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The interaction of α-synuclein and Tau: A molecular conspiracy in neurodegeneration?

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Abstract

α-synuclein and Tau are proteins prone to pathological misfolding and aggregation that are normally found in the presynaptic and axonal compartments of neurons. Misfolding initiates a homo-oligomerization and aggregation cascade culminating in cerebral accumulation of aggregated α-synuclein and Tau in insoluble protein inclusions in multiple neurodegenerative diseases. Traditionally, α-synuclein-containing Lewy bodies have been associated with Parkinson's disease and Tau-containing neurofibrillary tangles with Alzheimer's disease and various frontotemporal dementia syndromes. However, there is significant overlap and co-occurrence of α-synuclein and Tau pathologies in a spectrum of neurodegenerative diseases. Importantly, α-synuclein and Tau can interact in cells, and their pathological conformations are capable of templating further misfolding and aggregation of each other. They also share a number of protein interactors indicating that network perturbations may contribute to chronic proteotoxic stress and neuronal dysfunction in synucleinopathies and tauopathies, some of which share similarities in both neuropathological and clinical manifestations. In this review, we focus on the protein interactions of these two pathologically important proteins and consider a network biology perspective towards neurodegenerative diseases.

1 Introduction

1.1 Aberrant protein-protein interactions in neurodegenerative diseases

Dynamic protein-protein interactions (PPIs) that constitute multi-protein complexes and networks are at the core of all cellular functions. Abnormalities in protein complexes and PPI networks are associated with various pathological disorders [1]. Misfolding and subsequent aggregation of normally soluble proteins into insoluble filamentous aggregates is a pathological hallmark shared by many neurodegenerative diseases [2]. Cerebral accumulation of aggregated forms of microtubule-associated protein Tau, in the form of neurofibrillary tangles (NFT), is a common feature of Alzheimer's disease (AD) and frontotemporal degeneration [3]. The accumulation of aggregated forms of α-Synuclein (aSyn) in Lewy bodies (LB) is a hallmark of Parkinson's disease (PD) and dementia with Lewy bodies (DLB) [4].

Despite the fact that Tau and aSyn are distinct proteins and have been extensively studied in different pathological contexts, the mechanisms underlying their pathological aggregation and the consequences thereof appear to be converged and overlapping [5]. For example, both aSyn and Tau aggregation exhibit an inducible nucleation-elongation mechanism [2, 6]. aSyn and Tau are cytosolic proteins predominantly expressed in neurons but are also commonly found in cerebrospinal fluid (CSF) of human patients, and the pathological forms of these proteins are transmissible between cells [7]. Tau and aSyn neuropathologies rarely exist in isolation and are often found to be accompanied with at least one other amyloidogenic protein such as β-amyloid (Aβ), TDP-43 and huntingtin. More than half of AD cases show LBs, and co-morbid AD pathologies, particularly NFTs, are commonly

found in the brains of PD, DLB and PD with dementia (PDD) patients [5, 8]. The associated aggregated proteins may have an impact on the clinical symptoms and disease progression, thus further affecting the neuropathological classification of the diseases. Tau is also a risk factor and mediator of parkinsonism, even in the absence of aSyn pathology [9]. Importantly, aSyn and Tau can synergistically promote the aggregation and fibrillization of each other [10].

Pathologies associated with aSyn and Tau misfolding and aggregation may involve both gain-of-toxic-function features as well as loss-of-normal function features. Both proteins are normally predominantly localized in the axonal compartment of neurons where Tau functions as a microtubule-stabilizing protein and aSyn as a regulator of presynaptic vesicular trafficking [11, 12]. Thus, loss-of-function effects are most likely to primarily target axonal and presynaptic functions of neurons. Interestingly, several shared PPIs suggest that aSyn and Tau are involved in partially overlapping PPI networks. As the shared PPI networks are likely linked to cellular functions that are primarily affected when pathological aggregation of aSyn and Tau occurs, understanding the network biology connecting aSyn and Tau can provide new insight into disease mechanisms and therapeutic options. In this review, we will discuss the interactions between aSyn and Tau and provide an interactome perspective towards cellular dysfunction in tauopathies and synucleinopathies.

1.2 Propagation of proteinopathies

Both aSyn and Tau are natively unfolded proteins in monomeric form. Upon self-interaction or interaction with other proteins or membranes, both proteins are known to adopt more stable secondary and tertiary structures. Aggregation of aSyn and Tau occurs via misfolding, homo-oligomerization, and adoption of stable β-sheet structures [13, 14]. Importantly, the pathological conformations of aSyn and Tau are capable of templating further misfolding and aggregation [15].

