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REVIEW

Modelling mitochondrial dysfunction in Alzheimer's disease using human induced pluripotent stem cells

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Abstract

Alzheimer's disease (AD) is the most common form of dementia. To date, only five pharmacological agents have been approved by the Food and Drug Administration for clinical use in AD, all of which target the symptoms of the disease rather than the cause. Increasing our understanding of the underlying pathophysiology of AD will facilitate the development of new therapeutic strategies. Over the years, the major hypotheses of AD etiology have focused on deposition of amyloid beta and mitochondrial dysfunction. In this review we highlight the potential of experimental model systems based on human induced pluripotent stem cells (iPSCs) to provide novel insights into the cellular pathophysiology underlying neurodegeneration in AD. Whilst Down syndrome and familial AD iPSC models faithfully reproduce features of AD such as accumulation of A β and tau, oxidative stress and mitochondrial dysfunction, sporadic AD is much more difficult to model in this way due to its complex etiology. Nevertheless, iPSC-based modelling of AD has provided invaluable insights into the underlying pathophysiology of the disease, and has a huge potential for use as a platform for drug discovery.

Key words: Induced pluripotent stem cells; Alzheimer's disease; Mitochondria

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Core tip: Alzheimer's disease (AD) is a huge burden on the healthcare system and on society. At present, there are no therapeutic approaches that address the underlying causes of this devastating disease, largely because we lack understanding of the underlying molecular mechanisms. Induced pluripotent stem cells (iPSCs) from AD or Down syndrome patients can be used to elucidate these molecular mechanisms, therefore presenting a novel approach to this problem. In this review, we focus on the ability of iPSC models to gain insight into the mitochondrial dysfunction that occurs during AD and therefore identify novel drug targets.

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HYPOTHESES OF CAUSATION: THE AMYLOID HYPOTHESIS VS THE MITOCHONDRIAL CASCADE HYPOTHESIS

Alzheimer's disease (AD) is characterized by the presence of tangles of hyperphosphorylated tau and plaques of beta-amyloid (A β) in the central nervous system (CNS). However, it is not clear whether the tangles and plaques drive the pathophysiology of AD or whether they are symptomatic, caused by a common underlying process. The vast majority of people with AD present at 65 or older with "sporadic" AD (sAD). Around 1% of subjects present with atypical early onset familial AD (fAD), generally diagnosed between the ages of 30-60^[1,2]. Despite this, most research has focused on fAD since its etiology is the most straightforward to model. fAD is most frequently caused by mutations in the genes encoding the three components of the amyloid precursor protein (APP) processing pathway (Figure 1), the γ -secretase-component, encoding the genes presenilin (PSEN)-1 and PSEN-2, or the APP gene itself, whereas a growing consensus suggests that sAD is more likely to be caused by impaired clearance of A β ^[3-7].

The genetic basis of fAD suggests that the accumulation of A β in plaques is one, if not the only, cause of the disease, as was suggested by the "amyloid hypothesis" of AD^[8]. The amyloid hypothesis has evolved over the years and the most recent version distinguishes between soluble forms of A β , which are likely to accumulate in cells early in AD and be highly toxic, and insoluble fibrillary A β which is deposited later in the disease and is less toxic (reviewed in^[9-12]) (Figure 2). Interestingly, tau tangles are generally no longer posited as a primary cause for AD, despite being a major cause of neuronal death, since mutations in the tau gene (*MAPT*) do not cause AD (reviewed in^[13]), instead leading to frontotemporal dementia and parkinsonism. *MAPT* knockout mice are also relatively normal^[14]. Instead A β accumulation is thought to cause accumulation of tau tangles^[15], since treatment of AD neurons *in vitro* with A β -specific antibodies reverses the tau accumulation phenotype^[16], although the mechanism for this association is currently unknown^[17]. In support of the amyloid hypothesis, exposure of astrocytes and neurons to exogenous A β causes mitochondrial dysfunction, impaired glucose uptake and ultimately cell death^[18,19] whilst injecting A β ₄₂ into the CNS of healthy rats^[20] and primates^[21] causes impaired memory. In addition, APP duplications cause fAD^[22] and the incidence of AD-like dementia is almost universal in ageing Down's syndrome (DS) subjects, who have three copies of chromosome 21 and therefore of the APP gene^[23]. Approximately two thirds of people with DS will develop a dementia by the age of 60^[23], compared to an incidence closer to 1 in 10 in the general population at a similar age. Furthermore, Prasher *et al*^[24] described a 78-year-old woman with DS but without AD, in which the distal segment of chromosome 21 was translocated so that the APP gene, amongst others, was not triplicated^[24]. Despite extensive evidence for the role of A β in AD aetiology, various anti-amyloid drugs have failed in clinical trials^[25,26], as have anti-tangle drugs, which have also all failed phase II clinical trials^[27]. This, along with the observations that sAD patients do not harbor APP or PSEN mutations^[28], that many ageing individuals also have plaques and tangles at post mortem without signs of dementia^[29,30], and that triplication of all genes on chromosome 21 except APP in mice still leads to A β deposition and cognitive deficits in mice^[31], suggests that the pathophysiology underlying AD progression likely to be more complex. Thus, the search for the underlying mechanisms driving the pathophysiology of sAD and identification of novel candidate drug targets is urgent.

