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Invited review

Intercellular transfer of tau aggregates and spreading of tau pathology: Implications for therapeutic strategies

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ABSTRACT

Filaments made of hyperphosphorylated tau protein are encountered in a group of neurodegenerative disorders termed tauopathies. The most prevalent tauopathy, Alzheimer's disease (AD), additionally presents with extracellular deposits of the amyloid-β peptide (Aβ). Current symptomatic treatments have shown short term benefits in reducing cognitive symptoms as well as behavioral abnormalities in patients with mild to moderate AD but there is still no effective treatment to prevent or reverse AD. For decades, the amyloid cascade hypothesis of AD dominated basic research and focused pharmaceutical interest on Aβ. However, the existence of tauopathies that are devoid of Aβ deposits, together with the discovery of mutations in the tau gene leading to frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17*T*), confirmed the importance of tau *per se* in disease. Tau became an interesting disease target in its own right. We will review here recent research on cell-to-cell propagation of tau pathology, which we believe to be central to disease progression, and discuss tau immunotherapy in the light of these findings.

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1. Tau protein

In 1975, Weingarten et al. (1975), isolated from brain a protein and named it tau for its ability to bind to microtubules. Tau is extremely heat stable and controls the polymerization of microtubules as major structural component of the axonal transport and neurotransmission machinery. In the human brain, six protein tau isoforms are derived by alternative mRNA splicing from a single gene (*MAPT*) located on the chromosome 17q.21.31 (Andreadis et al., 1992; Goedert et al., 1989; Neve et al., 1986). These six CNS tau isoforms contain or not a 29- or 58-amino acid insert in the N-terminal half of the protein and either three or four repeat domains (3R- and 4R- tau, respectively) in the C-terminal part (Kosik et al., 1989; Lee et al., 1988, 1989). The repeats and some adjoining sequences constitute the microtubule-binding domains of tau with 4R tau being more efficient at promoting microtubule assembly than 3R tau (Goedert and Jakes, 1990). Tau is subject to various post-translational changes such as glycosylation, phosphorylation, nitration, and acetylation, of which phosphorylation constitutes the perhaps most important modification (Chen et al., 2004; Selden and Pollard, 1983). Whereas phosphorylation is fundamental for tau function in physiological conditions, a large number of neurodegenerative diseases features neurofibrillary lesions composed of tau in an abnormally phosphorylated state. This pathological phosphorylation of tau, assumed to result from deregulation of tau kinases or/and phosphatases, can either occur at sites that are normally phosphorylated, or at residues that do not undergo phosphorylation under physiological conditions (Bennecib et al., 2001; Buee Scherrer et al., 1996; Gong et al., 1995, 1993; Hanger et al., 1998; Kins et al., 2003; Liu and Yen, 1996; Patrick et al., 1999; Pei et al., 2003; Tomizawa et al., 2001). Abnormal phosphorylation of tau (or pretangle stage of tau pathology) dissociates it from microtubules, causing its redistribution from axonal to somatodendritic compartments. Consequently, the increased pool of hyperphosphorylated tau is thought to promote tau aggregation (or tangle stage).

2. Neurodegenerative disorders with tau pathology

Pathological tau inclusions are encountered in a large number of neurodegenerative diseases grouped under the convenient term 'tauopathies' (Goedert et al., 2010; Spillantini et al., 1997). They include Alzheimer's disease (AD), tangle-only dementia (TD), argyrophilic grain disease (AGD), progressive supranuclear

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palsy (PSP), corticobasal degeneration (CBD), Pick disease (PiD) as well as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17*T*), the latter being causally linked to mutations in the tau gene (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998) (Table 1). Despite common lesions such as gross brain atrophy, neuronal loss, gliosis, superficial spongiosis, ballooned neurons, and abnormal glial cells, these disorders present distinct tau pathological profiles. Thus, in AD and TD, both 3R- and 4R-tau make up the neurofibrillary lesions (Goedert et al., 1992; Noda et al., 2006; Schmidt et al., 2001), whereas in PiD 3R tau predominates in the neuronal inclusions (Delacourte et al., 1996); the assembly of 4R tau into filaments is characteristic of PSP, CBD and AGD (Flament et al., 1991; Ksiezak-Reding et al., 1994; Togo et al., 2002; Tolnay et al., 2002). In addition to specific isoform compositions, tau pathology also exhibits characteristic neuropathological aspects. In AD and TD, intracellular deposits of hyperphosphorylated tau proteins occur in the shape of neurofibrillary tangles (NFT) and neuropil threads (NT). In the case of NFT, tau lesions are located in the somatodendritic compartment, whereas NT are found in distal dendrites and axons. In AGD, abundant argyrophilic grains (ArGs) in neuronal processes, pretangle neurons in limbic areas as well as glial tau pathology both in astrocytes and oligodendrocytes make up the hallmark lesions (Tolnay and Clavaguera, 2004). In PSP, characteristic tau inclusions known as globose-type NFT and NT (Probst et al., 1988) are present in various brain regions, and besides neurons also affect astrocytes (in the shape of "tufted astrocytes") and oligodendrocytes (coiled bodies). CBD brains reveal intracytoplasmic pathological tau in NT, pretangle neurons or small NFT as well as in astrocytes (in the shape of "astrocytic plaques") and oligodendroglial coiled bodies (Ikeda et al., 2002; Tolnay and Probst, 2002; Uchihara et al., 1998). Argyrophilic Pick bodies composed of abnormally phosphorylated tau (Probst et al., 1996) are present in neocortical, hippocampal and subcortical neurons of patients with PiD. Neuropathologically, FTDP-17*T* presents with severe neuronal loss, astrocytic gliosis, and spongiosis, with filamentous tau inclusions affecting both neuronal and glial cells. Here, depending on the mutation site, tau aggregates may be composed predominantly of 3R, 4R or an admixture of 3R and 4R isoforms (Ghetti et al., 2011).

