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Brain Research

Research Report

Induced pluripotent stem cells from ALS patients for disease modeling

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ARTICLE INFO

Article history:
Accepted 3 September 2014
Available online 16 September 2014

Keywords:
Stem cell
iPSC
Motor neuron
Astrocyte
Non-cell autonomous
Human

ABSTRACT

The ability to reprogram adult somatic cells into pluripotent stem cells that can differentiate into all three germ layers of the developing human has fundamentally changed the landscape of biomedical research. For a neurodegenerative disease like Amyotrophic Lateral Sclerosis (ALS), which does not manifest itself until adulthood and is a heterogeneous disease with few animal models, this technology may be particularly important. Induced pluripotent stem cells (iPSC) have been created from patients with several familial forms of ALS as well as some sporadic forms of ALS. These cells have been differentiated into ALS-relevant cell subtypes including motor neurons and astrocytes, among others. ALS-relevant pathologies have also been identified in motor neurons from these cells and may provide a window into understanding disease mechanisms *in vitro*. Given that this is a relatively new field of research, numerous challenges remain before iPSC methodologies can fulfill their potential as tools for modeling ALS as well as providing a platform for the investigation of ALS therapeutics.

This article is part of a Special Issue entitled ALS complex pathogenesis.

Contents

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http://dx.doi.org/10.1016/j.brainres.2014.09.017
0006-8993/

1. Introduction

In vitro strategies to recapitulate disease mechanisms causing Amyotrophic Lateral Sclerosis (ALS) have been attempted for some time. Attempts to manipulate cell-types associated with the disease have included the study of primary dissociated motor neurons and glial cells from animal models, as well as other neural and non-neural cell lines. While many initial studies focused on motor neurons in culture, later work included the co-culture of non-neuronal cell types with motor neurons to allow for a dissection of individual cellular contributions to disease pathogenesis (Veyrat-Durebex et al., 2014).

Animal models of ALS have been generated to understand disease mechanisms as well as provide platforms for testing therapeutic strategies. The majority of ALS rodent models have been based on the use of transgenic overexpression of genes known to cause familial ALS. These have included the overexpression of mutations in the following genes: superoxide dismutase (SOD1), tar DNA protein 43 (TDP-43), fused in sarcoma (FUS), and valosin-containing protein (VCP). These *in vivo* models have taught us a great deal about the molecular cascades by which these specific genes may cause disease, the neural cell types that contribute to ALS pathogenesis, the complexities of genotype–phenotype correlations, and at least a window into using these animals for the study of therapeutics for ALS (McGoldrick et al., 2013). In part because animal models for understanding ALS disease mechanisms have demonstrated shortcomings with regard to recapitulating sporadic ALS and also have had limited capacity for predicting therapeutic efficacy of compounds in ALS, investigators have been seeking alternatives for addressing both issues (Benatar, 2007).

However, modeling ALS using rodents with ALS carrying disease causing mutations only represents a subset of the disease as a whole. Furthermore, as a slowly progressive neurodegenerative disease, modeling ALS using animal models also requires months of study, which results in an increase in study costs. In light of these limitations, the research community has shown great interest in the potential value of modeling ALS using induced pluripotent stem cells. These cells also have the advantage of being derived from humans, could be derived from ALS patients with both familial and sporadic forms, and could be versatile in allowing investigators to differentiate these cells into multiple cell subtypes.

Induced pluripotent stem cells (iPSC) were first characterized by Yamanaka and colleagues in 2006 with their reprogramming from mouse somatic cells (Takahashi and Yamanaka, 2006). This breakthrough was followed by the development of human iPSC in 2007 (Takahashi et al., 2007). Yamanaka and colleagues used cultured skin fibroblasts from adult individuals. Using four transcription factors (Oct4, Sox2, c-Myc, and Klf4) introduced *via* retroviral constructs, they reprogrammed these fibroblasts and demonstrated that the resulting cells had the capacity for self renewal, could differentiate into all three of the embryonic germ layers (endoderm, mesoderm, and ectoderm), and form teratomas following introduction into rodent hosts. The development of this technology has resulted in a fundamental change in the uses of stem cells for disease modeling and circumvented the ethical concerns regarding the use of embryonic stem cells (ESC). This work resulted in his being awarding a share of the Nobel Prize in Physiology or Medicine in 2012. (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/yamanaka-facts.html)

With the development of induced pluripotent stem cell methodologies came the opportunity to potentially investigate mechanisms of human ALS *in vitro*. IPSC can be differentiated into neural subtypes including neurons, motor neurons, astrocytes, oligodendrocytes, Schwann cells, and myoblasts among others. However, just as important as differentiating cells into these subtypes is that this technology allows us the first opportunity to develop cell subtypes from ALS patients with known genotypes and phenotypes. This was previously not feasible using embryonic stem cells since those cells would have to be derived from embryonic tissue prior to the manifestation of disease. While the use of ESC could be made from embryos known to harbor penetrant ALS gene mutations, there was no potential for using ESC to model sporadic ALS. In addition, the affected tissue (brain