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Cell-to-cell transmission of tau and α -synuclein

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Abstract

The stereotypical spread of pathological protein inclusions and clinicopathological heterogeneity are well described in neurodegenerative diseases. Accumulating evidence suggests that the former can be attributed to consecutive cell-to-cell transmission of pathological proteins between anatomically connected brain regions, while the latter has been hypothesized to result from the spread of conformationally distinct pathological protein aggregates, or strains. These emerging concepts have dramatically changed our understanding of neurodegenerative diseases. In this review, we first summarize the background and recent findings underpinning these concepts with a focus on two major pathological proteins—tau and α -synuclein. We then discuss their clinical implications for tauopathies and synucleinopathies and propose a working hypothesis for future research.

Keywords

tauopathies; synucleinopathies; Alzheimer's disease; Parkinson's disease; propagation; strains

Emerging Concepts in Tauopathies and Synucleinopathies

Tauopathies and synucleinopathies are neurodegenerative diseases pathologically characterized by deposition of tau and α -synuclein (α -syn) proteins in brains, respectively. Clinically, tauopathies and synucleinopathies show progressively deteriorating neurological functions such as cognition and motor function. Tauopathies and synucleinopathies comprise a large population of patients with neurodegenerative diseases. However, currently, no treatment can halt or even slow down the progression of these diseases.

Many studies have demonstrated that aggregation of tau and α -syn exerts neurotoxicity, and its spread in brains is associated with increasing severity of clinical symptoms [1]. Although the pathological mechanisms of this disease progression had been unclear, recent human and

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animal studies have repeatedly demonstrated that cell-to-cell transmission of pathological tau and α -syn underlies this process. This concept has been a platform to explore molecular mechanisms of disease progression and provided these incurable diseases with new therapeutic targets (see Clinician's Corner). Meanwhile, the origin of clinicopathological heterogeneity among the diseases caused by a single pathological protein (i.e. tau or α -syn) remains one of the unsolved mysteries in this field. Recent accumulating evidence suggests that spread of tau and α -syn aggregates with disease-specific conformation referred to as strains, at least partly, define distinct tauopathies and synucleinopathies. This concept highlights the necessity of strain-based, disease-specific studies which have just begun very recently and would expand this research field in the future.

Tau and α -syn share many similarities but have some key differences in terms of pathological roles under disease conditions. The purposes of this review are (1) to update evidence supporting those emerging concepts and (2) to discuss their therapeutic implications and future directions with a focus on tau and α -syn, which will be compared side-by-side to provide new insights into each research field.

Neuropathology of tauopathies and synucleinopathies

Tauopathies and synucleinopathies are characterized by formation of tau and α -syn inclusions in brains, respectively. While tau and α -syn exist as natively unfolded proteins, they form aggregates under disease conditions and are closely associated with neurodegeneration (Box 1, 2). Tauopathies and synucleinopathies are each subcategorized into several diseases based on histopathological characteristics including the temporal distribution, morphology, and affected cell types. For tauopathies, the tau isoforms present in pathology provide an additional distinguishing criterion for classification. The major tauopathies can therefore be subdivided into 3R, 4R, and 3R/4R tauopathies (Table 1). Alzheimer's disease (AD) is the most common neurodegenerative disease and the most prevalent cause of dementia. AD neuropathology is characterized by neurofibrillary tangles (NFTs), neuritic plaques (NPs), and amyloid- β (A β) plaques (Figure 1a,b) [2]. NFTs are tau inclusions within neuronal somas, and NPs are tau inclusions in dystrophic neurites within A β plaques. NFTs are primarily restricted in the entorhinal region and hippocampal formation in the early stages of disease but are widely seen in the neocortical areas in the late stages [3]. Extracellular A β plaques, the other pathological hallmark of AD, initially accumulate in the cortical areas, later extending to the subcortical areas and brainstem [4]. Pick's disease (PiD), which typically presents dementia, behavioral abnormalities, aphasia, and personality changes, is pathologically defined by round tau inclusions in neuronal perikarya called Pick bodies (Figure 1c) [5]. Although less often described, astrocytic and oligodendroglial tau inclusions have been also reported in PiD [6]. Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are distinct entities but share some similarities [7]. The major clinical manifestations of PSP are postural instability, dementia, and eye movement abnormalities, while those of CBD are asymmetric apraxia, rigidity, dystonia, and dementia. NFTs and globose tangles are observed in the basal ganglia and brainstem in PSP (Figure 1e). On the other hand, ballooned neurons and globose tangles are observed in the affected cortical areas and in the brainstem, respectively, in CBD (Figure 1f) [7]. Distinct astrocytic pathologies—tufted astrocytes in PSP and astrocytic plaques in CBD

—are regarded as pathological hallmarks, while both share common oligodendroglial pathology called coiled bodies (Figure 1d,g,h) [7]. Given that patients with PiD, PSP, and CBD often show symptoms common to other frontotemporal dementias (FTD), these diseases are subcategorized as frontotemporal lobar degeneration with tauopathy (FTLD-tau) [8]. Patients with chronic traumatic encephalopathy (CTE) have a history of repetitive brain injury and show neuropsychiatric symptoms. The pathology shows pathognomonic lesions consisting of hyperphosphorylated tau inclusions in neurons and astrocytes around small vessels at the depths of the cortical sulci [9]. Neuronal tau pathology is NFTs composed of 3R and 4R tau, while astrocytic tau pathology called thorn-shaped astrocytes is composed of 4R tau [10].

Parkinson's disease (PD) is the second-most common neurodegenerative disorder. Patients with PD show motor dysfunction including bradykinesia, rigidity, and resting tremor, collectively called parkinsonism. Pathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and intraneuronal α -syn inclusions called Lewy bodies (LBs) and Lewy neurites (LNs) [11] (Figure 1i,j, Table 2). Lewy pathology is restricted in the brainstem and olfactory bulb in the early stages, extending to the limbic system and neocortical areas in the late stages [12]. Patients with PD often develop dementia years after the onset of motor dysfunction, a diagnosis termed PD with dementia (PDD). LB pathology in the cortical areas correlates with development of dementia in PD [13]. Moreover, subjects with PDD tend to show more severe A β and NFT pathology in the cortical areas than subjects with PD [13]. Patients who develop dementia before or concurrently with motor symptoms are diagnosed as dementia with LBs (DLB). However, there is no clinical symptom or hallmark pathological feature that distinguishes DLB from PDD [14, 15]. LB diseases are used as an umbrella term of PD, PDD and DLB. Although it has received relatively little attention, astrocytic and oligodendroglial α -syn inclusions are also seen in LB diseases [16]. Multiple system atrophy (MSA) is clinically and pathologically distinct from LB diseases. Patients with MSA show parkinsonism, cerebellar ataxia, and autonomic failure, and their clinical condition declines faster than LB diseases [17]. The pathological hallmark of MSA is abundant oligodendroglial α -syn inclusions, referred to as glial cytoplasmic inclusions (GCIs), with rare neuronal inclusions (NIs) (Figure 1k,l, Table 2) [18]. The α -syn pathology and neuronal loss are observed mainly in the striatonigral or olivopontocerebellar system, correlating with clinical symptoms [17].

These unique neuropathological observations raise a number of fundamental questions regarding the pathogenesis of these disorders: How do tau and α -syn inclusions spread in brains? How do tau and α -syn cause diverse disease entities? Several concepts to address these questions are now emerging, as we will see in the following sections.

Cell-to-cell transmission in tauopathies and synucleinopathies from human studies

An expanding number of postmortem and epidemiological studies have implicated that tau and α -syn pathology spreads intercellularly. Systematic analyses of NFT pathology in

subjects with AD as well as healthy individuals revealed that NFTs first occur in the locus coeruleus and transentorhinal region, then spreading to the entorhinal region and hippocampal formation, and finally reaching the neocortical areas [3, 19, 20]. Most subjects follow this temporal distribution of the NFT pathology, which correlates with development of dementia [20]. This same approach was applied for subjects with PD and incidental LB cases, showing that Lewy pathology is initially present in the dorsal motor nucleus of the vagus nerve (dmX) and olfactory bulb, then spreading in the brain stereotypically [12]. In addition, since Lewy pathology is found in the enteric nervous system (ENS) even in incidental LB cases, it has been hypothesized that Lewy pathology in the ENS travels retrogradely to the dmX via the vagus nerve before proceeding in a caudo-rostral direction to reach the SNpc and other regions [12, 21]. These observations raise two possibilities: (1) vulnerable neuronal populations are consecutively affected with aging, defining the unique spatiotemporal distribution of pathology, or (2) the intercellular transfer of some pathogen(s) through preferential routes forms the stereotypical progression of pathology. Several human PD studies support the latter possibility. Most notably, transplanted mesencephalic dopaminergic neurons developed LBs in subjects with PD years after the transplantation, suggesting that certain pathogenic events in PD are not cell-autonomous, and that Lewy pathology can propagate from the host to grafted cells [22, 23]. Though they are not yet conclusive, recent epidemiological studies indicate that individuals who have undergone truncal vagotomy or appendectomy have a lower risk of developing PD, thus providing support for the gut-to-brain hypothesis of PD [24–27].

