Published in final edited form as:
Cell Motil Cytoskeleton. 2009 August ; 66(8): 635–649. doi:10.1002/cm.20388.

Cytoskeletal Pathologies of Alzheimer Disease

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Abstract

The histopathological hallmarks of Alzheimer disease are the extracellular amyloid plaques, composed principally of the amyloid beta peptide, and the intracellular neurofibrillary tangles, composed of paired helical filaments of the microtubule-associated protein, tau. Other histopathological structures involving actin and the actin-binding protein, cofilin, have more recently been recognized. Here we review new findings about these cytoskeletal pathologies, and, emphasize how plaques, tangles, the actin-containing inclusions and their respective building blocks may contribute to Alzheimer pathogenesis and the primary behavioral symptoms of the disease.

Keywords

Alzheimer disease; tau; microtubule; actin; cofilin; amyloid beta

I. Alzheimer Disease

A. Historical aspects and definition

Alzheimer Disease (AD) is currently diagnosed post mortem where the pathology found in brains is largely stereotypical and includes extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). Late stages of AD are characterized by hallucinations, paranoia, loss of verbal communication, loss of fine and later gross motor control often resembling Parkinson's disease, incontinence, and finally the patient lapses into a vegetative state where they remain until death. However, AD presents clinically as a steady decline in cognitive ability beginning with the loss of short-term memory and progressing through stages of increasing dementia. The severity of the symptoms varies dramatically among individuals and the time of progression through these stages may take anywhere from months to years.

B. Hallmarks of AD: senile plaques, neurofibrillary tangles and cofilin pathology

The amyloid, or senile, plaques are composed mainly of fibrils formed by amyloid beta (Aβ) peptides, whereas the NFTs principally comprise paired helical filaments (PHFs) made from the microtubule binding and stabilizing protein, tau. Hirano bodies, paracrystalline intracellular inclusions containing actin and actin binding proteins, are also a prominent feature of AD brain. However, both amyloid plaques and Hirano bodies are often found in brains of cognitively normal individuals suggesting that they are not the cause of the senile dementia. Other changes in the actin cytoskeleton have been described at synaptic sites as

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well as non-synaptic sites, which can be grouped and referred to as cofilin pathologies because of changes in cofilin activity or organization. Blockage in transport that leads to axonal swellings is a common feature of AD brain and is often initiated by specific cytoskeletal alterations that lead to abnormal protein inclusions; the formation and role of these inclusions in AD will be one focus of this review.

C. Genetic causes of Familial AD: The Amyloid hypothesis

Proteolytic cleavage of the full-length β-amyloid precursor protein (APP) by β- and γ-secretases gives rise to Aβ peptides ranging in length from 39-43 amino acids which form in part the extracellular senile plaques characteristic of AD (Glenner & Wong, 1984a; Hardy, & Selkoe, 2002; Mattson, 2004; Price, et al., 1995; Sisodia & Price, 1995; Tanzi, & Bertram, 2005). Mutations that lead to increased production of the more amyloidogenic $A\beta_{1\text{-}42}$ species are linked to early onset familial AD with high penetrance (Chartier-Harlin, et al., 1991a,b; Goate, et al., 1991; Murrell, et al., 1991; Price et al., 1995). Familial AD mutations have been identified in genes encoding APP, and in presenilins 1 and 2 (Tanzi & Bertram, 2005), components of the γ-secretase complex responsible for one of the proteolytic cleavages that gives rise to amyloid beta peptides. Furthermore, Down syndrome (DS; aka trisomy 21) patients living to age 40 or beyond develop all of the pathological hallmarks of AD (Glenner & Wong, 1984b). Chromosome 21 carries genes for both APP and a β-secretase (BACE-2), and DS patients have increased expression of both (Cataldo *et al.*, 2003). The BACE-2 gene has been excluded as a contributor to the pathogenesis of AD in DS patients, but an increase in BACE-1 activity, which occurs in DS patients, does contribute (Sun *et al.*, 2006 a, b). Although the molecular mechanism increasing BACE-1 activity has not been elucidated, it could arise as a result of increased expression of two other genes, named DSCR1 and DYRK1A, which lie within the critical region of chromosome 21; the products of these genes act synergistically to prevent nuclear occupancy of NFATc transcription factors (Arron *et al.*, 2006). BACE1 expression is regulated at least in part by NFATc which binds to several DNA sequences in the BACE1 promoter region (Cho et al., 2008). Additionally expression of a common polymorphism (ε4) found in apolipoprotein-E (ApoE) has been correlated with increased risk for late-onset AD (Schmechel *et al.*, 1993; Strittmatter *et al.*, 1993), shifting the onset age almost 10 years earlier in individuals homozygous for the ε4 allele (Nunomura et al., 1996). Interestingly, the size of the amyloid plaques did not increase in AD patients with the ε4 allele versus those with the ε3 allele, but rather plaque numbers increased, suggesting enhanced nucleation of plaque formation (Hyman et al., 1995). The “amyloid hypothesis” states that increasing cerebral accumulation of Aβ over years to decades exacerbates cognitive decline, neurodegeneration, and senile plaque deposition associated with AD and can be a result of mutations or allele expression patterns (or both) that enhance production/aggregation or decreased clearance/degradation of Aβ.

