Applications of the induced pluripotent stem cell technology in neurodegenerative diseases

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Introduction

Induced pluripotent stem cells (iPSCs) are pluripotent stem cells that can be obtained from somatic cells by the addition of four transcription factors: Oct4, Sox2, Klf4, C-Myc. As pluripotent stem cells, iPSC can differentiate into any cell type of the human body.

Therefore, iPSC technology allows for the generation of any adult cell type from a somatic cell.

The iPSC technology has two main applications in the treatment of neurodegenerative diseases

- The generation of *in vitro* models of disease
- The generation of a cell source to carry out regenerative medicine (cell therapy)

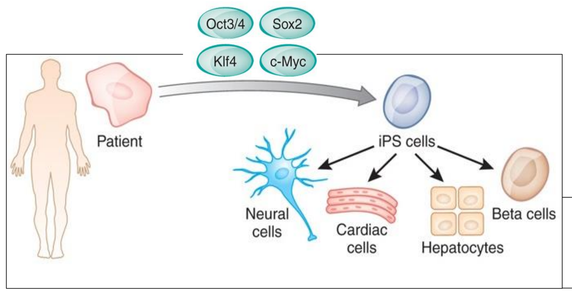


Figure 1: generation of iPSC (1)

The aim of this project is to review new findings and approaches, allowed by iPSC technology, that may be useful to treat neurodegenerative diseases.

In order to get a broad and accurate view four of the most relevant illnesses were studied, for which an overview of symptoms and causes is listed below:

Disease	Genetic defect	Symptoms and Causes
Alzheimer disease (AD)	Multifactorial or APP, PS1 or PS2 mutations	Progressive memory loss and cognitive disturbance Caused by the loss of cholinergic neurons in the hippocampus
Amyotrophic lateral sclerosis (ALS)	Multifactorial or SOD1, VAPB mutations	Weakness and paralysis Caused by the loss of motor neurons and neuromuscular degeneration
Huntington's disease (HD)	CAG repeat expansion in the huntingtin gene	Progressive chorea and dementia Caused by the loss of neurons in striatum and cortex
Parkinson's disease (PD)	Multifactorial or LRRK2, PINK1, PARKIN, SNCA mutations	Coordination difficulties, stiffness, tremor of hands… Caused by the loss of dopaminergic neurons in the *substantia nigra, pars compacta*

Materials and Methods

Search on PubMed database: scientific literature including published reviews and papers.

Selection of literature: by journal relevance, citations in later papers and publication date (most of the literature was published in the past 5 years).

Key words: induced pluripotent stem cells**,** iPSC, applications, neurodegenerative diseases, Alzheimer's disease, AD, Parkinson's disease, PD, Amyotrophic lateral sclerosis, ALS, Huntington's disease, HD, treatment, regenerative medicine, cell therapy, drug testing, amongst others.

Results

Models Of Disease

The iPSC technology allows for the generation of neurons from somatic cells of patients who suffer from neurodegenerative diseases.

The neurons yielded from patients recapitulate the disease phenotype and can be used as *in vitro* human models of disease, which have two main applications:

- Understanding the molecular basis of neurodegenerative diseases, still fairly unknown.
- Seek for new targets of treatments and drug testing.

Cell Therapy

The neuron loss is the most characteristic feature of neurodegenerative diseases. As previously mentioned, iPSC have the potential of generating neurons, which could be engrafted in the loss sites of patients in order to perform regenerative medicine.

- The main goal is the cell therapy with neurons or neural precursors obtained from patient somatic cells through the iPSC technology to carry out an autologous transplantation (lack of engraftment rejection).
- However, the possibility of teratoma formation or disease recapitulation hinder the use of this approach in humans.

