Human Induced Pluripotent Stem Cell Models of Neurodegenerative Disorders for Studying the Biomedical Implications of Autophagy

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Abstract

Autophagy is an intracellular degradation process that is essential for cellular survival, tissue homeostasis, and human health. The housekeeping functions of autophagy in mediating the clearance of aggregation-prone proteins and damaged organelles are vital for post-mitotic neurons. Improper functioning of this process contributes to the pathology of myriad human diseases, including neurodegeneration. Impairment in autophagy has been reported in several neurodegenerative diseases where pharmacological induction of autophagy has therapeutic benefits in cellular and transgenic animal models. However, emerging studies suggest that the efficacy of autophagy inducers, as well as the nature of the autophagy defects, may be context-dependent, and therefore, studies in disease-relevant experimental systems may provide more insights for clinical translation to patients. With the advancements in human stem cell technology, it is now possible to establish disease-affected cellular platforms from patients for investigating disease mechanisms and identifying candidate drugs in the appropriate cell types, such as neurons that are otherwise not accessible. Towards this, patient-derived human induced pluripotent stem cells (hiPSCs) have demonstrated considerable promise in constituting a platform for effective disease modeling and drug discovery. Multiple studies have utilized hiPSC models of neurodegenerative diseases to study autophagy and evaluate the therapeutic efficacy of autophagy inducers in neuronal cells. This review provides an overview of the regulation of autophagy, generation of hiPSCs via cellular reprogramming, and neuronal differentiation. It outlines the findings in various neurodegenerative disorders where autophagy has been studied using hiPSC models.

Mechanisms of Autophagy

Macroautophagy (referred herein as autophagy) is a highly conserved catabolic pathway, which delivers undesirable cytoplasmic materials to the lysosomes for their degradation. It plays a constitutive role in the quality control of intracellular macromolecules and organelles, thus imperative for the maintenance of cellular homeostasis that is vital for human health [1,2]. Though, it can be triggered under various environmental cues, such as stress conditions like starvation, hypoxia, and oxidative

stress, or pathogenic stimulation like viral and bacterial infection [3,4]. Over the last two decades, numerous studies have shown that autophagy predominantly acts as a cellular survival pathway. It is implicated in myriad human physiology, including development and immunity, whereas its malfunction contributes to the pathology of diverse human diseases, including neurodegeneration [5–7]. In recent years, a homeostatic role of autophagy has been attributed to the control of embryonic and adult stem cell functions by acting as a critical quality control mechanism [8,9].

The initiation of the autophagy process in mammalian cells involves the genesis of the phagophore, which is an isolation membrane structure that is derived from the endoplasmic reticulum (ER)-emanating membrane domains termed as "omegasome" and/or from other sources like trans-Golgi, recycling endosomes, plasma membrane and mitochondria [10,11]. The phagophore expands to engulf intracellular autophagic cargo that comprises unwanted macromolecules like protein aggregates or damaged organelles like mitochondria, thereby sequestering the cargo in a double-membrane structure called the autophagosome. The cargo-loaded autophagosome then matures through fusion with the lysosome to form autolysosome, thereby promoting the degradation of the autophagosomal content by the lysosomal digestive enzymes [12]. Autophagosome maturation is generally a multistep process wherein the autophagosome initially fuses with the late endosome to form a hybrid organelle called amphisome, which

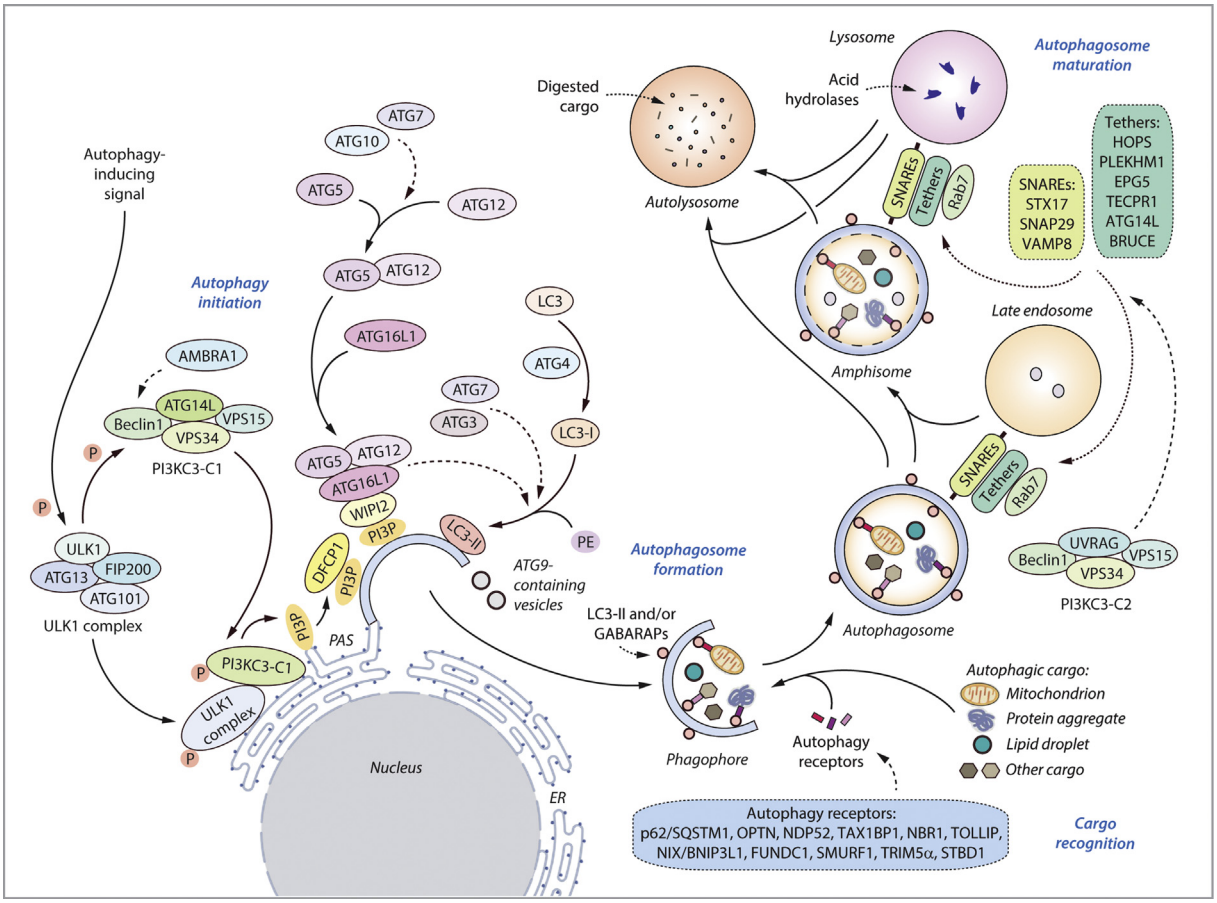

Fig. 1. Mechanism of the autophagy process. Autophagy encompasses multiple vesicular compartments and vesicle fusion events through which the autophagic cargo is degraded. This process initiates with the formation of phagophores at the phagophore assembly site (PAS). The autophagic machinery involving several autophagy-related (ATG) proteins enables the expansion of the phagophore to form autophagosomes. Autophagic cargo is engulfed in the autophagosomes during which specific autophagy receptors mediate selective cargo recognition. The autophagosomes either fuse with the late endosomes to form amphisomes and then with the lysosomes to form autolysosomes or directly fuse with the lysosomes forming autolysosomes. These vesicle fusion events during autophagosome maturation are mediated by various SNAREs, tethering proteins, and Rab7. The autophagic cargo is eventually degraded in the autolysosomes by the lysosomal acid hydrolases.

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acts as a sink for autophagic and endocytic cargo materials for delivery to the lysosomes; however, the autophagosome can also directly fuse with the lysosomes [13,14] (Fig. 1). The dynamic turnover of autophagosomes (autophagosome flux) and autophagic cargo (autophagic cargo flux) is collectively defined as autophagic flux.

Autophagy machinery

The quantum leap in the explication of the molecular machinery controlling autophagy came from the genetic studies in yeasts by Ohsumi and colleagues during the 1990s, in which autophagy-related (*Atg*) genes were identified [15]. Since then, numerous studies have elucidated that this dedicated cohort of ATG proteins assembles into functional complexes that are activated and recruited to specific membrane structures to initiate the autophagy process [16,17] (Fig. 1). The apical step in the initiation process involves the activation of the ULK1 (unc-51-like kinase-1) complex [18], which consists of the serine/threonine-protein kinase ULK1 (mammalian orthologue of yeast Atg1) and three scaffold proteins that include FIP200 (focal adhesion kinase family-interacting protein of 200 kDa; also known as RB1CC1), ATG13, and ATG101 [19]. Once activated, the ULK1 complex further phosphorylates a number of downstream targets, which culminate to promote autophagosome biogenesis from the phagophore assembly site (PAS) at the omegasome on the ER [20]. An important phosphorylation target of the ULK1 complex to trigger phagophore nucleation is the class III phosphatidylinositol-3-kinase complex 1 (PI3KC3−C1) [21], consisting of VPS34 (vacuolar protein sorting 34; the catalytic subunit), Beclin 1, ATG14L and VPS15 [22]. ULK1-mediated phosphorylation of the PI3KC3−C1 components, such as Beclin 1, activates the VPS34 lipid kinase that causes the production of the phospholipid, phosphatidylinositol 3-phosphate (PI3P), at the PAS [23]. PI3P then recruits the PI3P-binding proteins, such as WIPI2 (WD repeat domain phosphoinositide-interacting protein 2) and DFCP1 (double FYVE domain-containing protein 1) to support the expansion of the phagophore membrane [24,25]. Phosphorylation of ATG9 by ULK1 also mediates the translocation of ATG9-positive vesicles to the PAS, where they supply lipid membrane to the expanding phagophore [26].

The elongation of the phagophore is regulated by two ubiquitin-like conjugation systems, which generate modified complexes of autophagy regulators [27,28] (Fig. 1). The first ubiquitin-like reaction involves the conjugation of ATG12 to ATG5 that is catalyzed by the E1-like enzyme ATG7 and the E2-like enzyme ATG10. The ATG5-ATG12 complex then noncovalently interacts with ATG16L1 to form the ATG5-ATG12-ATG16L1 ternary complex. The second of the ubiquitin-like reactions involves the conjugation of ubiquitin-like molecules of the ATG8 family with membrane-resident phosphatidylethanolamine (PE) [16,29]. The human ATG8 family comprises of two subfamilies, microtubule-associated protein 1 light chain 3 (MAP1LC3 or LC3) and γ-aminobutyric acid receptor-associated proteins (GABARAPs), which are encoded by seven genes expressing LC3A, LC3B, LC3B2, LC3C, GABARAP, GABARAPL1 and GABARAPL2 (also called GATE-16) [30]. Prior to lipidation, the ATG8 protein is processed at its C-terminal by a family of cysteine protease, ATG4 [31]. Further, ATG7 and ATG3 acting as the respective E1 and E2 enzymes, and ATG12-ATG5-ATG16L1 complex serving as an E3 ligase, conjugate ATG8 to PE, resulting in the incorporation of ATG8-PE in the growing phagophore that aids in phagophore expansion, autophagosome formation, and cargo recognition [16,29]. One of the autophagosome markers generally used for studying autophagy is LC3B (referred herein as LC3), which via this conjugation reaction, gets converted from the cytosolic LC3-I form into the membrane-bound LC3-II form [32].

After biogenesis, the maturation of autophagosome occurs through fusion with the late endosome and lysosome that is primarily coordinated by three sets of proteins: Rab GTPases like Rab7, membrane tethering complexes, such as HOPS (homotypic fusion and protein sorting) complex, and SNARE (soluble N-ethylmaleimide-sensitive factor-attachment protein receptor) proteins like syntaxin-17 (STX17) and VAMP8 [13,14] (Fig. 1). Several effector proteins of active GTP-bound Rab7 drive autophagosome mobility and its fusion with the late endosomal and lysosomal compartments [33,34]. These include RILP (Rab-interacting lysosomal protein) [35] and FYCO-1 (FYVE and coiled-coil domain-containing protein 1) [36], which respectively recruit dynein and kinesin motor proteins for the perinuclear transport of mature autophagosome. Other Rab7 effectors enabling vesicle fusion include PLEKHM1 (Pleckstrin homology domain-containing family member 1), which acts as an adaptor by binding to both the HOPS complex and LC3/GABARAP [37], and EPG5 (ectopic P-granules autophagy protein 5 homolog) that binds to LC3 and stabilizes the autophagosomal SNARE complex [38]. Interestingly, class III phosphatidylinositol-3-kinase complex 2 (PI3KC3−C2), comprising of VPS34, Beclin 1, VPS15, and UVRAG (UV radiation resistance-associated gene protein), positively regulates autophagosome maturation via the association of UVRAG with the HOPS complex to activate Rab7 [39,40]. Besides HOPS, other tethering factors driving autophagosome fusion events are ATG14L [41] and TECPR1 (Tectonin beta-propeller repeat-

containing protein 1) [42]. The SNAREs involved in autophagosome maturation form a complex between the autophagosomal Q-SNAREs STX17 and SNAP29, and the late endosomal/lysosomal R-SNARE VAMP8 [43], which is mediated by ATG14L [41]. Additional regulators of autophagosome maturation are GABARAPs [44], myosin VI [45], BRUCE (Baculovirus IAP repeat-containing ubiquitin-conjugating enzyme) [44], and phosphoinositides like PI4P (phosphatidylinositol-4-phosphate) [46].

In the final steps, the inner membrane of the autophagosome and the engulfed cytoplasm-derived materials are degraded inside the autolysosome by the lysosomal acid hydrolases, which include proteases, such as cathepsins (Fig. 1). The breakdown products are then recycled and serve as inputs for bioenergetics and anabolic pathways [47].

Autophagy receptors for mediating selective autophagy

The autophagic response to starvation is the bulk degradation of cytosolic materials that occurs in a nonselective manner. However, other types of cellular stresses, such as damaged organelles, aggregated proteins, or pathogens, require their selective sequestration into the autophagosomes for degradation. Based on the remarkable substrate specificity, selective autophagy is classified into aggrephagy (clearance of protein aggregates), mitophagy (clearance of mitochondria), pexophagy (clearance of peroxisomes), ribophagy (clearance of ribosomes), nucleophagy (clearance of nuclear envelope), reticulophagy (clearance of ER), lysophagy (clearance of lysosomes), xenophagy (clearance of pathogens), lipophagy (clearance of lipid droplets), and glycophagy (clearance of glycogen) [48,49].

Selectivity in autophagy is conferred by the cargo receptor proteins, which tether the ubiquitinated cargo to the phagophore (Fig. 1). All cargo receptors share common domains: the ubiquitin-binding domain (UBD) through which they bind the specific cargo [50], and the LC3-interaction region (LIR) motif via which the interaction with the expanding phagophore occurs [51]. In mammalian cells, several cargo receptor proteins are recognized, which include p62 (sequestosome-1 or SQSTM1) [52], OPTN (optineurin) [53], NDP52 (nuclear dot protein of 52 kDa) [54], TAX1BP1 (tax1 binding protein 1) [55], NBR1 (neighbor of BRCA1 gene 1) [56] and TOLLIP (Toll-interacting protein) [57]. These receptors could be recruited to different cargos in varying proportions and/or may also cooperate in substrate selection. For instance, p62/SQSTM1, NBR1, optineurin, and TOLLIP play a role in executing aggrephagy [48]. Several studies have revealed an intrinsic connection between autophagy receptors and neurodegenerative diseases. Some of these findings reported that mutations in *SQSTM1* could modify the genetic susceptibility of Alzheimer's disease [58], frontotemporal dementia [59], and amyotrophic lateral sclerosis [60].

Apart from ubiquitin-dependent selective autophagy, there is an arsenal of receptor proteins, which perform the process independent of ubiquitination [61]. The most remarkable example is NIX, also known as BNIP3L1 (Bcl-2-interacting protein 3 like), which is a selective autophagy cargo receptor for mitophagy in reticulocytes during the final stage of erythroid maturation [62]. Others include FUNDC1 (FUN14 domain containing 1) [63], SMURF1 (SMAD-specific E3 ubiquitin-protein ligase 1) [64], TRIM5α (tripartite motif-containing protein 5α) [65] and STBD1 (starch-binding domain-containing protein 1) [66]. Besides the cargo receptors, there are several key players like ALFY (autophagy-linked FYVE protein, also known as WDFY3), which does not harbor the UBD domain but acts as a scaffold by getting associated with the ubiquitinated protein aggregates and autophagosomal markers to facilitate aggrephagy [67].

Signaling pathways regulating autophagy

Diverse signaling pathways regulate autophagy, but the most characterized one is nutrient signaling. Nutrient deprivation (starvation) induces autophagy by inhibiting the mechanistic target of rapamycin (mTOR), which is a serine/threonine-protein kinase that otherwise suppresses autophagy under nutrient sufficiency [68] (Fig. 2). mTOR forms two distinct protein complexes, which are mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [69], but only mTORC1 directly regulates autophagy by phosphorylating the ULK1 complex and suppressing the ULK1 kinase activity that is required to initiate autophagy [19]. Besides ULK1 phosphorylation, mTORC1 can also indirectly inhibit autophagy by phosphorylating AMBRA1 (activating molecule in Beclin 1-regulated autophagy protein 1), which, in turn, could reduce ULK1 stability and its kinase activity [70].

