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Review

The potential role of glial cells in driving the prion-like transcellular propagation of tau in tauopathies

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ABSTRACT

Dementia is one of the leading causes of death worldwide, with tauopathies, a class of diseases defined by pathology associated with the microtubule-enriched protein, tau, as the major contributor. Although tauopathies, such as Alzheimer's disease and Frontotemporal dementia, are common amongst the ageing population, current effective treatment options are scarce, primarily due to the incomplete understanding of disease pathogenesis. The mechanisms via which aggregated forms of tau are able to propagate from one anatomical area to another to cause disease spread and progression is yet unknown. The prion-like hypothesis of tau propagation proposes that tau can propagate along neighbouring anatomical areas in a similar manner to prion proteins in prion diseases, such as Creutzfeldt-Jacob disease. This hypothesis has been supported by a plethora of studies that note the ability of tau to be actively secreted by neurons, propagated and internalised by neighbouring neuronal cells, causing disease spread. Surfacing research suggests a role of reactive astrocytes and microglia in early pre-clinical stages of tauopathy through their inflammatory actions. Furthermore, both glial types are able to internalise and secrete tau from the extracellular space, suggesting a potential role in tau propagation; although understanding the physiological mechanisms by which this can occur remains poorly understood. This review will discuss the current literature around the prion-like propagation of tau, with particular emphasis on glial-mediated neuroinflammation and the contribution it may play in this propagation process.

As life expectancy increases, age-associated neurodegenerative disorders and related health complications, such as dementia, are becoming more prevalent. Dementia affects approximately 50 million individuals worldwide and it is expected that disease prevalence will continue to increase, with more than 131 million people living with dementia by the year 2050 (Ponjoan et al., 2019). In the context of health burden, dementia is responsible for 28.8 million disability-adjusted life years, and, is associated with a high rate of morbidity and mortality, being the fifth leading cause of death worldwide (Nichols et al., 2019). A major class of neurodegenerative disorders that are responsible for dementia-like symptoms are tauopathies. Tauopathies are characterised by the pathological aggregation and deposition of the microtubule associated protein, tau (Kovacs, 2015). Of this family, Alzheimer's disease (AD) is the leading cause of dementia in the ageing population; thus, a plethora of previous studies, more so than any other tauopathy, have primarily focused on better understanding the alterations in tau that occur in the course of AD, for the purpose of therapeutic targeting. Given this, much of this review paper will address tauopathy in relation to AD, with comparisons drawn to other tauopathies when applicable. Currently, effective treatment options for tauopathies are scarce, as there is still a prominent gap in understanding tau dynamics in the context of disease spread and progression (Khanna et al., 2016). While the link between the anatomical and disease progression in AD has been well established by the Braak staging method, proposed by Heiko Braak and colleagues (Braak and Braak, 1997), the mechanisms behind the propagation of tau remain poorly understood. In recent years, research has surfaced to suggest a role of supporting glial cells and associated neuroinflammation in tau pathology (Morales et al., 2013; Ghetti et al., 2015) with additional roles of these cells in tau propagation hinted at (Martini-Stoica et al., 2018; Hopp et al., 2018), but, remain poorly understood. This review will address tau dynamics in both rodent and human studies, with particular focus on extracellular tau and the key role that glial cells and associated neuroinflammation may play in driving its pathological, prion-like spread.

1. The microtubule-associated protein, tau

Tau is a microtubule-associated protein found predominantly within

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neuronal axons (Kempf et al., 1996), as well as in glial cells, including astrocytes (Papasozomenos and Binder, 1987) and oligodendrocytes (LoPresti et al., 1995). Under normal physiological conditions, tau controls cytoskeletal organisation and intracellular trafficking (Aamodt and Williams, 1984). Encoded by the *microtubule-associated protein tau* (*MAPT*) gene, found on chromosome position 17q21.3, tau has six isoforms based on alternative splicing of exon 2, 3 and 10[14] (Fig. 1A). Exons 2 and 3 are translated to the amino N-terminal projection domain, where alternative splicing produces four isoforms (0–3N) with different amino inserts playing an important role in microtubule-plasma membrane interactions (Park et al., 2016; Brandt et al., 1995). In the healthy adult brain, splicing of exon 10 produces an equal ratio between three microtubule-binding repeats (3R) and four microtubule-binding repeats (4R), which are located on the carboxyl terminal (C-terminal) and regulate polymerisation (Braak and Braak, 1991a; Lee et al., 1988) (Fig. 1). The affinity of tau for microtubules is modulated by an equilibrium between phosphorylation and dephosphorylation at 85 potential serine, threonine and tyrosine phosphorylation sites, allowing dynamic regulation by kinases and phosphatases (Brandt et al., 2005; Li and Gotz, 2017; Wagner et al., 1996). Under normal physiological conditions, the reduction of microtubule binding affinity by phosphorylation of tau promotes axonal transport mediated by kinesin and dyenein motor proteins; conversely, dephosphorylation of tau by phosphatases increases binding affinity to the microtubule, reducing cargo transport by creating an obstacle for translocation along the axon (Fig. 2) (Dixit et al., 2008; Chaudhary et al., 2018; Noble et al., 2013). Under pathological conditions, aggregation of tau in the cytosolic space, as a result of inherited mutations and post-translational modifications that result in the hyperphosphorylation of the protein, is a hallmark of tauopathies (Ghetti et al., 2015; Guillozet-Bongaarts et al., 2007).

2. Tauopathies and neurodegeneration

Tauopathies can be classified as either primary or secondary (Supplementary, S1), depending on whether tau is the primary hallmark causing the pathology or whether it is secondary to other pathological proteins, such as amyloid-beta (Aβ) in AD (Kovacs, 2015). Examples of primary tauopathies include progressive supranuclear palsy (PSP),