The concept that different isoforms and/or conformations of Aβ deliver independent signals to neurons is widely supported. Although the term Aβ is used to describe a spectrum of peptide species, the neurotoxic effects of different Aβ peptides are not the same. Investigations are beginning to elucidate differences in the biological activity of Aβ species. Amyloid $\beta_{1\text{-}40}$ fibrils ($fA\beta_{1\text{-}40}$) induce dystrophy in cultured cortical neurons, at least in part via activation of focal adhesion proteins (Busciglio *et al.*, 1992; Grace *et al.*, 2002; Grace & Busciglio, 2003). Treatment of human cortical neurons with 20 μM $fA\beta_{1\text{-}40}$ for 10 days produced progressive dystrophy and minimal neurotoxicity (Deshpande *et al.*, 2006). Focal adhesions provide a link to the actin cytoskeleton whereby integrin receptors can activate intracellular signals that regulate actin cytoskeletal dynamics (Calderwood *et al.*, 2000; Giancotti & Ruoslahti, 1999). However, most research today is focused on the smaller

soluble forms of Aβ and not the insoluble fibrils or large aggregates, whose sequestration into plaques may be neuroprotective.

Soluble species of Aβ (sAβ; also called ADDLs for Aβ-derived diffusible ligands) bind to synaptic sites on cultured hippocampal neurons (Gong *et al.*, 2003; Lacor *et al.*, 2004). Furthermore, ADDLs derived from synthetic Aβ are toxic to cultured neurons at nanomolar concentrations (Lambert *et al.*, 1998) and at 500 nM they prevent high frequency stimulation-induced LTP measured from the dentate gyrus in acute hippocampal slices (Wang *et al.*, 2002). sAβ has been linked to hippocampus-dependent temporal memory deficits in mice (Ohno *et al.*, 2006). Transgenic mice expressing mutant forms of human APP and presenilin-1 (Tg6799) or human mutant APP alone (Tg2675) both display elevated levels of sAβ and temporal memory deficits (Ohno *et al.*, 2006). Deletion of the BACE1 gene lowered the concentration of sAβ to wild type levels and rescued temporal memory deficits in Tg6799 mice, implying a direct role of Aβ formation in memory loss.

Recent work has identified a soluble form of Aβ with the chromatographic and electrophoretic properties of peptide dimers and trimers as the major species responsible for the synaptic deficits characteristic of AD (Shankar et al. 2007;Shankar et al., 2008). The Aβ-dimer has been extracted from human AD and DS brains but not from brains of patients with other forms of dementia that are unrelated to Aβ production (Shankar et al., 2008). Furthermore, the Aβ-dimer causes synaptic dysfunction at subnanomolar concentrations, which are 10^3 to 10^5 fold lower than what is commonly used for *in vitro* assays with fibrils or with oligomeric forms of synthetic Aβ. The assembly of synthetic Aβ into oligomers or fibrilsis so rapid at the typically used concentrations that little remains of the smaller, more pathophysiologically active species (Hung et al., 2008). Thus, the dimer/trimer fraction of amyloid beta that is secreted from cultured 7PAa cells, which stably express a mutated, pathogenic form of human APP (Walsh et al., 2002), or the dimer fraction isolated from postmortem human AD brain, contain the more physiologically relevant species at close to their naturally occurring concentrations (Cleary et al., 2005; Shankar et al., 2008). Single infusions of either of these fractions into adult rat brain cause transient memory and learning deficits (Cleary et al., 2005; Shankar et al., 2008). Treatment of hippocampal slices in culture with the these same fractions give rise to decreased long-term potentiation (LTP) and enhanced long-term depression (LTD), electrophysiological correlates of the learning and memory defects in the intact animal (Shankar et al., 2008).

D. Possible causes of sporadic AD

The vast majority of AD is sporadic with familial AD (FAD) accounting for fewer than 5% of all cases (Mattson, 2004; Tanzi & Bertram, 2005). One of the major challenges in AD research is to identify causative factors, other than the few point mutations known to induce Aβ accumulation in FAD, which will ultimately lead to the same common pathologies observed in sporadic and familial AD brains. Because AD is an age-related disorder, one early focus for its cause was mitochondrial dysfunction due to mitochondrial aging (Fukui and Moraes, 2008). Mitochondrial dysfunction also allowed for many other initiators of AD that could come from environmental sources, such as mitochondrial poisons (e.g. herbicides and insecticides) that have been implicated in Parkinson Disease (Hatcher et al., 2008). Mitochondrial dysfunction could itself give rise to the release of reactive oxygen species, initiating oxidative stress, or conversely, other initiators of oxidative stress could lead to mitochondrial dysfunction. Regardless of the initiator, mitochondrial insufficiency in CNS neurons leads to a decline in cellular ATP. Another potential AD initiator is increased extracellular glutamate, the major excitatory neurotransmitter in the CNS. In excess, glutamate can cause neuronal excitoxicity (Arias *et al.*, 1998; Lancelot & Beal, 1998). Excess accumulation of glutamate most likely occurs as a function of decreased glial cell uptake and conversion to glutamine for transfer to and re-utilization by neurons. Any of

these mechanisms for AD initiation could also be exacerbated by metabolic or age related changes in the cerebrovasculature, which could impact clearance and exchange mechanisms. Indeed there is a significant association between diabetes and dementia (Duron and Hanon, 2008), especially the insulin-resistant type II diabetes that may impact AD through excitotoxicity, aberrant calcium signaling, release of inflammatory cytokines and common signaling cascade intermediates (Zhao and Townsend, 2008). Furthermore, Aβoligomers impair neuronal insulin receptor signaling (Zhao et al., 2008).