Additionally, mTORC1 can prevent autophagy by phosphorylation-dependent cytoplasmic sequestration of TFEB (transcription factor EB), a master transcriptional regulator of genes involved in lysosomal biogenesis and autophagy [71] (Fig. 2). Particularly for the autophagy process, TFEB regulates the expression of genes required for autophagy initiation (*BECN1, ATG9B, WIPI1*), phagophore elongation (*GABARAP, MAP1LC3B*, *ATG5*), autophagosome maturation (*UVRAG, RAB7*) and cargo recognition

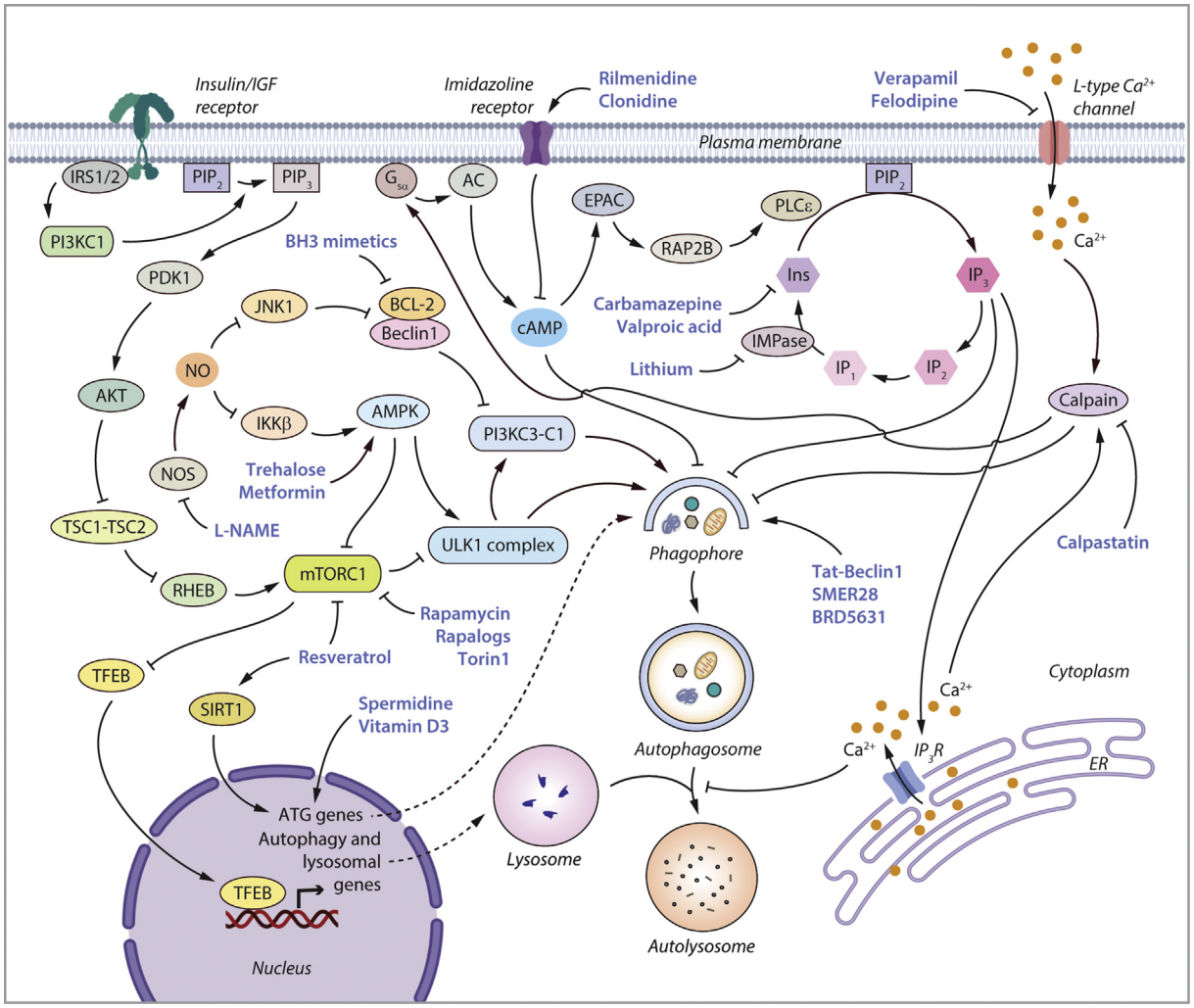

Fig. 2. Regulation of autophagy by mTOR-dependent and mTOR-independent signaling pathways. Autophagy is classically regulated by the mechanistic target of rapamycin (mTOR) pathway, in which the downstream mediators are the ULK1 and PI3KC3–C1 complexes. AMPK can also directly influence ULK1 to govern autophagy. In addition, autophagy is regulated by mTOR-independent pathways involving IP_3, cAMP, Ca^{2+}, and calpain. Various pharmacological inducers of autophagy acting on specific targets in these pathways are shown.

(*SQSTM1*) [72]. Likewise, another serine/threonine-protein kinase, Akt, can phosphorylate TFEB independently of mTORC1 and prevent its nuclear translocation [73]. Inhibition of mTORC1 or Akt activity promotes autophagy via nuclear localization of TFEB to enable the transcription of the target genes [73,74]. Nuclear translocation of TFEB can also occur via its dephosphorylation by the phosphatase calcineurin, which is activated during the release of lysosomal Ca^{2+} through the Ca^{2+} channel mucolipin 1 (MCOLN1) [75].

Another key regulator of autophagy is AMPK (AMP-activated protein kinase), which is activated during energy-deprived conditions [76]. Activated AMPK can indirectly stimulate autophagy by suppressing mTORC1 activity via phosphorylation of RAPTOR (regulatory-associated protein of mTOR) and TSC2 (tuberous sclerosis complex 2) [77,78]. However, AMPK can directly induce autophagy independently of mTORC1 via binding to and phosphorylating ULK1 [79,80] (Fig. 2). Furthermore, AMPK can phosphorylate Beclin 1 in PI3KC3–C1 that can be augmented by ATG14 to induce autophagy [22].

Apart from the regulation of autophagy by mTORC1 and AMPK, a number of mTORC1-independent autophagy pathways have also been described [81] (Fig. 2). Most of these pathways involve second messenger molecules that negatively influence autophagy when their intracellular levels rise. These include IP_3 (inositol 1,4,5-trisphosphate) [82], Ca^{2+} (calcium) [83,84], cAMP (3′,5′-cyclic adenosine monophosphate) [83], and NO (nitric oxide) [85]. While high levels of IP_3, cAMP,

and NO suppress autophagosome biogenesis, Ca^{2+} has complex effects on autophagy that are not fully understood. For example, increased cytosolic Ca^{2+} via influx from extracellular space through L-type Ca^{2+} channels inhibits autophagosome formation by activating the calpains (Ca^{2+}-dependent cysteine proteases), whereas efflux of stored ER Ca^{2+} via IP_3 receptors (IP_3R) blocks autophagosome maturation [83,84]. Some of these pathways are interconnected and form a cyclic loop, wherein high cAMP levels could increase IP_3 production via the cAMP sensor EPAC (exchange protein directly activated by cAMP), the small G-protein RAP2B and PLCϵ (phospholipase Cϵ), and subsequently IP_3 influences ER Ca^{2+} release through the IP_3R to elevate cytosolic Ca^{2+} (which also increases via L-type Ca^{2+} channels) that activates the calpains; which, in turn, could increase cAMP levels by cleaving and activating $G_{s\alpha}$ proteins [83]. Both mTORC1 and mTORC1-independent pathways can be targeted by small molecules for modulating autophagy.

Chemical modulators of autophagy

Chemical modulation of autophagy can be achieved via directly inhibiting mTORC1 or by targeting the mTORC1-independent pathways [81,86] (Fig. 2). Some of the mTOR inhibitors inducing autophagy include rapamycin [87] and its analogs (rapalogs) temsirolimus (CCI-779) [88] and everolimus (RAD-001) [89], and Torin 1 [90]. There are a number of mTOR-independent autophagy inducers acting via distinct mechanisms, which include lithium, carbamazepine, and valproic acid [82] (lowering intracellular inositol and IP_3 levels), trehalose [91,92] and metformin [93] (AMPK activation), verapamil [83], and felodipine [94] (reduction in cytosolic Ca^{2+} levels), rilmenidine [83], (decrease in cAMP levels), L-NAME [85] (inhibition of NO production), and SMER28 [95] (mechanism not clear), amongst many others. Additional means of inducing autophagy include the natural compounds or nutritional supplements, such as resveratrol [96,97] (activation of sirtuin 1 and inhibition of mTOR), spermidine [98] (increase in *ATG* gene expression), and vitamin D3 [99,100] (increase in Beclin 1 and *ATG* gene expression), or via the autophagy-inducing peptide Tat-Beclin 1 [101], or via BH3 mimetics like ABT737 [102] (disruption of Beclin 1−Bcl-2 interaction).

The pharmacological modulation of autophagy has attracted significant biomedical interests for the treatment of myriad human diseases, including neurodegenerative disorders [103]. For clinical applications, mTOR-independent autophagy inducers are considered to be safer with lesser side-effects as compared to the mTOR inhibitors [81,86]. This is because mTOR governs critical cellular processes like cell growth and protein synthesis [69], and thus, inhibiting mTOR for inducing autophagy may not be ideal for long-term drug administration.

Role of autophagy in neurodegenerative disorders

Autophagy is implicated in diverse human diseases, including neurodegenerative, infectious, inflammatory, and metabolic diseases, as well as myopathies and cancer [5,6]. Many of these pathologies occurring due to abnormal accumulation of undesirable macromolecules are broadly classified under macromolecule storage disorders, which encompass several neurodegenerative and lysosomal storage disorders [7,104,105]. Autophagy is required for maintaining cellular homeostasis in post-mitotic neurons, and improper functioning of this process contributes to neurodegeneration. This is evident from genetic studies in mice, where brain-specific deletion of essential autophagy genes, such as *Atg5* or *Atg7* to abrogate autophagy, resulted in neurodegenerative phenotype [106,107]. Indeed, autophagy dysfunction has been reported in almost all the neurodegenerative disorders investigated, and in certain conditions, induction of autophagy ameliorated the disease phenotypes in transgenic animal models [7,81,86,103,108]. These observations have led to the potential therapeutic possibilities for autophagy modulation in these contexts.

However, emerging studies suggest that the efficacy of autophagy modulators, as well as the nature of the autophagy defects, may be context-dependent. For example, a drug identified in immortalized human or mouse cell lines showing therapeutic benefits in transgenic animal models may not be effective in the target organs of the patients. With the advancements in human stem cell technology, it is now possible to establish disease-affected cellular platforms from patients for investigating disease mechanisms and drug discovery in the appropriate cell types, such as in neurons that are otherwise not accessible.

Human Induced Pluripotent Stem Cells: Potential and Progress in Human Disease Modeling and Drug Discovery

The intricate manner in which genetic components are entangled with environmental exposures, a factor, which constitutes the basis for virtually all human disease, poses a significant challenge to gaining a deeper understanding of pathologies, which is often a prerequisite for the development of novel therapies. To compound this, a large contributor to disease burden in the modern world are diseases, which are not monogenic [109]. Rather,

many pathologies arise when specific alleles of multiple genes with interconnected functions, although not always apparent, produce a genetic predisposition to develop a disease given a degree of certain environmental exposure within an anatomical system. Often the environmental element is also a temporal one, namely aging, which precedes the development of a disease. The mechanisms of pathology may come to light when the genetic background meets the environmental and temporal influences in the context of an elaborate biological structure. Therefore, it is these arenas with which any relevant disease model must grapple in the hopes of unveiling molecular workings of disease and ultimately discovering therapies. Since their derivation [110], human-induced pluripotent stem cells (hiPSCs) have demonstrated considerable promise in constituting a platform for effective disease modeling (Fig. 3), while work continues to be done in addressing these central aspects.

Nuclear reprogramming to pluripotency for generating patient-specific cell types

Cellular reprogramming and the direct conversion approach have been fascinating areas of research for the last two decades. The seeds of these research fields were sown in 1962 when Sir John Gurdon first reported that an adult nucleus could be reprogrammed by an egg to produce an embryo

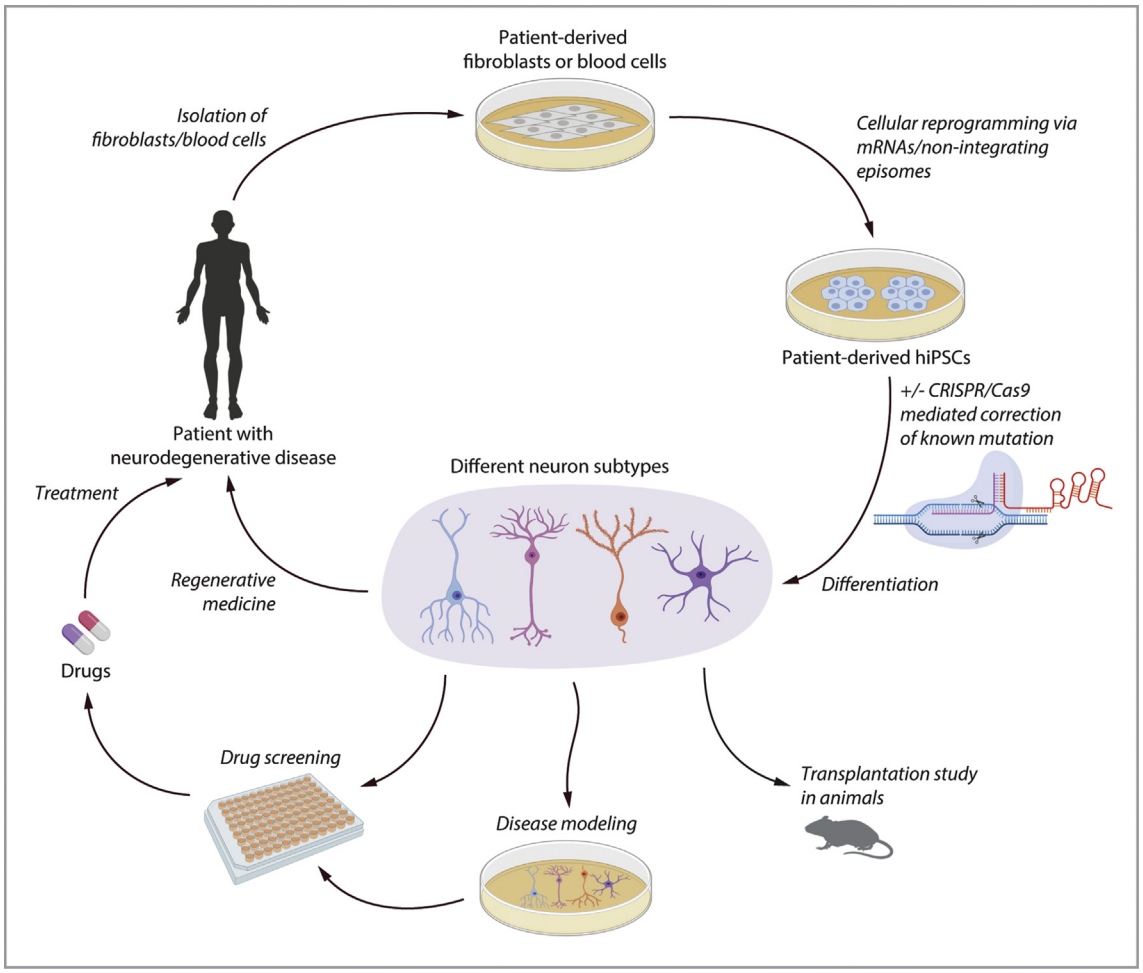

Fig. 3. Cellular reprogramming for hiPSC generation and possible applications for hiPSC-based disease modeling and drug discovery. A disease-affected patient serves as a source of easily obtained somatic cells, which can subsequently be reprogrammed into human induced pluripotent stem cells (hiPSCs). Genetic editing technology, such as CRISPR/Cas9 can be used to generate isogenic controls. hiPSCs are then differentiated into disease-relevant cell types, such as neurons, for the modeling of neurodegenerative diseases. Thus, disease modeling may be performed on a platform with a genetic load, which is identical to disease-bearing individuals. Such cells may be grown in two- or three-dimensional modeling conditions, engrafted into animals, and subjected to high-throughput screening for drug discovery. Ultimately, new therapeutic agents may be discovered, and a personalized therapy plan may be used to benefit the individual patient. Derived cells may also be used for autologous transplantation after correction with genetic editing.

[111]. This nuclear reprogramming technique, which was later termed somatic cell nuclear transfer (SCNT), challenged the Waddington landscape model in which the lineage of a committed cell was permanent [112]. Following this discovery, a series of studies in different models have demonstrated the power of transcription factors in forcing alternative cell fate. When ectopically expressed, some cell type-specific transcription factors were shown to induce a partial conversion process between two different cell types. A master regulatory role was attributed to these key master regulators in cell fate determination [113–115]. In 2006, a game-changing discovery was made by Takahashi and Yamanaka when they demonstrated that pluripotency is achievable through the overexpression of few master transcription factors, namely, OCT4, SOX2, KLF4, and MYC (OSKM) [110,116]. The resulting hiPSCs were similar to human embryonic stem cells (hESCs) in all examined parameters, including morphology, proliferation, gene expression profile, surface antigens, epigenetic marks of pluripotent cell-specific genes, and telomerase activity [117–120]. Furthermore, hiPSCs showed the same capacity as hESCs to differentiate into cells of the three embryonic germ layers via the teratoma assay and by *in vitro* differentiation [110,121]. Derivation of hESCs *in vitro* is not easily achieved due to limited access to early human embryos. Therefore, this astonishing ability to take fully adult cells and reprogram them to pluripotency opens the opportunity to utilize the reprogramming approach to produce hiPSCs for modeling human diseases and for drug discovery (Fig. 3).

