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REVIEW

Induced pluripotent stem cells for modeling neurological disorders

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Abstract

Several diseases have been successfully modeled since the development of induced pluripotent stem cell (iPSC) technology in 2006. Since then, methods for increased reprogramming efficiency and cell culture maintenance have been optimized and many protocols for differentiating stem cell lines have been successfully developed, allowing the generation of several cellular subtypes *in vitro*. Gene editing technologies have also greatly advanced lately, enhancing disease-specific phenotypes by creating isogenic cell lines, allowing mutations to be corrected in affected samples or inserted in control lines. Neurological disorders have benefited the most from iPSC-disease modeling for its capability for generating disease-relevant cell types *in vitro* from the central nervous system, such as neurons and glial cells, otherwise only available from post-mortem samples. Patient-specific iPSC-derived neural cells can recapitulate the phenotypes of these diseases and therefore, considerably enrich our understanding of pathogenesis, disease mechanism and facilitate the development of drug screening platforms for novel therapeutic targets. Here, we review the accomplishments and the current progress in human neurological disorders by using iPSC modeling for Alzheimer's disease, Parkinson's disease, Huntington's disease, spinal muscular atrophy, amyotrophic lateral sclerosis, duchenne muscular dystrophy, schizophrenia and autism spectrum disorders, which include Timothy syndrome, Fragile X syndrome, Angelman syndrome, Prader-Willi syndrome, Phelan-McDermid, Rett syndrome as well as Nonsyndromic Autism.

Key words: Neurological disorders; Induced pluripotent stem cells; Disease modeling; Human neurons; Drug screening

Core tip: Several diseases have been successfully

modeled using induced pluripotent stem cell (iPSC) technology. Neurological disorders are frequent targets of iPSC-disease modeling for its ability to generate *in vitro* disease-relevant cell types from the central nervous system, such as neurons and glial cells. Patientspecific iPSC-derived neural cells can recapitulate the phenotypes of these diseases, unveiling mechanisms and providing drug screening platforms for novel therapeutic targets. Here, we review the accomplishments and the current progress achieved in human neurological disorders by using iPSC modeling for Alzheimer's disease, Parkinson's disease, Huntington's disease, spinal muscular atrophy, amyotrophic lateral sclerosis, duchenne muscular dystrophy, schizophrenia and autism spectrum disorders.

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INTRODUCTION

Induced pluripotent stem cell (iPSC) technology was first described in 2006 by Takahashi and Yamanaka[1], when murine fibroblast cells were reprogrammed to a pluripotent stage, with the protocol being successfully applied to human fibroblast cells on the following year by the same group[2]. Since then, iPSCs have been greatly used by many laboratories for pathobiology studies, discovery of disease mechanisms and potential drug-screening platforms[3,4].

Neurological diseases have benefited enormously from iPSC technology for it allowing *in vitro* production of human cells that wouldn't be accessible otherwise, such as the brain, and protocols for generating well-defined neural cell types are already available, being used by several research groups. In our laboratory, the protocol described by Marchetto *et al*[5] for generating cortical neurons has been successfully reproduced. The steps for neuron generation are represented in Figure 1.

In this review, we introduce an overview of the use of iPSC technology for Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease, Spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), duchenne muscular dystrophy (DMD), autism (syndromic and nonsyndromic) and schizoprhenia as well as its application as a drug screening platform and potential therapeutic application.

AD

AD is the most common progressive neurodegenerative disease affecting the aging population in which patients display gradual memory loss and cognitive impairment. AD can be classified as sporadic late onset (S-AD), which mostly occur after the age of 65 and accounts for 95% of the cases, or more rarely familiar early onset (F-AD), developing in patients in as early as their 30 s. Both occurrences present similar clinical features and pathological phenotypes. For familial cases of AD, mutations in amyloid precursor protein (APP), presenilin 1 and 2 (PS1, PS2) were identified[6].