Swerdlow and Khan^[32] proposed the mitochondrial cascade hypothesis, suggesting that AD develops as a consequence of an individual's baseline mitochondrial function coupled with a decline in mitochondrial function with age^[33,34]. This might explain the role of ageing in the aetiology of sAD and is supported by various forms of experimental evidence. For example, evidence of oxidative stress can precede plaque formation in the brain^[35], AD has a strong maternal genetic contribution^[36,37] and cybrid cells, in which platelets from AD patients were fused with neuroblastoma/teratocarcinoma cell lines lacking mtDNA, develop molecular features of

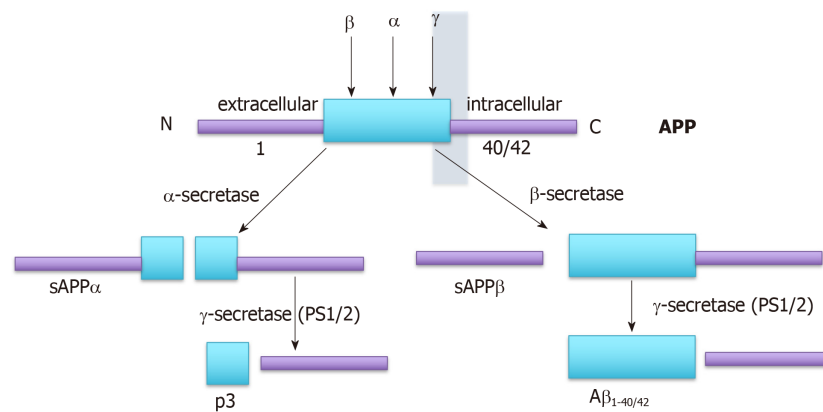


Figure 1 Amyloid precursor protein processing. Adapted from^[80].

AD including A β production^[38]. Exposure of HEK293 cells to the mitochondrial respiratory chain inhibitor antimycin A was associated with increased reactive oxygen species (ROS) generation, A β deposition and toxicity and this was reduced by expression of the alternative oxidase, which prevents antimycin A-induced ROS production^[39]. Furthermore, normal astrocytes exhibit intracellular accumulation of A β similar to that observed in DS astrocytes when mitochondrial metabolism is prevented by the uncoupler carbonyl cyanide m-chlorophenyl-hydrazone (CCCP)^[40].

The role of A β in AD remains controversial since, despite its toxicity, it can also protect cells, perhaps by virtue of an antioxidant role (reviewed in^[41,42]). This role, evidenced by the ability of aggregated A β_{42} peptide to abolish ROS formation in rat mitochondria exposed to FeSO₄ and ascorbate, has been proposed to be mediated by metal chelation by the peptide^[43]. In addition, soluble (s)APP α , generated by the non-amyloidogenic processing of APP (Figure 1), has been shown to be neuroprotective^[44]. It has been suggested that accumulation of A β_{40} and A β_{42} in AD may be a protective response to the oxidative damage caused by mitochondrial dysfunction^[45], consistent with the mitochondrial cascade theory. This idea is supported by the observation that the survival of DS neurons was increased by recombinant or astrocyte-produced A β ^[40]. It seems plausible that ageing (or premature ageing in DS^[46,47]) causes both A β accumulation, as a result of neurodegeneration, and mitochondrial dysfunction/oxidative stress and therefore that a vicious cycle develops whereby accumulation of A β into plaques causes oxidative stress which in turn increases the amyloidogenic processing of APP and A β deposition^[45]. Interestingly, tau phosphorylation also increases in response to disruption of mitochondrial function through inhibition of the electron transport chain^[48-50]. Both hypotheses are therefore likely to be correct at least to some extent.

MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS IN AD: MECHANISTIC INSIGHT

Various mechanisms by which A β plaques may cause oxidative stress have been proposed. For example, it has long been suggested that A β generates oxygen radicals directly in solution^[51], since A β coordinates with iron and copper, which can generate ROS^[52,53]. A β also has the capacity to form Ca²⁺-permeant channels in lipid bilayers^[54,55]. This property is dependent on the membrane cholesterol content of the bilayer^[56,57], leading to the selective generation of Ca²⁺ signals in astrocytes, but not neurons after exposure to A β , reflecting differences in membrane cholesterol content between the two cell types^[58]. This phenomenon may explain our previous observations, detailed below, in which we described mitochondrial dysfunction in astrocytes in response to A β , followed only later by the death of neurons. Interestingly, reactive astrocytes have been shown to actively induce neuronal death in the context of many neurodegenerative diseases, including AD^[59,60].

