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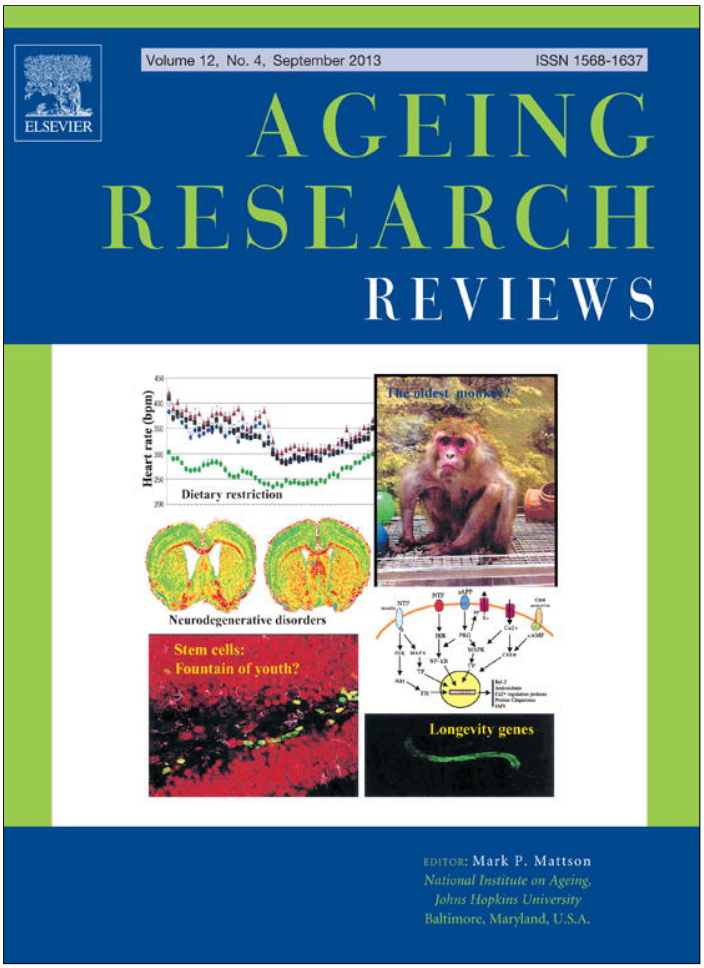

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Review

Commentary to the recently published review "Drug pipeline in neurodegeneration based on transgenic mice models of Alzheimer's disease" by Li, Evrahimi and Schluesener. Ageing Res. Rev. 2013 Jan;12(1):116–40

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ABSTRACT

Li and colleagues summarized the most frequently used Alzheimer's disease (AD) mouse models available for drug testing and the mediating effects of the different compounds. With almost 300 cited publications, authors present the research community's effort of the last 10 years in finding a new drug for the treatment of AD.

Some of the transgenic mouse lines mentioned by Li and colleagues are discussed only very briefly. Since we are convinced that a couple of these models indeed have a great value for AD research and the development of new AD drugs we will subsequently describe a few of them in more detail.

A suitable mouse model of AD does not only have to mimic major hallmarks of AD that are modifiable by different test substances as mentioned by the authors; they also have to be translational to clinical trials in humans. For the following discussion, we will therefore also include information on clinical trials of drugs previously tested in the different transgenic mice.

Contents

1. mThy1-APP751 (Line 41 and APP_{SL}) transgenic mice

Line 41 transgenic mice over-express the longest APP isoform 751 with the London (V717I) and Swedish mutation (K670M/N671L) under control of the murine Thy1 promoter (Rockenstein et al., 2001). These mice present with an early onset of plaque formation in the frontal cortex including the piriform and olfactory cortex, followed by the hippocampus and thalamus. The most prominent Aβ species of these mice is reported to be Aβ1–42 (Rockenstein et al., 2001), though numerous following preclinical studies found also high levels of Aβ1–40 and Aβ1–38. In two further publications the behavioral deficits of Line 41 transgenic mice were described in detail: 6 months old animals already show significant spatial working memory deficits, memory retention deficits and episodic like-memory discrepancies. These deficits are accompanied by changes in the activity, social novelty recognition and curiosity. The results were unbiased by any motor disturbances or unusual pain perception (Faizi et al., 2012; Havas et al., 2011). Havas et al. (2011) could additionally show that first plaques were already visible at an age of 3 months, followed by further Aβ accumulation in the cortex and hippocampus during aging. These data correlated with an increase in SDS and FA insoluble Aβ42.