The amyloid hypothesis of AD pathogenesis stems from the accumulation and aggregation of plaques in the brain comprised of β-amyloid (Aβ) peptides and a hyper phosphorylated form of microtubule associated protein Tau. Point mutations in PS1 or PS2, which form the major component of the γ-secretase complex, affect the γ-secretase-mediated processing of APP, increasing formation of Aβ42 within the neurons, wielding a toxic effect, obstructing neuronal communication and causing oxidative stress[7-9]. Nevertheless, it has been reported contradictory results in animal models for the role of APP in AD[10] and most drugs candidates in clinical trials have failed, implying that to prevent functional and cognitive decline, aiming Aβ alone may not be enough. Utilizing iPSCs in AD modeling allow to further investigate if the cause of neurodegeneration is due to accumulation of Aβ and provide a new method to relate S-AD pathogenesis and newly identified genetic risk variants[11].

Several groups have already successfully generated AD patient specific iPSC-derived neuron lines, providing a novel strategy to investigating the pathogen pathways of the disease[12-14]. Yagi *et al*[12] first generated neurons from iPSCs from F-AD patients carrying PS1 or PS2 mutations, which revealed elevated levels of Aβ, thus confirming the amyloid cascade hypothesis. Israel *et al*[14] generated iPSC from two F-AD patients harboring duplications of the *APP* gene and two S-AD patients and found higher levels of the pathological marker Aβ40, phosphorylated tau (Thr231) and active glycogen synthase kinase-3β, when compared to matched control iPSCs, in both F-AD patients and one S-AD patient. Further treatment of the cells with β-secretase inhibitor improved levels of Thr231 and GSK-23, indicating an APP-tau relationship. Although only one of the S-AD lines recapitulated F-AD phenotype (APP duplication), the autosomal-dominant mechanism forms of F-AD may provide insight into the pathogenesis of S-AD in future studies. Nevertheless, larger numbers of samples will be required in order to fully access their genetic heterogeneity.

Additional studies approaching drug and toxicity screenings in AD, used neuronal cells-iPSC derived, positive for forebrain markers and able to secrete functional proteins involved in Aβ, as well as APP, β-secretase and γ-secretase[15]. After treatment with β- and γ-secretase inhibitors, differences in susceptibility to drugs between the early and late differentiation stages of the cells were reported. Another group used AD iPSC-derived neurons to test for molecules effective against Aβ42 toxicity and revealed that cyclin-dependent kinase 2 inhibitor block Aβ toxicity in the differentiated neural cells[16]. Both studies show the potential that iPSC technology