We have previously shown that exogenous A β -mediated Ca²⁺ influx into rat astrocytes activate the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which generates superoxide. This results in DNA damage and large transient depolarizations of the mitochondrial membrane potential, driven by Ca²⁺ signals and opening of the mitochondrial permeability transition pore (mPTP)^[18,19,61]. We showed

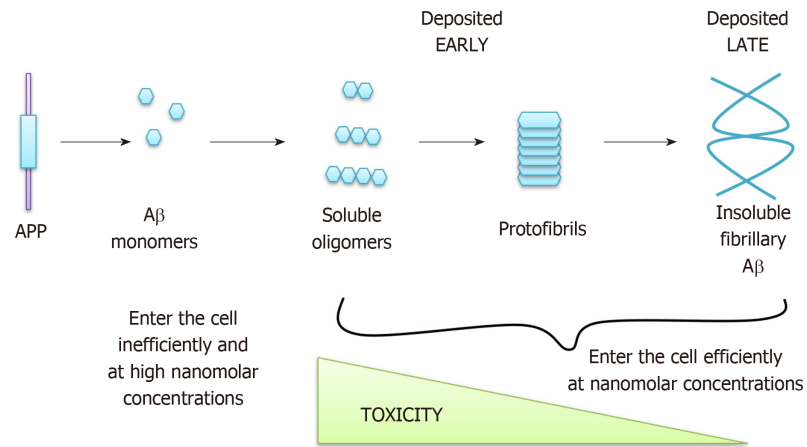


Figure 2 The different forms of Aβ. Adapted from^[178] with additional information from^[84].

that overactivation of Poly (ADP-ribose) polymerase (PARP)-1 in astrocytes and neurons in response to superoxide-driven DNA damage caused NAD⁺ depletion, failure of glycolysis in neurons and neuronal death. Neurons were rescued by inhibition of each step of this pathway - by NADPH oxidase inhibitors, PARP-1 inhibitors and by supply of metabolic substrates that bypass glycolysis, such as supplementation with methyl succinate or pyruvate^[18] (Figure 3). That these mechanisms are not simply an artefact of the experimental design and operate in the intact AD nervous system is suggested by a number of observations. For example, intercellular Ca²⁺ waves passing between astrocytes and initiated at Aβ plaques were described *in vivo* in a double transgenic mouse model of AD expressing APP and mutant PSEN^[62] and we found evidence for increased activation of the NADPH oxidase in the hippocampus of a triple transgenic AD mouse model^[18]. Similarly, Love *et al*^[63] reported evidence of increased PARP activity in post-mortem AD brains.

Impaired mitochondrial substrate supply may be exacerbated by decreased glucose uptake, a feature of the AD brain^[64], likely due to Aβ exposure, which impairs glucose uptake in astrocytes^[18]. This effect has been modelled in stem cell-derived neurons and astrocytes upon exposure to Aβ, which resulted in decreased levels of glucose uptake^[65]. Interestingly, glucose levels have been shown in some studies to increase in the AD brain^[66], which has been proposed to lead to decreased glucose uptake as an adaptive response. Whilst the mechanisms remain uncertain, Liu *et al*^[67] demonstrated decreased expression of the glucose transporters GLUT-1 (the blood-brain barrier and astrocytic glucose transporter) and GLUT-3 in the AD brain and Prapong *et al*^[68] have shown that Aβ inhibits neuronal glucose uptake by preventing the fusion of GLUT-3-containing vesicles with the plasma membrane.

Mitochondrial dysfunction in AD is well-established (reviewed in^[69]) and respiratory capacity is generally decreased across AD models^[70,71]. Mitochondrial dynamics also appear to be dysregulated in AD. Expression of the proteins mitofusin-1 and -2 and optic atrophy-1, which are involved in mitochondrial fusion, and dynamin-like protein-1, which mediates fission, are all downregulated in pyramidal neurons of AD patients^[72,73]. In addition, genes associated with autophagy and mitophagy are downregulated in fibroblasts derived from sAD patients^[73]. Despite this, Birnbaum *et al*^[74] demonstrated an upregulation of mitochondrial complex protein expression. Mechanistically, PTEN-induced putative kinase (PINK)1, which promotes removal of damaged mitochondria by mitophagy, is downregulated in AD and restoring its expression decreases Aβ production, oxidative stress and mitochondrial dysfunction in APP-overexpressing mouse brains^[75]. PINK1 mutations are associated with Parkinson's disease (reviewed in^[76,77]), highlighting the common mechanisms underlying the various neurodegenerative disorders.

