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Erik D. Roberson
Editor

Alzheimer's Disease and Frontotemporal Dementia

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Preface

Alzheimer's disease (AD) is the most common neurodegenerative disorder and one of the most feared diseases due to the manner in which it robs its victims of their memories. Frontotemporal dementia (FTD) is perhaps somewhat less well known among the public, but it is also a prominent cause of dementia that produces devastating changes in personality and a decline in interpersonal interactions. The two conditions are often considered siblings, for while they are distinct disorders targeting different brain regions and producing unique clinical symptoms, there is some overlap in their molecular neuropathology (such as the presence of inclusions containing the microtubule-associated protein tau) and genetic risk factors (such as apolipoprotein E).

Both conditions were originally described around the turn of the last century but languished without significant research effort for decades. In the 1980s, breakthroughs in pathobiochemistry and genetics led to identification of molecular players in these diseases, enabling a very fruitful period of biomedical research that continues to intensify. Recent years have seen a growing interest in the neurobiology of neuronal dysfunction in these conditions with increasing application of complex techniques from molecular and cellular neuroscience. Thus, the diversity and sophistication of methods and protocols used for research on AD and FTD continue to grow. It is not uncommon, and actually is expected in many journals, to see publications that include techniques as divergent in their required expertise as behavior, electrophysiology, confocal microscopy, and hardcore biochemistry. Consequently, projects in AD and FTD research may require individual investigators to branch out into complex approaches for which they have not received abundant hands-on training. The goal of this book is to make many of those techniques more accessible.

The book is intended for scientists of all kinds studying AD and FTD. Realizing that many of the approaches will be foreign to some users, the protocols are presented in a step-by-step fashion with complete materials lists and user notes describing the "real story" about how to make the method work.

The book begins with an overview of the two diseases and modern approaches to research on them. Many of the molecules associated with AD and FTD are notoriously difficult to work with, so the first half of the book (Chaps. 2–10) details specialized protocols for working with amyloid-β peptide, tau, and apolipoprotein E. The second part (Chaps. 11–18) focuses on experimental systems for studying AD and FTD, including cell and animal models, and outcome measures that can be used to assess neuronal function in these systems.

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Contents

Chapter 1

Contemporary Approaches to Alzheimer's Disease and Frontotemporal Dementia

Erik D. Roberson

Abstract

Alzheimer's disease and frontotemporal dementia are two of the most common neurodegenerative dementias. Here, we review the clinical presentation, genetic causes, typical neuropathology, and current treatments for these disorders. We then review molecules involved in their pathogenesis and protocols for working with these species and conclude with a discussion of experimental systems and outcome measures for studying these disorders.

Key words: Dementia, Mild cognitive impairment, Memory, Personality change, Disinhibition, Aging, Methods, Protocols, Aβ, β-Amyloid, Tau, Apolipoprotein E, Progranulin, TDP-43

1. Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease. Age is the strongest risk factor, and advances in health care that enable more people to live into their 80s and 90s have led to a steady increase in the incidence of AD (1).

Memory impairment is the earliest and most prominent symptom of AD. The typical patient might first notice mild problems with episodic memory, such as repeating themselves in conversation or forgetting recent events. Initially, the symptoms do not cause significant functional impairment, and at this stage the patient is considered to have amnestic mild cognitive impairment (aMCI). As the disease and symptoms worsen, functional impairment in daily activities becomes manifest, such as with problems balancing the checkbook, preparing meals, or managing medications. At this point, unless another likely cause is identified, the patient meets criteria for a clinical diagnosis of probable AD.

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The disease is inexorably progressive and fatal, with median survival about 12 years from onset of symptoms (2). Definite diagnosis is made neuropathologically, based on the presence of the pathological hallmarks of AD: amyloid plaques and neurofibrillary tangles.

Three genes have been identified as causes of rare, autosomal dominant, early onset AD. *APP*, encoding amyloid precursor protein, was the first to be identified (3), followed by *PSEN1* and *PSEN2*, encoding presenilin 1 and 2 (4–6). All three genes are involved in the production of amyloid-β peptide (Aβ). APP is the precursor protein from which Aβ is generated, and the presenilins are components of the γ-secretase enzyme complex that cleaves Aβ from APP (7, 8).