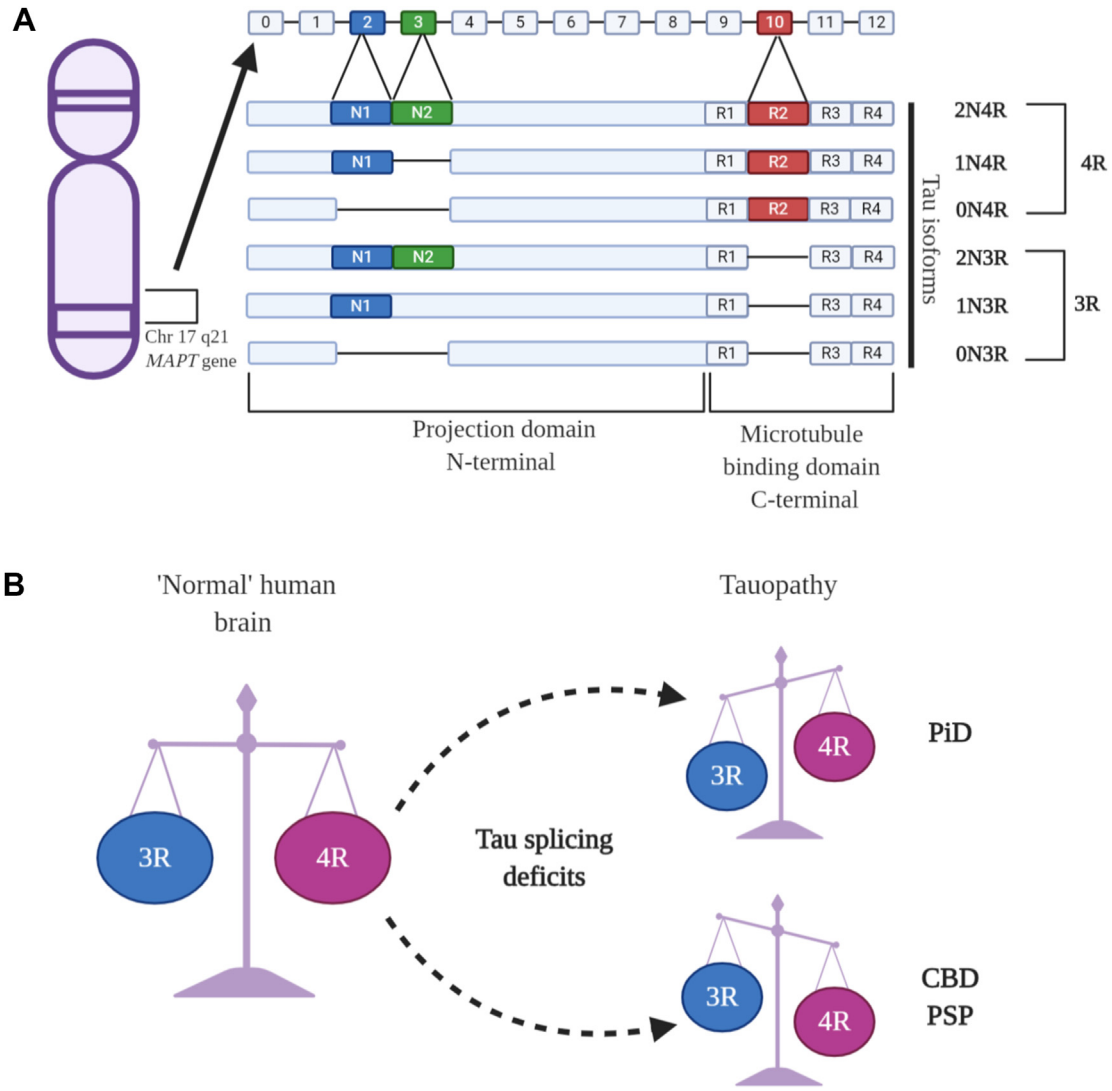

Fig. 1. Alternative splicing of the *microtubule-associated protein tau (MAPT)* gene implicated in tauopathy. **(A)** *MAPT* gene is located on chromosome 17, position q21 and exons 2, 3 and 10 are alternatively spliced producing six tau isoforms. Exon 2 (blue) and 3 (green) encode for amino acid inserts in the N-terminal projection domain; whilst, exon 10 encodes for amino acids at the R2 repeat (red) at the C-terminal microtubule binding domain. **(B)** Equal ratio between 3 and 4R carboxyl repeats in the healthy adult brain which is skewed in primary tauopathies to producing more of either 3R repeat, as observed in Pick's Disease (PiD), or 4R repeat, as observed in Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

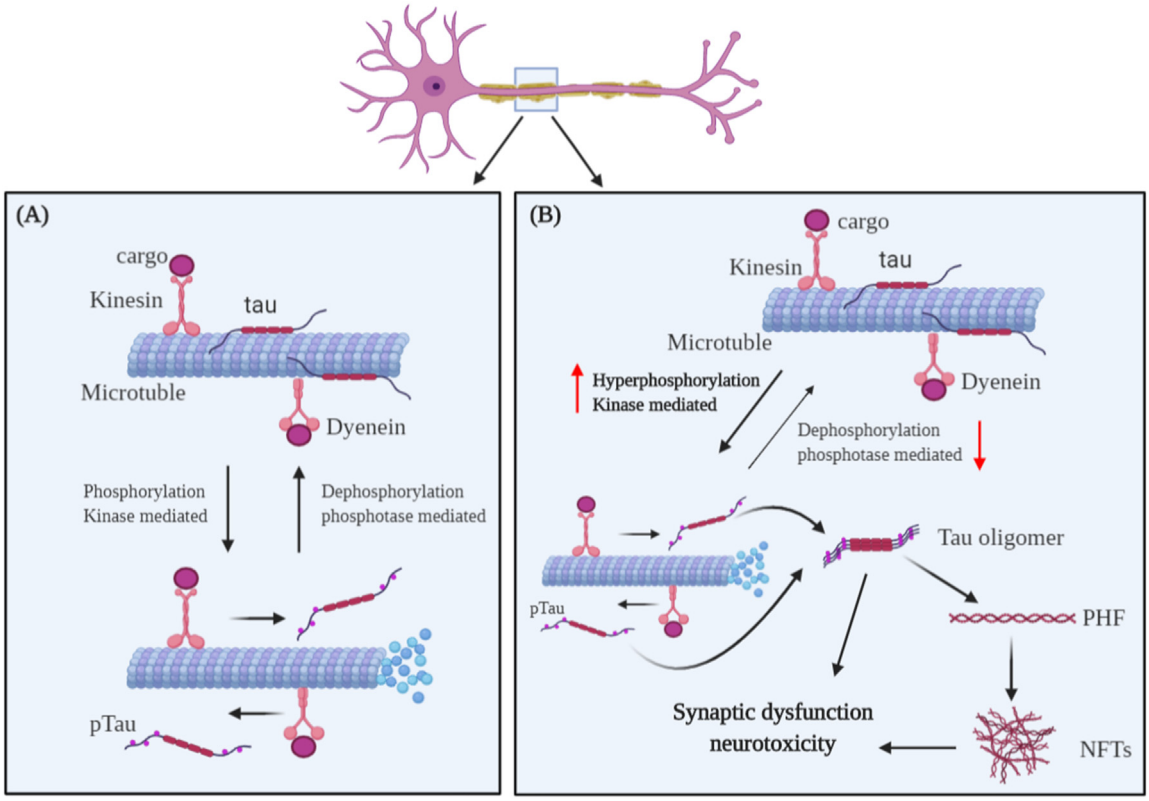

Fig. 2. Intracellular tau-mediated neurotoxicity in tauopathy. **(A)** Normal physiological function of tau. Tau proteins stabilise the microtubule via the C-terminal binding domain, which regulates microtubule dynamics. Tau proteins can prevent or reduce axonal transport (cargo) by acting as obstacles, halting anterograde cargo transport via kinesin or retrograde transport via dyenein. Tau binding is regulated by a phosphorylation/dephosphorylation equilibrium mediated by kinases and phosphatases, respectively. Tau unbinding via kinase regulated phosphorylation (pTau) allows for changes in microtubule dynamics, aiding in anterograde and retrograde axonal transport mediated by kinesin and dyenein motor proteins. **(B)** Tau-mediated neurotoxicity. In tauopathies, a disequilibrium favouring the hyperphosphorylation of tau, mediated by the hyperactivity of kinases and disregulation of phosphatases, leads to excessive accumulation of tau in the cytosolic space. Free tau is able to self-aggregate into tau oligomers via protein-to-protein binding domain interactions, causing synaptic dysfunction and neurotoxicity during early tauopathy. Additionally, tau oligomers can form paired helical filaments (PHFs) that can subsequently form neurofibrillary tangles (NFTs), which lead to synaptic dysfunction, neurotoxicity and cell death, predominantly during later stages of tauopathy.

corticobasal degeneration (CBD), Pick's disease (PiD), and frontotemporal dementia with parkinsonism in chromosome 17 (FTDP-17)[26]. While the majority of primary tauopathies do not arise from genetic mutation to the *MAPT* gene, FTDP-17 has been linked to specific inherited mutations in the *MAPT* gene located on chromosome 17[7, 27]. Primary tauopathies can have different ratios between the two types of microtubule-binding repeats (3R and 4R) on the C-terminal of tau, favouring either one or the other, which has been hypothesised to favour tau aggregation in some tauopathies. For example, PiD is predominantly a 3R tauopathy, whilst CBD and PSP are both 4R tauopathies (Fig. 1B); alternatively, FTD-17 is both 3R and 4R, similar to AD, a secondary tauopathy (Ghetti et al., 2015; Dickson, 2001; Williams and Lees, 2009; Kouri et al., 2011; Masters et al., 2015; Adams et al., 2010). For a more extensive insight on *MAPT* alternative exon splicing and the implications of this in tauopathy, refer to the review by Liu and Gong (2008) (Liu and Gong, 2008). In AD, conversely, tauopathy occurs as a secondary consequence of amyloid plaques, which are composed of aggregated Aβ peptides in the extracellular space that bind to neuronal dendrites and cause downstream effects on tau phosphorylation (Povova et al., 2012; Jack et al., 2013; Pierrot et al., 2006).

3. Intracellular tau in tauopathy

In tauopathies, tau dissociates from microtubules and aggregates in the cytoplasm forming insoluble paired helical filaments (PHFs) and neurofibrillary tangles (NFTs). NFTs are a key pathological marker in tauopathies, where the number of aggregated tangles correlate with neuronal toxicity and overall disease status (Lee et al., 2001). In support of this, in AD, the number of NFTs in the neocortex has been shown to be more predictive of cognitive performance and overall dementia status than the number of Aβ plaques (Giannakopoulos et al., 2003; Serrano--Pozo et al., 2011). PHFs and NFTs form due to conformational changes to tau, such as C-terminal truncation and hyperphosphorylation by elevated kinase activity (Fig. 2)[25, 40]. Truncation of the C-terminal domain is a post-translational modification mechanism that is associated with PHF formation in the early stages (Flores-Rodriguez et al., 2015), and extracellular NFT deposition during the later stages, of tauopathy (Irwin et al., 2012). C-terminal truncation and hyperphosphorylation leads to an increase in unbound free tau in the cytoplasm by decreasing its binding affinity for the microtubule and, subsequently, promotes tau-to-tau interaction and aggregation into PHFs and later into NFTs (Flores-Rodriguez et al., 2015).