For initiators of sporadic AD to ultimately cause the same final pathology seen in FAD, there must also be changes in the amount or form of Aβ peptides being generated, degraded or cleared from the body as a result of neuronal abnormalities. Because the activity of α-secretase is high in the lipid environment of the plasma membrane and the activity of β-secretase is enhanced in endosomes (Ehehalt et al., 2003), increasing endocytosis of the plasma membrane APP or decreasing the efficiency of transporting the APP- containing endosomes to site where they can fuse with lysosomes and degrade the newly formed Aβ are likely to enhance production of Aβ peptides. Although inhibition of APP trafficking by overexpressing tau protein to inhibit motor molecules from moving vesicles on microtubules did not increase the generation of Aβ peptides (Goldsbury et al., 2006), treatment of cultured neurons with excess glutamate, Aβ peptide oligomers, or peroxide all caused a blockage in transport (Hiruma et al., 2003; Maloney et al., 2005; Goldsbury et al., 2008), resulting in accumulation of retrogradely transported vesicles containing APP and β-secretase cleaved APP (Maloney et al., 2005) and, in the one case where it was quantified, a 2.5 fold increase in Aβ peptide secretion (Goldsbury et al., 2008). These findings suggest that the mechanism of transport inhibition, perhaps one allowing fusion of different endosomal vesicles during blockage and exocytosis, might be required to generate increased Aβsecretion. *In vivo* such vesicle fusion may be a very slow process. Enlarged early endosomes develop in neurons before birth in DS brains (Cataldo *et al.*, 2003) and appear years before significant formation of Aβ deposits and the neurofibrillary pathology associated with AD and DS (Cataldo *et al.*, 1997; Cataldo *et al.*, 2000; Cataldo *et al.*, 2004).

During AD and DS progression, both the size and number of basal forebrain cholinergic (BFC) neurons decrease (Whitehouse *et al.*, 1982; Mann *et al.*, 1984; Casanova *et al.*, 1985; Mufson *et al.*, 1989). BFC neurons depend upon NGF for their normal function and development. BFC neuronal loss, a classic feature of both AD and DS, results, at least in part, from defective retrograde transport of nerve growth factor (NGF) from the hippocampus (Cooper *et al.*, 2001). NGF produced in the hippocampus binds to receptors on BFC axons and is retrogradely transported as an active signaling endosome to the cell body (Sofroniew *et al.*, 2001). This early loss of transport in some axons in AD brain correlates with the appearance of “striated neuropil threads,” localized tandem arrays of swellings that occur along a neurite and which are packed with filament bundles, most of which immunostain for the microtubule associated proteins tau (Velasco et al., 1998). Thus abnormal cytoskeletal organization that brings about defects in transport may indeed be an early event in response to a sporadic AD initiator. How such initiators might bring about these changes in cytoskeletal organization is described below.

II. Cytoskeletal Pathologies

A. Paired helical filaments (PHFs), neurofibrillary tangles (NFTs) and tau

Structures corresponding to NFTs were first described more than a century ago by Alois Alzheimer, the discoverer and namesake of the now well known disease (Alzheimer 1907). More than 50 additional years passed before electron microscopy revealed that NFTs correspond to densely packed fibers, the PHFs (Kidd 1963), which subsequently were shown to be ~20 nm in diameter at their widest and of highly variable length (Wischik et al.

1985). The molecular composition of PHFs was finally resolved in the late 1980's, when tangles were immunolabeled by anti-tau *in situ*, and isolated tangles were found to elicit immune responses against tau, and to comprise a collection of epitopes and peptide sequences spanning virtually the entire tau molecule (Grundke-Iqbal et al. 1986; Kondo et al. 1988; Kosik et al. 1986; Kosik et al. 1988; Nukina and Ihara 1986; Wood et al. 1986). Although NFTs have also been reported to be immunoreactive with antibodies to neurofilament subunits (Anderton et al. 1982; Perry et al., 1985) and MAP2 (Kosik et al. 1984), *in vitro* reconstitution experiments established that full length tau or microtubule-binding tau fragments can self-assemble into straight filaments and PHF-like structures in the absence of any other protein species (Goedert et al. 1996; Kampers et al. 1996; King et al. 1999; Wilson and Binder 1997). The microtubule binding region of tau thus appears to be both necessary and sufficient to form the core structure of the PHF.

Human tau is encoded by a single gene (Neve et al., 1986), which is expressed primarily in neurons (Binder et al. 1985; Boyne et al. 1995). Within the brain, the only organ directly targeted in AD, tau accumulates preferentially in axons (Binder et al. 1985), and is encoded by alternatively spliced transcripts that yield 6 microtubule-binding isoforms ranging from 352-441 amino acid residues in length (Himmler 1989) and at least one smaller isoform that lacks the microtubule-binding region (Luo et al. 2004). The microtubule-binding region begins near the middle of the protein as a proline-rich domain followed C-terminally by 3 or 4 imperfect tandem repeats that are encoded by exons 9-12 and comprise 31 or 32 amino acid residues each (Lee et al. 1988; Goedert et al 1989a; Goedert et al. 1989b; Preuss et al. 1997). Interested readers are referred to the following recent reviews that illustrate and discuss tau gene and protein structure in greater detail (Andreadis 2005; Lee et al. 2001).

Polymerization into PHFs is not the only pathological response of tau in AD. Relative to tau in normal brain, AD tau is found throughout both the axonal and somatodendritic compartments (Grundke-Iqbal et al. 1986) in hyperphosphorylated (Grundke-Iqbal et al. 1986), C-terminally proteolyzed (Gamblin et al. 2003; Novak et al. 1993; Garcia-Sierra et al. 2001) and oxidized forms, such as the conformationally altered tau recognized by the Alz50 monoclonal antobody (Takeda et al. 2000). All tau isoforms contain at least 30 phosphorylation sites (reviewed in Buée et al. 2000), most of which are usually in the de-phospho form in normal tau, but many of which are frequently phosphorylated in AD tau (Lee et al. 2001). Tau phosphorylation, particularly at specific sites, like S262, reduces its affinity for MTs (Biernat et al. 1993), so it is not surprising that considerable attention has been paid to determining which protein kinases and phosphatases control tau phosphorylation. Numerous tau kinases have been found, including, but not restricted to MAPK (Drewes et al. 1992; Goedert et al. 1992), GSK-3β (Hanger et al. 1992; Mandelkow et al. 1992), MARK/PAR-1 (Drewes et al. 1995), and cdk2 and cdk5 (Baumann et al. 1993). In contrast, PP2A appears to be the major tau phosphatase *in vivo* (Goedert et al. 1995; Sontag et al. 1996; Sontag et al. 1999), although PP1, PP2B and PP2C are also capable of dephosphorylating tau *in vitro* (Buée et al. 2000), and presumably *in vivo* as well.