A ROLE FOR THE MITOCHONDRIAL mPTP IN AD

Supraphysiological increases in intra-mitochondrial Ca²⁺ can trigger opening of the mPTP, causing mitochondrial depolarization and cell death, especially if the Ca²⁺ signal is coincident with oxidative stress^[18,78-81]. It has been suggested that Aβ may directly contribute to the formation of the mPTP by binding cyclophilin D, the major regulator of mPTP opening, resident in the mitochondrial matrix^[82]. Alternatively, it

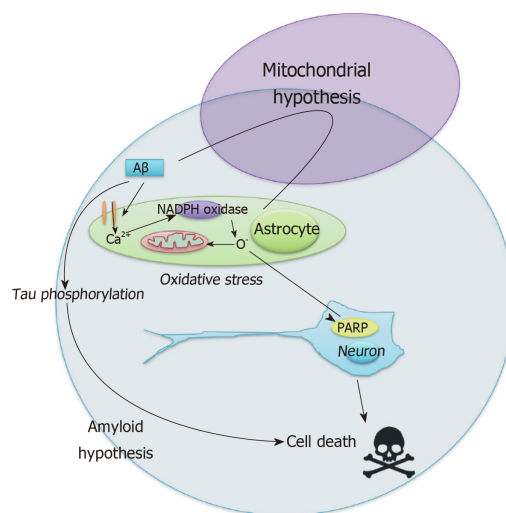


Figure 3 A proposed mechanism for the role of A β in neuronal death. Showing the intersection of the amyloid and mitochondrial hypotheses.

has been suggested that A β upregulates another putative regulator of mPTP opening, the voltage-dependent anion-selective channel-1^[83]. The concept that A β can be internalized into the cell was recently supported by a study which visualized its uptake using confocal microscopy^[84]. Interestingly, mitochondria in DS astrocytes were described as shorter, consistent with mitochondrial fragmentation and, possibly, mitochondrial swelling due to mPTP formation^[85]. Furthermore, a double transgenic AD mouse model crossed with a cyclophilin D knockout mouse (in which mPTP opening is suppressed), performed significantly better in various cognitive tasks^[82,86]. A β can also disrupt the mitochondrial respiratory chain directly through the inhibition of complex IV^[87-89], complex V (reviewed in^[42]) and/or by binding to A β -binding alcohol dehydrogenase^[88,90-94], all of which would contribute to mitochondrial dysfunction and potentially to increased ROS production^[95]. Moreover, deregulation of complex I has been shown to be regulated by tau^[96].

THE NEED FOR BETTER MODEL SYSTEMS

Much insight has been gained through animal models. However, the lack of effective disease modifying drugs for AD largely reflects the failure of these studies to translate to efficacy in humans^[97]. Reasons for this failure remain unclear, but certainly, the anatomy and genetics of the brain in rodents differ significantly from that of the human^[1]. sAD is especially difficult to model, as we know so little about the underlying mechanisms, and mouse models have been generated through genetic manipulation and are therefore representative of fAD than sAD^[98], with the hope that these will give insights into mechanisms of sAD. Even in the case of fAD they do not accurately mimic AD progression, for example by exhibiting full tau tangle pathology^[99]. Animal models do have the unique advantage of being able to model systemic physiological factors such as diet, obesity and hypertension, all of which play important roles in sAD (reviewed in^[100]). Mouse models also cannot realistically lend themselves to drug screens. Postmortem brain tissue from AD patients has also been used as a research tool. However, this is difficult to obtain^[101] and the ability to generate neural cultures from postmortem tissue is highly dependent on the quality of the tissue, which is often compromised during the later stages of the disease^[102].

Adding A β exogenously to cell cultures has been widely employed as a strategy and may have generated interesting data on the mechanisms of A β toxicity, but is also fraught with interpretational difficulties. It is difficult to know whether the levels or forms of A β that are used experimentally are (patho) physiologically relevant. In addition, various groups have added pre-aggregated tau fibrils to induced pluripotent stem cell (iPSC)-derived neurons to model AD, demonstrating that these fibrils efficiently enter the neurons^[103], are propagated intracellularly^[104] and that the tau aggregation phenotype that they induce can be rescued by treatment with autophagy inducers^[105]. The advantages and disadvantages of the different model systems are summarized in [Table 1](#).

Table 1 Advantages and disadvantages of different systems for modelling Alzheimer's disease^[178]

Model system	Advantages	Disadvantages
Animal models	Can be used to model physiological factors such as diet, obesity and hypertension	Findings may not be able to be directly extrapolated to humans
Postmortem tissue	Human-derived	Difficult to obtain; May be of poor quality due to the destructive effects of AD in its later stages
iPSC-based models	Human-derived; More easily obtained than post-mortem tissue	Cannot be used to model physiological or epigenetic factors; Large variation between sAD iPSC lines (may not exhibit phenotype); Neuronal derivatives may be akin to 'younger' neurons

AD: Alzheimer's disease; iPSC: Induced pluripotent stem cells.

