Acta Neuropathol (2014) 127:151–173
DOI 10.1007/s00401-013-1222-6

REVIEW

Human stem cell models of neurodegeneration: a novel approach to study mechanisms of disease development

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Received: 28 September 2013 / Revised: 11 November 2013 / Accepted: 21 November 2013 / Published online: 5 December 2013

Abstract The number of patients with neurodegenerative diseases is increasing significantly worldwide. Thus, intense research is being pursued to uncover mechanisms of disease development in an effort to identify molecular targets for therapeutic intervention. Analysis of postmortem tissue from patients has yielded important histological and biochemical markers of disease progression. However, this approach is inherently limited because it is not possible to study patient neurons prior to degeneration. As such, transgenic and knockout models of neurodegenerative diseases are commonly employed. While these animal models have yielded important insights into some molecular mechanisms of disease development, they do not provide the opportunity to study mechanisms of neurodegeneration in human neurons at risk and thus, it is often difficult or even impossible to replicate human pathogenesis with this approach. The generation of patient-specific induced pluripotent stem (iPS) cells offers a unique opportunity to overcome these obstacles. By expanding and differentiating iPS cells, it is possible to generate large numbers of functional neurons in vitro, which can then be used to study the disease of the donating patient. Here, we provide an overview of human stem cell models of neurodegeneration using iPS cells from patients with Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, Huntington's disease, spinal muscular atrophy and other neurodegenerative diseases. In addition, we describe how further refinements of reprogramming technology resulted in the generation of patient-specific induced neurons, which have also been used to model neurodegenerative changes in vitro.

Keywords iPS cells · ES cells · iN cells · Neurodegenerative diseases · Neurodegeneration

Introduction

Neurodegenerative diseases include a variety of neuropsychiatric and neurological disorders with limited therapeutic options. Advanced age is the biggest risk factor for the development of neurodegenerative changes, and because people are living increasingly longer life spans, treatment of patients with neurodegenerative diseases results in an increasingly significant socio-economic impact on society. For example, the global cost of dementia comprised 604 billion US dollars in 2010 (Alzheimer's Disease International). Hence, both medically and economically, it is urgently necessary to identify the mechanisms of neurodegeneration and to develop novel treatments to protect neurons against pathologic changes.

Directly studying living patient neurons is severely limited by the inaccessibility of the human brain. As a result, postmortem analyses of brain tissue have been performed, which yielded extensive insights into end-stage disease pathology. In order to study disease development, alternative approaches have been applied, which include the analysis of patients' fibroblasts or transformed cell lines that harbor disease-associated mutations. Although the ability to easily culture transformed cell lines has enabled detailed mechanistic studies to be carried out, the biology of cell lines does not resemble the biology of primary neurons. As

Electronic supplementary material The online version of this article (doi:10.1007/s00401-013-1222-6) contains supplementary material, which is available to authorized users.

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a result, it is often unclear whether the mechanisms studied are directly comparable to patients' pathology.

Another method of studying neurodegenerative disease is the creation of transgenic animal models—especially mice. For example, human mutations that cause familial forms of neurodegenerative diseases can be inserted into mice, and mechanisms of disease development can be studied. However, these models often do not accurately recapitulate human disease, as typical phenotypes are often underrepresented or even lacking [114]. As an example, in animal models of Alzheimer's disease (AD), overexpression of the human mutated amyloid precursor protein (APP) resulted in abundant plaque deposition and amyloid-associated pathology, but neurofibrillary tangles and significant neuronal loss as additional hallmarks of AD were not detected [69, 143]. Furthermore, animal models of the sporadic forms of neurodegenerative diseases cannot easily be established due to species-related differences in genetic susceptibility factors.

Therefore, understanding the mechanisms causing human neurodegeneration and developing effective therapies may require human-specific models, which more closely recapitulate human pathogenesis. Stem cell technologies enable the development of such models and encompassed the analysis of disease-affected human embryonic stem (ES) cells. ES cells are derived from the inner cell mass of pre-implantation stage embryos and, as pluripotent stem cells, have the ability of potentially unlimited self-renewal and of spontaneous differentiation into cells of the three germ layers: mesoderm, endoderm and ectoderm [180]. By applying sophisticated differentiation protocols, high numbers of functional neurons can be derived from undifferentiated ES cells, which behave similarly to primary neurons and which have been widely used in cell culture assays [9, 36, 44, 138, 169] (Fig. 1).

The most obvious approach to modeling neurodegenerative diseases with human ES cells is to use neurons derived from stem cells carrying disease-causing mutations. However, because ES cells are derived from embryos, this would involve using pre-implantation genetic diagnostic (PGD) testing to identify embryos harboring a genetic disease, as has been done for Huntington's disease (HD) or Down syndrome (DS). Neurons have been differentiated from these ES cells to analyze disease-associated phenotypes [19, 115, 123, 124, 186]. For instance, aggregates of Aβ42 protein or increased expression of phospho-tau have been observed in stem cell-derived neurons using this approach (Table S1). However, in addition to ethical concerns [60], the isolation of ES cells during PGD can only be used for diseases with very specific mutations and not for the vast majority of neurodegenerative diseases, which are sporadic and not clearly associated with a specific mutation. Thus, deriving human ES cells from embryos analyzed by PGD cannot be a standard procedure for modeling neurodegenerative diseases.

One alternative to PGD is to insert disease-causing mutations into existing human ES cell lines using endonuclease-mediated gene targeting (Fig. 1). For instance, zinc-finger nucleases introduce a double-strand break at a specific target sequence in the genome, which enables the insertion of specific donor sequences through homologous recombination as the cell repairs the break. Using this technique, the Parkinson's disease (PD)-associated mutations A53T and E46K were inserted into the α-synuclein (*SNCA*) locus of two different ES cell lines [168] (Table S1). These modified ES cells did not carry any additional off-site genetic modifications other than the targeted alteration within the *SNCA* locus and thus, the parental and modified ES cell lines were isogenic and differed only by a single mutation. As a result, whole-genome expression profiling of these stem cells demonstrated that isogenic ES cell lines had a much more similar expression profile compared with unrelated ES cell lines [168]. A major disadvantage of this technology, however, is related to the fact that cells of a patient may carry specific disease-associated genetic variants in addition to a specific mutation, which cannot be established in the gene-targeted stem cell and thus, mechanisms of disease development may not be modeled properly. Furthermore, this technique could not be applied to model sporadic diseases. Therefore, while these studies highlight the usefulness of human ES cells for research on neurodegenerative diseases, an alternative approach is needed that uses cells directly derived from patients with the disease of interest. This was accomplished by the application of patient-specific induced pluripotent stem (iPS) cells or the derivation of human induced neurons (iN cells) from patients, as reviewed in this article (Fig. 1).

Human stem cell models of neurodegeneration using patient-derived iPS cells

In 2006, Takahashi and Yamanaka [175] demonstrated a revolutionary technology in which fibroblasts could be reprogrammed into iPS cells simply by expressing the pluripotency-associated transcription factors Oct4, Klf4, Sox2 and c-Myc (Fig. 1). These iPS cells share the main characteristics of pre-implantation embryo-derived ES cells including the ability of unlimited self-renewal and the potential to differentiate into cells of the three germ layers. As a result, it is possible to derive fibroblasts from a patient with a neurodegenerative disease, to reprogram them into iPS cells and to expand them into large numbers. By applying differentiation protocols used for ES cells, iPS cells can be directed to differentiate into functional neuronal