Induction of pluripotency by different routes and delivery systems

Since the OSKM combination produces hiPSCs with low efficiency and with varying quality, researchers have attempted to optimize the reprogramming process by modification of the reprogramming factors, culture conditions, and cell type of origin [121–127] (Fig. 3). Given the assumption that it will be beneficial to reprogram cells without MYC, which is a strong oncogene, scientists have reprogrammed cells with OSK alone but with reduced efficiency [128–130]. In addition, it has been shown in human cells that both KLF4 and MYC can be replaced by NANOG and LIN28 [121]. While in the mouse system, many combinations were identified which replace OSKM and even produce higher quality cells [131–133], in the human system, it has been more difficult to discover such combinations. Interestingly, lineage specifiers were also shown to induce pluripotency. GATA3, a mesendodermal lineage specifier, was able to replace OCT4, while ectodermal lineage specifiers like ZNF521, SOX1, or SOX3 were able to replace SOX2 during reprogramming [134,135]. While the current dogma is that pluripotency is a result of a balanced cell state between opposing lineage-specification pathways [135], others proposed different explanations to the capability of these factors to induce pluripotency [136]. For example, the direct targets of the functionally selected lineage specifiers are pluripotency genes. Another explanation is that some of these lineage specifiers are expressed at a developmental stage that is similar to that of the preimplantation embryo, suggesting a potential role in reprogramming for these factors [136].

Besides transcription factors, a major focus was given to chromatin regulators, as cellular reprogramming involves the erasure of the epigenome of the cell of origin and the acquisition of an epigenetic landscape resembling that of ESCs [137–140]. For example, RCOR2, a member of a nucleosome demethylation complex, was shown to replace SOX2 in the classical Yamanaka factors [141]. Interestingly, inhibition of DOTL1 (H3K79 methyltransferase) by shRNA or pharmacological interventions could replace KLF4 and MYC in the Yamanaka factors during the induction of pluripotency [138]. These observations indicate that epigenetic modifiers can take over the role of master regulatory transcription factors in the establishment of pluripotency.

A recent study aimed to understand the essential genes that confer ESCs with growth and survival capabilities [142]. To that end, haploid human pluripotent stem cells (hPSCs) were subjected to a genome-wide CRISPR/Cas9-mediated knockout screen. Interestingly, many of the identified essential genes encoded for transcription factors and proteins related to cell cycle and DNA repair machinery, which are important for normal growth. Among the known pluripotency transcription factors, OCT4, PRDM14, SALL4, and DPPA3 were identified as part of the hPSC-essentialome [142]. These observations raise the question of whether the master regulators and drivers of pluripotency can be redefined in the context of somatic cell nuclear reprogramming in order to yield hiPSCs with more efficient and rapid reprogramming [142].

However, the reprogramming of fibroblasts into hiPSCs with integrated viral vectors harbors a limitation for regenerative medicine, since integrations into the genome might increase the possibility for genomic aberrations and cancer [121,129,143]. Therefore, considerable attempts have been made to generate hiPSCs that bypass integrated vector-based gene transfer. Successful reprogramming to hiPSCs was done using adenoviruses, microRNAs, episomal DNA, Sendai viruses, PiggyBac transposons, recombinant proteins, synthetic mRNAs, and minicircles [143–152]. Reprogramming to hiPSC was also shown to be possible with small molecules, and yielded a more efficient reprogramming process,

albeit with the need for episomal vector induction [153].

Primed *versus* naïve pluripotent stem cells

The hPSCs, which include both hESCs and hiPSCs, harbor some limitations, which need to be addressed. Conventional hESC derivation or hiPSC production gives rise to developmentally advanced or primed pluripotency cells in terms of their transcriptional signatures and epigenetic marks, defining their developmental stage to post-implantation [154–156]. Hence, producing hiPSCs resembling preimplantation naive epiblast might hold a higher potential for differentiation, as seen in the mouse [157–160]. The first attempts to generate authentic naïve hPSCs raised doubt as to their usefulness in disease modeling and clinical applications because they were found to have a higher degree of genomic instability when compared to primed hPSCs [161,162]. Moreover, loss of genomic imprinting existing in the current naïve hPSCs is associated with human disorders and can also potentially dysregulate the differentiation of hPSCs into specific cell fates for disease modeling purposes [163]. Therefore, optimization of culture conditions will be required in order to address these features in naïve hPSCs in order to use them as an intrinsic model for disease modeling [164].

Altogether, the process of direct reprogramming of fibroblasts into hiPSCs holds great promise for modeling human diseases and for generating patient-specific cell types for drug discovery. This cellular model alleviates the ethical issues that are linked with hESCs, and also solves the unavailability issues of these cells; hence, facilitating the flourishing of hiPSC-based therapies [165].

Achieving disease-relevant human cell cultures

The hPSCs (i.e., hESCs and hiPSCs) are capable of both self-renewal and differentiation into any cell of embryonic origin [166]. Therefore, hPSCs offer an effectively indefinite source of differentiated disease-relevant cells (Fig. 3). This is crucial in modeling human pathologies, as many cell types are near impossible to isolate and culture, both technically and ethically, and have a limited proliferative capacity. Furthermore, readily available human cells avoid discrepancies due to evolutionary divergence between humans and animal models. Still, the utility of hPSCs in this context hinges on the refinement of reliable differentiation protocols into relevant cell identities. It might be for this reason that neurological and neurodegenerative diseases are at the forefront of disease modeling using hPSCs, as protocols for neuronal differentiation from hPSCs are relatively advanced [167]. Besides these, other types of cells for which differentiation protocols have been developed include cardiomyocytes [168], pancreatic beta cells [169], hematopoietic cells [170], renal cells [171,172], intestinal cells [173,174], cells of the lung [175,176], and others. In this manner, the establishment of workable *in vitro* platforms for the study of specific disease-associated and disease-affected human cell types is attainable. Notwithstanding, while it is extremely useful to have established cultures of specific disease-affected cells, some phenotypes of a disease are not manifested in a two-dimensional culture system. Therefore, it is advantageous that more complex structures be utilized, ones in which the three-dimensional interactions between multiple cell subtypes are taken into account. This is partly being addressed by the development of three-dimensional organoid cultures, which replicate *in vivo* cell-cell interactions to some degree. Using PSCs to create human-animal chimeras, although provoking considerable ethical concerns [177], takes this a step further and allows for the consideration of interactions between different anatomical systems in the development of the disease. A comprehensive overview of current research in human disease modeling using three-dimensional culture and human-animal chimeras has been published recently [178].

hiPSCs for modelling genetically simple and complex human diseases

While hESCs are derived from an early embryo, hiPSCs are the product of cellular reprogramming of somatic cells, as discussed above. hESCs have been used to model genetic disease by way of gene expression knockdown [179], inducing a disease-relevant gene mutation [180], by employing hESCs derived from diseased embryos that have undergone preimplantation genetic diagnosis (PGD) [181] and by utilizing aneuploid hESCs that emerge spontaneously in culture [182]. Conversely, diseases that are genetically complex, have unknown genetic components and have no available preimplantation screening tests, cannot be modeled in the aforementioned methods. In such cases, patient-derived hiPSCs have the unique ability to serve as a platform, which is faithful to the genetic background of the patient, ensuring complete conservation of the genetic components of any particular disease in the disease model and without the need for genetic editing. Thus, the ability to produce patient-specific hPSCs is the crux of employing hiPSCs as powerful tools in disease modeling (Fig. 3). They also allow for the derivation of disease-relevant cells from patients of all ages. In this way, cell-level phenotypes, specifically in the patient-derived cells, have been uncovered in relatively genetically simple childhood diseases like spinal muscular atrophy (SMA) [183], and genetically complex adult-onset diseases, such

as schizophrenia [184,185]. Examples of diseases that have been studied using two- and three-dimensional hiPSC-derived culture systems include gastrointestinal diseases, such as Hirschsprung disease [186], autism spectrum disorder (ASD) [187,188], Parkinson's disease (PD) [189] and Alzheimer's disease (AD) [190], among many others.

hiPSCs in drug discovery and drug screening

Understanding the molecular mechanisms underlying pathology is an important step in the development of targeted therapies. Moreover, hiPSC-derived disease models can serve as a more direct platform for drug discovery, as candidate drugs can be directly tested using patient-derived cells. Differentiated disease-relevant cells from large cohorts or from individual patients can be subjected to treatment with specific candidate drugs, or simultaneously with a large number of compounds using high-throughput screening (HTS) (Fig. 3). In both cases, an observable phenotype, or set of phenotypes, must be defined in order to evaluate the efficacy and potency of tested compounds in the setting of the specific disease model. Numerous therapeutic agents have been tested in this way for multiple diseases, including amyotrophic lateral sclerosis (ALS) [191], AD [192], SMA [193], and achondroplasia [194]. In the case of HTS, this phenotype must be capable of being measured via automated analysis. This may not be suitable when the disease phenotype is difficult to quantify, or if a system which would allow automatic quantification would be extremely laborious to develop. In other cases, such as with quantification of cell proliferation or measurement of fluorescent signal of a reporter gene, which can be targeted in the iPSC state, HTS has the advantage of allowing testing of over one million compounds simultaneously [195], without the need for prior knowledge about the drug mechanism. This allows the possibility of testing a large number of drugs, which have already been approved for use in humans for possible repositioning thereof in other diseases, thereby expediting clinical trials and new treatment options. Such systems have been employed in the study of AD [196], familial dysautonomia [197], and ALS [195]. Achieving rapid drug-screening for patient-derived model systems could facilitate a breakthrough in personalized medicine, as the response to various drugs could be tested on individual patient cells. They also allow screening for drug toxicities on specific and possibly individual human tissues, most commonly hepatotoxicity [198], cardiotoxicity [199], and neurotoxicity [200]. Thorough reviews of current disease models and drug screening have been published previously [127,201].

hESCs *versus* hiPSCs: shared and distinct challenges

While the topic has been under some debate [202], it is generally believed that hiPSCs hold similar potentials to hESCs in their capacity to differentiate into various cell types. Still, in a few instances, diseases in which both hESC-based and hiPSC-based models have been developed, diverging phenotypes have been observed. Such is the case with fragile X syndrome (FXS), which was first modeled in hESCs derived from early embryos diagnosed using PGD [181] and later compared with a patient-derived hiPSC model [203]. In the hESC model, the FMR1 gene, which is aberrantly silenced in FXS, was active in undifferentiated cells and silenced upon differentiation. In contrast, in patient-derived undifferentiated hiPSC lines, the FMR1 gene was silenced. This highlights a potential difference between hESC and hiPSC disease models, especially in the context of diseases involving aberrant epigenetic processes. One reason for this could be variations in the reprogramming process, whereby some colonies may maintain aberrant epigenetic patterns, which do not fully mirror hESCs due to incomplete reprogramming, thus causing inconsistencies in expression between hiPSC colonies and hESCs [204]. Nevertheless, both models are potentially useful following differentiation into disease-relevant cells.

A further challenge, namely variations between hiPSCs derived from different individuals, must also be taken into account [205,206]. Therefore, strict controls must be employed to avoid confounding factors due to background genetic variability. When disease-relevant mutations are known, these should include isogenic controls generated using gene-editing techniques to correct the disease-inducing mutation [207]. In other cases, large cohorts of patient-derived iPSCs must be employed in order to identify authentic disease phenotypes. This endeavor is aided by the establishment of hiPSC repositories derived from a vast array of disease-affected individuals [208].

The development and progression of many diseases, such as AD and PD, are highly affected by aging [209]. These diseases are pertinent to study, especially in the context of an aging world population [210]. One drawback of using differentiated hPSCs as a basis for disease models is that the reprogramming of adult cells into hiPSC abolishes cellular aging. Thus, subsequently, differentiated cells tend to retain fetal characteristics, thus impeding the ability to model diseases in which aging is a central component. This phenomenon has been reported in differentiation into hematopoietic cells [211], neurons [212], pancreatic beta cells [213], intestinal organoids [214], and others. Because of this, various

strategies have been employed in an attempt to induce cellular aging in hPSC-differentiated cells [215]. One attempt to overcome this barrier is by forced expression of progerin, the truncated lamin A protein that accelerates aging in Hutchinson-Gilford progeria syndrome, in differentiated cells [216]. By overexpression of progerin, late-onset characteristics of PD were induced in neurons, which were differentiated from patient-derived hiPSCs [216]. Similarly, hiPSC-differentiated neurons in which telomere-shortening was employed also resulted in phenotypes characteristic of aging cells [217]. Interestingly, neurons derived from fibroblasts by the direct reprogramming method, rather than by achieving a pluripotent stage, did retain aging-associated gene signatures, unlike their hiPSC-derived counterparts [218,219].

Neural Differentiation of Human Pluripotent Stem Cells

Since the first derivation of hESCs [166,220], and later the advent of cellular reprogramming to hiPSCs [110], numerous studies have utilized these pluripotent stem cells (will refer collectively as hPSCs) for neural differentiation. The ability to generate human neurons from hPSCs allow researchers to study the

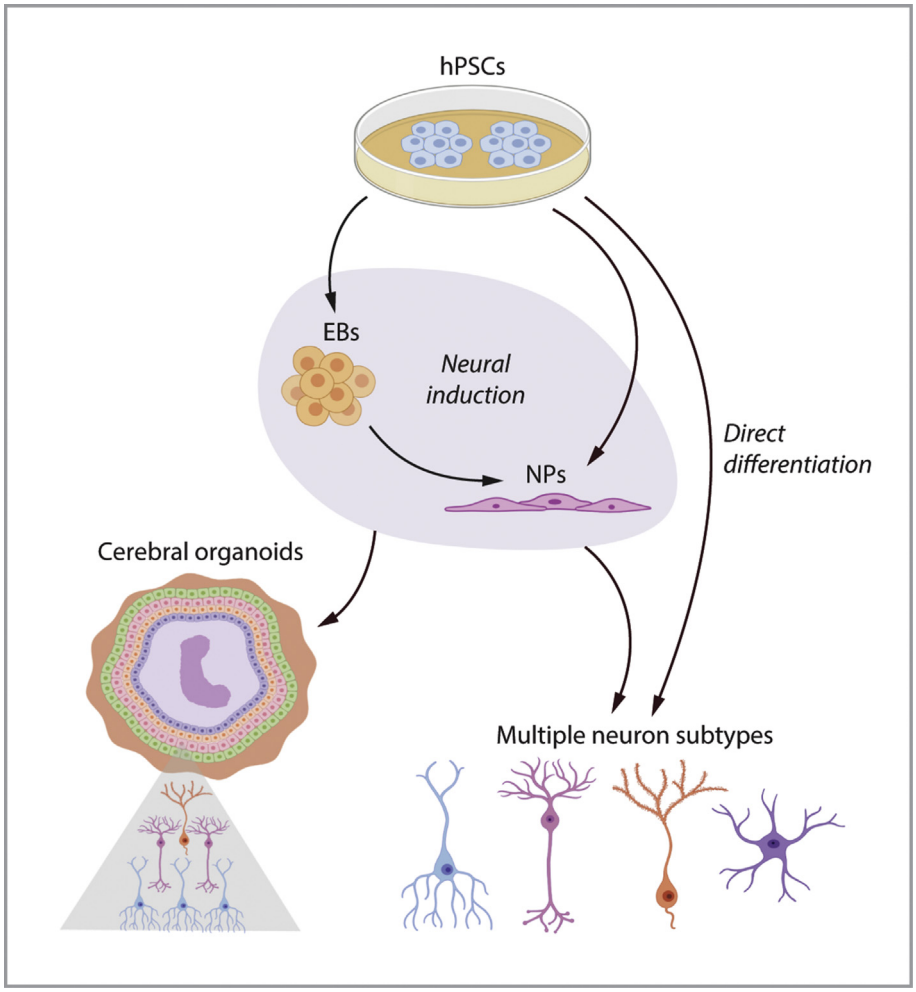

Fig. 4. Generation of human neurons from hPSCs. Classical approaches for the differentiation of human pluripotent stem cells (hPSCs) into the neural lineage involve neural induction in 2D (adherent) or 3D (through embryoid bodies; EBs) cultures into neural precursors (NPs). This can be followed by further differentiation and neural patterning into subtypes of neurons by exposing the cells to appropriate morphogens and/or relevant small molecules in adherent cultures. Directed and more rapid differentiation of hPSCs into neurons can be achieved by overexpression of a single or a combination of relevant transcription factors. Cerebral organoids are derived from 3D cultures of hPSCs-derived EBs or NP-clusters. These organoids represent a miniature of the developing human brain and may contain a similar neuronal complexity and tissue architectures. All these methods serve widely as platforms to differentiate hPSCs into the different cell types of the human brain, serving as a powerful system to study neurodevelopmental and neurodegenerative disease *in vitro.*

aspects of human neural differentiation, its pathologies in diseases, and to serve as a valuable source for cell therapy applications and drug development [221,222] (Fig. 4). These hPSC-derived neural cells also enable the studies on autophagy in physiological or disease-affected human cellular platforms that are relevant to human biology [223,224].

