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Review

Toward more predictive genetic mouse models of Alzheimer's disease

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ABSTRACT

Genetic mouse models for Alzheimer's disease (AD) have been widely used to understand aspects of the biology of the disease, but have had limited success in translating these findings to the clinic. In this review, we discuss the benefits and limitations of existing genetic models and recent advances in technologies (including high throughput sequencing and genome editing) that promise more predictive models. We summarize widely used biomarkers and behavioral tests for mouse models of AD and highlight best practices that will maximize translatability of preclinical findings.

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1. Introduction

With an aging population, Alzheimer's disease (AD) is on the increase with no current cures or effective treatments. Despite the obvious advantages of using mice to study complex, age-related diseases such as AD, it is a challenging time for mouse models. In some quarters, enthusiasm for using mice to model AD is waning, in part, because of the lack of success in translating findings in mouse models to the clinic. Current models utilize knowledge from early onset Alzheimer's disease (EOAD, or familial AD), incorporating mutant forms of amyloid precursor protein (APP), presenilins, Tau (Mapt) and other genes. These models have been essential in understanding the biology of key aspects of AD, most prominently the formation of amyloid plaques and neurofibrillary tangles, but have not proven particularly effective as preclinical models. Some of this is down to the lack of the critical hallmarks of AD, notably significant neuronal cell loss, in the current models. However, the lack of success is also due to a lack of standardization of models (such as inconsistent genetic background), underpowered experiments, and less than ideal end points. Additionally, there may be significant differences between early and late onset AD (LOAD, or sporadic AD) such that treatments tested in existing models may be useful for EOAD but not for the sporadic form of AD that is much more common in the patient population.

Encouragingly, times are changing. Advances in studies of patient populations and animal models should enable the creation of more predictive mouse models; these are summarized in Table 1 and described in detail below. Genome-wide association studies (GWAS), and more so high-throughput genome sequencing projects are identifying novel variants for late onset Alzheimer's disease that increase our knowledge of genetic susceptibility of LOAD (Fig. 1). Combine these advances with the revolution in genetic and genome engineering and, although there is much work still to do, the future looks bright for developing the next generation of AD models. In this review, we aim to provide recent updates regarding current mouse models relevant to AD as well as consider emerging strategies for the generation of improved models. We also discuss how the field is moving towards improved standards for experimental design and phenotyping to maximize the benefit of mouse models as researchers seek novel therapeutic targets for AD.

2. Modeling early-onset Alzheimer's disease

Genetic mouse models of early-onset Alzheimer's disease have been reviewed recently (Hall and Roberson, 2012) and are summarized in Table 2; we focus here on developments since then. A summary of existing AD mouse models is compiled and maintained by the Alzforum (http://www.alzforum.org/research-models). This important resource includes updated information regarding genetic construct, phenotype, and availability of each mouse model.

While traditional transgenic mouse models have been essential to our understanding of AD, they suffer from a variety of drawbacks: mis- or over-expression of transgenically expressed protein relative to the endogenous protein; developmental compensation for knocked-out or over-expressed genes; and inadvertent and unknown disruption of an endogenous gene by the transgenic construct. Most transgenic lines have been created on standard genetic backgrounds, which may not be the most suitable for expressing disease phenotypes (see discussion below). Perhaps most critically, the timing of expression off the transgenic promoter will not mimic the disease condition, so that mechanisms of disease onset cannot be studied in a realistic context. In addition, the utility of many of these models to the research community is limited due to legal restrictions on their availability and use, particularly for therapy development projects by for-profit companies (Bubela and Cook-Deegan, 2015).

Over the past few years, a variety of techniques have been used to attempt to generate improved mouse models of EOAD. In order to get away from the inherent technical issues with using traditional transgenic models, some groups have used a knock-in strategy. This has the advantage of providing more realistic expression patterns and levels, and avoids the complication of disrupting an unknown genomic locus. Perhaps due to the lack of over-expression of APP and/or tau or the relatively short lifespan of the mouse, these models have shown relatively mild, late onset phenotypes (Malthankar-Phatak et al., 2012; Saito et al., 2014; Plucinska et al., 2014).

Another recent approach to improving mouse models of EOAD has been to use systems that enable inducible expression of transgenic protein to study the half-life and reversibility of AD endophenotypes. When mutant APP expression was turned off after the formation of initial amyloid deposits, performance in some cognitive tasks improved (Melnikova et al., 2013). Likewise, suppression of transgenic mutant tau expression demonstrated that tau-induced impairments are reversible (Van der Jeugd et al., 2012). These studies provide justification for drug trials in AD patients, at least early in progression of the disease. A similar approach has been used to distinguish the effects of soluble Aβ relative to deposited amyloid (Fowler et al., 2014).

In addition, a recent paper using genetic mouse models (Willem et al., 2015) presents evidence that cleavage of the APP protein by other than the well-known beta and gamma secretase pathways results in forms of Aβ that may be important in APP pathology. This highlights the fact that we still do not fully understand which fragments of APP cause AD, and that genetic models are useful to dissect the physiological cleavage events.

Various labs now are using a transcriptomics approach to compare transcriptional profiles of mouse models to patient tissue, with varying conclusions (Jackson et al., 2013; Landel et al., 2014; Morihara et al., 2014; Burns et al., 2015).

One of the major benefits to the mouse model is that it is relatively easy to assay the effect of other genes/pathways to see if they impinge on an established AD endophenotype. There have been hundreds of publications showing that combining an existing AD model with an established genetic knockout can modify a specific phenotype (e.g., plaque load, performance in Morris water maze, etc.). Most prominently, genetic ablation of the *tau* (*Mapt*) locus in AD models has enabled dissection of the relative contributions of the Aβ and tau pathways to AD pathophysiology (Vossel et al., 2015). While this approach may be useful for identifying relevant disease pathways and even targets, it has not led to a model that recapitulates all aspects of the human disease.

3. Creating animal models for late-onset Alzheimer's disease

In contrast to creating mouse models for EOAD, generating models for late-onset Alzheimer's disease (LOAD) is more challenging.