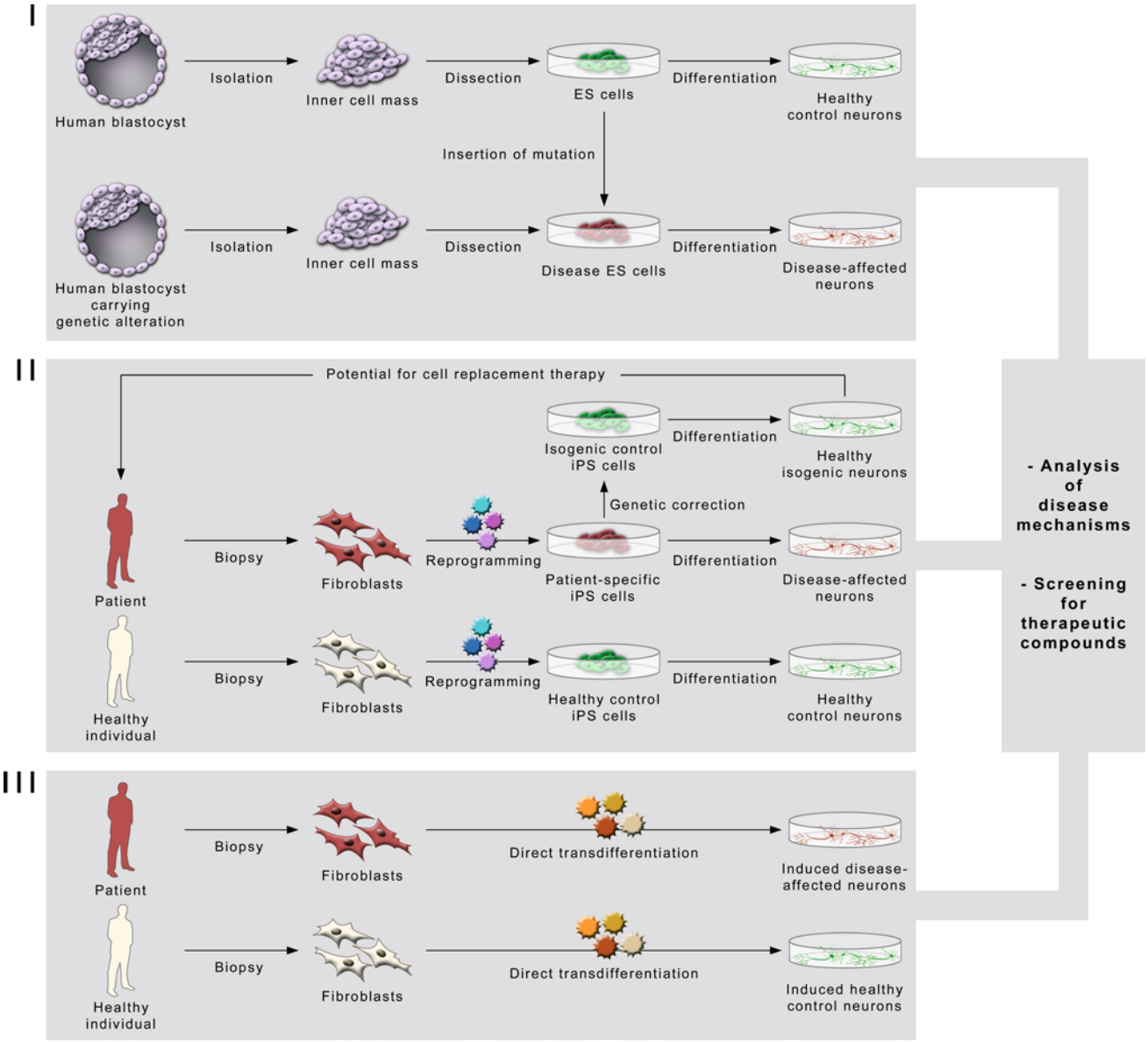

Fig. 1 In vitro modeling of neurodegenerative diseases using human embryonic stem cells, induced pluripotent stem cells and induced neurons. *I* Human ES cells are derived from human blastocysts after isolation and dissection of the inner cell mass and can be differentiated into mature neurons. It is possible to genetically modify ES cells and to introduce a disease-specific mutation in order to model neurodegenerative diseases after differentiation into disease-affected neurons. An alternative, but a less suitable approach, is to analyze ES cells already carrying a genetic defect. *II* Skin fibroblasts of patients can be reprogrammed into induced pluripotent stem (iPS) cells by ectopic expression of the transcription factors Oct4, Sox2, Klf4 and c-Myc. These patient-specific iPS cells can be differentiated into disease-affected neuronal subtypes. In cases of known genetic abnormalities causing the neurodegenerative disease, gene targeting can be applied to repair the genetic mutation thereby establishing isogenic control iPS cell lines. In addition, these genetically corrected iPS cells can be differentiated into neurons and, at least theoretically, subsequently used for cell replacement therapy. Alternatively, iPS cells derived from healthy individuals serve as a source of healthy control neurons. *III* Skin fibroblasts from patients with neurodegenerative diseases or from healthy individuals can be directly transdifferentiated into neuronal cells (so-called induced neurons or iN cells) through ectopic expression of transcription factors such as Ascl1, Brn2, Myt1l and NeuroD1

subtypes such as midbrain dopaminergic (DA) neurons [36, 44, 96, 122, 138, 139], glutamatergic cortical neurons [159], striatal GABAergic neurons [9] or cholinergic motor neurons [117, 138], which are at risk in PD, AD, HD or amyotrophic lateral sclerosis (ALS), respectively (Fig. 2). Because these differentiated neurons were generated from cells of a specific patient, the resulting phenotype of these cells can be used to model the pathology of neurons within the same individual. In addition, since iPS cells can produce specialized neurons in very large quantities, it is

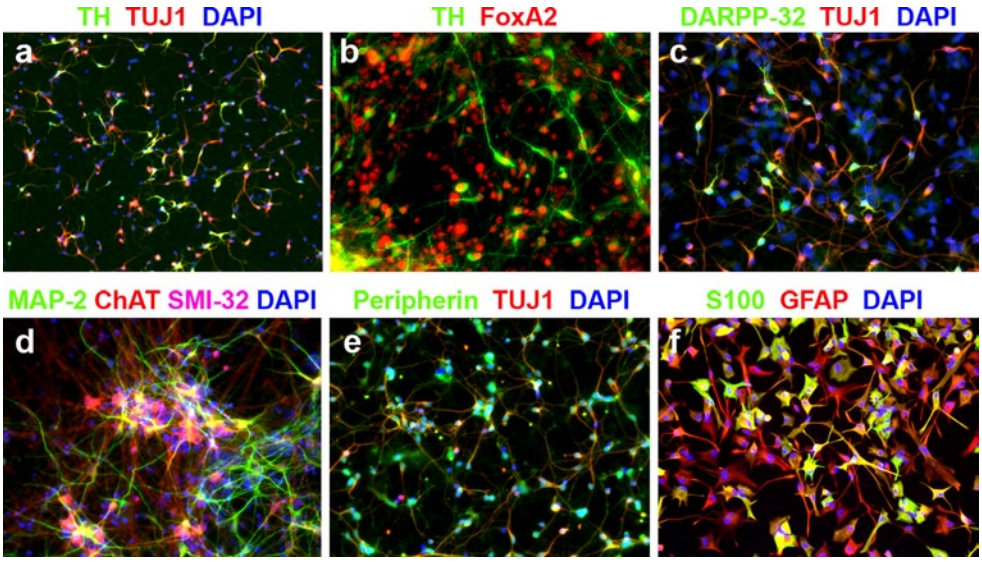

Fig. 2 Differentiation of human iPS cells into neural subtypes in vitro. By applying improved differentiation protocols, human iPS cells can be differentiated into several mature neuronal subtypes. **a** Dopaminergic neurons co-expressing tyrosine hydroxylase (TH) and βIII-tubulin (TUJ1) and **b** midbrain-like dopaminergic neurons co-expressing TH and FoxA2. **c** Striatal neurons co-expressing βIII-tubulin and the dopamine and cAMP-regulated phosphoprotein DARPP-32. **d** Motor neurons positive for microtubule-associated protein-2 (MAP-2), choline acetyltransferase (ChAT) and non-phosphorylated neurofilament H (SMI-32). **e** Peripheral neurons expressing peripherin and βIII-tubulin. **f** Human iPS cells can also be directed to differentiate into astrocytes expressing glial fibrillary acidic protein (GFAP) and S100

possible to apply these models to conduct detailed mechanistic studies, to develop cell therapies, or to identify new drug candidates [46, 73, 84, 111, 133].

The first iPS cell lines from patients with neurodegenerative diseases were described in 2008 [57, 128], and to date, more than 50 reports on iPS cell-based models of neurodegeneration have been published, most of which focus on familial forms of disease caused by specific mutations (Table S2). However, iPS cell models of sporadic forms of neurodegenerative diseases have also been established (Table S2). Interestingly, despite the usually late manifestation of degenerative changes in patients, disease phenotypes were described in patient-iPS cell-derived neurons only after a few weeks of culture and appeared either spontaneously or after challenge with stress-inducing compounds mimicking cumulative age- and disease-related insults to neurons in vivo.

Models of Alzheimer's disease using patient-derived iPS cells

AD is the most common neurodegenerative disease and the most common cause of dementia, affecting more than 30 million people worldwide [11]. Patients suffer from severe cognitive decline with progressive loss of memory function and of abilities to perform basic daily procedures properly. Pathologic hallmarks of AD are extracellular deposits of Aβ protein forming amyloid plaques and intracellular neurofibrillary tangles composed of aggregated and hyperphosphorylated tau protein [56, 72]. These pathologic changes within and around forebrain neurons have been modeled with AD patient-derived iPS cells in different studies.