Neural induction

The first step in neural differentiation of hPSCs is essentially switching from the self-renewal state to neural induction (Fig. 4). Historically, neural cultures of primary neural progenitors and stem cells involved the formation of neural spheroids [225]. Presumably, for that reason, the initial protocols for neural induction and differentiation of hPSCs to neural precursors (NPs) involved the formation of hPSCs aggregates. In these protocols, the switching from self-renewal state to neural induction was triggered by spontaneous, uncontrolled differentiation of prolonged culture of hPSCs as colonies or in three-dimensional, free-floating hPSCs-aggregates, termed embryoid bodies (EBs) or neurospheres, followed by lineage selection to NPs [226–228]. To further induce neural differentiation, some of the early methods used retinoic acid (RA), coculturing of hPSCs with mouse stromal cells, or mechanically dissecting "neural differentiating zones" of hPSCs colonies [226,227,229]. However, generating progenitor cells using these aggregation approaches displayed cells with a wide range of developmental stages. To this end, methods for further isolating neural tube-like structures, termed "neural rosettes," or sorting cells based on early neural markers (like PSA-NCAM) were applied to purify the NPs in cultures [226,228,230].

For better neural induction methods, researchers searched for growth factors, which will enable a more controlled and efficient neural induction of hPSCs. At first, the inhibition of bone morphogenetic protein (BMP) signaling was identified to significantly enhance the enrichment levels for NPs within the differentiating hPSCs by suppressing the differentiation of hPSCs into lineages other than the neural one [231–233]. Hence, initially, noggin-mediated blockage of endogenous BMP signaling and later by small molecules, such as LDN-193189 or dorsomorphin, were shown to support neural induction and differentiation of hPSCs to NPs. Next, a second pathway involving TGFβ was identified that could be targeted for more efficient conversion of hPSCs to NPs. The small molecule TGFβ inhibitor, SB431542, was shown to inhibit the Lefty/Activin/TGFβ pathways by blocking the phosphorylation of ALK receptors 4, 5, and 7. While the Activin/Nodal pathway has been implicated in the pluripotency of hPSCs [234], its inhibition by SB431542 enhanced the ability of hPSCs to exit their self-renewal; thereafter leading to improved neural induction efficiency of hPSCs [235].

Chambers and colleagues introduced the synergistic action of inhibition of both BMP and TGFβ pathways, leading to inhibition of their respective downstream SMAD effectors (SMAD1/5/8 for BMP, and SMAD2/3 for TGFβ signaling); hence, termed "dual-SMAD inhibition" by using the combination of Noggin (and later, LDN-193189) and SB431542 to greatly facilitate the differentiation of hPSCs to NPs and in a shorter time period [236,237]. Moreover, with the identification that EB-based protocols might present uneven distribution of growth factors and/or small molecules to the differentiating cells that could result in heterogeneous differentiation, Chambers and colleagues presented one of the first reports for differentiating hPSCs in monolayer cultures with highly efficient neural conversion; thus bypassing the hurdles associated with EBs [236]. Nowadays, most laboratories use mixed methods, which are mostly based on the EBs/neurospheres and the "dual-SMAD inhibition" protocols. Finally, the NPs could be further differentiated into different neural lineages, such as astrocytes, oligodendrocytes, and neurons, and to cells of the human retina.

Neuronal subtype specification

The NPs differentiated from hPSCs via the EB/neurospheres or dual-SMAD inhibition methods carry an anterior identity. When normally expanded and cultured in the presence of basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), these NPs will eventually be committed to forebrain fates. However, in the presence of different morphogens and/or small molecules, the NPs can acquire definitive regional identities [238]. Generally, WNT, FGF, and RA are used for caudalization (posterior identity). Activation of the WNT pathway showed a dose-dependent effect in patterning NPs to the forebrain (low concentrations), midbrain, hindbrain, and spinal cord (high concentrations) identities [239], while the gradients of RA and FGFs governed the spinal cord segmentation identities [240,241]. NPs can be specified not only along the anterior-posterior axis but also to the dorsoventral axis. Sonic hedgehog (SHH) is a ventralization morphogen, whereas BMPs and WNT are more dorsal morphogens [242,243]. Following these principles, the combinations of different morphogens permit to pattern the NPs into specific neural subtypes that are to be derived from these NPs, such as cortical neurons (forebrain; dorsal), dopaminergic neurons (midbrain; ventral) or motor neurons (spinal cord; ventral). The ability to differentiate hPSC-derived NPs into specific neural subtypes is of great potential for studying human neurodegenerative disorders in the most relevant, disease-affected human cell types, such as midbrain dopaminergic neurons for PD or motor neurons for ALS [244,245] (Fig. 4).

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Directed differentiation by transcription factors

In the last decade, multiple studies have shown efficient cell fate reprogramming only by forced expression of single or multiple transcription factors (Fig. 4). In an effort to produce neurons, forced expression of three transcription factors (Brn2, Ascl1, and Myt1) were proven to reprogram mouse fibroblasts into functional neurons, termed induced neurons (iN) [246]. This was immediately followed by several studies, which used a similar approach to directly differentiate hPSCs into neurons by forced overexpression of relevant transcription factors, thus bypassing the need to first differentiate to NPs and also significantly shortening the differentiation processes for generating neurons *in vitro*. These multiple studies showed that a single factor, such as ASCL1, NEUROD1, or NEUROG2, can efficiently drive hPSCs into pure excitatory neurons in less than two weeks [247,248]. This single factor-directed differentiation to human neurons gave rise to neurons with cellular, electrophysiological, and molecular characteristics of excitatory neurons. For inducing specific subtypes of neurons, the forced expression of a combination of transcription factors was utilized to drive reprogramming into specific neurons. For example, the coexpression of ASCL1and DLX2 was found to be sufficient to directly differentiate hPSCs into GABAergic interneurons, which are the inhibitory neurons that balance neuronal excitation in the brain [249]. Similarly, ASCL1, NURR1, and LMX1A were found to drive hPSCs directly into dopaminergic neurons, while coexpression of NEUROG1, NEUROG2, NEUROG3, NEUROD1, and NEUROD2 induced direct differentiation of hPSCs into motor neuron [250,251].

Cerebral Organoids

Specific neural subtypes derived from hPSCs may be valuable for disease modelling, drug discovery, and toxicity assays. However, these differentiated neurons still lack the complexity characteristic of the brain tissue. In order to apply a more holistic approach for studying human development using hPSCs, researchers invested their effort to develop an *in vitro* model of a complex tissue derived from hPSCs. A pioneering study first demonstrated the ability of self-organization of hPSCs aggregates to form complex, multicell type optic cup structures [252]. In a similar manner, another method was established to form a three-dimensional organoid culture-system from hPSC-derived EBs, termed cerebral organoids, which developed various discrete brain regions with self-organization and minimal exogenic cues [253]. Subsequent studies of multiple research-groups have shown that human organoid cultures enabled cells to differentiate into mature and functional neurons in structures and contexts resembling the developing human cortex [254–257]. This fast-growing field presented a "renaissance" to the EBs-based neural induction method. Multiple methods are now used to culture cerebral organoids from hPSCs and/or NPs aggregates in culture conditions for growing region-specific brain-like structures, i.e., the cerebellum, hypothalamus, or the hippocampus [258–260]. The cerebral organoid differentiation approach enables the study of different aspects of human diseases, such as microcephaly, dementia, autism, and Zika viral infection [261–265]. Moreover, these organoids can be cultured over a long period of time and provide access to a large diversity of cell types, including subtypes of neurons and cells of the astroglial lineages [266,267] (Fig. 4).

Human Pluripotent Stem Cell Models of Neurodegenerative Diseases as a Disease-Relevant Platform for Studying Autophagy

Autophagy has attracted significant attention for hiPSC-based studies of neurodegenerative disorders. Since impairment of this vital homeostatic process contributes to neurodegeneration, defective autophagy is being utilized in recent years as a phenotypic readout in hiPSC-derived neurons [223,224] (Fig. 5). This provides an appropriate disease-affected human cellular platform for investigating the mechanisms of autophagy dysfunction and the drug discovery of autophagy modulators in a manner relevant to human biology. Several hiPSC models of neurodegenerative diseases (Table 1), where impairment of autophagy has been studied (Table 2) and autophagy modulators, have been assessed for therapeutic benefits (Table 3), are described below.

Alzheimer's disease

Alzheimer's disease (AD) is the most common type of progressive dementia. AD is associated with abnormal metabolism of amyloid precursor protein (APP), which leads to the formation of extracellular senile plaques made of amyloid-β (Aβ) [268]. Autophagy is implicated in the production of Aβ depositions, as they have been shown to be generated inside the autophagosomes, where APP is processed by the enzyme presenilin-1 (PS1) into Aβ that is then either degraded or secreted in the extracellular space to form plaques [269–271]. This is supported by the accumulation of autophagosomes, characteristic for an autophagy block, observed in the post-mortem brain samples from AD patients, and in the neurites of *PS1/APP* mutant mice [272]. The AD-associated

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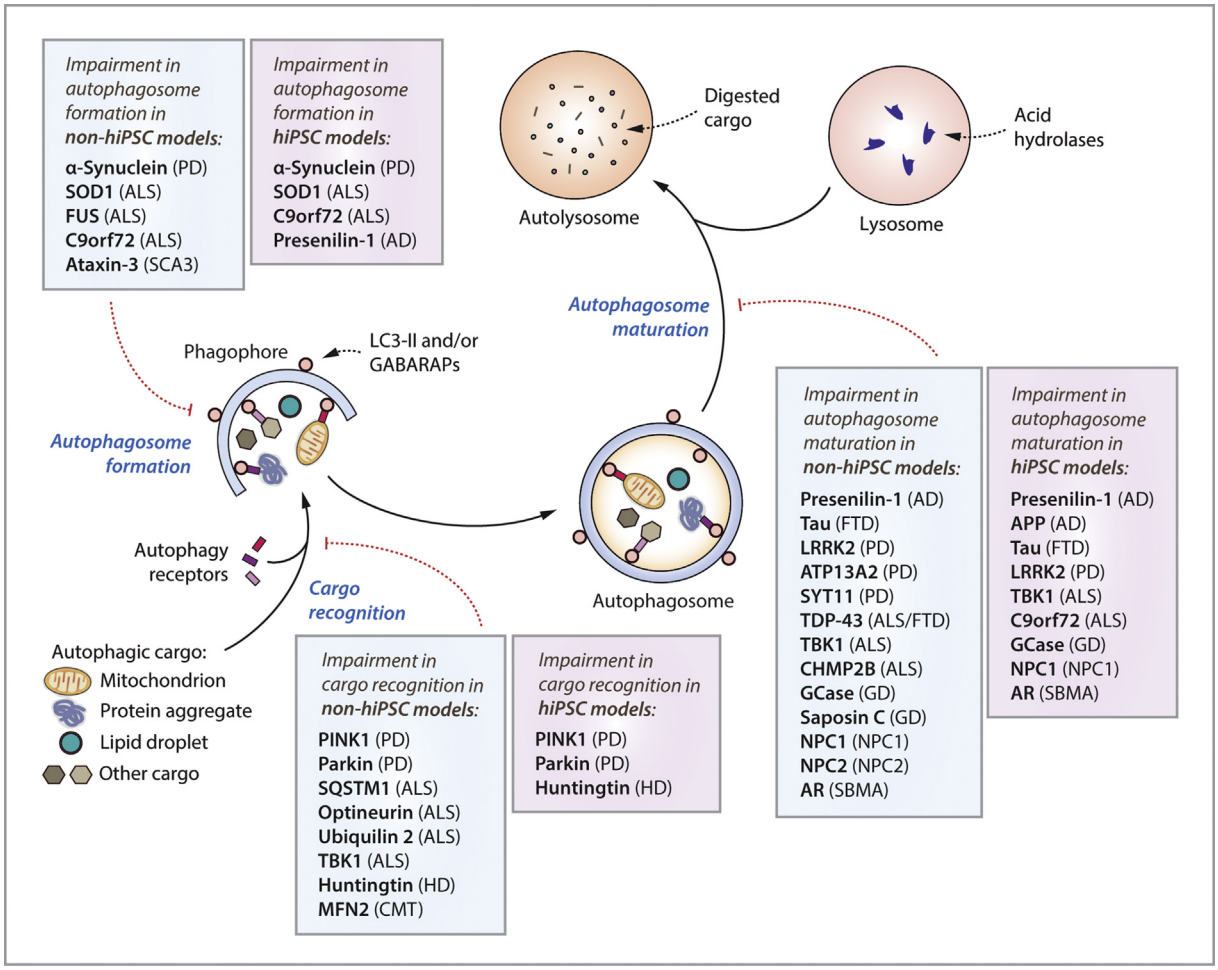

Fig. 5. Impairment of autophagy in neurodegenerative diseases. Impairment of autophagy at distinct stages of the process, such as at the level of autophagosome formation, cargo recognition, or autophagosome maturation, has been described in multiple neurodegenerative diseases. The impact on autophagy due to mutations or loss of disease-associated proteins in non-hiPSC and hiPSC models is indicated (by red arrows). In addition, the point mutants of α-synuclein and LRRK2 associated with PD also impair chaperone-mediated autophagy (not shown).

gene most studied for autophagy is *PSEN1*, the gene encoding for PS1, which has been suggested to be required for lysosomal targeting of the proton pump, v-ATPase V_0a_1 subunit, for maintaining the acidic pH, whereas mutant PS1 has been shown to impair lysosomal acidification and function that consequently block autophagosome maturation and autophagic flux in mammalian cell lines [273,274]. However, PS1/2 double knockout mouse embryonic fibroblasts (MEFs) displayed reduced autophagosome number due to impaired biogenesis, as well as dysregulation of nutrient sensing by mTORC1 and dysfunctional mTORC1/TFEB-driven CLEAR gene network activity [275]. Despite the autophagy defect, the pharmacological induction of autophagy was beneficial by clearing Aβ plaques and tau tangles, and rescuing the disease pathogenesis in various AD mouse models. These effects have been demonstrated in *APP/Tau/PS1* mutant (3xTg-AD) mice with rapamycin [276,277] and carbamazepine [278]; in *APP/PS1* mutant mice with rapamycin [279], trehalose [280], carbamazepine [281], and gypenoside XVII (GP-17) [282]; in *APP* mutant mice with rapamycin [283], trehalose [284], and latrepirdine [285]; and in *APOE4* mutant mice with rapamycin [286].

With the emergence of patient-derived hiPSC models, a number of hiPSC-based neuronal platforms have been generated to study the pathogenesis of AD. Since *PSEN1* is the most commonly mutated gene in familial AD (FAD), multiple studies have utilized AD patient-derived hiPSC models with *PSEN1* gene mutations. The autophagic block observed in cellular and *in vivo* models of AD with *PSEN1* mutations is consistent with some, but not all of the studies in AD hiPSC models carrying this

Table 1. List of patient-derived hiPSC lines of neurodegenerative disorders where autophagy has been studied.

