Applications of the induced pluripotent stem cell technology in neurodegenerative diseases

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Introduction

The 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 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 diseases were studied, for which an overview of symptoms and causes is listed below:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetic defect</th>
<th>Symptoms and Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer</td>
<td>Tau proteinopathies, P301L, V717L mutations</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>ALS</td>
<td>CAG repeat expansion in the huntingtin gene</td>
<td>ALS</td>
</tr>
<tr>
<td>PD</td>
<td>CAG repeat expansion in the huntingtin gene</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Huntington</td>
<td>CAG repeat expansion in the huntingtin gene</td>
<td>Huntington's disease</td>
</tr>
</tbody>
</table>

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 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.

Results

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 and PD, compiled in the following table and schematic representations:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phenotype in iPSC-Derived Progeny</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Amyloid β (Ab) secretion</td>
</tr>
<tr>
<td>ALS</td>
<td>Reduced levels and lack of/reduction of the v-executed protein (VAPB)</td>
</tr>
<tr>
<td>HD</td>
<td>Dysfunctional activity</td>
</tr>
<tr>
<td>PD</td>
<td>Increased oxidative stress</td>
</tr>
</tbody>
</table>

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

- γ-secretase inhibitors
- B-secretase inhibitors
- Dose-dependent acidosis (DHA)
- EGR1 inhibitors
- LRRK2 inhibitors
- General correction of the huntingtin gene by homologous recombination

Conclusions

- The use of iPSC-derived cells as in vitro models of disease have 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.

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.

References


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[Figure 1: generation of iPSC (S)]

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

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

[Figure 4: Reduced motor asymmetry of PD rats after transplantation of differentiated PD-iPSC cells (*)]