Experimental evidence for cell-to-cell transmission of tau and α -syn

While human studies have suggested that tau and α -syn pathology is transmissible intercellularly, the pathogen(s) responsible for this process had been unknown. However, it is now understood that pathological tau and α -syn themselves show **prion-like** behavior (see Glossary), that is, the ability to self-propagate via **templated misfolding** and intercellular dissemination. Seeded fibrilization of monomeric tau in cultured cells was demonstrated by exogenously adding tau fibrils to cells expressing tau [28]. In this study, transmission of differently tagged tau aggregates among cells was also demonstrated in a co-cultured system [28]. As is the case in tau, treatment with α -syn fibrils induces α -syn inclusions in cell lines and primary mouse neurons [29, 30]. Tagged α -syn also transmitted from donor cells to acceptor cells in a co-cultured system, forming α -syn inclusions in acceptor cells [31].

One of the initial demonstration of tau pathology in animals was performed by injection of brain extracts from mutant **P301S tau** transgenic mice, which develop tau inclusions in the brains, into the brains of wild-type tau transgenic ALZ17 mice, which do not spontaneously produce tau inclusions in the brain [32]. The brain extracts containing tau aggregates induced neuronal tau inclusions in ALZ17 mice, spreading in the brains over time [32]. Transmission of tau pathology was also reported in a tau transgenic mouse model. Transgenic expression of mutant **P301L tau** restricted to layer II of the entorhinal cortex under control of the neuropsin gene promoter first produced local tau inclusions, later inducing tau inclusions in the interconnected regions [33, 34]. Transmission of α -syn pathology *in vivo* was first demonstrated in a cell transplantation mouse model [31]. In a human α -syn transgenic line 61 mice, which develop neuronal α -syn inclusions in the

brains, the engrafted mouse neuronal precursor cells formed human α -syn inclusions 4 weeks after transplantation, suggesting host-to-graft transmission of human α -syn inclusions [31]. Later, it was demonstrated that injection of synthetic α -syn fibrils or brain extracts from DLB subjects into the brains of wild-type mice induces neuronal α -syn inclusions and their subsequent spread within interconnected brain regions [35–37]. Importantly, *Snca* knockout mice injected with α -syn fibrils did not exhibit any α -syn inclusions, indicating that templated misfolding of endogenous α -syn is required for the transmission processes [35].

Collectively, these lines of evidence support the concept that templated misfolding and intercellular dissemination of tau and α -syn inclusions underlie the pathological progression of tauopathies and synucleinopathies. Induction of tau and α -syn pathology and its subsequent spread by injecting pathological tau and α -syn aggregates into animals is now widely used to investigate pathological mechanisms of tauopathies and synucleinopathies (Box 3).

Cell-to-cell transmission and distinct tau and α -syn aggregates

There is a considerable heterogeneity in clinicopathological features of tauopathies and synucleinopathies. The mechanisms by which the same pathological proteins cause distinct diseases have been enigmatic in this field. Recent converging efforts have revealed that heterogeneity of these diseases is, at least partly, attributed to distinct conformations of a single protein referred to as **strains**. Injection of brain extracts from different tauopathy subjects into the brains of tau transgenic ALZ17 mice produced tau pathology characteristic of each tauopathy [38]. Later, injection of purified brain extracts containing higher concentrations of disease-associated tau made it possible to induce robust, disease-specific tau pathology even in wild-type mice [39, 40]. These results indicate that disease-specific tau aggregates in brain extracts maintain distinct bioactivity to induce disease-specific tau pathology upon seeded-fibrilization in the mouse brains. The relationship between disease-specific tau aggregates and tau isoforms has been unclear. A recent study demonstrated that injection of brain extracts from different tauopathy subjects into the brains of transgenic 6hTau mice expressing both human 3R and 4R tau isoforms induces tau inclusions composed of the same isoform(s) in the inoculum [41].

Distinct bioactivity and conformations of α -syn aggregates were first demonstrated in synthetic α -syn fibrils. α -syn fibrils generated by repetitive self-seeded fibrilization *in vitro* more efficiently cross-seeded tau fibrillization in mutant P301S tau transgenic PS19 mice compared with original α -syn fibrils [42]. Moreover, α -syn fibrils generated in different buffer conditions showed different cell-type preference and neurotoxicity in rats virally overexpressing human α -syn [43]. The difference in α -syn aggregates between PD and MSA was first shown by **seeding potency**. Brain extracts from MSA subjects, but not those from PD subjects, induced α -syn inclusions in α -syn-expressing cultured cells and mutant **A53T α -syn** transgenic M83 mice [44]. Later, it was shown that MSA brain extracts are ~1,000-fold more potent in inducing α -syn inclusions in cultured cells compared with those from LB diseases [45]. Curiously, unlike brain extracts from tauopathies, MSA brain extracts did not recapitulate disease-specific pathology, GCI-like oligodendroglial α -syn

inclusions, in mice [44, 45]. A recent study reported that oligodendroglial α -syn inclusions form in α -syn fibril-injected mice several months after injection, raising the possibility that longer incubation after injection of MSA brain lysates might recapitulate GCI-like pathology [46]. More recently, the differences in α -syn aggregates between MSA and α -syn aggregate-forming M83 mice have been reported [47]. Injection of MSA and M83 mouse brain lysates induced distinct α -syn pathology in M83 mice in terms of temporal distribution, morphology, and affected cell types [47].

In support of the notion that distinct tau and α -syn aggregates underlie different tauopathies and synucleinopathies, several studies have unveiled conformational differences in tau and α -syn aggregates among specific clinical disorders. **Partial protease digestion** of brain extracts from different tauopathy subjects revealed distinct protease-resistant cores of tau aggregates [48]. Moreover, recent advances in cryo-electron microscopy (EM) have enabled atomic-resolution structural analyses, revealing differences in the ultrastructural organization of tau aggregates in brain extracts from PiD, AD, CBD, and CTE subjects [49–53]. Likewise, conformational differences in α -syn aggregates between LB diseases and MSA have been suggested by partial protease digestion, showing that α -syn aggregates of MSA are more resistant to proteolysis [45]. A recent study has documented the biochemical, biophysical, and biological differences in α -syn aggregates generated by **protein misfolding cyclic amplification** from the cerebrospinal fluid (CSF) between PD and MSA [54]. Moreover, this study showed that the fluorescent signal from the amyloid fibril-binding dye thioflavin T can discriminate the samples of PD from those of MSA with a sensitivity of over 95% [54].

The origin of distinct tau and α -syn strains in human remains largely unknown. A recent study demonstrated that transduction of synthetic α -syn fibril into oligodendrocytes overexpressing human α -syn induces GCI-like α -syn aggregates in terms of seeding potency and biochemical property, suggesting that oligodendroglial cellular milieu convert one α -syn strain into a GCI-like strain [45]. Another recent study using cryo-EM along with mass spectrometry revealed distinct atomic structures of tau filaments superposed with posttranslational modifications (PTMs) in CBD and AD brain extracts, proposing that site-specific PTMs influence tau filament structure, contributing to structural diversity of tau aggregates [52].

Taken together, tau and α -syn aggregates of different tauopathies and synucleinopathies show distinct bioactivity and conformation. Given that distinct tau and α -syn aggregates induce different pathology in animal brains in terms of temporal distribution, morphology, and affected cell types, spread of distinct strains in brains in part defines heterogeneity of tauopathies and synucleinopathies.

Molecular mechanisms underlying transmission of tau and α -syn pathology

Various molecular mechanisms related to transmission of tau and α -syn pathology have been reported chiefly in the context of neuron-to-neuron transmission (Figure 2, Key Figure). However, there are some caveats to consider when interpreting the findings reported so far. First, the differences in mechanisms observed across the studies may be due to the

differences in experimental models or parallel mechanisms in play. Second, based on human and animal studies, tau and α -syn pathology seems to spread among neurons trans-synaptically, rather than in a proximity-dependent manner (i.e., passive diffusion; see Box 4). Thus, it may be necessary to carefully interpret the phenomenon observed in cell lines lacking synaptic connections. Finally, since most previous studies did not use patient-derived tau or α -syn aggregates, it remains unclear the extent to which these experimental models recapitulate the cell-to-cell transmission in human disease.

Release and uptake of pathological tau and α -syn

Both tau and α -syn can be detected in the interstitial fluid (ISF) of mouse and human brains, supporting the view that tau and α -syn secreted in the extracellular space mediate cell-to-cell transmission of pathology [55–57]. Several studies have reported **exosomal release** of pathological tau and α -syn in cultured cells [58–60] and that of pathological tau into the extracellular space of mouse brains [61]. In line with this, exosomes isolated from the CSF of patients with LB diseases showed higher seeding potency compared with those of neurological controls [62]. Direct translocation has also been reported as another mechanism for actively introducing pathological tau into the extracellular space [63].

