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Chapter 3

Tauopathy

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Abstract

Tauopathy is a category of neurodegenerative diseases that are caused or associated with pathological tau protein. Some of the diseases are relatively common, which include Alzheimer's disease (AD) and various Parkinsonism (PD). Tau protein is a type of microtubule-associated protein (MAP), encoded by the gene MAPT (microtubule-associated protein tau). Normally, tau binds to microtubule, supporting the assembling and structure of cytoskeletons. However, in tauopathy, normal tau protein undergoes abnormal posttranslational modifications and detaches from microtubule; furthermore, they may aggregate forming paired helical filaments (PHF) or straight filaments (SF). Abundant PHF could be observed under microscope as fibrillary tangles. In this chapter, we will introduce the pathogenesis process of tauopathy with regard to the posttranslational modifications of the protein, the animal models, and the developing treatments against tauopathy from a clinical prospective.

Keywords: tau, phosphorylation, truncation, kinases, Alzheimer's diseases, clinical trials

1. Introduction

Tauopathy is used to summarize all the diseases that the pathogenesis processes are related to tau protein. Tau is one of the most common proteins involved in neurodegenerative diseases. In many tauopathy cases, tau protein seeds and forms intracellular fibrillary tangles on itself, one of the pathological hallmarks of Alzheimer diseases [1]. The tangles formations are believed mostly due to altered posttranslational modifications of tau protein, which detaches from microtubules and binds each other forming aggregates. In several parkinsonism-associated movement disorders, including frontotemporal dementia with parkinsonism-17 (FTDP-17), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), mutations in tau have been identified, and those altered tau are prone to tangles formation [2]. The common

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involvement of tau protein in a range of neurological disorders makes it one of the most studied proteins. However, despite it has been studied for approximately 30 years since tau is coined as the major component of fibrillary tangles, concrete evidence that detail tauopathy in molecular and cellular levels is still limited [3], and most of the pathological data are obtained from studies using postmortem brain. Therefore, how tau protein and its dynamic changes affect the pathogenesis of various neurodegenerative diseases is still a mystery. Many outstanding questions are being stressed, including which posttranslational modifications are critical for it to gain toxicity, does other neurodegenerative diseases involved proteins interact with tau protein, which brain regions or cell types are most susceptive to the toxicity of tau and how the aggregates cause cellular dysfunction, and which forms of tau during the tangle formation process are toxic. In this process, some widely accepted concepts are being challenged. For example, traditionally, it is believed that hyperphosphorylation of tau induces it to detach from microtubule and increases its toxicity, but recent findings suggest some phosphorylations are protective instead [4, 5]. These findings will be emphasized in the following sections. Apparently, more efforts are needed before we can reach a definitive answer for these questions. Some exciting technological advances promise further exploration of some exist questions and more unexplored fields involving tau protein.

2. Tau biology and pathology

Tau pathology, namely fibrillary tangles, was observed way before the protein was identified. In fact, it was Alois Alzheimer who first described the heavy burdens of this never reported feature in his demented patient back to 1906 [6]. Seventy years later, tau protein was isolated as a factor that is critical for the re-polymerization of some depolymerized tubulins to form microtubules in vitro [7]. After another 10 years, a series studies confirmed that the tangles observed in AD brain are composed of tau [3, 8–10]. Since then, tau received significant attention in AD research. Nevertheless, as researchers soon realized tau pathology in a panel of neurological dysfunction, solving the underlying mechanism of tauopathy has been regarded as a unique field of neurobiology.

2.1. Tau biology

2.1.1. Tau's interaction with microtubule

The expression of tau protein varies in different tissues, but the brain has the most abundant level. In brains, tau is predominately expressed in neurons but can also be detected in glial cells, especially in oligodendrocytes [11]. In neurons, tau proteins are mainly localized in axons, but they are not excluded from dendrites [12]. Functional analyses in vitro demonstrated that tau plays critical roles in both microtubules assembly and maintaining the structural stabilization [7, 13]. But not until recently, researchers are starting to understand the interactions between tau and microtubule in real-time by adopting different newly developed techniques. By fusing a Halo-tag, a dehalogenase modified to bind certain fluorescent ligand; tau could be labeled and monitored in live imaging [14]. With tubulins being labeled

with photoactivatable green fluorescent protein (PAGFP), the interactions between tau and tubulins are viewed under total internal reflection fluorescence microscope (TIRF). With such high resolution and relatively short time frame, the live imaging revealed that tau moves on microtubule quickly without direction. In authors' words, it could "hops on and off" to another microtubule in milliseconds and moves along a microtubule with little dwindle time [14, 15]. In another study, under transmission electron microscope (TEM), it was found that tau could promote the microtubule assemble by laterally crosslinking protofilaments [13]. Moreover, tau showed a preference to bind GDP-tubulin over GTP-tubulin, but the reason behind it is not understood [13].

