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The therapeutic potential of cell identity reprogramming for the treatment of aging-related neurodegenerative disorders

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ABSTRACT

Neural cell identity reprogramming strategies aim to treat age-related neurodegenerative disorders with newly induced neurons that regenerate neural architecture and functional circuits *in vivo*. The isolation and neural differentiation of pluripotent embryonic stem cells provided the first *in vitro* models of human neurodegenerative disease. Investigation into the molecular mechanisms underlying stem cell pluripotency revealed that somatic cells could be reprogrammed to induced pluripotent stem cells (iPSCs) and these cells could be used to model Alzheimer disease, amyotrophic lateral sclerosis, Huntington disease, and Parkinson disease. Additional neural precursor and direct transdifferentiation strategies further enabled the induction of diverse neural linages and neuron subtypes both *in vitro* and *in vivo*. In this review, we highlight neural induction strategies that utilize stem cells, iPSCs, and lineage reprogramming to model or treat age-related neurodegenerative diseases, as well as, the clinical challenges related to neural transplantation and *in vivo* reprogramming strategies.

Abbreviations: 6-OHDA, 6-hydroxydopamine; Aβ, amyloid-β; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APOE4, apolipoprotein E4; APP, amyloid precursor protein; ASCL1, achaete-scute family basic helix-loop-helix transcription factor 1; ATP, adenosine triphosphate; BCL11B, B-cell CLL/Lymphoma 11B; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-Cas9; DLX1, distal-less homeobox 1; DLX2, distal-less homeobox 2; DNA, deoxyribonucleic acid; DOT1L, DOT1-like histone H3 methyltransferase; EGF + FGF2, epidermal growth factor and fibroblast growth factor 2; EN1, engrailed homeobox 1; ESC, embryonic stem cell; FOXA2, forkhead box A2; FOXG1, forkhead box G1; FUS, FUS ribonucleic acid binding protein; GABA, gamma-aminobutyric acid; GAD1, glutamate decarboxylase 1; GFAP, glial fibrillary acidic protein; GSK3B, glycogen synthase kinase 3 beta; H3K27, histone 3 lysine 27; H3K4, histone 3 lysine 4; HD, Huntington disease; HSPA, heat shock 70 kilodaltons protein family; HTT, Huntingtin; iPSC, induced pluripotent stem cell; ISL1, ISL LIM homeobox 1; KLF4, kruppel-like factor 4; LHX3, LIM homeobox 3; LIN28A, lin-28 homolog A; LMX1A, LIM homeobox transcription factor 1 alpha; LMX1B, LIM homeobox transcription factor 1 beta; LRRK2, leucine-rich repeat kinase 2; MAP2, microtubule-associated protein 2; MAPT, microtubule-associated protein tau; MKI67, marker of proliferation Ki-67; MNX1, motor neuron and pancreas homeobox 1; mRNA, messenger ribonucleic acid; MSN, medium spiny neuron; MYC, v-myc avian myelocytomatosis viral oncogene homolog; MYRF, myelin regulatory factor; MYT1, myelin transcription factor 1; MTY1L, myelin transcription factor 1-like; NEUROD1, neuronal differentiation 1; NEUROD2, neuronal differentiation 2; NEUROG2, neurogenin 2; NKX2-2, NK2 homeobox 2; NKX6-3, NK6 homeobox 3; NR4A2, nuclear receptor subfamily 4 group A member 2; NSC, neural stem cell; OLIG1, oligodendrocyte transcription factor 1; OLIG2, oligodendrocyte transcription factor 2; OTX2, orthodenticle homeobox 2; PARK2, parkin RBR E3 ubiquitin protein ligase; PARK3, Parkinson disease 3; PARK7, Parkinson protein 7; PD, Parkinson disease; PI3K, phosphatidylinositol 3-kinase; PINK1, PTEN induced putative kinase 1; PITX3, paired-like homeodomain 3; PN, projection neuron; POU3F2, POU class 3 homeobox 2; POU3F4, POU class 3 homeobox 4; POU5F1, POU class 5 homeobox 1; PPP1R1B, protein phosphatase 1 regulatory subunit 1B; RBFOX3, ribonucleic acid binding protein fox-1 homolog 3; RNA, ribonucleic acid; SNCA, synuclein alpha; SOD1, superoxide dismutase 1; SOX2, sex determining region Y-box 2; SOX10, sex determining region Y-box 10; SOX11, sex determining region Y-box 11; ST18, suppression of tumorigenicity 18; SUV39H1, suppressor of variegation 3-9 homolog 1; SYN1, synapsin 1; TALEN, transcription activator-like effector nuclease; TARDBP, TAR deoxyribonucleic acid binding protein; TCF3, transcription factor 3; TP53, tumor protein p53; TUBB3, tubulin beta 3 class III; UCHL1, ubiquitin carboxyl-terminal esterase L1; YY1, YY1 transcription factor; ZNF536, zinc finger protein 536.

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Contents

1. Introduction

Q5 The foremost aim of neural cell reprogramming is the treatment of age-related neurodegenerative disorders and the functional regeneration of neural circuits *in vivo*. This concept is particularly relevant to the central nervous system, which retains a limited capacity for self-regeneration in adulthood. The isolation of pluripotent embryonic stem cells (ESCs), *in vitro* neuronal differentiation, and transplantation of ESC-derived neurons to models of neurodegenerative disease marked the first milestones in the application of stem cell-related technologies to human diseases. Investigation into the molecular mechanisms underlying this pluripotency revealed that somatic cells could be reprogrammed to induced pluripotent stem cells (iPSCs) with a limited number of transcription factors. These cells enabled direct modeling of genetic and sporadic forms of Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and Parkinson disease (PD). Refined reprogramming strategies enabled the direct transdifferentiation of diverse neural linages and neuron subtypes both *in vitro* and *in vivo*. However, as an evolving technology, neural reprogramming still faces numerous challenges to clinical implementation. In this review, we highlight neural induction strategies that utilize stem cells, iPSCs, and transdifferentiated non-neuronal cells to model or treat age-related neurodegenerative diseases, as well as, the clinical challenges related to neuron transplantation and *in vivo* reprogramming strategies.

2. Stem cell-based neural induction strategies

2.1. Embryonic stem cells

2.1.1. Teratocarcinoma cells and embryonic stem cells

The isolation of mouse teratocarcinoma cells with properties highly similar to cells of the early mouse embryo provided the first *in vitro* experimental model of cellular pluripotency (Stevens, 1967). The *in vivo* transplantation of single teratocarcinoma cells isolated by enzymatic dissociation of embryonal carcinomas revealed that these cells are multipotential with the capacity to differentiate into diverse somatic lineages (Kleinsmith and Pierce,

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