A common feature of PHFs isolated from AD brain is the presence of C-terminally cleaved tau that ends with a glutamic acid corresponding to position 391 in the largest isoform of human brain tau (Novak et al. 1993). The protease responsible for cutting tau following E391 has not been identified, but this cleavage event may follow earlier proteolysis that yields tau terminating at D421. Cleavage at this position can be catalyzed by caspases 3, 7 and 8 to yield a truncated tau that assembles *in vitro* into PHF-like polymers more rapidly and efficiently than full length tau (Gamblin et al. 2003).

AD is the most common, but by no means only disease that involves tau pathology. At least 20 additional neurodegenerative disorders are associated with NFTs, hyperphosphorylated

tau, and impaired memory and cognition, but generally not with amyloid pathoogy (Lee et al. 2001). Perhaps most notable among these “non-Alzheimer tauopathies” are several that can be caused by tau mutations. Examples of such diseases include FTPD-17 (frontotemporal dementia with Parkinsonism linked to chromosome 17), and syndromes resembling progressive supranuclear palsy, corticobasal degeneration and Pick's disease (Lee et al. 2001). Tau mutations cause these non-Alzheimer tauopathies with very high penetrance, but have not been found to be associated with AD. Nevertheless, AD is always associated with the combination of amyloid pathology and tau pathology, whereas amyloid pathology in the absence of tau pathology is usually asymptomatic. It follows naturally that tau lies within a pathway, which if appropriately perturbed, leads with high probability to neurodegeneration, dementia and death.

B. Abnormalities in the actin cytoskeleton

Actin dynamics and regulation—The ability of globular actin (G-actin) to rapidly assemble and disassemble into filaments (F-actin) is critical to many cell behaviors. Among the most important regulators of actin dynamics are members of the ADF/cofilin family. Because mammalian neurons contain about 5-10 fold more cofilin than ADF (Minamide et al., 2000; Garvalov et al., 2007), henceforth we will just refer to cofilin. Cofilin can sever filaments and thus form more filament ends. Depending upon the local environment, the newly formed “barbed” ends may enhance nucleation and filament growth or the “pointed” ends may increase subunit dissociation and filament depolymerization (reviewed in Bamburg and Wiggan, 2002). ADF and cofilin's ability to increase actin filament dynamics is inhibited by their phosphorylation on ser 3 by LIM kinase and other kinases (Morgan et al., 1993; Agnew et al., 1995; Moriyama et al., 1996; Yang et al., 1998; Arber et al., 1998; Toshima et al. 2001). The active (dephosphorylated) cofilin, generated by specific and highly regulated phosphatases in the slingshot (Niwa et al., 2002; Eiseler et al., 2009) and chronophin (Gohla et al., 2005) families, binds to ADP-actin with higher affinity than to ATP-actin and stabilizes a slightly twisted form of actin (McGough et al., 1997; Galkin et al., 2001). Prolonged filament severing by cofilin is highest rate at low cofilin/actin ratios where low occupancy of the filaments creates boundaries between different twisted states. At higher cofilin/actin ratios severing is more transient during early stages of filament binding (Chan et al., 2009) and at even higher cofilin/actin ratios cofilin nucleates actin assembly (Chen et al., 2004; Andrianantoandro and Pollard, 2006) and stabilizes filaments from turnover (Andrianantoandro and Pollard, 2006; Bernstein et al., 2006; Chan et al., 2009). Thus, cofilin's influence on actin dynamics increases with active cofilin concentration to an optimal value at an intermediate cofilin/actin ratio. Shifting cofilin activity to enhance actin dynamics might require dephosphorylation (activation) in one region of a cell and phosphorylation (inactivation) in another.

During focal adhesion activation a multiprotein complex containing LIMK1 and its upstream activator PAK becomes recruited via P95PKL-mediated binding to paxillin (Turner, 2000; Chen *et al.*, 2005). Activated paxillin and focal adhesion proteins are found with high frequency associated with senile plaques in human AD brain (Grace & Busciglio, 2003). *Drosophila* paxillin positively regulates Rac, an activator of PAK, and negatively regulates Rho, thus paxillin is a modulator of the Rho family of GTPases that affect the LIMK pathway and cofilin phosphorylation (Chen *et al.*, 2005). Greater phosphorylation (inactivation) of cofilin by active LIM kinase in regions of $fA\beta_{1\text{-}40}$ contact with neurons may be responsible for the enhanced assembly of F-actin observed in these regions (Heredia et al., 2006). However, in some neurons that contact soluble Aβ cofilin undergoes dephosphorylation leading to cofilin-actin rods.

Cofilin-actin rods—Cofilin-actin enriched inclusions are a common pathological feature observed in a broad spectrum of neurodegenerative diseases (reviewed in Maloney et al., 2007; Bernstein et al., 2009). These often take the form of rod shaped bundles of filaments (cofilin-actin rods), as irregular aggregates (probably aggresomes), or as cytoplasmic paracrystalline lattices (Hirano bodies). Cofilin-actin rods form rapidly in response to neuronal stress (Minamide et al., 2000; Davis et al., 2009) but it is unclear if rods are intermediates in the formation of the other aggregates. Actin aggresomes may be an intermediate in formation of Hirano bodies via the activity of a macroautophagic pathway that is upregulated in transgenic mouse models of AD (Yu et al., 2005).