In tauopathies, this association is exacerbated due to the hyperphosphorylation of tau driven by an increase in kinase activity and the dysregulation of phosphatase activity (Fig. 2B) (Alavi Naini and Soussi-Yanicostas, 2015; Vogelsberg-Ragaglia et al., 2001a; Park et al., 2018). The ratio of phosphorylation per mole of tau driven by elevated kinase regulation and activity can be four times higher in tauopathy when compared to physiological conditions (Li and Gotz, 2017; Köpke et al., 1993). In AD, for example, an upregulation of GSK3β and Cdk5 kinase activity occurs as a downstream effect of Aβ oligomers binding to the dendritic spines of the neuron and increasing intracellular calcium levels, which has a direct up-regulatory effect on kinase activity (Pierrot et al., 2006). Furthermore, this increase in kinase activity has been shown

to impair a barrier for tau diffusion within the axonal initiation segment, which normally plays an important role in retrograde tau transport from the soma to the axon. This, consequently, leads to tau retention and mis-localisation within the soma and dendrites (Zempel et al., 2017). The mis-localisation of tau from the axon into the somatodendritic regions has been shown to impair synaptic function, leading to neuronal damage (Hoover et al., 2010). Interestingly, in the primary tauopathy PiD, the hyperphosphorylation of tau drives the mis-sorting of tau into the somatoaxonal region, causing neuronal damage, rather than the somatodendritic mis-localisation observed in AD, as well as FTD-17, another tauopathy; however, whether this is via a direct effect on the axonal initiation segment remains unknown (Hoover et al., 2010; Probst et al., 1996; Bodea et al., 2016). In addition to an increase in kinase activity, phosphatase dysregulation can also result in a disequilibrium favouring the hyperphosphorylation of tau and subsequent tau pathology. A decrease in protein phosphatase 2A (PP2A) gene and protein expression which, under normal physiological condition, mediates approximately 70% of tau dephosphorylation has been observed in *post mortem* AD samples (Vogelsberg-Ragaglia et al., 2001b; Sontag et al., 2004; Liu et al., 2005). In primary tauopathy FTD-17, *MAPT* gene mutations at multiple exon regions were shown to reduce the binding affinity of tau to PP2A suggesting a contribution to hyperphosphorylation and tau pathology (Goedert et al., 2000).

Taken together, hyperphosphorylation, which is a driving post-translational mechanism common amongst all tauopathies, increases the levels of cytoplasmic tau phosphorylated at serine/threonine and tyrosine positions and, hence, can drive C-terminal interaction, self-aggregation and formation of PHFs and NFTs (Alavi Naini and Soussi-Yanicostas, 2015; Bodea et al., 2016; Buée Scherrer et al., 1996; Vega et al., 2005; Stöhr et al., 2017). In support of hyperphosphorylation driving self-aggregation of tau, in a FTD-17 transgenic mouse model with mutant human tau P301L, GSK3β induced phosphorylation was inhibited with lithium and subsequently decreased tau aggregation (Noble et al., 2005). Conversely, in another study, phosphorylation via GSK3β of tau at the C-terminal, which is suggested to be involved in protein-to-protein interaction (Stöhr et al., 2017), was shown to promote self-aggregation *in vitro* (Liu et al., 2007).

Although NFT formation has shown to be a good predictor of overall dementia status in tauopathies (Braak and Braak, 1991a), more recent data based on two-photon imaging in P301L transgenic mice showed the presence of NFTs even in healthy functioning neurons (Kuchibhotla et al., 2014). These findings suggest that the number of tangles may not have a direct correlation with neurotoxicity during early tauopathy as previously explained (Kuchibhotla et al., 2014; Braak and Braak, 1995). Similarly, in P301L transgenic mice, the aggregation of tau into NFTs had no association with synaptic dysfunction, cognitive decline or neuronal death during the early stages of tauopathy, suggesting a poor correlation between NFT numbers and early disease events (Berger et al., 2007; Spires et al., 2006). Instead, the presence of tau oligomers, which are small insoluble aggregates of tau that later form NFTs (Fig. 2B), were shown to be more toxic to neurons than NFTs (Takashima, 2013). In support of this, tau oligomers exert neurotoxic effects on neurons both *in vitro* and *in vivo,* even in the absence of NFT pathology (Lasagna-Reeves et al., 2012; Shafiei et al., 2017). Brain-derived tau oligomers isolated from human AD samples *in vitro,* as well as 3 month old C57BL/6 mice *in vivo* were shown to exert neurotoxic effects in the hippocampal CA1 and CA3 regions, impairing long term potentiation (Lasagna-Reeves et al., 2012). These results suggest that tau oligomers, which are found both intracellularly and extracellularly, could be better pathological markers of early tauopathy than NFTs.

4. Extracellular tau, a new focus

The observation that tau oligomers can be found extracellularly conflicts with the traditional understanding that tau is localised intracellularly as a cytosolic protein within neurons and supporting glial structures (Kempf et al., 1996; Papasozomenos and Binder, 1987; LoPresti et al., 1995). The presence of extracellular tau was originally speculated to be a consequence of neuronal death (Gomez-Ramos et al., 2006); however, as first observed in the anterior bulbar neurons of a lamprey overexpressing human tau, the protein is able to be secreted from neurons by multiple secretary mechanisms and is found in the extracellular space, irrespective of neuronal apoptosis (Kim et al., 2010). In support of this, in culture studies, secreted tau was phosphorylated and truncated at the C-terminal, which differs from the non-truncated full--length tau and tau fragments found in the media after neuronal apoptosis, suggesting tau secretion occurs independent of cell death (Plouffe et al., 2012; Kanmert et al., 2015). Under culturing conditions, both the SH-SY5Y neuroblastoma cell line and mouse cortical cultures have been shown to secrete endogenous total tau, as well as hyperphosphorylated tau, into the extracellular space in response to increases in intracellular calcium levels (Karch et al., 2012). The role of extracellular tau under normal physiological conditions remains a mystery, but may be a by-product released as a result of tau turnover, as the protein has a predicted half-life between 10 and 30 days (Sato et al., 2018). Notably, tau has been identified in the interstitial (ISF) and the cerebrospinal fluid (CSF) in both animal and human models. An *in vivo* model on P301S human transgenic mice utilising microdialysis showed tau to be released by neurons and found in the ISF (Yamada et al., 2011). Tau in the ISF was present prior to neurodegeneration and decreased with the progression of neurodegeneration, possibly due to an uptake of tau by glial cells for degradation or for clearance (Yamada et al., 2011). Under pathological conditions, such as acute stroke (Hesse et al., 2001), prion disease (Otto et al., 1997) and AD (Riemenschneider et al., 2003; Hampel and Teipel, 2004), tau, in particular phosphorylated tau, has also been shown to be elevated in the CSF. In AD, for example, both total and phosphorylated tau levels are increased in human CSF samples (Vanmechelen et al., 2000; Hampel et al., 2005, 2010; Barten et al., 2011). In particular, levels of tau phosphorylated at threonine position 181 in the CSF has been used as a biological marker to assess AD progression. Recently, another phosphorylated tau isoform, pT217, has been identified in the CSF and has shown to be a better and more specific biomarker for both preclinical and late stage AD (Barthélemy et al., 2020). pT217 has also been detected in the blood plasma and shows promising and exciting results to be used as a new biomarker to test for preclinical stage AD (Palmqvist et al., 2020). When considering other tauopathies, such as FTD-17, there are discrepancies in the literature, with some studies reporting an elevation in CSF tau (Green et al., 1999), whilst others show no elevation in levels of tau in the CSF, but rather a possible increase in ISF tau (Grossman et al., 2005), potentially due to the nature of FTD being remote from ventricular CSF spaces in early stages of degeneration (Riemenschneider et al., 2002). Although this discrepancy suggests variability in CSF levels of tau, it is evident that tau can be secreted by neurons and found within the extracellular space, in either the ISF or CSF, under both normal physiological conditions and in disease states.