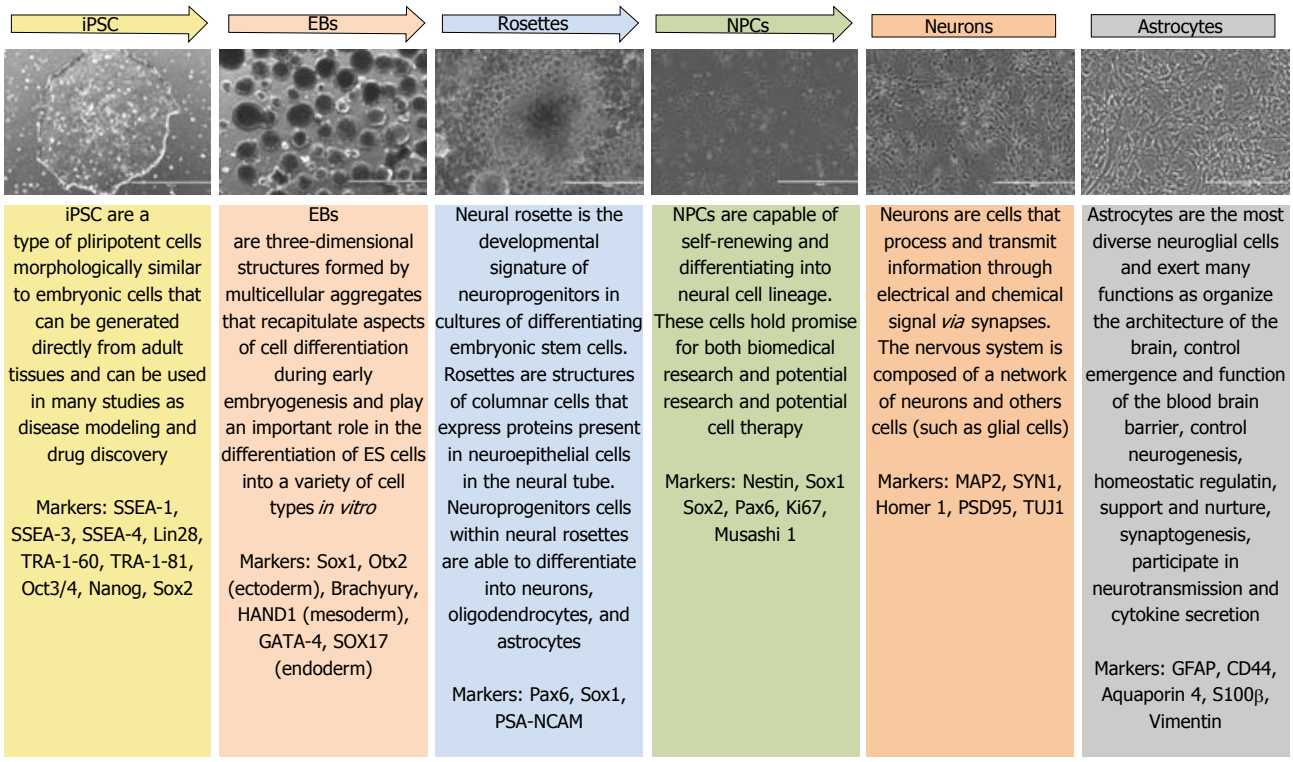

Figure 1 Steps for neuronal and glial differentiation protocol. NPCs: Neural progenitor cells; iPSC: Induced pluripotent stem cells; EBs: Embryoid bodies.

represents in modeling AD and allow to examine patient-specific phenotypes *in vitro* reflecting the familial and sporadic forms of Alzheimer's disease, as they are often indistinguishable clinically.

PD

PD is the second most common neurodegenerative disease, behind only to AD, and it's characterized by progressive loss of dopaminergic neurons (DA) from substantia nigra. Patients display progressive motor dysfunction, such as tremor, rigidity, akinesia and bradykinesia. Most cases of PD are sporadic, but about 20% of patients display familial monogenic forms of the disease[17]. Pathological hallmarks of PD are characterized by presence of Lewy bodies composed of alpha-synuclei (α-syn) protein beyond the nigra and the cortex.

The first dominantly inherited familial PD genetic cause identified was linked to alpha synuclei encoded by the *SNCA* gene[18], with four mutations currently described[19-22], which causes a misfolding of the protein leading to neuronal dysfunction. Alpha-synuclei is believed to participate in pre-synaptic functions of DA neurons, though the complete actual role of α-SYN is still unknown. DA neurons were generated from iPSCs from a family who carried a triplication of the SNCA locus and expressed double the amount of α-SYN when compared to healthy controls[18]. Further analysis on iPSC-derived DA neurons from the same family, showed increases in mRNA for genes associated with oxidative stress, such as haemoxygenase 2 and monoamine oxidase, and when these neurons were exposed to hydrogen peroxide, increased activation of caspase-3 was detected, suggesting that high levels of α-SYN may present a toxic effect on DA neurons under stress[23].

Another mutation, in *A52T SNCA* gene, was corrected using zinc finger nuclease (ZFN) technology, both in mutated and control iPSC lines in order to correct the mutation and generate isogenic control lines, respectively. However, the iPSC-derived DA neurons generated were not evaluated, but authors showed the proof of principle that isogenic cell lines are important to evaluate consequences of mutated genes[24].

Two other dominant forms later characterized were linked to mutations in glucocerebrosidase and leucine rich repeat kinase 2 (*LRRK2*) genes[25-27]. Mutations in *LRRK2* gene, usually G2019S, are the most common cause of familial PD, being intensively investigated with use of iPSC technology[28-32]. Increased expression of alpha-synuclein in iPSC-derived DA neurons from LRRK2-mutant lines was found[28], fact observed by other studies[29,32], suggesting a connection between these risk genes, as well as increased expression of oxidative stress genes and increased activation of caspase-3 after treatment with H_2O_2. Another study used ZFN technology in G2019S-iPSC and health control iPSC lines to correct and add the G2019S mutation, respectively, observed the reversal of the pathogenic phenotype associated with the G2019S mutations[33].