Mutant gene	Mutant protein	Patient-derived hiPSC lines of neurodegenerative disorders	Gene mutation	Origin of patient-derived hiPSC lines	Reference
Alzheimer's disease (AD)					
PSEN1	Presenilin-1	PSEN1 Y115C	*PSEN1*$^{(Y115C)}$	Patient dermal fibroblasts	[288]
		PSEN1 M146I	*PSEN1*$^{(M146I)}$	Patient dermal fibroblasts	[288]
		PSEN1 Intron4	*PSEN1*$^{(Intron4)}$	Patient dermal fibroblasts	[288]
		PS1-M146L	*PSEN1*$^{(M146L)}$	Patient dermal fibroblasts	[275]
		PS1-A246E	*PSEN1*$^{(A246E)}$	Patient dermal fibroblasts	[275]
		PS1 M146L (7889(S)B)	*PSEN1*$^{(M146L)}$	Patient dermal fibroblasts	[291]
		FAD1 iPSC (7671C)	*PSEN1*$^{(A246E)}$	Patient dermal fibroblasts	[287]
		PS1-4 iPSC	*Not specified*	Patient dermal fibroblasts	[290]
		PS1-E120K	*PSEN1*$^{(E120K/wt)}$	Patient blood mononuclear cells	[289]
APP	APP	APP V717I	*APP*$^{(V717I)}$	Patient dermal fibroblasts	[288]
		APP^{dup}	*APP*$^{(Duplication)}$	Patient dermal fibroblasts	[288]
		Ts21	*Trisomy chromosome 21*	Patient dermal fibroblasts	[288]
Tauopathies, including frontotemporal dementia (FTD)					
MAPT	Tau	19-L3-RC3	*MAPT*$^{(A152T\ -/+)}$	Patient dermal fibroblasts	[308]
		19-L5-RC6	*MAPT*$^{(A152T\ -/+)}$	Patient dermal fibroblasts	[308]
		Tau6-1-RC1	*MAPT*$^{(A152T\ -/+)}$	Patient dermal fibroblasts	[308]
GRN	Progranulin	GRN-1	*GRN*$^{(R493X)}$	Patient dermal fibroblasts	[310]
		GRN-2	*GRN*$^{(R493X)}$	Patient dermal fibroblasts	[310]
		GRN-3	*GRN*$^{(R198GfsX19)}$	Patient dermal fibroblasts	[310]
Parkinson's disease (PD)					
SNCA	α-synuclein	A53T SNCA #1 (SFC828-03)	*SNCA*$^{(A53T)}$	Patient dermal fibroblasts	[338]
		A53T SNCA #2 (SFC829-03)	*SNCA*$^{(A53T)}$	Patient dermal fibroblasts	[338]
		A53T SNCA #3 (SFC830-04)	*SNCA*$^{(A53T)}$	Patient dermal fibroblasts	[338]
		SNCA Tripl #1,2,3 (SFC831-03)	*SNCA*$^{(Triplication)}$	Patient dermal fibroblasts	[338]
LRRK2	LRRK2	LRRK2-PD (SP05) #1,2)	*LRRK2*$^{(G2019S)}$	Patient keratinocytes and dermal fibroblasts	[342]
		LRRK2-PD (SP06) #1,2)	*LRRK2*$^{(G2019S)}$	Patient keratinocytes and dermal fibroblasts	[342]
		LRRK2-PD (SP12) #3,4)	*LRRK2*$^{(G2019S)}$	Patient keratinocytes and dermal fibroblasts	[342]
		LRRK2-PD (SP13) #2,4)	*LRRK2*$^{(G2019S)}$	Patient keratinocytes and dermal fibroblasts	[342]
		LA iPSC #5,11	*LRRK2*$^{(I2020T)}$	Patient dermal fibroblasts	[345]
		LB iPSC #16,21	*LRRK2*$^{(I2020T)}$	Patient dermal fibroblasts	[345]
		LRRK2-G2019S	*LRRK2*$^{(G2019S)}$	Patient dermal fibroblasts	[328]
		LRRK2 G2019S-iPSC	*LRRK2*$^{(G2019S)}$	Patient dermal fibroblasts	[344]
Amyotrophic lateral sclerosis (ALS)					
SOD1	SOD1	ALS1 (SOD1 L144FVX) (A3316)	*SOD1*$^{(L144FVX)}$	Patient dermal fibroblasts	[387]
		ALS2 (SOD1 L144FVX) (A3536)	*SOD1*$^{(L144FVX)}$	Patient dermal fibroblasts	[387]
		ALS3 (SOD1 G93S) (A37228)	*SOD1*$^{(G93S)}$	Patient dermal fibroblasts	[387]
		SOD1 iPSC	*SOD1*$^{(N139K)}$	Patient dermal fibroblasts	[392]
TARDBP	TDP-43	TDP-43 M337V iPSC	*TARDBP*$^{(M337V)}$	Patient dermal fibroblasts	[195]
C9orf72	C9orf72	C9-T2 #6,7	*C9orf72*$^{(510-690\ R.E.\ \#6,\ 420-640\ R.E.\ \#7)}$	Patient dermal fibroblasts	[390]
		C9-7245 #1,3	*C9orf72*$^{(1210\ R.E.\ \#1,\ 1380\ R.E.\ \#3)}$	Patient dermal fibroblasts	[390]
		C9-02 #2,10	*C9orf72*$^{(1000\ R.E.\ \#1,\ \#3)}$	Patient dermal fibroblasts	[390]
		C9orf72 iPSC #1,2,3	*C9orf72*$^{(\sim 800\ R.E.)}$	Patient dermal fibroblasts	[392]
		iPS21c1	*C9orf72*$^{(R.E.)}$	Patient dermal fibroblasts	[395]
		iPS21cx	*C9orf72*$^{(R.E.)}$	Patient dermal fibroblasts	[395]
		iPS31c8	*C9orf72*$^{(R.E.)}$	Patient dermal fibroblasts	[395]
		Carrier 1 #5,6	*C9orf72*$^{(>1000\ R.E.)}$	Patient dermal fibroblasts	[391]
		Carrier 2 #1,11	*C9orf72*$^{(>1000\ R.E.)}$	Patient dermal fibroblasts	[391]
TBK1	TBK1	mTBK1-I	*TBK1*$^{(T77WfsX4)}$	Patient keratinocytes	[389]
		mTBK1-II	*TBK1*$^{(E643del)}$	Patient keratinocytes	[389]
		mTBK1-FUS	*TBK1*$^{(Y185X)}$	Patient keratinocytes	[389]
Huntington's disease (HD)					
HTT	Huntingtin	HD-iPS^{hom} 4F #1,2	*HTT*$^{(42/44\ CAG\ repeats)}$	Patient dermal fibroblasts	[409]
		HD-iPS^{hom} 3F #1,2	*HTT*$^{(42/44\ CAG\ repeats)}$	Patient dermal fibroblasts	[409]
		HD-iPS^{het} 3F #1	*HTT*$^{(17/45\ CAG\ repeats)}$	Patient dermal fibroblasts	[409]
		iPSHD22	*HTT*$^{(47/16\ CAG\ repeats)}$	Patient dermal fibroblasts	[410]
		D-HD-iPSC	*HTT*$^{(109\ CAG\ repeats)}$	Patient dermal fibroblasts	[411]
		F-HD-iPSC	*HTT*$^{(50\ CAG\ repeats)}$	Patient dermal fibroblasts	[411]

(continued on next page)

Table 1 (*continued*)

Mutant gene	Mutant protein	Patient-derived hiPSC lines of neurodegenerative disorders	Gene mutation	Origin of patient-derived hiPSC lines	Reference
		iPSC-HDQ47	*HTT*$^{(47\ CAG\ repeats)}$	Patient dermal fibroblasts	[412]
Multiple System Atrophy (MSA)					
(Sporadic)	(Sporadic)	MSA-P1	(Sporadic)	Patient dermal fibroblasts	[423]
		MSA-P2		Patient dermal fibroblasts	[423]
		MSA-C1		Patient dermal fibroblasts	[423]
		MSA-C2		Patient dermal fibroblasts	[423]
Gaucher disease (GD)					
GBA1	GCase	GD-1 #1 (MNG-09-232)	*GBA1*$^{(N370S/N370S}$	Patient dermal fibroblasts	[441]
		GD-2a #13,16 (MNG-09-246)	*GBA1*$^{(W184R/D409H)}$	Patient dermal fibroblasts	[441]
		GD-2b #3,4 (MNG-10-257)	*GBA1*$^{(L444P/RecNcil)}$	Patient dermal fibroblasts	[441]
		GD-3 #1,4 (MNG-98-12-9)	*GBA1*$^{(L444P/L444P)}$	Patient dermal fibroblasts	[441]
		GBA-PD-1 #1,2 (MK071)	*GBA1*$^{(N370S/wt)}$	Patient dermal fibroblasts	[442]
		GBA-PD-2 #1 (MK088)	*GBA1*$^{(N370S/wt)}$	Patient dermal fibroblasts	[442]
		GBA-PD-3 #1,2 (SFC-834-03)	*GBA1*$^{(N370S/wt)}$	Patient dermal fibroblasts	[442]
		GD	*GBA1*$^{(N370S/84GG)}$	Patient dermal fibroblasts	[436]
		PD-1	*GBA1*$^{(RecNcil/wt)}$	Patient dermal fibroblasts	[438]
		PD-2	*GBA1*$^{(L444P/wt)}$	Patient dermal fibroblasts	[438]
		PD-3	*GBA1*$^{(N370S/wt)}$	Patient dermal fibroblasts	[438]
		PD-4	*GBA1*$^{(N370S/wt)}$	Patient dermal fibroblasts	[438]
		GD-1	*GBA1*$^{(L444P/L444P)}$	Patient dermal fibroblasts	[438]
		GD-2	*GBA1*$^{(N370S/N370S)}$	Patient dermal fibroblasts	[438]
Niemann-Pick type C1 (NPC1) disease					
NPC1	NPC1	NPC1-1 #4,13 (WIBR-IPS-NPC1$^{I1061T/I1061T}$)	*NPC1*$^{(I1061T/I1061T)}$	Patient dermal fibroblasts	[454]
		NPC1-2 #9,26 (WIBR-IPS-NPC1$^{P237S/I1061T}$)	*NPC1*$^{(P237S/I1061T)}$	Patient dermal fibroblasts	[454]
		NPC1-3 #4,47 (WIBR-IPS-NPC1$^{1920\Delta G/1009G>A}$)	*NPC1*$^{(1920\Delta G/1009G>A)}$	Patient dermal fibroblasts	[454]
		NPC1-4 #17,20 (WIBR-IPS-NPC1$^{1920\Delta G/1009G>A}$)	*NPC1*$^{(1920\Delta G/1009G>A)}$	Patient dermal fibroblasts	[454]
		hNPC #3,17	*NPC1*$^{(P237S/I1061T)}$	Patient dermal fibroblasts	[450]
		NPC1	*NPC1*$^{(P237S/I1061T)}$	Patient dermal fibroblasts	[455]
Spinocerebellar Ataxia (SCA)					
ATXN3	Ataxin-3	SCA3-iPS #1,2	*ATXN3*$^{(81\ CAG\ repeats)}$	Patient dermal fibroblasts	[470]
PRKCG	PKCγ	SCA14-H36R-1 #1,18	*PRKCG*$^{(H36R\ exon\ 1)}$	Patient dermal fibroblasts	[471]
		SCA14-H36R-2 #3,12	*PRKCG*$^{(H36R\ exon\ 1)}$	Patient dermal fibroblasts	[471]
		SCA14-H101Q-1 #1,10	*PRKCG*$^{(H101Q\ exon\ 4)}$	Patient dermal fibroblasts	[471]
		SCA14-H101Q-2 #3,14	*PRKCG*$^{(H101Q\ exon\ 4)}$	Patient dermal fibroblasts	[471]
Spinal bulbar muscular atrophy (SBMA)					
AR	Androgen receptor	SBMA-1-AR-CAG44 #C1,C3,C4	*AR*$^{(44\ CAG\ repeats)}$	Patient dermal fibroblasts	[474]
		SBMA-2-AR-CAG50 #C1,C2,C5	*AR*$^{(50\ CAG\ repeats)}$	Patient dermal fibroblasts	[474]
		SBMA-3-AR-CAG48 #C2,C3,C4	*AR*$^{(48\ CAG\ repeats)}$	Patient dermal fibroblasts	[474]
		SB6 #MP2,MP3	*AR*$^{(62\ CAG\ repeats)}$	Patient dermal fibroblasts	[486]
		SB18	*AR*$^{(68\ CAG\ repeats)}$	Patient dermal fibroblasts	[486]
Charcot-Marie-Tooth (CMT) disease					
MFN2	Mitofusin 2	CMT2A-1 #1,2,3	*MFN2*$^{(A383V)}$	Patient dermal fibroblasts	[493]
		CMT2A-2 #1,2,3	*MFN2*$^{(A383V)}$	Patient dermal fibroblasts	[493]

Abbreviations – AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; APP: Amyloid-β precursor protein; AR: androgen receptor; C9orf72: Chromosome 9 Open Reading Frame 72; CMT: Charcot-Marie-Tooth disease; FTD: Frontotemporal dementia; GCase: Glucocerebrosidase; GD: Gaucher disease; HD: Huntington's disease; HTT: Huntingtin; iPSC: induced pluripotent stem cells; LRRK2: Leucine-rich repeat kinase 2; MSA: Multiple system atrophy; NPC1: Niemann-Pick type C 1; PD: Parkinson's disease; PKCγ: Protein kinase Cγ; PS1: presenilin-1; R.E.: Repeat expansion; SBMA: Spinal bulbar muscular atrophy; SCAs: Spinocerebellar ataxias; SOD1: superoxide dismutase 1; TBK1: TANK-binding kinase 1; TDP-43: TAR DNA-binding protein 43.

mutation. Autophagic flux assays in hiPSC-derived neurons from AD patients carrying PS1$^{(A246E)}$ [287], PS1($^{Y115C)}$ [288], PS1$^{(M146I)}$ [288], PS1-$^{(E120K)}$ [289], or FAD-PS1 [290] mutations have suggested a block in autophagy at the late stage due to impaired autophagosome maturation. This autophagic defect was characterized by an increase in LC3-II, p62 and lysosomal load [287–290], and disruption in lysosomal function [288], with the exception of PS1$^{(E120K)}$ mutant neurons, in which, the elevation in LC3-II was not associated with accumulation of p62 [289]. Similar dysregulated autophagic and lysosomal phenotypes were found in AD hiPSC-derived neurons with APP mutations (V717I, trisomy 21, and duplication) [288]. While impaired lysosomal functionality could be a causative factor for the autophagic block, increased activity of acid

Table 2. Defective autophagy phenotypes in non-hiPSC and patient-derived hiPSC models of neurodegenerative diseases.

Neurodegenerative disease	Mutant protein	Autophagy phenotype in non-hiPSC models	Autophagy phenotype in patient-derived hiPSC models	hiPSC-derived cell type where autophagy is studied
Alzheimer's disease (AD)	Presenilin-1	Defective autophagy due to impaired autophagosome maturation [272–274] via improper lysosomal acidification and function [273,274]	Defective autophagy due to impaired autophagosome maturation [287–290] possibly via disruption in lysosomal function [288]; defective autophagy due to impaired autophagosome formation possibly via TFEB inactivation [275]	AD hiPSC-derived neurons [275,287,290] and cortical neurons [288,289]
	APP	Perturbation in autophagy (nature of the defect not clear) [272]	Defective autophagy due to impaired autophagosome maturation possibly via disruption in lysosomal function [288]	AD hiPSC-derived cortical neurons [288]
Tauopathies, including frontotemporal dementia (FTD)	Tau	Defective autophagy possibly due to impaired autophagosome maturation via disruption of axonal transport [298,299]	Defective autophagy possibly due to impaired autophagosome maturation [308]	FTD hiPSC-derived cortical neurons [308]
Parkinson's disease (PD)	α-synuclein	Defective autophagy (by α-synuclein gene multiplication) due to impaired autophagosome formation [320,321] via ATG9 mislocalization [320] and cytoplasmic retention of TFEB [321]; defective CMA (by α-synuclein point mutations A53T or A30P) due to blockage of substrate uptake [325]	Defective autophagy possibly due to impaired autophagosome formation [338]	PD hiPSC-derived dopaminergic neurons [338]
	PINK1, Parkin	Defective mitophagy due to impaired mitochondrial targeting to autophagosomes [316–319]	Not studied	Not studied
	LRRK2	Defective CMA due to disruption of the CMA translocation complex [327]; Defective autophagy possibly due to impaired autophagosome maturation [328]	Defective CMA [327,346]; Defective autophagy possibly due to impaired autophagosome maturation [342,346]	PD hiPSC-derived dopaminergic neurons [327,342] and astrocytes [346]
Amyotrophic lateral sclerosis (ALS)	SOD1	Defective autophagy possibly due to impaired autophagosome maturation [352–354]	Defective autophagy (nature of the defect not clear) [387]	ALS hiPSC-derived motor neurons [387]
	TDP-43	Defective autophagy due to impaired autophagosome maturation possibly via downregulation of dynactin 1 [356]; defective autophagy due to impaired autophagosome formation possibly via destabilization of ATG7 mRNA [355]	Not studied	Not studied
	FUS	Defective autophagy due to impaired autophagosome formation via impairment in omegasome formation and ATG9 recruitment [358]	Not studied	Not studied
	SQSTM1, Optineurin, Ubiquilin 2	Defective autophagy and mitophagy due to impaired cargo recruitment to autophagosomes	Not studied	Not studied

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Table 2 (*continued*)

Neurodegenerative disease	Mutant protein	Autophagy phenotype in non-hiPSC models	Autophagy phenotype in patient-derived hiPSC models	hiPSC-derived cell type where autophagy is studied
		[60,362–366], and disruption of myosin VI-mediated intracellular trafficking by optineurin [369]		
	TBK1	Defective mitophagy possibly due to impaired phosphorylation of optineurin [367,368]	Defective autophagy possibly due to impaired autophagosome formation [389]	ALS hiPSC-derived motor neurons [389]
	CHMP2B	Defective autophagy due to impaired autophagosome maturation via disruption of ESCRT machinery [370,371]	Not studied	Not studied
	C9orf72	Defective autophagy possibly due to impaired autophagosome formation via disruption of its interaction with ULK1 and SMCR8/WDR41 complexes [373–376]	Defective autophagy [373,390,391] possibly due to impaired autophagosome formation [373]	ALS/FTD hiPSC derived-neurons [391], motor neurons [390] and iNeurons [373]
Huntington's disease (HD)	Huntingtin	Defective autophagy due to impaired recognition and recruitment of autophagic cargo [401] and dysfunction in axonal transport of autophagosomes [402]	Perturbation in autophagy (nature of the defect not clear) [409,410]	HD hiPSC-derived neurons [409] and GABAergic medium spiny neurons [410]
Multiple system atrophy (MSA)	(Sporadic)	Defective autophagy (nature of the defect not clear) [416,419,420]	Defective autophagy possibly due to impaired autophagosome maturation [423]	MSA hiPSC-derived dopaminergic neurons [423]
Gaucher disease (GD)	GCase	Defective autophagy possibly due to impaired autophagosome maturation [426–428,432,433] likely via disruption in lysosomal function [427,432]	Defective autophagy due to impaired autophagosome maturation [438,441–443] likely via inefficient lysosomal function [441]	GD iPSC-derived neurons [441,443], dopaminergic neurons [438,442] and neuronal precursor cells [443]
	Saposin C	Defective autophagy possibly due to impaired autophagosome maturation [426,430] likely via inefficient cathepsin activity [430]	Not studied	Not studied
Niemann-Pick type C1 (NPC1) disease	NPC1	Defective autophagy due to impaired autophagosome maturation [449,450] via disruption in SNARE machinery [449], reduction in sphingosine kinase activity and VEGF levels [450]	Defective autophagy due to impaired autophagosome maturation [450,454,455]	NPC1 hiPSC-derived neurons [450,454,455] and hepatic cells [454]
Spinocerebellar ataxia 3 (SCA3)	Ataxin-3	Defective autophagy due to impaired autophagosome formation [459,461] via degradation of Beclin 1 [459], reduction in Sirtuin-1 [464]	Defective autophagy (nature of the defect not clear) [470]	SCA3 hiPSC-derived neurons [470]
Spinal bulbar muscular atrophy (SBMA)	Androgen receptor	Defective autophagy possibly due to impaired autophagosome maturation [474–476] via suppression of TFEB transactivation and downregulation of autophagy-related genes [474]	Defective autophagy possibly due to impaired autophagosome maturation [474] possibly via downregulation of TFEB target genes [474]	SBMA hiPSC-derived neuronal precursor cells [474]
Charcot-Marie-Tooth (CMT) disease 2A	Mitofusin 2	Defective mitophagy due to inefficient Parkin recruitment [491]	Increased autophagic flux (mechanism not known) [493]	CMT2A hiPSC-derived motor neurons [493]

Abbreviations – CHMP2B: charged multivesicular body protein 2B; CMA: chaperone-mediated autophagy; C9orf72: Chromosome 9 Open Reading Frame 72; ESCRT: Endosomal sorting complexes required for transport; FUS: Fused in sarcoma; GCase: Glucocerebrosidase;; hiPSC: Human induced pluripotent stem cells; mTOR1: Mechanistic target of rapamycin complex1; SMCR8: Smith-Magenis syndrome chromosome region, candidate 8; SNARE: Soluble N-ethylmaleimide-sensitive factor attachment protein receptor; SOD1: superoxide dismutase 1; SQSTM1: Sequestosome 1; TBK1: TANK-binding kinase 1; TDP-43: TAR DNA-binding protein 43; TFEB: Transcription factor EB; ULK1: Unc-51 like autophagy activating kinase 1; VEGF: Vascular endothelial growth factor; WDR41: WD repeat domain 41.