2.1.2. Tau structures and functions

Tau is encoded by the gene MAPT (microtubule-associated protein tau), which is located on chromosome 17q21. *MAPT* has 15 exons, and the alternative splicing of the mRNA resulted in six different isoforms. The longest one among these has 441 amino acids, which is often referred as full-length tau. In late 1980s, the basic protein structure of tau was defined [16, 17], and it was realized that the C-terminus of tau protein contains repeated domains responsible for the binding of microtubules [17]. The basic structure and functions of each functional region of it are summarized as follow:

On the N terminal side (1–150), it has two N-terminal domains. Each has 29 amino acids, one from 45 to 74 and another from 75 to 103. The physiological functions of N terminal domain are largely unknown, and speculations on that including it could play roles in signal transduction as tau could co-immunoprecipitated with phospholipase C gamma through the binding sites within N terminus [18].

The N terminal side is followed by two proline-rich domains, one from 151 to 198 followed by another from 199 to 243. Studies showed that this region interacts with src kinase family members, such as fyn serving for signal transductions [19, 20]. Furthermore, it was shown that tau could interact with beta and gamma actins, which are the subtypes of actins commonly seen in neurons [21]. A panel of different truncated and or mutated tau was generated to test the interactions of it with actins, and it was found that the proline-rich regions were responsible for this interaction [21].

The proline-rich region is followed by microtubule binding region (244–370), which is composed of four repeated domains and each one of them contains 18 highly conserved amino acids. The microtubule binding region directly binds to tubulin, which plays the most critical role in microtubule interaction [22]. Because the N terminal side does not bind to microtubule and was thought to interact with other proteins, the N terminal side plus the first proline-rich domain is often referred as projection domain of tau. The rest residues, including the second proline-rich domain and microtubule binding domains as well as the C terminal tail, are often referred as microtubule assembly domain [23].

Because the full-length tau has all these N terminal regions (2 N) and C terminal repeats (4R), it is also referred as "2N4R" tau. The rest of other tau isoforms found in brain are the combinations of either lacks one (the second N terminal domain; 1 N) or two N terminal

domains (0 N) or does not contain the second microtubule-binding domain (3R). Therefore, isoforms "1N4R", "0N4R", "2N3R", "1N3R," and "0N3R" are simply denoting the major functional domains of tau [22, 23]. The dominate forms found in human brain are 2N4R and 2N3R. Under physiological conditions, the ratio of isoforms with 4R and 3R is around 1 [24]. While in pathological conditions, the expression of tau isoforms could favor one form, especially 2N4R for most tauopathies. Researchers have long noticed the ratio alterations in disease conditions, but the exact meaning and the reason behind this change are still unknown [25].

Under physiological condition, tau exists in an unfolded state, and 80% of the proteins interact with microtubule in neurons [22, 26]. When tau is not interacting with other proteins, it may curl on its own, and this random curled state is believed important for preventing interactions with other tau proteins by masking the possible interacting sites [27, 28]. The protein itself is bipolar; the N-terminal side is highly negatively charged in normal physiology, while the proline-rich domain and C-terminal end are positively charged, allowing it to interact with the negatively charged C-terminal of tubulins [22, 29]. Various posttranslational modifications could alter its charge. Paired helical filaments (PHFs) are relatively acidic compared to normal full-length tau, which is believed due to the phosphorylation of the amino acid residues [30, 31]. Tau is also very hydrophilic, containing only a small portion of hydrophobic residues [27]. Both the net charge changes and a possible shift from being hydrophilic to hydrophobic are speculated of contributing to its aggregation behavior under pathological conditions [28, 31]. Also, normal tau proteins only exhibit transient secondary structures [27]. Phosphorylation of certain residues may prompt tau to form secondary structures, which is revealed by pseudophosphorylation of all the residues that could be recognized by phospho-tau specific antibodies AT8, AT100, and PHF1 and are shown by the structural changes in nuclear magnetic resonance spectroscopy [32]. But how normal tau proteins are transformed to form aggregates remains a mystery.

Given that tau may exist in various forms and structures, one shall be mindful not to overstate the possible role of tau based on data derived from truncated/engineered tau, which may only have the N terminal side or the C terminal side [18, 33–35]. Nevertheless, we have gained more understanding of tau and its function from previous works, but better manipulations are needed before we can be comfortable about applying those bench-side results to tauopathies treatment.

2.2. Tau pathology

Tauopathies feature a variety of pathological brain defects, such as neurites dystrophy, cell loss of certain brain regions, and brain shrinkage. The patients show associated symptoms like the decline of cognitive function, memory loss, and defects of the visual system. In the postmortem brains of most affected patients, tau aggregations are commonly found.

2.2.1. Formation of fibrillar tangles

The fibrillar tangle is the hallmark of tauopathy. The formation process of this aberrant salient could generally be categorized into several stages described as follow:

Step 1. Conformational change of tau: Certain sites phosphorylation and other posttranslational modifications or genetic mutation of MAPT rendering tau bind to tubulins with reduced affinity and detaches from microtubules no longer support the microtubule assemble, increasing the free tau protein pool [22, 36].