Endocytosis is a main pathway of internalizing tau and α -syn fibrils [31, 64–66]. A study demonstrated that both tau and α -syn fibrils bind heparan sulfate proteoglycans (HSPGs) on the cell surface and then are taken up via **macropinocytosis**, a form of endocytosis [65]. Another study demonstrated that α -syn fibrils are recognized by lymphocyte activation gene 3 (LAG3) receptor on the cell surface, then internalized via receptor-mediated endocytosis [66]. Internalized tau and α -syn fibrils are transported to the endo-lysosomal pathway, some of which are degraded in lysosomes [67, 68]. Tau and α -syn fibrils are released through the ruptured lysosomes into the cytosol, where fibrils presumably act as templates for fibrillization of monomeric tau and α -syn [69]. Upon exosomal uptake, exogenous exosomes could be incorporated into endogenous endosomes and subsequently undergo axonal transport, transferred to interconnected neurons [70].

Aside from release and uptake mechanisms, tunneling nanotube (TNT)-mediated cell-to-cell transfer of pathological tau and α -syn aggregates has also been reported [71, 72]. Exogenously added α -syn fibrils were incorporated in lysosomes of donor cells and then transferred through TNTs to acceptor cells, subsequently forming inclusions by recruiting endogenous α -syn in acceptor cells [72]. However, whether TNTs connecting neurons are present *in vivo* remains unclear.

Neuronal activity and transmission

The association of neuronal activity with spread of tau pathology has been well studied. Tau release by primary rat neurons into the conditioned medium was correlated with neuronal activity [73]. Consistent with this, *in vivo* microdialysis revealed that the amount of extracellular tau in brain ISF depends on neuronal activity [74]. Moreover, optogenetic and chemogenetic stimulation accelerated formation of tau pathology in mutant tau P301L transgenic mouse models [75]. Since A β plaques render nearby neurons hyperactive in A β plaques-forming transgenic mice [76], it is possible that A β pathology exacerbates spread of

tau pathology in AD. Interestingly, a recent study demonstrated that manual and chemogenetically-driven sleep deprivation enhances neuronal activity and increases tau concentration in brain ISF [77]. Chronic sleep deprivation promoted spread of tau pathology in the brains of mutant P301S tau transgenic PS19 mice injected with tau fibrils [77]. This study also showed sleep deprivation increases both tau and α -syn in CSF of cognitively normal human subjects [77]. The correlation of neuronal activity with α -syn release into the extracellular space was also demonstrated in primary mouse neurons and in mouse brains [78].

Glial involvement in neuron-to-neuron transmission

Microglia and astrocyte have phagocytic clearance functions in the central nervous system, presumably playing a protective role against spread of tau and α -syn pathology. Several studies reported microglial and astrocytic phagocytic clearance of pathological tau and α -syn in cultured cells and mice [79–84]. By contrast, microglia might facilitate spread of tau pathology by exosomal release of pathological tau. Pharmacological depletion of microglia or inhibition of exosome synthesis suppressed spread of tau pathology in mice virally overexpressing tau [61].

Formation and transmission of glial pathology

The mechanisms of glial pathology formation have been one of the major questions in tauopathies and synucleinopathies. A few recent studies have provided insights into the association of cell-to-cell transmission with formation of glial pathology (Figure 3). Analyses of wild-type or neuron-specific tau knockout mice injected with PSP and CBD brain extracts revealed that astrocytic tau pathology was correlated closely with nearby neuronal tau pathology, suggesting that astrocytic tau pathology results from local astrocytic uptake of tau aggregates released by neurons [40, 85]. On the other hand, oligodendroglial tau pathology appears to spread along white matter tracts over time despite lack of neuronal tau pathology in neuron-specific tau knockout mice injected with CBD brain extracts, consistent with oligodendroglia-to-oligodendroglia transmission of tau pathology [85]. Long-term observation of wild-type mice injected with α -syn fibrils revealed oligodendroglial α -syn pathology in white matter involved in spread of neuronal α -syn pathology, suggesting axon-to-oligodendroglia transmission of α -syn pathology [46]. Moreover, the amount of oligodendroglial α -syn pathology increased over time even after most neuronal α -syn pathology disappeared, raising the possibility of oligodendroglia-to-oligodendroglia transmission of α -syn pathology [46].

Therapeutic implications

Given the accessibility of antibodies to extracellular pathological proteins, one attractive therapeutic approach to inhibit cell-to-cell transmission of tau and α -syn is immunotherapy. Two common approaches to immunotherapy have been explored: (1) active immunotherapy, which attempts to induce an immune response against tau and α -syn (e.g., generation of protective antibodies), and (2) passive immunotherapy, which involves the administration of antibodies engineered against tau and α -syn. The mechanisms of action likely vary depending on the individual antibody used and include promoting microglial clearance [81,

83], inhibiting neuronal uptake [86], and preventing disease-associated truncation in the extracellular space [87]. Several studies have reported the efficacy of immunotherapy in animal studies: active immunotherapy [88] and passive immunotherapy [89, 90] in tau transgenic and AD brain extract-injected mouse models, and active immunotherapy [91] and passive immunotherapy [86, 87, 92] in α -syn transgenic and synthetic α -syn fibril-injected mouse models. Based on the positive results of these studies, several clinical trials are currently ongoing (clinical trials are reviewed elsewhere [93, 94]). However, conformational differences in tau and α -syn aggregates among diseases are only beginning to be examined in animal studies. Validating the efficacy of immune-therapies towards inhibiting pathology formation induced by disease-specific tau and α -syn strains should increase their probability of success in clinical trials.

Aside from extracellular pathological tau and α -syn, the mechanisms involved in their release and uptake also represent potential therapeutic targets. For instance, heparinoids block HSPG-mediated uptake of tau aggregates in cultured cells and mice [65, 95]. Sertraline, an antidepressant, has the effect against dynamin, inhibiting transmission of pathological α -syn in a co-culture system [96]. LAG3 was reported to mediate uptake of α -syn fibrils, and an antibody against it inhibited neuronal uptake of α -syn fibrils and subsequent formation of α -syn pathology in mice injected with α -syn fibrils [66]. Modulation of neuronal activity is another potential therapeutic approach given that a number of drugs (e.g., antiepileptics) modify neuronal excitability or neurotransmission and can be repurposed. Reduction of expression level of tau and α -syn is the other therapeutic strategy to prevent fibrilization after uptake and before subsequent dissemination step. Several studies demonstrated that gene silencing approach is effective in reduction of tau and α -syn pathology formation in disease models [97–99].

Concluding Remarks

Emerging evidence supports the concept that cell-to-cell transmission and disease-selective strains underlie disease progression and heterogeneity in tauopathies and synucleinopathies. Our current understanding of the pathological mechanisms of distinct tauopathies and synucleinopathies are summarized and proposed as a working hypothesis in Figure 4. Spread of tau and α -syn pathology (i.e. spatiotemporal distribution, morphology, and affected cell types) in the nervous system is defined by several factors. These factors should differently influence spread of pathology among strains, thereby causing distinct disease entities. Therefore, it may be necessary to use disease-specific aggregates in experiments in order to identify therapeutic targets which may be unique among these diseases. However, considering limited availability of autopsied brains, it would be indispensable to develop new methodology which makes it possible to provide enough disease-specific aggregates to promote each disease research. The origin of distinct tau and α -syn aggregates in humans still remains largely unknown and one of the major questions in this field. Problems to be urgently solved are summarized under Outstanding Questions.

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Glossary

A53T α -syn

An α -syn missense mutation which causes early-onset familial PD

Exosomal release

Exosomes are extracellular membrane vesicles between 40 and 100 nm in diameter, transferring cytosolic proteins, lipids, and RNAs between cells. When late endosomes containing the intraluminal vesicles (ILVs) fuse with the plasma membrane, ILVs are released into the extracellular space as exosomes

Partial protease digestion

A biochemical technique to examine protein structures by incubating the protein with some proteases, which cut the protein at the recognition sites of exposed regions. Distinct digested patterns seen by SDS-PAGE presumably reflect different exposed regions, or conformational differences of the protein

Macropinocytosis

A form of endocytosis which engulfs external fluid by protruding the plasma membrane, forming large (>200 nm in diameter) organelles called macropinosomes

Protein misfolding cyclic amplification

A biochemical technique to detect minute amounts of protein aggregates in biological samples by incubating them with monomers of the protein. The kinetics of seeded fibrilization of monomers are usually monitored by fluorescent signal of Thioflavin T

Prion

Prion protein (PrP) is causative of scrapie in sheep, bovine spongiform encephalopathy in cattle, and Creutzfeldt–Jakob disease in humans. An abnormal β -sheet-rich conformer of PrP (PrP^{Sc}) functions as a template which triggers conformational conversion of normal PrP (PrP^C) into PrP^{Sc}. In addition to this self-propagating cycle, PrP^{Sc} can be transmitted from affected to healthy, unaffected cells, extending the disease process in the brain. One of the differences among prion, tau, and α -syn is that prion is infectious through ingestion and iatrogenesis, while tau and α -syn are not

P301S tau

A tau missense mutation which causes early-onset familial FTD

P301L tau

A tau missense mutation which causes early-onset familial FTD

Receptor-mediated endocytosis

A form of endocytosis in which a variety of transmembrane receptors and their ligands are packaged into clathrin-coated pits which evolve into vesicles (~100 nm in diameter) in a dynamin-mediated manner

Seeding potency

The potency of inducing specific protein pathology, usually evaluated by measuring the amount of pathology in cultured cells or mouse brains treated with pathological protein aggregates

Strains

This concept was first described in prion diseases. Prion strains retain their identity even after propagation in an inoculated animal and show strain-specific neuropathology and incubation time between initial infection and the development of symptoms. Current evidence suggests that these differences mainly come from conformational differences among prion strains.