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Table 3. Therapeutic benefits with autophagy inducers in non-hiPSC *in vivo* models and in patient-derived hiPSC models of neurodegenerative disorders.

Neurodegenerative disease	Autophagy inducer	Mechanism of autophagy induction	Efficacy in non-hiPSC *in vivo* models	Efficacy in patient-derived hiPSC models
Alzheimer's disease (AD)	Rapamycin	Induces autophagy via mTORC1 inhibition [88]	AD mice [276,277,279,283,286]	Not tested
	Trehalose	Induces mTOR-independent autophagy [91] via AMPK activation [92]	AD mice [280,284]	Not tested
	Carbamazepine	Induces mTOR-independent autophagy via reduction in inositol and IP_3 [82]	AD mice [278,281]	Not tested
	Gypenoside XVII (GP-17)	Induces autophagy via promoting TFEB nuclear translocation [282]	AD mice [282]	Not tested
	Latrepirdine	Induces autophagy via inhibition of mTORC1 signaling [285]	AD mice [285]	Not tested
	Bexarotene	Induces autophagy [291]; mechanism not known	AD mice [496][a]	AD hiPSC-derived neural stem cells [291]
	OM99-2	Induce autophagy possibly via inhibition of β-secretase activity [288]	Not tested	AD hiPSC-derived cortical neurons [288]
Tauopathies, including frontotemporal dementia (FTD)	Rapamycin	Induces autophagy via mTORC1 inhibition [88]	Tauopathy mice [302–304], Tauopathy *Drosophila* [300], FTD mice [305]	Tauopathy hiPSC-derived cortical neurons [308]
	Trehalose	Induces mTOR-independent autophagy [91] via AMPK activation [92]	Tauopathy mice [306,307]	FTD hiPSC-derived neurons [310]
	Carbamazepine	Induces mTOR-independent autophagy via reduction in inositol and IP_3 [82]	FTD mice [305]	Not tested
Parkinson's disease (PD)	Rapamycin	Induces autophagy via mTORC1 inhibition [88]	PD mice [330–335]	PD hiPSC-derived dopaminergic neurons [341]
	Trehalose	Induces mTOR-independent autophagy [91] via AMPK activation [92]	PD mice [335]	PD hiPSC-derived dopaminergic neurons [341]
	6-Bio	Induces autophagy via inhibition of mTORC1 signaling [336]	PD mice [336]	Not tested
	Piperlongumine	Induces autophagy by Bcl-2 phosphorylation and Bcl-2–Beclin1 dissociation [337]	PD mice [337]	Not tested
	GSK621	Induces autophagy via AMPK activation [340]	Not tested	PD hiPSC-derived neurons [340]
	A769662	Induces autophagy via AMPK activation [340]	Not tested	PD hiPSC-derived neurons [340]
	CMA activator	Induces CMA via inhibition of RARα signaling [497]	Not tested	PD hiPSC-derived dopaminergic neurons and astrocytes [346]
Amyotrophic lateral sclerosis (ALS)	Rapamycin	Induces autophagy via mTORC1 inhibition [88]	(Accelerated disease phenotypes in ALS mice [384] and ALS/FTD *Drosophila* [356])	ALS hiPSC-derived motor neurons [387]
	Trehalose	Induces mTOR-independent autophagy [91] via AMPK activation [92]	ALS mice [379,380]	Not tested
	Bosutinib (SKI-606)	Possibly induces autophagy via Src/c-Abl inhibition [387]	Not tested	ALS hiPSC-derived motor neurons [387]
	Fluphenazine	Induces autophagy [195] possibly via mTORC1 inhibition [498]	Not tested	ALS/FTD hiPSC-derived motor neurons and astrocytes [195]
	Methotrimeprazine	Induces autophagy [195]; mechanism not known	Not tested	ALS/FTD hiPSC-derived motor neurons and astrocytes [195]
Huntington's disease (HD)	Rapamycin	Induces autophagy via mTORC1 inhibition [88]	HD *Drosophila* [88], HD zebrafish [83,85]	Not tested
	Temsirolimus (CCI-779)	Induces autophagy via mTORC1 inhibition; rapamycin ester analogue [88]	HD mice [88]	Not tested
	Trehalose	Induces mTOR-independent autophagy [91] via AMPK activation [92]	HD mice [403][a]	Not tested
	Rilmenidine	Induces mTOR-independent autophagy	HD mice [404]	Not tested

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Table 3 (*continued*)

Neurodegenerative disease	Autophagy inducer	Mechanism of autophagy induction	Efficacy in non-hiPSC *in vivo* models	Efficacy in patient-derived hiPSC models
		via reduction in cAMP [83]		
	Clonidine	Induces mTOR-independent autophagy via reduction in cAMP [83]	HD *Drosophila* [83], HD zebrafish [83]	
	Calpastatin	Induces mTOR-independent autophagy via calpain inhibition [83]	HD mice [405], HD zebrafish [83]	Not tested
	Felodipine	Induces mTOR-independent autophagy via reduction in cytosolic Ca^{2+} [94]	HD mice [94]	Not tested
	Verapamil	Induces mTOR-independent autophagy via reduction in cytosolic Ca^{2+} [83]	HD *Drosophila* [83], HD zebrafish [83]	Not tested
	Plerixafor (AMD3100)	Induces autophagy via reduction in ZBTB16 and increase in Atg14L [406]	HD mice [406]	Not tested
	SMER28	Induces mTOR-independent autophagy [95]; mechanism not known	HD *Drosophila* [95]	Not tested
	L-NAME	Induces mTOR-independent autophagy via NOS inhibition [85]	HD *Drosophila* [85], HD zebrafish [85]	Not tested
	Valproic acid	Induces mTOR-independent autophagy via reduction in inositol and IP_3 [82]	HD *Drosophila* [83]	Not tested
	AUTEN-67, AUTEN-99	Induces autophagy via MTMR14 inhibition [407,408]	HD *Drosophila* [407,408]	Not tested
	EVP4593	Possibly affects autophagy via inhibition of store-operated Ca^{2+} entry [410]	Not tested	HD hiPSC-derived neurons [410]
	AST487	Possibly induces autophagy via HIPK3 inhibition [412]	Not tested	HD hiPSC-derived neurons [412]
Gaucher disease (GD)	Rapamycin	Induces autophagy via mTORC1 inhibition [87]	GD *Drosophila* [432]	(Toxic in GD iPSC-derived neurons) [441]
	Torin 1	Induces autophagy via ATP-competitive inhibition of mTORC1 inhibition [90]	Not tested	GD iPSC-derived neurons [443]
Niemann-Pick type C1 (NPC1) disease	Rapamycin	Induces autophagy via mTORC1 inhibition [87]	Not tested	NPC1 hiPSC-derived neurons and hepatic cells [454]
	Carbamazepine	Induces mTOR-independent autophagy via reduction in inositol and IP_3 [82]	Not tested	NPC1 hiPSC-derived neurons and hepatic cells [454]
	Trehalose	Induces mTOR-independent autophagy [91] via AMPK activation [92]	Not tested	NPC1 hiPSC-derived neurons [454]
	Verapamil	Induces mTOR-independent autophagy via reduction in cytosolic Ca^{2+} [83]	Not tested	NPC1 hiPSC-derived neurons [454]
	BRD5631, BRD2716, BRD34009	Induces mTOR-independent autophagy; mechanism not known [456]	Not tested	NPC1 hiPSC-derived neurons [456]
	MβCD	Induces autophagy via mTORC1 inhibition and AMPK activation [455]	Not tested	NPC1 hiPSC-derived neurons [455]
Spinocerebellar ataxia 3 (SCA3)	Temsirolimus (CCI-779)	Induces autophagy via mTORC1 inhibition; rapamycin ester analogue [88]	SCA3 mice [466]	Not tested
	Calpeptin	Induces mTOR-independent autophagy via calpain inhibition [83]	SCA3 zebrafish [467]	Not tested
	Lithium chloride	Induces mTOR-independent autophagy via inhibition of IMPase and reduction in inositol and IP_3 [82]	SCA3 *Drosophila* [468]	Not tested
	Sodium valproate	Induces mTOR-independent autophagy via reduction in inositol and IP_3 [82]	SCA3 *Drosophila* [469]	Not tested

Abbreviations – AMPK: 5′ adenosine monophosphate-activated protein kinase; Atg: Autophagy-related; ATP: Adenosine triphosphate; Bcl-2: B-cell lymphoma 2; Ca^{2+}: Calcium; cAMP: 3′, 5’ -cyclic adenosine monophosphate; CMA: Chaperone-mediated autophagy; IP3: Inositol 1,4,5-triphosphahe; HIPK3: Homeodomain interacting protein kinase 3; hiPSC: Human induced pluripotent stem cells; MTMR14: Myotubularin-related protein 14; mTORC1: Mechanistic target of rapamycin complex1; NOS: Nitric oxide synthase; RARα: Retinoic acid receptor α; SMER: Small molecule enhancer of rapamycin; TFEB: Transcription factor EB; ZBTB16: Zinc finger and BTB domain-containing protein 16.

[a] These studies do not show the autophagy-inducing properties of the compounds for the therapeutic effects *in vivo*.

sphingomyelinase (ASM) in hiPSC-derived FAD-PS1 neurons has also been shown to block autophagic flux possibly via lysosomal depletion [290].

However, studies in hiPSC-derived neurons from AD patients carrying PS1(M146L) mutation or hiPSC-derived neurons with PS1 depletion [275], and in hiPSC-derived neural stem cells (NSCs) with

PS1(M146L) knock-in [291] or *PSEN1* gene knockout [292], have reported reduction in autophagosomes and LC3-II levels [275,291,292], low TFEB expression [291,292], and attenuation in CLEAR gene network activity [275]. These data indicate a possible suppression of autophagy at an early stage due to impaired autophagosome formation. This apparent discrepancy in the nature of autophagic defect could be due to the fact that loss of PS1 in hiPSC-derived neurons might be perturbing autophagy via different mechanisms. For example, PS1/2 deficiency has been suggested to lower nuclear Ca^{2+} and CaMKIV/pCREB signaling, resulting in the reduction of sestrin2 (a stress-inducible protein) that led to excessive lysosomal tethering of mTORC1, and consequently, dysregulation of mTORC1 activity and dynamics. This caused hyperphosphorylation and inactivation of TFEB and subsequent suppression of the CLEAR gene network activity, thereby decreasing LC3 expression [275]. An additional factor could be high levels of the amino acid, homocysteine, which is associated with an increased risk of developing AD [293]. Treatment of hiPSC-derived neurons with homocysteine increased mTORC1 activity and suppressed TFEB-mediated CLEAR gene network activity, thereby preventing autophagosome formation and reducing autophagic flux that caused accumulation of Aβ and phosphorylated tau filaments [294].

Defective autophagy is likely to retard mitophagy, which has been demonstrated in hiPSC-derived PS1(A246E) neurons [287] and PS1(M146L) NSCs [291]. Of biomedical relevance, induction of autophagy promoted Aβ clearance and improved neuronal viability in hiPSC-derived neurons, such as with rapamycin and Tat-Beclin 1 treatment in hyperhomocysteinemic conditions [294]. Bexarotene could also stimulate autophagic flux and rescue the autophagy and mitophagy defects in hiPSC-derived PS1(M146L) NSCs [291]. Interestingly, inhibition of β-secretase activity with OM99-2 corrected the autophagic defects by promoting the degradative capability of autophagy and reduced Aβ levels in multiple hiPSC-derived neurons from AD patients with the various APP or PS1 mutations [288].

Overall, a wide range of *PSEN1* mutations has shown a blockage in autophagic flux due to impaired autophagosome maturation in hiPSC-derived neurons, consistent with the results seen in other cellular and animal models. This autophagic defect is likely due to impairment in lysosomal function. On the contrary, complete loss of PS1/2 or the PS1(M146L) mutation caused inhibition of autophagosome formation in hiPSC-derived neurons, and this might be due to specific effects on the protein function. Further studies are required to assess whether autophagy inducers would have a positive impact on neuronal viability in multiple AD hiPSC models since autophagy induction had beneficial effects in cellular and animal models of AD.

Tauopathies, including frontotemporal dementia

Another key hallmark of AD is the formation of intracellular neurofibrillary tangles made of hyperphosphorylated microtubule-associated tau protein, which is encoded by the *MAPT* gene. Accumulation of mutant tau is characteristic of tauopathies, including frontotemporal dementia (FTD) [295]. FTD affects the frontal and temporal lobes of the brain and is also associated with the accumulation of TAR DNA-binding protein 43 (TDP-43) [296]. In addition, mutations in *GRN* encoding for progranulin cause FTD, while complete loss of this gene causes a lysosomal storage disorder (LSD) called neuronal ceroid lipofuscinosis (NCL) [297]. Mutant tau, which contributes to neuronal cell death, is thought to impair autophagosome maturation. Studies in FTD *Drosophila* and mouse models have shown that mutant tau deregulated the retrograde axonal transport on the microtubule and prevented the fusion of autophagosomes with lysosomes [298,299]. On the other hand, mutant tau could undergo autophagic degradation [300,301]. The pharmacological induction of autophagy was shown to rescue the disease pathogenesis in tauopathy and FTD mouse models. Therapeutic benefits, including a reduction in tau tangles, have been demonstrated with rapamycin in mutant tau mice [302–304], mutant TDP-43 mice [305], and mutant tau *Drosophila* model [300], with carbamazepine in mutant TDP-43 mice [305], and with trehalose in mutant tau mice [306,307].

Autophagy has been studied in tauopathy hiPSC lines, such as 19-L3-RC3, 19-L5-RC6, and Tau6-1-RC2, which were generated from patients carrying the $tau^{(A152T)}$ mutation that increases the risk of FTD [308]. Tau levels, as well as phosphorylation at AT8 and AT108, were increased in $tau^{(A152T)}$ hiPSC-derived cortical neurons compared to the control neurons, and their distribution was predominantly somatodendritic; consistent with what was seen in tauopathies and AD. The autophagy (LC3-II, ATG12-ATG5) and lysosomal (LAMP1, LAMP2a) markers were upregulated in $tau^{(A152T)}$ neurons [308], suggesting a possible induction of autophagy. However, the autophagy substrate p62, as well as polyubiquitinated proteins, were also accumulated in these neurons [308], indicating that autophagic flux might be retarded, and this could be due to impaired autophagosome maturation causing an increase in autophagosomes (LC3-II). Nonetheless, induction of autophagy with rapamycin in $tau^{(A152T)}$ neurons reduced the cellular load of mutant tau and improved cell viability in the presence of external stressors like mitochondrial toxins, proteasome inhibitors, and $A\beta_{42}$; effects that were also seen with CRISPR/

Cas9-mediated tau gene disruption for reducing the mutant protein level [308]. Another hiPSC tauopathy model has been developed by transducing tau$^{(P310L)}$ mutation into neural progenitor (NP) cells that were differentiated from hiPSCs derived from healthy donors [309]. Since spontaneous tau aggregation was not observed in NP-derived cortical neurons expressing tau$^{(P310L)}$, this phenotype was enforced by seeding the cells with mutant tau preformed fibrils (K18). Consistent with other studies, autophagy inducers, such as rapamycin and trehalose, reduced the levels of tau aggregates and the phosphorylation at the AT8 site that promotes their aggregation [309]. Trehalose also increased autophagosome formation and progranulin expression in hiPSC-derived neurons carrying *GRN* mutations causative of progranulin haploinsufficiency [310].

Although the studies in hiPSC tauopathy models do not clearly define the status of autophagic flux for which further analysis is required, it might be possible that this is affected due to impaired autophagosome maturation, as reported in non-hiPSC models. Importantly, autophagy inducers rescued the disease phenotypes in both mouse and hiPSC-derived neuronal models, suggesting that autophagy induction could be beneficial in tauopathies.