Step 2. Oligomer formation: The detached tau proteins form globular oligomers, which are composed of 40 monomers in vitro in the presence of heparin [37]. The mainstream opinion speculates that the detached/modified tau proteins, especially the hyperphosphorylated types, are prone to interact with each other. The phosphorylation on the residues of C-terminal and proline-rich domains neutralizes the charges of the region and reduces the net charge of the protein by which it may contribute to losing the natively unfolded property and prohibit the intramolecular interactions of tau protein [22, 38, 39]. On the other hand, it was reported that the two cysteine residues on tau, cysteine-291 and cysteine-322, play a pivotal role in the tau dimerization [40] because oxidation of the residues may lead to the disulfide bond formation between tau monomers, which potentially seeds for the oligomerization process. This theory is supported by the frequent observation of oxidative stress in tauopathies [41]. Moreover, a recent study showed a compound which could effectively inhibit heparin-induced tau oligomerization was through its interaction with the cysteine residues [37]. However, tau can also form cysteine-independent oligomers [40]. Another recent study adopted tau fragment (aa. 297–391), which is the core of PHF, to study the role of cysteine in the polymerization of tau in the absence of heparin [42]. The results showed that replacement of the cysteine residue or in the presence of reducing agents, the polymerization process was accelerated rather than decelerated [42].

It is noteworthy that most of these studies used anionic agents like heparin to induce the oligomerization of different recombinant tau isoforms or fragments to test the intrinsic properties and the effects of the modifications in vitro. But to what extent could this artificially induced tau oligomerization reflects the real pathological process is questionable. A recent study showed that heparin-induced recombinant tau tangles have little seeding ability in the wild-type mouse. In contrast, tau tangles isolated from patients have a strong seeding ability, and the pathology could spread quickly to different brain regions, shedding lights on the difference between in vitro generated tau tangles and in situ harvested tau tangles [43].

Step 3. PHF formation: Tau oligomers may further develop into more complex structures like PHF or straight filaments (SF) [44]. It has been shown that in different tauopathies, the ratio of PHF/SF and their sizes may vary [45, 46]. For example, in Alzheimer's disease, PHF is more commonly observed than SF [45]. On the other hand, in progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and pick's disease (PiD), SF is predominately found [46]. In certain cell types beyond neurons, tau inclusions may exhibit different morphologies and have been given different names to describe their shapes [47]. With the help of Cryo-Electron Microscopy (Cryo-EM), we are now able to identify the structures with high resolutions [48]. It becomes clear that the cores of the filaments are composed of eight β-sheets which requires some hydrophobic interactions between individual peptides; the difference between PHF and SF is due to the lateral interactions between the sheets. However, disulfide bonds formed in the structures remain to be determined [48]. The β-sheets formed in tau oligomers and PHF could be detected with thioflavin T or S staining [28].

2.2.2. Uniqueness of different tauopathies

As mentioned above, tau inclusions are found in different types of cells in different tauopathies. In Alzheimer's disease (AD), tau inclusions are found in neurons as neurofibrillary tangles (NFT). While in many other tauopathies, the inclusions are found both in neurons and glia cells. Also, the compositions of the inclusions are different. In many tauopathies, the inclusions are mainly composed by 4R tau, while in PiD, 3R tau is the dominant form in the inclusions. In AD, the ratio of 3R/4R is close to 1 albeit the expression favors 2N4R [46]. How the different tau tangles are constructed and what the chemical and physical factors attributing the assembled pattern are still an enigma. Moreover, the locations where the aggregates are first found are also different, following different transmission pathways [46]. Together these indicate that although tau aggregate is the hallmark for all tauopathies, the properties of the inclusions are different and the factors that trigger various pathological changes may also be different [43, 46].

2.2.3. Tau degradation

Normally, the lifetime of tau is short. It was tested in cultured cells that the lifetime of tau is within 24 hours [49, 50]. It is presumed that tau proteolysis is mainly controlled by proteasomes degradation and in vitro studies also support this notion [51]. Since many endogenous proteolytic enzymes can cleave tau proteins, it is likely there is some coordination which may exist among them and also with the proteasomes [51]. Nevertheless, in tau pathology, the turnover time for tau significantly increased. It has been reported that tau phosphorylation inhibits the protein degradation [52], which could explain its pathogenic link. Recently, studies showed autophagy is involved in the digestion of tau, especially for those bulky inclusions that are probably hard to be digested by the proteasome [53]. It was found hyperphosphorylated tau co-localized with LC3 positive vesicles, a critical autophagy adaptor protein, in postmortem brains of different tauopathies [54]. More importantly, many evidence directly shows that both proteasome and autophagy systems are impaired in tauopathies, likely resulting from the assault of tau aggregation [55, 56].

For proteasome-mediated degradation of tau, different studies have shown that proteasome activities are decreased in tauopathies. Both in a tauopathy animal model or AD brains, isolated tau of sarkosyl-insoluble fraction was co-immunoprecipitated with proteasome subunits [57, 58]. Furthermore, incubating proteasome with fibrillar tau or tau oligomers decreased the activities of the proteasome, whereas when it was incubated with monomer tau, the activities were not affected, demonstrating that pathological tau might cause proteasome dysfunction [57]. It was observed that the ubiquitinated protein levels are increased in a tauopathy model, and PHF tau was also ubiquitinated in both animal models and AD brains [57, 59, 60]. While these results demonstrate a nice correlation between proteasome function and tau degradation, whether the turnover of normal or pathological tau depends on proteasome or not is still unclear [61].

