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Novel Key Players in the Development of Tau Neuropathology: Focus on the 5-Lipoxygenase

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Abstract

Tauopathies belong to a large group of neurodegenerative diseases characterized by progressive accumulation of hyperphosphorylated tau. Tau is a microtubule binding protein which is necessary for their assembly and stability. However, tau affinity for microtubules mainly depends on its phosphorylation status, which is the result of a delicate balance between kinases and phosphatases activity. Any significant changes in this equilibrium can promote tau fibrillation, aggregation, neuronal dysfunction, and ultimately neuronal loss. Despite intensive research, the molecular mechanism(s) leading to tau hyperphosphorylation are still unknown and there is no cure for these diseases. Development of an effective strategy that successfully prevents tau excessive phosphorylation and/or tau aggregation may offer a real therapeutic opportunity for these less investigated neurodegenerative conditions. Beside tau, chronic brain inflammation is a common feature of all tauopathies and 5-lipoxygenase, an inflammatory enzyme, is upregulated in brain regions affected by tau pathology. Recently, *in vitro* studies and preclinical investigations with animal models of tauopathy have implicated 5-lipoxygenase in the regulation of tau phosphorylation through activation of the cyclin-dependent kinase 5 pathway, supporting the novel hypothesis that this protein is a promising therapeutic target for the treatment of tauopathies. In this article, we will discuss the contribution of the 5-lipoxygenase signaling pathway in the development of tau neuropathology, and the promising potential that drugs targeting this enzyme activation hold as a novel disease-modifying therapeutic approach for tauopathies.

Keywords

5-lipoxygenase; phosphorylation; tau protein; tauopathies

INTRODUCTION

Most of the very common neurodegenerative diseases are characterized by aberrant protein aggregation, subsequent intracellular precipitation and ultimately inclusion body formation. Hyperphosphorylation and aggregation of the microtubule-associated protein tau is the major pathological signature of a group of neurodegenerative disorders collectively referred

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to as tauopathies, which includes Alzheimer's disease (AD), Pick's disease, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) [1]. Clinically, tauopathies present a heterogeneous phenotype which may include both motor dysfunction and cognitive impairments. The tau protein is normally associated with microtubules and is necessary for their assembly and stabilization. However, when it becomes highly phosphorylated, its affinity for microtubule decreases and tau starts to polymerize into paired helical filaments (PHFs) which then accumulate and precipitate forming neurofibrillary tangles (NFTs) leading to microtubules disassembly, synaptic dysfunction and ultimately neuronal death [2]. Although several mutations of the gene coding for tau (MAPT gene) have been linked to rare familial forms of these disorders, tauopathies are mostly sporadic diseases and the etiological factors that trigger the pathological tau metabolism, initiate the abnormal conformation and intracellular accumulation in these cases are poorly understood [2].

In addition to tau pathology, neuroinflammation is another common feature of these disorders [3]. Previous research suggested that neuroinflammation is an early event and that activation of the inflammatory response exacerbates microtubule-associated protein tau (or tau) phosphorylation, tau pathology and cognitive deficits in several mouse models of tauopathy [3–5]. The 5-lipoxygenase (5LO) is a pro-inflammatory protein enzyme, widely expressed in the central nervous system (CNS) and is found to be upregulated in the brain of tauopathy patients [5]. Previous studies have provided evidence that this enzyme is significantly involved in age-associated neurodegenerative diseases. In fact, 5LO has shown to influence AD-like neuropathology, modulating both amyloid- β and tau metabolism in APP transgenic mice and in a mouse model with amyloid plaques and tau tangles [5–8]. Moreover, genetic or pharmacological modulation of 5LO activity influences memory impairments, synaptic dysfunction, and pathology and directly modifies tau phosphorylation in transgenic mouse models of tauopathies [5, 9]. Since altered tau metabolism and disrupted function have unequivocally been shown to be central to the neurodegenerative process in tauopathies, the prevention of tau phosphorylation and aggregation represents the main focus of the current drug development research approach in this specific area. However, the identification of a valid target able to efficiently affect these aspects of tau neurobiology and subsequent development of the associated neuropathology has proven to be rather challenging.