Templated misfolding

The process in which ordered assemblies of a protein serve as templates to recruit the same protein and faithfully replicate the original conformation

References

1. Brettschneider J et al. (2015) Spreading of pathology in neurodegenerative diseases: a focus on human studies. *Nat Rev Neurosci* 16 (2), 109–20. [PubMed: 25588378]
2. Hyman BT et al. (2012) National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement* 8 (1), 1–13. [PubMed: 22265587]
3. Braak H et al. (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol* 112 (4), 389–404. [PubMed: 16906426]
4. Thal DR et al. (2002) Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 58 (12), 1791–800. [PubMed: 12084879]
5. Uchihara T et al. (2003) Pick body disease and Pick syndrome. *Neuropathology* 23 (4), 318–26. [PubMed: 14719549]
6. Komori T (1999) Tau-positive glial inclusions in progressive supranuclear palsy, corticobasal degeneration and Pick's disease. *Brain Pathol* 9 (4), 663–79. [PubMed: 10517506]
7. Dickson DW (1999) Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol* 246 Suppl 2, Ii6–15. [PubMed: 10525997]
8. Lashley T et al. (2015) Review: an update on clinical, genetic and pathological aspects of frontotemporal lobar degenerations. *Neuropathol Appl Neurobiol* 41 (7), 858–81. [PubMed: 26041104]
9. McKee AC et al. (2016) The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol* 131 (1), 75–86. [PubMed: 26667418]
10. Kovacs GG et al. (2017) Evaluating the Patterns of Aging-Related Tau Astroglipathy Unravels Novel Insights Into Brain Aging and Neurodegenerative Diseases. *J Neuropathol Exp Neurol* 76 (4), 270–288. [PubMed: 28340083]
11. Dickson DW et al. (2009) Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. *The Lancet Neurology* 8 (12), 1150–1157. [PubMed: 19909913]
12. Braak H et al. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24 (2), 197–211. [PubMed: 12498954]
13. Irwin DJ et al. (2012) Neuropathologic substrates of Parkinson disease dementia. *Ann Neurol* 72 (4), 587–98. [PubMed: 23037886]
14. Lippa CF et al. (2007) DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology* 68 (11), 812–9. [PubMed: 17353469]

15. Jellinger KA and Korfczyn AD (2018) Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? *BMC Med* 16 (1), 34. [PubMed: 29510692]
16. Braak H et al. (2007) Development of alpha-synuclein immunoreactive astrocytes in the forebrain parallels stages of intraneuronal pathology in sporadic Parkinson's disease. *Acta Neuropathol* 114 (3), 231–41. [PubMed: 17576580]
17. Krismer F and Wenning GK (2017) Multiple system atrophy: insights into a rare and debilitating movement disorder. *Nat Rev Neurol* 13 (4), 232–243. [PubMed: 28303913]
18. Trojanowski JQ and Revesz T (2007) Proposed neuropathological criteria for the postmortem diagnosis of multiple system atrophy. *Neuropathol Appl Neurobiol* 33 (6), 615–20. [PubMed: 17990994]
19. Braak H and Del Tredici K (2011) The pathological process underlying Alzheimer's disease in individuals under thirty. *Acta Neuropathol* 121 (2), 171–81. [PubMed: 21170538]
20. Braak H and Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 82 (4), 239–59. [PubMed: 1759558]
21. Braak H et al. (2006) Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett* 396 (1), 67–72. [PubMed: 16330147]
22. Li JY et al. (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med* 14 (5), 501–3. [PubMed: 18391963]
23. Kordower JH et al. (2008) Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nat Med* 14 (5), 504–6. [PubMed: 18391962]
24. Svensson E et al. (2015) Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 78 (4), 522–9. [PubMed: 26031848]
25. Killinger BA et al. (2018) The vermiform appendix impacts the risk of developing Parkinson's disease. *Sci Transl Med* 10 (465).
26. Lu HT et al. (2019) Lack of association between appendectomy and Parkinson's disease: a systematic review and meta-analysis. *Aging Clin Exp Res*.
27. Liu B et al. (2017) Vagotomy and Parkinson disease: A Swedish register-based matched-cohort study. *Neurology* 88 (21), 1996–2002. [PubMed: 28446653]
28. Frost B et al. (2009) Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem* 284 (19), 12845–52. [PubMed: 19282288]
29. Luk KC et al. (2009) Exogenous alpha-synuclein fibrils seed the formation of Lewy body-like intracellular inclusions in cultured cells. *Proc Natl Acad Sci U S A* 106 (47), 20051–6. [PubMed: 19892735]
30. Volpicelli-Daley LA et al. (2011) Exogenous alpha-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* 72 (1), 57–71. [PubMed: 21982369]
31. Desplats P et al. (2009) Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci U S A* 106 (31), 13010–5. [PubMed: 19651612]
32. Clavaguera F et al. (2009) Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol* 11 (7), 909–13. [PubMed: 19503072]
33. de Calignon A et al. (2012) Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron* 73 (4), 685–97. [PubMed: 22365544]
34. Liu L et al. (2012) Trans-synaptic spread of tau pathology in vivo. *PLoS One* 7 (2), e31302. [PubMed: 22312444]
35. Luk KC et al. (2012) Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science* 338 (6109), 949–53. [PubMed: 23161999]
36. Luk KC et al. (2012) Intracerebral inoculation of pathological alpha-synuclein initiates a rapidly progressive neurodegenerative alpha-synucleinopathy in mice. *J Exp Med* 209 (5), 975–86. [PubMed: 22508839]
37. Masuda-Suzukake M et al. (2013) Prion-like spreading of pathological alpha-synuclein in brain. *Brain* 136 (Pt 4), 1128–38. [PubMed: 23466394]