For autophagy, it was observed that the dystrophic neuritis of postmortem AD brains contains huge amounts of autophagic-like vacuoles, which are presumably to be autophagosome

or autolysosomes. These observations imply a significant upregulation of autophagy activities preceded by certain stimuli like cytoskeletal dysregulation or oxidative stress, likely causing the neurons to initiate apoptosis and contribute to neurites dystrophy [55, 56, 62]. Dense lysosome proteases staining results in AD brains also indicate defective degradation of major intracellular protein aggregates. Moreover, in the familial AD, presenilin 1 mutation is one of the most common mutations causing the disease. Traditionally, it is believed the pathogenic mechanism is that the expression of presenilin 1 mutations results in the generation of Amyloid-beta, as this molecule constitutes the active domain of γ-Secretase. However, presenilin 1 also plays a critical role in autophagy that functions as an ER chaperon transporting enzyme subunit critical for lysosome protease activation. Deletion of presenilin 1 could abolish autophagy [56]. All these results support the notion that tau aggregation may cause upregulation of autophagy activity.

3. Pathogenesis of tauopathy

There are two forms of tauopathy, familial and sporadic. Familial tauopathy is linked with genetic mutations of tau, and sporadic tauopathy is often associated with altered posttranslational modifications. Since the pathogenesis of the two forms is different, so they are discussed separately in the sections below.

3.1. Genetic mutations of tau

3.1.1. Tau mutations in neurodegenerative disorders

Genetic mutations of tau can cause familial tauopathies, which are commonly found in frontal temporal dementia (FTD), including a range of clinical conditions like Pick's disease, corticobasal dementia, and progressive supranuclear palsy [63, 64]. Mutations of tau were first discovered in the late 1990s in inherited FTD families [65], and it was the first known monogenic mutations that could cause FTD [63, 64]. Epidemiological surveys showed MAPT mutations are responsible for 5–20% FTD cases [63]. Since MAPT is localized to chromosome 17 and the subject showed FTD with parkinsonism syndrome, it was named frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) to refer tau mutations-associated FTD [66]. More than a hundred tau mutations have been identified, and not all of them are pathogenic. A detailed mutations list and their associated impacts can be found online at Alzforum.org [67]. Tau mutations are rarely found in Alzheimer's disease (AD) and normally are not considered as a major genetic risk factor for the disease's familial form. But certain mutations could contribute to the pathogenesis of AD, and some found that mutations' pathogenicity has not been integrated yet [67, 68].

3.1.2. Tauopathy animal models

Pathogenic tau mutations typically result in either RNA splicing variation causing the ratio change of 3R/4R or a structure change, which will further affect its binding affinity with

microtubule and other proteins or promote its self-assembly [66, 67, 69]. The mutation sites cover the whole protein and could also be in the introns affecting the RNA splicing [67]. Some much more common mutations have been selected in generating transgenic models for studying tauopathies [70]. To date, 28 tauopathy mouse models have been reported according to Alzhforum.org and many of which are overexpressing models [67]. Other tauopathy animal models in *Drosophila*, zebrafish, and *C. elegans* also help the field to untangle the molecular and cellular complexity of this clinical condition [71–74].

Transgenic expression of normal human tau in mouse models with either 3R or 4R forms were unable to induce significant pathological changes [75]. While with strong pan-neuronal promoters could induce more pathological features, this approach also raises a concern of overwhelmed tau expression, which may lead to possible artificial effects by causing heavy burdens on protein degradation systems, which obviously deviated from the progressive pathogenesis that is responsible for the sporadic tauopathy [75–77]. Notably, a recent study created transgenic mice expressing an N-terminal truncated tau under the control of human tau promoter so to mimic the normal expression level and by which recapitulated some major pathological features of tauopathies [76]. The authors claimed that a similarly truncated tau could be found in postmortem progressive supranuclear palsy brains, which makes this finding quite interesting.

In comparison, expressing disease-linked mutant tau can induce more pronounced pathological effects, and some of the models are widely used in basic or pre-clinical research settings if not in combined with other tauopathy-related protein expression [67, 70, 75, 77]. The most commonly adopted tau mutations in transgenic animal models are P301L, P301S, R406W, and V337 M [59, 77]. All these mutants were found in FTD patients, and their expression showed reduced binding affinity to the microtubule. Importantly, all of them could efficiently induce tau filaments formations in mouse models, although the composition of the filaments may be different for different tau mutations [66, 70]. Among them, three mouse models stand out in terms of their wide usage in basic research, as well as in the pre-clinical tests of drug development. These are P301L, PS19, and rTg4510 (r for regulatable), all of which were developed in the mid-2000s [78–80]. P301L mice overexpress 2N4R tau with P301L mutation under the pan-neuronal driver Thy1 [78]. PS19 mice overexpress 1N4R tau with P301S mutation driven by mouse prion protein promoter [79], and rTg4510 adopts the tet-off system to overexpress 0N4R tau bearing P301L mutation only in the absence of tetracycline that controlled by Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) promoter [80]. In general, rTg4510 and PS19 mice show more massive pathology burdens in comparison with to P301L. Although overt tau aggregations were observed in all three types of mice and showed cognitive defects, only rTg4510 and PS19 were reported to induce significant neuronal loss [79, 80]. PS19 mice showed severe hippocampus shrinkage at the age of 9 months, while rTg4510 mice showed gross forebrain atrophy at the age of 10 months [79, 80]. It is noteworthy that human tau expression levels were several times higher than the endogenous mouse tau levels for all three models [78–80].