In this review, we will focus on new exciting findings which underscore the functional role that the 5LO signaling pathway plays, as a key regulator of tau phosphorylation and pathology, in the pathogenesis of these neurodegenerative diseases. Additionally, we will discuss the potential that 5LO has as a novel therapeutic target, and the promise that pharmacological inhibitors of this protein enzyme may have as a viable and disease-modifying treatment of human tauopathies.

TAU AND TAUOPATHIES

Tau protein

The microtubule associated protein tau, which in this article we will refer simply as tau protein, is encoded by the MAPT gene located on the human chromosome 17. In human, tau gene is composed of 16 exons and alternative splicing of exons 2, 3, and 10 that generate 6

isoforms that differ depending on the presence of the 3 or 4 conserved repeats (3R-tau, 4R-tau) through which tau binds to the microtubules [2]. In addition to alternative RNA splicing, tau can undergo extensive post-translational modifications including phosphorylation, glycosylation, glycation, ubiquitination, and cleavage or truncation. Due to its high content of serine and threonine residues, tau is a good substrate to a large number of protein kinases such as glycogen synthase kinase 3 β (GSK-3 β), cyclin-dependent kinase 5 (CDK5), mitogen activated protein kinases p38 MAPK, c-Jun amino-terminal kinase (JNK), ERK/MAPK, and different protein phosphatases such as PP1, PP2A, PP2B, and PP2C [10]. The phosphorylation status of tau is critical for the regulation of its function and subcellular localization and distribution. In fact, phosphorylation generally reduces or inhibits its microtubule binding property, while de-phosphorylation tends to restore its affinity for the microtubules (Fig. 1) [11]. In neurons, tau is found mainly in the axon associated to the microtubules where is required for microtubule assembly, axons growth and integrity and also for transport of molecular cargo to the synapses [2]. However, accumulating evidence suggest also a physiological role for tau at the synapse level and in the nucleus. Tau is present at both pre-and post-synaptic level and can modulate synaptic neurotransmitter receptor signaling and synaptic plasticity [2,10]. Our understanding of tau function at the nuclear level is less clear but its interaction with several nuclear proteins seems to be important for nucleolar organization and genome stability [2, 10].

Tau in neurodegeneration

Previous studies on animal models of tauopathy have established that the development of tau excessive phosphorylation and tau pathology cause abnormal neuronal and synaptic function and cognitive deficits [12]. In fact, tau reduction has been shown to prevent neuronal loss, reverse pathological tau deposition, and to prolong survival in a transgenic mouse model of tauopathy expressing human tau mutant P301S, the P301S mice [13] revealing the crucial role of tau in mediating neurodegeneration. Notably, both brain imaging studies and CSF measures in AD patients have confirmed that the extent of tau neuropathology strongly correlates with the levels of dementia and memory loss [14]. More than 80 MAPT mutations have been linked to frontotemporal dementia with parkinsonism associated with chromosome 17 (FTD-17), CBD, and PSP but they only account for less than 5% of the total cases, thus what triggers tau abnormal phosphorylation and dysfunction in the sporadic forms of these disorders is still not clear [2]. The disruption of the equilibrium between tau kinases and tau phosphatases observed in tauopathies can significantly contribute to tau aggregation and toxicity. When highly phosphorylated, tau affinity for microtubule decreases and it starts to polymerize into PHFs which then accumulate forming NFTs leading to microtubules disassembly and tau mislocalization which impairs synaptic function (Fig. 1) [15]. Among all the kinases involved in tau phosphorylation, GSK-3 β and CDK5 are probably the most investigated and today considered the most important ones, and their expression is in fact higher in the brain of tauopathies patients when compared with matched controls [16]. The role of these candidate kinases in the pathogenesis of tauopathy has been widely investigated in several relevant mouse models. For instance, when the P301L tau transgenic *JNPL3* mice are crossed with mice transgenic for the CDK5 activator p25, tau phosphorylation is increased at the putative CDK5 epitopes pThr181 (as recognized by the antibody AT270), pSer202, pThr231, and pSer396/pSer404 (AD2/PHF-1) and the number of

