injections

Target cells are located in the intestines where oral drugs will be most effective

Requires the targeting of only one gene

Intestinal stem cells have a rapid turnover rate

Uses patient's own cells, mitigating risk of an immune response

Lower teratoma (cancer) risk than other stem cell based strategies
*Production of a FoxO1 inhibitor will be much cheaper than production of insulin-producing cells in culture and subsequent transplantation into a patient

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