Toward an attractive strategy is arising in the field of cell reprogramming, it consists in the direct conversion or transdifferentiation of terminally differentiated somatic cells into other adult cells, bypassing the pluripotent state. This strategy is useful to side-step recent controversal data derived from the use of Induced Pluripotent Stem Cells. Although this technology is relatively recent, it stands as a potential method to be applied in the field of regenerative medicine, once having solved the challenges it faces. The aim of this bibliographic research is to develop an updated review of transdifferentiation, highlighting advantages and disadvantages of this method, its achievements, the multiple procedures to transdifferentiate an adult cell and its application in β-cell generation in order to treat type II Diabetes Mellitus.

**MATERIALS AND METHODS**

In this review, the most recent publications, either reviews or conventional articles, related to transdifferentiation were studied.

- Firstly, a search of the terms transdifferentiation, reprogramming, direct conversion and β-cell was held in Pubmed and Scopus® and the articles found were ordered by preference and impact.
- Secondly, the most important and recent articles were read and summarized, and their bibliography extensively analyzed.
- Finally, high-impact journals were periodically examined in the search of new publications.

**GENERAL ASPECTS OF CELL REPROGRAMMING**

Waddington’s epigenetic landscape is an interesting schematic representation of how differentiation takes place in vivo (Fig. 1, black arrow). C. H. Waddington gave emphasis to those points or bifurcations which he named ‘chreodes’, where a cell must choose a path and therefore became inevitable committed, in a natural state. In 2005, when Yamanaka turned upside down the concept of reprogramming, several strategies involving transdifferentiation (Fig. 1, grey arrow) were unearthed, such as:

- Short-range transdifferentiation
- Long-range transdifferentiation
- Induced Pluripotent Stem Cell-transcription factor based transdifferentiation
- Transdifferentiation from multipotent stem cells

Transdifferentiation avoids several problems that induced Pluripotent Stem Cells (iPSC) display, such as, tumorigenesis or difficulty to be maintained (iPSC) in culture. However, transdifferentiation also has its own drawbacks, such as, formation of immortal intermediates.

**APPLICATIONS**

Successfully reprogrammed cells have three main applications:

- Cell replacement therapy and organogenesis
- Drug discovery and toxicology
- Developmental biology understanding

**GENERAL STRATEGIES**

A broad understanding of the elements involved in determination and differentiation of lineage-specific stem cells into unipotent cells in vivo is the key point to develop a reliable strategy to convert any kind of somatic cell into the target cells (Table 2).

**Overexpression of transcription factors**

Overexpression of a single or a group of transcription factors (TF) is the most utilized method in transdifferentiation, TF that occupy the very top of a regulatory hierarchy, which therefore are not under regulation of other TF, are known as master regulatory factors (MRF), for example, MyoD (Fig. 3). MRF are very useful, because with only one transduction of a viral vector carrying the MRF, a cell can be fully reprogrammed. When more than one TF need to be transduced, it is important to introduce them hierarchically, simulating natural expression, in order to improve efficiency. Recently, some authors demonstrated that cells could be temporally co-cultured with IPSC-transcription factor (IPSC-TF) and lineage-specific TF in order to transdifferentiate cells faster and more efficiently, compared to classical transdifferentiation, and also allowing clinical expansion. In this case, the direct stimulation with IPSC-TF is not sufficient to generate IPSC. It has been hypothesized that IPSC-TF erase the epigenetic identity of the starting cell. This technology has been used to generate cardiomyocytes, neural progenitors and definitive endoderm.

**“DNA-free” strategies**

These strategies consist of the utilization of small chemical soluble molecules involved in methylation/demethylation of DNA and histones, heterochromatin regulators or interfering RNA (RNAi). Some “DNA-free” strategies have become a substitute to IPSC-TF, and that is why these molecules could be applied in IPSC-TF based transdifferentiation.

**Selection of the origin cell**

Defining the origin cell is as crucial as the election of transdifferentiation elements. Accessible cells, such as fibroblasts, might be more suitable for translational applications. It’s relevant that cells which do not share a common progenitor are characterized by a more complex molecular mechanism underlying cellular transitions (Fig. 4).

**ACHIEVEMENTS**

Few of the most relevant achievements of transdifferentiation: MASC: Muscle-derived stem cells, iPSC-TF: induced pluripotent stem cell transcription factors.

**DIRECT CONVERSION OF β-CELLS**

Type 2 Diabetes Mellitus (T2D) is characterized by hyperglycemic episodes caused by an autoimmune destruction of β-cells. A suitable cure for T2D must consider two aspects: suppression of immune response against β-cells and replacement of cell loss.

An extensive understanding of organogenesis is essential to develop new reprogramming strategies (Fig. 5). In order to determine if a cell has been reprogrammed into a β-like cell, Glucose Stimulated Insulin Secretion (GSIS) tests or in vivo alleviation of hyperglycemia experiments are held.

**Short-range or intralineage transdifferentiation of pancreatic β-cells**

There are three relevant studies on transdifferentiation using definitive endoderm-derived cells as origin cells:

- The first transdifferentiation of β-cells was achieved in the in vivo setting in mice as early as 1969 by Pitorski and co-workers.
- The second study carried out in transdifferentiation was done in 2008, when Ferber and co-workers identified, using clonal expansion, in this case, the brief stimulation with BMP4, Gata4, Mef2c, Tbx5 in vivo.
- The third one was published in 2011 by Pagliuca and colleagues, identifying three TF (Mash1, Nurr1, Lmx1a) Ex vivo and converting islet cells in vitro by adenoviral vector transduction (Fig. 6).

**Long-range direct conversion from fibroblasts to β-cells**

A combination of PAX4 and small chemical molecules (β-Amylase and Fondaparinux) that modify the histone code has been used to transdifferentiate human fibroblasts into β-cells for the first time.

**IPSC-TF based transdifferentiation**

The most inspiring achievement in β-cell direct conversion was published in 2014. In this study, Definitive Endoderm-like Cells (DELC) were derived from teratogenic mouse embryonic fibroblasts using a combination of IPSC-TF co-cultured with Activin A and Lithium Chloride. After that, DELC were cultured with neural and other small molecules in order to obtain functional β-cells (Fig. 7).

**REFERENCES**