These data collectively show that while significant tau aggregates can be induced by expressing mutant tau, the models are different from sporadic tauopathy, especially in terms of studying

the pathogenesis and treatment methods for tauopathy with a mouse. Another major concern is related to the modulation of endogenous enzymes at the time of human tau expression, which is an issue difficult to control. Some key features related to general pathogenesis process were missed from the transgenic mice models, including robust tau propagation and significant cell apoptosis [48, 81]. In one study, by injecting insoluble tau to mouse hippocampus, it was found that the seeding and propagation ability of the synthesized insoluble tau are much weaker than the insoluble fraction of isolated tau from the AD in vivo [48]. Together, it shows there is still a long way to go before using these animal models to find a strategy for detour tauopathy.

Recent advances in human stem cell research may provide a solution for tauopathy and related research. By grafting human stem cell-derived neuron to express amyloid-beta in mouse brain, a study revealed that the human neurons are more susceptible to the toxicity of amyloid-beta than mouse neurons [81]. This observation proved the discrepancy of cells from the two organisms. Therefore, if the quality of the grafted cells and the surrounding microenvironment represent the physiological conditions in the human brain, shall we also expect human neurons are more susceptible to the toxicity of tau?

3.2. Posttranslational modifications of tau

Most patients who suffer from tauopathies carry wild-type MAPT. Therefore, posttranslational modifications of tau are believed to be the key of tau pathogenesis and have been the major area of tauopathy research for years. Understanding the posttranslational modifications of tau not only helps us to pin down the pathogenic mechanism but also offers a viable path for drug screen by targeting certain enzymes that modifying tau. As mentioned in the above sections, altered posttranslational modifications of tau could render the protein to lose its native unfolded structure and by which to promote aggregate formation. In this process, the modifications also changed the interactions between tau and other proteins in addition to tubulins. So far, 10 types of tau posttranslational modifications have been documented [82], among which phosphorylation and truncation are most found, representing the majority of the modifications, while other modifications (ubiquitylation, oxidation, glycosylation, glycation, nitration, acetylation, and sumoylation) are either not often discussed in this setting or just recently founded. In total, over 100 sites on a tau protein have been proposed that could be modified if not considering the truncation [83].

3.2.1. Phosphorylation

In one of the pioneer studies aimed to prove that neurofibrillary tangles are made of tau, the researchers found treating the tissue section with phosphatase could dramatically increase the antibody labeling of tau on the tangles [9], and the researchers coined the staining as “atypical phosphorylated” tau. Since then, the “hyperphosphorylated” tau under pathological conditions received a great deal of attention. Many protein kinases have been proposed to play roles in tau phosphorylation, and some of them have been confirmed by in vivo studies [9, 84]. Recent developments have proposed to try out some kinase inhibitors as potential tauopathy therapeutics [85]. For a 2N4R tau protein, it consists of 45 serine residues, 35 threonine

residues, 12 histidine residues, and 5 tyrosine residues. Current postulated phosphorylation sites have essentially covered most of the available sites, and indeed many of these residues are found being phosphorylated under physiological conditions. Therefore, the widespread, and likely dynamic, tau phosphorylation appears to serve for certain uncovered functions. Nevertheless, it also indicates that the differences in general phosphorylation and changes of phosphorylation state in certain residues may play a critical role in tauopathies [83, 84]. Moreover, hyperphosphorylated tau could also be detected in other pathological conditions aside from tauopathy. It was found that phosphorylated tau proteins are co-aggregated with alpha-synuclein in Parkinson disease and Lewy bodies dementia [86]. In some reports, phosphorylated tau aggregation can be found in Huntington disease and amyotrophic lateral sclerosis brains [87, 88]. In traumatic brain injury patients, the levels of phosphorylated tau, but not total tau, are significantly increased [89]. Recently, it is also suspected that tau phosphorylation may play a role in type 2 diabetes, rendering the patients incline to have cognitive defects [90]. These data collectively indicate hyperphosphorylation of tau has a strong correlation with a variety of brain pathologies, not just tauopathies.

However, the scenario of pathogenesis in tau hyperphosphorylation is more than merely the activation of some kinases or down-regulation of some phosphatase. As a matter of fact, different kinases are interacting, regulating, and even competing with each other for acting or interfering on same sites [91, 92], it is conceivable that the dynamics of transferring/removing phosphate groups on tau protein could be complex. Besides, kinases have multiple substrates, and some of them have important roles in normal cell functions [91]. The activities change of a kinase could lead to a domino effect toward the change of cellular activities. Last but not least, not all phosphorylations are toxic as some of them are required for normal tau functions, and certain sites phosphorylation may even serve as a protective effect in tauopathies [4, 5]. Therefore, a systemic dissection of disease-prone tau phosphorylations and their regulation is a pre-requisite before aiming such complex regulation for a therapeutic exploration.

To study the phosphorylations, many antibodies recognizing specific phosphorylated residues on tau have been generated, and a list can be found on Alzforum.org [93]. For analyzing the effect of phosphorylation, recombinant MAPT constructs bearing site-specific mutations to mimic potential phosphorylation status of tau are regularly utilized in tauopathy research, which provides some insights regarding the genotoxic and structural impacts upon modifications [94]. However, even with the recombinant tau with or without pseudo-phosphorylations, it is hard to generate significant polymerization in vitro postulated due to a lack of "nucleation" process, although pseudo-phosphorylated tau may be prone to aggregate [95].