38. Clavaguera F et al. (2013) Brain homogenates from human tauopathies induce tau inclusions in mouse brain. *Proc Natl Acad Sci U S A* 110 (23), 9535–40. [PubMed: 23690619]
39. Guo JL et al. (2016) Unique pathological tau conformers from Alzheimer's brains transmit tau pathology in nontransgenic mice. *J Exp Med* 213 (12), 2635–2654. [PubMed: 27810929]
40. Narasimhan S et al. (2017) Pathological Tau Strains from Human Brains Recapitulate the Diversity of Tauopathies in Nontransgenic Mouse Brain. *J Neurosci* 37 (47), 11406–11423. [PubMed: 29054878]
41. He Z et al. (2020) Transmission of tauopathy strains is independent of their isoform composition. *Nat Commun* 11 (1), 7. [PubMed: 31911587]
42. Guo JL et al. (2013) Distinct alpha-synuclein strains differentially promote tau inclusions in neurons. *Cell* 154 (1), 103–17. [PubMed: 23827677]
43. Peelaerts W et al. (2015) alpha-Synuclein strains cause distinct synucleinopathies after local and systemic administration. *Nature* 522 (7556), 340–4. [PubMed: 26061766]
44. Prusiner SB et al. (2015) Evidence for alpha-synuclein prions causing multiple system atrophy in humans with parkinsonism. *Proc Natl Acad Sci U S A* 112 (38), E5308–17. [PubMed: 26324905]
45. Peng C et al. (2018) Cellular milieu imparts distinct pathological alpha-synuclein strains in alpha-synucleinopathies. *Nature* 557 (7706), 558–563. [PubMed: 29743672]
46. Uemura N et al. (2019) Slow Progressive Accumulation of Oligodendroglial Alpha-Synuclein (alpha-Syn) Pathology in Synthetic alpha-Syn Fibril-Induced Mouse Models of Synucleinopathy. *J Neuropathol Exp Neurol* 78 (10), 877–890. [PubMed: 31504665]
47. Lau A et al. (2020) alpha-Synuclein strains target distinct brain regions and cell types. *Nat Neurosci* 23 (1), 21–31. [PubMed: 31792467]
48. Taniguchi-Watanabe S et al. (2016) Biochemical classification of tauopathies by immunoblot, protein sequence and mass spectrometric analyses of sarkosyl-insoluble and trypsin-resistant tau. *Acta Neuropathol* 131 (2), 267–280. [PubMed: 26538150]
49. Fitzpatrick AWP et al. (2017) Cryo-EM structures of tau filaments from Alzheimer's disease. *Nature* 547 (7662), 185–190. [PubMed: 28678775]
50. Falcon B et al. (2019) Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. *Nature* 568 (7752), 420–423. [PubMed: 30894745]
51. Falcon B et al. (2018) Structures of filaments from Pick's disease reveal a novel tau protein fold. *Nature* 561 (7721), 137–140. [PubMed: 30158706]
52. Arakhamia T et al. (2020) Posttranslational Modifications Mediate the Structural Diversity of Tauopathy Strains. *Cell* 180 (4), 633–644 e12. [PubMed: 32032505]
53. Zhang W et al. (2020) Novel tau filament fold in corticobasal degeneration. *Nature*. doi: 10.1038/s41586-020-2043-0.
54. Shahnawaz M et al. (2020) Discriminating alpha-synuclein strains in Parkinson's disease and multiple system atrophy. *Nature* 578 (7794), 273–277. [PubMed: 32025029]
55. Marklund N et al. (2009) Monitoring of brain interstitial total tau and beta amyloid proteins by microdialysis in patients with traumatic brain injury. *J Neurosurg* 110 (6), 1227–37. [PubMed: 19216653]
56. Yamada K et al. (2011) In vivo microdialysis reveals age-dependent decrease of brain interstitial fluid tau levels in P301S human tau transgenic mice. *J Neurosci* 31 (37), 13110–7. [PubMed: 21917794]
57. Emmanouilidou E et al. (2011) Assessment of alpha-synuclein secretion in mouse and human brain parenchyma. *PLoS One* 6 (7), e22225. [PubMed: 21779395]
58. Saman S et al. (2012) Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease. *J Biol Chem* 287 (6), 3842–9. [PubMed: 22057275]
59. Wang Y et al. (2017) The release and trans-synaptic transmission of Tau via exosomes. *Mol Neurodegener* 12 (1), 5. [PubMed: 28086931]
60. Emmanouilidou E et al. (2010) Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. *J Neurosci* 30 (20), 6838–51. [PubMed: 20484626]

61. Asai H et al. (2015) Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nat Neurosci* 18 (11), 1584–93. [PubMed: 26436904]
62. Stuenkel A et al. (2016) Induction of alpha-synuclein aggregate formation by CSF exosomes from patients with Parkinson's disease and dementia with Lewy bodies. *Brain* 139 (Pt 2), 481–94. [PubMed: 26647156]
63. Katsinelos T et al. (2018) Unconventional Secretion Mediates the Trans-cellular Spreading of Tau. *Cell Rep* 23 (7), 2039–2055. [PubMed: 29768203]
64. Lee HJ et al. (2008) Assembly-dependent endocytosis and clearance of extracellular alpha-synuclein. *Int J Biochem Cell Biol* 40 (9), 1835–49. [PubMed: 18291704]
65. Holmes BB et al. (2013) Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. *Proc Natl Acad Sci U S A* 110 (33), E3138–47. [PubMed: 23898162]
66. Mao X et al. (2016) Pathological alpha-synuclein transmission initiated by binding lymphocyte-activation gene 3. *Science* 353 (6307).
67. Gibbons GS et al. (2017) GFP-Mutant Human Tau Transgenic Mice Develop Tauopathy Following CNS Injections of Alzheimer's Brain-Derived Pathological Tau or Synthetic Mutant Human Tau Fibrils. *J Neurosci* 37 (47), 11485–11494. [PubMed: 28986461]
68. Karpowicz RJ Jr. et al. (2017) Selective imaging of internalized proteopathic alpha-synuclein seeds in primary neurons reveals mechanistic insight into transmission of synucleinopathies. *J Biol Chem* 292 (32), 13482–13497. [PubMed: 28611062]
69. Flavin WP et al. (2017) Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathol* 134 (4), 629–653. [PubMed: 28527044]
70. Polanco JC et al. (2018) Exosomes taken up by neurons hijack the endosomal pathway to spread to interconnected neurons. *Acta Neuropathol Commun* 6 (1), 10. [PubMed: 29448966]
71. Tardivel M et al. (2016) Tunneling nanotube (TNT)-mediated neuron-to neuron transfer of pathological Tau protein assemblies. *Acta Neuropathol Commun* 4 (1), 117. [PubMed: 27809932]
72. Abounit S et al. (2016) Tunneling nanotubes spread fibrillar alpha-synuclein by intercellular trafficking of lysosomes. *Embo j* 35 (19), 2120–2138. [PubMed: 27550960]
73. Pooler AM et al. (2013) Physiological release of endogenous tau is stimulated by neuronal activity. *EMBO Rep* 14 (4), 389–94. [PubMed: 23412472]
74. Yamada K et al. (2014) Neuronal activity regulates extracellular tau in vivo. *J Exp Med* 211 (3), 387–93. [PubMed: 24534188]
75. Wu JW et al. (2016) Neuronal activity enhances tau propagation and tau pathology in vivo. *Nat Neurosci* 19 (8), 1085–92. [PubMed: 27322420]
76. Busche MA et al. (2008) Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science* 321 (5896), 1686–9. [PubMed: 18802001]
77. Holth JK et al. (2019) The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* 363 (6429), 880–884. [PubMed: 30679382]
78. Yamada K and Iwatsubo T (2018) Extracellular alpha-synuclein levels are regulated by neuronal activity. *Mol Neurodegener* 13 (1), 9. [PubMed: 29467003]
79. Martini-Stoica H et al. (2018) TFEB enhances astroglial uptake of extracellular tau species and reduces tau spreading. *J Exp Med* 215 (9), 2355–2377. [PubMed: 30108137]
80. Loria F et al. (2017) alpha-Synuclein transfer between neurons and astrocytes indicates that astrocytes play a role in degradation rather than in spreading. *Acta Neuropathol* 134 (5), 789–808. [PubMed: 28725967]
81. Funk KE et al. (2015) Distinct Therapeutic Mechanisms of Tau Antibodies: Promoting Microglial Clearance Versus Blocking Neuronal Uptake. *J Biol Chem* 290 (35), 21652–62. [PubMed: 26126828]
82. Bolos M et al. (2016) Direct Evidence of Internalization of Tau by Microglia In Vitro and In Vivo. *J Alzheimers Dis* 50 (1), 77–87. [PubMed: 26638867]
83. Lee SH et al. (2016) Antibody-Mediated Targeting of Tau In Vivo Does Not Require Effector Function and Microglial Engagement. *Cell Rep* 16 (6), 1690–1700. [PubMed: 27475227]

