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Review

Alzheimer's disease: Old problem, new views from transgenic and viral models

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ABSTRACT

Alzheimer's dementia is developing ever more as a complex syndrome with various unknown genetic and epigenetic contributions. These are compounded on and exacerbating the underlying amyloid and tau pathology that remain the basis of the pathological definition of Alzheimer's disease. Here, we present a selection of aspects of recent bigenic and virus-based mouse strains, developed as pre-clinical models for Alzheimer's disease. We discuss newer features in the context of the characteristics defined in previously validated transgenic models. We focus on specific aspects of single and multiple transgenic mouse models for Alzheimer's disease and for tauopathies, rather than providing an exhaustive list of all available models. We concentrate on the content of information related to neurodegeneration and disease mechanisms. We pay attention to aspects and defects that are predicted by the models and can be tested in humans. We discuss implications that help translate the fundamental knowledge into clinical, diagnostic and therapeutic applications. We elaborate on the increasing knowledge extracted from transgenic models and from newer adeno-associated viral models. We advocate this combination as a valuable strategy to study molecular, cellular and system-related pathogenic mechanisms in AD and tauopathies. We believe that innovative animal models remain needed to critically test current views, to identify and validate therapeutic targets, to allow testing of compounds, to help understand and eventually treat tauopathies, including Alzheimer's disease.

1. Introduction and background

1.1. Alzheimer disease

Alzheimer's disease (AD) is the most prevalent form of dementia among the elderly accounting for more than 70% of all dementia cases [1]. The clinical disease stages are initially announced by mild cognitive impairment (MCI) that gradually progresses from subtle cognitive and memory problems to severe deficits, inevitably ending in deep dementia. The composite clinical picture at any stage is variable among AD patients, including cognitive and memory problems, and mild to severe changes in social behavior with mood swings and altered personality and character, including apathy, depression, irritability, agitation, psychosis, aggression.

Current treatments for AD are purely symptomatic and hardly effective. The development of disease-modifying therapies is extremely urgent because of the exponential increase in AD with age. This poses a direct and major medical and social threat for current and all future generations with our ever-increasing life expectancy. Diagnosis of AD is not uniformly accepted or applied, and based on variable combinations of neurological examination, CSF-biomarkers, mental and memory tests, MRI and PET brain-imaging. Needless to state that, even when effective therapy becomes available, diagnosis of AD should be made as early as possible in the disease process to help the patient, the family and caretakers.

The development of efficient diagnostic and therapeutic means relies entirely on scientific progress made in understanding the fundamental mechanisms that cause and underlie AD. Progress then remains heavily dependent on studies in animal models that recapitulate the disease at least in essentials aspects, if not as exact and complete phenocopies.

Moreover and in addition, early objective diagnosis of AD is essential for many reasons. Today it is profoundly hampered, if not made impossible by problems of accuracy and safety, specificity and reproducibility of current methods and tests, ranging from cognitive examination tests, lumbar puncture and ELISA for CSF-biomarkers, PET-imaging for amyloid load and glucose metabolism, MRI for brain region-specific atrophy. Many tests detect problems (too) late in the disease process to allow effective treatment, provided it was available. Diagnostic problems therefore reverberate into therapeutic tests, because of difficulties with recruiting properly diagnosed AD patients, and of proper stratification by genetic, clinical or biochemical parameters. This is currently technically impossible and prevents

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personalized therapeutic strategies that would be more effective and less costly. The same problems plague experimental therapies that are hampered by the objective estimation of the rate of decline of cognition. Finally, stratification based on genetic parameters remain largely limited to defining the ApoE genotype, and is used often only post-hoc. The many genetic, epigenetic and environmental factors that are claimed as potential risk-factors to AD are intensely debated, but none generally accepted or implemented as objective parameters in clinical studies — with exceptions on the obvious parameter of age and gender.

Despite all the technical progress, the post-mortem brain pathology described by Alzheimer more than a century ago, still defines AD. The microscopic pathology remains the only final diagnosis, unfortunately post-mortem: extracellular amyloid plaques made up of aggregated amyloid peptides and intracellular neurofibrillary tauopathy resulting from aggregated phosphorylated protein tau. The associated parameter of inflammation, also noted by Alzheimer, remains the third important hallmark in AD brain.

1.2. AD and amyloid

A panoply of data corroborates the amyloid cascade hypothesis that proposes a primary, causal role for amyloid peptides in the pathogenesis of AD. The experimental proof is, however, still not conclusive despite 25 years of molecular and cellular analysis since the discovery of amyloid peptides [2]. Amyloid peptides (Aβ) accumulate in the brain of AD patients because of increased production or of impaired elimination. The peptides are produced from the amyloid precursor protein (APP) by a complex set of sequential endoproteolytic cleavages [3].

Amyloidogenic processing of APP is initiated by β-secretase (BACE) that produces the secreted APPsβ ectodomain and the cell-bound C99 fragment, which is then cleaved by γ-secretase to release the intracellular domain (AICD). This process also produces various amyloid peptides for as yet unknown biological reasons, because no physiological function is unequivocally assigned to any of the amyloid peptides.