There are three early onset autosomal recessive forms of PD, caused by mutations in Parkin (PARK2), PTEN induced kinase 1 (PINK1) and DJ1 (PARK7)[34-36]. Parkin is believed to mediate mitophagy on a system dependent on PINK1 and account for most cases of

early-onset PD[37]. Studies done by different groups in PD iPSC-derived neurons found impaired Parkin recruitment after mitochondria depolarization and observed indications that mutations in PARK2 may predispose neurons to oxidative stress, though details of the exact phenotype remains unclear[38-41].

Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, affecting approximately 1:10000 persons[42]. Mutations in the *huntingtin* gene (HTT) lead to poliglutamine repetitions (CAG), causing psychiatric and physiologic alterations[43,44]. Patients with HD display progressive motor and cognitive impairments, change in personality, loss of function along with a decrease in number of neurons, among other symptoms[44,45].

The development of iPSC technology applied to human cells[2] helped elucidate the mechanisms of several devastating neurologic diseases, as HD. Cells from HD patients were first reprogrammed into iPSC in 2010[46], and alterations in electrophysiology, cell metabolism, adherence and toxicity were reported. Expansion of a CAG repeat alters the transport and release of BDFN and increases glutamate receptors, producing toxicity and oxidative stress in neuron and glial cells[44,46,47]. HD iPSC-derived astrocytes displayed 34% more vacuoles when compared to healthy control astrocyte cell lines[42] and on HDN177-82Q mice model, it was observed that mutation in gene *HTT* causes severe neurological phenotypes and dysfunction in glia cells[48].

Another study created genetically corrected HD iPSCs lines and further differentiated them into neural stem cells (NSC), which displayed normalized pathogenic TGF-β and cadherin signaling pathways. When these genetically corrected NSCs were transplanted into a transgenic HD mice model, it was observed that they were able to populate the striatum after a two week post-transplantation period, uncovering advancements for a potential stem cell replacement therapy[49].

SMA

SMA is an autosomal recessive neurodegenerative disease caused by mutations in survival of motor neuron gene (*SMN-1*), characterized by a selective and progressive loss of lower motor neurons resulting in degeneration of motor neurons in the spinal cord and muscular atrophy on limbs and trunk[50-52].

In order to uncover what is really happening from an inside perspective of the patient's body, iPSC technology can be used to elucidate this disease mechanism[53]. This was first demonstrated by Ebert *et al*[50] using fibroblast cells from SMA patients, which were reprogrammed into iPSCs by lentiviral infection carrying Oct4, Sox2, Nanog and Lin28 factors. When these iPSCs were further differentiated into motor neurons, it was observed they displayed smaller soma size and incomplete synapses formation. Valproic acid (1 mmol/L) and Tobramycin (320 umol/L) drugs, both previously described in the treatment of SMA patients[54], were tested and appeared to increase the production of SMN protein in iPSC-derived motor neurons. Valproic acid and anti-sense oligo treatment help improve defects in AChR clustering, increasing levels of SMN transcripts[55].

The neuronal differentiation of SMA iPSCs show reduced capacity to produce motor neurons[51], therefore, applying gene correcting technology may aid in overcoming these methodological shortcomings. The correction of *SMN* gene, using single-stranded oligonucleotide, was shown to restore the *SMN* gene profile in neurons derived from SMA-iPSC, converting SMN2 in SMN1[56]. Furthermore, these corrected-gene cells were transplantated in SMA rat models, improving the animals' disease phenotype and life extension. The possibility of generating genetically corrected, patient-specific SMA-iPSC derived motor neurons and the positive results observed from transplantation in this study, open the path for therapeutic application of autologous cell therapy for SMA patients[57].

ALS

ALS is a late adult onset neurodegenerative disease characterized by a progressive degeneration of motor neurons in the cortex, brainstem and bone marrow[58,59]. ALS is a devastating disease; the loss of motor neurons and muscle atrophy confine patients to a wheelchair very rapidly, followed by respiratory failure. The cause of ALS is not yet elucidated, however, mutations in genes *SOD1, C9orf72, TDP-43, FUS/TLS*, angiogenin, Matrin 3[60-65] and others, have been associated with ALS. Moreover, familial inheritance accounts for about 10% of the cases of patients diagnosed with ALS[65].