NFT is five times higher when compared to the single transgenic mice confirming that this kinase plays an important role in this process [17]. In the normal human brain, tau has also been localized in both pre- and post-synaptic compartments where interact with the post-synaptic density protein 95/NMDA receptor complex [18, 19]. The potential mechanisms by which tau affects synaptic function is not clear; however, tau could play as a scaffold promoting interaction between the post-synaptic density protein 95/NMDA receptor complex and the tyrosine kinase *fyn*, thus regulating the NMDA-receptor signaling [2]. To this end, when tau is hyperphosphorylated, this interaction could be compromised leading to synaptic dysfunction. Beside phosphorylation, an imbalance in the 3R/4R ratio has been also observed in various tauopathies [2, 16]. Under normal physiologic condition, 3R-tau and 4R-tau are present in equal amount in the adult human brain. However, some recent studies have shown that 4R-tau isoforms, which generally have a greater microtubule-binding affinity than the 3R-tau isoforms, are more efficient at promoting microtubule assembly. For this reason, today it is also believed that abnormal alternative splicing can also be involved in the promotion of tau dysregulated phosphorylation and ultimately pathological aggregation [16].

Tauopathies

Tauopathies are chronic neurodegenerative disorders clinically characterized by progressive loss of memory and learning ability (cognition), and impairments of motor functions. Although, several mutations of the gene coding for tau have been identified, the majority of tauopathies are mainly sporadic and thought to arise from the interaction of both environmental and genetic risk factors [11]. Currently, despite the major effort in the tauopathies research field, there are no effective therapies to cure or delay the progression of these disorders. From a pathological point of view, human tauopathies are quite heterogeneous syndromes [1]. In fact, although they all display hyperphosphorylation and accumulation of fibrillary tau in the CNS, tauopathies differ with respect to tau specific phosphorylation sites, cellular distribution, and isoforms found in the fibrillary lesions [1]. Furthermore, tauopathies can be categorized as primary or secondary depending on whether tau pathology is associated with other factors that may contribute to its development and progression of the disease or is the only pathological lesion found in the brains of these individuals [1, 2]. Primary tauopathies includes frontotemporal lobar degeneration, Pick's disease, PSP, and CBD. By contrast, AD represents the typical example of a secondary tauopathy. A further classification is based on the ratio of 3R/4R isoforms of tau which are essential for microtubules binding: PSP and CBD are 4R tauopathies; Pick's disease is 3R tauopathy; but AD typically displays an equal amount of the two isoforms (Table 1). Interestingly, no tau mutations have ever been identified in subjects with AD. Finally, different types of tau aggregates and cellular localization can be distinguished in these disorders. In AD, tau is mainly found in neurons as PHF, whereas in PSP and CBD, tau also accumulate in oligodendrocytes and astrocytes, in form of pre-neurofibrillary tangles in PSP but less filamentous in CBD [1, 2, 20].

Tau pathology and neuroinflammation

Increased neuroinflammation is strongly associated with NFT formation but whether it precedes or is driven by tau pathology *per se* is still not clear. Activated microglia and

astrocytes co-localize with tau oligomers in the postmortem brain tissues of various human tauopathies including AD, FTD, PSP, and CBD [21, 22]. Moreover, the severity of brain inflammation correlates with disease progression, neuronal cell death, and cognitive impairments. What initiate tau phosphorylation and dysfunction is still not known but neuroinflammation seems to play an active role in this neurodegenerative process [3]. In fact, recent findings have demonstrated that microgliosis precede tangle formation in two mouse models of tauopathy: the hTau and P301S mice [5, 23]. Moreover, current research has shown that induction or inhibition of the inflammatory response can modulate tau pathology *in vivo*. The administration of lipopolysaccharide, the Toll-like receptor 4 ligand, can trigger tau hyperphosphorylation in the 3xTg AD mouse model [24], while administration of FK506, an immunosuppressant drug, decrease microgliosis in the P301S transgenic mouse model [23]. On the other hand, alterations in microglial phenotypes are also driven by tau dysfunction. Misfolded truncated tau is reported to activate the innate immune response via activation of the MAPK kinase pathway and to induce the release nitric oxide and other powerful pro-inflammatory cytokines (i.e., Interleukin-1 β , Interleukin-6 and Tumor Necrosis Factor- α) [25, 26]. Finally, loss of tau in neurons and microglia provides protection against lipopolysaccharide-induced neurotoxicity, which under normal conditions triggers tau hyper-phosphorylation, tau pathology and ultimately cell loss and neurodegeneration [27].