MODELLING AD USING IPSCS

The use of patient-derived iPSCs may be able to address many of these challenges, since they are derived from human subjects and are easier to obtain than postmortem tissue. In addition, tau phosphorylation has been demonstrated both in AD patient iPSC-derived neurons^[106,107] and cerebral organoids generated from these cells^[108] while GSK3 β , a major tau kinase, has been shown to be upregulated in AD iPSC-derived neurons^[17,107].

iPSCs were first generated from mouse^[109] and human^[110] fibroblasts in 2006 and 2007 respectively. The pioneering work of Prof. Yamanaka's group in Japan demonstrated that pluripotency, the ability to give rise to the three germ layers, could be induced in these cells through the forced expression of four key "Yamanaka factors", OCT4, SOX2, KLF4 and cMYC. The original Yamanaka factors are still in use today, with the optional addition of LIN28, p53 shRNA and NANOG to increase efficacy and the substitution of LMYC in the place of cMYC. The substitution of the latter factor is for safety reasons, since cMYC is a known oncogene^[111]. In addition, pTAT-mcMYC^[112] or fluorescence-activated cell sorting for differentiation markers^[102] can be used to prevent uncontrolled proliferation.

Importantly, the epigenetic landscape is largely reset by the reprogramming process^[113]. This will inevitably limit the use of iPSC-derived neurons to study the role of epigenetic factors in AD. Despite this phenomenon, some iPSC lines have been shown to exhibit an "epigenetic memory" of their cell type of origin^[114]. This observation, along with the high degree of variability between iPSC clones (reviewed in^[115]), may mean that they exhibit differing abilities to differentiate down a particular lineage, which should be taken into account when using iPSCs in this way. To address these issues, various groups have published protocols for the direct conversion of fibroblasts into induced neural precursor cells (iNPCs^[116]) and induced neuronal cells (iNs^[117]), in which case the epigenetic changes a cell has obtained over the lifespan of the individual are maintained. The choice of whether to use iPSC-derived neurons or iNPCs/iNs will depend on whether the researchers intend to study the genetic basis of the disease only or both genetic and epigenetic factors. However, the cell type of origin, usually fibroblasts, may still be an issue depending to what extent this cell type is affected by the disease and ageing in comparison to the neurons and astrocytes of the brain that are directly affected by the disease in the patient.

Since their original discovery a decade ago, iPSCs have proven to be an invaluable tool for studying disease progression "in a dish". Diseases that have been modelled in this way include amyotrophic lateral sclerosis^[118], familial dysautonomia^[119], Rett syndrome^[120], schizophrenia^[121], spinal muscular atrophy^[122,123], DS^[124], Huntington's disease^[125], Duchenne muscular dystrophy, Parkinson's disease, AD, type 1 diabetes^[126] and Gaucher disease^[125]. These diseases all have a genetic basis, which is necessary to allow recapitulation of the disease phenotype in iPSCs and their derivatives.

sAD may be included in this category to some degree since it is linked to SNP variants in particular genes in 60%-80% of cases^[102] (reviewed in^[127]). Interestingly, in two recent studies only one of two sAD patient lines studied demonstrated an AD phenotype in the iPSC-derived neurons, including altered APP expression and A β secretion^[17,53], demonstrating the high variability of results obtained using sAD patient-derived iPSCs. This variability is likely to reflect the different genetic backgrounds of the two different patients and highlights the importance of maximising the number of cell lines used, particularly in the case of sAD where phenotypes are so variable. The maximum number of cell lines used in the studies described here is Young *et al*^[128] who use seven lines. However, studies of other

diseases have been identified that use almost 30 disease lines to ensure that the statistical power of their findings is sufficient^[129]. These types of studies will be important, at least initially, to identify subtypes of patients with similar phenotypes and therefore to potentially allow particular therapies to be targeted to these subtypes. Variations in the neural differentiation protocols used are also likely to represent another potential source of variation between studies. This may lead to different neural cell phenotypes and therefore possibly to different mechanistic findings.

Encouragingly, however, Hossini *et al*^[130] have demonstrated AD-like gene expression profiles in sAD patient iPSC-derived neurons, including alterations in the response to oxidative stress. In addition, AD-associated phenotypes such as the presence of large RAB5+ early endosomes, which indicate impaired autophagy, increased susceptibility to cell death, abnormal calcium influx and altered axonal transport have all been observed in cells derived from patients with both fAD and sAD^[17,53,131,132], reinforcing the validity of iPSC sAD models.