84. Venezia S et al. (2017) Toll-like receptor 4 stimulation with monophosphoryl lipid A ameliorates motor deficits and nigral neurodegeneration triggered by extraneuronal alpha-synucleinopathy. *Mol Neurodegener* 12 (1), 52. [PubMed: 28676095]
85. Narasimhan S et al. (2020) Human tau pathology transmits glial tau aggregates in the absence of neuronal tau. *J Exp Med* 217 (2).
86. Tran HT et al. (2014) Alpha-synuclein immunotherapy blocks uptake and templated propagation of misfolded alpha-synuclein and neurodegeneration. *Cell Rep* 7 (6), 2054–65. [PubMed: 24931606]
87. Games D et al. (2014) Reducing C-terminal-truncated alpha-synuclein by immunotherapy attenuates neurodegeneration and propagation in Parkinson's disease-like models. *J Neurosci* 34 (28), 9441–54. [PubMed: 25009275]
88. Boutajangout A et al. (2010) Immunotherapy targeting pathological tau prevents cognitive decline in a new tangle mouse model. *J Neurosci* 30 (49), 16559–66. [PubMed: 21147995]
89. Yanamandra K et al. (2013) Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo. *Neuron* 80 (2), 402–414. [PubMed: 24075978]
90. Dai CL et al. (2018) Tau passive immunization blocks seeding and spread of Alzheimer hyperphosphorylated Tau-induced pathology in 3 x Tg-AD mice. *Alzheimers Res Ther* 10 (1), 13. [PubMed: 29386065]
91. Mandler M et al. (2014) Next-generation active immunization approach for synucleinopathies: implications for Parkinson's disease clinical trials. *Acta Neuropathol* 127 (6), 861–79. [PubMed: 24525765]
92. Henderson MX et al. (2019) Characterization of novel conformation-selective alpha-synuclein antibodies as potential immunotherapeutic agents for Parkinson's disease. *Neurobiol Dis* 136, 104712. [PubMed: 31837422]
93. Cummings J et al. (2019) Anti-Tau Trials for Alzheimer's Disease: A Report from the EU/US/CTAD Task Force. *J Prev Alzheimers Dis* 6 (3), 157–163. [PubMed: 31062825]
94. Zella SMA et al. (2019) Emerging Immunotherapies for Parkinson Disease. *Neurol Ther* 8 (1), 29–44. [PubMed: 30539376]
95. Stopschinski BE et al. (2020) A synthetic heparinoid blocks tau aggregate cell uptake and amplification. *J Biol Chem*.
96. Konno M et al. (2012) Suppression of dynamin GTPase decreases alpha-synuclein uptake by neuronal and oligodendroglial cells: a potent therapeutic target for synucleinopathy. *Mol Neurodegener* 7, 38. [PubMed: 22892036]
97. DeVos SL et al. (2017) Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. *Sci Transl Med* 9 (374).
98. Luna E et al. (2018) Differential alpha-synuclein expression contributes to selective vulnerability of hippocampal neuron subpopulations to fibril-induced toxicity. *Acta Neuropathol* 135 (6), 855–875. [PubMed: 29502200]
99. Uehara T et al. (2019) Amido-bridged nucleic acid (AmNA)-modified antisense oligonucleotides targeting alpha-synuclein as a novel therapy for Parkinson's disease. *Sci Rep* 9 (1), 7567. [PubMed: 31110191]
100. Llorens-Martin M et al. (2012) Tau isoform with three microtubule binding domains is a marker of new axons generated from the subgranular zone in the hippocampal dentate gyrus: implications for Alzheimer's disease. *J Alzheimers Dis* 29 (4), 921–30. [PubMed: 22337826]
101. Zhang Y et al. (2014) An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci* 34 (36), 11929–47. [PubMed: 25186741]
102. Qiang L et al. (2018) Tau Does Not Stabilize Axonal Microtubules but Rather Enables Them to Have Long Labile Domains. *Curr Biol* 28 (13), 2181–2189. e4. [PubMed: 30008334]
103. Monroy BY et al. (2018) Competition between microtubule-associated proteins directs motor transport. *Nat Commun* 9 (1), 1487. [PubMed: 29662074]
104. Burre J et al. (2014) alpha-Synuclein assembles into higher-order multimers upon membrane binding to promote SNARE complex formation. *Proc Natl Acad Sci U S A* 111 (40), E4274–83. [PubMed: 25246573]
105. Bartels T et al. (2011) alpha-Synuclein occurs physiologically as a helically folded tetramer that resists aggregation. *Nature* 477 (7362), 107–10. [PubMed: 21841800]

106. Kaji S et al. (2018) Pathological Endogenous alpha-Synuclein Accumulation in Oligodendrocyte Precursor Cells Potentially Induces Inclusions in Multiple System Atrophy. *Stem Cell Reports* 10 (2), 356–365. [PubMed: 29337114]
107. DeWitt DC and Rhoades E (2013) alpha-Synuclein can inhibit SNARE-mediated vesicle fusion through direct interactions with lipid bilayers. *Biochemistry* 52 (14), 2385–7. [PubMed: 23528131]
108. Abeliovich A et al. (2000) Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron* 25 (1), 239–52. [PubMed: 10707987]
109. Sun J et al. (2019) Functional cooperation of alpha-synuclein and VAMP2 in synaptic vesicle recycling. *Proc Natl Acad Sci U S A* 116 (23), 11113–11115. [PubMed: 31110017]
110. Mukrasch MD et al. (2009) Structural polymorphism of 441-residue tau at single residue resolution. *PLoS Biol* 7 (2), e34. [PubMed: 19226187]
111. Wille H et al. (1992) Alzheimer-like paired helical filaments and antiparallel dimers formed from microtubule-associated protein tau in vitro. *J Cell Biol* 118 (3), 573–84. [PubMed: 1639844]
112. Conway KA et al. (1998) Accelerated in vitro fibril formation by a mutant alpha-synuclein linked to early-onset Parkinson disease. *Nat Med* 4 (11), 1318–20. [PubMed: 9809558]
113. Dettmer U et al. (2015) Parkinson-causing alpha-synuclein missense mutations shift native tetramers to monomers as a mechanism for disease initiation. *Nat Commun* 6, 7314. [PubMed: 26076669]
114. Nuber S et al. (2018) Abrogating Native alpha-Synuclein Tetramers in Mice Causes a L-DOPA-Responsive Motor Syndrome Closely Resembling Parkinson's Disease. *Neuron* 100 (1), 75–90. e5. [PubMed: 30308173]
115. Morsch R et al. (1999) Neurons may live for decades with neurofibrillary tangles. *J Neuropathol Exp Neurol* 58 (2), 188–97. [PubMed: 10029101]
116. Yoshiyama Y et al. (2007) Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* 53 (3), 337–51. [PubMed: 17270732]
117. Cowan CM et al. (2010) Soluble hyper-phosphorylated tau causes microtubule breakdown and functionally compromises normal tau in vivo. *Acta Neuropathol* 120 (5), 593–604. [PubMed: 20617325]
118. Ittner LM et al. (2010) Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. *Cell* 142 (3), 387–97. [PubMed: 20655099]
119. Lasagna-Reeves CA et al. (2011) Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice. *Mol Neurodegener* 6, 39. [PubMed: 21645391]
120. Winner B et al. (2011) In vivo demonstration that alpha-synuclein oligomers are toxic. *Proc Natl Acad Sci U S A* 108 (10), 4194–9. [PubMed: 21325059]
121. Osterberg VR et al. (2015) Progressive aggregation of alpha-synuclein and selective degeneration of lewy inclusion-bearing neurons in a mouse model of parkinsonism. *Cell Rep* 10 (8), 1252–60. [PubMed: 25732816]
122. Wang Y and Mandelkow E (2016) Tau in physiology and pathology. *Nat Rev Neurosci* 17 (1), 5–21. [PubMed: 26631930]
123. Wong YC and Krainc D (2017) alpha-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. *Nat Med* 23 (2), 1–13.
124. Mirbaha H et al. (2018) Inert and seed-competent tau monomers suggest structural origins of aggregation. *Elife* 7.
125. Sharma AM et al. (2018) Tau monomer encodes strains. *Elife* 7.
126. Pieri L et al. (2016) Structural and functional properties of prefibrillar alpha-synuclein oligomers. *Sci Rep* 6, 24526. [PubMed: 27075649]
127. Evans LD et al. (2018) Extracellular Monomeric and Aggregated Tau Efficiently Enter Human Neurons through Overlapping but Distinct Pathways. *Cell Rep* 22 (13), 3612–3624. [PubMed: 29590627]
128. He Z et al. (2018) Amyloid-beta plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. *Nat Med* 24 (1), 29–38. [PubMed: 29200205]

129. Bassil F et al. (2020) Amyloid-Beta (Abeta) Plaques Promote Seeding and Spreading of Alpha-Synuclein and Tau in a Mouse Model of Lewy Body Disorders with Abeta Pathology. *Neuron* 105 (2), 260–275. e6. [PubMed: 31759806]
130. Zanier ER et al. (2018) Induction of a transmissible tau pathology by traumatic brain injury. *Brain* 141 (9), 2685–2699. [PubMed: 30084913]
131. Rey NL et al. (2016) Widespread transneuronal propagation of alpha-synucleinopathy triggered in olfactory bulb mimics prodromal Parkinson's disease. *J Exp Med* 213 (9), 1759–78. [PubMed: 27503075]
132. Rey NL et al. (2018) Spread of aggregates after olfactory bulb injection of alpha-synuclein fibrils is associated with early neuronal loss and is reduced long term. *Acta Neuropathol* 135 (1), 65–83. [PubMed: 29209768]
133. Manfredsson FP et al. (2018) Induction of alpha-synuclein pathology in the enteric nervous system of the rat and non-human primate results in gastrointestinal dysmotility and transient CNS pathology. *Neurobiol Dis*.
134. Uemura N et al. (2018) Inoculation of alpha-synuclein preformed fibrils into the mouse gastrointestinal tract induces Lewy body-like aggregates in the brainstem via the vagus nerve. *Mol Neurodegener* 13 (1), 21. [PubMed: 29751824]
135. Kim S et al. (2019) Transneuronal Propagation of Pathologic alpha-Synuclein from the Gut to the Brain Models Parkinson's Disease. *Neuron*.
136. Van Den Berge N et al. (2019) Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. *Acta Neuropathol*.
137. Uemura N et al. (2020) Limited spread of pathology within the brainstem of alpha-synuclein BAC transgenic mice inoculated with preformed fibrils into the gastrointestinal tract. *Neurosci Lett* 716, 134651. [PubMed: 31783082]
138. Braak H and Del Tredici K (2016) Potential Pathways of Abnormal Tau and alpha-Synuclein Dissemination in Sporadic Alzheimer's and Parkinson's Diseases. *Cold Spring Harb Perspect Biol* 8 (11).
139. Ahmed Z et al. (2014) A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. *Acta Neuropathol* 127 (5), 667–83. [PubMed: 24531916]
140. Franzmeier N et al. (2020) Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat Commun* 11 (1), 347. [PubMed: 31953405]
141. Mason DM et al. (2016) Transmission of alpha-synucleinopathy from olfactory structures deep into the temporal lobe. *Mol Neurodegener* 11 (1), 49. [PubMed: 27363576]
142. Henderson MX et al. (2019) Spread of alpha-synuclein pathology through the brain connectome is modulated by selective vulnerability and predicted by network analysis. *Nat Neurosci* 22 (8), 1248–1257. [PubMed: 31346295]
143. Taguchi K et al. (2014) Differential expression of alpha-synuclein in hippocampal neurons. *PLoS One* 9 (2), e89327. [PubMed: 24586691]
144. Mezas C et al. (2020) Neural connectivity predicts spreading of alpha-synuclein pathology in fibril-injected mouse models: Involvement of retrograde and anterograde axonal propagation. *Neurobiol Dis* 134, 104623. [PubMed: 31628991]