4.1. Regulation of tau secretion

It has been proposed that tau secretion is regulated by increased neuronal activity and a defect in the autophagy-lysosomal pathway. In line with this, an increase in neuronal activity as a result of calcium-mediated AMPA receptor activation has been shown to induce tau release *in vivo* (Pooler et al., 2013). In the context of tauopathies, where neuronal hyperexcitability can be observed, tau release is elevated (Pooler et al., 2013; Bakker et al., 2012; Wu et al., 2016; Yamada et al., 2014). Similarly, in the Tau P301S transgenic mouse model, which expresses mutant human MAPT, increased neuronal activity and subsequent presynaptic glutamate release have been shown to drive tau release into the ISF (Yamada et al., 2014). Independent of neuronal excitability, intracellular tau can also be released by cortical neurons by cellular insults, such as the induction of autophagy and lysosomal dysfunction (Mohamed et al., 2014). In support of this, autophagic and lysosomal

markers are found in *post mortem* samples in patients with both primary (PSP and CBD) and secondary (AD) tauopathies, indicating a potential defect in the autophagy-lysosomal pathway that could contribute to tau secretion (Piras et al., 2016). In a more recent study, the activity of lysine acetyltransferase p300 and its homolog CBP, which regulate the acetylation and accumulation of tau, were elevated in HEK293T cells and human iPSC-derived neurons causing autophagy-lysosomal dysfunction and thus increasing tau secretion (Chen et al., 2020). Taken together with the evidence described above, the presence of tau in the extracellular space suggests a potential role of the protein aggregate in the pathological spread of tauopathies.

5. Prion-like propagation of tau

Disease spread and progression of tauopathy was originally hypothesised to be a consequence of vulnerability of neighbouring anatomical regions prone to NFT formation (Morrison et al., 1998); however, this idea has since been challenged by a plethora of work supporting the notion that extracellular tau is able to spread along neighbouring anatomical regions in a similar way to the pathological prion protein (PrP), as reviewed by Jucker and Walker (2013) (Jucker and Walker, 2013). In prion diseases, such as Creutzfeldt-Jacob disease (CJD), PrPs, in contact with the non-pathogenic prions expressed in many human cell types, act as templates, leading to conformational changes and seeding subsequent missfolding of the healthy protein, transforming them into PrPs and leading to disease spread and progression (Prusiner, 1998; Pan et al., 1993; Head and Ironside, 2012). The prion-like propagation of tau was first observed *in vivo* by utilising tau extract from transgenic mice that carried one FTD tau mutation and injecting it into healthy mice, which led to the development of tau NFTs and associated pathology (Clavaguera et al., 2009). Results from this study demonstrated the ability for tau to propagate between neurons and pioneered research into the prion-like propagation of tau, with the aim of better understanding the pathophysiological mechanisms by which this can occur, for purposes of therapeutic targeting. Following this study, phosphorylated tau in culture was observed to act as a seed for further missfolding of normal functioning tau, promoting aggregation of NFTs (Alonso Adel et al., 2006). Furthermore, tau extracted from patients with tauopathies, such as AD, CBD and PSP, and injected into the brain of mice showed positive inclusions of similar structure to human tau in the mouse hippocampal and cortical areas, suggesting cell to cell extracellular tau propagation and seeding (Narasimhan et al., 2017). It is important to note that abnormal tau propagation does not necessarily require template missfolding of healthy endogenous tau. A study testing whether the lack of endogenous tau is protective against tau aggregation *in vivo* showed that, although the absence of endogenous tau blunts neurotoxicity, aggregated tau oligomers can still propagate from one cell to another (Wegmann et al., 2015). This suggests that while tau propagation may behave in a prion-like manner, unlike PrPs it does not dependent on endogenous protein recruitment and template missfolding (Jucker and Walker, 2013); although, this seems to pivotal for tau induced neurotoxicity.

5.1. Synaptic and non-synaptic propagation of tau

There is accumulating evidence supporting that the spread of tau oligomers follows a prion-like pattern from one neuron to another, suggesting a key role of trans-synaptic propagation between damaged neurons and neighbouring neuronal connections. In artificial neuronal networks utilising microfluidic devices, synaptic cell-to-cell transmission was shown to play an important role in tau propagation, highlighting the significance of synaptic contacts in facilitating tau pathology (Calafate et al., 2015). In primary and secondary neuronal cultures, synaptic tau propagation has been linked to secretion of phosphorylated tau in exosomes (Wang et al., 2017). Similarly, in tau P301S mutant transgenic mice, injection of synthetic preformed tau fibrils (PFFs) into both the striatum and the hippocampus led to a distinct ipsilateral and contralateral synaptic spreading pattern between site of injection and neurons in the hippocampal CA1 and CA3 regions, as well as the caudal enterohinal cortex, beginning 1 month post-injection (Iba et al., 2013). Moreover, models restricting human tau expression to the entorhinal cortex show that tau is able to propagate from affected entorhinal cortex neurons to neighbouring neurons in the hippocampus, dentate gyrus and other anatomical regions (Liu et al., 2012; de Calignon et al., 2012). These results support the Braak staging scheme used as the gold standard for classifying the degree of tau pathology in AD, which suggests that tau deposition begins in the entorhinal cortex before later spreading to associated cortical areas (Braak and Braak, 1991b). Although it is evident that direct synaptic connections are important for transcellular propagation of tau, non-synaptic mechanisms may also contribute to tau propagation and pathology. The use of real-time visualisation of tau pathology in AD patients using PET tracers that bind to fibrillar forms of tau suggests a wide spread development of tau aggregates, rather than a region-to-region synaptic spread, during early pathology (Lowe et al., 2018). This finding suggests an alternative pathway by which tau can propagate independent of synapse-to-synapse transmission during early pathology, one in which supporting glial cells and associated neuroinflammation may play a key role.

5.2. Mechanisms for tau secretion, common modality of transport with PrP

Tau secretion into the extracellular space can occur via multiple pathways (Fig. 3) that can be exploited in tauopathy and are also utilised in prion disease. The most studied mechanism of tau release into the extracellular space is the exosomal-dependant pathway of secretion (pathway 1; Fig. 3). Exosomes are small intraluminal vesicles formed within late endosomal multivesicular bodies (MVBs), which are defined by multiple internal vesicles budding inwards, enclosed in an outer endosomal membrane (Denzer et al., 2000). These MVBs are able to then fuse with the plasma membrane and secrete proteins captured from the cytosol, such as tau, into the extracellular space, packaged within exosome vesicles (Denzer et al., 2000). In support of this, although under-characterised in many tauopathies, in patients with AD, CSF samples have been shown to contain elevated levels of phosphorylated tau in exosomes (Saman et al., 2012). Similarly, when human tau is overexpressed in both the non-neuronal cell line COS-7 and the neuroblastoma cell line M1C, tau is secreted and co-localised with exosomes (Saman et al., 2012; Simón et al., 2012). While the exact mechanisms of this are still unknown, neuronal hyperexcitability and tau mis-localisation due to pathological increases in phosphorylation may play a key role (Yamada et al., 2014). Within both cultured primary neurons and the neuronal cell line N2A, neuronal excitability has been shown to promote the release of phosphorylated tau via exosomes (Wang et al., 2017).

Tau mis-localisation into the somatodendritic region of the neuron, as a result of axonal initiation segment impairment due to kinase hyperactivity, may also increase the likelihood of tau being secreted in exosomes from the somatodendritic region in addition to the presynaptic terminal (Zempel et al., 2017). In both the soma and dendrites of the neuron, MVBs are approximately 50 times more common than in the neuronal axon (Altick et al., 2009). This would suggest that in tauopathies, such as AD and FTD-17, where tau mis-localisation into the somatodendritic is observed (Bodea et al., 2016; Li and Götz, 2017; Zempel et al., 2010; Van der Jeugd et al., 2012), tau is more likely to be packaged within MVBs and secreted out of the cell in exosomes; whilst in PiD, where tau can mis-sort into the somato-axonal region, alternative pathways could be exploited. Interestingly, the exosomal-dependant pathway is utilised in other neurodegenerative conditions to secrete their pathological hallmark protein extracellularly. For example, both α-synuclein in Parkinson's disease and PrP in prion disease have been shown to be secreted by exosomes, suggesting a common mechanism for secretion across multiple different pathologies (Emmanouilidou et al., 2010; Fevrier et al., 2004).In addition to vesicle secretion of tau via exosomes, tau can also be