Table 1
Diseases with Tau inclusions.

Alzheimer's disease
Amyotrophic lateral sclerosis and parkinsonism-dementia complex
Argyrophilic grain disease
Chronic traumatic encephalopathy
Corticobasal degeneration
Diffuse neurofibrillary tangles with calcification
Down's syndrome
Familial British dementia
Familial Danish dementia
Frontotemporal dementia and parkinsonism linked to chromosome 17 (caused by *MAPT* mutations)
Frontotemporal lobar degeneration (some cases caused by *C90RF72* mutations)
Gerstmann–Sträussler–Scheinker disease
Guadeloupean parkinsonism
Myotonic dystrophy
Neurodegeneration with brain iron accumulation
Niemann-Pick disease, type C
Non-Guamanian motor neuron disease with neurofibrillary tangles
Pick's disease
Postencephalitic parkinsonism
Prion protein cerebral amyloid angiopathy
Progressive subcortical gliosis
Progressive supranuclear palsy
SLC9A6-related mental retardation
Subacute sclerosing panencephalitis
Tangle-only dementia
White matter tauopathy with globular glial inclusions

During the clinical course of AD and AGD, filamentous tau inclusions propagate throughout the brain following a stereotypical pattern, thereby providing the basis for disease staging. In AD, tau pathology is staged using a six-tiered system of criteria defined by Braak and Braak (1991). Braak stages I and II correspond to the appearance of NFT in the transentorhinal and entorhinal cortex and are not associated with clinical dementia. More pronounced involvement of both transentorhinal and entorhinal regions and formation of NFT in the hippocampus are characteristics of stages III-IV. The degree of neuronal damage at stages III-IV may lead to the appearance of first clinical symptoms. Stages V and VI correspond to abundant spreading of NFT to isocortical association areas. Patients with Braak stages V and VI are severely demented, and meet the neuropathological criteria for the diagnosis of AD. Many tau inclusions survive the death of the affected nerve cells as extracellular or ghost tangles. In AGD, the earliest changes are restricted to the ambient gyrus (stage I according to the classification proposed by Saito et al. (2004), from where the pathological process extends to the anterior and posterior medial temporal lobe (stage II), followed by the septum, insular cortex and anterior cingulate gyrus (stage III). Stage III is characteristic of patients with a clinical diagnosis of dementia (Saito et al., 2004).

3. Experimental transmission of tauopathy

The propagation of tau pathology during the clinical course of tauopathies points to the existence of intercellular tau aggregate transfer mechanisms. Over the past years, this notion has been experimentally substantiated through the description of cell-to-cell propagation of tau filaments, both *in vivo* and *in vitro* (Clavaguera et al., 2009; Frost et al., 2009a). In addition, in parallel to classical prion diseases, the characteristics and specifics of the different tauopathies are consistent with the existence of tau strains.

To determine whether the aggregation of tau protein can be induced *in vivo*, we injected P301S brain homogenates bearing numerous tau filaments into the hippocampus and the overlying cerebral cortex of ALZ17 mice that never develop tau deposits (Allen et al., 2002; Clavaguera et al., 2009; Probst et al., 2000) (Fig. 1). Such injection induced the assembly of wild-type human tau of ALZ17 mice into filaments, in neurons and in oligodendrocytes in the form of NFT, NT and oligodendroglial coiled bodies similar to those found in the human tauopathies. Strikingly, induced tau filaments were not restricted to the injection sites but progressed over time to neighboring and more remote, but anatomically connected, brain regions (Fig. 1). Signs of neurodegeneration were not observed for up to 18 months after the injection of P301S tau brain homogenates. This supports the suggestion that the molecular tau species responsible for propagation and toxicity are different (Clavaguera et al., 2009). These findings were confirmed and extended by additional work *in vivo*. Lasagna et al. (Lasagna-Reeves et al., 2012) have isolated tau oligomers from AD brains by immunoprecipitation and injected them into the hippocampus of wild-type C57BL/6 mice. Eleven months after injection, Gallyas silver-positive staining was present in the brains of injected mice in the hippocampus but also in neighboring brain regions such as cortex, corpus callosum, and hypothalamus, confirming the propagation of the induced filamentous tauopathy. More recently, Iba et al. (2013) demonstrated that pure synthetic fibrils prepared from recombinant human mutant tau protein were able to induce in a dose- and time-dependent manner NFT-like tau inclusions when injected into the brains of young mutant tau transgenic mice. Again, the induced tau pathology propagated to brain regions