Many groups have modelled AD using fAD^[15-17,53,98,101,108,131,133-140], sAD^[17,53,98,128,129,136,141] or DS^[15,124,142-147] iPSCs (Table 2). Indeed, fAD iPSC-derived neurons appear to faithfully reproduce the A β overproduction/tau hyperphosphorylation phenotype^[15,16]. Interestingly, AD iPSCs differentiate into NPCs with indistinguishable growth rate and morphology to control cells and show a comparable efficacy of terminal differentiation into neurons^[98], as do DS iPSCs^[124].

Neural differentiation of iPSCs also presents the unique opportunity to model disease progression from an early stage. For example, it has been shown that A β secretion increases throughout neural differentiation of both fAD patient and control iPSCs^[16]. Moreover, DS iPSC-derived neurons are electrophysiologically active; DS and control cell lines show no significant differences in this respect^[144] and neural cultures develop AD-like pathologies after relatively short periods in culture. Despite this, iPSC-derived neurons have been shown to be more similar to late fetal neurons than late adult neurons which may limit the expression of tau isoforms^[148]. In addition, iPSC-derived astrocytes from both sAD and fAD patients exhibited defective localization of astroglial markers in comparison to control cell lines^[98] and fAD iPSC-derived astrocytes exhibited increased A β production, dysregulated calcium homeostasis and were more inflammatory, producing more ROS^[98,149]. Birnbaum *et al*^[74] also showed oxidative stress in iPSC-derived neurons from sAD patients, even in the absence of A β and tau pathology, providing support for the mitochondrial cascade hypothesis. Hibaoui *et al*^[143] showed that DS iPSC-derived neurospheres contained a reduced number of NPCs, likely related to the observation that NPC proliferation was decreased and levels of apoptosis increased in the patient-derived cells. Upon neural maturation, they observed decreased expression of neuronal markers and increased expression of astroglial markers in DS cells in comparison to isogenic controls. These defects could be rescued by inhibition of dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A, suggesting that its triplication in DS is responsible for the phenotypes observed.

AD MODELLING IN 3D CULTURE SYSTEMS

In addition to 2D disease modelling, various groups are attempting to model AD in 3D cultures, in order to recreate the interactions between neurons and glia in the brain^[99,108,141]. Lancaster *et al*^[150] were the first to generate cerebral organoids, paving the way for 3D studies by demonstrating that these “mini brains” recapitulate the development of the fetal brain and can be used to model diseases such as microcephaly. 3D culture may have benefits over 2D culture. For example, Choi *et al*^[99] describe accelerated A β and tau pathologies in 3D compared to 2D cultures, arguing that A β aggregates get “trapped” in the 3D structure rather than being released into the culture medium as they would in 2D and therefore that 3D cultures more accurately model the disease. This assumes that aggregated extracellular species are the toxic entity as opposed to soluble oligomers or intracellular accumulation. However, current drawbacks of 3D modeling include their heterogeneity and lack of developmental maturity^[150-152]. Jorfi *et al*^[153] have recently addressed the heterogeneity issue by demonstrating the derivation of more uniform neurospheroids which may be of use in future studies.

DRUG TESTING USING AD IPSCS

One of the major potential applications of AD derived iPSCs is in drug discovery. This

Table 2 List of studies that have used induced pluripotent stem cells to model Alzheimer's disease

