Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 849–857

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

3

Reprogramming of human exocrine pancreas cells to beta cells

Willem Staels, MD, PhD, Student [a, b, 1],
Yves Heremans, PhD, Senior Research Assistant [a, 1],
Harry Heimberg, PhD, Professor and Principal Investigator [a, *]

[a] Diabetes Research Center, Vrije Universiteit Brussel, 1090 Brussels, Belgium
[b] Department of Pediatrics, Division of Pediatric Endocrinology, Ghent University Hospital, and Department of Pediatrics and Genetics, Ghent University, Ghent, Belgium

ARTICLE INFO

Article history:
Available online 9 October 2015

Keywords:
diabetes
pancreas
beta cell
reprogramming
transdifferentiation

ABSTRACT

One of the key promises of regenerative medicine is providing a cure for diabetes. Cell-based therapies are proving their safety and efficiency, but donor beta cell shortages and immunological issues remain major hurdles. Reprogramming of human pancreatic exocrine cells towards beta cells would offer a major advantage by providing an abundant and autologous source of beta cells. Over the past decade our understanding of transdifferentiation processes greatly increased allowing us to design reprogramming protocols that fairly aim for clinical trials.

Introduction

The ridges in Waddington's illustrious epigenetic landscape that represent the process of cellular decision-making during development have flattened and morphed into an “epigenetic disc” [1]. Waddington proposed his conceptual landscape in 1957, but the “creodes” he coined as a metaphor for unidirectional lineage commitment were soon challenged by paradigm shifts [2]. Spemann originally conceived the fantastical experiment of somatic cell nuclear transfer (SCNT) to answer the question

* Corresponding author. Diabetes Research Center, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium. Tel.: +32 2 4774473; Fax: +32 2 4774472.
E-mail address: Harry.Heimberg@vub.ac.be (H. Heimberg).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.beem.2015.10.001
1521-690X/

whether the nucleus of a differentiated cell retains the genomic capacity to direct all types of differentiation [3]. Nuclear transplantation was elaborated in experiments performed by Briggs and King, but the factual possibility of transition between epigenetic states in differentiated cells was first demonstrated in Gurdon's seminal paper [4]. In addition to SCNT, stressful conditions that endanger cell integrity and longevity, whether due to isolation of cells from their *in vivo* restrictive niches or in response to *in vivo* tissue damage, have been shown to result in extreme fate changes (plasticity) such as dedifferentiation (return to stemness) and reprogramming (interconversion of differentiated cell types) in an attempt to escape from damage and contribute to regeneration of the damaged tissue as soon as the risk has subdued (reviewed in [5,6]). A further blow to the concept of a hierarchical organization of cell differentiation was delivered with the demonstration of transcription factor (TF) induced reprogramming, typically exemplified by *Myod1*-mediated reprogramming of fibroblasts into myotubes [7]. The value of this groundbreaking concept (reviewed in [8]) has been demonstrated extensively, especially in the blood system ([9–13], reviewed in [14]). One of the most spectacular experiments in developmental biology in the 1990's was arguably the ectopic expression of *eyeless* in various imaginal disc primordia of Drosophila, causing the formation of ectopic, morphologically normal and stimulus-sensitive eyes on the wings, legs, and antennae [15]. Since a single TF could induce morphogenesis of such a complex structure as the insect eye, great expectations were directed towards the general use of master control genes for reprogramming purposes in regenerative medicine. Although the underlying cellular and molecular mechanisms remain largely elusive, a two-way relationship between transcription factor binding and chromatin structure is essential during the reprogramming process ([16–18], reviewed in [19,20]). Reprogramming approaches should not only envisage the overexpression of TFs imposing a particular target cell fate, but also TFs disturbing the differentiation status of the original cell and TFs antagonizing genes inappropriate for the desired cell type [21–24]. Diabetes has been one of the prime interests of regenerative medicine as it is a major and increasing public health problem which could be cured by the replacement of a single cell type, the pancreatic beta cell [25]. Moreover, with the notable exception of persistent hyperinsulinemic hypoglycemia of infancy [26], the existence of an inherent regenerative potential of the human (type 1) diabetic pancreas is probably one of the most controversial aspects of current diabetes research [27]. This review will focus on the current knowledge on reprogramming of human pancreatic exocrine cells towards beta cells.

Reprogramming exocrine cells of the adult human pancreas

For several reasons, pancreatic duct and acinar cells represent particularly useful targets for reprogramming into beta cells as a cell replacement therapy for diabetes. First, cellular reprogramming is considered more efficient when the cells of origin share a similar ontogeny as the envisioned final cell type. The epigenetic memory, defined as the retention of regulatory labels on DNA and DNA-interacting proteins in the origin cell, is considered a hurdle to reprogramming. Obviously, this hurdle is less difficult to cross between cells with similar epigenetic landscapes (reviewed in [28]). Indeed, duct and acinar cells follow a similar developmental trajectory as their pancreatic endocrine counterparts and, although the exact origin of adult human beta cell progenitors remains uncertain, a substantial amount of evidence has put forward the “trunk” cells lining the early ducts as plausible candidates (reviewed in [29,30]). Second, both duct cells ([31], reviewed in [32]) and acinar cells (reviewed in [33]) show a high degree of cellular plasticity. Although this phenomenon has been mostly studied in rodents, recent studies have uncovered plasticity of human exocrine cells as well ([34–37], reviewed in [38,39]). A theoretical framework has been proposed for the therapeutic application of induced metaplasia, referring to reversal of harmful metaplasias on the one hand and generation of useful reprogrammed cells on the other [40]. Third, besides non-beta cells, pancreatic exocrine cells share the most similar microenvironment with beta cells as compared to any other cell type. Since the differentiated state of a mature cell is most stable when the cell resides in its native environment, *in situ* reprogramming of pancreatic exocrine cells to beta cells is likely favorable over reprogramming in an environment other than pancreas, in order to avoid an altered phenotype or function of the reprogrammed cells [41]. Sufficiency of the pancreatic microenvironment in promoting endocrine differentiation has been suggested as acinar to endocrine conversion was seen in zebra fish