Several studies using reprogrammed cells generated from patients of different diseases have been described since 2008[66,67] and they have and still contribute to the understanding, from a physiological point of view to prospective treatments, of these diseases. The first group to generate ALS-derived iPSCs reprogrammed fibroblast cells and further differentiated them into motor neuron cells, opening the path to studies on ALS pathogenesis, yield in a model for testing novel compounds and for autologous cell replacement therapy[67].

iPSC-derived motor neuron cells have been shown to be physiologically active *in vitro* after reprogramming[68,69] and were immunopositive for ISL^+ (motor neuron marker)[68], MNX1 (motor neuron and pancreas homebox protein 1)[69] and also, displaying a phenotype for cholinergic transmitters, positive for ChAT (acetylcholine marker)[68,69].

Neural progenitor cells, which can be generated from iPSC, have become a promising source for cell therapy for ALS. These cells have been transplanted in the lumbar spinal cord in ALS mice models, further differentiated into neurons and astrocytes, and were shown to be able to improve the quality and lifespan of these mice[70,71].

Recently, the world has drawn attention to the ALS

"Ice bucket" campaign[72], gaining scientific research strength and raising public awareness about the disease. ALS iPSC research can contribute as a platform to developing new therapeutics, clinical application with cell and gene therapies, enabling new opportunities for future patients' treatments.

DMD

Mutations in the dystrophin gene, located on X chromosome in region p21, lead to dysfunctions in the production of dystrophin, resulting in a misfolded protein. Partial expression or total loss of the dystrophin cause weakness and progressive degeneration of skeletal muscles, reported symptoms of the DMD, whose prevalence is high, affecting approximately 1 in 3300 males[73].

Dystrophin provides support between the actin filaments and cell membrane (sarcolemma) in muscle cells but may also be found in other cellular types, such as in the retina, liver, heart, brain, *etc.*[74]. Moreover, dystrophin appears to act in the central nervous system. Some studies have reported that DMD patients have difficulties in tests requiring attention and verbal repetition, as well as deficits in speech processing and reading, suggesting DMD may be a cerebellar disorder[75,76]. Approximately one third of DMD patients show cognitive impairment[77,78], in which the mutations in the dystrophin gene seem to alter the efficiency of the brain-cerebellum path, as well as change the neuronal and brain architecture, leading to cognitive deficits in these patients[75-77].

Modeling DMD *in vitro* will help disclose the neurological mechanism of this disease and even allow to correct the dystrophin deficit in the muscle. To date, cardiomyoblast cells, muscle cells and neurons have been generated from iPSC cells[79-82]. The first group to reprogram cells from DMD patients was Park *et al*[66] in 2008, followed by other groups modeling DMD *in vitro* and whose primary objective was to correct the dystrophin in muscle cells. Furthermore, studies applying human artificial chromosome, CRISPR/Cas9 and TALEN technologies[82-84] reported to have restored the expression of dystrophin, observed *in vitro* and *in vivo*.

Neuromuscular diseases like DMD have been the focus of iPSC modeling disease studies, which allow the creation of platforms to correct genetic mutations as well as for drug discovery, opening doors to personalized medicine.

AUTISM

Autism spectrum disorder (ASD) is a group of complex neurodevelopmental disorders, affecting 1% of the world's population, characterized by qualitative communication impairment, atypical social interaction and restricted and repetitive patterns of behavior[85-87]. Autism can be categorized in syndromic and nonsyndromic types. Syndromic autism is definied by an identified neurological disorder, harboring a set of associated phenotypes, where the genetic cause is known and gene mutation is identified. Syndromic forms of ASD are Timothy syndrome (TS), Fragile X syndrome (FXS), Angelman syndrome (AS), Prader-Willi syndrome (PWS), Phelan-McDermid and Rett syndrome (RTT)[5,88-91]. Studies using iPSC technology have already been reported for all of these diseases. Nonsyndromic autism, or simple called ASD, is a group of comorbidities whose genetic cause is not well defined yet, although some genes involved are known, and accounts for the majority of autism cases.

