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Tau Pathology and Neurodegeneration: An Obvious but Misunderstood Link

André Delacourte
Inserm Unit 837 – JPARC, 1, Place de Verdun, 59045 Lille cedex, France
E-mail: andre.delacourte@lille.inserm.fr

Abstract. Most dementing disorders result from a degenerating process named tauopathy. Alzheimer disease is the most frequent one, but only one among the large spectrum of tau-related diseases. Cognitive impairment is related, first of all, to the neocortical location of this degenerating process. However, the nature and the mechanisms leading to tauopathy can be very different. This is demonstrated by familial mutations on the tau gene as well as by the different morphological and biochemical patterns of tau lesions. Therefore there is no doubt that tau is an etiological agent. But the persistent and unsolved question is the basic mechanism leading to neurodegeneration: is it due to the toxic effect of aggregated tau, or a loss of tau function, or both? Some answers may come from a more focused interest towards sporadic tauopathies. Most of them are characterized by a degenerating process starting in a specific and vulnerable brain area and consuming the connected neuronal network, like a chain reaction. In other words, sporadic tauopathies are mostly a destabilization of specific neuronal networks that should be modeled for an efficient therapeutic approach.

Keywords: Alzheimer, loss of function, mutation, neurodegeneration, phosphorylation, proteinopathy, tauopathy, toxicity

INTRODUCTION

Tau pathology was discovered by studying the brain lesions found in Alzheimer's disease (AD). From neurofibrillary tangles well described by Alois Alzheimer [1], their ultrastructural filaments components [28], their basic component protein tau [9,12, 19], the description of a hyperphosphorylated state [20] and pathological tau species in AD [16], these major findings have shown the importance of this degenerating process. This was just the beginning. Indeed, tau pathology is present in most neurodegenerating dementing disorders, and there is a code-bar of aggregated tau species able to distinguish five types of tau syndromes [37]. Moreover, a subset of frontotemporal dementia (FTD), FTDP-17, is characterized by mutations on tau gene [25,39] while Dementia Lacking Distinctive Histology (DLDH) has an abnormal low level of normal tau proteins with no tau aggregates [43]. These discoveries generated the concept of tauopathies [4, 18]. Altogether, tauopathies present a classical pattern observed in many syndromes, with a small part which is familial and a big part corresponding to a cluster of sporadic diseases. This is also true for synucleopathy, prion diseases, amyotrophic lateral sclerosis, amyloidopathy of AD and many other diseases. For all these syndromes, the etiological agent is affected by pathological mutations and is also the basic component of the characteristic lesions. This is true for tau for tauopathies, amyloid-β protein precursor (AβPP) for AD, synuclein for parkinsonian syndromes, prion protein for prion diseases, etc. But for all of them, the same question arises: What is the basic etiological event leading to neurodegeneration? Is it the toxic effect of the proteinous aggregates observed in brain lesions or is it a loss of function of the etiologic agent? (for example, see the opposite concepts developed by [22, 38]). The right answer will give the right therapeutic strategy [42].

THE DIFFICULTY TO SET UP RELEVANT MODELS OF TAUOPATHIES

Models developed for all the known proteinopathies generate in fact more questions than answers. Indeed,

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for tauopathies, transgenic mice with wild type tau gene are not able to mimic tau aggregation [5,40]. Transgenic mice with tau mutations are modeling familial tau lesions, but are the phenotypic defects resulting from these models really relevant of familial tauopathies [29, 35]? Indeed, one can note that the mutated tau transgene is dramatically overexpressed (not in the human disease) and the delivery of overexpressed and mutated tau in the nerve cell compartments is not regulated. Modeling tau pathology in sporadic and familial AD is even more complicated. There is now an agreement that AD is defined as a dementia with neocortical amyloidopathy and tauopathy [26]. But transgenic mice with AD mutation genes (APP*+PS1*) develop numerous amyloid plaques but no trace of tauopathy [11, 24,36]. Therefore, it was logical to add a mutated tau gene in addition to trying to get closer to the human pathology [30]. But are transgenic mice with three mutated genes, each gene having two of the most powerful pathological mutations found in humans, relevant to model familial tauopathy? Moreover, what about modeling sporadic AD, which represents 99.7% of all AD cases [10]?