Outstanding Questions

- What molecular entities (monomers, oligomers, and fibrils) are most responsible for cell-to-cell transmission of tau and α -syn pathology *in vivo*?
- What release and uptake mechanisms are most strongly associated with transmission of tau and α -syn pathology *in vivo*?
- What molecular mechanisms link neuronal activity to release of pathological tau and α -syn?
- To which direction (anterograde, retrograde, or both) do pathological tau and α -syn spread at synapses? If they spread to both directions, which direction is more associated with spread of pathology?
- Are the release and uptake mechanisms different between anterograde and retrograde transmission?
- What is the origin of distinct tau and α -syn aggregates *in vivo*?
- What are the roles of glial pathology in disease progression of tauopathies and synucleinopathies?
- Can tau and α -syn aggregates extracted from diseased brains be amplified? If it becomes possible, it would promote research on disease/conformation-specific pathological mechanisms.

Clinician's Corner

- Patients with tauopathies (i.e. Alzheimer's disease, etc.) and synucleinopathies (i.e. Parkinson's disease, etc.) show progressively declining neurological function, which is associated with spread of tau and α -syn pathology in functionally related brain areas. Recent studies have demonstrated that cell-to-cell transmission of pathological tau and α -syn plays a key role in this spread of pathology.
- Tauopathies and synucleinopathies each include several distinct disease entities. Recent accumulating evidence suggests that these distinct diseases are caused by conformational differences of tau and α -syn aggregates referred to as strains in the diseased brains. Indeed, injection of disease-specific tau and α -syn aggregates into the animal brains recapitulates disease-specific pathology.
- The concept of cell-to-cell transmission has provided new therapeutic targets for these incurable diseases. The process of cell-to-cell transmission is comprised of (1) release of pathological proteins by donor cells into the extracellular space and (2) uptake of the extracellular pathological proteins by acceptor cells. Clinical immunotherapy trials which target extracellular tau and α -syn to inhibit the transmission are currently ongoing. The molecular mechanisms of release and uptake are also promising therapeutic targets, and several therapeutic approaches targeting them have shown efficacy in animal models.
- Studies about disease-specific tau and α -syn aggregates have just begun very recently and would expand this research field in the future. This emerging concept would be a new platform to develop novel diagnostic approaches, to explore different pathological mechanisms among distinct diseases, and to develop more effective therapies for each disease.

Box 1.**Structure and physiological functions of tau and α -syn**

Tau is a microtubule-associated protein (MAP) encoded by the *MAPT* gene. Tau is composed of four major domains: the amino-terminal region, the proline-rich domain, the microtubule-binding domain, and the carboxy-terminal region (Figure 1a). The microtubule-binding domain mediates the interaction with microtubules and forms core in tau aggregates. The majority of mutations that causes familial tauopathies clusters around this domain. Tau is expressed as six isoforms in the normal human brain resulting from alternative splicing. Each isoform is named after the numbers of inserts in the amino-terminal region (0N, 1N, 2N) and tandem repeat sequences in the microtubule-binding domain (3R, 4R). The expression of tau isoforms is developmentally regulated. The fetal brain expresses exclusively the 0N3R isoform, while the adult brain expresses all six isoforms with a similar expression level of 3R and 4R isoforms. In mice, new-born neurons express 3R isoforms, while the adult brain expresses 4R isoforms [100]. Tau is highly expressed in neurons, where tau is mainly localized in axons with a small amount in dendrites and nuclei (Figure 1b), but it is also expressed at low levels in glial cells [101]. As tau was first found as a MAP, its well-studied functions are regulating microtubule dynamics and axonal transport. Tau is enriched on the labile domain of the microtubule to promote microtubule assembly [102] and regulates kinesin and dynein motility competing with some other MAPs [103].

α -syn, encoded by the *SNCA* gene, is composed of three major regions: amphipathic α -helix region, hydrophobic non-amyloid-component (NAC) domain, and acidic region (Figure 1c). α -syn monomer exists in equilibrium between cytosolic, unfolded form and membrane-bound α -helical form in the cytoplasm [104]. α -syn has also been reported to exist as helically folded tetramers under physiological conditions [105]. The NAC domain is hydrophobic and necessary for α -syn aggregation. Missense mutations causative of familial PD concentrate in the amino-terminal region. α -syn is predominantly expressed in neurons, where α -syn distributes mainly in presynaptic terminals with a small amount in nuclei (Figure 1d), but it is also expressed at low levels in glial cells [106]. Several studies have documented its physiological function in inhibiting synaptic vesicle (SV) release and disruption of soluble SNARE complex-mediated lipid membrane fusion [107, 108]. A recent study also demonstrated that α -syn directly interacts with VAMP2 to promote physiological clustering of SV pools, restricting their egress to the presynaptic plasma membrane, thus attenuating SV recycling [109].

Box 2.**Tau and α -syn aggregation and neurotoxicity**

Tau and α -syn are natively unfolded proteins but form β -sheet-rich amyloid fibrils under disease conditions [104, 110]. Tau shows hardly any tendency to aggregate in physiological buffer conditions, but tau assembly is accelerated in the presence of polyanions such as heparin, RNA, and acidic peptides [111]. On the other hand, α -syn easily aggregates in physiological buffer conditions [112]. In the aggregation process, tau and α -syn first form soluble oligomers and subsequently insoluble fibrils (Figure II). It has been reported that physiological tetramers of α -syn are protective against α -syn aggregation, and PD-causing missense mutations unfold tetramers into monomers [113, 114]. What molecular entities of tau and α -syn aggregates cause neurotoxicity in the aggregation process still remains unclear. A line of evidence suggests that neuronal loss, synaptic dysfunction, or behavioral abnormalities precede formation of NFT or tau inclusions in humans and animal models [115–117]. Rather, tau hyperphosphorylation and oligomerization, and/or consequent loss of normal functions of tau cause neurotoxicity [117–119]. On the other hand, both α -syn oligomers and fibrils have been reported to cause neuronal loss [120, 121]. Detailed mechanisms of cytotoxicity were extensively reviewed elsewhere [122, 123]. Minimal units of pathological tau and α -syn which serve as templates for fibrilization of monomers also remain elusive. A recent study demonstrated that even tau monomers generated from tau fibrils by sonication have unique conformations and seeding potency [124]. Tau monomers purified from brain extracts from patients with tauopathies also showed seeding potency and strain-specific bioactivity [124, 125]. On the other hand, large stable α -syn oligomers composed of more than ~15 α -syn monomers seed the aggregation of soluble α -syn, while low-molecular weight and unstable oligomers do not [126]. It may be important to identify molecular entities responsible for cell-to-cell transmission of tau and α -syn pathology *in vivo* because different molecular entities (monomers, oligomers, and fibrils) may transmit intercellularly by different mechanisms. Indeed, it has been shown that tau fibrils and monomers are differentially taken up by cultured cells [28, 127], and a cell surface receptor LAG3 specifically recognizes and internalizes α -syn fibrils over α -syn monomers [66].

