Livesey *Alzheimer's Research & Therapy* 2012, **4**:44
http://alzres.com/content/4/6/44

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REVIEW

Stem cell models of Alzheimer's disease and related neurological disorders

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Abstract

Human models of Alzheimer's disease (AD) have the potential to complement existing animal models for carrying out functional studies of AD pathogenesis and the development of novel therapies. An effective human cellular model of AD would use the appropriate cell types and ideally neural circuits affected by the disease, would develop relevant pathology and would do so in a reproducible manner over a timescale short enough for practical use. A pressing question for the usefulness of this approach is whether neurological diseases that take decades to become manifest in humans can be successfully modelled over a reasonable timescale. We discuss here whether these models can do more than simply replicate what is already known about AD, and evaluate some of their potentially unique advantages.

Stem cell models in neurology – the opportunity

Stem cell biology is commonly predicted to hold great potential for the study and treatment of neurodegenerative disease [1]. The development of technologies to generate human embryonic stem cells (ESCs) raised the possibility of producing large numbers of defined classes of neurons for research and for transplantation. More recently, the development of methods to reprogram adult somatic cells, including fibroblasts, into induced pluripotent stem cells (iPSCs) [2-4] has made it possible to generate patient-specific pluripotent stem cells (PSCs) [5].

In neurology, this approach has now been used to generate *in vitro* models for a number of genetic conditions, early examples being spinal muscular atrophy [6] and familial dysautonomia [7]. Similar approaches have been taken to inherited and sporadic forms of a range of human neurodegenerative conditions, including Parkinson's disease and Alzheimer's disease (AD) [8-13].

The degree to which those neurons develop pathologies varies, both in terms of whether disease development has to be induced by external stressors and the severity of those pathologies. A number of questions remain over the utility of this approach, including the degree to which stem cell models will be of use in diseases such as AD in which several different neuronal types in discrete regions of the nervous system are affected by the disease process [14]. We review here current progress in applying this approach to generating human models of AD and the potential for such models in the AD field.

Current approaches to cellular and molecular AD studies

As in many diseases, animal models continue to be critical to understanding the pathogenesis of AD. A number of different transgenic mice expressing human AD-causing mutations in single genes have been generated, most notably using the human *Tau*, *APP* and *PSEN1* genes [15]. Those animals develop many different aspects of the AD phenotype, although there are often notable gaps – including, for example, the absence of neuronal loss in many models and the difficulty in generating neurofibrillary tangles [15]. Clearly, no one animal model completely models sporadic AD and there is an ongoing need for tractable systems to study AD pathology both *in vitro* and *in vivo*.

One challenge for modelling AD, and therapies based on those models, is our incomplete understanding of the cell and molecular biology underlying the initiation and progression of the disease. A common working theory for AD pathogenesis, the amyloid hypothesis [16], was formulated based on the genetics of familial or inherited AD. Familial AD makes up less than 1% of cases of AD, and disease-causing mutations either increase production of longer forms of Aβ peptides, particularly Aβ42, or increase the tendency of Aβ to form oligomers and fibrils [17,18]. Familial AD mutations are found in genes encoding components of the gamma-secretase complex, most commonly *PSEN1*, and less frequently *PSEN2*, or in *APP* itself [18]. Duplication of the *APP* gene itself is also a

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cause of autosomal dominant familial AD [19]. Mutations in the gene encoding the microtubule-associated protein tau, the major component of neurofibriallary tangles, do not cause AD, but instead underlie frontal temporal dementia and progressive supranuclear palsy [20], diseases that are clinically distinct from AD.

A consensus view for the initiation and progression of AD is that altered APP processing and Aβ peptide production changes occur early in the disease process, resulting in synaptic dysfunction and neuronal cell death, and that tau hyperphosphorylation and neurofibrillary tangles occur late in the disease process, possibly as a downstream response to changes in Aβ production. Recent functional data indicate that tau may be important for mediating many of the neurotoxic effects of Aβ peptides in the early stages of the disease [21]. Furthermore, tau can transfer between neurons in newer mouse models [22,23] and Aβ aggregates trigger large-scale amyloid aggregate formation when injected into the mouse central nervous system [24], suggesting that both Aβ and tau may contribute to mechanisms by which the disease spreads through the nervous system. Those findings also suggest that the relationship between Aβ, tau and disease progression may not be a simple linear one.

One possible limitation of mouse models is their ability to model the much more common sporadic form of AD. In sporadic forms of AD, the complex genetic contribution to disease pathogenesis is very challenging to model in mice, even when the genetics are well characterised, as is becoming the case in AD [25]. In contrast, patient-specific stem cell lines already have genomes that contain the genetic contribution to the development of AD, and as such are ideal starting material for disease modelling, although it is not yet known whether it is possible to model environmental and epigenetic influences on disease initiation and progression. Human AD models therefore clearly have considerable potential to enable functional studies of disease pathogenesis and progression.