Cofilin-actin rods form in the cytoplasm of many types of cultured cells in response to heat shock (Iida, & Yahara 1986; Iida et al., 1986; Iida et al., 1992; Nishida et al., 1987; Ohta, et al., 1989), osmotic stress (Iida, & Yahara 1986; Nishida et al., 1987), and ATP rundown (Ashworth, et al., 2003; Bershadsky, et al., 1980; Minamide, et al., 2000). In fibroblasts or epithelial cells, rods are generally reversible and do not appear to cause permanent damage to the cell. However, rods form primarily in the axons and dendrites of neurons where there clearance is more problematic and their affect on cell function more acute. Neurons stressed by treatment with peroxide, glutamate, or ATP-depleting medium, form rods, usually in tandem arrays within the neurite processes where cofilin and actin concentrations are high (Minamide et al., 2000). Tandem arrays of cofilin-immunostaining occur in the hippocampus and frontal cortex of human AD but not human control brain (Minamide et al., 2000) and in transgenic mouse models of AD (Maloney et al., 2005). Rods can be induced in axons and dendrites of rat and mouse hippocampal and cortical neurons in dissociated cultures (Minamide et al., 2000) and in organotypic hippocampal slices (Davis et al., 2009). Similar filamentous structures have been observed in electron micrographs of human AD brain (S. Siedlak and G. Perry, personal communication; Figure 1). Rods block transport within neurites (Maloney et al., 2005).

Treatment of cultured rat hippocampal neurons with $A\beta_{1\text{-}42}$ induces rod formation in ~20% of the total population (Maloney *et al.*, 2005). Rod formation in neurons treated with $A\beta_{1\text{-}42}$ is slower than for the inducers mentioned above, reaching 50% of the maximum response within 6 h in neurons treated with 1 μM synthetic $A\beta_{1\text{-}42}$ oligomers ($sA\beta_{1\text{-}42}$), and by 12-24 h when treated with $sA\beta_{1\text{-}42}$ at concentrations of 10-100 nM, a time course similar to the decline in ATP levels observed in human cortical neurons exposed to 100 nM Aβ (Deshpande *et al*., 2006). Aβ-treatment causes the dephosphorylation (activation) of cofilin within the soma and neurites of only those neurons that form rods (Maloney *et al.*, 2005). The Aβ-responsive sub-population of hippocampal neurons is most prominent in the dentate gyrus (Davis et al., 2009). Aβ-induced rods are reversible and disappear completely by 24 h after washout (Davis et al., 2009), which is in contrast to the persistent rods that form within 24 h of a transient 30 min ATP-depletion and washout. Rod persistence may result from an inadequate recovery of mitochondrial function within affected neurites (Minamide et al., 2000).

Synaptic dysfunction is the most established correlate of cognitive decline in AD (Masliah, 2000; Mucke *et al.*, 2000). Recent studies using *Aplysia kurodai* neurons found that microinjection of cofilin led to rod formation, synapse loss and, distal to the rod, impairment of synaptic plasticity measured by electrophysiological methods (Jang *et al.*, 2005). While introducing excess cofilin did not affect the gross morphology of the neuron, a decrease in the number of pre-synaptic varicosities was observed. In addition, excess cofilin impaired both basal synaptic transmission and LTP. Neither cell death nor induction of an apoptotic cascade was found to be responsible for these effects.

In addition to its role in rod formation and transport inhibition, cofilin also has direct effects on the structure and dynamics of the postsynaptic terminals known as dendritic spines. Spine dynamics are driven by the actin cytoskeleton which shows treadmilling within the spine (Honkura et al., 2008), probably mediated by cofilin and its ability to compete for actin binding with drebrin, an F-actin stabilizing protein (Kojima and Shirao, 2007). A balance between drebrin and cofilin binding to F-actin seems to be important in modulating spine dynamics. Dendritic spines undergo shape changes in response to stimulation that accompany increased insertion of neurotransmitter receptors, part of synaptic plasticity associated with memory and learning (Carlisle et al., 2008). These changes are dependent upon transmembrane signals mediated by pathways that directly modulate cofilin activity (see signaling section below). In AD brain, there is a downregulation of upstream modulators of cofilin phosphorylation, which could lead to enhanced cofilin activity and excessive release of drebrin, which also occurs in AD brain (Zhao et al., 2006). Cofilin-actin rods sequester active cofilin, which could be required for maintaining spine plasticity. Thus, the synaptic dysfunction in human AD brain could result directly from changes in local cofilin regulation within spines, from rod formation sequestering spine cofilin and blocking transport to spines, or from a combination of these effects.

Hirano Bodies—ADF, cofilin and actin are also major components of Hirano bodies (Maciver, & Harrington, 1995). Hirano bodies are unique intracytoplasmic inclusions consisting of a paracrystalline ordered array of parallel regularly spaced 6-10 nm filaments in orthogonal layers encircled by a less structured actin dense region (Schochet, & McCormick, 1972; Tomonaga, 1974). Hirano bodies were first described in patients with amyotrophic lateral sclerosis and Parkinsonism-dementia complex (ALS-PDC) on Guam (Hirano, 1994; Hirano et al., 1968). Because Hirano bodies are found in aged human brain from individuals with normal cognitive abilities, their link to various ailments in which they occur more frequently is tenuous. These include AD (Gibson, & Tomlinson, 1977; Mitake et al., 1997), in which AD patients of the same age as controls displayed a significantly greater number of Hirano bodies (Schmidt, Lee, & Trojanowski,1989). Although Hirano bodies have been found in multiple areas of the brain, they are most frequently found in Sommer's sector of Ammon's horn (Hirano et al., 1968), a region of the brain where AD neurofibriliary tangles and Pick bodies are also enriched (Hirano, 1994). Since this brain region is involved in the development of new memories, the formation of inclusion bodies in this region could contribute to the cognitive impairment found in patients of AD, as well as in many other neurodegenerative disorders (Hirano, 1994). Phalloidin, a probe that recognizes F-actin but not that saturated with cofilin (Minamide et al., 2000), stains Hirano bodies (Galloway et al., 1987). Hirano bodies also contain epitopes for microtubule-associated proteins, including tau, and the actin-associated proteins, α-actinin, vinculin, tropomyosin, and ADF/cofilin (Galloway et al., 1987; Maciver, & Harrington, 1995; Peterson et al., 1988). Thus, it is believed that these structures are primarily composed of actin and actin binding proteins. Although the mechanism of Hirano body formation from endogenous proteins is unknown, expression in mammalian cells of a C-terminal (CT) fragment of an actin cross-linking protein from *Dictyostelium discoideum* induces structures morphologically identical to Hirano bodies (Maselli et al., 2002) and has provided a model system for their study (Davis et al., 2008).