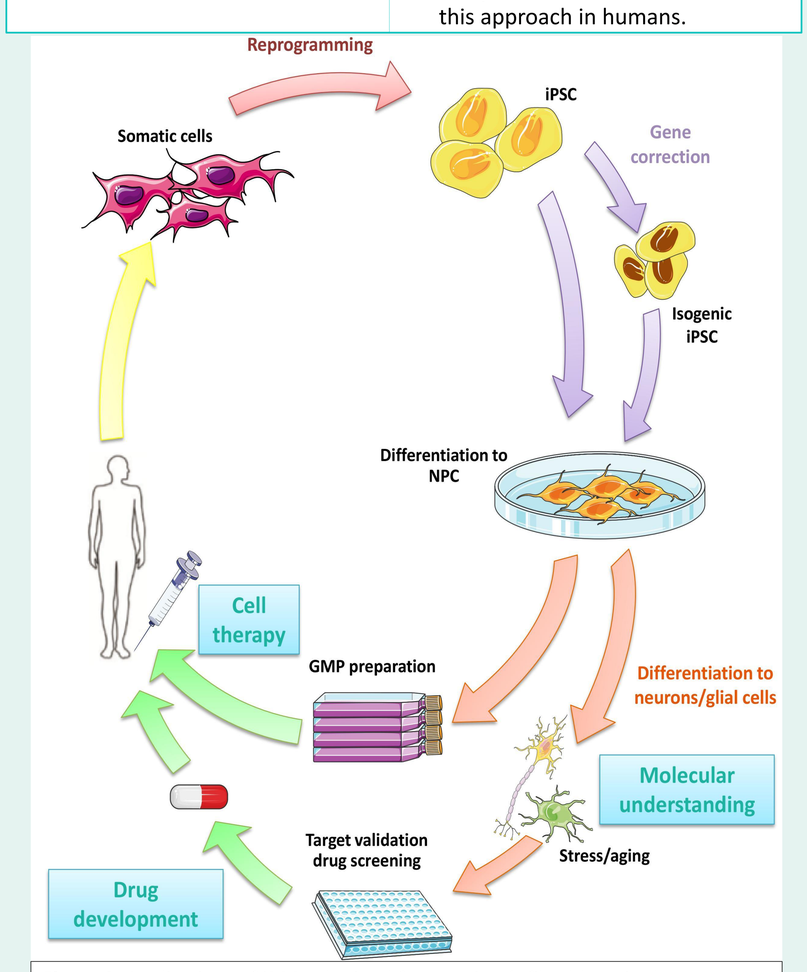


Figure 2: Applications of iPSCs obtained from patient's fibroblasts in the treatment of neurodegenerative diseases (*)

Models of disease

MOLECULAR FINDINGS

The generation of neurons from patient somatic cells through the iPSC technology has allowed the discovery of molecular alterations that lead to cell death in AD, ALS, HD and PD; compiled in the following table and schematic representations:

Disease	Phenotype in iPSC-Derived Progeny
AD	⇧Amyloid β (Aβ) secretion ⇧Tau phosphorylation Active glycogen synthase kinase 3 (GSK3) — GSK3 phosphorylates tau when activated by Aβ oligomers
ALS	Reduced levels and lack of inclusions of the vamp associated protein B (VAPB)
HD	⇧Lysosomal activity Susceptibility to stress which increases cell death ⇩TGFβ and N-cadherin
PD	⇧Sensitivity to oxidative stress Presence of α-synuclein bodies Impaired mitochondrial function and autophagy pathways

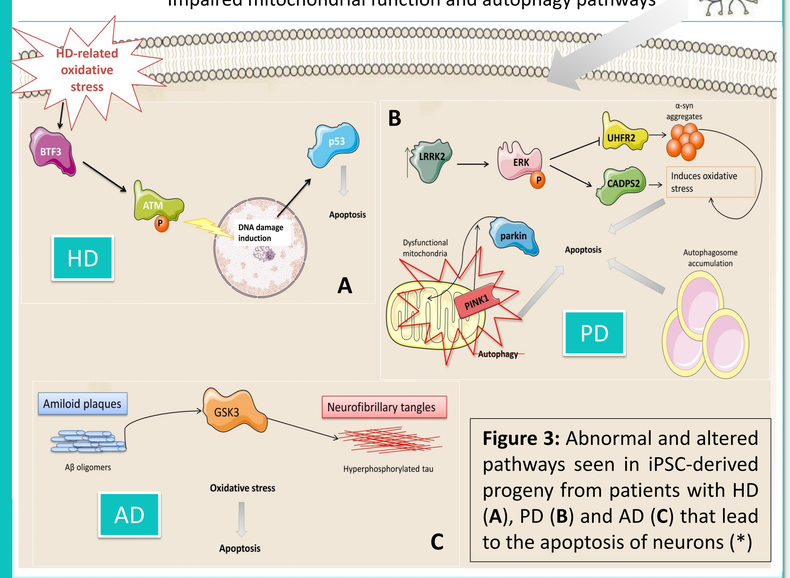
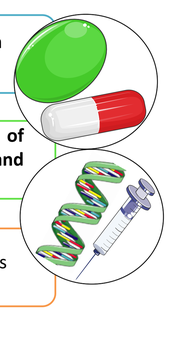


Figure 3: Abnormal and altered pathways seen in iPSC-derived progeny from patients with HD (**A**), PD (**B**) and AD (**C**) that lead to the apoptosis of neurons (*)