Study	Disease	Key findings	Advantages	Disadvantages
Yagi <i>et al.</i> ^[133] , 2011	fAD	Relevant expression of APP and secretase subunits in iPSC-derived neurons	Obvious AD phenotype observed	fAD only represents ~5% patients
Shi <i>et al.</i> ^[124] , 2012a	DS	AD pathology (such as aberrant A β production and hyperphosphorylated Tau) developed over months in culture, as opposed to years in vivo	Show tau (advanced) phenotype	Findings may not be able to be extrapolated to AD
Israel <i>et al.</i> ^[17] , 2012	fAD, sAD	fAD neurons and one out of two sAD neurons exhibit altered APP expression and A β secretion and swollen endosomes	Comparison of fAD and sAD, in essence using fAD lines as positive control	High levels of variation between cell lines
Koch <i>et al.</i> ^[101] , 2012	fAD	Key steps in proteolytic APP processing are recapitulated in hES and iPSC-derived neurons	Obvious AD phenotype observed	High levels of variation between cell lines
Maclean <i>et al.</i> ^[146] , 2012	DS	Disturbance of multilineage myeloid haematopoiesis in T21 at fetal liver stage	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Kondo <i>et al.</i> ^[53] , 2013	fAD, sAD	A β oligomers accumulated in iPSC-derived neurons and astrocytes in fAD and one out of two sAD patients, also observed ROS	Comparison of fAD and sAD, in essence using fAD lines as positive control	High variation between sAD cell lines
Xu <i>et al.</i> ^[66] , 2013	Exogenous A β	Cell cycle re-entry in iPSC-derived neurons treated with A β	Used pharmacological inhibitors to demonstrate rescue of phenotype	May not be physiologically relevant
Weick <i>et al.</i> ^[142] , 2013	DS	Compensatory responses to oxidative stress in T21 neurons, also reduced synaptic activity	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Woodruff <i>et al.</i> ^[139] , 2013	fAD	PSEN1 mutations impair γ -secretase activity but do not disrupt γ -secretase-independent functions	Obvious AD phenotype observed	fAD only represents ~5% patients
Hibaoui <i>et al.</i> ^[143] , 2014	DS	Abnormal neural differentiation, likely caused by DYRK1A on chromosome 21	Used fetal fibroblasts to generate iPSCs (less acquired mutations)	Findings may not be able to be extrapolated to AD
Muratore <i>et al.</i> ^[16] , 2014	fAD	iPSC-derived neurons have increased A β 42 and A β 38, along with increased levels of both tau and phosphorylated tau	Obvious AD phenotype observed	fAD only represents ~5% patients
Mahairaki <i>et al.</i> ^[134] , 2014	fAD	Increased A β 42:A β 40 ratio in fAD iPSC-derived neurons	Obvious AD phenotype observed	fAD only represents ~5% patients
Sproul <i>et al.</i> ^[135] , 2014	fAD	Identified 14 genes that are differentially regulated in PSEN1 mutant NPCs relative to controls	Obvious AD phenotype observed	fAD only represents ~5% patients
Duan <i>et al.</i> ^[131] , 2014	fAD	iPSC-derived neurons with ApoE3/4 mutations showed typical AD features	Obvious AD phenotype observed	fAD only represents ~5% patients
Liu <i>et al.</i> ^[67] , 2014	fAD	Treatment with NSAID reduced A β 42:A β 40 ratio	Obvious AD phenotype observed	fAD only represents ~5% patients
Young <i>et al.</i> ^[128] , 2015	sAD	Human neurons with SORL1 mutations associated with sAD show a reduced response to BDNF, at the level of both SORL1 expression and APP processing	Many cell lines used ($n = 7$)	Only one type of sAD mutation examined; unlikely to be able to be extrapolated to a large patient cohort

Hossini <i>et al</i> ^[130] , 2015	sAD	Genes associated with AD expressed in sAD iPSC-derived neurons (including oxidative stress response). Treatment with a γ -secretase inhibitor reduced levels of Tau.	Show AD-like gene expression patterns	Only one patient line used ($n = 1$)
Chang <i>et al</i> ^[147] , 2015	DS	Tau mislocalisation	Show advanced (tau) phenotype	Findings may not be able to be extrapolated to AD
Murray <i>et al</i> ^[144] , 2015	DS	Slower proliferation of NPCs, increased A β production, a decrease in mitochondrial membrane potential and increased no. and abnormal appearance of mitochondria, also increased no. of ds DNA breaks in T21 neurons	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Moore <i>et al</i> ^[15] , 2015	fAD, DS	APP mutations increase levels of tau and phosphorylated tau whereas PSEN mutations do not	Obvious AD phenotype observed	Tested drugs (β -secretase and -secretase inhibitors) that have failed clinical trials
Tubsuwan <i>et al</i> ^[177] , 2016	fAD	Description of model	Obvious AD phenotype observed	fAD only represents ~5% patients
Raja <i>et al</i> ^[108] , 2016	fAD	Brain organoids from AD patients exhibit amyloid aggregation, pTau and endosome abnormalities, treatment with β and γ -secretase inhibitors reduced this pathology	Obvious AD phenotype observed	fAD only represents ~5% patients
Li <i>et al</i> ^[140] , 2016	fAD	Characterisation of an iPSC line	Obvious AD phenotype observed	fAD only represents ~5% patients
Lee <i>et al</i> ^[119] , 2016	sAD	Secretase inhibitors decreased A β generation but less potency in 3D	High number of sAD lines used ($n = 5$)	Tested generic drugs (BACE1 and -secretase inhibitors) that have failed clinical trials
Yang <i>et al</i> ^[136] , 2017	fAD	Premature neuronal differentiation with decreased proliferation and increased apoptosis in AD-NPCs, Wnt-Notch pathway involvement	Obvious AD phenotype observed	fAD only represents ~5% patients
Dashinimaev <i>et al</i> ^[145] , 2017	DS	Increased A β secretion and upregulation of <i>APP</i> gene, also increased <i>BACE2</i> , <i>RCAN1</i> , <i>ETS2</i> , <i>TMED10</i> expression in T21 neural cells compared to controls	Reproducible phenotype because clear genetic link	Findings may not be able to be extrapolated to AD
Jones <i>et al</i> ^[98] , 2017	fAD, sAD	Astrocytes derived from iPSCs from both fAD and sAD patients exhibit a pronounced pathological phenotype	Comparison of fAD and sAD, in essence using fAD lines as positive control	Only one line each fAD and sAD used ($n = 1$)
Armijo <i>et al</i> ^[137] , 2017	fAD, sAD	fAD neurons have increased susceptibility to A β in comparison to sAD (and control) neurons	Comparison of fAD and sAD, in essence using fAD lines as positive control	Only one line each fAD and sAD used ($n = 1$)
Ochalek <i>et al</i> ^[107] , 2018	fAD, sAD	sAD iPSC-derived neurons reveal elevated tau hyperphosphorylation, increased amyloid levels and GSK3 β activation	Show tau (advanced) phenotype	Differentiation protocol requires 10 weeks at least
Birnbaum <i>et al</i> ^[74] , 2018	sAD	sAD iPSC-derived neurons display oxidative stress and increased mitochondrial protein expression which doesn't correlate with A β /tau	Occurs in ~95% of AD cases	Hard to explain why the oxidative stress and increased mitochondrial protein expression don't correlate with A β /tau