AD caused by mutated APP

AD-specific iPS cells have been derived from patients with familial forms of AD (fAD) carrying a duplication of the *APP* locus (*APP*^{dp}) [80] or the E693Δ mutation in *APP* [94] (Table S2). APP is a transmembrane protein with important physiological functions including cell signaling, synapse formation and neurogenesis [100]. However, when gene dosage is increased or in the case of certain point mutations, the amyloidogenic pathway generates more pathologic Aβ protein with subsequent deposition of senile Aβ-positive plaques [177]. Similarly, APP^{dp}-AD and E693Δ-AD patient-derived iPS neurons expressed increased levels of Aβ40 protein when compared to neurons from non-demented control individuals [80, 94]. Furthermore, APP^{dp}-AD-iPS cell-derived neurons expressed higher amounts of active GSK-3β and phosphorylated tau protein at Thr231 indicating neurodegenerative changes within patient-derived neurons in vitro [80]. Also, APP^{dp}-AD-derived neurons contained significantly increased numbers of RAB5-positive endosomes, which is in line with observations that RAB5-positive

endosomes accumulate within neurons of a subset of AD patients [33, 34, 80]. These pathologic changes could be significantly reduced after application of β-secretase inhibitors to patient-derived neurons. However, the application of γ-secretase inhibitors only significantly reduced the level of Aβ40 protein, but not the levels of active GSK-3β and phospho-tau protein, indicating that products of APP processing other than Aβ40 protein may regulate the induction of GSK-3β activity and phospho-tau protein in AD [80].

Since APP is encoded on chromosome 21, a duplication of the *APP* gene is present also in neurons from individuals with DS, which is caused by trisomy of chromosome 21. AD-like neurodegenerative changes have been described in people with DS [25], which could be due to duplication of the *APP* gene and/or due to duplication of other genes such as *Dyrk1A* kinase, known to phosphorylate tau protein at Thr212 [192]. DS-iPS cell-derived cortical neurons expressed higher amounts of both Aβ40 and Aβ42 protein with an increased Aβ42/Aβ40 ratio, formed insoluble intracellular and also extracellular amyloid aggregates, accumulated AT8-positive phosphorylated tau protein and secreted phospho-tau, thereby mimicking changes seen in patients with AD [158].

AD caused by mutant PS1 and PS2

Mutations in the presenilin 1 gene (*PS1*) and in the presenilin 2 gene (*PS2*) are common causes of fAD [48, 157] and have been described to enhance the production of Aβ protein, especially of Aβ42 [153]. AD-iPS cells have been derived from a patient with the A246E mutation in the *PS1* gene and from a patient with the N141I mutation in the *PS2* gene [193] (Table S2). When differentiated into neurons, both PS1-AD-iPS cells and PS2-AD-iPS cells secreted Aβ40 and Aβ42 into the medium supernatant with an increased Aβ42/Aβ40 ratio as seen in postmortem tissue from fAD patients [193]. These changes could be reversed by γ-secretase inhibition [193].

Sporadic AD

Most AD patients suffer from the sporadic, non-familial form of AD, which is not linked to a specific genetic mutation. However, genetic risk variants have been discovered in genome-wide association studies, among which apolipoprotein E isoform *E4* showed the highest consistency. Other genes include *Picalm*, *CR1*, *Clusterin* and *SORL1* [74, 99, 144, 196]. IPS cells were recently generated from two individuals with sporadic AD [80]. Neurons from one of the patients behaved like non-demented control neurons, while neurons from the other sporadic AD patient showed the same AD pathology as seen in cells from the APP^{dp}-AD patients described above [80] (Table S2). It will be very interesting to analyze pathologic neurodegenerative changes in iPS cell-derived neurons from sporadic AD patients with different genetic risk variants for apolipoprotein E isoform *E4*, *CR1*, *Clusterin* and *SORL1* and to use these stem cells to obtain better mechanistic insights into the pathogenesis of different forms of sporadic AD.

Models of Parkinson's disease using patient-derived iPS cells

Among all neurodegenerative diseases, PD has been modeled most frequently with iPS cells (Fig. 3; Table S2). PD is the second most common neurodegenerative disease and affects approximately 1 % of people over 60 years of age and approximately 4 % of people over 80 years of age [50]. A minor fraction of PD patients, about 5–10 % have a familial form of PD (fPD), which is the result of inheriting specific mutations. Mutations in *SNCA* were the first to be linked to fPD and cause pathology in an

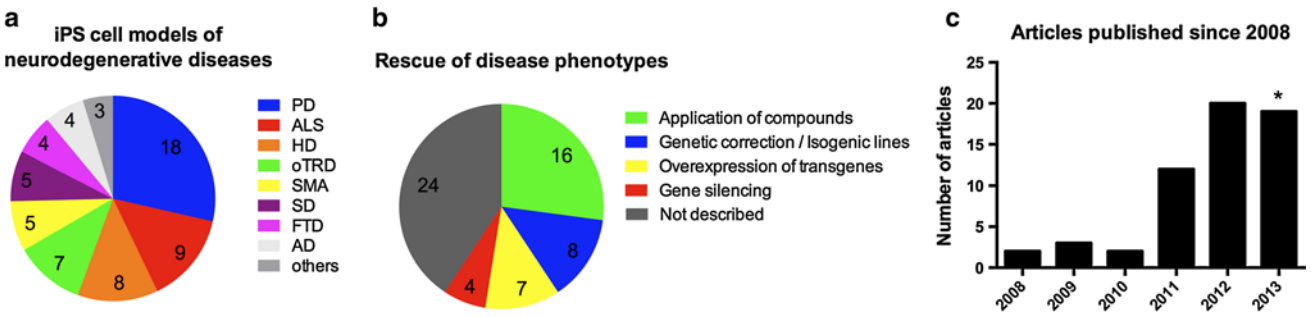

Fig. 3 Statistics on human iPS cell models of neurodegeneration. **a** Number of articles published on human iPS cell models of neurodegenerative diseases. *PD* Parkinson's disease, *ALS* amyotrophic lateral sclerosis, *HD* Huntington's disease, *oTRD* other triplet repeat diseases, *SMA* spinal muscular atrophy, *SD* storage diseases, *FTD* frontotemporal dementia, *AD* Alzheimer's disease. **b** Number of articles describing (partial) rescue of disease phenotypes through different approaches. **c** Number of articles published from 2008 to 2013. *Asterisk* as of November 2013

autosomal-dominant fashion [131]. Subsequently, mutations in Leucine-Rich Repeat Kinase 2 (*LRRK2*) were identified as causing autosomal-dominant PD and are the most common known genetic causes of PD [43]. Mutations in PTEN-induced Putative Kinase 1 (*PINK1*), *DJ-1* or *PARKIN* result in autosomal-recessive fPD (for review see [105]). In addition, duplication and triplication of the *SNCA* locus cause fPD [105, 163]. However, the majority of PD patients suffer from sporadic PD, which is most likely caused by a combination of environmental and genetic susceptibility factors. Indeed, genome-wide association studies revealed that variants in the gene loci of *SNCA*, *MAPT*, *PARK16* and *LRRK2* comprise risk factors for sporadic PD [105, 162]. Histopathologically, severe degeneration of DA neurons within the substantia nigra pars compacta is typical and Lewy bodies, which comprise intracellular aggregates of proteins including SNCA, are seen in most, though not all PD patients [43, 172].

Sporadic PD

The first PD-specific iPS cell lines were derived from a donor with sporadic PD [128] (Table S2). Derivation of additional iPS cell lines from five sporadic PD patients demonstrated that the neuronal differentiation potential of these cells was comparable to those of control iPS cells from healthy donors [167]. However, PD patient-derived neurons had a reduced number and length of neurites, expressed significantly increased levels of cleaved caspase 3 protein after prolonged culture in vitro and were more vulnerable to MPP^+, a neurotoxin to midbrain DA neurons [147]. These findings were attributed to an accumulation of autophagic vacuoles due to an impaired maturation of autophagosomes into autophagolysosomes in patient-derived DA neurons [147].

PD caused by mutant LRRK2

Mutations in *LRRK2* result in a late-onset form of PD with clinical symptoms comparable to those of patients with sporadic PD. *LRRK2* encodes a multidomain protein with kinase and GTPase activities, which are mediated through a kinase domain and a ras of complex GTPase domain, respectively [43]. To date, more than 50 mutations in the *LRRK2* gene have been described in PD patients, but the most common is G2019S, which occurs within the kinase domain and results in increased kinase activity [43]. Consequently, disease phenotypes were analyzed in G2019S-LRRK2-iPS cells, which had been differentiated into neural progenitor cells [108] and into DA neurons [45, 122, 126, 138, 139, 147, 148] (Table S2).

