The “tangles” pathway to Alzheimer’s disease

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Introduction

The “tangles” component of the classic Alzheimer’s “plaques and tangles” pathology may be key to developing the first drug to halt the progression of Alzheimer’s disease.

Support for this hypothesis comes from 1) a growing library of animal research by many scientists, 2) the first human clinical trial results and preclinical data, from Allon Therapeutics’ drug AL-108, that associate reduction of tangles to improved cognition, and 3) concerns over clinical failure of drugs that target amyloid plaques, such as Myriad Genetics’ drug Flurizan.

Allon’s clinical trial data is being presented to the International Conference on Alzheimer’s Disease and Related Disorders (ICAD 2008) in Chicago at an ICAD 2008 sponsored news conference and at scientific sessions on July 28 and July 30 (Presenters: Dr. Donald E. Schmechel, Duke University, principal investigator; Professor Illana Gozes, Chief Scientific Officer at Allon Therapeutics).

In addition, animal data from Allon and collaborators is being presented to an ICAD 2008 scientific symposium on July 30 (Dr. Yasuji Matsuoka, previously at Georgetown University).

(News releases at: www.alz.org/icad and www.allontherapeutics.com.)

AL-108 is being developed by Allon Therapeutics (TSX: NPC), a Canadian biotechnology company located in Vancouver. The drug was discovered by Prof. Gozes of the Sackler Faculty of Medicine at Tel Aviv University. Prof. Gozes also heads up research activities at Allon Therapeutics. Collaborative research led by Prof. Gozes has been supported by Tel Aviv University and the U.S. National Institutes of Health. Among numerous collaborators are Dr. Paul Aisen, University of California San Diego, and Dr. Matsuoka, until recently at Georgetown University in Washington, D.C.

Tangles and plaques in Alzheimer’s disease

The two key hallmarks of Alzheimer’s disease (AD) are the appearance of amyloid plaques and neurofibrillary tangles. It is the presence of these two characteristics in post-mortem brains that provides a definitive diagnosis of AD. Plaques are comprised of aggregated amyloid-beta protein while tangles are made principally from aggregated tau protein, a microtubule-associated protein. (1. LaFerla et al, 2005)

The neurodegeneration cascade in Alzheimer's disease

Despite a great deal of research in AD, the causative events leading to the generation of plaques and tangles are unclear. However, published reports clearly show that the cognitive decline in amnestic mild cognitive impairment, a precursor to AD, and in AD is associated with tangle accumulation and not plaques (2. Markesbery et al, 2006; 3. Petersen et al, 2006).

Microtubules and tau play a number of critical roles in normal neuron function

Neurofibrillary tangles are the result of degeneration of microtubules, key components of the communication and transport pathways inside brain cells (neurons). Tangles occur when tau protein, which normally acts to hold microtubules together, converts from a soluble to an insoluble form, a process known as hyperphosphorylation.

The primary function of tau is to stabilize microtubules. With its ability to modulate microtubule dynamics, tau directly or indirectly influences critical cellular functions. For example, the action of tau on stability of the microtubule network is key in maintaining the appropriate structure of neurons, of which the axons and processes typically extend over significant distances. Furthermore, the microtubule skeleton allows appropriate transport of signaling molecules, trophic factors and other essential cellular constituents, including organelles (for example, mitochondria and vesicles) along the axons (axonal transport). The presence of tau on microtubules has significant effects on axonal transport and, hence, on the function and viability of neurons. (4. Ballatore et al, 2007)

Neurofibrillary tangles occur when the cytoskeleton of neurons collapses

In healthy neurons, tau binds to microtubules and stabilizes neuronal structure and function. Regulation of this complex structural network can go awry in several pathological conditions, including AD, resulting in deposition of paired-helical fragments of tau and eventually larger aggregates known as neurofibrillary tangles (4. Ballatore et al, 2007). These tangles are formed when tau dissociates from microtubules and clusters to form an insoluble mass containing hyperphosphorylated tau.

Hyperphosphorylation makes tau dissociate from microtubules, leading to tangles

The activity of tau and its binding to microtubules is controlled by a number of factors, the foremost of which is phosphorylation (the addition of a phosphate group to specific amino acids in the tau protein). Phosphorylation occurs on a number of different parts of the protein and an increase in phosphorylation generally reduces tau binding to microtubules. In AD, extremely high levels of phosphorylation are seen (hyperphosphorylation) and can be used as a marker for progression to AD. It is the hyperphosphorylation of tau that transforms it from its normal function towards a pathological role.

