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Molecular Insights into Cell Type-specific Roles in Alzheimer's Disease: Human Induced Pluripotent Stem Cell-based Disease Modelling

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Abstract—Alzheimer's disease (AD) is the most common cause of dementia resulting in widespread degeneration of the central nervous system with severe cognitive impairment. Despite the devastating toll of AD, the incomplete understanding of the complex molecular mechanisms hinders the expeditious development of effective cures. Emerging evidence from animal studies has shown that different brain cell types play distinct roles in the pathogenesis of AD. Glutamatergic neurons are preferentially affected in AD and pronounced gliosis contributes to the progression of AD in both a cell-autonomous and a non-cell-autonomous manner. Much has been discovered through genetically modified animal models, yet frequently failed translational attempts to clinical applications call for better disease models. Emerging evidence supports the significance of human-induced pluripotent stem cell (iPSC) derived brain cells in modeling disease development and progression, opening new avenues for the discovery of molecular mechanisms. This review summarizes the function of different cell types in the pathogenesis of AD, such as neurons, microglia, and astrocytes, and recognizes the potential of utilizing the rapidly growing iPSC technology in modeling AD.

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Key words: Alzheimer's disease, induced pluripotent stem cells, disease modeling, tau, amyloid.

INTRODUCTION

Alzheimer's disease (AD) is a fatal neurodegenerative disease characterized by progressive loss of cognitive function including learning and memory (Tarawneh and Holtzman, 2012). More than 46 million people suffer from dementia worldwide and AD accounts for at least half of these patients with expected growing numbers in future decades due to extended life expectancy. Thus, AD places a severe burden on patients and families as well as healthcare systems as society ages. Taking advantage of human genetic studies, rodent models carrying AD mutations successfully mimic the age-related neurodegenerative aspect of AD and they have provided invaluable molecular insights into cell type-specific mechanisms of AD pathogenesis (Penney et al., 2020). However, attempts to translate these insights from rodent studies to clinical trials in AD patients have failed, highlighting the need for better models (Ceyzeriat et al., 2020). The expression and cellular regulation of several key AD-related proteins differ significantly between humans and rodents, which may have contributed to negative outcomes (Maloney et al., 2007; Hernández et al., 2020; Zhou et al., 2020). Emerging evidence has suggested the importance of utilizing human cells, such as iPSC-derived brain cells, to model human neurodegenerative diseases (Penney et al., 2020). The iPSC technology was introduced more than a decade ago and allows for the generation of pluripotent stem cells from differentiated patient-derived cells, such as fibroblast from a skin biopsy or peripheral blood mononuclear cells from a blood draw, by overexpressing the reprogramming factors *Oct4*, *Klf4*, *Sox2* and *c-Myc* in these cells (Takahashi et al., 2007). By applying robust and improved maturation protocols, these human iPSCs can be efficiently differentiated into various cell types of interest such as cortical neurons (Shi et al., 2012; Zhang et al., 2013), astrocytes (Serio et al., 2013; Hallmann et al., 2017; Zhao et al., 2017; Guttikonda et al., 2021), oligodendrocytes (Ehrlich et al., 2017) and microglia (Muffat et al., 2016; Haenseler et al., 2017; McQuade et al., 2018; Marton et al., 2019) (Fig. 1). Thus, patient-derived iPSCs have been successfully used to model various neurodegenerative diseases including primary tauopathies (Lines et al., 2020; Kuhn

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Abbreviations: AD, Alzheimer's disease; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; DAM, disease-associated microglia; FAD, familial AD; SAD, sporadic AD; GWAS, genome-wide association studies; HPC, hematopoietic precursor cells; iPSC, induced pluripotent stem cell; NPs, neuritic plaques; PQBP1, polyglutamine binding protein 1.

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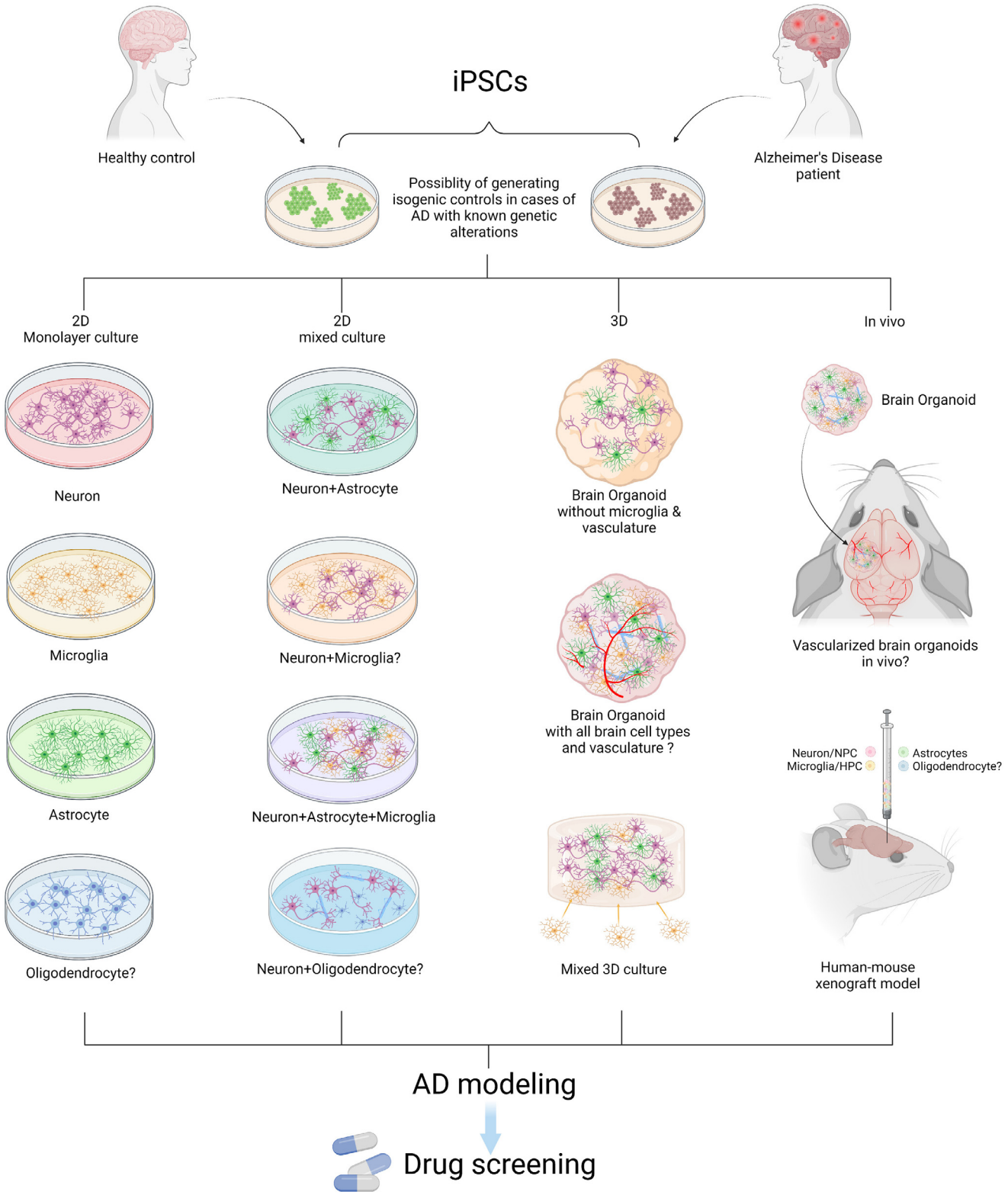