TS

TS is a rare genetic disorder caused by *de novo* missense mutation in the *CACNA1C* gene[92,93] and it is associated with developmental delay and autism[92]. This gene encodes the α-subunit of the voltage-gated calcium channel $Ca_v1.2$. This channel plays a central role in regulating and signaling network that is essential for neuronal function[94-96].

Cortical neuronal precursor cells and neurons were first differentiated from iPSCs generated from patients with Timothy syndrome by Pasca *et al*[88]. Intracellular calcium (Ca^{2+}) signals were examined in these cells and a significant increase in TS neurons was observed. Furthermore, TS patient specific-iPSCs were generated to study the effects of the mutation on dendritic arbors. The results found in these cells were then compared to a TS rodent model and revealed an aberrant activity-dependent dendritic retraction in both human derived neurons and animal neurons[97].

Mutations in ion channel genes have been associated with cardiac arrhythmias and TS, but the pathophysiological process is little known. TS iPSC-derived cardiomyocyte cells displayed an erratic and slow contraction behaviour when compared to healthy controls, as well as abnormal calcium handling and irregular and prolonged action potential patterns[98].

FXS

FXS is the most common form of syndromic ASD and mental retardation[89]. FXS is caused by loss of expression of the fragile X mental retardation gene 1 (*FMR1*) located in the X-chromosome, where an expanded CGG repeats in the 5'-untranslated region of the *FMR1* gene is present[89,99]. FXS has no cure and patients display developmental impairment, learning and cognitive disabilities, as well as physical and behavioral phenotypes such as stereotypic movements[100,101].

FMR1 gene is associated with synaptogenesis and the FMRP protein can be detected at synapses and dendritic spines[102]. The first FXS iPSC model was derived from fibroblasts and described by Urbach *et al*[89]. Their findings reported the *FMR1* gene remained inactive and highlighted crucial differences between ES and iPS cells. Another study reported variable levels of FMR1 silencing and expression in multiple FXS iPSC lines. Furthermore, these lines showed reduced FRM1 expression during

neuronal differentiation[99].

FMRP expression works as an indicator for drug discovery for FXS. In a recent drug screening study, 6 compounds were shown to increase *FMR1* gene expression in neural stem cells differentiated from a FXS iPSC line. Despite none of these compounds resulted in clinically relevant levels of FMR1, these findings support the idea this assay can be used as a drug screening platform for FXS[101].

Another study showed that iPSC-derived neurons from FXS patients displayed fewer synaptic protein levels and synapses, reduced neurite length and abnormal functionality, with increased calcium transients[103]. Reduced neurite was also observed in forebrain neurons derived from FXS iPSCs[104].

AS and PWS

AS and PWS are neurodevelopmental disorders associated with autism caused by deletions in chromosome 15q11-q13[105]. AS is caused by reduced expression of the ubiquitin-protein ligase E3A gene (*UBE3A*) of the maternal chromosome[106-108] whereas PWS occurs by the same deletion on the paternally inherited allele[109]. They both share same behavioral and neurological phenotypes. However, cognitive and neurologic impairments are more severe in AS, including seizures, while behavioral problems are more severe in PWS[109].

The first study to model AS and PWS using iPSC-derived from patients was done by Chamberlain *et al*[105]. Although the authors found no phenotypic differences between AS and control neurons, they observed the UBE3A imprinting occurred during neuronal differentiation in AS cells.

Recently, iPSCs from a PWS patient with an atypical microdeletion on paternal chromosome 15q11-q13 were generated[90], revealing they expressed UBE3A-ATS, typically restricted to neurons as is, consequently, the imprinted expression of UBE3A observed in these iPSCs, as well[90].

Another study generated iPSCs from patients with duplications of chromosome 15q11-q13.1 (Dup15q syndrome) and were further differentiated into functional neurons. Gene expression analysis was performed and compared to AS neurons, revealing they shared common neuronal pathways disrupted in both Angelman and Dup15q syndromes[110].