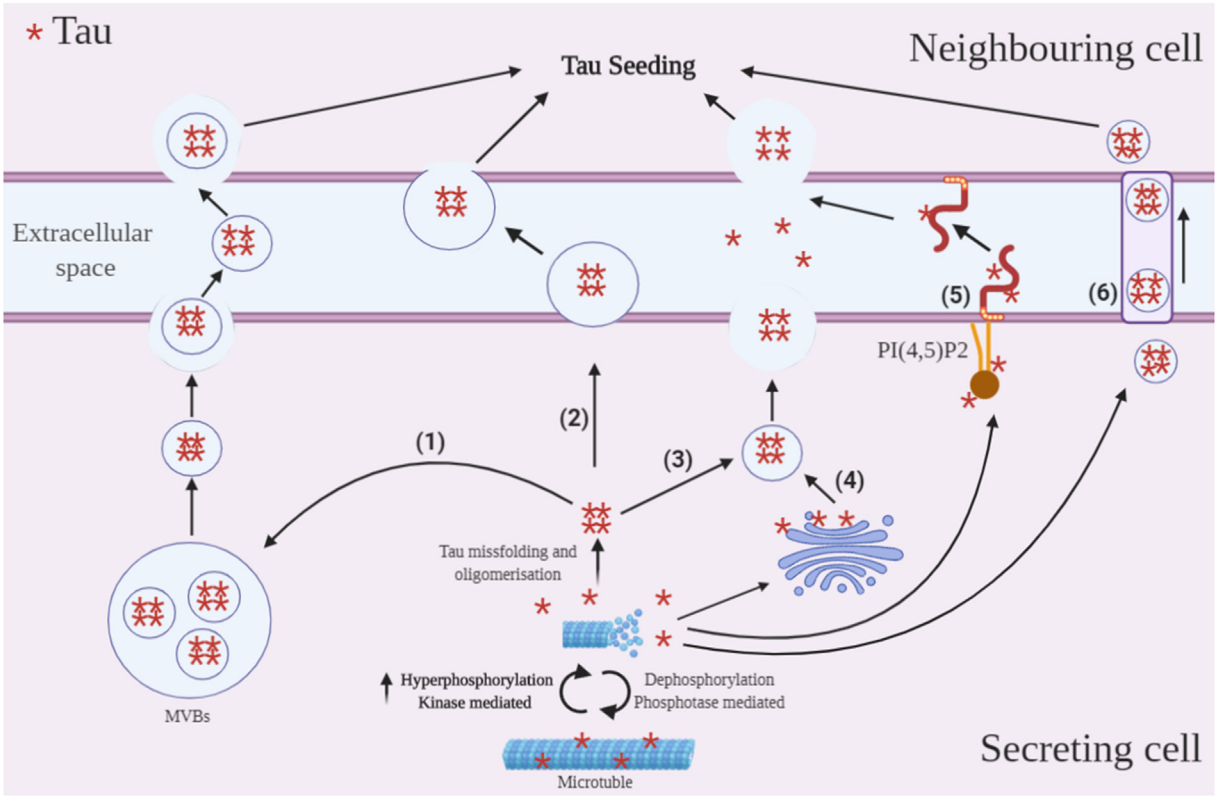

Fig. 3. Mechanism for tau secretion in tauopathy. Tau aggregation into oligomers as a result of hyperphosphorylation leads to secretion of tau into the extracellular space by multiple secretory pathways. (1) Free cytosolic tau can be packaged into exosome vesicles within MVBs for secretion through the plasma membrane. (2) Tau can be packaged and secreted into the extracellular space via larger vesicles known as ectosomes that form at the plasma membrane and can be taken up by neighbouring cells via endocytosis. (3) Free tau can be released into the extracellular space in a vesicle free form after being packaged into endo-lysosomes and released at the plasma membrane. (4) Tau localised to the Golgi apparatus can be trafficked and packaged into endo-lysosomes before release at the plasma membrane. (5) Tau can be secreted directly through the plasma membrane by binding to PI(4,5)P2 on the cytosolic side of the membrane, altering membrane integrity and being captured by HSPGs on the extracellular side before secretion. (6) A direct transfer of tau from the secreting cell to the neighbouring cell can occur via tunnelling nanotubules connecting the cytoplasm of the two cells, bypassing the extracellular space. Tau released within the extracellular space can be taken up by recipient neighbouring cells.

secreted in larger vesicles, known as ectosomes (pathway 2; Fig. 3). Rather than inward budding of vesicles closed in an outer endosomal membrane, as seen in MVBs, ectosomes are defined by the outward budding of the plasma membrane itself. In the ISF of wild-type mice, tau was found to be secreted by ectosomes in addition to exosomes (Dujardin et al., 2014).

Although it seems that the vesicle-dependant pathway could be favoured for the secretion of tau in tauopathy, alternative pathways that can potentially be exploited by tauopathies for disease spread and progression have also been identified. Studies that show the secretion of tau via vesicles also note a percentage of secretion in a vesicle-free form, suggesting secretion is not restricted to vesicle packaging alone (Dujardin et al., 2014; Yan et al., 2016; Chai et al., 2012). In line with this, in both Hela and SH-SY5Y cell lines, tau has been shown to be released in a vesicle-free form (Karch et al., 2012). The presence of vesicle free tau in the extracellular space has been suggested to be a result of an endo-lysosomal pathway of secretion. During stress to the cell, the translocation and capturing of misfolded tau to endo-lysosomes, either by protein trafficking pathways or through macroautophagy, which is suggested to facilitate secretion of cytosolic proteins, could occur (pathway 3; Fig. 3)[122]. This process would consequently lead to the fusion of the endo-lysosome with the plasma membrane, leading to the secretion of the protein in a vesicle free form (Kang et al., 2019; Lee and Ye, 2018). Notably, PrPs have also been shown to utilise the endo-lysosomal pathway for transportation and secretion, illustrating another common pathway for secretion between tauopathy and prion disease (Magalhães et al., 2005). Alternatively, tau, being a cytosolic protein, is proposed to associate with the Golgi apparatus membrane (Mohamed et al., 2017). This suggests the possibility of tau being secreted into the extracellular space via vesicular packaging of tau and consequent secretion by fusion into endosomes before secretion (Ponnambalam, 2003) (pathway 4; Fig. 3).

More recently, data elucidates an alternative pathway for tau secretion involving direct translocation and release across the plasma membrane of the cell (Merezhko et al., 2018). Tau aggregating in the cytoplasm as a result of hyperphosphorylation has been shown to bind to cholesterol and lipids, such as phosphatidyl inositol 4,5 phosphate (PI(4,5)P_2) and sphingolipids, allowing for local alterations in membrane integrity. The secretion of tau is then mediated by heparin sulfate proteoglycans (HSPGs) found on the extracellular surface of the plasma membrane, which capture and secrete tau into the extracellular space in a vesicle-free form (Merezhko et al., 2018; Katsinelos et al., 2018) (pathway 5; Fig. 3). This mechanism of tau secretion is similar to the secretory pathway observed for a well-studied signalling molecule, fibroblast growth factor (FGF2). FGF2, like tau, is translocated across the plasma membrane via binding to PI(4,5)P_2, where it is captured and retained by HSPG on the cell surface before secretion (Zehe et al., 2006). In the context of prion disease, PrPs have also shown to bind to HSPGs for secretion and propagation. Additionally, HSPGs on neighbouring cells have shown to be associated with binding and internalising PrP via endocytosis from the extracellular environment (Horonchik et al., 2005; Schonberger et al., 2003); a similar mechanism for cellular uptake of tau (Stopschinski et al., 2018). Notably, tau binding onto HSPGs is dependent on specific sulfation of the glycosaminoglycan chain whilst other

pathological aggregates such as Aβ in AD, and, alpha-synuclein in Parkinson's disease only require an overall sulfation of the polysaccharide to bind and initiate internalisation (Stopschinski et al., 2018).

Notably, tau secretion is not limited to extracellular-mediated pathways, but can additionally be transported from one neuron to another via an intracellular mechanism involving tunnelling nanotubules (Tardivel et al., 2016). Connecting the cytoplasm of one cell with another, tunnelling nanotubules are found within neurons and astrocytes and play an important role in cell-to-cell communication by facilitating the selective transfer of vesicles (Rustom et al., 2004; Rostami et al., 2017) (pathway 6; Fig. 3). Unlike gap junctions, tunnelling nanotubules are long-range communication pathways formed in abundance under different forms of cellular stress, covered in depth by Matejka and Reindl (2019). Interestingly, tunnelling nanotubules and lysosomes have been shown to play a role in mediating the neuron to neuron transfer of pathological proteins, such as α-synuclein in Parkinson's disease (Dieriks et al., 2017) and PrP in prion disease (Victoria and Zurzolo, 2017; Gousset et al., 2009). With respect to tau, the number of tunnelling nanotubules between cells are shown to increase in the presence of tau aggregates suggesting an intracellular pathway for tau propagation that can be exploited in tauopathy (Abounit et al., 2016).