Fig. 1. Modeling AD with patient iPSCs. AD patient or healthy control-derived iPSCs can be differentiated into different brain cell types including neurons, microglia, astrocytes, and oligodendrocytes. *In vitro* and *in vivo* AD modeling strategies can be utilized to model AD and they can be applied for drug screening. "?" indicates available technology yet to be used in AD research.

et al., 2021) and secondary tauopathies such as AD (Yagi et al., 2011; Israel et al., 2012; Lee et al., 2020; Penney et al., 2020; Cenini et al., 2021). The application of genome editing tools, such as CRISPR/Cas9 to generate isogenic, gene-corrected control cells or to introduce AD-associated mutations in control cells, comprises an addi-

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tional powerful approach to interrogate the molecular mechanisms of tauopathies in different human brain cell types *in vitro* (Jehuda et al., 2018). Furthermore, mixed neuron-glia co-culture systems have been established to study disease pathogenesis (Jehuda et al., 2018; Lee et al., 2020; Penney et al., 2020; Cenini et al., 2021) and rapid growing 3D/brain organoid culture techniques and human-mouse chimeric disease models provide prevailing disease modeling systems to study AD in a 3D/*in vivo* environment (Zhang et al., 2014; Purhonen et al., 2020; Sharma et al., 2020; Xu et al., 2020; Preman et al., 2021) (Fig. 1).

This review summarizes key findings of the molecular mechanisms of different brain cell types in contributing to the pathogenesis of AD. Reviewing mechanistic studies in genetically modified animal models and the phenotypes of iPSC-derived brain cell types, this review provides molecular insights into the pathogenesis of AD and emphasizes the promising potential of utilizing iPSC technology for better translational approaches.

ALZHEIMER'S DISEASE

AD is characterized by a progressive decline in at least two cognitive domains that commonly include episodic memory and executive function (Tarawneh and Holtzman, 2012). Pathological features of AD include extracellular deposition of amyloid plaques and formation of intracellular neurofibrillary tangles containing hyperphosphorylated tau (p-tau), accompanied by extensive gliosis, synaptic dysfunction, and neuronal loss (Serrano-Pozo et al., 2011). Amyloid plaques are formed by the Aβ peptide, which is sequentially cleaved from β-amyloid precursor protein (APP) by β- and γ-secretase that generates toxic Aβ species (Chow et al., 2010; Bernabeu-Zornoza et al., 2019). APP can also be sequentially cleaved by α- and γ-secretase, resulting in the generation of non-amyloidogenic fragments (Chow et al., 2010). Aβ is mainly produced in neurons due to the abundant expression of APP and β-secretase (Zhou et al., 2011; Das and Yan, 2017). Among all the Aβ species, $A\beta_{42}$ and $A\beta_{40}$ are the most common isoforms present in amyloid plaques of human AD brains and are a major focus of the research effort in the field of AD (Braak and Braak, 1991; Hardy and Allsop, 1991; Serrano-Pozo et al., 2011; Masters and Selkoe, 2012). $A\beta_{42}$ has a higher rate of fibrillization and insolubility and is deposited in dense-core plaques in the brain parenchyma. The more soluble $A\beta_{40}$ is the most abundantly produced Aβ species and is the major constituent of amyloid deposition in blood vessel walls leading to cerebral amyloid angiopathy (CAA). A decreased ratio of $A\beta_{42}/A\beta_{40}$ in cerebrospinal fluid (CSF) is a strong biomarker for AD, reflecting reduced Aβ clearance through CSF and increased accumulation of amyloid plaques in the brain parenchyma (Shaw et al., 2009). Emerging evidence supports the idea that soluble $A\beta_{42}$ oligomers are more neurotoxic compared with Aβ deposited in amyloid plaques, interrupting glutamatergic neurotransmission, inducing synapse loss, and contributing to dysregulation of synaptic plasticity in AD (Benilova et al., 2012). In addition to the toxicity induced by Aβ, several lines of research also support mechanistic roles of altered APP metabolism and loss-of-function of γ-secretase in contributing to the pathogenesis of AD (Shen and Kelleher, 2007; Kametani and Hasegawa, 2018).

Tau pathology usually follows Aβ pathology in AD and can be induced by Aβ (Stancu et al., 2014). Tau is a microtubule-associated protein that is encoded by the *MAPT* gene. Under physiological conditions, tau plays important role in microtubule stabilization, in regulating the dynamics of microtubule assembly, and in assisting axonal transportation (Mietelska-Porowska et al., 2014). Alternative splicing of the exons 2, 3, and 10 of the *MAPT* gene produces six tau isoforms (Trabzuni et al., 2012). Splicing of exons 2 and 3 produces tau proteins with 0–2 N domains and splicing of exon 10 determines the expression of tau with three or four microtubule-binding domains (3R- or 4R-tau) (Park et al., 2016). Tau pathology propagates in a prion-like manner following a stereotypical pattern during the pathogenesis of AD, striking earliest in the locus coeruleus of the brain stem and the integrity of which indicates the neuropathology and cognitive function of AD patients (Jacobs et al., 2021). From the locus coeruleus, tau pathology then emerges in the entorhinal cortex, spreading to the hippocampus and neocortex (Braak and Braak, 1991; Clavaguera et al., 2015). A recent study has identified the Wolframin-1 expressing neurons in the entorhinal cortex that are responsible for propagating toxic tau to hippocampal neurons (Delpech et al., 2021). The severity of tau pathology closely correlates with neurodegeneration and cognitive decline in AD, further highlighting the neurotoxicity of pathological tau (Jack Jr et al., 2010). Interestingly, a recent report showed that the replication rather than the spreading of toxic tau between brain regions are the main driver of tau accumulation in AD (Meisl et al., 2021).