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system, characterized by cognitive deterioration and motor deficits. The hallmark of PD is the presence of intracellular inclusions of abnormal protein aggregates called Lewy bodies [311]. PD is a multigenic disorder, in which, the genes that are commonly mutated encode for Parkin, PINK1 (PTEN induced putative kinase 1), α-synuclein, and LRRK2 (leucine-rich repeat kinase 2). These and other PD-associated mutant proteins have been shown to cause dysfunction of autophagy and mitophagy [312–314]. Extensive studies have elucidated the role of wild-type PINK1 and Parkin in regulating mitophagy for the maintenance of mitochondrial quality control. Selective mitophagy of damaged mitochondria is initiated by PINK1 stabilization on the outer mitochondrial membrane (OMM), where it phosphorylates and activates the E3 ubiquitin ligase Parkin, which ubiquitinates OMM proteins for enabling mitochondrial targeting to the autophagy pathway [313,315]. This process was disrupted by the PD-associated mutations in PINK1 and Parkin that lead to mitochondrial dysfunction, mitochondrial DNA mutations, and oxidative stress [316–319]. On the other hand, the overall autophagy process was impaired by mutant α-synuclein in multiple ways. Accumulation of α-synuclein, such as occurring during its gene multiplication, has been shown to suppress autophagosome biogenesis via ATG9 mislocalization [320] and cytoplasmic retention of TFEB [321]. However, the Lewy bodies comprising of α-synuclein inclusions retarded autophagosome maturation without causing lysosomal malfunction [322]. Other PD-associated mutant proteins, such as VPS35, ATP13A2, and STY11, have also been reported to impair autophagy [323,324]. Furthermore, α-synuclein$^{(A53T)}$ and α-synuclein$^{(A30P)}$ point mutants could prevent chaperone-mediated autophagy (CMA), a process distinct from macroautophagy involving protein translocation across the lysosomal membrane [325,326]. In addition, LRRK2 mutants, including LRRK2$^{(G2019S)}$ also impaired CMA that could compromise the clearance of mutant α-synuclein [327], as well as possibly impaired autophagosome maturation [328]. While autophagic dysfunction occurs in PD via multiple mechanisms, pharmacological induction of autophagy could facilitate mutant α-synuclein clearance [329] *in vitro* and *in vivo,* and exert beneficial effects in animal models of PD. Stimulating autophagy with rapamycin, either alone [330–334] or in combination with trehalose [335], as well as with other autophagy-inducing compounds like 6-Bio [336] and piperlongumine [337], demonstrated neuroprotective effects and improved motor functions in toxin-induced or α-synuclein transgenic mouse models of PD.

Multiple hiPSC lines from PD patients carrying different gene mutations have been utilized to study autophagy. Dopaminergic neurons generated from PD hiPSCs with α-synuclein mutations, such as *SNCA*$^{(A53T)}$ or *SNCA*$^{(triplication)}$, exhibited a reduction in LC3-II levels that were associated with an elevation in p62 levels in some of the lines; suggesting a possible impairment in autophagosome formation, as seen in cell models [338]. These mutant α-synuclein neurons also showed dysfunction in mitochondrial bioenergetics and lipid homeostasis [338]. Furthermore, in the *PARK10* susceptibility locus associated with late-onset PD, a gene encoding for USP24 (ubiquitin specific peptidase 24) that was elevated in the brain of idiopathic PD patients has been suggested to suppress autophagy, since knockdown of *USP24* induced autophagic flux in hiPSC-derived dopaminergic neurons [339]. However, consistent with α-synuclein inclusions preventing autophagosome maturation in cell models, the treatment of hiPSC-derived neurons with exogenous α-synuclein preformed fibrils, but not monomeric α-synuclein, caused time-dependent accumulation of α-synuclein inclusions, autophagosomes, and p62 [340]. Induction of autophagy with AMPK activators, such as GSK621 and A769662, restored the autophagic flux and enhanced the clearance of α-synuclein inclusions [340]. Additionally, in hiPSC-derived dopaminergic neurons, where mitochondria were compromised by rotenone treatment, inducing

autophagy with rapamycin and trehalose rescued mitochondrial neurotoxicity and dysfunction [341].

Defects in CMA have been reported in hiPSC-derived dopaminergic neurons of PD patients with *LRRK2*$^{(G2019S)}$, where abnormal accumulation of α-synuclein probably occurred due to its impaired CMA clearance [327]; consistent with the findings from noniPSC experimental systems. Additionally, dopaminergic neurons generated from multiple hiPSC lines with familial PD with *LRRK2*$^{(G2019S)}$ mutation or idiopathic PD, also exhibiting elevated α-synuclein levels, showed impairment in autophagic flux due to defective autophagosome maturation, as evident from accumulation of LC3-II and p62, and reduction in the colocalization between autophagosomes and lysosomes, as well as increased mitochondrial fragmentation [342–344]. A similar autophagic block was found in PD hiPSC-derived dopaminergic neurons with *LRRK2*$^{(I2020T)}$ mutation [345]. In *LRRK2*$^{(G2019S)}$ neurons, mutant LRRK2-mediated phosphorylation of leucyl-tRNA synthetase was suggested to impair autophagy [328], whereas the increased activity of RAC1 (Rac family small GTPase 1) was shown to rescue the autophagy defects, α-synuclein accumulation, and cell death [343]. Similar to the neuronal phenotypes, PD hiPSC-derived astrocytes with *LRRK2*$^{(G2019S)}$ mutation exhibited impaired CMA, autophagic block, and accumulation of α-synuclein [346]. Interestingly, a contribution of the astrocytes to noncell-autonomous neurodegeneration in PD has also been suggested. *LRRK2*$^{(G2019S)}$ mutant astrocytes promoted neurodegenerative features like shortened neurites, α-synuclein accumulation, and decreased viability in control iPSC-derived dopaminergic neurons during coculture; and conversely, control astrocytes partially rescued these phenotypes when cocultured with *LRRK2*$^{(G2019S)}$ mutant neurons [346]. Tagging the endogenous α-synuclein with a FLAG peptide in control astrocytes resulted in the accumulation of FLAG-tagged α-synuclein in mutant dopaminergic neurons during the coculture, suggesting a direct transfer of astrocytic α-synuclein to the neurons [346]. Enhancing the lysosomal activity with a CMA activator (CA) decreased α-synuclein levels in *LRRK2*$^{(G2019S)}$ astrocytes, and also partially prevented the neurodegenerative features in control dopaminergic neurons during coculture [346].

PD is a multigenic disorder, and thus, the nature of the autophagy defects and the underlying mechanisms vary depending on the gene mutations. Chemical induction of autophagy has been shown to be beneficial in cellular and animal models of PD, but the cytoprotective effects of autophagy inducers in hiPSC-derived dopaminergic neurons from PD patients remain to be thoroughly investigated.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder, primarily sporadic but also familial, in which the motor neurons, located in the motor cortex, brainstem, and spinal cord, are affected that lead to muscle weakness and progressive loss of voluntary muscle movement [347]. Certain clinical symptoms, disease phenotypes, and genetic causes are overlapping between ALS and FTD [348]. Several genes associated with ALS cause autophagy dysfunction or encode for misfolded proteins that can undergo autophagic degradation [349]. Mutations in genes encoding for SOD1 (superoxide dismutase 1), TDP-43 (TAR DNA-binding protein 43), and FUS (fused in sarcoma) lead to accumulation of misfolded proteins that can be degraded by autophagy, although these mutant proteins could dysregulate this process [349,350]. Mutant SOD1$^{(G93A)}$ has been suggested to suppress autophagy and mitophagy via a reduction in TFEB, Beclin 1, or lysosomes [351,352], and possibly cause an autophagic block in transgenic mice, as evident from the accumulation of autophagosomes and autophagy substrates [352–354]. Mutation or loss of TDP-43 has also been shown to impair autophagy via its inability to bind and stabilize ATG7 mRNA and prevent autophagosome maturation via downregulation of dynactin 1 [355,356]. However, mutant FUS, which accumulates in stress granules to be degraded via autophagy [357], prevented autophagosome biogenesis, possibly due to impairment in omegasome formation and recruitment of ATG9 to the growing autophagosomes [358]. Other ALS-associated genes include *SQSTM1* [359], *OPTN* [360], and *UBQLN2* [361] that encode for the autophagy receptors p62, optineurin, and ubiquilin 2, respectively. Disease-causing mutations in these autophagy receptors decreased autophagic flux and mitophagy via impairment in cargo recruitment to the autophagosomes, thereby preventing the clearance of SOD1, TDP-43, and damaged mitochondria [60,362–366]. ALS-associated mutations in TBK1 (TANK-binding kinase 1), which normally phosphorylates optineurin to promote mitophagy, also caused inefficient mitochondrial clearance [367,368]. Additionally, ALS-linked mutations in optineurin disrupted myosin VI-mediated autophagosome maturation, causing a block in autophagic flux [369]. Defective autophagosome maturation also resulted from ALS-associated mutations in CHMP2B (charged multivesicular body protein 2B) via disruption of the ESCRT (endosomal sorting complexes required for transport) machinery [370,371], which plays a role in the late stages of autophagy, as well as in autophagosome closure

[372]. One of the most common causes of ALS is the hexanucleotide repeat expansion in a noncoding region of *C9orf72* (Chromosome 9 Open Reading Frame 72) gene, which has been shown to regulate autophagy. A role of C9orf72 in autophagosome formation and maturation has been implicated via its interaction with ULK1 and Rab1a [373,374], and also via its GEF (guanine nucleotide exchange factor) effector activity for Rab GTPases through a complex formation with SMCR8 (Smith-Magenis syndrome chromosome region, candidate 8) and WDR41 (WD repeat domain 41) [375,376]. Accordingly, depletion or loss of C9orf72 inhibited autophagy and decreased autophagic flux in mammalian cell lines, primary mouse and rat neurons, and *in vivo* in knockout mice [373–376], as evident from reduction in autophagosomes and accumulation of autophagy substrates; whereas a contrary study suggested enhanced autophagic flux in *C9orf72* knockout mice [377]. However, an autophagic block was apparent in C9ALS/FTD patient-derived fibroblasts with *C9orf72* hexanucleotide repeat expansions due to the accumulation of both LC3-II and p62 [378].

The pharmacological induction of autophagy showed conflicting outcomes in ALS mice. While trehalose and lithium ameliorated the disease phenotypes in *SOD1*$^{(G93A)}$ transgenic mice [379–381], other studies in these mice showed no therapeutic benefits with lithium [382,383], and even acceleration of the disease progression by rapamycin and rilmenidine in *SOD1*$^{(G93A)}$ mouse and TDP-43-depleted *Drosophila* models [356,384,385]. However, autophagy activation in cell models with rapamycin [357], rilmenidine [385], fluphenazine [195], methotrimeprazine [195], and berberine (a natural herb) [386] was neuroprotective by enhancing the clearance of misfolded TDP-43 and SOD1, and FUS-positive stress granules.

Several studies utilizing ALS patient-derived hiPSC models carrying various ALS-linked gene mutations have demonstrated autophagy defects. Reduction in autophagic flux was shown in *SOD1*-$^{(L144FVX)}$ hiPSC-derived motor neurons where induction of autophagy with rapamycin or the Src/c-Abl inhibitor, bosutinib, reduced misfolded SOD1 levels and improved cell viability [387]. Similarly, induction of autophagy by methotrimeprazine and fluphenazine was attributed to their neuroprotective effects in motor neurons and astrocytes derived from ALS hiPSCs carrying a pathogenic TARDBP$^{(M337V)}$ mutation encoding for mutant TDP-43 [195]. Likewise, mTOR inhibitors like rapamycin and torkinib, as well as certain other antipsychotic and antidepressant drugs known to induce autophagy, reduced FUS-associated stress granules in genome-edited hiPSCs, and hiPSC-derived neurons expressing EGFP-tagged FUS$^{(P525L)}$, where rapamycin also improved neuronal survival [388]. Autophagic flux was also retarded, possibly due to inhibition of autophagosome formation, in motor neurons generated from various ALS hiPSC lines carrying different heterozygous *TBK1* mutations, where an accumulation of cytosolic p62 aggregates was found [389]. Likewise, cortical and motor neurons generated from multiple ALS hiPSC lines with *C9orf72* hexanucleotide repeat expansions exhibited a reduction in autophagic flux, resulting in accumulation of LC3-II, p62, and stress granules [390,391]. Autophagosome formation was markedly suppressed in C9ALS/FTD patient-derived induced neurons (iNeurons) with *C9orf72* expansion mutation [373]; consistent with the autophagy phenotype in *C9orf72* depletion cellular models. Furthermore, elevated levels of the insoluble fraction of optineurin were found in motor neurons derived from ALS hiPSCs with *SOD1*, *TDP-43,* or C9orf72 mutations [392]. Like in PD, astrocytes have been suggested contributing to noncell-autonomous neurodegeneration in ALS [393,394]. Conditioned medium from hiPSC-derived astrocytes with *C9orf72* repeat expansions was toxic, specifically on hiPSC-derived motor neurons, and also impaired autophagic flux in mammalian cells that could be rescued by rapamycin [395].

Multiple genes associated with ALS encode mutant proteins that differentially affect autophagy. Some of the autophagic defects have been characterized in ALS patient hiPSC-derived motor neurons. However, it is not entirely clear whether autophagy induction would be beneficial in ALS. Although certain autophagy inducers were cytoprotective in cell and hiPSC models, some others had deleterious effects *in vivo* in transgenic models. Further studies are warranted using mTOR-independent autophagy inducers, which are considered relatively safer for inducing autophagy compared to using mTOR inhibitors.

Huntington's disease

Huntington's disease (HD) is an autosomal-dominant, monogenic neurodegenerative disorder characterized by motor, cognitive, and psychiatric impairments. HD is caused by the excessive expansion of the CAG trinucleotide repeat in the *HTT* gene, encoding for the protein huntingtin, in which, the addition of the N-terminal polyglutamine repeats makes the protein aggregation-prone and cytotoxic [396]. Mutant huntingtin is an established autophagy substrate [397,398], and its autophagic clearance could be conformation-dependent [397], while its wild-type counterpart acts as a scaffold for recruiting autophagic proteins during aggrephagy and mitophagy [399,400]. Autophagy is impaired in HD, characterized by an accumulation of autophagosomes, which is considered primarily due to failure in the recognition and recruitment of autophagic cargo [401], as well as defective axonal transport of the autophagosomes [402]. Of

biomedical relevance, induction of autophagy is a promising treatment strategy in HD, as evident from the extensive studies in transgenic *in vivo* models, where chemical autophagy inducers ameliorated the disease phenotypes. These include rapamycin [88], trehalose [403], rilmenidine [404], calpastatin [405], AMD3100 (G-protein-coupled receptor antagonist) [406], and felodipine [94] in HD mice; and SMER28 [95], verapamil [83], valproic acid [83], L-NAME [85], AUTEN-67 [407], and AUTEN-99 [408] in HD *Drosophila* models, amongst others.

Perturbations in autophagy have been observed in a few HD patient-derived hiPSC models. The *HTT* mutation did not affect the reprogramming or neuronal differentiation, and the CAG repeat numbers were stable during these processes [409]. Accumulation of autophagosomes and lysosomes were found in neurons differentiated from HD hiPSC lines, namely HD-iPS^{hom} 4F-1 (42/44 CAG repeats), HD-iPS^{het} 3F-1 (17/45 CAG repeats) [409], and iPSHD22 (47/16 CAG repeats) [410], as well as increased cytoplasmic vacuolation in astrocytes generated from HD iPSC line, D-HD-iPSC (109 CAG repeats) [411]. In addition, increased Ca^{2+} entry via store-operated channels (SOC) was seen in HD iPSC (iPSHD22)-derived neurons, an effect consistent with Ca^{2+} excitotoxicity in HD animal models, where EVP4593 (SOC Ca^{2+} channel inhibitor) improved Ca^{2+} homeostasis that was associated with a reduction in autophagosomes [410]. Moreover, since mutant huntingtin is an autophagy substrate, its autophagic degradation might be regulated by kinases, such as HIPK3 (homeodomain interacting protein kinase 3) [412], which inhibits autophagy via DAXX [413]. Knockdown of *HIPK3* increased autophagic flux and lowered mutant huntingtin load in HD iPSC (iPSC-HDQ47)-derived neurons, and this reduction of mutant huntingtin levels was also achieved with the HIPK3 inhibitor, AST487 [412].

The autophagy defect and the therapeutic benefits of autophagy inducers have been robustly demonstrated in mammalian cell and animal models of HD [7,81,88,108,401]. However, the hiPSC-related studies did not portray a clear picture of the nature of the autophagy dysfunction due to a lack of rigorous analysis, although the accumulation of autophagosomes was a common feature. Extensive analysis of autophagic flux and the therapeutic evaluation of established autophagy inducers would be important next steps to undertake in HD hiPSC-derived neurons to aid clinical translation.

Multiple system atrophy

Multiple system atrophy (MSA) is a sporadic adult-onset neurodegenerative disorder characterized by autonomic dysfunction, parkinsonism, and ataxia. The hallmark of MSA is the presence of glial cytoplasmic inclusions (GCIs), primarily made of α-synuclein, in oligodendrocytes, and thus, MSA falls under the spectrum of synucleinopathies [414,415]. As in other neurodegenerative disorders, the autophagy pathway is affected in MSA. Neuropathological studies in MSA patient brain samples have shown elevation in LC3-II, autophagy receptors (p62 and NBR1), and AMBRA1 (mediator of autophagy initiation) that colocalized with the GCIs [416–419]. Transgenic mice with oligodendrocyte-specific expression of human α-synuclein (hαSYN) under proteolipid protein (PLP) gene promoter (PLP-hαSYN mice), which exhibits MSA-like GCIs, also revealed accumulation of LC3-II [420]. However, the levels of GABARAPs were reduced in the cerebellum of MSA patient brains, where they did not localize to the GCIs [419]. Moreover, TFEB was decreased in MSA patient brains, whereas oligodendroglial overexpression of TFEB, but not neuronal, exerted neuroprotective effects, and enhanced autophagic flux in PLP-hαSYN mouse model [421]. Furthermore, impaired mitophagy and mitochondrial function have been reported in MSA patient fibroblasts [422]. Although the precise nature of the autophagy defect is unclear, it is possible that the dysfunction of autophagy could cause oligodendroglial accumulation of α-synuclein that might contribute to the formation of GCIs and neurodegeneration in MSA.