Current treatments for AD have only modest benefits (9). Around the time of diagnosis, one of three widely available cholinesterase inhibitors is often used to boost cholinergic function. In the middle stages of the disease, these agents are often paired with memantine, which prevents overstimulation of NMDA-type glutamate receptors. Many other agents specifically targeting the molecular processes involved in pathogenesis (and developed using some of the techniques described in his volume) are currently in clinical trials, and there is hope that some of these agents will provide more dramatic therapeutic benefit (10).

2. Frontotemporal Dementia

Frontotemporal dementia (FTD) is a term variably used to refer either to a specific clinical syndrome (more specifically called "behavioral variant FTD" or bvFTD) or to a family of neurodegenerative conditions that includes bvFTD and several related disorders (a group also called "frontotemporal lobar degeneration" or FTLD) (11, 12).

The clinical disorders falling under the umbrella of FTLD include bvFTD, semantic dementia, progressive nonfluent aphasia, and FTD with motor neuron disease (FTD-MND) (13). The bvFTD is characterized by personality changes and loss of insight, emotion, and social interactions (14). In semantic dementia, patients develop a fluent aphasia with loss of semantic knowledge about objects (15). Patients with progressive nonfluent aphasia exhibit progressive deterioration in expressive language with agrammatic, effortful speech (16). FTD-MND produces a combination of behavioral symptoms and frontal executive dysfunction in combination with weakness due to motor neuron degeneration (17).

Just as the clinical syndromes associated with FTD are more diverse than in AD, the neuropathology of FTD is also more complex (18). About half of the cases have some form of

tau-positive inclusions, while most of the others have inclusions composed of ubiquitinated TAR DNA-binding protein of 43 kDa (TDP-43). A small percentage have inclusions of the "fused in sarcoma" (FUS) gene product (19).

Families in which FTD is inherited in an autosomal dominant manner have also provided important clues to the molecular pathogenesis of the disease (20). Roughly 5% of all FTD cases are due to mutations in the *MAPT* gene encoding tau; all of these cases have tau pathology (21–24). Roughly 5% of FTD cases harbor mutation in the *GRN* gene encoding progranulin (25–27); these cases display TDP-43 pathology (28). Other, much less common genetic causes of FTD include mutations in *CHMP2B* (29, 30) or *VCP* (31, 32).

There are no FDA-approved treatments for FTD, although selective serotonin reuptake inhibitors are often used (33, 34). The lack of effective treatments for FTD underlines the need for intense research to develop new therapeutic strategies for targeting this disorder.

3. Molecules Involved in AD and FTD

As described in Subheadings 1 and 2, the identification of proteins accumulating in inclusion bodies and of genes causing inherited disease has greatly advanced our understanding of the molecular basis of AD and FTD.

Aβ is a 40- or 42-amino acid fragment of APP, which has normal functions in regulating synaptic transmission (35, 36), but which accumulates to toxic levels in AD. One of the most important properties of Aβ is its ability to aggregate into multimers, including dimers and trimers (37, 38), dodecamers (39), larger oligomers (40), protofibrils, and the long fibrils that compose amyloid plaques. The size of an Aβ aggregate is a critical determinant of its toxicity (41, 42). Unfortunately, the diverse array of possible aggregation states makes working with Aβ very challenging. In Chapter 2, Mary Jo LaDu and colleagues present protocols for preparing synthetic Aβ monomers, oligomers, and fibrils. In Chapter 3, Dominic Walsh, Dennis Selkoe, and colleagues describe purification of small Aβ oligomers (dimers and trimers) from cultured cells and from CSF and brain tissue. In Chapter 4, Sylvain Lesné and colleagues describe the isolation of Aβ*56, a larger oligomer shown to correlate with cognitive deficits in a mouse model of AD (39). In Chapter 5, Justin Legleiter describes protocols for using atomic force microscopy to evaluate the aggregation state of Aβ.