Blood–brain barrier (BBB) dysfunction is another key pathological feature of AD and emerging evidence indicated that the degeneration of pericytes of BBB is associated with neurovascular malfunction and exacerbated Aβ and tau pathology (Sagare et al., 2013; Halliday et al., 2016; Sweeney et al., 2016). Interestingly, Aβ can also signal to pericytes to restrict capillaries in AD which correlates with Aβ deposition (Nortley et al., 2019). Important work has been done to convert adult human brain pericytes into neurons, which could potentially be applied as an AD treatment strategy (Karow et al., 2018).

The two main forms of AD include early-onset familial AD (FAD), which is caused by known mutations involved in Aβ production, and sporadic AD (SAD) (Hardy and Allsop, 1991; Chow et al., 2010; Holtzman et al., 2011). Mutations in genes involved in Aβ production leading to FAD include the *APP* gene and γ-secretase catalytic subunits encoding genes, *PSEN1* and *PSEN2,* encoding presenilin 1 and presenilin 2, respectively (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995; Haass et al., 2012). More than 200 pathogenic mutations have been described in *PSEN1*, while around 30 and 20 mutations have been reported in the *APP* and *PSEN2* loci, respectively (Lanoiselee et al., 2017). Pathological mutations of these FAD genes all increase either total $A\beta_{42}$ or

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the ratio of $A\beta_{42}/A\beta_{40}$ (Fernandez et al., 2014). FAD consists of around 1–5% of all AD cases and the majority of AD cases are sporadic. In an attempt to elucidate the molecular pathways that contribute to the pathogenesis of AD, genome-wide association studies (GWAS) were conducted and have identified more than 40 AD risk genes, including *APOE4*, *TREM2*, *ABCA7, CD33*, and *SORL1* which are highly expressed in glia (Kamboh et al., 2012; Tábuas-Pereira et al., 2020). These findings underscore a highly relevant role of non-cell-autonomous mechanisms, potentially involving astrocytes and microglia, that contribute to neurodegeneration in AD. Both FAD and SAD cases present with an accumulation of amyloid pathology that precedes tau pathology, followed by cognitive impairment (Holtzman et al., 2011; Selkoe and Hardy, 2016).

NEURONS

Early studies have provided evidence that human iPSC-derived neurons express key components and regulators of the APP processing machinery such as β- and γ-secretase, as well as different APP isoforms and several isoforms of Aβ including $A\beta_{37}$, $A\beta_{38}$, $A\beta_{39}$, $A\beta_{40}$, $A\beta_{42,}$ and N-terminally truncated $A\beta_{2\text{-}40}$ (Koch et al., 2012; Bergström et al., 2016). In addition, the formation of the different tau isoforms, both 3R- and 4R-tau, in human iPSC-derived neurons follows a developmental pattern (Iovino et al., 2015; Sposito et al., 2015). While the fetal 3R tau isoform appears earliest during differentiation, all 6 isoforms are expressed in mature neurons after several months of differentiation *in vitro.* Thus, iPSCs are suitable cell sources to study AD-associated pathologic changes in human neurons (Table 1).

Excitatory neurons are preferentially affected in AD. The increased rate of seizures in Alzheimer's patients hints towards a disruption of the excitatory/inhibitory (E/I) balance in AD brains (Born, 2015). Multiple AD mouse models carrying FAD or SAD mutations/variances show dysregulation of synaptic transmission and prominent neuron hyperexcitability (Klein et al., 2014; Kazim et al., 2017; Varela et al., 2019; Qu and Li, 2020; Müller et al., 2021). Increased electrophysiological E/I balance has recently been demonstrated in the forebrain circuits of post-mortem human AD brains (Lauterborn et al., 2021). Differential gene expression analyses and protein assays also confirmed an increased expression of excitatory synaptic markers (Lauterborn et al., 2021). Interestingly, another report showed that excitatory and inhibitory neurons exhibit different vulnerabilities to tau pathology in human AD brains (Fu et al., 2019). Furthermore, single-nucleus RNA-seq (snRNA-seq) analysis of human AD brains revealed a tau homeostasis signature in excitatory neurons and identified BCL-2 associated athanogene3 (BAG3), an autophagy facilitator, as a master regulator of this tau homeostatic gene signature in these neurons (Fu et al., 2019). Increased neuronal activity enhances the propagation of tau and facilitates the development of tau pathology in a tauopathy mouse model as well as in human iPSC-derived cortical neurons (Wu et al., 2016; Lauterborn et al., 2021). Recently, the low-density lipoprotein receptor-related protein 1 (LRP1) has been identified as the receptor that controls the endocytosis and spread of tau, as also shown in human iPSC-derived neurons (Rauch et al., 2020). Consistent with these studies, ablation of tau in mice shows reduced baseline activity of excitatory neurons and enhanced excitability of inhibitory neurons, suggesting that tau plays a differential role in excitatory and inhibitory neurons (Chang et al., 2021). An abnormally enhanced electrophysiological activity can be recapitulated in human iPSC-derived cortical neurons and organoids carrying FAD mutations in *PSEN1* (PS1 ΔE9 mutation and M146V mutation) and *APP* (KM670/671NL; Swedish mutation), when compared with their isogenic WT controls (Ghatak et al., 2019). The aberrant neuronal activity in iPSC-derived neurons correlates with ion channel dysfunction and reduced neurite length, closely mimicking the early synaptic dysfunction and hyperexcitability in human AD brains (Ghatak et al., 2019). While it may be difficult to recapitulate age-dependent neurodegenerative phenotypes in iPSC-derived neurons, a recent report showed significant overlap of gene expression and correlation of Aβ and tau species between iPSC-derived neurons and the brains of their AD iPSC donors, highlighting the suitability of using iPSC to interrogate the molecular mechanisms of AD pathogenesis in humans (Lagomarsino et al., 2021).

Characterization of iPSC-derived neurons that carry FAD mutations has provided insights into the molecular mechanisms underlying AD pathogenesis. Accumulating evidence suggests that Aβ triggers pathological tau formation and accumulation in the pathogenesis of AD in animal models (Bloom, 2014), and this pathological feature can be recapitulated in iPSC-derived neurons. iPSC-derived forebrain neurons harboring the *APP* London mutation (V717I) demonstrate altered APP cleavage and increased production of Aβ, leading to elevated levels of total tau and p-tau (Muratore et al., 2014). Increased levels of tau can be rescued by early Aβ antibody treatment. These findings suggested that tau pathology is downstream of Aβ raising the possibility that targeting Aβ early in the course of AD may be a promising therapeutic strategy. Similarly, increased levels of Aβ-induced p-tau have been reported in WT neurons and in several additional studies on iPSC-derived neural progenitor cells (NPCs) and neurons that carry FAD or SAD mutations/-variants including FAD mutations in the *APP*, *PSEN1*, *PSEN2*, and *APOE (APOE4)* loci (Israel et al., 2012; Sproul et al., 2014; Ortiz-Virumbrales et al., 2017; Yang et al., 2017; Lin et al., 2018; Bassil et al., 2021).