The 5-lipoxygenase pathway

The 5LO protein is an enzyme that produces potent pro-inflammatory mediators such as leukotrienes by oxidation of the carbon in position 5 of free or esterified fatty acids, such as arachidonic acid [28]. Immediate product of 5LO enzymatic action is the 5-hydroxy-peroxieicosatetraenoic acid (5-HPETE), which is then metabolized into 5-hydroxy-eicosatetraenoic acid (5HETE) or leukotriene A₄ (LTA₄), depending on the cellular milieu. LTA₄ is a substrate for the LTA₄ hydrolase or LTC₄ synthase generating LTB₄ or LTC₄, respectively. LTC₄ can be then further metabolized by γ -glutamyl-transferase 1, and LTD₄ dipeptidase to produce LTD₄ and LTE₄ (Fig. 2). Collectively LTC₄, LTD₄, and LTE₄ are known as the cysteinyl-leukotrienes which signal through the activation of G-protein-coupled-receptors (GPCRs), cysteinyl leukotriene receptors (CysLT1, CysLT2) to modulate chemokine production, immune cell activation and inflammation [29]. The 5LO enzymatic activity is strictly dependent and regulated by the availability of another protein, 5LO-activating protein (FLAP), which is necessary for the delivery of arachidonic acid to 5LO at the nuclear membrane level and for 5LO full activation (Fig. 2) [29].

The 5LO is widely expressed in the cardiovascular system and CNS and its levels are upregulated with aging, a common risk factor for the development of both cardiovascular and neurodegenerative diseases. In fact, upregulation of 5LO is implicated in vascular inflammation, and myocardial infarction [4, 30]. Furthermore, this enzymatic pathway has been reported to increase after cerebral ischemia and variants of the ALOX5AP, the gene encoding the 5LO-activating protein, have been shown to be associated with a greater risk of stroke compared with matched controls [31, 32].

The role of 5LO in tauopathy

In the CNS, the 5LO is expressed by both neurons and glia cells [29, 34]. Interestingly, post-mortem studies have shown that 5LO levels are upregulated in AD and PSP patients, as well as in relevant mouse models of AD and other tauopathies in areas of the brain more vulnerable to neurodegeneration, such as cortex and hippocampus [5, 33–35]. Following this discovery, in recent years, our group has demonstrated that 5LO is a key player in the development of the full pathological phenotype of these neurodegenerative disorders [7, 8]. First, we showed that in a transgenic mouse model of AD with plaques and tangles, the 3xTg AD mice, 5LO pharmacological inhibition or genetic deletion reduces amyloidosis and tau pathology and restores memory loss and synaptic dysfunction. On the other hand, we saw that the same mice overexpressing 5LO display worsening of their memory performance, greater A β and tau phosphorylation accumulation, and increased neuroinflammation [8]. In particular, we demonstrated that the effect on tau phosphorylation was mediated by the activation of the CDK-5 kinase pathway [8]. In fact, 5LO inhibition or knockout specifically reduces not only expression levels of the two CDK5 coactivators, p35 and p25, but also CDK5 kinase activity *ex vivo*. By contrast, 5LO overexpression results in a significant increase in tau phosphorylation upon increased levels and activity of the CDK5 kinase pathway [5–8]. Additionally, inhibition of CDK5 activity prevents 5LO-induced phosphorylation of tau in an *in vitro* model of AD, thus confirming that 5LO acts through CDK5 to induce tau pathological changes.