Pathological protein aggregation is a cascade of events, starting from a natively unfolded protein and culminating in the formation of insoluble protein aggregates and mature fibrils (Figure 1). The pathological protein conformers can further transfer from one cell to another and seed aggregation of healthy proteins, thus transmitting the disease from one cell to another. Emerging evidence on the spread of various disease-associated proteins in a "prion-like" manner *in vitro* and *in vivo* have implicated the existence of a common mechanism in the spread of pathology of neurodegenerative diseases [16]. The "prion-like propagation" paradigm holds that pathological conformers of amyloidogenic proteins, such as aSyn, Tau, Aβ, TDP-43, SOD1 and huntingtin, transmit between cells and spread pathology into distinct but connected brain regions with a mechanism similar to prion proteins. The exact mechanisms of cell-to-cell transfer and seeding of the disease-associated proteins remain poorly understood and generally involve four main stages: gain of seeding property, release from donor cells, uptake by recipient cells and templated misfolding of normal proteins in the recipient cells. Importantly, it should be considered that not only does the protein aggregation propagate from one cell to another but also the associated alterations in PPI networks of the affected proteins likely contribute to cellular dysfunction in the newly affected cells.

2 Protein-protein interactions of normal vs pathological α-synuclein and Tau

2.1 α-synuclein interactions in health and disease

2.1.1 α-synuclein aggregation

aSyn is a 140-amino acid protein encoded by the *SCNA* gene and forms the synuclein gene family together with the β- and γ-synuclein. Aggregated aSyn is the major component of Lewy Bodies in various neurodegenerative diseases (synucleinopathies)[17]. There has been much controversy on the structure of normal aSyn protein and it seems that aSyn may context-dependently adopt secondary and quaternary structures [18]. Under normal circumstances, aSyn may exist in an equilibrium between unfolded monomers and folded multimers composed of 2-4 aSyn units [19]. Destabilization of the tetrameric forms of aSyn may serve as a mechanism for disease initiation by decreasing the solubility and increasing the toxicity of aSyn, as was shown for PD-causing aSyn mutations E46K and A53T [20]. Pathological forms of aSyn occur as ring- or pore-shaped oligomers, β-sheet intermediates and larger insoluble fibers and aggregates [2]. Oligomerization of misfolded aSyn results in aggregation that eventually leads to formation of inclusions, such as LBs (Figure 1)[21]. aSyn seems to favour α-helical structure upon binding to phospholipid membranes [22]. Lipid membrane serves as a 2D scaffold which modulates the local concentration and aggregation of aSyn [23].

Many factors contributing to aSyn aggregation are directly linked to aSyn structure. Some genetic mutations and post-translational modifications, such as partial proteolytic cleavage, can alter aSyn structure to favour aggregation [2]. Other factors, such as phosphorylation, oxidative stress, fatty acids and distorted protein clearance mechanisms, can indirectly promote accumulation of aSyn aggregates. Proteins with chaperone activity towards aSyn, such as Hsp70 and several other heat-shock proteins, and some presynaptic proteins like Munc18-1 are important regulators of aSyn aggregation and toxicity [24, 25]. In addition, there are other aSyn-interacting proteins with enzymatic activities, such as peptidyl prolyl isomerases FKBP12 and FKBP52 and prolyl oligopeptidase PREP, that interact with and promote oligomerization and aggregation of aSyn [26-28].

The non-amyloid component fragment (NAC) of aSyn composes the 35-amino acid (61-95) central hydrophobic region of the protein, which plays a major role in aSyn oligomerization and aggregation [29]. This hydrophobic motif may get exposed during misfolding and initiate aggregation. Mutation or deletion of this region significantly reduces aSyn filament assembly [30].

The mutations that are associated with familial forms of PD are mostly found at the N-terminal helix of aSyn. A30P, E46K, H50Q, G51D and A53T mutations at the N-terminus have been associated with acceleration of aSyn fibrillization and increased aSyn toxicity [31]. These mutation-mediated effects were suggested to be a result of altered aSyn secondary structure (A30P, A53T), enhanced aSyn binding to phospholipids (E46K) and formation of aSyn fibrils that are more prone to activate proapoptotic pathways (G51D)[32-36].

C-terminal truncation of aSyn is a common post-translational modification, and the C-terminally truncated aSyn was found to be significantly enriched in Lewy bodies [37]. Tissue-specific expression of C-terminally truncated aSyn in nigral dopamine neurons was shown to markedly reduce dopamine levels in a transgenic mouse model, suggesting a failure to maintain aSyn-regulated dopamine homeostasis [38].