AD: Alzheimer's disease; iPSC: Induced pluripotent stem cells; DS: Down's syndrome; APP: Amyloid precursor protein; NPC: Neural precursor cells; A β : Beta-amyloid.

relies on the establishment of a reliable and robust readout that associates unequivocally with AD pathophysiology that is suitable for screening on high throughput

platforms. Various groups have used AD iPSC-derived neurons to test γ -secretase inhibitors, with some efficacy^[16,132,154]. Additional drugs that have been tested in this way include docosahexaenoic acid (DHA), which reduces ROS production by an unknown mechanism. Interestingly, treatment with this drug increased the survival time of AD iPSC-derived neurons^[53]. Since A β -induced toxicity has been linked to aberrant cell cycle re-entry, CDK2 inhibitors^[155] and avermectins^[156] have also been shown to be effective blockers of A β -induced toxicity in AD iPSC-derived neuronal models, although the mechanism of action of avermectins is unknown other than they increase the relative production of shorter A β peptides and that this action is unrelated to γ -secretase activity^[156]. In addition, a combinatorial approach may be useful. For example, Kondo *et al.*^[154] have used human iPSC-derived neurons to identify three drugs (bromocriptine, cromolyn and topiramate) from a screen of 1258 compounds that had the most potent A β -reducing effects in both fAD and sAD iPSC-derived neurons.

FUTURE AVENUES OF RESEARCH AND THERAPY

One particular benefit of iPSC technology is the ability to model the heterogeneity of sAD. Many AD-linked SNPs have been identified by genome-wide association studies^[157], and so use of iPSCs may allow particular treatments to be targeted to groups of individuals based on the SNPs they harbor. This field of personalized medicine, known as pharmacogenomics, may mean that drugs that have failed in clinical trials of large cohorts may be effective when applied to specific patient groups (as discussed in^[158]).

Human cell models, including those based on iPSCs, are the most appropriate for modelling the human genetic variation underlying sAD since they are derived directly from sAD patient cells. Despite this, disease phenotypes are not observed in all sAD iPSC lines^[17,53]. Moreover, some cell lines exhibit extracellular A β accumulation whereas other lines exhibit intracellular A β and only the latter were responsive to DHA treatment^[53], suggesting an additional parameter that should be considered when designing personalized treatments. Part of the issue here understands which of these readouts most reliably reflects meaningful AD pathophysiology. The lack of a “disease phenotype” observed in some cell lines is likely due to the “rejuvenation” of markers of ageing that occurs during iPSC reprogramming and includes not only epigenetic signatures but also telomere length, mitochondrial function and the levels of oxidative stress^[159-161]. To address this challenge it has been suggested that “ageing” could be accelerated in cell cultures by exposure to toxins including hydrogen peroxide or compounds that trigger mitochondrial stress such as CCCP or rotenone^[162,163]. Interestingly, it has been suggested that rotenone (an inhibitor of complex I of the respiratory chain) treatment may mimic Parkinson’s disease (PD)^[164], again showing similar molecular mechanisms underlying neurodegeneration between AD and PD. Alternatively, the epigenetic signature could be maintained by generating iNs instead of iPSCs as described previously^[117,165,166]. Importantly, Mertens *et al.*^[167] showed that iNs from donors aged 0-89 retained ageing-associated molecular signatures whereas iPSCs did not. Another potential approach to combat this problem is to overexpress Progerin which re-establishes age-related markers in iPSC-derived fibroblasts and neurons^[159].

Despite the huge promise of personalized medicine, therapeutics with wider applicability will be more cost-efficient. Due to the widespread mitochondrial dysfunction observed not only across sAD and fAD but also across various different neurodegenerative disorders it is likely that mitochondrial disease targets may constitute a more global approach.

CONCLUSION

Recent advances in iPSC technology have highlighted the importance of metabolic dysfunction in the progression of AD. Our hope and expectation is that understanding the molecular mechanisms underlying this metabolic dysfunction will reveal novel therapeutic targets for this devastating disease^[168-177].

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