Approaches to generating human neurons and neural circuits

The combination of novel, powerful stem cell technologies, most notably cellular reprogramming [2-4], with the maturation of the field of developmental biology has enabled considerable progress in our ability to generate specific neuronal cell types *in vitro*. Directed differentiation of PSCs (ESCs and iPSCs, collectively referred to as PSCs) has been the primary approach to this end. Currently, there are methods for the directed differentiation of PSCs to a number of neural lineages, including the neural crest, dopaminergic neurons, motor neurons, interneurons, forebrain neurons and cortical projection neurons [26-30]. However, the efficiency of production of specific cell types varies among these methods, such that, for example, dopaminergic neuron differentiation typically generates between 25 and 50% dopaminergic neurons, with the remaining neurons being of a variety of other cell types [29].

Direct transdifferentiation of neurons from adult somatic cell types, mainly dermal fibroblasts, is becoming a popular approach [31-33]. Several groups have reported the direct programming of rodent and human fibroblasts to functional neurons [34]. The potential advantages of this approach are a notable shortening of the time required to generate cells of interest, and targeted generation of defined cell types. Potential drawbacks are: the relatively low efficiency of this method, although this is likely to improve as techniques become optimised; a reduction in cellular complexity, which complicates the production of neural circuits; and that neurons are a nonrenewable resource, requiring transdifferentiation for each experiment. A promising variant on this approach is direct transdifferentiation to neural progenitor and stem cells, which then can be used to generate neurons [35,36]. Although the nature of such progenitor cells remains to be explored, in terms of the classes of neurons they can generate, such approaches solve the problems of lack of renewability of transdifferentiated neurons and, potentially, of reduced neuronal complexity.

A recurring practical question about the use of these systems for modelling neurological disease is that of the functional maturity of neurons generated *in vitro* from PSCs. This question speaks to the fundamental issues of whether such neurons are truly the equivalent of neurons generated from primary neural stem cells or whether there are features of neural differentiation that are not captured by *in vitro* systems. An emerging theme from several groups is that this is not a significant problem, as long as one bears in mind that human cellular systems take an inherently long period of time to acquire functional maturity, compared with their rodent equivalents [30]. Methods are currently being developed to accelerate the entire differentiation process, including neuronal maturation, using small molecules in place of recombinant proteins to more efficiently manipulate cell signalling systems [37].

Given that many of the major diseases of the cerebral cortex, including AD, are diseases of synaptic function, a goal of the field is to generate cortical networks *in vitro* that closely resemble those found *in vivo*. To date, there has been little research published characterising the functional properties of neural networks formed by PSC-derived neurons, with some notable exceptions [38]. In this relatively early phase, the field has focused on the production of specific cell types rather than on developing representative neural networks, although this is rapidly changing. This is an important issue for the future

exploitation of stem cell models for functional studies of synaptic function in AD and also for the potential generation of models of AD progression through the central nervous system. Clearly, models to study AD initiation and progression in the context of different human neural circuits *in vitro*, including cortico-cortical, cortico-thalamic and cortico-hippocampal, have considerable potential for functional studies of AD pathogenesis and testing of therapeutic intervention strategies. The availability of powerful optogenetic techniques to control neuronal firing [39], combined with recent advances in genome engineering in stem cells [40], offer the potential for accurate control of circuit inputs, activity and outputs in healthy and AD-affected circuits. A related issue is the potential generation of models of greater cellular complexity to study the contribution of different cell types to AD pathogenesis, including astrocytes and microglia. Such a system could also be extended to studying the roles of different AD-associated risk alleles in different cell types during AD initiation and progression.

Stem cell models of Alzheimer's disease

Initially, the majority of neurological stem cell disease modelling studies have used genetic forms of disease, typically single gene disorders. Cellular or molecular pathologies have been observed in a number of conditions, including Rett syndrome, Parkinson's disease, schizophrenia, spinal muscular atrophy and familial dysautonomia [6,7,11,12,41,42]. These proof-of-principle studies suggested that neuronal models generated from patient-specific somatic cells could be a potentially powerful approach to studying AD initiation and progression.

Cellular models of AD and AD-related disorders have been reported in the past year by several research groups [8-10,13]. Those studies clearly demonstrated that neurons generated from genetic forms of AD both from iPSCs and by direct transdifferentiation recapitulate key aspects of AD pathology, particularly altered APP processing and Aβ peptide production. Although there are significant differences among the studies, discussed below, collectively these reports demonstrate the utility and promise of this approach for generating human cellular models for AD research.