As seen in neurons from patients with sporadic PD, G2019S-LRRK2 neurons also showed impaired neurite outgrowth [122, 139, 147]. This observation is consistent with studies linking mutant LRRK2 protein to altered neurite extension [112] and linking LRRK2 overexpression to depolymerization of microtubules [107]. Furthermore, iPS cell-derived G2019S-LRRK2 DA neurons showed an increased expression of cleaved caspase 3 protein and the oxidative stress-response genes *HSPB1*, *NOX1* and *MAOB* [122, 147]. These neurons revealed increased damage of mitochondrial DNA [148] and were more susceptible to toxins such as hydrogen peroxide, 6-hydroxydopamine, rotenone, MPP^+, valinomycin, concanamycin A and MG-132, when compared to control cells from healthy donors [45, 122, 138, 139, 147]. These findings indicated an increased vulnerability of G2019S-LRRK2 DA neurons to stressors due to disturbances in pathways involving the mitochondrial oxidative complexes I and IV, the clearance of mitochondria via autophagosomes and the degradation of proteins through the proteasome complex, respectively. In addition, G2019S-LRRK2 DA neurons had impaired autophagosome clearance and an increased expression of stress-response genes, even when cultured over prolonged period of time and without application of oxidative stressors as similarly described for iPS cell-derived DA neurons from patients with sporadic PD [147]. An application of the antioxidant coenzyme Q10, the pro-survival AKT activator rapamycin and the LRRK2 inhibitors GW5074 and IN1 could partially rescue stress phenotypes in G2019S-LRRK2 iPS cell-derived neurons [45, 139].

iPS cell-derived G2019S-LRRK2 neurons accumulated SNCA protein, a major component in Lewy bodies in substantia nigra DA neurons of PD patients [122, 139, 147]. This is consistent with previous findings linking LRKK2 mutation to increased SNCA expression in human cells [32] and is in line with the observation that most patients with LRRK2 mutations present with α-synucleinopathy [43]. The accumulation of SNCA protein in G2019S neurons could be related to defects in autophagy [126, 139] and proteasomal function [139], which were observed in differentiated G2019S-LRRK2-iPS cells.

Further mechanistic insights into G2019S-mediated PD pathogenesis were provided by a recent publication by Reinhardt et al. [139] on patient-specific iPS cells. The expression of *CPNE8*, *MAP7*, *ANXA1* and *CADPS2*, genes that are implicated in neurotransmission and microtubule dynamics [24], was significantly increased in G2019S-iPS cell-derived midbrain DA neurons and siRNA-mediated knockdown of these genes was followed by decreased DA neurodegeneration. Phosphorylated microtubule-associated protein tau was also significantly upregulated in G2019S-DA neurons, further supporting a critical role of LRRK2 in microtubule function and cellular integrity. In contrast, E3 ubiquitin ligase *UHRF2*, which is involved in clearance of polyglutamine aggregates [81], was significantly

downregulated in G2019 DA neurons. UHRF2 could have a similar function in protein clearance in midbrain DA neurons, which might be impaired in G2019S neurons from patients with PD. In line with the observation that the G2019S mutation causes an increased activity of the kinase domain [43], dysregulated expression of *CPNE8*, *UHRF2* and *CADP2* in G2019S DA neurons was caused by LRRK2-dependent ERK phosphorylation [139]. Observed disease phenotypes were ameliorated by inhibition of ERK protein in G2019S neurons and by zinc finger-mediated correction of the genetic defect in G2019S-LRRK2-iPS cells. These observations are particularly important since they show that phenotypes appeared as a result of the genetic defect and not due to any unspecific confounding factors [139].

Mutations in the GTPase domain of the *LRRK2* gene have also been identified in fPD [43]. When compared to control cells, R1441C-iPS cell-derived DA neurons presented with dysfunctional intracellular transport of mitochondria [45], again highlighting an important role of LRRK2 in microtubule function. Furthermore, R1441C neural cells presented with increased damage of mitochondrial DNA [148] and with increased cell death after application of valinomycin and concanamycin A, as similarly seen for G2019S iPS cell-derived neural cells. These findings indicated enhanced vulnerability of PD patient-derived R1441C cells through mechanisms, which, at least in part, are also involved in degeneration of neural cells carrying the G2019S LRRK2 mutation [45].

PD caused by mutant SNCA

SNCA point mutations A53T, A30P and E46K [106, 197] and the more frequent *SNCA* duplications and triplications cause an early-onset form of PD [163]. One study reported the derivation of iPS cells from a patient with the A53T *SNCA* mutation and was the first to demonstrate that patient-derived iPS cells can be genetically modified via zinc finger-mediated gene transfer to replace the mutation-bearing sequence with a healthy sequence thereby generating isogenic control iPS cell lines [168]. In a follow-up study, disease phenotypes were discovered in iPS cell-derived A53T cortical neurons and comprised an accumulation of nitric oxide (NO), increased levels of endoplasmic reticulum (ER) stress and an accumulation of ER-associated substrates, such as glucocerebrosidase and nicastrin [39]. These substrates were also elevated in postmortem cortical tissue from a patient carrying the A53T-*SNCA* mutation [39]. Elevated levels of NO and ER-associated substrates in A53T-iPS cell-derived neurons were changed to normal levels after application of NAB2, which has previously been identified as a compound to rescue SNCA-mediated toxicity [178].

Three independent groups reported the derivation of iPS cells from patients with a *SNCA* triplication [27, 53, 194] (Table S2). DA neurons differentiated from iPS cells with triplicated SNCA contained significantly increased amounts of SNCA protein compared to healthy controls [27, 53, 194]. In addition, these neurons expressed elevated levels of *DNAJA1*, *HMOX2*, *UCHL1*, *HSPB1* and *MAO-A* mRNA [27], suggesting increased oxidative stress in the PD-derived DA neurons. Consistent with this observation, DA neurons with the SNCA triplication expressed higher levels of cleaved caspase 3 protein in response to H_2O_2 when compared to healthy controls [27].

PD caused by mutant PINK1 or PARKIN

Mutations in the *PINK1* and *PARKIN* genes cause fPD in an autosomal-recessive fashion. *PINK1* encodes a kinase localized at the outer mitochondrial membrane, while *PARKIN* encodes an E3 ubiquitin ligase found in the cytosol [119, 161, 188]. Mitochondrial damage activates PINK1 kinase activity, which recruits PARKIN protein and stimulates autophagy of the damaged mitochondria [120, 188]. Consequently, models of PD induced by mutant *PINK1* or *PARKIN* examined mitochondrial function as well as neurodegeneration [45, 79, 85, 155] (Table S2).

DA neurons differentiated from mutant *PINK1* iPS cells demonstrated significantly reduced translocation of PARKIN to mitochondria when treated with the mitochondrial stressor valinomycin [155]. Furthermore, these valinomycin-treated neurons showed an increased mitochondrial DNA copy number as well as increased biogenesis of mitochondria, which could indicate compensatory mechanisms for impaired mitochondrial function [155]. The mitochondrial disease phenotypes could be rescued by viral delivery and expression of wildtype (WT) *PINK1* in patient-derived neurons [155].

In addition, iPS cells have been derived from PD patients with either a homozygous deletion of exon 3 [85], exons 2-4 [79], exons 6 and 7 [79] or with a compound heterozygous deletion of exons 3 and 5 of *PARKIN* [85]. DA neurons with mutant *PARKIN* had increased spontaneous DA release and decreased DA uptake compared to healthy controls [85]. These neurons also expressed higher levels of *MAO-A* and *MAO-B* mRNA, which produce significant amounts of reactive oxygen species through the oxidative deamination of DA [85, 160]. As demonstrated for iPS cells with mutant PINK1, the cellular phenotypes in mutant *PARKIN* iPS cell-derived neurons could be reversed by overexpression of WT *PARKIN* [85]. Together, these results indicated that *PARKIN* suppresses DA oxidation and controls neurotransmission in human midbrain DA neurons. Furthermore, mutant *PARKIN* DA neurons revealed an increased response to oxidative stress, showed altered

morphology of mitochondria and impaired mitochondrial homeostasis [79], and expressed higher levels of NRF2 and NQO1 proteins, which are part of the same cytoprotective pathway and are activated in postmortem tissue of PD patients [79, 136]. Interestingly, the extent of disease phenotypes in iPS cell-derived DA neurons was directly correlated with postmortem pathology within the donor's brain. Indeed, the accumulation of SNCA protein was only found in those iPS cell-derived neurons with mutant PARKIN, whose donor presented with SNCA-positive Lewy bodies. SNCA pathology was not detected in iPS cell-derived DA neurons generated from a family lacking Lewy body formation [79].

Models of amyotrophic lateral sclerosis using patient-derived iPS cells

ALS is a rapidly progressing neurodegenerative disease with a prevalence of 2 in 100,000 people affecting motor neurons in the spinal cord and the motor cortex. While the majority of patients suffer from the sporadic form of ALS, about 10 % of patients present with familial ALS caused by mutations in one of at least 32 known genetic loci [174] including superoxide dismutase 1 (*SOD1*; [145]), TAR DNA-binding protein 43 (*TDP-43*; [5, 121]), fused in sarcoma (*FUS*; [98, 185]) and *C9ORF72* [51, 141].