However, since data in the literature have shown that A β itself can promote tau phosphorylation [36, 37], our observation did not address the important biological question of a direct or indirect (i.e., via A β) role that 5LO plays in tau phosphorylation. To this end, and to finally establish that 5LO effect on tau is independent from A β , the possible modulation of tau phosphorylation by the 5LO signaling pathway has recently been investigated in two different models of pure tauopathy: the hTau mice in which mouse tau is substituted by non-mutated human tau [11], and the P301S mice, carrying the MAPT P301S mutation which is associated with FTD [38]. In both models, 5LO is significantly upregulated in an age-dependent manner, and brain region-dependent fashion with hippocampus and cortex showing higher levels compared with controls, whereas no differences were detected when cerebellum of the two groups was compared [5]. The observation regarding the region-specific increase in 5LO levels confirm the findings we previously observed in AD brains. Interestingly, in P301S mice, levels of LTB₄, an indirect measure of 5LO activity, are also significantly increased in both regions as early as 2 months of age, when tau pathology is not detectable yet. This finding suggests that the activation of this enzymatic pathway is an early event during the development of the phenotype in this mouse model of human tauopathy [5].

Further studies have demonstrated the beneficial effect of 5LO inhibition in hTau mice, using zileuton, a selective and specific 5LO inhibitor which is approved by the FDA for the treatment of asthma since it prevents leukotrienes formation. In this relevant tauopathy model, pharmacological targeting of 5LO enzymatic activity results in reduced levels of tau phosphorylation without affecting total tau expression levels [5]. In addition to these changes in phosphorylation, mice receiving zileuton display significant less insoluble tau

and less immunoreactivity for MC1, an antibody which specifically recognizes pathological tau conformation [39], indicating that 5LO inhibition also prevents alteration of tau folding associated with PHF formation [5, 40]. Recently, to rule out the possibility of potential zileuton offtarget effects, these data have been reproduced in the tau transgenic mice where 5LO was genetically deleted. In this study we showed that the absence of this enzyme is accountable for a significant reduction of tau phosphorylation at specific epitopes without influencing total tau expression [9]. As mentioned previously, this effect is mediated via inhibition of the CDK5 kinase pathway, as demonstrated by reduction of p35 and p25 expression, in tau mice lacking the 5LO gene. These results have been confirmed also using an *in vitro* approach, in primary neuronal cells stably expressing the whole human tau transgene (Fig. 3) [5, 9].

Pleiotropic effect of 5LO in tauopathy

Considering that tau neuropathology induces defects in synaptic plasticity, learning, and memory, it comes with no surprise that beyond tau phosphorylation, the 5LO enzymatic pathway is also implicated in modulating synaptic function and cognitive impairments. Behavioral and electrophysiological analyses of transgenic tau mice have shown that tau hyperphosphorylation and aggregation particularly affects synapses and causes significant reduction in the long-term potentiation responses [41]. However, pharmacological inhibition or genetic absence of 5LO enzyme rescues these brain functions. In fact, zileuton treatment as well as 5LO knockout in hTau and P301S mice results in better working and spatial memory [5, 9] and protects from tau-induced synapsis dysfunction as measured by long term potentiation recording at both 10 and 120 minutes [5].

Together with these functional aspects of the synapse, manipulation of the 5LO pathway can also modulates the expression of several markers of synaptic integrity such as post-synaptic density protein 95, synaptophysin, and microtubule-associated protein 2 (MAP2) [42–45]. Thus, compared with controls transgenic tau mice chronically receiving the 5LO inhibitor, or born genetically deficient for the 5LO gene manifested significant improvements in these different synaptic proteins suggesting a modulatory ability of 5LO toward this important aspect of the tauopathy phenotype. Lastly, genetic deletion of the 5LO enzymatic pathway results in reduced activation of microglia and astrocytes, commonly found around NFTs-rich areas [46, 47] as demonstrated by a decrease in glial fibrillary acidic protein and cluster of differentiation 45 steady state levels and brain immunoreactivity to these proteins [5, 9]. Current animal models of neurodegenerative diseases have shown that the activation of the local inflammatory response is an early event and strongly influences the rate of disease progression suggesting that a viable therapeutic approach should potentially address both neuroinflammation and tau pathology. In this regard, 5LO represents an attractive target for the treatment of both aspects of the disease phenotype. Employing pharmacological inhibition, gene knockdown and overexpression of 5LO, these recent studies have validated the crucial role of this enzyme in the modulation of several aspects of tau pathology including tau phosphorylation, synaptic function and plasticity and memory in different mouse models of tauopathy [5, 9].