3.2.1.1. GSK3β

It is well acknowledged that glycogen synthase kinase 3 beta (GSK3β) plays a pivotal role in tau hyperphosphorylation [96, 97]. An early study showed that recombinant tau and microtubule-associated GSK3β that were harvested from bacterial lysates could be co-eluted in immunochromatography with anti-GSK3β and co-immunoprecipitated [98]. A subsequent study found active GSK3β co-localized with tau inclusions in tauopathy brain tissues, and the amount of active GSK3β was significantly increased in the patients [99]. Moreover, in vitro

study found active GSK3β could efficiently facilitate tau tangles formation after tau are initially polymerized in the presence of arachidonic acid [100]. It should be noticed that effects of GSK3β in tau-mediated toxicity are unsettled; a report found that overexpression of GSK3β in tauopathy models may not necessarily lead to shortened lifespan or accelerate pathological burden in the animal model [101]. In contrast, results from some studies hinted that activation of GSK3β is critical for exacerbating tauopathy [102, 103]. These observations should be interpreted carefully as the tau models used or compared are not in the same background.

GSK3β is a constitutively active protein that can autophosphorylate its tyrosine residues like Tyr 216 to increase the enzyme stability [104]. The activity of GSK3β is mainly regulated by insulin and Wnt signaling pathways [105]. When insulin pathway is activated, protein kinase B/Akt will be activated, which in turns phosphorylate serine 9 on GSK3β and causes its inactivation. In the case of activated Wnt signaling pathway, the inhibition of GSK3β activity would alleviate the degradation of β-catenin, whose nuclear translocation is responsible for the downstream genes activation of the pathway, but the precise mechanism regarding tauopathy modulation is still unknown [106, 107]. Nevertheless, a report showed both pathways are being downregulated in AD [96].

It was postulated that the phosphorylation by GSK3β requires the priming of adjacent proline residue as GSK3β is a member of proline-directed kinase family [84]. So far, more than 40 sites in tau, either serine or threonine, have been reported could be phosphorylated by GSK3β, and some of them are exclusively found in pathological conditions [84]. Among these sites, in vitro study first identified tau could be phosphorylated by GSK3β at the sites S202, S396, and S404 [108]. Since then, different studies reported many different phosphorylation sites with the availability of the corresponded phospho- site-specific antibodies. Some in vitro/in vivo studies later confirmed that frequent phosphorylation sites include S262, S396, and S404 [101, 109]. The phosphorylation of some residues may play important roles in affecting the binding affinity between tau and tubulins or regulating synaptic plasticity [4, 110, 111]. However, it is still unknown which residues are most frequently phosphorylated by GSK3β under different pathological states in contrast to normal condition, and if there is any protective effect by GSK3β phosphorylation against tau from forming the aggregates. Probing these questions is a major challenge but will help our understanding of the role of GSK3β in tau-associated disease conditions.

3.2.1.2. Other kinases

Besides GSK3β, other kinases such as p38, cyclin-dependent kinase 5 (CDK5), c-Jun N-terminal kinase (JNK), extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A), casein kinase (CK), protein kinase A (PKA), and Ca2+ /calmodulin-dependent protein kinase II (CAMKII) have been reported to involve in directing tau phosphorylation [4, 84, 112–114]. Although the possible phosphorylation sites mediated by these kinases, especially in tauopathy conditions, may be less than GSK3β, it is fair to say that their roles in modulating tau toxicity are less well studied, thus whether the modulations by these kinases are less critical than GSK3β in tauopathy remain to be addressed. Indeed, a recent study found P38γ overexpression could ameliorate excitotoxicity

induced by amyloid-beta in a tau-dependent manner. Further experiments showed that the effect was mediated by the phosphorylation of tau S205 through the action of P38γ, and the phosphorylation of this residue could abolish the interaction between tau and Fyn and PSD95, which otherwise could form a complex interacting with NMDA receptor to induce excitotoxicity [4]. This result strongly suggests different kinases may have different roles in tauopathy, and not every up-regulated tau phosphorylations under pathological conditions are for enhancing the toxicity. Given such complex modifications, more studies shall emphasize the difference of activity among these kinases under physiological and pathological conditions, as another recent study showed that ERK1/2 does not phosphorylate tau under physiological condition [115]. Furthermore, since the pathology development in tauopathy usually takes years, whether there is any sequential activation of the kinases appears to be another intriguing issue. Indeed, a recent study examining tau-staining in the postmortem AD brains of different stages showed that N-terminal side of tau is preferentially phosphorylated at early stages [116].

3.2.2. Truncation

Proteases including calpain and caspases are involved in tauopathy pathogenesis [117, 118]. They are activated in tauopathies, either directly cleave tau or indirectly cleaving its associated kinases, affecting the structure/function of tau [118–121]. While less commonly reported, other proteases are suspected to play roles in tauopathy-related protein truncations [122].