ALS caused by mutant SOD1

Mutations in the *SOD1* gene are found in about 20 % of patients with familial ALS and in approximately 2 % of all ALS patients [17, 23]. SOD1-related ALS has been the most studied form of ALS and presents with motor neuron degeneration as a result of mitochondrial dysfunction, protein misfolding, defects in axonal transport and disturbed signaling through the IGF1/PI3K/AKT pathways (for review see [88]). The first ALS-iPS cell lines were derived from two siblings, an 82- and an 89-year old, with an L144F mutation within the *SOD1* gene [57] (Table S2). These iPS cells were differentiated into $HB9^+$ and $islet\text{-}1^+$ motor neurons and into $GFAP^+$ astrocytes in vitro but disease phenotypes were not analyzed. In a follow-up study, the same group published additional iPS cell lines with the L144F mutation and also iPS cell lines with a G85S mutation in the *SOD1* gene, and the neural differentiation potential of six ALS-iPS cell lines was compared to ten control iPS cells lines from healthy donors [18]. No differences in motor neuron differentiation were observed between these lines, although two ALS-iPS cell lines and one control iPS cell line could be differentiated into motor neurons only using an alternative differentiation protocol including dual inhibition of SMAD signaling in differentiating cells [18]. Furthermore, ALS-iPS cells carrying the L144F mutation were used to test the effect of a substance, kenpaullone, which appeared to be neuroprotective in a high-throughput screen of about 5,000 different compounds on motor neurons derived from mouse ES cells [195]. In this study, kenpaullone, an inhibitor of GSK-3 and HGK kinases, strongly improved the survival of motor neurons derived from L144F-SOD1-ALS-iPS cells and was more active than two compounds that recently failed in clinical trials on ALS patients [195]. These results highlight that patient-derived iPS cells may play a crucial role in drug discovery and in pre-clinical drug testing for the benefit of patients with neurodegenerative diseases.

As both cell-autonomous and non-cell-autonomous mechanisms of neurodegeneration have been found to contribute to ALS pathogenesis, stem cell-based models have been applied to address these effects in vitro. It is known that mutant SOD1 in astrocytes causes mitochondrial dysfunction and oxidative stress in neighboring motor neurons (non-cell-autonomous mechanism), while initiation of neuronal degeneration in SOD1-ALS is thought to be caused by an intrinsic, cell-autonomous mechanism within motor neurons themselves [15, 17, 55]. Non-cell-autonomous, mutant SOD1-mediated detrimental effects on motor neurons were shown in mouse [55] and also human [54] pluripotent stem cells that had been differentiated into mature motor neurons in vitro. Indeed, these studies demonstrated that pluripotent stem cell-derived motor neurons had an increased vulnerability and showed increased cell death when co-cultured with astrocytes derived from mice carrying the SOD1-G93A mutation [54, 55].

ALS caused by mutant TDP-43

TDP-43 is the transactive response (TAR) DNA-binding protein with a molecular weight of 43 kDa, a nuclear protein that plays a significant role in RNA metabolism including RNA transcription, splicing and transport [101, 130, 182]. Furthermore, TDP-43 is found in proteinaceous inclusion bodies in the cytosol of motor neurons in most forms of ALS, and mutations in the *TDP-43* locus have been linked to the development of familial and sporadic ALS [173]. Indeed, more than 30 different mutations, including the M337V mutation, have been described in ALS patients so far [89, 173]. As seen in independent studies, motor neurons derived from M337V-TDP-43-iPS cells were more susceptible to cellular stress and showed increased vulnerability in different in vitro-culture assays including growth factor withdrawal, antagonism of the PI3K pathway or the application of the cytotoxic stressor arsenite [13, 63, 195] (Table S2). However, contradictory results were obtained regarding the viability of M337V-TDP-43 neurons under basal culture conditions eliciting discussions about clonal variations and the use of appropriate viability assays in

the context of iPS cell-based disease modeling [13, 14, 63, 64]. M337V-TDP-43 motor neurons contained significantly higher amounts of soluble [13] and detergent-resistent, insoluble TDP-43 protein [13, 63] and demonstrated redistribution of TDP-43 protein from the nucleus to the cytosol with the formation of cytosolic TDP-43^{+} pre-inclusion-like aggregates [63]. In line with the role of TDP-43 in RNA metabolism, gene expression profiles in purified TDP-43-iPS cell-derived motor neurons revealed alterations in pathways mediating RNA processing, binding and splicing [63]. As seen in postmortem tissue of ALS patients, ALS-iPS cell-derived motor neurons expressed cytoskeletal intermediate filaments at lower levels when compared to control neurons and had impaired neurite outgrowth as similarly seen in a zebrafish model of ALS [63, 89]. Interestingly, these changes were also observed in iPS cell-derived motor neurons from ALS patients with the Q343R and the G298S *TDP-43* mutations, which are also located within the glycine-rich domain of the TDP-43 protein [63, 129]. Similarly, intracellular TDP-43 aggregates were recently observed in iPS cell-derived motor neurons from patients with sporadic ALS [26]. Notably, a reversal of disease phenotypes in TDP-43-iPS cell-derived motor neurons could be achieved through the application of anacardic acid, an inhibitor of histone acetyl transferase [63].

While non-cell-autonomous effects have been demonstrated for SOD1-ALS, it is still unclear, if such mechanisms would also apply to other forms of ALS. Recently, a study by Serio et al. [156] addressed this topic and investigated the influence of M337V-TDP-43-iPS cell-derived astrocytes on healthy iPS cell-derived motor neurons. As shown for motor neurons with the M337V-TDP-43 mutation, M337V-TDP-43-iPS cell-derived astrocytes were more vulnerable and contained increased levels of soluble TDP-43 protein that was mislocalized from the nucleus to the cytoplasm [13, 156]. When co-cultured with M337V-TDP-43-iPS cell-derived astrocytes, however, healthy motor neurons did not show an increased vulnerability but behaved like neurons that had been co-cultured with healthy iPS cell-derived astrocytes. These iPS cell-based results demonstrated that neurodegeneration did not occur in a non-cell-autonomous fashion in M337V-TDP-43-ALS [156].

Models of frontotemporal dementia using patient-derived iPS cells

Pathological TDP-43 has also been linked to the development of frontotemporal lobe degeneration (FTLD-TDP), an ubiquitin-positive but tau- and SNCA-negative form of frontotemporal dementia (FTD). FTD is the second most common pre-senile dementia after AD and is clinically characterized by deficits in cognition, language and behavior due to pronounced atrophy in the frontal and temporal lobes [166]. In addition to mutations in the TDP-43 locus, mutations in the progranulin (*PGRN*) gene, intronic hexanucleotide repeat expansions within the *C9ORF72* locus and mutations in the *MAPT* gene, besides others, have been linked to the development of FTD (for review see [135]).

FTD caused by mutant progranulin

PGRN mutations are seen in about 10 % of all FTD cases and cause haploinsufficiency of the *PGRN* gene with concomitant loss of *PGRN* function [6, 10, 47]. A recent publication by Almeida et al. [3] investigated pathologic alterations in iPS cell-derived cortical neurons from sporadic FTD patients and from FTD patients with the heterozygous S116X *PGRN* mutation (Table S2). This study demonstrated that patient-derived cortical neurons from both sporadic and S116X-PGRN-FTD patients were more susceptible to tunicamycin, an inhibitor of protein *N*-glycosylation within the ER, and to lactacystin, an inhibitor of the proteasome. Furthermore, S116X-PGRN-FTD-iPS cell-derived cortical neurons were more vulnerable towards staurosporine, towards the two PI3K-inhibitors wortmannin and LY294002 and towards the MEK/MAPK inhibitor PD98059 [3] demonstrating involvement of these pathways in PGRN-FTD pathogenesis. Interestingly, FTD-iPS cell-derived neurons exhibited stress-induced translocation of nuclear TDP-43 protein to the cytoplasm and this translocation of TDP-43 was observed in PGRN-FTD-iPS cell-derived neurons even in the absence of cellular stressors. These findings are in line with observations that the brains of FTD patients with *PGRN* mutations have TDP-43 pathology including accumulation of TDP-43 protein within the cytoplasmic compartment [6, 121]. As seen for other iPS cell models of neurodegeneration involving loss of gene function due to genetic mutations (e.g. *PARKIN* or *PINK-1*), genetic correction of *PGRN* haploinsufficiency through lentiviral overexpression of *PGRN* in PGRN-FTD-iPS cell-derived neurons resulted in reversal of most of the phenotypes described above [3].