AD-like pathology is observed in individuals with Down syndrome (DS) and this pathology is attributed to the supernumerary copy of the *APP* gene (Wisniewski et al., 1985). Interestingly, deletion of one of these copies in DS patient-derived neurons corrects Aβ pathology and rescues altered neuronal gene expression but is unable to alter levels of p-tau or apoptosis, challenging the view that Aβ-related pathology is the sole contributor to p-tau pathology in DS (Ovchinnikov et al., 2018).

In addition to Aβ and tau pathology, iPSC-derived neurons from FAD patients also show several perturbed cellular pathways including altered cellular trafficking

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Table 1. Major AD disease phenotypes in iPSC-derived neurons

Model system	Mutations/variants	Phenotypes	References*
2D culture	FAD mutations including APP Lon APP Swe APP Dup PSEN1 M146L PSEN1 A246E PSEN1 E120K PSEN2 N141I SAD variant of APOE4 WT exposed to exogenous Aβ	• Increased total Aβ production or increased $A\beta_{42}/A\beta_{40}$ ratio • Increased total tau or p-tau	(Israel et al., 2012) (Muratore et al., 2014) (Sproul et al., 2014) (Yang et al., 2017) (Ortiz-Virumbrales et al., 2017) (Lin et al., 2018) (Bassil et al., 2021)
	APP Swe PSEN1 ΔE9 PSEN1 M146V PSEN1 A246EPSEN1 E120K PSEN1 R307S	• Enhanced excitability • Synaptic dysfunction	(Ghatak et al., 2019)
		• Increased oxidative stress • Lysosomal dysregulation • DNA damage	(Martin-Maestro et al., 2017) (Yang et al., 2017) (Wezyk et al., 2018) (Li et al., 2018)
3D culture	Overexpression of APP Swe, APP Lon, PSEN1 ΔE9	• Formation of Aβ plaque-like structures • Formation of neurofibrillary tangles	(Choi et al., 2014) (Park et al., 2018) (Kwak et al., 2020)
Organoid	APP Swe PSEN1 M146V APOE4	• Increased total Aβ production or increased $A\beta_{42}/A\beta_{40}$ ratio • Increased p-tau • Lysosomal dysregulation • Synaptic dysfunction	(Raja et al., 2016) (Gonzalez et al., 2018) (Lin et al., 2018) (Zhao et al., 2020)
Xenotransplant in APP/PS1 mice	WT	• Amyloid plaque-associated neurite dystrophy • Increased p-tau and tau conformational changes • Decreased neuronal survival with increased plaque formation within grafts	(Espuny-Camacho et al., 2017)
Xenotransplant in APOE4 KI mice	APOE4	• Elevated production of Aβ aggregates • Dysregulated gene expression profiles including p53 signaling, cellular senescence pathway, and apoptosis	(Najm et al., 2020)

*Selected references.
Reports on mixed neuron-glial co-cultures and additional 3D cultures are listed in Table 2.

and lysosomal degradation, increased oxidative stress, and elevated DNA damage, as similarly shown in rodent models of AD (Martin-Maestro et al., 2017; Yang et al., 2017; Li et al., 2018; Wezyk et al., 2018) (Table 1). Interestingly, an accelerated neural differentiation and an impaired proliferation of NPCs were described in iPSC neural cells derived from SAD cases without known AD-related mutations and in iPSC neural cells with introduced APOE4 (Meyer et al., 2019). This phenotype was linked to a loss of function of REST, a transcription factor, that showed impaired nuclear translocation and chromatin binding in both neural cell types, suggesting a shared phenotype in regards to epigenetic dysregulation in these cells (Meyer et al., 2019).

In conventional 2D culture, human AD neurons contain elevated levels of p-tau but they do not form amyloid plaques or neurofibrillary tangles, which are the key pathological features in AD. Using a 3D culture system, human neuronal progenitor cells overexpressing FAD *APP* and *PSEN1* mutations show an elevated $A\beta_{42}/A\beta_{40}$ ratio that drives the formation of neurofibrillary tangles (Choi et al., 2014; Park et al., 2018; Kwak et al., 2020), indicating the importance of a 3D environment in recapitulating key AD pathological features (Table 1). A 3D environment can also be achieved by the formation of brain organoids which have been applied to model AD. As such, FAD and SAD iPSC-derived brain organoids demonstrated accumulation of β-amyloid, the elevation of p-tau, lysosomal dysregulation, and synaptic dysfunction (Raja et al., 2016; Gonzalez et al., 2018; Lin et al., 2018; Zhao et al., 2020) (Table 1). A recent report generated hippocampal spheroids from FAD patient-derived iPSC that exhibit AD pathologic changes with an increased $A\beta_{42}/A\beta_{40}$ ratio, elevated p-tau, reduced expression of synaptic makers as well as electrophysiologically altered synaptic transmission (Pomeshchik et al., 2020). A limitation of utilizing brain organoids for disease modeling used to be the relative lack of cells that are not of ectodermal origin including microglia and vasculature (Papaspyropoulos et al., 2020). Microglia are innate immune cells of the brain that play an important role in the pathogenesis of AD and will be discussed in a later section. Vasculature delivers oxygen and endothelial cells form part of the BBB, which is dysfunctional in AD (Sweeney et al., 2018). Emerging efforts are invested in vascularizing brain organoids with the help of microfluidic devices for potential applications *in vitro* and in immunosuppressed mice *in vivo* (Daviaud et al., 2018; Cakir et al., 2019; Matsui et al., 2021; Zhang et al., 2021). Future studies may take advantage of these sophisticated 3D models to study the pathogenesis of AD.

Human-mouse chimeric transplantation models of AD have been established using human iPSC-derived neurons as single-cell suspensions (Espuny-Camacho

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et al., 2017; Najm et al., 2020). WT iPSC-derived human neuronal precursor cells transplanted into immunocompromised rodent brains mature *in vivo* and form connections and active synapses that appeared more mature compared to those *in vitro*-cultured cells (Gaspard et al., 2008; Espuny-Camacho et al., 2013). In a later study, human WT iPSC-derived neuronal progenitor cells were transplanted into an immunosuppressed mouse model of AD, in which injected cells differentiated into mature neurons and were exposed to Aβ plaques (Espuny-Camacho et al., 2017). Notably, grafted neurons exhibited key AD pathological features including amyloid plaque-associated neurite dystrophy, abnormal tau phosphorylation, and conformational changes, decreased neuronal survival as well as the acquisition of an AD transcriptome signature (Espuny-Camacho et al., 2017).