Our team replicated this transgenic mouse model also using the longest APP isoform 751 with London and Swedish mutation under control of the murine Thy-1 promoter in a C57BL/6 background. The resulting APP_{SL} transgenic mice present with the same behavioral deficits, plaque load and Aβ levels compared to Line 41 mice. Furthermore, we could observe that progressive plaque deposition is accompanied by a strong neuroinflammation as evident by astrogliosis and activated microglia and age-dependent increasing oxidative stress (unpublished data).

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Within the last ten years, these two very similar mouse lines with Swedish and London mutation, Line 41 and APP_{SL}, were frequently used for AD related drug trials. Next to analyze the effect of a NADPH oxidase inhibitor (Lull et al., 2011), animals were also used to test Cerebrolysin™ (Rockenstein et al., 2002), neprilysin (Spencer et al., 2011), ACAT inhibitors (Hutter-Paier et al., 2004; Huttunen et al., 2010, 2009), γ-secretase modulator CHF5074 (Imbimbo et al., 2009), Neuropeptide Y (Rose et al., 2009), glutaminyl cyclase inhibitor (Schilling et al., 2008), UBITh® amyloid-β vaccine (Wang et al., 2007), CDK5 inhibitor Roscovitine (Crews et al., 2011) and EFRH-Phage (Lavie et al., 2004). All of these substances were able to modify at least one AD-like feature of these mice, like cognitive deficits, plaque burden or Aβ concentrations in specific brain regions. Furthermore, in some of these studies, drug effects on the neuroinflammation were analyzed: Imbimbo and colleagues observed increased activated microglia in APP_{SL} mice and CHF5074 as well as Ibuprofen were able to reduce the activated microglia (Imbimbo et al., 2009); Huttunen and colleagues published suppression of astrogliosis and enhanced microglia activation after ACAT inhibitor treatment in APP_{SL} mice (Huttunen et al., 2010). Rockenstein and colleagues observed an increase in total microglia levels in Line 41 compared to non-transgenic littermates, and these levels were modifiable by Cerebrolysin™ (Rockenstein et al., 2011).

The substances PQ912, UBITh®, Cerebrolysin™ and CHF5074 are test compounds that were already tested in one of these two transgenic mouse models and clinical trials. The phase 1 clinical studies with PQ912 and UBITh® (NCT00965588; http://clinicaltrials.gov/) for the treatment of AD, were just recently successfully completed; Cerebrolysin™ was proven to be effective for the treatment of AD (Alvarez et al., 2011), vascular dementia (Muresanu et al., 2008), and traumatic brain injury (Alvarez et al., 2008). First clinical trials with the γ-secretase modulator CHF5074 for the treatment of AD are just completed (NCT01303744, NCT01203384; http://clinicaltrials.gov/), but further clinical trials are ongoing.

Since compound tests in Line 41 and APP_{SL} transgenic mice were already very successful and some of the substances are currently tested in clinical trials, it can be concluded that these mice are a very promising AD mouse model mimicking the most prominent features of AD pathology.

2. Human tau (Htau) transgenic mice

Within the last 10 years, researchers put increasing effort in analyzing the physiological and pathological function of tau (MAPT) as hallmark of neurofibrillary tangles in tauopathies, including AD. By now, the research community consents on the importance of tau as pathological factor for the development of AD, clearing the way for the development of tau specific drugs and thus the need of transgenic human tau animal models for drug trials. First generation human tau transgenic mouse models often presented with moderate to severe motor deficits, e.g. Allen et al. (2003). This disadvantage compromises most cognitive behavioral tests, a read-out variable of major interest to assess the potential clinical efficacy of new compounds. When selecting a human tau transgenic model for AD drug trials, thus not only disease specific pathologies should be considered, but also disease unspecific pathologies, like motor deficits, excluded.