FTD caused by mutant MAPT

Mutations in *MAPT* encoding the microtubule-associated protein tau constitute another cause of familial FTD and result in the accumulation of phosphorylated tau in neurons and glia in several brain areas including the frontal and temporal cortex as well as the substantia nigra [132, 165, 171]. Fong et al. [67] derived iPS cells from an individual with a heterozygous A152T *MAPT* mutation and generated isogenic control iPS cell lines using zinc-finger technology (Table S2). With this approach, pathologic changes were

observed, which comprised increased fragmentation and enhanced phosphorylation of tau protein (Ser 202 and Thr 205) in mutated iPS cell-derived neurons, which were significantly reduced in gene-corrected cells [67]. On the other hand, introducing a second mutation in patient-derived iPS cells instead of genetic correction resulted in homozygous A152T *MAPT* and in even more pronounced pathologic changes in iPS cell-derived neurons, as evidenced by increased phosphorylation and enhanced fragmentation of tau protein [67].

FTD caused by mutant C9ORF72

The most common mutation in FTD and ALS is the GGGGCC hexanucleotide repeat expansion in the noncoding region of *C9ORF72* [51, 113, 141]. Recently, several research groups generated iPS cells from patients carrying expanded *C9ORF72* GGGGCC repeats and described disturbed RNA metabolism as a contributing pathogenic factor in C9ORF72-FTD/ALS [2, 58, 152] (Table S2). Indeed, while GGGGCC repeats showed instability upon reprogramming and during neuronal differentiation [2], a subset of patient-derived iPS cells [2] and neurons [2, 58, 152] exhibited nuclear RNA foci containing GGGGCC repeats, which were not detected in healthy control cells but have been described in some patients with C9ORF72-FTD [51]. To characterize potential binding partners of these intranuclear GGGGCC RNA transcripts, a proteome analysis on 16,368 proteins was performed on C9ORF72-iPS cell-derived neurons [58]. This screen revealed 19 candidates and included the RNA-binding protein ADARB2, which also colocalized to GGGGCC RNA foci in postmortem CNS tissue of C9ORF72 patients [58]. C9ORF72 neurons contained non-ATG translation (RAN) di-peptide (poly-Gly-Pro) repeats [2, 58], that have recently been observed in patients with FTD/ALS [8, 118]. These data indicated that pathologic changes in C9ORF72-FTD/ALS patients could be modeled in patient-specific iPS cells. That was further supported by the fact that C9ORF72-iPS cell-derived neurons revealed dysregulation of specific genes, which were similarly misexpressed in CNS tissue of C9ORF72 patients including *NEDD4L*, *FAM3C*, *CHRDL1*, *SEPP1* and *SERPINE2* [58]. Neurons also accumulated p62, a component in neuronal inclusions in C9ORF72 patients and a substrate of the autophagy pathway [1, 2]. In line with that, neurons had compromised autophagy function, as indicated by an increased vulnerability after exposure to the autophagy inhibitors chloroquine and 3-MA [2], and revealed an increased susceptibility to excitotoxic stress induced by glutamate [58]. Importantly, C9ORF72-associated RNA toxicity could be rescued by application of antisense oligonucleotides (ASO) targeting either the intronic GGGGCC repeat sequence or a *C9ORF72* downstream sequence in exon 2 and appeared to be independent of *C9ORF72* mRNA levels and accumulating RAN products [58]. An ASO-mediated rescue of repeat-associated neuronal disease phenotypes was similarly described in an independent study on C9ORF72-iPS cells [152].

Models of Huntington's disease using patient-derived iPS cells

HD is a monogenetic, autosomal-dominant disease caused by CAG trinucleotide expansions in exon 1 of the huntingtin (*HTT*) gene [41]. It is characterized by a degeneration of medium-sized spiny projection neurons within the striatum and, at later stages of the disease, also by degeneration of neurons within the cerebral cortex [137].

IPS cells have been generated from patients carrying enhanced numbers of CAG repeats within the *HTT* gene ranging from 45, 60, 72 and 109 to 180 repeats [4, 29, 35, 38, 42, 84, 128, 198] (Table S2). In addition, iPS cells have been derived from patients with rare homozygous *HTT* CAG extensions (39/43 and 42/44 CAG repeats, respectively; [29]). These studies revealed disease phenotypes, which have previously been tied to HD pathogenesis, validating these stem cell-based models of HD. Indeed, it has been demonstrated that mutant HTT, through interaction with other HTT-binding proteins, causes decreased levels of intracellular ATP and increased caspase activity, disturbed mitochondrial function, impaired signaling by brain-derived neurotrophic factor (BDNF), perturbation of Ca^{2+} signaling and eventually excitotoxicity [49, 75, 199]. Likewise, HD-iPS cell-derived neurons showed increased caspase activity and cell death after prolonged culture or upon growth factor deprivation [4, 35, 42, 198], especially after removal of BDNF from the cell culture medium [42]. Furthermore, these cells presented with a decreased oxygen consumption rate along with decreased intracellular ATP concentrations, indicating an impairment of mitochondrial bioenergetics in patient-derived cells [4, 42]. In addition, HD-iPS cell-derived neural cells were more susceptible to H_2O_2-mediated oxidative stress and to excitotoxicity induced by pulsatile or chronic treatment with glutamate [42]. This effect was accompanied by disturbed Ca^{2+} homeostasis in challenged cells [42]. Finally, HD-iPS cell-derived neurons revealed an increased basal lysosomal activity [29] and an increased susceptibility to 3-MA [42]. These findings are in line with the observation that an increased number of autophagosome-like structures and thus disturbed protein clearance is found in the brains of HD patients [49, 150].

Disease-associated changes in stress-response levels could already be detected in undifferentiated iPS cells from HD patients [4, 35]. Comparative proteomic analysis among hES cells, healthy donor-derived iPS cells and iPS

cells from HD patients revealed 26 proteins that were dysregulated in patient-derived cells. Among these proteins, the antioxidant enzymes SOD1, glutathione transferase (GST) and glutathione peroxidase 1 (Gpx1) were significantly downregulated, while the oxidative stress-response proteins Prx1, Prx2 and Prx6 were found in higher quantities in undifferentiated HD-iPS cells [35]. Notably, similar findings have also been observed in the striatum of HD patients [170]. Furthermore, gene array analysis was performed on undifferentiated iPS cells from HD patients that had been genetically corrected through bacterial artificial chromosome (BAC)-mediated homologous recombination to derive isogenic control lines [4]. This study demonstrated that TGF-β pathway molecules, cadherin family members and caspase-related signaling molecules were significantly altered in non-corrected HD-iPS cells as opposed to gene-corrected HD-iPS cells [4]. These pathways were also altered in alternative models of HD and in the brain of HD patients [12, 90, 140].

Whole-genome expression analysis was also performed on control- and HD-iPS cells that had been differentiated into neural precursor cells in vitro [42]. In this study, 1,601 genes were differentially regulated between control and patient-derived neural precursor cells and gene ontology analysis revealed dysregulated pathways involved in proliferation, cell cycle regulation, cell signaling, axonal guidance and cellular assembly [42]. Consistent with alterations in postmortem tissue from HD patients and HD transgenic mice, dysregulated genes in HD-iPS cell-derived neural precursor cells included *UCHL1*, *EGFR* (epidermal growth factor receptor), *TRK* (tyrosine kinase) receptors, *p53*, *Syndecan4*, *SRPX* and also the HMG box protein 1, which was found to accumulate in the brains of patients suffering from AD [42, 176].

The onset of HD and disease severity are dependent on the number of CAG repeats within the *HTT* gene. Thus, an interesting question was if disease phenotypes in HD-iPS cell-derived neural cells were also dependent on the length of CAG repeats. This question was addressed by the HD iPSC Consortium by comparing disease phenotypes in iPS cells derived from HD patients with either 60, 109 or 180 CAG repeats [42]. They found that all HD-iPS cell lines shared a similar cumulative risk of cell death and an impaired energy metabolism when compared to the control lines but they also observed that certain disease phenotypes such as responses to BDNF withdrawal and toxicity upon glutamate exposure were much more pronounced and robust in the HD-iPS cell line carrying the highest number (180) of CAG repeats in the *HTT* gene [42]. These results were thus consistent with observations and models of HD pathogenesis.

Intracytoplasmic and intranuclear aggregates of HTT protein are pathological hallmarks of HD [7]. Hence, it was examined if such changes also occur in differentiated iPS cells from HD patients. While intracellular aggregates did not appear under normal differentiation conditions in vitro, such inclusions were induced through the application of the proteasome inhibitor MG-132 to differentiating HD-iPS cells [38, 84]. Furthermore, intracellular aggregates of HTT protein were observed 33 weeks after injection of differentiated HD-iPS cells into the lateral ventricle of postnatal P2 mice [84]. These data show that pathological hallmarks were elicited in patient-derived neural cells and underscore that genetic correction of cells prior to transplantation might be necessary if cells were to be used for cell replacement therapy in regenerative paradigms. In this context, it should be noted that gene-corrected HD-iPS cell-derived neurons survived after transplantation in the striatum of R6/2 HD mice [111] and that HD-iPS cell-derived neurons mediated functional recovery in the quinolinic acid model of HD [84].

