BRAIN RESEARCH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

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Review

New approaches for direct conversion of patient fibroblasts into neural cells

Q1 *Suhasni Gopalakrishnan, Pooja Hor, Justin K. Ichida*

Q2 *University of Southern California, Department of Stem Cells and Regenerative Medicine, Eli and Edythe Broad, CIRM Center for Regenerative Medicine and Stem Cell Research at USC, Los Angeles, CA 90033, USA*

ARTICLE INFO

Article history:
Accepted 5 October 2015

Keywords:
Q3 Induced neuron
Reprogramming
Direct conversion
Lineage conversion
Disease modeling
Neurological disease

ABSTRACT

Recent landmark studies have demonstrated the production of disease-relevant human cell types by two different methods; differentiation of stem cells using external morphogens or lineage conversion using genetic factors. Directed differentiation changes embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) into a desired cell type by providing developmental cues in an in vitro environment. Direct reprogramming is achieved by the introduction of exogenous lineage specific transcription factors to convert any somatic cell type into another, thereby bypassing an intermediate pluripotent stage. A variety of somatic cell types such as blood, keratinocytes and fibroblasts can be used to derive iPSC cells. However, the process is time consuming,laborious, expensive and gives rise to cells with reported epigenetic heterogeneity even amongst different iPSC lines from same patient which could propagate phenotypic variability. A major concern with the use of pluripotent cells as starting material for cell replacement therapy is their incomplete differentiation and their propensity to form tumors following transplantation. In comparison, transcription factor mediated reprogramming offers a direct route to target cell types. This could allow for rapid comparison of large cohorts of patient and control samples at a given time for disease modeling. Additionally, transcription factors that drive maturation may yield more functionally mature cells than directed differentiation. Several studies have demonstrated the feasibility of generating of cell types such as cardiomyocytes, hepatocytes, and neurons from fibroblasts. Here, we will discuss recent advances and key challenges regarding direct reprogramming of somatic cell types into diverse neural cells.

This article is part of a Special Issue entitled SI: Exploiting human neurons.

Published by Elsevier B.V.

Contents

http://dx.doi.org/10.1016/j.brainres.2015.10.012
0006-8993/Published by Elsevier B.V.

1. Introduction

Cellular reprogramming, the ability to convert one cell type into another desired cell type, can be achieved by either directed differentiation of pluripotent stem cells or direct reprogramming of somatic cells. Directed differentiation changes embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) into a desired cell type by providing developmental cues in an *in vitro* environment. Direct reprogramming is achieved by the introduction of exogenous lineage specific transcription factors to convert any somatic cell type into another, bypassing an intermediate pluripotent stage. A variety of somatic cell types such as blood, keratinocytes and fibroblasts can be used to derive iPSCs (Aasen and Izpisua Belmonte, 2010; Su et al., 2013; Takahashi et al., 2007). However, the process is time-consuming, laborious, expensive and gives rise to cells with reported epigenetic heterogeneity even amongst different iPSC lines from same patient which could propagate phenotypic variability (Egawa et al., 2012; Israel et al., 2012). A major concern with the use of pluripotent cells as starting material for cell replacement therapy is their incomplete differentiation and their propensity to form tumors following transplantation (Kim et al., 2010; Miura et al., 2009). In comparison, transcription factor mediated direct reprogramming strategy offers a direct route to target cell types. The feasibility of direct reprogramming in other cell types such as cardiomyocytes, hepatocytes, and neurons from fibroblasts has been successfully demonstrated (Ieda et al., 2010; Sekiya and Suzuki, 2011; Son et al., 2011; Vierbuchen et al., 2010). In addition, direct reprogramming yields more functionally mature cells than directed differentiation (Lujan and Wernig, 2013). This could allow for rapid comparison of large cohorts of patient and control samples at a given time for disease modeling. It is likely the target neural cell types derived from direct reprogramming preserve their genomic integrity in contrast to cells obtained through directed differentiation because of prolonged culturing of iPSCs, which might lead to higher chances of introducing mutations.

2. Direct reprogramming as a tool to derive functional neurons and neuronal cell types

2.1. Neurons

Many neurological disorders have specific subtypes of neurons that are affected. The earliest report of direct reprogrammed neurons described the use of three transcription factors Ascl1, Brn2, Myt1L to reprogram mouse fibroblasts into excitatory functional neurons. These induced neurons (iNs) could fire repetitive specific action potentials and exhibited glutamatergic and GABAergic phenotype (Vierbuchen et al., 2010). Addition of NeuroD1 to the three factors could generate functional human induced neurons (Pang et al., 2011). Subsequently, several groups have successfully generated many clinically relevant neuronal subtypes such as dopamine neurons, motor neurons, medium spiny neurons, nociceptors and retinal ganglions from fibroblasts using direct reprogramming methods (Table 1) (Blanchard et al., 2015; Caiazzo et al., 2011; Hu et al., 2015; Kim et al., 2011b; Li et al., 2015; Liu et al., 2012; Meng et al., 2013; Pfisterer et al., 2011; Sheng et al., 2012a; Son et al., 2011; Victor et al., 2014; Wainger et al., 2015).

2.2. Neural stem cells

One of the earliest studies to induce a cell type with proliferative and progenitor like phenotype was the induction of neural progenitor cells from mouse fibroblasts (Kim et al., 2011a). In comparison to post-mitotic induced neurons which are directly converted from fibroblasts, induced neural progenitor cells (iNPCs) and/or neural stem cells (iNSCs) have the advantage of being expandable *in vitro* and have the ability to give rise to multiple neuronal subtypes and glial cells (Table 1) (Cheng et al., 2014; Han et al., 2012; Kim et al., 2011a; Lujan et al., 2012; Thier et al., 2012; Zhu et al., 2014). Transient induction of pluripotency factors (Oct4, Sox2, Klf4, and c-Myc (OKSM) in murine fibroblasts in the presence of appropriate signaling inputs can promote selective lineage conversion to induce neural stem cell state (Kim et al., 2011a). Since then, several reports have generated expandable

Please cite this article as: Gopalakrishnan, S., et al., New approaches for direct conversion of patient fibroblasts into neural cells. Brain Research (2015), http://dx.doi.org/10.1016/j.brainres.2015.10.012