Aβ is not the only important product generated from its precursor, APP. The initial step in the production of Aβ from APP is

the cleavage of the extracellular portion of APP, which generates carboxy-terminal fragments (CTFs). The second step is the cleavage of the CTFs by γ-secretase, which produces Aβ and the APP intracellular domain (AICD). Thus, production of Aβ is coupled to generation of other biologically active species, and independent assays for each of these species can aid in the interpretation of data from experiments in which multiple APP fragments are present. In Chapter 6, Luke Esposito describes a method for quantifying CTFs and for examining different sized Aβ fragments using acid urea gels. And in Chapter 7, Sanjay Pimplikar and colleagues describe a protocol for detecting AICD in cell lysates.

The microtubule-associated protein tau, a component of the cytoskeleton, aggregates into neurofibrillary tangles, the other pathological hallmark of AD (43–46). Tau is also the most common genetic cause of FTD (20) and accumulates in about half of all FTD cases. One important aspect of tau biology is its level of expression; reducing tau expression was shown to be beneficial in mouse models of both AD and FTD (47, 48). In Chapter 8, Chad Dickey et al. describe an in-cell western assay that they have used to screen for regulators of tau expression (49). Another important aspect of tau is its ability to aggregate; in Chapter 9, Gail Johnson and colleagues describe a method they have developed using split GFP technology to quantitatively measure the effect of various agents on tau aggregation (50).

ApoE is the main genetic risk factor for AD; relative to the more common ε3 allele, the more pathologic ε4 allele increases AD risk several-fold (51). ApoE also has an influence on the evolution of FTD (52). As a lipoprotein, the biochemistry of apoE is quite sophisticated. In Chapter 10, Karl Weisgraber and colleagues describe a biochemical purification protocol they have developed to generate different apoE isoforms for use in experiments.

4. Experimental Systems for AD and FTD

A variety of experimental systems can be used to study these diseases. Many questions related to the effects of Aβ can be addressed using primary cultured neurons and a protocol for assessing the toxic effects of Aβ on cultured cells is presented by Adrianna Ferriera and colleagues in Chapter 11. Viral vectors have also proved an important tool for modeling neurodegenerative diseases, and in Chapter 12, Li Gan and colleagues detail a method for using lentivirus in the central nervous system. And of course, mouse models are a mainstay of research on these diseases (53). Given the myriad models available, the choice of which to use in a given situation can be dizzying, and in Chapter 13, Jeannie Chin provides a summary of important features of

major AD models and a discussion of factors to consider in choosing a mouse model.

After choosing a model system, it is important to define outcome measures with which to gauge the severity of impairments and/or the effects of potential treatments. Some, such as determining amyloid plaque burden, are well established. But it has become clear that plaques often are not a reliable indicator of neuronal function (39, 54–60); so other functional methods are increasingly applied. The ultimate functional measure is behavior, and the Morris water maze is a classic test of hippocampus-dependent memory function. Murine neurobehavioral assessment can be intimidating to newcomers in the field, so in Chapter 14, Kimberly Scearce-Levie presents a step-by-step guide to acquiring and analyzing water maze data. In Chapter 15, Jorge Palop and colleagues describe a detailed method for in situ hybridization to quantify and localize gene expression changes in the brain. Axonal transport impairment has been demonstrated in both AD and FTD, as well as in animal models (61); in Chapter 16, Bianxiao Cui and colleagues present a method for real-time evaluation of axonal transport. Recent findings have highlighted the importance of epileptiform activity in AD-related cognitive impairment (62, 63), and in Chapter 17, Jorge Palop et al. outline immunohistochemical biomarkers of this aberrant activity, which correlate well with behavioral impairment. Finally, one of the new frontiers in neurobiology, especially learning and memory, is the role of epigenetics: covalent modifications of DNA and histone proteins (64). There is now early evidence of a role for epigenetic changes in neurodegenerative disease (65, 66), and in Chapter 18, Courtney Miller and colleagues describe how to purify histone proteins and assess epigenetic post-translational modifications.

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