Models of spinal muscular atrophy using patient-derived iPS cells

Spinal muscular atrophy (SMA) is an autosomal-recessive neurodegenerative disease caused by mutations in the survival motor neuron 1 gene (*SMN1*) [104]. These mutations result in a significant reduction of the SMN1 protein and cause a selective degeneration of lower motor neurons within the anterior horn of the spinal cord. The SMN protein has several functions, including splicing of pre-messenger RNA and the biogenesis of small nuclear ribonucleoprotein particles [68, 82]. It also interacts with the 3′-untranslated region of β-actin mRNA in the axonal compartment of motor neurons [146]. Although SMA patients carry an intact *SMN2* gene encoding an SMN2 protein with overlapping function to the SMN1 protein, only about 10 % of the SMN2 protein remains functional due to alternative splicing and degradation of truncated SMN2 protein, which cannot compensate for significantly reduced SMN1 protein levels in patients. The first human iPS cell models of SMA were published in 2009 by Ebert et al. [62] (Table S2). In this study, iPS cells were derived from a 3-year-old boy suffering from SMA. IPS cells from his unaffected mother served as controls. Quantification of full-length SMN1 protein revealed significantly decreased levels in SMA-patient-derived fibroblasts and iPS cells, while the levels of alternatively spliced *SMN2* gene transcripts were unchanged in these cells. Thus, these findings highlighted that the typical transcriptional regulation of the *SMN1* and *SMN2* genes found in SMA patients in vivo was also reflected in patient-derived iPS cells in vitro [62]. The SMA- and control iPS cells were differentiated into $HB9^+$, $SMI\text{-}32^+$ and $ChAT^+$ motor neurons, and motor neuron degeneration was observed in

SMA-patient-derived cultures after 8, but not 4 weeks of differentiation [62]. This was indicated by reduction of the size, percentage and synaptic coverage of SMA motor neurons when compared to control iPS cell-derived neurons. These findings could be reproduced by other groups [37, 46] and also with iPS cells from a second patient, a 23-month-old boy with SMA [37, 151]. In addition, these studies demonstrated reduced neurite outgrowth in SMA-iPS cell-derived motor neurons [37, 46] and showed that motor neuron degeneration was associated with increased expression of the pro-apoptotic marker molecules cleaved caspase-3, cleaved caspase-8 and Fas ligand but not Bax, Bcl-2, cleaved caspase-9 or the apoptosis-inducing factor AIF [151]. These findings indicated death-receptor-mediated apoptosis rather than mitochondria-associated apoptosis in SMA-iPS cell-derived motor neurons [151]. In addition, SMA-iPS cell-derived astrocytes showed morphological changes and functional impairment, supporting the hypothesis that glial pathology might contribute to SMA development [116]. Some of the observed neuronal disease phenotypes could be rescued by the application of valproic acid and tobramycin to SMA-iPS cells [62], which increased the level of SMN protein in the context of SMA [22, 190], further indicating that SMA-iPS cells may constitute a suitable cell population for in vitro drug testing and screening in SMA. An overexpression of SMN protein in SMA-iPS cells resulted in correction of impaired neurite outgrowth and improved survival of SMA-iPS cell-derived motor neurons [37]. Furthermore, genetic modification of the *SMN2* locus towards a more *SMN1*-like state was followed by the rescue of several disease phenotypes [46]. In this report, single-stranded DNA oligonucleotides with coding sequences of the *SMN1* gene were introduced into undifferentiated SMA-iPS cells to generate isogenic control iPS cell lines with increased amounts of functional full-length SMN1 protein. This approach not only resulted in prevention of iPS cell-derived motor neuron degeneration but also in increased formation of neuromuscular junctions between motor neurons and myotubes in in vitro-co-culture assays [46]. Furthermore, gene array analysis on gene-corrected cells revealed rescued expression of differentially regulated genes involved in RNA metabolism, axonal guidance and motor neuron development. Notably, gene-corrected SMA-iPS cell-derived motor neurons showed improved engraftment after intraspinal transplantation into a mouse model of SMA and caused prolonged survival of these animals when compared to the transplantation of non-modified SMA-iPS cell-derived motor neurons [46]. These data again highlight the regenerative potential of gene-corrected patient-iPS cell-derived neurons in the context of cell therapy in neurodegenerative diseases.

Models of other rare neurodegenerative diseases using patient-derived iPS cells

IPS cell models of other monogenetic neurodegenerative diseases included models of triplet repeat diseases, lysosomal storage diseases and additional rare degenerative diseases of the central or peripheral nervous system (Table S2).

Triplet repeat diseases other than Huntington's disease

Spinocerebellar atrophy type 3 (SCA-3) or Machado–Joseph disease is a slowly progressive neurodegenerative disease caused by CAG repeat expansions in the ataxin 3 (*ATXN3*) gene, which lead to deficits in gait coordination and to poor control of speech, eye and hand movements [70]. SCA-3-iPS cells were derived from four patients ranging between 38 and 42 years of age and were differentiated into mature neurons along with healthy control iPS cells. This report demonstrated formation of ATXN3-positive, SDS-insoluble aggregates in patient-iPS cell-derived neurons, which are typically found in patients' tissue. The formation of aggregates was dependent on L-glutamine-induced excitation and on functional Na^+ and K^+ channels in addition to functional ionotropic and voltage-gated Ca^{2+} channels. Indeed, formation of SDS-insoluble ATXN3 aggregates was not observed in SCA3-fibroblasts, undifferentiated SCA3-iPS cells or SCA3-iPS cell-derived glial cells, consistent with the neuron-specific phenotype in SCA3. Furthermore, this report provided mechanistic insights into aggregate formation, as excitation-induced aggregation was preceded by Ca^{2+}-dependent proteolysis of ATXN3. Notably, these SDS-insoluble ATXN3 aggregates disappeared after inhibition of calpain, but not after caspase inhibition, confirming a significant role of calpain protease in ATXN3 aggregation in the context of SCA3-disease development [93].

Friedreich ataxia (FA) is a disease with progressive spinocerebellar neurodegeneration due to GAA·TTC repeat expansions in the first intron of the frataxin (*FXN*) gene [31]. This mutation causes reduced expression of FXN protein within mitochondria and leads to altered cellular iron metabolism, mitochondrial dysfunction and increased sensitivity to oxidative stress [30, 154]. Several groups derived iPS cells from FA patients [61, 76, 97, 109] and found epigenetic silencing of the *FXN* locus [97] and decreased levels of *FXN* transcripts in undifferentiated [76, 97, 109] and differentiated iPS cells [76]. In addition, neurons presented with delayed maturation and decreased mitochondrial membrane potential [76]. Furthermore, these studies demonstrated instability of GAA·TTC repeats during reprogramming with extensions [61, 76, 97, 109] and contractions [76, 109] of these repeats, and also described GAA·TTC repeat extensions during prolonged culturing of iPS cells in vitro [61, 76]. These changes

were associated with increased expression of the mismatch repair enzymes MSH2 and MSH6, as shRNA-mediated silencing of these two factors resulted in reduced GAA·TTC extensions during culture in vitro [61, 97]. These findings were consistent with the fact that GAA·TTC repeats in FA are genetically highly unstable and with the observation that mismatch repair enzymes are involved in the instability of trinucleotide repeat diseases [59, 95, 110]. Notably, such instability was not found in other iPS cell models of triplet repeat diseases including models of SCA-3 [93], spinal and bulbar muscular atrophy [125] or dentato-rubral-pallido-luysian dystrophy [125] (Table S2).

Storage diseases

Gaucher's disease (GD) is a lysosomal storage disease caused by a mutation in the *GBA-1* gene encoding acid-β-glucocerebrosidase [87]. This enzyme cleaves glucosylceramide into glucose and ceramide [20]. However in GD patients, the enzymatic activity is significantly decreased leading to the accumulation of glucosylceramide and glucosylsphingosine in lysosomes as well as to cellular degeneration in multiple brain areas [191]. So far, stem cell models of the acute (type 2) and the chronic (type 3) neuronopathic form of GD have been published [128, 181] (Table S2). While iPS cells from type 3 GD patients were characterized only at the undifferentiated stage [128], Tiscornia et al. [181] derived iPS cells from type 2 GD patients and described decreased levels of acid-β-glucocerebrosidase in iPS cells and differentiated DA neurons. Decreased acid-β-glucocerebrosidase activity in neurons was rescued by enzyme overexpression in undifferentiated cells and by the application of the two chaperone compounds 6S-AdBI-NJ and NOI-NJ, which were suggested to stabilize protein levels and to facilitate protein trafficking to the lysosome [181]. Thus, such iPS cell models could be useful in finding and testing potential small molecules as alternatives to enzyme replacement and substrate reduction therapy in GD patients. Other stem cell models of storage diseases included models of Pompe disease [78], Niemann–Pick type C1 disease [183] and X-linked adrenoleukodystrophy [83, 189]. Notably, intracellular accumulation of disease-specific products such as glycogen in Pompe disease [78], cholesterol in Niemann–Pick type C1 disease [183] or very long chain fatty acids in X-linked adrenoleukodystrophy [83] was recapitulated in patient-derived iPS cells, neurons or oligodendrocytes, respectively (Table S2).