Neurons that carry AD-associated variants have also been explored in a human-mouse chimeric model of AD. Human iPSC-derived neurons carrying APOE4 were injected into human APOE4 knock-in (KI) mouse brains and exhibited dysregulated gene expression profiles related to p53 signaling, cellular senescence, and apoptosis (Najm et al., 2020). Interestingly, APOE4 iPSC-derived neurons produce more Aβ *in vitro* compared with APOE3 but neither form Aβ aggregates *in vitro* (Wang et al., 2018). In contrast, both transplanted APOE3 and transplanted APOE4 human neurons produced Aβ aggregates *in vivo* (Najm et al., 2020). Furthermore, APOE4 human neurons produced more Aβ aggregates in APOE4 KI mice than in APOE3 KI mice, which was attributed to impaired phagocytosis of Aβ by APOE4 murine microglia (Najm et al., 2020).

While it is important to continously optimize differentiation protocols to shorten the oftentimes time-intensive and laborious differentiation of iPSCs into mature neurons, these studies clearly highlight that iPSC-derived neurons are suitable to study the pathogenesis of AD. They also suggest that characterizing iPSC-derived neurons in an *in vivo* environment might be beneficial to study mechanisms of disease development in AD. Future studies could utilize these models to further interrogate cell–cell interactions by co-transplanting different human iPSC-derived brain cells, for instance, neurons with glial cells such as astrocytes or microglia.

MICROGLIA

Microglia are innate immune cells of the brain that serve important roles throughout life, including facilitating neurodevelopment, modulating synaptic plasticity, and responding to injury and pathological insults to the central nervous system (Ransohoff and El Khoury, 2015). Human genetic studies have identified several risk genes for AD that are highly expressed in microglia including *APOE*, *TREM2*, and *CD33*, highlighting the significant contribution of microglial dysfunction in the pathogenesis of AD (Kamboh et al., 2012; Dos Santos et al., 2017; Tábuas-Pereira et al., 2020). In healthy brains, microglia maintain a homostatic state defined by their unique gene signature. In AD, microglia alter transcriptomic programs that transform them into functional activation states, including the state of disease-associated microglia (DAM) (Keren-Shaul et al., 2017; Krasemann et al., 2017). Microgliosis is prominent especially around amyloid plaques in the brain where microglia cluster around the plaques and form a barrier to prevent their expansion (Casali et al., 2020). Amyloid plaques facilitate the accumulation of p-tau in dystrophic neurites which are a component of neuritic plaques (NPs) (He et al., 2018), and at the initial tau seeding stage, microglia regulate the spread and accumulation of toxic p-tau in these NPs (Leyns et al., 2019; Delizannis et al., 2021; Gratuze et al., 2021).

Tau released from neuronal synapses can be phagocytosed by microglia and is sensed by the polyglutamine binding protein 1 (PQBP1) on microglia that triggers a microglial inflammatory response contributing to cognitive impairment (Jin et al., 2021). In addition to direct uptake of tau, microglia can phagocytose tau aggregate-bearing neurons alive (Brelstaff et al., 2018; Pampuscenko et al., 2020). Toxic tau species force microglia to enter a senescent-like, hypofunctional state that intensifies their pro-inflammatory response and results in the release of toxic tau seeds (Hopp et al., 2018; Brelstaff et al., 2021). Interestingly, microglia directly contribute to neuronal loss at a late stage of neurodegeneration, which could be prevented by genetically deleting *APOE* and *TREM2* in mice (Leyns et al., 2017; Shi et al., 2019; Gratuze et al., 2020; Shi et al., 2021; Wang et al., 2021).

Animal studies have provided invaluable insights into the molecular mechanisms of the pathogenesis of AD but conflicting conclusions are often reported in AD mouse models carrying modified AD risk genes including *APOE* and *TREM2* (Shi and Holtzman, 2018; Wolfe et al., 2019; Qu and Li, 2021). Notably, snRNA-seq analyses revealed that mouse DAM signatures only partially match with the microglial transcriptome in the human AD brain, indicating species-specific changes in microglial responses in AD (Mathys et al., 2019; Zhou et al., 2020).

Emerging evidence has supported the suitability of utilizing iPSC-derived microglia to study AD (Abud et al., 2017; Hasselmann and Blurton-Jones, 2020) (Table 2). However, microglia differentiation from iPSCs is challenging due to their unique embryonic origin. Microglia are derived originally from progenitors located in the yolk sac during primitive hematopoiesis and later from mesoderm that migrate into the neural tube (Ginhoux et al., 2013). Therefore, microglial cells have a different embryonic origin than neurons, astrocytes, and oligodendrocytes, which are derived from neuroectoderm and can be differentiated from NPCs (Csobonyeiova et al., 2019). Providing crucial factors to mimic the embryonic development of microglia, multiple protocols have been established to produce human iPSC-derived microglia through lineage states resembling hematopoietic precursor cells (HPC) *in vitro* (Muffat et al., 2016; Abud et al., 2017; Douvaras et al., 2017; Haenseler et al., 2017; Pandya et al., 2017; Takata et al., 2017; Brownjohn et al., 2018; Garcia-Reitboeck et al., 2018; Konttinen

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Table 2. AD disease phenotypes in iPSC-derived glial cells

Cell type	Model system	MutationsVariants	Phenotype	References
Microglia	2D culture	APOE4	• Reduced ramified morphology • Upregulated expression of inflammatory genes • Impaired uptake of Aβ • Altered metabolism	(Lin et al., 2018) (Konttinen et al., 2019a)
		PSEN1 ΔE9APP Swe	• Altered PSEN1 endoproteolysis and accelerated chemokinesis but limited impact overall	(Konttinen et al., 2019a)
		Loss-of-function TREM2	• Reduced phagocytosis • Altered inflammatory gene expression • Decreased metabolic capacity	(Brownjohn et al., 2018) (Garcia-Reitboeck et al., 2018) (Piers et al., 2020) (Hall-Roberts et al., 2020) (Reich et al., 2020)
	2D co-culture	WT microglia with WT astrocyte(Immune response induced by APP Swe AD neurons/ exogenous Aβ treatment)	• Secretion of complement components including C1q and C3 • Internalization and exocytosis of $A\beta_{42}$	(Bassil et al., 2021) (Guttikonda et al., 2021)
	3D culture (microfluidic platform)	WT microglia with neurons and astrocytes overexpressing APP Swe, APP Lon, PSEN1 ΔE9	• Migration towards AD neurons and astrocytes • Secretion of pro-inflammatory factors including NO, IL-6, TNF-α • Fragmentation of neurites • Induction of loss of astrocytes and neurons	(Park et al., 2018)
	Xenotransplant in 5xFAD mice	WT	• Phagocytosis of amyloid plaques • Upregulation of DAM markers near amyloid plaque, including APOE and TREM2	(Abud et al., 2017) (Hasselmann et al., 2019)
	Xenotransplant in 5xFAD mice	Loss-of-function TREM2	• Locked in homoeostatic status • Reduced phagocytosis • Fail to cluster around amyloid plaques • Reduced accumulation of lipid droplets	(McQuade et al., 2020)(Claes et al., 2021)
Astrocyte	2D culture	PSEN1 M146L PSEN1 ΔE9	• Atrophic morphology • Increased release of inflammatory cytokines • Aberrant calcium signaling • Increased oxidative stress	(Jones et al., 2017) (Oksanen et al., 2017) (Konttinen et al., 2019b)
		APOE4	• Atrophic morphology • Increased release of inflammatory cytokines • Reduced uptake of Aβ • Disrupted lipidomics • Lipid droplet accumulation	(Jones et al., 2017) (Lin et al., 2018) (Sienski et al., 2021)
	2D co-culture	PSEN1 L286VPSEN1 R278I(astrocytes/neurons)	• Altered processing of APP • Increased oxidative stress	(Elsworthy et al., 2021)
		APOE4 astrocytes/APOE3 neurons	• Reduced neurotrophic support to APOE3 neurons	(Zhao et al., 2017)
	Xenotransplant in APP/PS1 mice	WT	• Morphological changes of astrocytes near amyloid plaques	(Preman et al., 2021)