6. Neuroinflammation and tauopathy

Neuroinflammation can be defined as an inflammatory response initiated to protect the central nervous system from acute insult and injury; however, persistent inflammation can prove detrimental to cellular homeostasis as implicated in neurodegenerative disorders (Kempuraj et al., 2016). Given tau propagation can be independent of synapse-to-synapse transmission during early pathology (Lowe et al., 2018), this suggests a role of neuroinflammation associated with the reactivity of supporting glial cells in the prion-like propagation of tau. Neuroinflammation has been shown to be a critical marker in tauopathies, preceding both NFT formation and neuronal loss (Yoshiyama et al., 2007) and highlighting a potential role of glial cells, including microglia and astrocytes, in early pre-clinical stages of tauopathy (Yoshiyama et al., 2007; Cook et al., 2015; Schwab et al., 2010). Notably, inflammation feeds into the neurodegenerative nature of tauopathies by exacerbating tau phosphorylation (Collins-Praino and Corrigan, 2017). In several primary tauopathies, including FTD-17 and CBD, overexpression of the pro-inflammatory cytokines interleukin 1β, interleukin-6 and tumour necrosis factor-α have been shown to potentiate tau pathology by increasing kinase activity such as cdk5, promoting tau hyperphosphorylation (Morales et al., 2013; Ghetti et al., 2015; Quintanilla et al., 2004). Similarly, in AD murine mouse models, inflammation induced via lipopolysaccharide administration preceded NFT deposition and caused an increase in tau phosphorylation via the increased activation of GSK3β and release of pro-inflammatory cytokines, such as interleukin-1 β (Li et al., 2003; Sy et al., 2011). Conversely, the propagation of tau oligomers, as highlighted in this review, can initiate inflammation by interacting with and activating inflammatory glial cells, such as astrocytes and microglia (Morales et al., 2013; Nilson et al., 2017). In *post mortem* brain samples of FTD-17 and AD patients, tau oligomers were in close proximity and co-localised with reactive astrocytes and microglia. Additionally, in the same study, high motility group box 1 (HMGB1), a chromatin protein that can be secreted as a proinflammatory cytokine by astrocytes (Passalacqua et al., 1998) and microglia (Fonken et al., 2016), was significantly increased in the frontal cortex of FTD-17 and AD patients in comparison to control. Notably, HMGB1 was observed to co-localise with tau oligomers suggesting that tau oligomers are closely associated with inflammation (Nilson et al., 2017). This cyclic relationship between neuroinflammation and tau pathology elucidates an interesting concept: that tau propagation also propagates neuroinflammation, which can potentiate the formation of more tau oligomers, thus increasing prion-like disease spread and associated degeneration. This association between neuroinflammation and the prion-like spread of tau could be carried via the ability of supporting astrocytes and microglial cells to internalise and secrete tau oligomers to neighbouring neuronal networks, potentiating tau spread and disease progression.

7. A potential role of astrocytes in tau neuroinflammation and propagation

7.1. Reactive astrocytes in tauopathy

Astrocytes play diverse and critical roles in brain circuitry. During early development, the maturation of astrocytes and ramification of their processes occurs in parallel with synaptogenesis and synaptic pruning, establishing "quad-partite synapses", a close association between astroglia, microglia and neuronal connections (Araque et al., 1999; Schafer et al., 2013). Through this dynamic interaction, astrocytes are able to modulate synaptic plasticity via the buffering of potassium ions (Pannasch et al., 2011), regulation of extracellular space volume (Murphy et al., 2017), clearing and recycling o neurotransmitters back into the presynaptic terminal (Allen, 2014) and metabolism of glucose to lactate for neuronal energy (Turner and Adamson, 2011). Astrocytes also play an integral role in the composition of the blood brain barrier, where their end-feet cover cerebrovascular capillaries, facilitating glucose and oxygen delivery to neuronal networks, in addition to regulating ionic and water homeostasis (Liu et al., 2018). Additionally, in response to neurotransmitter release from neighbouring neuronal cells, astrocytes are able to release their own subset of gliotransmitters, such as glutamate and ATP, to regulate synaptic transmission (Halassa et al., 2007; Li et al., 2013). Under physiological conditions, astrocytes are connected to one another by gap junctions, forming a functional reticular system known as a syncytium in the brain parenchyma, with little overlap between neighbouring astrocytes and their processes (Kiyoshi and Zhou, 2019). Under pathological conditions, however, astrocytes undergo astrogliosis and become reactive, leading to a change in morphology that allows them to penetrate into neighbouring brain areas as a defensive mechanism to control and maintain homeostasis of the microenvironment (Bushong et al., 2002; Schiweck et al., 2018). Reactive astrocytes become hypertrophic, upregulate their expression of the glial fibrillary acidic protein (GFAP) and ramify their processes, extending them to neighbouring environments (Wilhelmsson et al., 2006). As a result, astrocytes can become scar-forming, in order to isolate damaged areas and promote regeneration; while this can be reversible acutely, persistent astrocytic scarring, such as that observed in tauopathy (Perez-Nievas and Serrano-Pozo, 2018), can be a detriment to neuronal functioning (Schiweck et al., 2018; Burda et al., 2016). In *post mortem* brain tissue samples of patients with AD, astrogliosis was observed in the entorhinal cortex, the hippocampus, and in layers II-III and V in the temporal cortex (Taipa et al., 2018). Interestingly, astrocytes derived from the superficial cortical layers of P301S transgenic mice during the early post-natal age express high levels of GFAP (Sidoryk-Wegrzynowicz et al., 2017). This suggests a potential decreased neuroprotective function by astrocytes in early tauopathy that could contribute to neuronal damage and disease progression (Sidoryk-Wegrzynowicz et al., 2017).

7.2. Astrocyte inclusions in tauopathy

Astrocytes with tau inclusions are displayed in tauopathies and correlate closely with anatomical regions of degeneration, such as the hippocampus CA1 region and the cerebral cortex (Komori, 1999). Thorn-shaped astrocytes, which are morphologically similar to reactive astrocytes, but which are predominantly localised to the subpial region and temporal lobe white matter, are present in several tauopathies, such as CBD, PiD and PSP (Komori, 1999; Ikeda et al., 1995). In PSP, tau has also been shown to accumulate in a distinct population of astrocytes, termed tufted astrocytes, which are localised to the motor cortex and striatum and are characterised by tau-positive fibrils, which form tufts

(Ikeda et al., 1995; Matsusaka et al., 1998). While the implications of these different populations of astrocytes for disease pathogenesis are yet to be investigated, the identification of tau aggregations within astrocytes suggests that astrocytes are capable of internalising tau (Fig. 4). This astrocytic internalisation of tau may occur to maintain microenvironment homeostasis by facilitating the clearance through the perivascular pathway between the CSF and the ISF, termed the glymphatic system by Illif and colleagues (Iliff et al., 2012, 2015). Tau clearance through this system could occur through channel-dependant mechanisms, such has already been observed for the internalisation and clearance of Aβ plaques observed in AD (Qi and Ma, 2017), in which membrane channels, such as the lipoprotein receptor-related protein 1 (LRP1) (Kanekiyo and Bu, 2014) and aquaporin 4^{176}, play a key role.

7.3. Potential role of astrocytes in tau propagation

In recent years, it has been demonstrated that this internalisation of tau oligomers by astrocytes may occur via the lysosomal pathway. In line with this, transcription factor EB, which is an important regulator and stimulator of lysosomal biogenesis (Napolitano and Ballabio, 2016), enhanced astroglial uptake of fibrillar tau via endosomes (Martini-Stoica et al., 2018). Monomeric tau is also able to be internalised by astrocytes; however, the mechanism is unknown and appears to be independent of HSPGs (Perea et al., 2019), which are important for neuronal tau uptake (Holmes et al., 2013). Interestingly, astrocytes internalise and accumulate tau before neuronal toxicity and associated clinical symptoms occur (Ling et al., 2016) and may actually drive neuronal toxicity. As evidence of this, in a primary co-culture study, increases in intracellular calcium signalling in astrocytes following internalisation of tau oligomers affected the calcium dependant release of gliotransmitters, in particular ATP, causing neuronal toxicity via reducing synaptic vesicle release and neuronal excitation (Piacentini et al., 2017). Recently, tau was observed to accumulate in hippocampal astrocytes in AD patients when compared to age matched controls. Accumulation of the 1N3R tau isoform in astrocytes was shown to disrupt mitochondrial function, and, subsequently impairing neighbouring inhibitory neurons and adult neurogenesis in the dentate gyrus; an anatomical region involved in encoding spatial memory (Richetin et al., 2020). These findings suggest that, tau accumulation and associated toxicity in astrocytes may play an important role in driving neurotoxicity.