The Abeliovich laboratory reported the production of human neurons carrying mutations in either *PSEN1* (A246E) or *PSEN2* (N141I), the two genes most commonly mutated in familial AD. Rather than by iPSC generation, neuron production was by direct transdifferentiation of human fibroblasts to glutamatergic neurons. This transdifferentitation was achieved with the introduction of four transcription factors involved in neural development (Brn2, Mytl1, Zic1 and Ascl1) [10]. As these neurons were generated from fibroblasts deposited in the Coriell Cell Repository [43], clinical data on the individual donors are, by necessity, incomplete. In this system, in which approximately 30% of surviving cells are neurons, the levels of secreted Aβ, Aβ40 and Aβ42 were increased, and the ratio of Aβ42/Aβ40 was narrowed in cultures of familial AD neurons. In addition, the authors reported cell biology studies of the subcellular localisation of APP in the mutant neurons, as well as on endosomal sizes, both of which were altered in familial AD neurons. The increase in endosomal vesicle size in the familial AD neurons was rescued by introduction of wildtype *PSEN1*, and phenocopied in control neurons by gamma-secretase inhibition. Those data suggest that this aspect of the phenotype was not due to increased Aβ production, and may be secondary to some form of loss of function of gamma-secretase.

With respect to iPSC models of AD, two groups have reported generation of familial AD iPSCs and disease-related phenotypes. Yagi and colleagues generated glutamatergic neurons from control and AD iPSCs carrying mutations in *PSEN1* and *PSEN2* [13], using the same starting fibroblast lines from the Coriell repository as used in the report from the Abeliovich group [10]. Those neurons demonstrated changes in the Aβ40/Aβ42 ratio, with a trend towards an increased production of Aβ40 and Aβ42 peptides, although this varied among lines and was not significantly different compared with control cells [13]. Confirming the relevance of this model, the authors found that the change in the Aβ ratio was corrected by pharmacological inhibition of the gamma-secretase complex.

Detailed pathology was reported in neuronal models generated from two patients with duplications of APP, another cause of autosomal dominant familial AD, by Israel and colleagues [9]. In this case, cultures of iPSC-derived neurons of a mixture of neurotransmitter types showed an increase in Aβ40 production, compared with nondiseased controls, although Aβ42 levels were found to be below the level of detection in this system [9]. In contrast to the paper from Yagi and colleagues, in which no tau pathologies were observed, Israel and colleagues observed an increase in tau phosphorylation in the APP duplication neurons. Gamma-secretase and beta-secretase inhibition both revert the increased Aβ40 production by APP duplication neurons. However, an unexpected finding from this study was that only beta-secretase inhibition also prevented the increased GSK3β activation and tau phosphorylation. The authors interpreted this latter finding as suggesting that there may a role for increased production of the C-terminal fragment of APP generated by beta-secretase in AD progression [9]. Finally, this group also observed an increase in the number of large early, Rab5-positive endosomes in

neurons generated from an APP duplication iPSC line, consistent with the findings from the Abeliovich group.

A different approach was taken by our group, in which we used our understanding of cerebral cortex development to direct differentiation of iPSCs and ESCs to cortical glutamatergic neurons at high efficiency [30]. For modelling AD, we focused our studies on Down syndrome/Trisomy 21, due to the very high incidence of AD in people with Down syndrome [8], thought to be primarily due to the presence of the *APP* gene on chromosome 21 [44]. Using Trisomy 21/Down syndrome ESCs and iPSCs, we found that cortical neurons generated from that genotype recapitulated many aspects of early AD: greatly increased production of both Aβ40 and Aβ42, Aβ42 aggregate formation, increased neuronal cell death, and tau hyperphosphorylation and localisation to cell bodies and dendrites. As in other studies, gamma-secretase inhibition prevented the increased Aβ40 and Aβ42 production by Down syndrome cortical neurons. In contrast to those studies, Down syndrome neurons formed relatively large aggregates of Aβ42 and also underwent significantly higher levels of neuronal cell death than nondiseased controls.

Next steps

At this stage, it could be argued that stem cell models have not yet provided novel mechanistic insights into AD. Questions have therefore been raised about the usefulness of this approach, beyond these initial proofs of principle. In the longer term, these centre on the contributions that such models can make to our understanding of AD. In the medium term, a pressing question is the extent to which these models recapitulate the disease process, rather than its initiation, and whether they will have other applications in mechanistic studies of AD. There are obvious applications for using iPSC lines generated from individuals with genetic forms of AD to produce more complex cellular models in which familial AD neurons are used as initiator cells for the disease, whereas neuronal and non-neuronal cells of other genotypes are used to study their roles in disease progression. Such studies are dependent on the development of more complex cellular models of the human central nervous system *in vitro*, which combine neurons, astrocytes, oligodendrocytes and microglia. This application also crosses over into the use of these models for studying the majority of AD – the late-onset, sporadic form.