et al., 2019a; Guttikonda et al., 2021). iPSC-derived microglia resemble human primary microglia in that they express microglia-specific markers, secrete cytokines, prune synapses, and are capable of phagocytosing exogenous Aβ (Muffat et al., 2016; Abud et al., 2017; Xu et al., 2019; Guttikonda et al., 2021). These robust and reproducible HPC/microglia differentiation protocols have been utilized to assess microglial function *in vitro* and human-mouse chimeric models to further interrogate molecular mechanisms of AD.

Human iPSC-derived microglia carrying the APOE4 variant, the highest genetic risk factor for SAD, showed reduced ramified morphology, upregulation of pro-inflammatory genes, and impaired uptake of Aβ from the conditional medium of both APOE4 neurons and APOE4 brain organoids compared to their isogenic APOE3 controls (Lin et al., 2018). Interestingly, an independent report also demonstrated that APOE4 profoundly influences function in iPSC-derived microglia in regards to phagocytosis, metabolism, and inflammatory response,

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whereas the *PSEN*1 ΔE9 and *APP* London FAD mutations had limited impact on microglia function overall, suggesting potentially differential roles of microglia in SAD and FAD (Konttinen et al., 2019a).

Impaired microglial phagocytosis as well as altered expression of inflammatory genes and decreased metabolic capacity have been reported in iPSC-derived microglia carrying loss-of-function variants of *TREM2*, a microglia-specific gene that confers high-risk for AD (Brownjohn et al., 2018; Garcia-Reitboeck et al., 2018; Konttinen et al., 2019a; Hall-Roberts et al., 2020; Piers et al., 2020; Reich et al., 2020). iPSC-derived microglia have also been used to study signaling mechanisms of AD-related genes. For instance, the P522R gain-of-function variant of PLCG2 provides protection against AD (Sims et al., 2017). It was recently discovered that TREM2 and PLCG2 knockout iPSC-derived microglia show shared disease phenotypes with an increased lipid accumulation, impaired phagocytosis, and reduced cell survival (Andreone et al., 2020). In line with this observation, this study on these genetically modified iPSC-derived microglia also demonstrated that PLCG2 is required for TREM2 downstream signaling (Andreone et al., 2020). Collectively, these iPSC-based studies highlight intrinsic microglial dysfunction in AD.

Co-culture iPSC-derived microglia with other brain cell types revealed a non-cell-autonomous role of microglia in the pathogenesis of AD. For instance, human microglia were applied in a 3D AD culture model that contains iPSC-derived neurons and astrocytes overexpressing FAD mutations to recapitulate the human AD brain environment with the formation of Aβ plaque-like aggregates and p-tau in neurites and soma (Park et al., 2018) (Table 2). This AD brain-like environment recruits and activates human microglia resulting in the fragmentation of neurites of co-cultured neurons and in the secretion of pro-inflammatory factors that exacerbate neuron and astrocyte loss (Park et al., 2018). In addition, the co-culture of human iPSC-derived WT microglia and astrocytes with iPSC-derived neurons that harbor the *APP* London FAD mutation revealed that microglia initiate cellular cross-talk with astrocytes through complement C3 (Guttikonda et al., 2021), which is implicated in synapse loss in AD (Hong et al., 2016; Lian et al., 2016). Utilizing an automated culturing system, a recent report generated iPSC-derived neurons, astrocytes, and microglia as a triculture model of AD induced by exogenous $A\beta_{42}$ oligomers that harbor key pathological features of AD including the formation of Aβ-positive plaques, induction of p-tau and neurite dystrophy, and neuroinflammation (Bassil et al., 2021). Timelapse imaging of microglia in this system revealed that microglia first internalize soluble $A\beta_{42}$ oligomers and then exocytose $A\beta_{42}$ to initiate plaque nucleation with the formation of Aβ plaque-like structures. Utilizing these co-culture systems, future studies could further explore AD-relevant molecular mechanisms such as tau seeding and propagation of tau.

The recent development of human-mouse chimeric models has provided unique opportunities to study human microglia in an *in vivo* environment. Human microglia require human colony-stimulating factor 1 (CSF1) to survive in immunodeficient mice (Svoboda et al., 2019). Human WT iPSC-derived microglia transplanted into the brain of adult mice were ramified and mobile and express microglial markers that resemble phenotypes of resting microglia (Abud et al., 2017). Also, WT microglial progenitor cells were successfully injected into neonatal mice and functionally integrated into the developing brain (Hasselmann et al., 2019; Svoboda et al., 2019; Xu et al., 2020). In fact, these microglia were capable of responding to exogenous stimuli including injury and demyelination. Single-cell RNA sequencing (scRNA-seq) analyses revealed that these transplanted iPSC-derived microglia retained their identity and displayed a heterogeneous gene expression signature that closely resembles primary human microglia (Svoboda et al., 2019). Similar microglia transplantation models using human embryonic stem cells have also been reported (Mancuso et al., 2019; Fattorelli et al., 2021).

Human microglia transplantation models have also been utilized to study AD. In the brains of immunocompromised AD mice, injected human iPSC-derived WT microglia phagocytose amyloid plaques (Abud et al., 2017). Furthermore, xenografted human WT microglia near plaques upregulate several key DAM markers including APOE and TREM2 (Hasselmann et al., 2019). Notably, comparing the gene expression signature from these grafted human microglia with the expression profile of the murine microglia in this AD mouse model revealed a high degree of discordance in differentially expressed genes, emphasizing the importance of modeling human disease using human cells.