The accumulation of tau within astrocytes could overburden and damage the cell, in a similar way that Aβ does (Söllvander et al., 2016), consequently causing the secretion of tau oligomers to its neighbouring neuronal networks and aiding in the propagation and spread of the protein (Nagele et al., 2004). Similar to what is observed in neurons, this could occur via the exosomal-dependant pathway (pathway 1; Fig. 3), suggesting a commonality in mechanisms of tau secretion and prion-like propagation between neurons and astrocytes (Fauré et al., 2006). Alternatively, similar to neurons (pathway 6; Fig. 3), astrocytes also contain tunnelling nanotubules, which are known to play a key role in prion-like transfer and propagation of alpha-synuclein from astrocytes in Parkinson's disease (Rostami et al., 2017). Thus, this same route of cytoplasm-to-cytoplasm transfer could also be exploited in tauopathy and used to transfer tau from astrocytes to other cells in a similar manner as what has been observed to occur in the intracellular propagation of tau in neurons (Tardivel et al., 2016; Abounit et al., 2016) and PrPs in prion

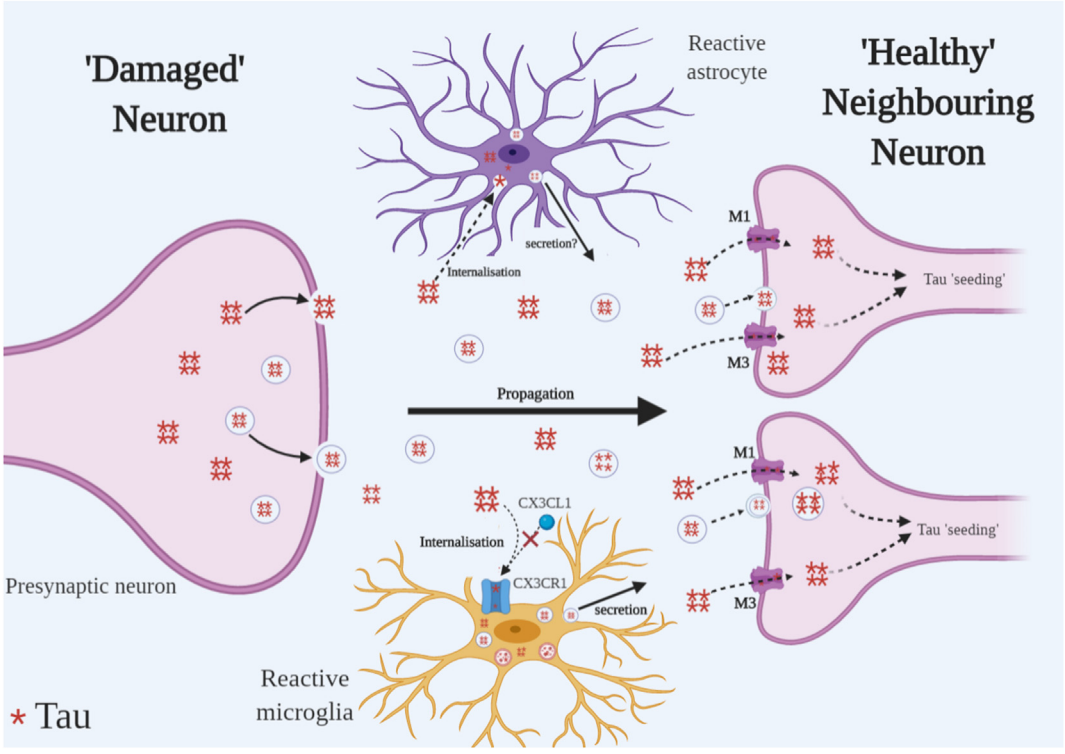

Fig. 4. An overview of the prion-like propagation and internalisation of tau. Aggregated tau can be secreted from the pre-synaptic terminal of a damaged neuron into the extracellular space by mechanisms of secretion shown in Fig. 3. Once in the extracellular space, tau can be internalised by nearby reactive astrocytes, but, bulk internalisation may result in toxicity and consequent secretion of tau to the neighbouring neuronal environment possibly via the exosomal-dependant pathway. Reactive microglia also internalise tau via competing with CX3CL1 for binding and uptake through the CX3CR1 channel for degradation; however, similar to what can occur with Aβ in astrocytes, abundant tau internalisation could be toxic to the cell, leading to the secretion of tau from microglia via exosomes. Both vesicle bound and free tau can then be internalised by the dendrites of nearby healthy neurons via endocytosis of the protein or by the binding and uptake through muscarinic receptor M1 and M3 or by LRP1 receptors. Internalised tau can then 'seed' existing tau structures, causing conformational changes and leading to both NFT formation and the production of more tau oligomers which can, in turn, be secreted and propagated in a prion-like manner. In this manner, tau pathology can spread throughout the brain in tauopathies. Secretion is denoted by arrows whilst internalisation is represented by dashed arrows.

disease (Gousset et al., 2009). Future research is required to verify and understand the mechanisms by which tau secretion can occur via astrocytes to better define their role in the prion-like propagation of tau.

8. A potential role of microglia in tau neuroinflammation and propagation

8.1. Reactive microglia in tauopathy

Microglia are the resident macrophages of the central nervous system and play a key role in actively surveying the brain parenchyma, interacting with neuronal and other glial subtypes, carrying out an innate immune response in response to neuronal damage (Ginhoux et al., 2013; Hanisch and Kettenmann, 2007; Gomez-Nicola and Perry, 2015). In response to a variety of neuronal insults, including neurodegeneration, microglia become reactive, actively motile, phagocytic and proliferative, facilitating an inflammatory response and engulfing neuronal debris (Hanisch and Kettenmann, 2007; von Bernhardi et al., 2015). For a detailed review on microglial function in both the neurologicall healthy and diseased brain, refer to the review by Gomez-Nicola and Perry (2015). Reactive microglia can be generally characterised into an inflammatory (M1) phenotype or an anti-inflammatory, neuroprotective (M2) phenotype. Interestingly, during the progression of AD pathology, reactive microglial phenotypes are shown to be skewed to an M1 phenotype, releasing more pro-inflammatory cytokines and nitric oxide (Hanisch, 2002). In support of this, administration of LPS *in vitro* to stimulate inflammation shows a phenotype switch from M2 reactive microglia to M1 reactive microglia, favouring neuroinflammation (Varnum and Ikezu, 2012; Chhor et al., 2013).

In the context of tau pathology, reactive microglia have been found near tau aggregations in the primary tauopathies, CBD and PSP, with early studies suggesting a parallel distribution of cortical microglia with NFT-bearing neurons (Sheffield et al., 2000; Sheng et al., 1997; Cras et al., 1991; Gerhard et al., 2004, 2006). In AD, reactive microglia are observed around NFTs (Cras et al., 1991; DiPatre and Gelman, 1997) and are shown to co-localise with tau oligomers for potential internalisation and degradation (Nilson et al., 2017), suggesting an intricate association between neuroinflammation and tauopathy. Tau aggregates in the form of oligomers or fibrils can directly activate microglia *in vitro*, subsequently increasing the secretion of the pro-inflammatory cytokine interleukin-6[6]. Interestingly, tau secretion in non-phosphorylated forms (Karch et al., 2012) has also been shown to activate microglia, initiating inflammation (Perea et al., 2018). This hints at the possible importance of neuroinflammation in the early progression of tauopathy. Additionally, oxidative stress, which is suggested to be a key event in tangle formation during early AD, can be closely associated with microglial reactivity and release of reactive oxygen species (ROS) (Mondragón-Rodríguez et al., 2013). For a detailed understanding of ROS production in reactive microglia and the association with oxidative stress in neurodegenerative disease, refer to the recent review by Simpson and Oliver (2020). In brief, oxidative stress can cause tau hyperphosphorylation and subsequent aggregation via the direct interaction and upregulation of kinases, such as GSK3β[202], or the downregulation of phosphatases, such as PP2A[203]. Notably, similar to astrogliosis, which has been observed to play a role in early tauopathy (Sidoryk-Wegrzynowicz et al., 2017), reactive microglia can also precede synaptic loss and NFT (Yoshiyama et al., 2007) formation, further supporting that neuroinflammation may play an important role in early disease progression. Furthermore, in P301S and SHR72 transgenic mice expressing truncated forms of tau, phosphorylated and truncated tau are both able to trigger neuroinflammation, as indicated by microglial reactivity and the upregulation of inflammatory cytokines (Bellucci et al., 2004; Zilka et al., 2009). This further supports a cyclic relationship between tau and the inflammatory cascade initiated by microglia, were neuroinflammation may precede tau pathology but, once present, tau aggregates can worsen neuroinflammation.