To fully recapitulate AD *in vitro*, an ideal human cellular model of AD would use the appropriate cell types and neural circuits, including microglia, would develop relevant molecular pathology – that is to say, altered APP processing, Aβ aggregation and tau hyperphosphorylation – and would do so in a reproducible manner over a timescale short enough for practical use. However, it could be argued that for these models to be worthwhile additions to the available models for AD, they should do more than simply recapitulate the biochemical aspects of AD. For example, as the early stages of AD are marked by synaptic dysfunction, these models could enable functional studies of synaptic activity and network behaviour in human cortical systems. Such models could also potentially be used to study the cell autonomous and nonautonomous aspects of AD initiation, particularly in familial AD, and the related issues of AD transmission between neurons and disease spread through the nervous system.

Sporadic AD makes up over 99% of cases of AD and is highly heritable, estimated at 60 to 70% [25]. As part of their AD modelling study, the Goldstein group generated iPSC lines from two individuals with late-onset, sporadic AD [9]. When differentiated to neurons, lines from one individual consistently developed phenotypes similar to those observed in the familial AD (APP duplication) lines: increased Aβ40 production, tau phosphorylation and an increase in the number of large early endosomes. In contrast, lines from a second individual did not develop AD-related phenotypes [9]. Given the small number of cases, it is hard to generalise from these initial experiments the likely phenotypes observed when generating models from a larger cohort of individuals with well-genotyped, late-onset AD. The significant heritability of AD does, however, suggest that modelling sporadic AD is feasible, if only in the subset of patients with a larger genetic contribution to their disease. As it is not currently possible to prospectively identify those patients, one possibility is that *in vitro* disease modelling can be used to identify empirically those patients with a particularly significant genetic contribution to disease initiation or progression.

Genome-wide association studies (GWAS) in sporadic AD have identified one major susceptibility gene, the ε4 allele of ApoE, and several additional susceptibility loci, including PICALM, BIN1, SORL1, Clusterin/ApoJ and CR1 [45]. Some of the genes encoded by these loci may alter APP processing or directly interact with Aβ peptides, but all may have functions independent of APP. A variety of biological pathways has been implicated from GWAS, including endocytosis/trafficking, lipid metabolism and inflammation [45].

The functional importance of these GWAS findings remains to be tested in disease models, but it is becoming clear that genes implicated in AD development form functionally related groups. For example, PICALM, BIN1 and SORL1 all encode proteins that are involved in endocytosis and vesicle trafficking [25,46,47]. With the completion of additional GWAS with increased power and the addition of further AD-associated genetic variants, the involvement of different cellular pathways in

AD progression will probably become clearer. Using those GWAS findings to inform the generation of patient-specific models of AD carrying each of those functional variants will be a powerful tool for testing the functional contribution of those genes and pathways and different cell types to the disease process.

An alternative approach to generating individual patient-specific lines for testing the functional contribution of variants to AD pathogenesis will be to use a small subset of well-characterised, ideally genome sequenced, lines as a template for genome engineering of specific combinations of gene variants. Such an approach would allow for fine control over the combinations of genetic variants, avoiding potentially confounding effects from the variety of genetic backgrounds inherent in studying a large population of different individuals. By analogy with the use of inbred strains of mice for gene targeting for isolating the effects of genes, as well as controlling for background genome effects, this would enable standardisation of studies among laboratories.

Conclusion

The publications over the past year have demonstrated the feasibility of modelling several aspects of AD in human neurons. Common themes in these reports include the neuron-specific nature of the APP processing phenotypes, the response to beta-secretase and gamma-secretase inhibition, changes in tau phosphorylation and altered endosome size and number. These are positive and encouraging findings, which are particularly promising for the feasibility of using these models for compound screening. Key issues for this area of research are whether these models can be exploited for mechanistic studies of AD progression, for functional studies of disease-associated genetic variants and, ultimately, for modelling late-onset, sporadic AD.

Abbreviations

Aβ, Abeta fragment of APP protein; AD, Alzheimer's disease; APP, amyloid precursor protein; ESC, embryonic stem cell; GWAS, genome-wide association study; iPSC, induced pluripotent stem cell; PSC, pluripotent stem cell.

Competing interests

The author declares that he has no competing interests.

Acknowledgements

Research in the author's group is supported by the Medical Research Council, Alzheimer's Research UK and the Wellcome Trust , and subject to a patent filing from the University of Cambridge, PCT/GB2011/001144.

Published: 6 November 2012

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doi:10.1186/alzrt147
Cite this article as: Livesey FJ: Stem cell models of Alzheimer's disease and related neurological disorders. *Alzheimer's Research & Therapy* 2012, **4:**44.