Several different human tau transgenic mice are published so far. Next to the already mentioned models by Andorfer and Santacruz (Andorfer et al., 2003; Santacruz et al., 2005) that were used to test minocycline (Garwood et al., 2010), HSP90-CHIP complex (Dickey et al., 2007), passive immunization (Chai et al., 2011) and sulfobenzoic acid derivative AK1 (Spires-Jones et al., 2012), respectively, a couple of other human tau models are available and partially also used for drug efficacy studies. The transgenic human tau model with P301L mutation as model of tauopathies expresses the transgene under control of a Thy-1.2 promoter (Gotz et al., 2001) and is characterized by hyperphosphorylated tau, astrocytosis and neuronal apoptosis. These so-called pR5 mice were already successfully used to analyze the effect of an active immunization against tau (Bi et al., 2011) as well as that of sodium selenate (van Eersel et al., 2010). Both substances were able to improve the phenotype of mice by reducing NFT pathology and hyperphosporylation of tau.

TMHT mice, express human tau441 with V337M and R406W mutations under control of the murine Thy-1 promoter (Flunkert et al., 2012). They are characterized by high levels of soluble and sarcosyl insoluble tau, hyperphosphorylated at different disease relevant residues and pronounced spatial memory and olfactory deficits uncompromised by motor disturbances. So far, only two preclinical trial studies are published. Treatment of TMHT mice with sodium selenate led to de-phosphorylation of tau, decrease of phosphorylated and total tau levels and improved cognitive function (Corcoran et al., 2010), reproducing the positive outcome reported for the pR5 model (van Eersel et al., 2010). Treatment of TMHT mice with a grape-seed polyphenol extract (GSPE) reduced tau neuropathology by potentially preventing tau aggregation (Wang et al., 2010).

Next to these models, a couple of human tau mouse models are published, that were so far not used for drug trials but are of great value due to their different phenotypes, including human tau with V337M mutation (Tanemura et al., 2001), THY-Tau22 (Schindowski et al., 2006), human tau R406W under control of the αCAMKII promoter (Tatebayashi et al., 2002), and human tau G272V under control of a prion promoter-driven expression system with an autoregulatory transactivation loop (Götz et al., 2000). For an even more complete and detailed list of human tau transgenic mouse models, please see (Wisniewski and Boutajangout, 2010) or visit: http://www.alzforum.org/res/com/tra/tau/default.asp.

The translational value of preclinical studies to human trials remains to be proven. But also the correct experimental design will be critical for predictive validity of animal models. When testing transgenic AD models the full spectrum of potential behavioral deficits should be analyzed, including clinically relevant cognitive tests such as spatial learning (Morris water maze) or social recognition tests for mice (Nadler et al., 2004), respectively. Additionally, the other way around, clinical tests should have a high translational value, like the human maze (blue velvet arena) that resembles the navigation tasks used in preclinical development (Gazova et al., 2012; Laczo et al., 2012).

3. Outlook

The value of transgenic mouse models for basic research in neurodegenerative diseases is beyond debate. In contrast, prediction of potential therapeutic efficacy based on preclinical data started to be heavily discussed since most clinical trials in AD failed so far in spite of promising results in animals. Li, Evrahimi and Schluesener diligently summarized the majority of publications about successful preclinical studies however, without the relation to clinical outcome the value remains vague. A final conclusion about the value of results from proof of concept studies in mice for the prediction of clinical usefulness is impossible, because of a plethora of unpublished negative and positive data. Being aware that especially information about negative outcome is, to say at least, precarious for compound developing parties, thinking of a future perspective of objectified preclinical study data bases should be allowed. But also a discussion about minimal experimental standards, like

blinding, power calculation and appropriate control groups, needs to be started to increase the predictive value of preclinical studies for later clinical development. This could certainly accelerate the availability of new drugs against AD in the future.

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