CONCLUSIONS

Tauopathies are a group of chronic neurodegenerative disorders characterized by progressive cognitive deficits and dementia. Aberrant phosphorylation of the microtubule associated protein tau has clearly been linked to the development of these neurodegenerative processes and several disease-causing mutations of the tau gene have been identified in some of these patients. However, tauopathies are mainly sporadic diseases, and the molecular and cellular mechanisms responsible for aberrant tau function in these cases are poorly understood. The prevention of increased tau phosphorylation and subsequent aggregation is currently the main focus of an intense drug development effort approach, but the research of a valid target able to directly modulate tau pathology and delay the progression of these diseases has failed so far. Beside tau, neuroinflammation is an active player in the neurobiology of these disorders. Growing evidence have shown that microgliosis and astrogliosis, two markers of cellular neuroinflammation, are strongly associated with NFTs deposition and neuronal toxicity, but whether activation of the inflammatory response is primary or secondary to the development of tau pathology is not clear.

Having established that 5LO, a pro-inflammatory enzyme, is upregulated in the brain of PSP patients and mouse models of tauopathy, and that knockout or pharmacological inhibition of 5LO activation is sufficient to reduce tau phosphorylation and to restore memory and synaptic function in several relevant models of the disease, this signaling pathway has recently emerged as a novel therapeutic target for the treatment of tauopathy. The successful completion of the initial step for the pre-clinical evaluation of a pharmacological inhibitor of this enzyme has now clearly paved the way for next step in this field: the investment in further research and development of this class of drugs (5LO inhibitors) as novel and potentially disease modifying agents with neuroprotective effects for human tauopathies.

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Fig. 1.

The neurobiology of microtubule associated protein tau. In physiological conditions, tau is associated with microtubules to stabilize them and to keep healthy axonal transport and neurite outgrowth. However, in the brain of tauopathy patients, the disruption of normal phosphorylation events results in aberrant phosphorylation of tau which negatively affects its affinity for the microtubules and leads to microtubule destabilization. Once detached from the microtubules, hyper-phosphorylated tau tends to aggregate into paired helical tau filaments, which eventually become insoluble and precipitate inside the cells generating the neurofibrillary tau tangles.

Fig. 2.

The 5 lipoxygenase enzymatic pathway. Following cellular activation, 5-LO migrates from the cytosol to the nuclear membrane where it is able to interact with the 5LO activating protein (FLAP) and by oxidizing arachidonic acid on carbon 5 generates first 5hydroperoxyeicosatetraenoic acid (5-HPETE), which can then be converted to 5-hydroxyeicosatetraenoic acid (5-HETE), or leukotriene A4 (LTA4). LTA4 can be metabolized in leukotriene B4 (LTB4) by the action of a hydrolase, or into leukotriene C4 (LTC4) by the action of a synthase. LTC4 in turn can be transformed into leukotriene D4 (LTD4) by the γ -glutamyl transferase-1 and then into leukotriene E4 (LTE4) by the LTD4 dipeptidase enzyme. LTB4 action is mediated by bonding to the leukotriene B receptors (BLT1, and LTB2), whereas the LTC4, LTD4 and LTE4 action is mediated by their binding to the cysteinyl leukotriene receptors (CysLT). In both cases, the binding will elicit a GPCR-dependent intracellular signaling biological event resulting in immune activation and inflammatory responses.

Fig.3.

Working model depicting the role that the 5-Lipoxygenase plays in the development of tau neuropathology. 5LO activation promotes tau phosphorylation via the CDK5 kinase and results in neuroinflammation, memory and synaptic dysfunction. Pharmacological inhibition of 5LO enzyme activity by zileuton by preventing activation of the CDK5 kinase reduces tau phosphorylation, synaptic dysfunction, neuroinflammation, neuronal loss and ultimately disease onset.

Table 1

Most prevalent tauopathies and associated tau isoforms

Disease	Predominant isoform
Primary tauopathies	
PSP	4R
Argyrophilic grain disease	4R
Corticobasal degeneration	4R
Pick's disease	3R
FTDP-17	4R/3R
PEP	4R/3R
PDC Guam	4R/3R
Guadeloupean parkinsonism	4R
Secondary tauopathies	
Alzheimer's disease	4R/3R
Down's syndrome	4R/3R