NEW TREATMENTS

The following treatments and drugs have been tested in iPSC-derived neurons from patients of AD, HD and PD and have shown promising results:

AD	• γ-secretase inhibitors • β-secretase inhibitors • Docosahexaenoic acid (DHA)	**Prevent the formation of Aβ oligomers**
PD	• ERK inhibitors • LRRK2 inhibitors	**Prevent the formation of α-syn aggregates and oxidative stress**
HD	• Genetic correction of the huntingtin gene by homologous recombination	



Cell Therapy

Studies in which neurons or neural precursor cells (NPC) from animals', human donor's and patient's somatic cells (obtained through the iPSC technology) were engrafted in mice and rat models of ALS, HD and PD showed the following results:

	Cell Therapy With iPSC-derived neurons or NPC		
Disease	iPSC from animal models	iPSC from human healthy donors	iPSC from human patients
ALS	-	Moderated amelioration of the disease pathology due to the production of VEGF and AKT activation Motor function and life span significantly improved due to an increased production of neurotrophic factors and a reduction in the immune response	-
HD	-	-	Improvement of the pathology Recapitulation of the disease long term post engraftment
PD	Improvement in the motor behaviour Teratoma formation rescued	Not statistically representative motor recovery and formation of teratomas	Improvement of behavioural and motor impairments

AUTOLOGOUS TRANSPLANTATION POTENTIAL

Neurons obtained through the iPSC technology from PD patient's fibroblasts were engrafted in the striatum of the PD rat model and improved its altered behaviour. Therefore, neurons obtained from patient somatic cells could be useful to treat their own disease.

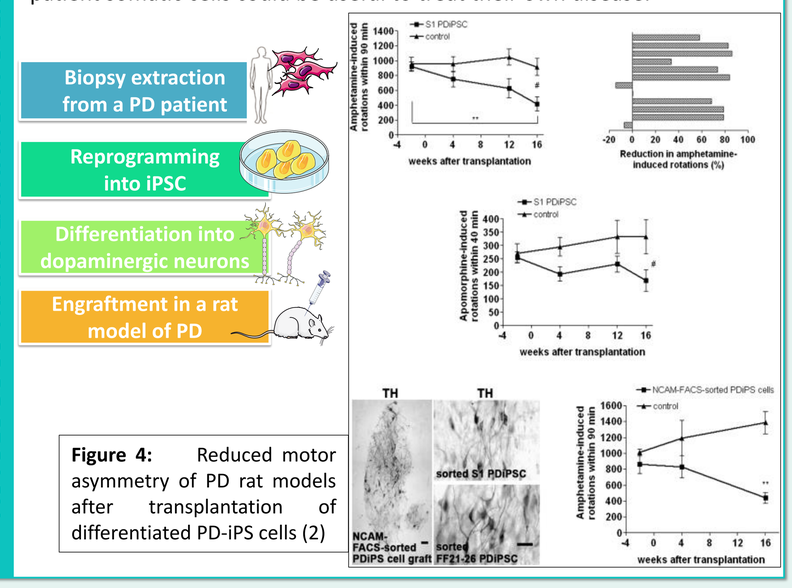
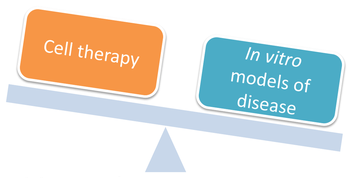


Figure 4: Reduced motor asymmetry of PD rat models after transplantation of differentiated PD-iPS cells (2)

Conclusions



- The use of iPSC-derived cells as *in vitro* models of disease has allowed the elucidation of a lot of abnormal pathways and molecular alterations in ALS, PD, HD and AD. Furthermore, it has been an useful tool to test the efficacy of innovative treatments. It is the only feasible application of iPSCs in humans currently.
- Regarding the use of the iPSC technology in cell therapy some approaches have been developed and have shown promising results. However, there is still a lot of work ahead until this application can be performed in human patients.

References

1. Yamanaka S. Ekiden to iPS Cells. Nat Med [Internet]. Nature Publishing Group; 2009;15(10):1145–8.
2. Hargus G, Cooper O, Deleidi M, Levy A, Lee K, Marlow E, et al. Differentiated Parkinson patient-derived induced pluripotent stem cells grow in the adult rodent brain and reduce motor asymmetry in Parkinsonian rats. Proc Natl Acad Sci U S A. 2010;107(7):15921–6.

(*) Figures created by the author