iPSCs and their potential in the treatment of diabetes mellitus

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Induced pluripotent stem cells (iPSCs) hold great promise in all the fields of regenerative medicine. In this review, a retrospective of the progress in the potential treatment for diabetes mellitus is offered. The challenges this technology encounters are also assayed and future directions examined in order to bypass these issues.

INTRODUCTION

The progress made during the end of the last century in reprogramming by nuclear transfer and fusion lead to Takahashi and Yamanaka to hypothesize that there should be certain factors that determine the differentiation fate of cells. Thus iPSCs were created in 2006 and a new scientific stream started developing. Despite their origin, iPSCs are very similar to embryonic stem cells (ESCs), avoiding most of the issues related to the latter, and may be even able to replace them in a future. This technology is in its early days, but lots of possible applications have already been found. One of them is the production of β-like cells in order to treat and study diabetes mellitus (DM).

β-CELL GENERATION AND MATURATION

Through functional genomics the role of some transcription factors have been identified. These have been used to differentiate hESCs and iPSCs into β-like cells (Figure 1), although we still need a wider understanding to develop fully mature β-cells.

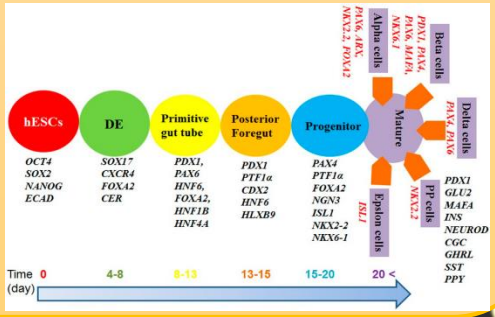


Figure 1. Timeline of differentiation of pluripotent stem cells into β-cells and expression of several genes[1]

FIRST REPORTS AND MOVING FORWARD

Soon after the discovery of iPS cells, a series of reports suggested that developing insulin producing β-like cells from iPSCs was feasible. One of the most remarkable reports was in 2010 when Alipio's group was able to stably engraft these cells into the liver of 30 T2DM and 6 T1DM mice and normalize their blood glucose levels for more than 3 months[2]. Jeon was able to repeat the experiment with very similar results on T1DM mice[3] (Figure 3).

Since then, a vast amount of research has been done in order to improve the technology and bypass its main issues. A combination of small molecules like DNA methyl transferase inhibitor 5-aza-2'-deoxycytidine (5-AZA) can guide the cellular reprogramming and even the generation of β cells, thus avoiding immunogenicity[4].

Another important breakthrough was made by Pagliuca's group (Figure 2) with the discovery of a strategy for large-scale production of functional β-cells allowing the cultivation of 300 million cells per single 500 ml flask[5].

CHALLENGES AND FUTURE DIRECTIONS

Nevertheless, the technology is not prepared for clinical trials and many issues have to be taken care of first (Figure 4 and Table 1):

CHALLENGES	& FUTURE DIRECTIONS
Variability of reprogramming	Should be minimized and quality ensured by the use of stringent criteria in order to standardize and take to clinical trials.
Generation of safe iPSCs	Use of tumorigenic integrating viral vectors is widespread due to their high efficiency. Other non-integrating or DNA-free methods are being developed.
Reprogramming efficiency	Both steps from somatic cells to iPSCs and then to mature β-cells should be optimized in order to have the highest yield possible.
Differentiation efficiency	Cells must be mature in order to respond correctly to stimulus. Immature cells have a risk of tumor formation. In vivo studies suggest there are other factors that help differentiating the cells further.
Autoimmunity	An obstacle in T1DM. An alternative to immunosuppressants should be found, such as the encapsulation of islets or modulation and genetic modification of the graft.

Table 1. Proposed future directions in order to bypass the current challenges in diabetes treatment with iPSCs.

Figure 2. Reprogramming steps from iPSCs to β-cells and graphical representation of the transplantation result[5]

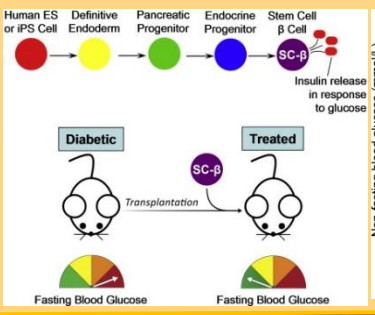
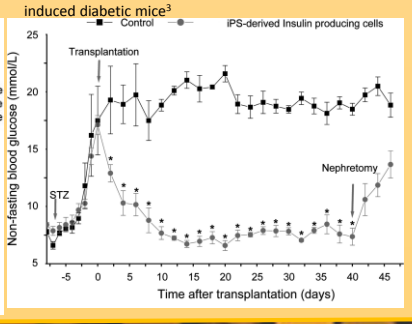


Figure 3. Blood glucose levels in transplanted STZ-induced diabetic mice[3]



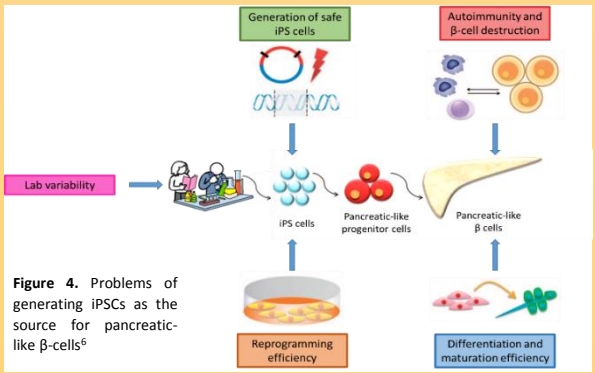


Figure 4. Problems of generating iPSCs as the source for pancreatic-like β-cells[6]

CONCLUSIONS

iPSC technology offers a promising solution for the understanding and treatment of DM and it has become a pillar of regenerative medicine. The main challenges have been clearly defined which allows for better approach strategies and more structured research.

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