Neuroscience 228 (2013) 47–59

POTENTIAL THERAPEUTIC APPLICATIONS OF DIFFERENTIATED INDUCED PLURIPOTENT STEM CELLS (iPSCS) IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

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Abstract—Difficulties in realizing persistent neurogenesis, inabilities in modeling pathogenesis of most cases, and a shortage of disease material for screening therapeutic agents restrict our progress to overcome challenges presented by neurodegenerative diseases. We propose that reprogramming primary somatic cells of patients into induced pluripotent stem cells (iPSCs) provides a new avenue to overcome these impediments. Their abilities in self-renewal and differentiation into various cell types will enable disease investigation and drug development. In this review, we introduce efficient approaches to generate iPSCs and distinct iPSCs differentiation stages, and critically discuss paradigms of iPSCs technology application to investigate neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Although iPSCs technology is in its infancy and faces many obstacles, it has great potential in helping to identify therapeutic targets for treating neurodegenerative diseases.

Key words: induced pluripotent stem cells, neurodegerative diseases, cell therapy, reprogramming factors, differentiation, immunogenicity.

Contents

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Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; ALS, amyotrophic Lateral Sclerosis; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; BM-MSCs, bone marrow-derived MSCs; DNA, deoxyribonucleic acid; EBs, embryoid bodies; ESC, embryonic stem cells; HD, Huntington's disease; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells; NPC, neural precursor cell; NSCs, neural stem cells; PD, Parkinson's disease; RA, retonic acid; RNA, ribonucleic acid; RNAi, RNA interference; SHH, sonic hedgehog; SMA, spinal Muscular Atrophy; SMN, survival Motor Neurons; SOD1, superoxide dismutase 1; TDP-43, transitive response DNA-binding protein 43; VAPB, vamp-associated protein B/C.

INTRODUCTION

Since first generated from mice cells in 2006 by Yamanaka's group and subsequently from human somatic cells by Thompson's group in 2007, induced pluripotent stem cells (iPSCs) have generated a lot of excitement. Adult mouse fibroblasts (Takahashi and Yamanaka, 2006) and human dermal fibroblasts (Takahashi et al., 2007) were reverted into pluripotent-state cells called iPSCs with the help of a limited set of transgenes including Oct3/4, Sox2, c-Myc, and Klf4. To reduce the potential adverse effects of c-Myc such as tumor formation or cell transformation, human somatic cells were reprogrammed with the help of Oct4, Sox2, Nanog, and LIN28 (Yu et al., 2007). These reprogramming methods for generating iPSCs do not use traditional approaches to induce pluripotency, such as cell fusion with embryonic stem cells (ESCs) or transfer of somatic nuclei into oocytes (Yamanaka and Blau, 2010).

To produce both normal and pathological human tissues *in vitro* for the purpose of systematic disease pathophysiology investigation, Daley's group (Park et al., 2008) generated a large number of iPSCs from patients with a variety of genetic diseases such as Parkinson's Disease (PD), Huntington's Disease (HD), juvenile-onset type I diabetes mellitus (JDM), ty, and Down's syndrome (DS). It was shown that these disease-associated iPSCs were genetically matched to their parental somatic cells, and the consistency of the genotypes facilitated disease investigation and clinical trials. In yet another study, iPSCs were induced to differentiate into functional dopamine neurons with midbrain character and implanted into Parkinsonian rats, which ameliorated their symptoms (Wernig et al., 2008).

0306-4522/12 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2012.09.076

Such encouraging studies have thus opened a new avenue for neurodegenerative diseases treatments.

Compared to embryonic stem cells (ESC), the therapeutic use of iPSCs is considered to be ethically more advantageous, because it does not involve the destruction of human embryos. Although iPSCs retain a memory of the somatic cell types they come from and display some non-CG methylation in regions proximal to centromeres and telomeres that change certain gene expression states (Lister et al., 2011), ESCs and iPSCs have almost the same potential for differentiation. Because of their clear advantages, considerable effort has been invested in creating iPSC-based disease models to establish etiologies of genetically-inherited or sporadic