A chimeric microglia transplantation model of AD has also been utilized to study the molecular mechanisms of microglia that harbor AD risk genes, such as *TREM2*. In this model, *TREM2*-deficient human iPSC-derived microglia displayed impaired phagocytosis of APOE and they failed to surround amyloid plaques, recapitulating key pathological features in *TREM2*-deficient human AD brains (McQuade et al., 2020). Furthermore, scRNA-seq analyses showed that transplanted TREM2-deficient microglia fail to upregulate human DAM genes, as similarly seen in previous TREM2 loss-of-function studies (Zhou et al., 2020). In another study, human iPSC-derived microglia from an individual carrying the TREM2 R47H mutation were injected into the brains of neonatal mice revealing a diminished response to amyloid plaques as well as reduced accumulation of lipid droplets (Claes et al., 2021), further highlighting the important role of TREM2 in the context of AD.

Collectively, these studies showed promising disease modeling approaches using iPSC-derived microglia. However, some technical limitations are associated with the application of these human microglia. For instance, microglial transcriptomic changes are sensitive to medium composition (Hasselmann and Blurton-Jones, 2020) and interaction of microglia with other brain cell types is difficult to study in a controlled culture environment. Chimeric human microglia mouse models require specific mouse strains, and the presence of innate murine microglia might complicate the interpretation of results. Thus, these technical limitations need to be addressed

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in future studies to further optimize disease modelling using human iPSC-derived microglia.

ASTROCYTES

Astrocytes are the most abundant glia in the brain that serve pivotal roles in supporting brain homeostasis, assisting neuronal signaling, and maintaining the blood–brain barrier (Linnerbauer et al., 2020). Reactive astrogliosis is prominent near amyloid plaques and, in response to AD pathology, astrocytes secrete inflammatory cytokines including interferon-γ (IFN-γ), interleukin-1β (IL-1β), and tumor necrosis factor α (TNF-α), all of which may contribute to neurotoxicity in AD (Hu et al., 1998; Johnstone et al., 1999; Frost and Li, 2017). Interestingly, astrocytes can also produce small levels of Aβ and due to their abundance in the brain, astrocytes contribute significantly to the Aβ burden in AD (Zhao et al., 2011). Astrocytes are the major source of APOE in the brain and they actively communicate with microglia through complement activation (Koistinaho et al., 2004; Lian et al., 2016). Toxic oligomeric tau species can induce astrocyte senescence in AD brains that contribute to neuroinflammation and cognitive impairment (Gaikwad et al., 2021). In addition, pathological tau accumulates in hilar astrocytes of the dentate gyrus of AD patients, which may directly contribute to an impairment of learning and memory (Richetin et al., 2020). Despite the limited expression of tau in astrocytes, bidirectional transmission of toxic tau species between neurons and astrocytes has been proposed as one of the mechanisms that facilitate tau propagation in AD (Maté de Gérando et al., 2021).

Astrocytes can be differentiated from human iPSCs and they have been used for studying AD-related disease mechanisms (Tchieu et al., 2019; Penney et al., 2020; Guttikonda et al., 2021) (Table 2). iPSC-derived astrocytes that harbor *PSEN1* mutations show atrophy, increased secretion of Aβ, altered inflammatory response, aberrant calcium signaling, increased oxidative stress, and impaired neuronal support (Jones et al., 2017; Oksanen et al., 2017; Konttinen et al., 2019b; Elsworthy et al., 2021). Furthermore, astrocytes derived from SAD patients carrying APOE4 presented with morphological alterations with an increased release of inflammatory cytokines, reduced uptake of Aβ, disrupted lipid homeostasis, and accumulation of lipid droplets (Jones et al., 2017; Lin et al., 2018; Sienski et al., 2021). iPSC-derived astrocytes respond to exogenous Aβ treatment and form fibrous Aβ aggregates, suggesting a potential role of astrocytes in the compaction of Aβ (Bassil et al., 2021).

Cross-talk between astrocytes and other cells types has also been explored in human iPSC models. Astrocytes co-cultured with neurons show increased arborization and promote neuronal survival but this function is compromised if astrocytes harbor APOE4 (Zhao et al., 2017; Park et al., 2018; Bassil et al., 2021). Also, co-cultures of astrocytes and neurons carrying mutant *PSEN1* (L286V and R278I) demonstrate altered processing of APP as well as increased oxidative stress (Elsworthy et al., 2021). iPSC-derived astrocytes can be activated by TNF-α secreted by microglia and they cross-talk with microglia through complement C3 (Guttikonda et al., 2021). In response to AD-related cues, astrocytes also secrete interleukin-3 (IL-3) that recruits and activates microglia to clear Aβ and tau (Guttikonda et al., 2021; McAlpine et al., 2021).

A few studies explored the engraftment of human astrocytes in the brains of mice and showed promising results to utilize the chimeric model to study human astrocytes. Transplantation of human glial progenitor cells into the mouse forebrain gave rise to mature human astrocytes in these mice resulting in enhanced synaptic plasticity and memory (Han et al., 2013). Furthermore, human iPSC-derived astrocytes injected into AD mouse brains showed morphological atrophy or hypertrophy in response to Aβ plaques but interestingly, this phenotype was APOE variant-independent (Preman et al., 2021). Future studies could take advantage of similar transplantation models to further determine functional and molecular changes in astrocytes in response to AD pathology.

OLIGODENDROCYTES

Oligodendrocytes generate myelin sheets that surround axons, facilitate neuronal signaling, and provide trophic support (Simons and Nave, 2015). Myelin loss is an early pathological feature of AD that may precede Aβ and tau pathology as a result of excessive oxidative stress and neuronal dysfunction (Butt et al., 2019; Papuc and Rejdak, 2020). Myelin debris is toxic to neurons and impaired clearance of myelin debris by microglia is closely linked to cognitive decline in aging (Gabande-Rodriguez et al., 2020). Myelin loss is associated with amyloid plaques in AD, and it has been reported that seeding and spreading of tau also occur in oligodendrocytes in the mouse brain (Ferrer et al., 2019). In line with that observation, a recent study showed that the propagation of toxic tau, isolated from patients with progressive supranuclear palsy and corticobasal degeneration, two other tauopathies, in oligodendrocytes is independent of neuronal tau, suggesting that an oligodendrocyte network may be sufficient to propagate tau resulting in myelin loss (Narasimhan et al., 2020). Multiple AD risk genes are also linked to myelin pathology including APOE and TREM2 (Bartzokis et al., 2007; Qu and Li, 2021). Collectively, these studies indicate a potential contribution of oligodendrocyte dysfunction to AD pathogenesis.