WHAT IS OR WHAT ARE THE ROLE(S) OF TAU?

The complexity of the problem is revealed by the fact that tau proteins are phosphoproteins, with numerous possible phosphorylation sites whose physiological or pathological significance is difficult to understand. Indeed, tau is a thermometer of the cell whose phosphorylation state varies as a function of the temperature [2,32], the metabolism [34], different types of stress [27,31], etc. Even worse, pathological tau epitopes thought to be specific of AD can be expressed in other conditions such as glucose deprivation [33]. Despite this complexity, once again pathological mutations give some answers. Indeed, recently, it has been shown that a mutation on a gene encoding tau tubulin kinase 2 (TTBK2) is able to generate a neurodegenerating process [23]. This finding suggests that a dysregulation of phosphorylation as an early event in the etiological cascade of neurodegeneration should be considered seriously

SPORADIC TAUOPATHIES GIVE VALUABLE LESSONS FOR THE DEVELOPMENT OF MORE RELEVANT MODELS

One way to circumvent this bulk of data that generate more questions than answers is to look more closely human sporadic tauopathies. They tell us lessons useful to understand the most common forms of tauopathies and synucleopathies; AD and parkinsonian sporadic disorders represent more than 80% of all dementing disorders. These diseases start with a degenerating process in very precise brain areas: the limbic system for AD [6, 13], the brain stem and substantia nigra for Parkinson disease [7]. These vulnerable brain areas are always affected in aging. At the age of 70 years, a few tangles or Lewy bodies are systematically found in these corresponding areas. The reason why these brain areas are vulnerable is unknown. Of course, the aggregated material could contribute as a nucleated seeding toxic effect. But the pathology really starts when the intensity of tauopathy or synucleopathy dramatically increases in these vulnerable areas and begin to spread in other brain areas, along neuronal networks linked to the primer vulnerable area [8]. This progressive collapse, this chain reaction of neurodegeneration, this domino effect tells us that specific trophic factors are lacking or that the trophic cross-talk between neurons of the same network is broken. The real pathology really starts when the incipient vulnerability is exacerbated by an additional deleterious process. This process could be linked to AβPP dysmetabolism in both AD and Parkinson's disease, due to a loss of its trophic functions [14, 15]. A similar process of tauopathy progression along neuronal connections of a subcortico-cortico network is also observed in progressive supranuclear palsy and corticobasal degeneration [3,21,41]. These observations suggest that the basic mechanism of **sporadic** tauopathies is a two-step pathogenic mechanism: the first one is a seed, revealed by a proteinopathy in a subset of neurons affected by an age-related vulnerability. The second one is definitely pathogenic, with a progressive and irreversible extension of proteinopathy and neurodegeneration along the connected neuronal network. The fact that this extension of neurodegeneration is not at random, but along cortico-cortical or subcortico-cortical connections, strongly suggests that "stabilizing" factors of neuronal networks are lost following tauopathy. This link is a therapeutic avenue.

CONCLUSION

The main message of this paper would be that it is time to adapt our research to the most common forms of neurodegenerative disorders [17]. The clear cul-de-sac approach is to develop strategies based uniquely on familial diseases, because the transgenic approach is, in

a way, easy or convenient. This transgenic approach is likely to be very useful if it takes into account the physiopathology of sporadic diseases. Indeed, using this transgenic approach, an induced localized tauopathy in the hippocampal area that would spread in neocortical areas under the burden of amyloidopathy is certainly a relevant model for all forms of AD. Also, in cellulo, in a network of neuronal or neuron+glia cells, the set up of a domino-effect propagation of a tau-related stress would be interesting for a relevant pharmacological screening of tau drugs. The aim would be the search for drugs able to stop or prevent the propagation of tauopathy as observed in sporadic diseases.

Altogether, maybe it is time for scientists to demonstrate more neuronal plasticity, or to be humble before the complexity of neuronal networks especially involved in sporadic tauopathies.

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