Two truncated tau proteins have caught attention in tauopathy, as they are abundant in the postmortem AD brains [123]. In fact, truncated tau could also found in other tauopathies beyond AD. Importantly, researchers used live multiphoton imaging combined with thioflavin S administration and a dye for activated caspases and observed that the tangle formation was preceded by caspases activation in a classic P301L tauopathy mice (tg4510) [124], indicating a close tight between tau cleavage and toxicity. Currently, two truncation sites, E391 and D421, have been characterized and both are on the C-terminus. We also learned that the truncation on D421 is mediated by caspases, mainly by Caspase-3. D421-truncated tau is associated with lysosome in AD brain, indicating that the truncated tau may be favored to be degraded through autophagy or maybe impairing the autophagy system [124]. However, it is still unclear what kind of proteases are responsible for the cleavage at E391, albeit the site was the first-identified cleavage site in tau, and its C-terminal cleavage product appears in PHF core [118, 123, 125–128]. While various reports have suggested that caspase and calpain are capable of cleaving tau and both present as an early event in pathogenesis and could aggravate tau toxicity [124, 129, 130], an important issue should be solved in studying tau truncation that is whether the aberrant increase of tau truncation is a consequence of tau aggregation or actually the cause that induces tau aggregate formation [124].

3.2.2.1. Calpains

Calpains are cytosolic calcium-dependent cysteine proteases. In an analysis of a postmortem brain lysates, calpain 1 was found to activate at early stages of AD, close to the stage when GSK-3β and CDK5 were activated [130]. The human genome has two identified calpain family members, calpain 1 and calpain 2. Calpain 1 is mainly expressed by neurons and thus received

most attention by researchers concerning neurodegeneration, and calpain 2, on the other hand, is mostly expressed by glial cells. Studies have shown that calpain 1 can cleave p35 to generate p25, which could further induce prolonged activation of CDK5 [120]. Calpain can also cleave GSK3β to generate a C-terminal truncated form, which makes its inhibitory site less likely to be phosphorylated and thus produces a dominant-active GSK3β [121, 131]. Also, calpain can directly process tau and generate small fragments. However, the physiological or pathological impacts of those cleaved calpain products in regarding tauopathy are unclear, and the calpain-mediated tau cleavage site(s) remains elusive [120, 127, 132].

3.2.2.2. Caspases

Among the caspases, executive caspases, especially caspase-3, play a critical role in the direct processing of tau at the site D421. As mentioned above, D421-truncated tau can be found in AD brains, and this cleaved form is suspected to facilitate tau aggregate formation and thus enhancing the toxicity [124, 129, 133, 134]. Phosphorylation at S422 could prevent the truncation, which could be mediated by JNK and TTBK-1 [114, 135, 136]. Nevertheless, JNK and TTBK-1 could also phosphorylate tau at the sites other than S422, which complexes the protective scenario [114, 136]. Caspase 3 can also regulate the phosphorylation of tau through cleaving and activates protein kinase B and thereby activates GSK3β [119].

Besides caspase-3, other caspases may involve in tauopathy as well. A recent study showed that caspase-2 could cleave tau at the site D314. This truncated tau could not participate in tau aggregation but is existing in the brains of P301L mice by a significant amount. Pseudophoshorylation of this site prevented caspase-2 cleavage and consequently caused memory and cognitive defects of the mice [137].

3.2.3. Acetylation

Tau lysine residues could be acetylated by certain endogenous acetyltransferase, and such modulations were first demonstrated by p300 and Creb-binding protein (CBP) [138, 139]. Importantly, the insoluble tau protein fraction isolated from postmortem brains of the AD patients could be recognized by an anti-acetylated tau antibody [138]. Since then, tau acetylation studies start to emerge, and up to date, four tau acetylation sites, K174, K274, K280, and K281, have been confirmed in pathological conditions [140]. Acetylation of K280 and K281 reduced tau binding affinity to microtubules in vivo and facilitated tau aggregation in vitro [140, 141]. Moreover, acetylation of K280 exacerbated tau toxicity in a *Drosophila* model, and acetylation of K174 worsened neurodegeneration and behavior defects in PS19 mice [142, 143]. An overall tau acetylation effect is likely to aggravate tau toxicity. A study showed the administration of salsalate, a drug that could inhibit p300, ameliorated the tau pathology and memory defects in PS19 mice [143]. Interestingly, a recent study reported acetylation of K321 could impede S324 phosphorylation, a frequent modification in postmortem AD brains. This observation leads to an intriguing prospect that some switches from acetylation to phosphorylation might affect disease progression [144]. Altogether, these studies bring up questions including to what extent tau acetylation could affect tau toxicity and whether there are interactions between tau acetylation and other posttranslational modifications.

3.2.4. Other posttranslational modifications

So far, our understanding of other tau modifications is still limited [82]. Take glycosylation as an example, glycosylation of tau was only found under pathological conditions but not physiological conditions [145], indicating that this type of posttranslational modification has a significant impact toward cell function. However, probed glycosylation sites of tau are limited, and some of the proposed sites might overlap with the known phosphorylation sites, suggesting a potential competition between glycosyltransferase and phosphorylation kinases [145]. The role of glycosylation in tauopathy is unknown [82]. A recent study using *Drosophila* showed that different gene locus of glycosyltransferases might have a different impact on tauopathy [146].