The reactivity of microglia and associated inflammation can also influence astrocytic reactivity, perpetuating neuroinflammation contributing to early tau pathology (Liddelow et al., 2017). Once reactive, microglia are able to induce the formation of A1 and A2 reactive astrocytes via the release of IL-1α, TNF and complement component 1q (Liddelow et al., 2017). Whilst A2 astrocytes play a neuroprotective role via the release of neurotrophic factors, A1 astrocytes, on the contrary, are associated with neurotoxicity, playing a negative role in synaptic formation and function (Liddelow et al., 2017; Baldwin and Eroglu, 2017). In the hippocampus and cortex of IL-10 knockout mice, a higher level of proinflammatory IL-1β, IL-6 and TNFα cytokine expression was associated with A1 reactive astrocytes (Zhang et al., 2020). In AD, over half of GFAP-positive astrocytes are A1[206], further supporting the notion that neuroinflammatory glial cells are key contributors to tau pathology. Notably, the negative role of A1 astrocytes on synaptic formation and functioning would not contradict the proposed prion-like propagation of tau, since as mentioned earlier, tau spread is not strictly dependent on synaptic connections (Lowe et al., 2018).

8.2. Potential role of microglia in tau propagation

In respect to the prion-like propagation of tau, a few studies hint at the potential role of microglia in this process. Recent work in the field has explored the ability of microglia to actively phagocytose phosphorylated tau from the extracellular space for degradation both *in vitro* and in P301S transgenic mice *in vivo* (Bolós et al., 2016; Luo et al., 2015). Interestingly, tau can be internalised by microglia via the CX3CL1 (fractalkine) microglial receptor CX3CR1[211] (Fig. 4). Under normal physiological conditions, CX3CL1 is expressed by neurons and binds to CX3CR1 on microglia, allowing for cellular cross-talk and keeping the microglia in an "off" state through inhibition of the release of proinflammatory cytokines (Biber et al., 2007). This neuronal-microglia cross-talk plays an important role during synaptic pruning in early development, with *in vivo* models lacking the CX3CR1 receptor exhibiting reduced synaptic pruning and immature synapses (Paolicelli et al., 2011; Hoshiko et al., 2012). In tauopathy, extracellular tau has been suggested to compete with CX3CL1 to bind to CX3CR1; once it binds, tau is internalised (Fig. 4)[211]. Thus, tau is not only internalised by microglia via CX3CR1, but, by interfering with neuronal-microglial cross-talk, may actually lead to disinhibition of proinflammatory cytokine release, further exacerbating neuroinflammation (Bolós et al., 2017). Further research is needed to understand the implications of tau binding and internalisation via CX3CR1 and the role that this may play in the prion-like propagation of the protein.

Similar to what can occur with Aβ internalisation by astrocytes, where accumulation can overwhelm the cell, causing subsequent secretion in microvesicles leading to neurotoxicity (Söllvander et al., 2016), reactive microglia can potentially be overburdened and unable to adequately degrade internalised tau (Hopp et al., 2018). Under these conditions, microglia can secrete the tau, prompting the prion-like propagation of the protein (Hopp et al., 2018; Nagele et al., 2004). Interestingly, the favoured pathway for tau secretion under pathological conditions in microglia is suggested to be the exosomal-dependant pathway (Asai et al., 2015) (Fig. 4). In support of this, a study using P301 transgenic mice investigating the propagation of tau, showed that, inhibiting exosome synthesis in microglia significantly decreases tau propagation (Asai et al., 2015).

9. Tau uptake and 'seeding'

The ability for neighbouring neurons to internalise extracellular tau, which act as 'seeds' within these neurons, recruiting and missfolding endogenous naïve tau proteins to form PHFs and subsequently NFTs, supports the notion of prion-like propagation (Guo and Lee, 2011; Wu et al., 2013; Frost et al., 2009; Evans et al., 2018; Morozova et al., 2019). Culture studies utilising QBI-293 cells show both truncated and

full-length tau can be internalised via co-localising with dextran, a marker for fluid-phase endocytosis (Fig. 4); a non-specific endocytic uptake mechanism normally utilised by immune cells for cleaning and surveying the microenvironment (Frost et al., 2009; Norbury, 2006). Concerningly, only a small amount of internalised tau aggregates can seed and recruit large amounts of endogenous tau to form fibrils (Guo and Lee, 2011; Frost et al., 2009). This suggests that tau uptake causes a ripple effect, where only minimal tau needs to be internalised to cause conformational changes and aggregation in a prion-like fashion; consequently, leading to disease spread and progression.

Additionally, in both hippocampal and cortical primary neurons, low molecular weight tau aggregates were shown to be internalised via endosomes at both the post-synaptic terminal and at the somatodendritic regions of neighbouring neurons (Fig. 4), suggesting that tau uptake is not confined to synaptic connections alone (Wu et al., 2013). In contrast to smaller tau aggregates, which enter neighbouring neurons via endosomes, larger tau oligomers are able to be internalised by binding to HSPGs and entering through the formation of large intracellular vacuoles known as micropinosomes, a process termed micropinocytosis (Holmes et al., 2013). It is important to note that, although the mechanisms by which extracellular tau is internalised appear to be dependent on its size, tau seeding of endogenous tau and consequent fibril formation remains the same.

Interestingly, more recent studies *in vitro* (Morozova et al., 2019) and *in vivo* (Rauch et al., 2020) elucidated a receptor-mediated mechanism for tau uptake involving muscarinic M1 and M3 receptors and LRP1 (Fig. 4). When either monomeric or phosphorylated tau was added to the culture media of non-neuronal HEK293 cells, which naturally express muscarnic receptors, tau was internalised by the cells. By treating cells with atropine, a muscarinic receptor antagonist, tau uptake was reduced by approximately 80%; a similar result was also shown by treating the cells with the M1 antagonist pirenzepene. These results suggest that the majority of tau uptake could occur via interaction with and internalisation through muscarinic receptors; however, further studies should investigate the interaction between the protein and M1 receptors to better understand how this receptor-mediated uptake works. Furthermore, it would be interesting to observe whether these results could be replicated in neuronal cell lines that naturally express M1 receptors, such as the SH-SY5Y neuroblastoma cell (Fowler et al., 1989). Given that M1 is the predominant muscarinic acetylcholine receptor in the hippocampus and pyramidal cells in the neocortex (Levey, 1996; Abrams et al., 2006), and, in tauopathies such as AD, pathogenesis leads to dysfunction of glutamatergic synapses in these regions (Wang and Reddy, 2017), this suggests that, M1 mediated tau uptake may potentiate tau pathology and subsequent neurotoxicity and neuronal loss. Interestingly, M1 receptors are localised to the somatodendritic region of pyramidal neurons, where tau mis-localisation can occur in AD and FTD-17[47, 48, 50], further hinting at a potential role of the receptor in tau pathology. Also, given that astrocytes and microglia have both also been shown to express muscarinic M1 receptors (Pannell et al., 2016; Shelton and McCarthy, 2000); future studies should investigate whether tau uptake into these glial cells occurs via M1 receptors (Morozova et al., 2019) for potential identification of therapeutic target for tauopathy treatment. In addition to the proposed muscarinic receptor-mediated uptake of tau, LRP1 channels are also suggested to play an important role in tau internalisation and thus propagation. Tau internalisation by LRP1 is suggested to occur by lysine interactions between the proteins (Rauch et al., 2020). In support of this, LRP1 knockout mice showed a reduction in tau propagation between neurons (Rauch et al., 2020), further supporting the importance of receptor-mediated internalisation of tau and the potential avenue for therapeutic targeting.

10. Conclusions and future prospects

Tau pathology is intimately associated with the cognitive and motor impairments observed in tauopathies (Brunello et al., 2019). In recent years, the understanding of how aggregated forms of tau are able to spread and lead to neuronal impairment has evolved from thinking it is due to vulnerability of specific brain areas to tau aggregation to knowledge of the existence of extracellular tau, which can be propagated and internalised by nearby healthy neurons in a prion-like manner (Jucker and Walker, 2013). As a result, a new branch of tauopathy research has arisen, which shifts the focus from intracellular tau pathology to extracellular tau propagation and seeding. Given that much of this work is still in its infancy, critical gaps in understanding remain, particularly in relation to the role that neuroinflammatory glial cells may play in this process. Mechanisms by which astrocytes and microglia are able to internalise and secrete tau to potentiate the prion-like spread of the protein are poorly understood, but, hold promise for the discovery of new and selective therapeutic interventions. Furthermore, a better understanding of the specific interactions that occur between internalised tau aggregates and endogenous tau within the healthy neighbouring neuron warrants investigation. Finally, it is important to note that many of the studies performed in this area to date have been *in vitro* in nature, and thus subject to the limitations of this sort of work, including culture conditions, choice of cell line, etc. Thus, more work is needed in order to understand the dynamic interactions that occur between neurons and glia in driving the propagation of tau in pre-clinical models. Taken together, this work has the potential to lead to the identification of promising novel therapeutic targets, potentially even leading to a disease modifying treatment for tauopathy.

Declaration of competing interest

The Authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100242.

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