Non-amyloidogenic processing of APP results in the secreted APPsα ectodomain and the C83 fragment, following cleavage by α-secretase, an activity exerted mainly by ADAM10 [4]. The C83 fragments are also processed by γ-secretase to yield the same AICD fragment, but also the harmless p3 peptides instead of the amyloid peptides [3].

Disease-modifying therapies in clinical tests today are mostly aimed at reducing the amyloid peptide concentrations in brain, either (i) by inhibition of β- or γ-secretases, (ii) by increasing elimination by active or passive immunization, (iii) by preventing peptide aggregation, or (iv) by increasing proteolytic degradation. Despite the many drawbacks and problems in these different approaches, the amyloid peptides remain prime target for therapy, and prime suspects for the pathogenic mechanism in AD [5].

Interestingly, PET-imaging using specific amyloid-ligands demonstrated high amyloid-load in the brain of cognitive non-compromised elderly and concluded to 20–40% false amyloid-positive cases pending the study [6–8]. These findings imply that even brain amyloid load does not equate to impaired cognition or failing mental capabilities.

1.3. AD and tau: not an innocent by-stander

In contrast to many primary tauopathies, wherein tau is accountable for neurodegeneration and its consequences, AD is classified as a secondary tauopathy downstream of amyloid pathology. Protein tau is yet to be generally accepted as being important in the overall disease process.

Tauopathy is typified by neurofibrillary tangles and neuropil treads composed of phosphorylated protein Tau and constitutes the second post-mortem diagnostic hallmark in AD but in contrast to amyloid pathology, is not specific for AD. Tauopathy is diagnostic for a variety of neuro-degenerative diseases that differ widely clinically, biochemically and pathologically [9–11].

Importantly, tauopathy is invariably present in all AD cases, including the early onset familial cases (EOFAD) that are associated with dominant mutations in the genes coding for APP or presenilins. These presenile AD-cases are by definition caused by excess production of deviating amyloid peptides. Consequently, the associated tauopathy in these obligate amyloid AD cases, must be closely linked to the cognitive demise and dementia of the Alzheimer type. Arguably, this is the strongest argument for an essential pathological contribution of the tauopathy in AD, rather than an innocent by-stander phenomenon. In addition, long-standing observations maintain that the typical brain-regional occurrence and progression of tau pathology in AD patients correlates temporally and spatially more closely with neuronal and cognitive dysfunction than amyloid pathology in AD [12,13].

Interestingly, no familial “amyloid-only” AD-cases have been described, while more than 40 mutations in the gene coding for human protein tau (the MAPT gene on chromosome 17) are associated with many sub-types of frontotemporal dementia [14,15] (cfr www.alzforum.org). These mutations are either exonic and expressed as a mutant protein tau, or intronic, which affect splicing of the tau mRNA to include or exclude exon10 that codes for the second microtubule binding domain. Importantly, intronic mutations produce normal protein Tau, but at deviating levels, which disturbs physiological functions that lead to synaptic and neuronal failure and degeneration.

1.4. Protein Tau, microtubule binding and tauopathy

While the amyloid cascade hypothesis [5] emphasizes the importance of amyloid peptides to the underlying pathology in AD, it does not provide an explanation for the inherent tauopathy associated with all AD cases. In addition, as discussed in the previous section, transgenic mouse with amyloid pathology caused by neuronal expression of any APP, wild-type or mutant, do not develop authentic tauopathy.

The aggregation of phosphorylated protein Tau into filamentous inclusions, eventually tangles, is the characteristic pathological feature of many neurodegenerative disorders known as Tauopathies, including Pick's disease, progressive supranuclear palsy, frontotemporal dementia (FTD) and many others [10,11,16–18]. Familial forms of tauopathy are associated with exonic and intronic mutations in the *MAPT* gene coding for protein tau on chromosome 17 in humans. The mutations are linked to various subtypes of fronto-temporal dementia, typified by extensive tau pathology in frontal and temporal brain regions, largely without any other associated pathology, i.e. no amyloid deposits.

The two most prevalent isoforms of tau, Tau3R and Tau4R, originate by alternative splicing of exon10 and have 3 or 4 microtubule binding repeats [19]. Tauopathies are differentiated biochemically by the ratio of Tau4R/Tau3R as well as by the relative composition of all tau-isoforms in the aggregates or tangles. In the case of familial FTD, the associated mutations are the defining factor, e.g. P301L, G272V, N279K, V337M, R406W, among others. To understand the mechanisms causing the familial forms of tauopathy linked to the MAPT gene, we must define an aberration in protein tau that is both needed and sufficient to cause neurodegeneration — in the absence of amyloid. The eventual understanding of the problem is even more concerned by the fact that many intronic mutations in specified FTD-families are located in intron-exon splice sites flanking exon10, encoding the second microtubule binding domain in protein tau. These intronic mutations evidently produce normal wild-type protein Tau, and their contribution to FTD can only be a distorted ratio of tau-isoforms in CNS.

The only known physiological action of protein tau is binding to microtubules, and its affinity is proportional to the number of microtubule binding domains: Tau4R binds stronger than Tau3R. Tau3R predominates in embryonic and fetal development, which is thought to allow greater plasticity and remodeling of the cytoskeleton of