A study in MSA patient-derived hiPSC models reported impairment in autophagy and mitochondrial function in hiPSC-derived dopaminergic neurons [423]. In these MSA neurons, the levels of LC3-II, p62, and mitochondrial load were increased, indicative of a block in autophagic flux possibly at the late stage of autophagy, while the activities of the mitochondrial respiratory chain complexes were decreased [423]. Further studies are needed to understand how autophagy is affected in MSA and the mechanism underlying this defect, and importantly, whether pharmacological inducers of autophagy would be beneficial.

Gaucher disease

Gaucher disease (GD) is an autosomal recessive disease that manifests neurological, splenic, and hepatic dysfunctions. It is one of the most prevalent lysosomal storage disorder (LSD) caused by mutations in the *GBA1* gene, encoding for glucocerebrosidase (GCase), and in rare cases by mutations in the *PSAP* gene, leading to a deficiency of the GCase activator, saposin C [424,425]. The GCase enzyme normally hydrolyzes glucosylceramide, and the lysosomal accumulation of glucosylceramide and glucosylsphingosine in GD is suggested to deregulate the later stages of the autophagic process. Consistent with the features of a block in autophagic flux, accumulation of autophagosomes and

autophagy substrates accompanied by dysfunctional cathepsin activity, impaired mitophagy, and mitochondrial function have been reported in patient fibroblasts, and in *Drosophila* and mouse models of GD with GCase or saposin C deficiency [425–434]. Interestingly, GD patients carrying GBA1 mutations are prone to neurodegeneration with a higher risk of acquiring Parkinson's disease (PD) [429,435] because defective autophagy underlying GCase deficiency could accumulate α-synuclein, while upregulation of α-synuclein in idiopathic PD might disrupt GCase activity [436–439]. This pathogenic link could be rescued by enhancing autophagy with rapamycin or C2-ceramide that suppressed mutant GBA-induced α-synuclein accumulation in cell models [437,440]. Moreover, the induction of autophagy with rapamycin enhanced autophagosome formation in saposin C-deficient patient fibroblasts [430], as well as rescued the disease phenotypes and extended the life span in a dGBA1-deficient *Drosophila* model of GD [432].

Multiple studies have utilized GD patient-derived hiPSC models to gain insights into the disease mechanisms, including autophagy. In neurons differentiated from several GD iPSC lines with GBA1 mutations, defective autophagic flux due to impaired autophagosome maturation and lysosomal dysfunction was evident from the accumulation of autophagosomes and autophagy substrates, such as p62, reduced autophagosome–lysosome fusion and inefficient activity of lysosomal enzymes like cathepsins [438,441–443]. Increased mTORC1 activity, downregulation of TFEB, and depletion of lysosomes were reported in neuropathic GD iPSC-derived neurons and neuronal precursor cells (NPCs) where the reduction in lysosomal compartments could contribute to ineffective autophagosome clearance [441,443]. In these GD neurons, treatment with recombinant GCase rescued the lysosomal and autophagic defects, effects that were augmented when coupled with TFEB overexpression [441]. Additionally, pharmacological inhibition of glucosylceramide synthase with the compound GZ-161, which prevents the production of glucosylceramide, rescued mTORC1 hyperactivation in GD NPCs, thereby suggesting a possible role of lipid substrate accumulation in influencing mTORC1 activity [443]. In contrast, other studies found increase in the number and size of lysosomes in dopaminergic neurons generated from GD or PD patients with GBA1 mutations [438,442]. These GBA1 mutant dopaminergic neurons exhibited a reduction in GCase activity, as well as the accumulation of glucosylceramide and α-synuclein, thus highlighting the pathogenic link between GD and PD [436,438,442]. Multiple cellular phenotypes were shown in these mutant cells, including abnormal lipid profiles, ER stress [442], increased neuronal calcium-binding protein 2 (NECAB2), elevated cytosolic Ca^{2+}, and dysfunctional Ca^{2+} homeostasis [438] that could also affect autophagic flux [83,84,444]. In addition, accumulation of α-synuclein could also impair lysosomal function by disrupting the trafficking and activity of the hydrolase, as demonstrated in GD and PD iPSC-derived neurons, where overexpression of Rab1a rescued these cellular phenotypes [445].

Surprisingly, the induction of autophagy via mTOR inhibition with rapamycin was found to be toxic in GD iPSC-derived neurons [441]; however, Torin1 was shown to induce TFEB nuclear translocation and improve autophagic clearance [443]. More studies are required to extensively evaluate the therapeutic potential of mTOR-dependent and mTOR-independent autophagy inducers in order to understand whether enhancing autophagy is beneficial in GD. Nonetheless, a block in autophagic flux has been a consistent feature in animal and iPSC models of GD.

Niemann-Pick type C disease

Niemann-Pick type C (NPC) disease is a rare, autosomal recessive LSD characterized by neurodegeneration and hepatosplenomegaly, and is associated with mutations predominantly in the *NPC1* gene (~95%) causing NPC1 disease or in the *NPC2* gene (~5%) causing NPC2 disease [446]. These genes encode NPC1 and NPC2 proteins, which respectively are lysosomal cholesterol transporter and lysosomal glycoprotein that play a role in the transport of cholesterol from late endosomes and lysosomes. Mutations in these genes lead to abnormal accumulation of unesterified cholesterol and other lipids like sphingolipids in the brain, liver, and spleen [447,448]. As in other LSDs [104], autophagic flux is retarded due to defective autophagosome maturation, as shown in mutant mouse and human cellular models of NPC1 and NPC2 disease, which are also associated with defective mitophagy and mitochondrial function [449–452]. Multiple mechanisms shown for dysregulated autophagy in NPC1 disease include disruption of SNARE complex formation between autophagosomes and late endosomal/lysosomal compartments involving Syntaxin-17 and VAMP8 to prevent autophagosome maturation [449], accumulation of sphingosine arising from diminished activity of sphingosine kinase and decreased levels of vascular endothelial growth factor (VEGF) to prevent autophagosome–lysosome fusion [450], and reduction in lysosomal Ca^{2+} stores [453]. Despite a block in the multistep route of autophagosome maturation, autophagy inducers improved autophagic flux in *Npc1* mutant mouse cells by facilitating direct autophagosome–lysosome fusion (bypass mechanism), which consequently also increased cell survival but did not reduce the cholesterol load [449].

As in nonhiPSC models, defective autophagic flux due to impaired autophagosome maturation, characterized by accumulation of autophagosomes and autophagy substrates like p62, was found in neurons and hepatic cells differentiated from multiple NPC1 hiPSC lines that also exhibited elevation in cholesterol [450,454,455]. Genetic correction of a disease-causing *NPC1*$^{(I1061T)}$ mutation rescued the cellular phenotypes of defective autophagy and cholesterol accumulation in these NPC1 hiPSC-derived cells [454]. Autophagic block associated with impaired mitophagy and mitochondrial fragmentation was also found in neurons derived from hESCs with shRNA-mediated NPC1 knockdown [452]. Of therapeutic relevance, stimulating autophagy with rapamycin and various mTOR-independent autophagy inducers, such as carbamazepine, trehalose, verapamil, and BRD5631, restored autophagic flux and improved cell viability in NPC1 hiPSC-derived neurons; however, only rapamycin and carbamazepine were effective in NPC1 hiPSC-derived hepatic cells [454,456]. The autophagy inducers were cytoprotective on their own without co-treatment of any cholesterol-lowering agents. In addition, recombinant VEGF treatment imparted similar beneficial effects in NPC1 neurons [450]. Interestingly, while the cholesterol-lowering agent, 2-hydroxypropyl-β-cyclodextrin (HPβCD), further augmented the autophagic block that could be detrimental [449,454,457], the HPβCD analogue called methyl-β-cyclodextrin (MβCD) improved the defective autophagic flux in NPC1 hiPSC-derived neurons [455].

In a nutshell, a block in autophagic flux due to impaired autophagosome maturation is a consistent phenotype across various NPC1 disease models, including iPSC-derived neurons where autophagy inducers rescued the autophagy defect and improved neuronal survival. However, further studies in *Npc1* mutant mice are necessary to examine the *in vivo* efficacy of autophagy induction and a combination treatment strategy with cholesterol depletion.

Spinocerebellar ataxias

Spinocerebellar ataxias (SCAs) are a group of genetic, progressive neurodegenerative diseases associated with loss of coordination of gait and muscle movements. Impairment in autophagy has been reported in some of the SCAs associated with polyglutamine (CAG)-expanded aggregation-prone proteins. These include SCA3 (Machado–Joseph disease) and SCA7 that are caused by the expansion of the polyglutamine tract in ataxin-3 and ataxin-7, respectively, and thus, are also known as polyglutamine or trinucleotide repeat disorders [396,458]. The polyglutamine domain of the wild-type ataxin-3 was found to interact with the pro-autophagic protein Beclin 1, whereby the deubiquitinase activity of ataxin-3 prevented the proteasomal degradation of Beclin 1 to facilitate autophagy; an effect that was suppressed by polyglutamine-expanded mutant ataxin-3 or huntingtin [459]. Indeed, decreased levels of Beclin 1 were found in SCA3 transgenic mice and patient fibroblasts [459–461], whereas overexpression of Beclin 1 improved autophagic flux and exerted neuroprotective effects in SCA3 rat neuronal cultures [460]. In addition, the reduction in sirtuin-1, which deacetylates autophagy proteins to induce autophagy [462,463], was seen in the SCA3 mouse model [464]. These effects were associated with inhibition of autophagosome formation in SCA3 [459,461]. Likewise, the levels of autophagy-associated proteins, Beclin 1, Atg7, Atg12, and Atg16, were reduced in the brain of the SCA7 mouse model [465]. Similar to the protective effects of autophagy activation in other polyglutamine disorders like HD via enhancing the clearance of aggregation-prone proteins, autophagy inducers were also beneficial in multiple *in vivo* SCA3 models. These include CCI-779 (temsirolimus) in SCA3 mice [466], calpeptin (calpain inhibitor) in SCA3 zebrafish [467], and lithium chloride and sodium valproate in SCA3 *Drosophila* models [468,469].

A study with SCA3 patient-derived hiPSC model confirmed that the autophagic flux was impaired in hiPSC-derived neuronal cells, as evidenced by the accumulation of p62 [470]. In these SCA3 neurally differentiated cells, rapamycin-induced autophagy to promote the clearance of mutant ataxin-3 without any significant effects on its wild-type counterpart [470]. Autophagy and lysosomal impairment were also suggested in SCA14 hiPSCs, although these cells were not differentiated into neurons [471]. Overall, although dysfunctional autophagy has been reported in animal and hiPSC models of SCA3, where autophagy induction is cytoprotective, more studies are required to investigate the role of autophagy in other SCAs.

Spinal bulbar muscular atrophy

Spinal bulbar muscular atrophy (SBMA, also known as Kennedy disease) is an X-linked neurodegenerative inherited disease caused by the expansion of polyglutamine (CAG) repeat in the gene encoding for androgen receptor (AR). SBMA is characterized by motor neuron loss in the brainstem and spinal cord and is associated with muscle weakness, atrophy, and endocrine manifestations [472]. Proteasomal and autophagic dysfunctions have been reported in SBMA [473]. Wild-type AR was shown to interact with and act as a coactivator of TFEB, whereas mutant AR prevented TFEB transactivation and downregulated its target genes in mouse embryonic motor neurons stably expressing mutant AR [474]. This effect was suggested to be

causing dysfunctional autophagic flux associated with the accumulation of autophagosomes in these mutant cells, as well as in motor neurons of symptomatic SBMA mice (YAC AR100) [474]. Autophagic flux was also possibly retarded in the skeletal muscle of SBMA mice (AR113Q knock-in) and in mouse immortalized motor neuron-like cell line, where autophagosomes, insoluble and aggregated p62, and ubiquitinated proteins were elevated [475,476]. However, in inducible PC12 cells expressing mutant AR, autophagic flux was shown to be increased via inhibition of the mTOR pathway along with higher nuclear TFEB and cytoplasmic translocation of the repressor ZKSCAN3 [475]. Likewise, TFEB target genes are upregulated in skeletal muscle biopsies of SBMA patients [475]. One plausible explanation of these contrasting results could be due to the cell type specificity. Despite alterations in autophagy, mutant AR and the associated aggresomes could be selectively targeted for autophagic degradation mediated via the HSPB8 (heat shock protein B8) and BAG3 (Bcl-2-associated athanogene 3) complex [476–478]. HDAC6 (histone deacetylase 6) plays a role in microtubule-assisted delivery of the lysosomes and aggregated proteins, including mutant AR, to the microtubule organizing center (MTOC), where it enables autophagosome maturation and cargo clearance [479–481]. Enhancing autophagy for facilitating the clearance of mutant AR was cytoprotective in primary motor neurons from SBMA mice and immortalized motor neuron-like mouse cell lines, as seen with trehalose [476,482,483], phenoxazine (AKT inhibitor) [482] and 17-AAG (HSP90 inhibitor) [484], as well as with trehalose in immortalized mouse myoblasts [485] and HDAC6 overexpression in SBMA *Drosophila* model [479].

Autophagic defects have been suggested in patient-derived hiPSC models of SBMA. Accumulation of autophagosomes without an increase in autolysosomes, reduction in the expression of TFEB target genes, and mitochondrial depolarization were observed in neuronal precursor cells differentiated from different SBMA hiPSC lines that also exhibited buildup of insoluble mutant AR [474]. In these mutant cells, TFEB overexpression improved autophagosome flux and mitochondrial membrane potential [474]. Furthermore, increased α-tubulin acetylation, reduced HDAC6 activity, and decreased lysosomal enrichment around MTOC, all of which could impact autophagy, were seen in SBMA hiPSC-derived motor neurons [486]. Another study using these SBMA motor neurons only measured the mRNA levels of autophagy-related genes, and thus, any changes in autophagy could not be assessed [487]. None of these studies, however, have robustly evaluated autophagic flux in hiPSC-derived neurons, and therefore, robust characterization is required to determine the extent and nature of autophagic dysfunction in these disease-affected cellular platforms.

Charcot-Marie-Tooth disease

Charcot-Marie-Tooth (CMT) disease is an inherited peripheral neuropathy, which affects motor and sensory neurons and is associated with atrophy and weakness in the distal extremities. There are two types of CMT as per electrophysiological criteria: CMT type 1 (CMT1) is the demyelinating form, whereas CMT2 is the axonal form [488]. Although there are multiple CMT-associated genes, mutations in *MFN2* cause CMT2A [489]. This gene encodes for mitofusin 2, a GTPase located on the outer membrane of the mitochondria regulating mitochondrial network homeostasis by mediating mitochondrial fusion, as well as mitophagy [490]. During mitochondrial damage, PINK1-phosphorylated mitofusin 2 recruits parkin, which, in turn, ubiquitinates mitofusin 2 that acts as a signal to initiate mitophagy, whereas depletion of *MFN2* impaired this process [490–492].

On the contrary, a study with CMT2A hiPSC model reported opposite results. Motor neurons generated from CMT patient-derived hiPSC lines carrying $MFN2^{(A383V)}$ mutation displayed increased autophagic flux accompanied with a reduction in mitochondrial content, although mitochondrial distribution was altered as seen clustering around the nucleus and the axonal movement of mitochondria was slower [493]. It is plausible that this mutation in mitofusin 2 may act via a gain-of-function mechanism that is distinct from the knockdown or knockout effects with mitofusin 2, and also the mutant protein may favor mitophagy by altering mitochondrial localization. Further confirmation of the impact on autophagy and mitophagy processes may come from future studies involving multiple hiPSC models, as well as any therapeutic benefits of autophagy stimulation in this condition.

Concluding Remarks

Autophagy is essential for neuronal health, and deregulation of this vital homeostatic process contributes to neurodegeneration. While impairment in autophagy has been reported in almost all the neurodegenerative disorders studies, the nature of the autophagic defects is sometimes different between nonhiPSC and hiPSC-based experimental systems (Fig. 5 and Table 2). The use of patient-derived hiPSC models to generate disease-affected cell types, such as neurons, may provide insights in a manner relevant to human biology. These cellular platforms are particularly important to evaluate the therapeutic potential of autophagy inducers that could be applicable to the patients (Table 3). Several

studies have been undertaken by utilizing hiPSC models of various neurodegenerative disorders, as described above (Table 1). However, further investigation is warranted in hiPSC-derived disease-affected cell types of most diseases to precisely characterize the nature of the autophagy dysregulation, elucidate the underlying mechanisms causing the autophagy defects, and assess the therapeutic benefits with established autophagy inducers as a proof-of-principle concept to understand whether induction of autophagy is beneficial to the specific disease-relevant contexts.

The promise of hiPSCs in disease modeling and drug discovery is vast, with significant advances being made in recent years. The ability to create human patient-derived model systems is an opportunity not only in understanding disease mechanisms like autophagy as discussed above but also in drug screening and facilitating patient-specific treatment. On the horizon, there is also an autologous hiPSC-derived cell transplant for the treatment of disease [494,495]. Although there are considerable challenges still to be overcome, global initiatives, such as the establishment of international hiPSC repositories for various diseases, developing novel ways to induce cellular aging, refinement of hPSC differentiation techniques and development of increasingly complex three-dimensional and chimeric disease model systems are valuable in furthering the extensive benefits to be derived from hiPSC disease modeling.

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