III. Signaling Pathways Activated by Neurodegenerative Signals Affecting the Cytoskeleton

A. Pathways involving tau

AD tau has been known to be hyperphosphorylated for more than 20 years (Grundke-Iqbal et al. 1986), but little is known about the upstream signals that disrupt the normal balance

between tau kinases and phosphatases in favor of the former. Although the role of tau phosphorylation in PHF assembly *in vivo* has prompted much speculation, it is clear from *in vitro* studies that non-phosphorylated tau is fully capable of polymerizing into PHF-like filaments (Goedert et al. 1996; Kampers et al. 1996; Wilson and Binder 1995). Furthermore, assembly of PHF-like filaments in cultured cells appears to be modulated by tau phosphorylation, but does not depend on it (Wang et al. 2007). Thus, in a purely biochemical sense, phosphorylation of tau is not required for its self-assembly, and the extent, if any, to which phosphorylation promotes tau assembly in the brain *in vivo* remains to be determined. One idea worth considering takes into account that the tau-tau interaction site in PHFs is coincident with the binding site on tau for microtubules (Goedert et al. 1996). Because phosphorylation of tau at key sites weakens its affinity for microtubules (Biernat et al. 1993), phosphorylation at those sites might represent a switch from an intracellular environment that is non-permissive for tau self-assembly to one that is permissive (Sontag et al. 1999).

Regardless of how phosphorylation influences tau assembly into PHFs, an equally important issue is how PHFs affect cell behavior. The most direct evidence comes from a recently developed system for assembly of transfected tau fragments into PHF-like structures in neuroblastoma cells. Within in a few days after transgene expression begins, appreciable cell death is evident in cultures that express assembly-competent versions of tau, but not in cells expressing tau mutants that fail to self-assemble (Khlistunova et al. 2006; Wang et al. 2007). It thus seems likely that tau filaments are inherently cytotoxic.

But must tau assmble into filaments in order to compromise cell function or viability? An emerging body of evidence suggests otherwise. Indeed, it seems that many toxic effects of β-amyloid requires expression of soluble tau (King et al. 2006; Rapoport et al. 2002; Roberson et al. 2007).

The first proof of tau-dependent amyloid toxicity came from a study of cultured primary neurons grown in the presence of fAβ40 (Rapoport et al. 2002). Over the course of 24-96 hours of exposure to the amyloid, neurite retraction and cell death progressively increased in wild type, tau-expressing neurons, and nearly 90% of the cells were dead within 4 days. Accompanying these effects was an increase in the activated form of the MAP kinase, ERK2. Remarkably, none of these responses were observed in comparably treated primary neurons from tau knockout mice unless they were transfected to express tau. These results demonstrate that tau is essential for fAβ-induced neurotoxicity, at least in cultured neurons, and reinforce earlier *in vivo* mouse studies placing Aβ upstream of tau in a pathogenic cascade (Götz et al. 2001; Lewis et al. 2001).

The *in vivo* relevance of these cultured neuron results was recently confirmed by a study of transgenic mice (Roberson et al. 2007). Compared to wild type mice, hAPP transgenics that expressed endogenous mouse tau at normal levels and overexpressed human APP with a pathogenic mutation had impaired memory and learning, were more susceptible to excitotoxin-induced seizures, and had shorter mean lifespans. Although abundant amyloid plaques accumulated in the brains of these mice, NFT pathology was not evident. The hAPP mice were crossed with tau knockout mice and the hybrids were back-crossed to yield all possible genotypes, which were then evaluated for amyloid pathology, learning, memory, excitotoxin response and viability. Mice that lacked tau but overexpressed the human APP mimicked wild type mice for memory and learning, frequency of excitotoxin-induced seizures and lifespan. In contrast, the lack of tau had no effect on amyloid plaque deposition. Bearing in mind the limitations of modeling human AD in mice, these *in vivo* results imply that tau is required for transducing toxic signals from Aβ in human AD pathogenesis, and that this occurs independently of tau assembling into PHFs.

Why is tau required for Aβ toxicity? The answer to this question is far from resolved, but an important clue comes from another recent cultured cell study (King et al. 2006). Exposure of cells to "pre-fibrillar Aβ", which contained a mixture of monomeric peptides and variably sized Aβ oligomers, was found to cause microtubule loss within 1-3 hours, but only in cells that expressed tau. This set of results was observed in fibroblasts, which expressed tau by transfection to overcome their normally silent tau gene, and in primary neurons, whose endogenous tau could be reduced to trace levels by siRNA. These results identify tau as an essential component of a microtubule disassembly pathway that is initiated by pre-fibrillar Aβ. Further work is required to establish whether monomeric Aβ or any particular subset of Aβ oligomers can induce microtubule depolymerization, but tau clearly functions downstream of the active Aβ form(s) in this pathway.