Other rare degenerative diseases of the central or peripheral nervous system

Hereditary spastic paraplegia (HSP) is a group of neurodegenerative diseases associated with spasticity of the lower limbs as a result of degeneration of corticospinal motor neurons and the pyramidal tract [66]. The most common form of HSP (SPG4) is caused by an autosomal-dominant mutation in the *SPAST* gene encoding spastin. Similar to neurons in the brains of HSP patients [91], HSP-iPS cell-derived forebrain neurons presented with axonopathic changes including axonal swelling and an impairment of fast axonal transport of mitochondria along axons [52]. Interestingly, axonopathic changes in iPS cell-derived neurons could be rescued by vinblastine, which has previously been applied to reduce axonal swelling in SPG4-deficient primary neurons [65].

Familial dysautonomia (FD) is associated with a degeneration of neurons of the peripheral nervous system and is caused by a mutation in the I-κ-B kinase complex-associated protein (*IKBKAP*) [77]. As a consequence, missplicing of *IKBKAP* and a decrease of normal *IKBKAP* transcripts lead to impaired migration of disease-affected cells [40]. Several FD-iPS cell lines were differentiated into neural crest precursor cells and peripheral neurons [102]. Interestingly, FD-iPS cell-derived neural precursor cells also showed defects in *IKBKAP* splicing and impairment of migration in scratch wound assays. In addition, these cells presented with impaired differentiation into peripheral neurons, altogether providing an excellent human in vitro-model of FD. In an initial experiment, the plant hormone kinetin [164] proved successful in reducing the level of misspliced *IKBKAP* transcripts in FD-iPS cell-derived neural crest precursor cells. Furthermore, kinetin improved the differentiation of FD-iPS cells into peripheral neurons [102]. Based on this study, the same group performed high-throughput screenings on FD-iPS cell-derived neural crest precursor cells with approximately 7,000 compounds and found eight substances that decreased the levels of misspliced *IKBKAP* transcripts, while increasing the levels of WT-*IKBKAP* transcripts [103]. This study also unraveled the molecular targets of one of these hits, compound SKF-86466, highlighting the usefulness of patient-derived iPS cells for large-scale screening of compounds for the potential treatment of neurodegenerative diseases [103].

Human cell culture models of neurodegeneration using iN cells

During the last few years, progress has been made towards generating neuronal cell types from fibroblasts without passing through a stage of pluripotency. This can be achieved by transduction of fibroblasts with the neural transcription factors Ascl1, Brn2, Myt1l and NeuroD1 resulting in the derivation of functional neurons, which were termed induced neurons or iN cells [127] (Fig. 1). These iN cells were electrophysiologically active and expressed typical

neuronal marker molecules such as MAP2, NeuN and synapsin [127]. Importantly, this technology can be applied to adult human fibroblasts isolated from skin biopsies of patients or healthy control individuals and thus has been used, with slight modifications, to model neurodegenerative changes in vitro (Table S3).

One report demonstrated the derivation of iN cells from two patients with familial forms of AD, who carried the A246E mutation in the *PS1* gene or the N141I mutation in the *PS2* gene, respectively [134]. These AD-iN cells were generated within 3 weeks of culture through transduction with the transcription factors Ascl1, Brn2, Myt1l, Olig2 and Zic1. AD-iN cells and control iN cells expressed markers of glutamatergic forebrain neurons and formed synaptic connections in in vitro-co-culture assays [134]. In comparison to their parental fibroblasts, iN cells from the AD patients and iN cells from control individuals expressed higher levels of APP and sAPPβ, while only the AD-iN cells expressed significantly higher amounts of Aβ40 and Aβ42 protein. Importantly, the Aβ42/Aβ40 ratio was significantly enhanced in AD-iN cells when compared to control iN cells, thus mimicking findings obtained from studies on AD-iPS cell-derived neurons described above. Likewise, AD-iN cells presented with an enlarged endocytic compartment with increased numbers of APP^{+} intracellular punctate [134]. Notably, this disease phenotype was rescued by transfection of AD-iN cells with a plasmid encoding non-mutated PS1 [134].

iN cells have also been derived from two patients with PD [28]. One patient carried a duplication of the *SNCA* locus, while the other PD patient had a mutation in the *PARKIN* gene. This study highlighted that functional DA neurons can be derived from human fibroblasts by direct transdifferentiation, which was achieved by transduction of fibroblasts with doxycycline-inducible lentiviruses encoding Ascl1, Nurr1 and Lmx1a. These DA-iN cells expressed typical DA marker molecules such as TH, ALDH-1A1, AADC, VMAT2 and DAT and showed electrophysiological activity [28]. Since DA-iN cells from PD patients and from control individuals were derived with similar efficiencies, these cells provide a suitable cell source for an in-depth analysis of disease-related phenotypes as described above for iPS cell-based models of PD.

These studies show that important progress has been made towards modeling neurodegenerative diseases using human cell-based systems. As iN cells are generated within only weeks by direct transdifferentiation of patients' fibroblasts, disease modeling assays can be performed in a shorter time frame when compared to assays using iPS cells. However, due to rapid cell-type conversion, it is possible that cells do not properly pass through a neuronal step-by-step maturation program and that unconverted fibroblasts and partially reprogrammed cells remain in culture, which may influence outcomes of disease modeling assays using iN cells (for reviews see [149, 187]). Current research addresses these challenges. For instance, further development of this technology led to the derivation of neural progenitor cells termed induced neural stem cells (iNSCs), which can be propagated over long periods of time and which have the potential to differentiate into mature neuroectodermal cell types such as neurons, astrocytes and oligodendrocytes at higher numbers in vitro [71, 92, 142, 179]. Although human iNSC-based stem cell models of neurodegeneration have not been established yet, this technology could constitute a very important approach towards research and therapy in neurodegenerative diseases and could complement research on patient-derived iPS cells.

Conclusions

Research on patient-derived iPS cell lines has significantly increased in the past years (Fig. 3). Other neurologic diseases have also been modeled with iPS cells and include neurodevelopmental disorders such as Rett syndrome [96] or fragile X syndrome [184] and neuropsychiatric diseases such as schizophrenia [21]. Importantly, not only early-disease phenotypes of genetic, but also of sporadic, diseases can be captured with this approach and several studies have presented significant neuropathological changes in patient-iPS cell-derived neurons. These changes point towards underlying pathogenic mechanisms of disease development, as presented in this article. It is desirable that iPS cell research translates into clinical applications, where compounds are first tested in high-throughput screening systems to modify disease-affected pathways in vitro, and where suitable candidates would then be applied in clinical trials with the goal to facilitate the development of new therapies for the benefit of patients. While further improvements of neural differentiation protocols are needed to reduce cellular heterogeneity and to continuously refine sensitivities of assays and drug responses, other challenges have to be carefully addressed, which may critically impinge the discovery of disease phenotypes in patient-specific iPS cells. For instance, the heterogeneity of the patient pool, possible differences in the quality of fibroblasts for reprogramming and potential variabilities in differentiation capacities of iPS cells have to be considered. Hence, an analysis of a single iPS cell clone from only one single patient could yield different results when compared to an analysis of several iPS cell clones from several different patients with the same disease. This would, in turn, result in erroneous conclusions in disease modeling experiments (for review see [149]). Furthermore, the choice of control cell lines has a strong influence on disease modeling

assays. The use of iPS cells from gender- and age matched control individuals and from individuals genetically related to the patient might not always be the most appropriate approach. When modeling monogenetic neurodegenerative diseases, isogenic, gene-corrected control cell lines can be generated, which carry the same genetic variants as their parental patient-derived cells and which differ from these cells only by the disease-causing mutation [149]. Hence, further progress has recently been pursued to more easily derive isogenic control lines, for example through the application of transcription activator-like effector nucleases (TALENs) [16] or by taking advantage of CAS/clustered regularly interspaced short palindromic repeats (CRISPR)-mediated genomic editing [86].

Altogether, these recent studies on human stem cell models of neurodegeneration demonstrate that iPS cell technology, in particular, carries a strong potential for biomedical research on human neurodegenerative diseases.

Acknowledgments We would like to thank Dr. Jared Sterneckert, Dr. Holm Zaehres and Dr. Vincent Ruland for critical reading of this manuscript and Dr. Peter Reinhardt for providing images of differentiated neural cells. This work was supported by the IMF at University Hospital Münster (I-HA-111219; to GH) and the German Research Foundation (DFG; SFB-TRR128-B7; to TK).

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