Phelan-McDermid syndrome

Phelan-McDermid syndrome (PMDS) is a rare disorder associated with deletions in chromosome 22q13[91,111]. PMDS is a monogenic form of ASD with a frequency of at least 0.5% of ASD cases and is resulted by deletions in SH3 and multiple ankyrin repeat domains 3 (SHANK3)[112]. This gene plays an important role in synaptic function and is involved in the organization of postsynaptic density[113,114]. PMDS patients display some autistic features as severe language delay and intellectual disability[115]. Animal models for ASD carrying SHANK3 mutations display synaptic dysfunction, abnormal social behavior, repetitive and communication behavior patterns and deficient learning and memory[116].

Recently, Shcheglovitov *et al*[117] generated iPSC-derived neurons from individuals with PMDS carrying large 22q13 deletions that included SHANK3. These neurons displayed fewer synapses and altered electrophysiology. The group reported that excitatory synaptic transmission in PMDS neurons can be corrected by restoring SHANK3 expression or by treating neurons with insulin-like growth factor 1[117].

RTT

RTT is a progressive neurodevelopmental disorder caused by mutations in the X-linked gene methyl CpG-binding protein 2 (MeCP2)[5,118]. RTT syndrome affects more females with an incidence of 1 in 10000[118]. Rett patients display a normal development until 18 mo of age, but thereafter, progressive neurological abnormalities begin to emerge[119]. Neurologic pathologies as autistic behavior, stereotypies, loss of speech, microcephaly, seizures and hypotonia have been described in RTT patients[120].

Several studies utilizing RTT-derived iPSC have been published in the past years. The first RTT-derived iPSC lines were generated by the Ellis group[121], however, the first group to make use of iPSC for disease modeling of RTT syndrome was by Marchetto *et al*[5]. In this work, iPSC-derived neurons from four different RTT patients were generated. Neuronal phenotypes displayed reduced dendritic spine density, smaller soma size, altered electrophysiology, alterations in Ca^{2+} influx and fewer synapses. Furthermore, insulin-like growth factor 1 (IGF-1) was able to rescue the synaptic defects in these neurons after treatment[5]. Reduced soma and nuclear size phenotypes from RTT iPSC-derived neurons were also observed by another group[122] as well as defects in neuronal maturation[123].

IPSC-derived neurons from heterozygous Mecp2308 mice showed defects in glutamatergic synaptic transmission and generation of action potentials and decreased action potential amplitude. These phenotypes were observed in neurons derived from WT and hemizygous mutant iPSC lines, indicating that these deficits are caused by MeCP2 deficiency[124].

The first isoform-patient specific iPSC model of RTT was reported by Dijuric *et al*[125]. iPSC-derived neurons from RTTe1 maintain an inactive X-chromosome and express only the mutant allele. Mutant neurons exhibited reduced dendritic complexity, decreased soma size and cell capacitance.

Recently, astrocytes derived from RTT iPSCs were generated by William *et al*[126]. The group demonstrated that these mutant astrocytes can affect directly the neurons and induce abnormalities. IGF-1 and GPE (an IGF-1 peptide) can partially rescue the morphological defects[126].

RTT syndrome has become a popular target for iPSC studies and this technology has greatly contributed to a

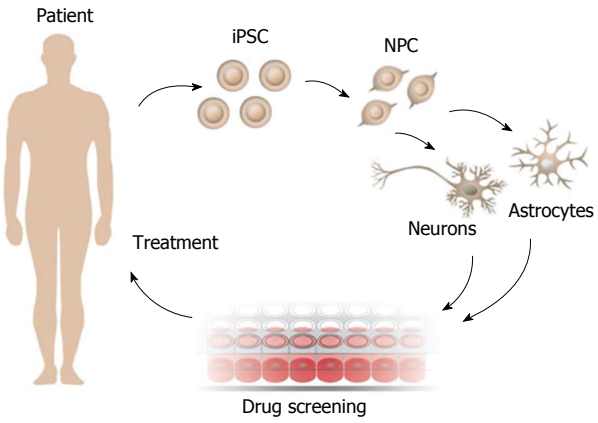

Figure 2 Scheme of neurological disease modeling using induced pluripotent stem cell technology for future personalized treatments. NPC: Neural progenitor cells; iPSC: Induced pluripotent stem cell.

better understanding of the disease.