Formation of tangles results in loss of microtubule/tau function and appearance of toxic species

The loss of tau from microtubules has dual effects, both of which lead to neuronal dysfunction and ultimately cell death: 1) The loss of tau reduces microtubule integrity and reduces cell viability, and 2) The tau forms into aggregates and tangles that are toxic to the neurons. In this way, a lack of proper tau control leads to both loss of microtubule function and an increased toxic insult, both of which lead to cell death.

Neurofibrillary tangles are evident in the brains of MCI and AD patients and correlate with cognitive loss

Markesbery et al. (2006) found that neurofibrillary tangles were significantly elevated in all four ventromedial temporal lobe structures in patients with mild cognitive impairment (MCI) patients and early AD compared to subjects with normal cognition. This comparison revealed a relative increase of tangles in frontal and temporal lobes, amygdala, and subiculum in the MCI and AD patients. The change in cognitive memory performance in normal subjects, MCI and early AD patients appeared to correlate with tangles in the hippocampal CA1 region and the entorhinal cortex.

A study by Petersen et al. (2006) independently found that tangles correlated best with the degree of clinical impairment in amnestic MCI patients, and the brain structure most affected was the medial temporal lobe structure which may account for memory impairment.

Neurofibrillary tangles can cause neurodegeneration in the absence of plaques

A number of neurodegenerative disorders, known collectively as tauopathies, show a build-up of tangles in the absence of amyloid plaques. These conditions (including Pick's disease and frontotemporal dementia) show a progressive accumulation of filamentous tau aggregates leading to brain dysfunction and degeneration (5. Lee et al, Ann Rev Neurosci, 2001). Tangles are therefore a critical element of neurodegeneration in various conditions, including AD and those where amyloid beta plays no role.

Cited articles:

1. LaFerla FM, Oddo S. Alzheimer's disease: Abeta, tau and synaptic dysfunction. Trends Mol Med. 2005 Apr;11(4):170-6.

Alzheimer's disease is a progressive neurodegenerative disorder that is characterized by two hallmark lesions: extracellular amyloid plaques and neurofibrillary tangles. The role that these lesions have in the pathogenesis of AD has proven difficult to unravel, in part because of unanticipated challenges of reproducing both pathologic hallmarks in transgenic mice. Recent

advances in recapitulating both plaques and tangles in the brains of transgenic mice are leading to novel insights into their role in the degenerative process, including their impact on synaptic activity and plasticity. Transgenic mice that harbor both neuropathological lesions are also facilitating the elucidation of the relationship of these proteinaceous aggregates to one another and providing a crucial in vivo system for developing and evaluating therapies.

2. Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. Arch Neurol. 2006 Jan;63(1):38-46.

OBJECTIVE: To define the neuropathologic findings in amnestic mild cognitive impairment (MCI) and early Alzheimer disease (EAD). METHODS: The mean numbers of diffuse plaques, neuritic plaques (NPs), and neurofibrillary tangles (NFTs) in 4 neocortical regions and 4 ventromedial temporal lobe regions were counted in 10 patients with amnestic MCI and compared with the mean numbers in 23 normal control subjects and 10 patients with EAD, and then were compared with memory performance. All of the controls and patients were followed longitudinally.
RESULTS: Patients with MCI showed no significant difference (P>.05) in the number of diffuse plaques from that in normal controls or patients with EAD. In patients with MCI, the number of NPs was significantly elevated in all 4 neocortical regions and amygdala compared with controls (P<.01 to <.001). There were no significant differences (P>.05) in the number of NPs between MCI and EAD cerebral cortex, but significant increases were present for NPs in EAD amygdala and subiculum compared with MCI (P<.01). In patients with MCI compared with controls, the only significant increase in NFTs in the neocortex was in the parietal lobe. However, the number of NFTs was significantly elevated in MCI in all 4 ventromedial temporal lobe structures compared with controls (P<.01 to <.001). In comparing MCI with EAD, there were significant increases in NFTs in EAD in frontal and temporal lobes, amygdala, and subiculum (P<.01). The numbers of NPs and NFTs were significantly elevated in all of the neocortical regions and ventromedial temporal lobe regions in patients with EAD compared with controls (P<.001). Memory function was significantly correlated with NFTs in CA1 of the hippocampus (P<.01) and the entorhinal cortex (P<.05).
CONCLUSIONS: In patients with amnestic MCI who were followed longitudinally, the early changes of Alzheimer disease were present. The NFTs were slightly more prominent than beta-amyloid peptide deposition in the progression from normal to MCI to EAD. entromedial temporal lobe NFTs probably represent the substrate for memory decline in MCI. From a neuropathologic perspective, it appears that amnestic MCI is, in reality, EAD.

3. Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H, Kokmen E. Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol. 2006 May;63(5):665-72.

BACKGROUND: The neuropathologic substrate of amnestic mild cognitive impairment (aMCI) is not known. OBJECTIVE: To determine the neuropathologic features of patients who died while their clinical classification was aMCI. DESIGN: Cohort study. SETTING: Community based. PARTICIPANTS: Sixty-six individuals, including 15 who had memory impairment beyond that allowed for aging but who were not demented, were studied along with 28 clinically healthy individuals and 23 patients with probable Alzheimer disease (AD) for comparison. MAIN OUTCOME MEASURES: Standard neuropathologic techniques and classification according to Khachaturian, Consortium to Establish a Registry for Alzheimer Disease, and National Institute on Aging-Reagan criteria were used to analyze autopsy tissue from 15 individuals who died while their clinical diagnosis was aMCI. For comparison, autopsy data on age-matched groups of clinically healthy individuals and patients with probable AD were analyzed. RESULTS: Most patients with aMCI did not meet the neuropathologic criteria for AD, but their pathologic findings suggest a transitional state of evolving AD. All the patients with aMCI had pathologic findings involving medial temporal lobe structures, likely accounting for their memory impairment. In addition, there were many concomitant pathologic abnormalities, including argyrophilic grain disease, hippocampal sclerosis, and vascular lesions. CONCLUSIONS: The neuropathologic features of aMCI matched the clinical features and seemed to be intermediate between the neurofibrillary changes of aging and the pathologic features of very early AD.

4. Ballatore C, Lee VM, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat Rev Neurosci. 2007 Sep;8(9):663-72.

Advances in our understanding of the mechanisms of tau-mediated neurodegeneration in Alzheimer's disease (AD) and related tauopathies, which are characterized by prominent CNS accumulations of fibrillar tau inclusions, are rapidly moving this previously underexplored disease pathway to centre stage for disease-modifying drug discovery efforts. However, controversies abound concerning whether or not the deleterious effects of tau pathologies result from toxic gains-of-function by pathological tau or from critical losses of normal tau function in the disease state. This Review summarizes the most recent advances in our knowledge of the mechanisms of tau-mediated neurodegeneration to forge an integrated concept of those tau-linked disease processes that drive the onset and progression of AD and related tauopathies.

5. Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci. 2001;24:1121-59.

The defining neuropathological characteristics of Alzheimer's disease are abundant filamentous tau lesions and deposits of fibrillar amyloid beta peptides. Prominent filamentous tau inclusions and brain degeneration in the absence of beta-amyloid deposits are also hallmarks of neurodegenerative tauopathies exemplified by sporadic corticobasal degeneration, progressive supranuclear palsy, and Pick's disease, as well as by hereditary frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Because multiple tau gene mutations are pathogenic for FTDP-17 and tau polymorphisms appear to be genetic risk factors for sporadic progressive supranuclear palsy and corticobasal degeneration, tau abnormalities are linked directly to the etiology and pathogenesis of neurodegenerative disease. Indeed, emerging data support the hypothesis that different tau gene mutations are pathogenic because they impair tau functions, promote tau fibrillization, or perturb tau gene splicing, thereby leading to formation of biochemically and structurally distinct aggregates of tau. Nonetheless, different members of the same kindred often exhibit diverse FTDP-17 syndromes, which suggests that additional genetic or epigenetic factors influence the phenotypic manifestations of neurodegenerative tauopathies. Although these and other hypothetical mechanisms of neurodegenerative tauopathies remain to be tested and validated, transgenic models are increasingly available for this purpose, and they will accelerate discovery of more effective therapies for neurodegenerative tauopathies and related disorders, including Alzheimer's disease.