An early *in vitro* study demonstrated that the residues S87 and S129 of aSyn are constitutively phosphorylated [39]. However, it was later shown that aSyn phosphorylation is dynamic and that both phosphorylated forms of aSyn are significantly increased in Lewy bodies in both patient samples and

animal models [40, 41]. Phosphorylation of S87 was found to increase the conformational flexibility of aSyn, which leads to reduced binding affinity to lipid membranes and reduced potential to form fibrils [42]. In pathological conditions, aSyn forms phosphorylated at S129 are also often ubiquitinated. It appears that S129 phosphorylation plays a critical role in regulating cellular clearance of aSyn [43].

2.1.2 Altered α-synuclein interactome in pathological conditions

In pathological conditions, the aSyn interactome can be altered resulting in both loss and gain of functions. As part of an effort to restore proteostasis, misfolded aSyn displays increased interactions towards a variety of chaperone proteins, with several examples from the Hsp90, Hsp70, Hsp60 and Hsp40 families (reviewed in [44]). Not surprisingly, increased levels or activity of chaperones has therapeutic effects in preclinical models of synucleinopathies [44].

At the presynapse, aSyn is normally associated with synaptic vesicles and interacts with SNARE proteins synaptobrevin-2 and VAMP2, promoting SNARE complex assembly. Via its role in presynaptic vesicle formation and fusion, aSyn regulates the release of neurotransmitters [12]. aSyn can also regulate dopamine (DA) transmission pathways via other mechanisms. aSyn interacts with and inhibits tyrosine hydroxylase (TH), the rate-limiting enzyme in DA synthesis [45]. It may block TH phosphorylation directly via PPIs or activate protein phosphatase 2A to dephosphorylate TH [46, 47]. Synaptic deficits in aSyn overexpressing neurons and transgenic mice are thus likely related to altered synaptic functions of aSyn leading to a reduction in dopamine levels and catecholamine release as well as the presence of abnormal presynaptic vesicles [45, 48, 49].

Disease-associated aSyn mutations and altered post-translational modifications can alter aSyn PPIs. For example, the A53T mutation alters the secondary structure and conformational flexibility of the aSyn protein [50]. Consequently, aSyn A53T mutant protein shows enhanced interaction with neurofascin, an adhesion protein involved in maintenance of axonal integrity, and aSyn toxicity and the associated axonal degradation can be attenuated by neurofascin overexpression [51, 52]. Some disease-associated aSyn mutations, including the E46K, A30P and G51D, alter the interactions of aSyn with lipids and membranes [53]. NMR data suggest that binding to the phospholipid membrane results in exposure of the hydrophobic areas of aSyn A30P and G51D mutants, which likely affects both protein aggregation mechanisms and PPIs of the mutant proteins [54]. Also, nuclear localization and histone interaction of aSyn was reported to associate with cellular dysfunction and toxicity, with A30P and A53T mutations exhibiting increased nuclear targeting [55].

Aberrant phosphorylation of aSyn impairs multiple important aspects of aSyn function and is associated with LB deposition of aSyn [41]. S129 phosphorylation is an important regulator of those interactions of aSyn that are involved in membrane interaction and vesicle trafficking [43]. In pathological conditions, aSyn hyperphosphorylated at S129 is extensively ubiquitinated, and S129 phosphorylation appears to play a critical role in mediating proteasomal degradation of aSyn [56]. In addition, phosphorylation at S129 and Y125 were shown to result in reduced interactions with proteins involved in mitochondrial electron transport chain complex while having increased interactions with proteins involved in cytoskeletal organization, vesicular trafficking and serine phosphorylation [57]. Interestingly, aSyn has been suggested to modulate apoptotic response to oxidative stress via its interactions with the mitochondria [58].

Homo-oligomerization is a process centrally involved in development of aSyn pathology. aSyn monomers and oligomers were shown to have different PPI profiles in synaptosomes [59]. Interestingly, majority of the synaptosomal aSyn-interacting proteins had a binding preference to aSyn

oligomers. Many of these oligomer-interacting proteins are involved in cytoskeletal organization, such as actin, p25α, tubulin and mortalin, others are involved in calcium regulation, translation, vesicular trafficking, mitochondrial homeostasis and lysosomal degradation. Better understanding of which PPIs are specific for the pathologically misfolded aSyn oligomers in human brain should provide new insight into the PPI network perturbations occurring in synucleinopathies.