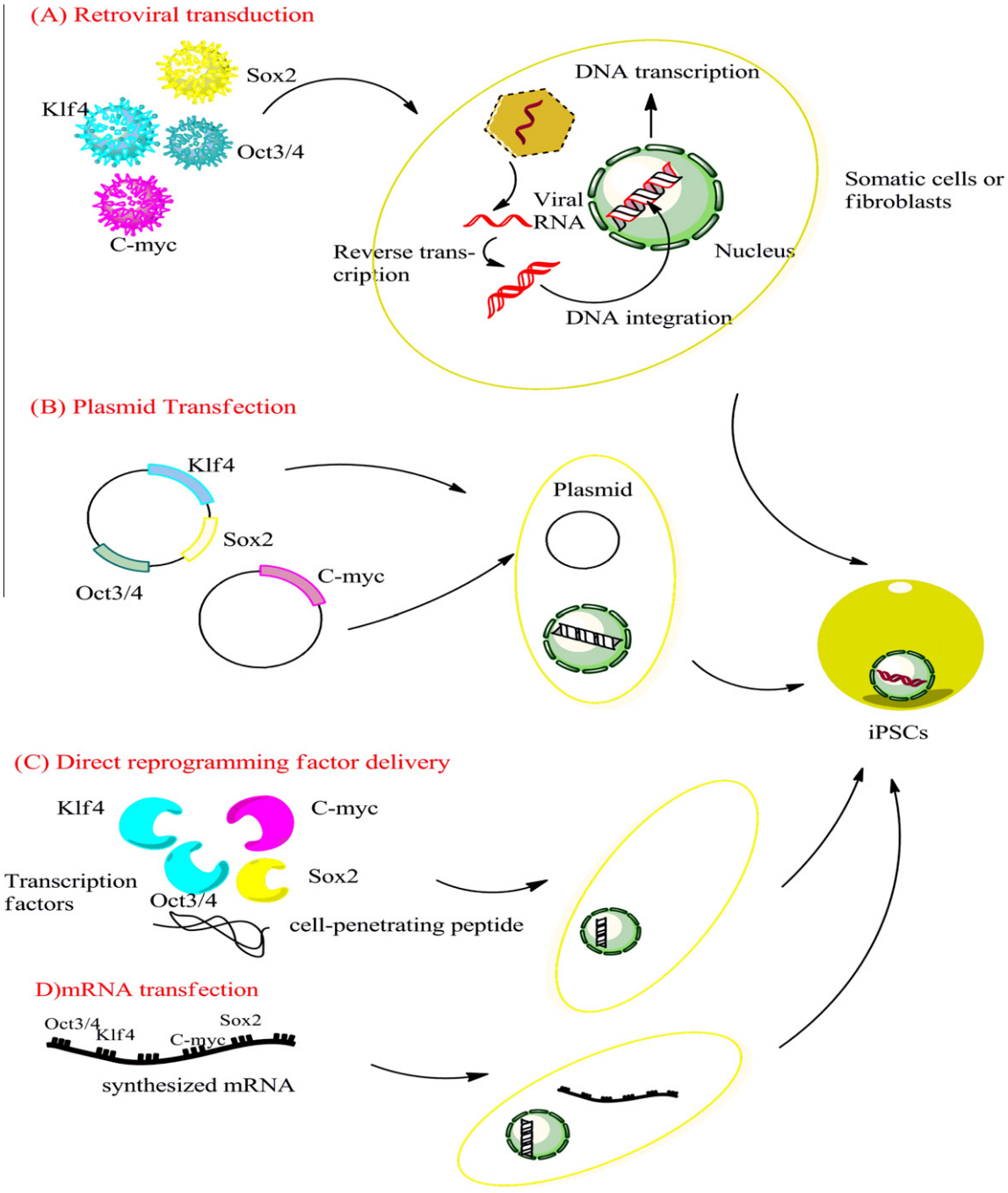

Fig. 1. Schematic models of three approaches to generate iPSCs using Oct3/4, Klf4, C-myc, and Sox2 genes as an example. (A) The use of retroviruses, most commonly lentivirus, to transduce reprogramming genes. Viral genes integrate into chromosomal DNA and transgene transcription induces pluripotency of somatic cells. (B) Plasmid transfections to avoid tumorigenicity. Repeated transformations with two plasmids, one encoding Sox2, Oct3/4, and Klf4, and the other encoding c-myc are sufficient to reprogram differentiated cells. (C) Direct delivery of reprogramming proteins and cell-penetrating peptides to generate protein-based iPSCs avoids the use of gene materials and is a safe method for iPSCs production. (D) Introduction of mRNA molecules encoding transcription factors into somatic cells efficiently induces pluripotency.