If such a pathway were to operate *in vivo* in the brain, neurons would be the principal cells that experience Aβ-induced microtubule loss because tau is expressed primarily in neurons (Binder et al. 1985). Microtubule loss would have the devastating effect of leading directly to synaptic dysfunction or the loss of synaptic connections altogether. This is because virtually all proteins located at the axon terminal are synthesized in or near the neuronal perikaryon, but perform their specialized functions many centimeters away from where they are made (Tytell et al. 1981). Transport of pre-synaptic terminal proteins across such distances by diffusion would require thousands of years, and to enable axonal transport to occur in a more biologically acceptable time frame of hours to days, neurons use microtubules as high speed intracellular highways (Bloom and Goldstein 1998). Microtubules are therefore essential for maintaining synaptoc integrity, and the fact that neurons express tau at uniquely high levels make them especially vulnerable to the microtubule-depolymerizing activity of pre-fibrillar Aβ. Although dendrites are known to support abundant protein synthesis, particularly in their proximal segments, it is easy to imagine how a global reduction or loss of microtubules in neurons could affect the functional integrity not only of pre-synaptic terminals, but of post-synaptic sites as well.

B. Pathways mediating actin dynamics

Regulating actin dynamics in spines—Previous studies have identified multiple pathways that link cofilin activity to memory and learning. For normal synaptic consolidation at excitatory medial perforant path granule cell synapses in the DG, synthesis of the immediate early gene activity-regulated cytoskeletal-associated protein (Arc) is required (Bramham, 2007). Arc is induced by brain-derived neurotrophic factor (BDNF) or high frequency stimulation that induces long-term potentiation (LTP) in the rat DG *in vivo*. The Arc mRNA is transported into dendrites where it is translated. Prolonged synthesis of Arc leads to phosphorylation (inactivation) of cofilin and decreased cofilin activity is suggested to cause a local expansion of actin filament structures and synaptic stabilization (Bramham, 2007). Spine architecture is regulated through actin dynamics downstream of the GTPase activating protein SynGAP, which has recently been shown to regulate both steady-state and activity-dependent cofilin phosphorylation (Carlisle et al., 2008).

In an opposing pathway, Aβ has been shown to down regulate the expression of Pak1 (Zhao *et al.*, 2006). The presence of bifurcating pathways to activate both phosphorylation and dephosphorylation of cofilin may be necessary to spatially regulate cofilin activity through a cycle of phosphorylation and dephosphorylation in response to a single extracellular ligand. Evidence for bifurcating pathways leading to cofilin phosphocycling was first obtained in serum stimulated fibroblasts (Meberg *et al.*, 1998), but also has been reported in neuronal growth cone pathfinding in gradients of bone morphogenic protein 7 (Wen *et al.*, 2007). Thus, its importance in dendritic spine morphology in response to glutamate signaling through the NMDA receptor (Carlisle et al., 2008), a known synaptic target of Aβ (DeFelice

et al., 2007), suggests that rapid effects on brain slice electrophysiology by Aβ extracted from human AD brain (Shankar et al., 2008), could arise from modulation of cofilin activity in spines.

As mentioned earlier, excess active cofilin will displace the actin filament stabilizing protein drebrin from spines, which alters spine dynamics (Kojima and Shirao, 2007). Drebrin levels are reduced in brains of patients with AD and Down syndrome (Shim and Lubec, 2002), especially in regions where cofilin is activated (Zhao *et al.*, 2006). Thus the activation of cofilin that occurs within the DG in response to treatment with Aβ1-42 oligomers may cause rapid alterations in synaptic function through its direct effects on the dynamics of the actin core of spines, perhaps mediated by the Ras family GTPase SynGAP (Carlisle et al., 2008), or through formation of rods within the neurite. Rod formation has the dual property of blocking delivery of material required for normal spine function and sequestering cofilin so that it is less able to participate in spine dynamics.

Rod formation—Pathways mediating neuronal rod formation from several different rod-inducing stimuli have been partially elucidated. ATP-depletion causes the release of the cofilin phosphatase chronophin (CIN) from Hsp90 (Huang et al., 2008). CIN is inhibited when bound to Hsp90 so its release causes a net dephosphorylation of cofilin. The Hsp90 inhibitor 17AAG, a galdanamycin analog, also causes the release of CIN from Hsp90, again activating cofilin and leading to rod formation in neurons that are so treated. Silencing of CIN in neurons with siRNA decreases the rate and extent of rod formation in response to both ATP-depletion and 17AAG, but does not eliminate it (Huang et al., 2008), suggesting that other phosphatases may eventually be recruited for this purpose.

The $A\beta_{1\text{-}42}$ signaling pathways may not be identical in all neurons and are likely complex. A conditional brain knock-out of cdc42 was previously shown to be inhibitory to axonogenesis and to increase the pool of phosphorylated cofilin (Garvalov et al., 2007). Knock-out of cdc42 or inhibition of cdc42 activity by dominant negative cdc42 expression reduced by about 50% the percentage of neurons forming rods in cells treated with 1 μM synthetic $A\beta_{1\text{-}42}$ (Davis et al., 2009), suggesting that extracellular $A\beta_{1\text{-}42}$ activates cofilin in a subpopulation of hippocampal neurons through multiple pathways, only one of which requires cdc42.

