Insulin-secreting human α cells for the treatment of diabetes

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Article based on the work of the Pedro L. Herrera research group, published at: https://www.nature.com/articles/s41586-019-0942-8

Discussion of articles group 2205 section A, subject physiology

Edited by: Raúl Sampieri-Cabrera

Diabetes mellitus is one of the top concerns of public health worldwide. According to the World Health Organization, the prevalence of diabetes in 2014 was of 422 million adults (a number that has doubled since 1980)[1]. Complications of diabetes are very severe, including vision loss, increased risk of cardiovascular events, lower extremity amputations, end-stage renal disease and many others.

The regeneration of damaged tissues has shown to be an innovative approach for the treatment of diverse pathologies. Given the relevance nowadays of chronic-degenerative diseases such as diabetes, it is of interest to explore alternatives for the reprogramming of pancreatic cells to reconstitute the production of insulin. In diabetic mice, the ability of α-cells of the pancreatic islet to recover insulin production has been described. There are three main transcription factors involved in the development, maturation and function of β-cells: PDX1, MAFA and NKX6-1 which are necessary to maintain the insulin secretion function.

The protocol by Furuyama et al.[2] started with the selection of pancreatic cells with flow cytometry, transduction of the transcription factors PDX1, MAFA and NKX6-1, reaggregation of these cells in monotypic pseudoislets to promote insulin secretion, as well as in vitro and in vivo analysis of the functions of these cells after conversion. After the cells were cultured, their capability to produce insulin in a high glucose medium and the expression of the transcription factors of β-cells in α-cells was assessed, giving evidence of the reprogramming-cell process. The reaggregation and reprogrammed α-pancreatic cells, in the presence of MSCs and HUVECs, managed to display glucose-stimulated insulin secretion comparable to the levels produced by the native islets. Similarly, γ-pancreatic cells reprogrammed with these same transcription factors were able to obtain even better insulin secretion by stimulation with glucose than the reprogrammed α-pancreatic cells.

To evaluate the *in vivo* functions of these cells, the α cells pseudoislets were transferred into diabetic mice, finding a significant improvement in glucose tolerance and insulin secretion stimulated by glucose. Later, to test the stability of these reprogrammed pseudoislets, one month after insertion in the mice, the molecular signature of these cells was analyzed both at mRNA level and at protein level, finding that the reprogrammed α-pancreatic cells showed an overexpression of mRNA and proteins characteristic of insulin-producing β-cells, including several molecules crucial for their characteristic functions. It's important to consider that even though α-cells express transcription factors, mRNA and proteins similar to β-cells, they still conserve their own molecular make-up that characterize them as α-cells.

Additionally, RNA-sequencing on αPM pseudoislets 1 month after transplantation showed that pathways related to hormone synthesis, secretion and innervation were further increased. Cells could be classified as early, mid and late progression states depending on the stage of cell conversion by the patterns of genes expression. However, some genes related to α-cells function remained unchanged or even overexpressed. αPM pseudoislets. Can gene therapy tackle the "refractory genes" to enhance the αPM pseudoislets insulin-secretion function? Further changing the phenotype to β-cells can increase the immunogenicity? Is molecule screening a worthy approach to find potential targets that promote conversion to a β-cell phenotype by modulating gene expression?

Finally, the authors performed cytotoxic T lymphocytes (CTL) killing assays to determine if insulin producing α-cells could be targets in type 1 diabetes. The authors found that preproinsulin (PPI) directed CTLs targeted αPM pseudoislets while β-cell specific anti-defective ribosomal product (DRiP) CTL did not. This could confer αPM pseudoislets with a protective advantage over dispersed human β-cell islets, since they are only targeted by PPI directed CTLs. Contrary to expectation, this does not seem to be a feature of αPM pseudoislets per se because they too found that β-cells pseudoislets are only targeted by PPI directed CTLs. Therefore, it appears it´s a feature of pseudoislets. Can this feature of pseudoislets be exploited beyond DM1? Despite this positive result, it is important to test the *in vivo* immunogenicity of αPM pseudoislets. To prevent an immune response to human antigens, the authors used immunodeficient mice. In the future, how can you overcome this challenge to test immunogenicity *in vivo*?

The successful reprogramming of pancreatic islet cells demonstrates the capability of plasticity by human cells.

https://doi.org/10.6084/m9.figshare.7885403.v1

Recovery in insulin secretion stimulated by glucose is observed both *in vitro* and *in vivo*, and the cells appear to show stability and efficiency in this function. This report of a successful reprogramming of pancreatic cells opens a window of opportunity for the treatment of diabetes from a tissue regeneration approach, showing a long-term alternative to promote insulin secretion and improve dysregulated physiological conditions in this disease. However, can cell plasticity constitute a therapeutic potential for other diseases?

References

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2. Furuyama, K. et al. Diabetes relief in mice by glucose-sensing insulinsecreting human α-cells. Nature, doi:10.1038/s41586-019-0942-8 (2019).

Additional information

Competing interests

None

Funding

None

https://doi.org/10.6084/m9.figshare.7885403.v1