Box 3.**Pathological mechanisms of disease progression from animal models**

Induction of tau and α -syn pathology and its subsequent spread by injecting synthetic fibrils or brain extracts into animals is used to investigate pathological mechanisms of disease progression in tauopathies and synucleinopathies. In AD, A β plaques are the other pathological hallmark than tau pathology, but the underlying mechanisms linking A β plaques to tau pathology have been enigmatic. Injection of brain extracts from AD subjects induced NFTs, but not NPs, in the brains of wild-type mice [39]. However, A β plaque-forming transgenic mouse models injected with AD brain extracts developed NPs surrounding A β plaques at early time points followed by abundant NFTs at later time points, more faithfully replicating tau pathology seen in AD [128]. These results suggest that A β plaques prime tau fibrilization around them and recapitulate tau pathology characteristic of AD [128]. Similarly, A β plaques exacerbate spread of α -syn pathology induced by injection of α -syn fibrils in the mouse brains, which presumably explains the high prevalence of A β pathology in patients with PDD and DLB [15, 129]. A CTE mouse model induced by a single brain trauma developed tau pathology in the brains, the amount of which was increased over time [130]. The transmissibility of tau aggregates in this model was demonstrated by injection of brain extracts from these mice into the non-treated mice, which subsequently developed tau pathology in the brains [130]. Taking advantage of injection methodology which can trigger pathology at certain brain regions or body parts, the routes of pathological progression have been investigated. Injection of α -syn fibrils in the olfactory bulb, one possible initiation site of Lewy pathology in PD, induced α -syn inclusions in the olfactory pathway and limbic system at early time points, later spreading even to the brainstem in mice [46, 131, 132]. Interestingly, injection of α -syn fibrils into the gastrointestinal tract, the other possible initiation site in PD, induced α -syn inclusions in the brains in several animal models, supporting the hypothesis of gut-to-brain spread of Lewy pathology [133–137].

Box 4.**Spreading direction of tau and α -syn pathology**

There are multiple possible pathways for the transmission of pathological tau and α -syn between neurons: proximity-dependent transmission (Figure IIIa) and anterograde/retrograde transsynaptic transmission (Figure IIIb,c). It may be important to determine which pathway is most strongly involved in the transmission processes since release and uptake mechanisms potentially differ among pathways. Autopsy studies and animal studies have demonstrated that tau and α -syn pathology seemingly spreads transsynaptically, but not in a proximity-dependent manner [37, 138, 139]. In line with this, a recent imaging study combining resting-state functional MRI with longitudinal tau-PET demonstrated similar rates of tau accumulation between functionally connected regions in patients with AD [140]. Transsynaptic transmission includes anterograde and retrograde transmission, but it is still debated which contributes to pathological progression of tau and α -syn. The pathological staging systems in AD and PD in combination with neural connections suggest that NFT pathology may progress anterogradely, while Lewy pathology may progress in both directions [138]. Transgenic expression of tau restricted to layer II of the mouse entorhinal cortex induces tau pathology in the granular layer of dentate gyrus earlier than other brain regions, suggesting anterograde transmission [33]. However, it is likely that injection of AD brain extracts or α -syn fibrils into the brains of WT mice initially induce chiefly retrograde transmission of tau or α -syn pathology with some predilution [39, 141]. Recently, two studies which mathematically analyzed distribution of α -syn pathology in mouse models injected with α -syn fibrils have been reported. One study demonstrated that neuronal connectivity and regional α -syn expression level well define spatiotemporal distribution of α -syn pathology [142]. Indeed, it has been reported that glutamatergic neurons show higher levels of α -syn expression and form more abundant α -syn pathology when treated with α -syn fibrils compared with GABAergic neurons [98, 143]. This study also suggested that α -syn pathology spreads primarily in a retrograde manner after injection of α -syn fibrils [142]. The other study analyzed α -syn fibril-injected mice for longer period and suggested that spread of α -syn pathology initially follows neural connections retrogradely and later switches to preferential anterograde direction [144]. Consistent with this, α -syn bacterial artificial chromosome transgenic rats injected with α -syn fibrils into the duodenum wall exhibited retrograde transmission to the first-order regions and then bidirectional transmission to the second or higher-order regions [136]. These lines of evidence raises the possibility that the mechanisms of uptake of injected aggregates may differ from those of subsequent interneuronal transmission. This needs further investigation.

Highlight

- Tauopathies and synucleinopathies consist of clinically and pathologically heterogeneous entities. Pathological heterogeneity includes temporal distribution, morphology, and affected cell types.
- Consecutive cell-to-cell transmission of pathological tau and α -syn between anatomically connected brain regions underlies the stereotypical spread of tau and α -syn pathology.
- Distinct tau and α -syn aggregates called strains induce different neuropathology in animal brains. Spread of distinct strains in brains in part defines heterogeneity of tauopathies and synucleinopathies.
- Several release and uptake mechanisms of pathological tau and α -syn between cells have been proposed. Neuronal activity and glial cells are also involved in these transmission processes. These could provide therapeutic opportunities in tauopathies and synucleinopathies.

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Figure 1. Distinct pathology in tauopathies and synucleinopathies

Phosphorylated tau immunohistochemistry (PHF1) (a–e,g,h). Hematoxylin-eosin staining (f). Misfolded α -syn immunohistochemistry (Syn303) (i–l). (a,b) NFTs and NP in the hippocampus of an AD subject. (c) Pick bodies in the dentate gyrus of a PiD subject. (d) Tufted astrocyte in the frontal cortex of a PSP subject. (e) Globose tangles in the medulla oblongata of a PSP subject. (f) Ballooned neuron in the amygdala of a CBD subject. (g,h) Coiled bodies and astrocytic plaque in the angular cortex of a CBD subject. (i) LB in a pigmented neuron in the SNpc of a PD subject. (j) LBs in the cingulate cortex of a DLB subject. (k) GCIs in the cerebellum of a MSA subject. (l) NI in the medulla oblongata of a MSA subject. Scale bar 40 μ m.

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Figure 2. Molecular mechanisms of cell-to-cell transmission

Schematic representation of cell-to-cell transmission of pathological tau and α -syn. Molecular mechanisms related to transmission of pathology are summarized in the context of neuron-to-neuron transmission. (a) Exosomal release of pathological tau [58, 59] and α -syn [60]. (b) Direct translocation of pathological tau [63]. (c) Macropinocytosis of pathological tau and α -syn [65]. (d) Receptor-mediated endocytosis of pathological α -syn [64, 66]. (e) Transportation of pathological tau [67] and α -syn [68] into endolysosomes. (f) Release of pathological tau and α -syn into cytosol through ruptured lysosomes [69]. (g) Templated misfolding of endogenous monomeric tau or α -syn. (h) Some exosomes containing pathological tau are incorporated in endosomes and are transmitted to the interconnected neuron of the acceptor neuron [70]. (i) Enhanced neuronal activity promotes release of pathological tau though the molecular mechanisms remain unclear [75, 77]. (j) Phagocytic clearance of pathological tau [79] and α -syn [80] by astrocytes. (k) Phagocytic clearance of pathological tau [81–83] and α -syn [84] by microglia. (l) Microglia release exosomes containing pathological tau and promote transmission [61].

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Figure 3. Formation and transmission of glial pathology

Schematic representation of the formation and transmission of glial pathology. Arrows indicate the direction of transmission of tau or α -syn pathology. (a) Neuron-to-astrocyte transmission of tau pathology [40, 85]. (b) Axon-to-oligodendroglia transmission of α -syn pathology [46]. (c) Oligodendroglia-to-oligodendroglia transmission of tau and α -syn pathology [46, 85].

Figure 4. Working hypothesis to investigate the pathological mechanisms of distinct tauopathies and synucleinopathies

Several factors highlighted in green define spread of tau and α-syn pathology in brains.

These factors differently influence spread of pathology among distinct strains, thereby causing distinct disease entities. A few factors highlighted in blue could be the causes of distinct tau and α-syn strains, but the origin of strains remains largely unknown.

Figure I.
Structure and Intraneuronal Localization of Tau and α -Syn.

Figure II.
Aggregation and Molecular Entities of Tau and α -Syn.

Trends in Molecular Medicine

Figure III.
Spreading Direction of Tau and α -Syn Pathology.

Table 1.

Summary of pathology in tauopathies

Disease	Tau isoform	Gross pathology	Neuronal pathology	Astrocytic pathology	Oligodendroglial pathology
Alzheimer's disease	3R/4R	Atrophy in the medial temporal and parietal lobes	Neurofibrillary tangles, Neuritic plaques		
Pick's disease	3R	Atrophy in the frontal and temporal lobes	Pick bodies	Ramified astrocytes	Coiled bodies
Progressive supranuclear palsy	4R	Atrophy in the midbrain and depigmentation of the substantia nigra	Neurofibrillary tangles, Globose tangles	Tufted astrocytes	Coiled bodies
Corticobasal degeneration	4R	Asymmetric atrophy in the temporal and parietal lobes, depigmentation of the substantia nigra	Ballooned neurons, Globose tangles	Astrocytic plaques	Coiled bodies
Chronic traumatic encephalopathy	3R/4R		Neurofibrillary tangles	Thorn-shaped astrocytes	

Table 2.

Summary of pathology in synucleinopathies

Disease	Gross pathology	Neuronal pathology	Astrocytic pathology	Oligodendroglial pathology
Parkinson's disease, Dementia with Lewy bodies	depigmentation of the substantia nigra and locus coeruleus	Lewy bodies Lewy neurites	α -syn immunoreactive astrocytes	Coiled bodies
Multiple system atrophy	Atrophy in the striatum or cerebellum, depigmentation of the substantia nigra	Neuronal inclusions		Glial cytoplasmic inclusions