Cofilin pathology in both AD and DS is spatially and temporally associated with marked reduction of PAK protein levels and activity (Zhao *et al.*, 2006). In postmortem human and Tg2576 mouse brains, activated phospho-PAK (pPAK) immunostaining resembles staining of intraneuronal $A\beta_{1\text{-}42}$ that accumulates along with APP-carboxy-terminal fragments (APP-CTFs) within enlarged endosomal and lysosomal structures (Yang *et al.*, 1995; Zhao *et al.*, 2006). Persistent reduction in pPAK was observed as early as 2 h following treatment of dissociated rat hippocampal neurons with soluble $A\beta_{1\text{-}42}$ oligomers and occurred at synthetic Aβ oligomer concentrations as low as 10 nM (Zhao et al., 2006). Pak1, an effector of the GTP-bound form of cdc42, is an activator of LIM kinase (Edwards *et al.*, 1999), which keeps cofilin in an inactive state; thus depletion of Pak1 may result in an over activation of cofilin (Zhao *et al.*, 2006). Application of a PAK inhibitory peptide to cultured neurons induced the formation of cofilin rods. Intracerebroventricular (i.c.v.) injection of this peptide into wild type mice induced rod-like cofilin pathology and social recognition memory deficits (Zhao et al., 2006). These findings suggest that a loss of pPAK may lead to local pathology related to the formation of cofilin aggregates similar to those observed in human AD and Tg2576 mouse brain, and may contribute to impaired cognitive function. However, the mechanism by which this occurs in AD brain is not yet clear. LIM kinase is activated by phosphorylation by either PAK or the rho-activated kinase, Rock. A decline in active (phosphorylated) PAK occurs in cdc42 knockout brain but surprisingly is

accompanied by an increase in phosphorylated (active) LIM kinase and phospho-cofilin (Garvalov et al., 2007). Although in chick retinal neurons activation of cdc42 leads to cofilin dephosphorylation through inhibition of a ROCK-dependent pathway (Chen et al., 2006), in cdc42 knockout mouse brains Rho and Rock activity do not appear to change. Thus the mechanism by which LIMK becomes activated is unknown. Cdc42 null neurons also have a decreased cofilin-specific phosphatase activity (Garvalov et al., 2007), which could also contribute to the increased phospho-cofilin pool, and presumably could also enhance the phosphorylated LIM kinase pool since at least one cofilin phosphatase, slingshot 1L, has been shown to dephosphorylate both (Soosairajah et al., 2005).

IV. Relationships Among Aβ, Neurofibrillary Tangles and Cofilin-actin Rods

Major unresolved questions in AD research pertain to the interrelationships between the different pathologies. Do Aβdimers or other forms of Aβ initiate the cofilin and tau pathologies that affect intracellular transport and synaptic dysfunction? Do the changes in intracellular transport alter APP processing leading to enhanced production, dimerization, and/or secretion of Aβ that can spread the zone of degeneration? Are pathways for tau hyperphosphorylation and cofilin dephosphorylation (activation) related and does one precede the other? Answers to some of these questions are actively being pursued and may ultimately change the way we think about how AD pathology develops.

In the brains of flies carrying the mutant human tauR406W transgene and in the brains of mice carrying the mutant human tauP301L transgene, both of which are linked to fronto-temporal dementia, cofilin-actin rods are observed to co-localize with tau deposits that stain for phosphorylated tau species associated with paired helical filaments (Fulga et al. 2007). Human mutant tau has the ability to bind and bundle F-actin *in vitro* and it could be responsible for the formation of actin bundles observed in cells. However, the *in vitro* bundles were formed in the presence of phalloidin (Fulga et al., 2007); phalloidin competes with cofilin for binding actin (Hayden et al., 1993) and fluorescent phalloidins will not stain cofilin-actin rods induced in dissociated neurons or organotypic hippocampal slice (Minamide et al., 2000; Davis et al., 2009). Thus, *in vivo* we still do not know if mutant human tau is the inducer of actin reorganization or if cofilin-actin rods, formed as a result of the stress of mutant tau expression, serve as a sink for binding the tau. The answer to this question could be extremely important in designing therapeutics. Soluble forms of synthetic Aβ-oligomers as well as soluble Aβ-extracts from human AD brain induce AD type of tau hyperphosphorylation in cultured neurons (DeFelice et al., 2008). One of the earliest pathological features within the brains of AD patients is a tandem array of axonal swellings called “striated neuropil threads.” These structures immunostain for tau epitopes (Velasco et al., 1998) but they have the pattern of formation and the size of stress-induced cofilin-actin rods, such as those induced by Aβ (Maloney et al., 2005). They could represent an early link between cofilin and tau pathologies (Whiteman et al., 2008). Regardless of whether tau is required for Aβ-induced actin rod formation, axonal transport is likely to be severely compromised by both the tau-dependent microtubule loss and cofilin-actin rod assembly that can be induced by certain forms of Aβ. It is therefore worth considering the possibility that onset of these cytoskeletal defects represent seminal cell biological events in AD pathogenesis.

Acknowledgments

The authors gratefully acknowledge support from the National Institutes of Neurological Diseases and Stroke, NIH, grants NS40371 and NS43115 (JRB) and NS051764 (GSB), The Alzheimer's Association (GSB), The Owens Family Foundation (GSB) and the Ivy Fund (GSB). The authors wish to thank Chi Pak for helpful comments and discussions and Judy Boyle, Colorado State University and Sandra Siedlak and George Perry, University of Texas at San Antonio for the electron micrographs.

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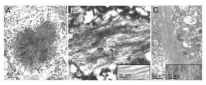

Figure 1. Pathological features of human AD brain as seen by electron microscopy

(A). Extracellular amyloid plaque. (B) Tau-containing 20 nm wide paired helical filaments; the twisted ribbon-like structure is better seen in the magnified inset. (C) A likely cofilin-actin rod with a morphology identical to those induced in rat brain organotypic slices (Davis et al., 2009). Inset at higher magnification shows filaments are thinner (8-9 nm) than paired helical filaments. Images were kindly provided by Judy Boyle (A and B) and George Perry and Sandra Siedlak (C).