4. Tauopathy treatment

To date, no drug targeting tauopathies has entered the market [147]. Over the past two decades, a dozen representative drugs have been pursued in the clinical trials [148], and these drugs represented the major therapeutic approaches in tauopathy treatment, including tau aggregation inhibitors, tau phosphorylation-related kinase inhibitors, microtubule stabilizers, and immunotherapy against tau. However, since these strategies have yet to show significant benefit, new approaches are being probed, among which a scheme to enhancing protein homeostasis is an intriguing approach [147, 149]. Other alternative approaches including using traditional Chinese medicine are also being pursued [150].

4.1. Treatment approaches target features of tauopathy

Five treatment approaches mentioned above have been scrutinized in clinical trials, and only microtubule stabilization and immunotherapy against tau are still active tau aggregation inhibitors, and phosphorylation kinase inhibitors, including GSK3β inhibitors and CDK5 inhibitors, were once favored, but they showed little efficacy in clinical trials [151].

4.1.1. Tau aggregation inhibitors

The direct inhibition of tau aggregation was the major therapeutic strategy being developed and had entered the clinical trials [151]. The development of tau aggregation inhibitor was initiated in the mid-1990s. The first platform to screen the drugs was reported in 1996 with the discovery of phenothiazine, a relatively potent tau aggregation inhibitor in vitro [152]. In this platform, recombinant PHF core tau fragment was incubated in wells, by reciprocal treating the wells with recombinant full-length tau, the protease-resistant tau aggregation could form [152]. By incubating the wells with compounds, the goal was to identify inhibitors that could effectively disrupt tau aggregation through the high-throughput assay, and phenothiazine showed a strong potency [152]. Unfortunately, phenothiazine was found no efficacy in clinical trials, and it was blamed for its poor absorption and was difficult to be transported into the brain [153]. Years later, a renewed platform was designed [153]. In this platform, fibroblasts

overexpressing a cocktail of different tau isoforms were incubated in wells. This setting could yield tau aggregations inside the cells, and compounds were tested to compare the labeled tau immunofluorescence as the readout [153]. Although this platform was a lower throughput, it overcame the shortages of the first platform in which cytotoxicity was unknown [153, 154]. With this platform, TRx0237 was later selected to be the lead candidate and went into clinical trials [151]. Unfortunately, the drug did not work in phase 3 as it failed to slow cognitive decline in AD patients [155].

Biochemically, the inhibitors could be categorized into two types, covalently and no-covalently tau aggregation inhibitors [156]. However, although they are called "tau" inhibitors, these chemicals are most likely inhibitors to other protein aggregations, and their selectivity is highly questionable [151]. Therefore, a highly selective with high-affinity tau inhibitor is still waiting to be discovered [151, 156].

4.1.2. Tau immunotherapy

The aim of immunotherapy is to clear pathological tau through the immune system [157]. It could be achieved either by applying antibodies that could recognize pathological tau or by vaccination to elicit activation of antigen presenting cells and subsequently the B cells and T cells to clear up pathological tau [157, 158]. Ten years have passed since the publication of the first study on tau immunotherapy [159]. In the study, the researchers showed that inoculation of a tau peptide aa R379-L408, which covers two critical phosphorylation sites S396 and S404 that being phosphorylated in P301L tau mice, could successfully elicit endogenous immune system to generate antibodies against tau, and the animal showed ameliorated symptoms of tauopathy-related behavior and decreased tau aggregation [160]. Multiple different antibodies or vaccines aiming at different tau epitopes have been developed since then, and some have entered the early phases of clinical trials [157].

4.2. Novel treatment approaches

Molecular chaperones play important roles in protein homeostasis. It was reported that inhibiting heat shock protein 90 (Hsp90) could inhibit tau toxicity in tauopathy model [160]. The mechanism behind could involve Hsp90 stabilize p35, the activator of CDK5, GSK3β, and tau, inhibiting their degradation [160, 161]. On the other hand, Hsp70 could facilitate protein ubiquitination and degradation by the proteasome [162]. Overexpression of Hsp70 in cells could decrease tau aggregation in vitro [163]. Recently, it is also suggested that targeting co-chaperones of Hsp90 could offer another approach to ameliorate tauopathy [164].

Several traditional Chinese medicines have been suggested that might be useful for treating tauopathies [150, 165]. Huannao Yicong Decotion was shown to improve learning and memory in rat AD model. Immunolabeling showed the expression levels of GSK3β, CDK5, and TTBK1 in CA1 region of the hippocampus are downregulated in the drug treatment groups [150]. Interestingly, it was also suggested that some traditional Chinese medicines, including Huperzine A and Tianma, could induce upregulation of ubiquitin ligases, indicating that they might facilitate protein degradation through ubiquitin-proteasome pathway [166].

5. Conclusion

In this chapter, we discussed major basic aspects of tauopathy, from tau normal functions to pathology formation process and from tau genetic mutations to posttranslational modifications. Finally, we discussed currently proposed tauopathy treatment methods. With the findings showing tau proteins are involved in many brain pathology conditions beyond tauopathy and more evidences showing the roles of tau in Alzheimer's disease are critical, it is expected to receive more basic research attentions in the future [167, 168]. Better animal models tailored for different tauopathy are of pursuit, which will benefit both basic research and clinical drug developments.

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