Nonsyndromic autism

Research on syndromic autism provides us with data that can contribute to the understanding of nonsyndromic autism cases, where the genetic causes are still unknown. Furthermore, animal models provide valuable information on ASD, with recent studies showing similar synaptic phenotypes in nonsyndromic and syndromic mouse models of autisms[127].

The first iPSC model of nonsyndromic autism was recently generated by Griesi-Oliveira *et al*[128]. In this study, the group investigated the molecular and cellular phenotypes in iPSC-derived neurons from an ASD individual carrying a mutation in the *TRPC6* gene, which encodes for protein channel transient receptor potential Canonical 6. TRPC6 protein operates in a calcium channel in the brain, controlling the functioning of neurons, in particular neuronal synapses[128]. *In vitro* analysis revealed that this mutation leads to a reduction of synapses and morphological changes in mouse neurons. These data showed phenotypes in common with findings from syndromic autism[5,88,89,105,117], where the studies demonstrated neuronal abnormalities such as altered morphology and synaptic deficits. The group was also able to rescue some of the neuronal abnormalities using candidate drugs as, IGF-1 and hyperforin. This study brings valuable information to the understanding of autism disorder, despite this mutation occurs in less than 1% of patients with ASD and the genetics of autism is quite complex and involves several genes[129].

Schizophrenia

Schizophrenia (SCZD), like nonsyndromic autism, is a complex neurological disorder where the genetic causes are still unclear, affecting a large number of individuals (1.1% of the world's population)[130,131]. It is considered to stem from a polygenic basis, with an estimated heritability of approximately 80%[130,132,133], and genetic and epigenetic processes underlying the disease, as it was observed in a discordant monozygotic twin study[133]. Moreover, environmental stressors like drug use, being cannabis the most frequently studied, birth complications, maternal immune response, among others, may contibute to SCZD[134-137].

People with SCZD have a lower life expectancy average, mostly to increased health problems and higher suicide rate, and individuals may experience symptoms like hallucinations, delusions, abnormal social behavior (inability to speak, express emotions or find pleasure) and cognitive impairment (deficits in attention, memory and planning)[131,132].

The very first study published with iPSC derived from SCZD patients did not produce neurons[138]. A different group published that same year a study using iPSC technology for SCZD modeling. In this study, iPSC-derived neurons were characterized and revealed defects in neuronal connectivity, reduced outgrowth from soma, reduced PSD95 dendritic protein levels and some altered gene expression. Furthermore, phenotypes in SCZD neurons were ameliorated after treatment with Loxapine, an antipsychotic drug[139].

Another work using SCDZ iPSC-derived neurons carrying 22q11 deletions observed a high L1 copy number in these cells, confirmed by neuronal genome analysis, validating the use of iPSC technology in the study of SCZD condition[140]. Notwithstanding these evidences and taking into consideration SCZD heterogeneity, more studies should be carried out bearing in mind the use of more homogeneous populations, by selecting subjects with rare genetic variants or with similar clinical manifestations[141].

Perspectives

The path for disease treatment and prevention is through the unveiling of pathogenesis and physiological mechanisms that ultimately result in the phenotypic symptoms of diseases. Analysis of live and post-mortem samples, as well as animal models, are great sources for disease study outlines. Despite the importance and relevance of the use of animal models in research, they sometimes are inadequate to fully recapitulate the pathology as it is in humans, and consequently, many drug candidates that once showed to be therapeutically promising in animal models, failed in clinical trials in humans[142].

The development of iPSC technology has come to aid to fill in the gap between pathogenesis and *in vivo* phenotypes. Since the first human iPSC line was established, this methodology has been used by many laboratories for the study of neurological and psychiatric disorders.

Neuroscience research has taken a significant step with iPSC disease modeling. The possibility of generating patient-specific cell lines and differentiating them into various cellular subtypes *in vitro*, allow the creation of future personalized therapeutical treatments. This procedure is represented in Figure 2.

Although iPSC technology holds great potential for disease modeling and research, it is still in its initial phase. This promising technology provides a useful platform for a better understanding of neurological diseases mechanisms, drug discovery and future therapeutical applications.

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