Oligodendrocytes can be differentiated from human iPSCs and incorporation of human iPSC-derived oligodendroglial cells in brain organoids as well as successful cell survival after transplantation into myelin basic protein-deficient mouse brains has been reported (Hu et al., 2009; Ehrlich et al., 2017; Madhavan et al., 2018; Marton et al., 2019). However, iPSC models of AD oligodendrocytes have not been reported so far to study the function of oligodendrocytes during AD pathogenesis.

CONCLUSIONS

The recent development of generating human iPSC-derived brain cells and the creation of reproducible

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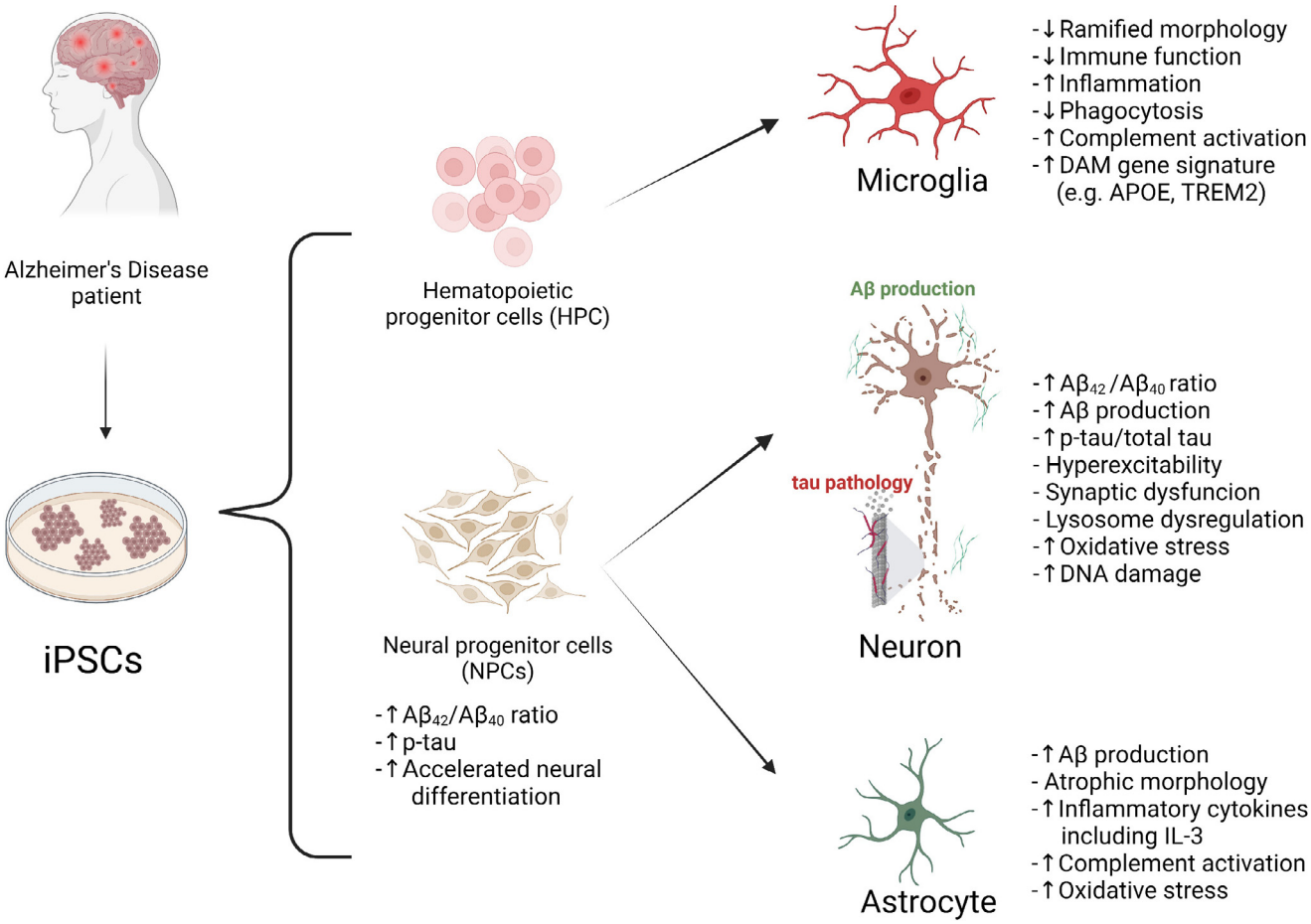

Fig. 2. Summary of disease phenotypes in AD iPSC-derived brain cells. AD-related phenotypes have been described mainly in neurons, microglia, NPCs, and astrocytes.

in vitro and *in vivo* AD models have provided a powerful toolkit to study the biology of different brain cell types in AD (Fig. 1). The phenotypes in AD-patient-derived cells have provided insights into cell type-specific mechanisms of AD pathogenesis (Tables 1 and 2, Fig. 2). In addition to determining cell-intrinsic and cell type-specific pathology in AD, a better understanding of the molecular cross-talk between different cell types will benefit future treatment strategies and may require the application of mixed cultures, generation of brain organoids or other 3D culture models as well as an analysis of grafts of different neuronal and glial cell types *in vivo*. The iPSC field is relatively young and some limitations still need to be addressed. For example, the overall number of patients in iPSC studies is relatively low and the *in vitro* environment does not resemble the microenvironment of AD patient brains with the formation of amyloid plaques and neurofibrillary tangles. Many of the iPSC differentiation protocols are time-consuming and costly to generate cultures of mature neural cells including neurons expression all six different tau isoforms or functional glial cells. Variabilities between different stem cell clones may influence the differentiation of iPSCs into various cell types. Also, microglia and oligodendrocytes are often missing from brain organoids and few studies investigated vascularizing brian organoids to model AD (Papaspyropoulos et al., 2020). In fact, BBB dysfunction is a key pathological feature of AD that should be further explored in AD iPSC models. Given the importance of pericytes in AD and the existence of iPSC-derived pericyte differentiation protocols (Kumar et al., 2017; Delsing et al., 2020; Aisenbrey et al., 2021), future research efforts may benefit from incorporating pericytes along with endothelial cells in these stem cell models of AD. Emerging efforts are underway to address these limitations including generation of isogenic stem cell lines, further improvement of differentiation protocols as well as utilization of 3D culture systems. In addition, *in vivo* applications of iPSC-derived brain cells in AD murine models can provide a more physiological microenvironment to study patient cells over months to years. Overall, the iPSC technology carries a very strong potential to model neurodegenerative diseases, including AD. It can be applied to drug screening *in vitro* and *in vivo* and, potentially, for the development of patient-specific treatment strategies. These models can also be used to validate key findings in rodent studies and to further explore many unsettled questions including the function of AD risk factors in different brain cell types. Combining iPSC technology with genetic and molecular studies in human AD patients and animal models should lead to important

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advancements in both the understanding and treatment of this devastating disease.

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