Changes in aSyn interacting proteins may also indirectly trigger aSyn misfolding and development of aSyn pathology. Mutations in *GBA1*, a gene that encodes glucocerebrosidase (GCase) enzyme with glucosylceramidase activity, lead to Gaucher disease, a lysosomal storage disorder [60]. It has been estimated that *GBA1* mutations confer a 20- to 30-fold increased risk for PD, and that at least 5-10% of PD patients carry a *GBA1* mutation [61]. Under physiological conditions aSyn interacts with GCase selectively at the low pH of the lysosomal environment but the interaction is significantly reduced with the GCase N370S mutation [62]. The relationship between aSyn and GCase is complex as decreased GCase activity increases the levels and aggregation of aSyn but also aberrant aSyn species have been reported to downregulate GCase activity further contributing to disease progression [63, 64].

Another interesting example of a disease-associated mutation in an aSyn-interacting protein is ATP13A2. Loss-of-function mutations in this endolysosomal transport ATPase result in an early-onset form of PD due to enhanced aSyn aggregation and increased exosomal secretion of aSyn that culminates in accelerated cell death and neurodegeneration [65, 66]. Altogether, functional studies of GBA1 and ATP13A2 mutations suggest that impaired lysosomal function and altered aSyn PPIs in this compartment can lead to pathological accumulation of aSyn.

2.2 Tau interactions in health and disease

2.2.1 Tau aggregation

Tau has been long known for its physiological role in regulating microtubule assembly and stability [11]. It is a protein of 440 amino acids at full length and belongs to the microtubule-binding protein (MAP) family. Tau is encoded by the *MAPT* gene on chromosome 17q21 and has six splicing isoforms [67]. Isoforms that have four instead of three microtubule-binding domains (MBD) appear to be more prone to aggregation. Tau protein is structurally divided into acidic region, proline-rich region, microtubule-binding repeat region and C-terminal region [68]. The four regions constitute two functional domains: the N-terminal projection domain (N-domain) and the microtubule-binding domain (R-domain).

Tau aggregation follows a similar pattern of nucleation-elongation mechanism as aSyn. Several factors contributing to the aggregation process are shared between aSyn and Tau, such as structural characteristics favouring aggregation – mutations, truncations and post-translational modifications [6]. Also, several biomolecules, such as heparin and free fatty acids, are known to promote Tau aggregation [69, 70].

It is widely recognized that hyperphosphorylation is a major contributor to Tau aggregation [6]. As the longest Tau isoform has >80 potential phosphorylation sites, the phosphorylation patterns of Tau are highly complex and remain incompletely understood. Under physiological conditions, Tau binds and stabilizes microtubules, and its phosphorylation homeostasis is maintained by transient interactions with kinases and phosphatases. However, abnormal phosphorylation of Tau occurs when the phosphorylation/dephosphorylation cycle is disturbed resulting in accumulation of hyperphosphorylated, non-microtubule-associated Tau in cells [6]. These forms of Tau can further

oligomerize, eventually forming fibrils known as paired helical filaments (PHF), which are further organized to NFTs, the neuropathological hallmark of tauopathies [71]. However, it should be noted that reversible hyperphosphorylation of Tau without development of pathology has been observed in the brains of hibernating animals indicating that hyperphosphorylation alone may not be sufficient to trigger Tau aggregation [72].

While natively unfolded Tau monomers are structurally highly dynamic, Tau aggregates are generally packed into well-ordered β-sheet-like structures [73, 74]. Two hexapeptides VQIINK and VQIVYK on second and third MBDs of Tau are essential for the formation of "zipper-like" interdigitated β-sheet structures, and thus play a key role in mediating Tau aggregation [75]. Certain FTDP-17 mutations, e.g. P301L, promote β-sheet formation and accelerate Tau aggregation [76, 77].

Truncation is one of the post-translational modifications that are closely linked with the aggregation properties of tau. There are multiple potential protease cleavage sites on full-length tau. Truncations of Tau lead to various fragments containing the microtubule-binding region that are highly prone to aggregation [6]. Inoculation of mice with truncated forms of Tau induces aggregation of endogenous Tau and development of neurofibrillary pathology [78, 79].

2.2.2 Altered Tau interactome in pathological conditions

The N-terminal projection domain of Tau interacts with a variety of signalling proteins including Src-family kinases, phospholipase C-γ, Grb2 and Pin1 [80]. The microtubule-binding domain functions primarily through the four highly conserved MBDs that mediate the interaction of Tau with microtubules [73]. Tau physiologically interacts with several proteins abundant in the postsynaptic termini including Fyn kinase, PSD-95 and NMDA receptor, suggesting that Tau could be involved in synaptic plasticity. Silencing of Tau in mice impairs long-term potentiation further implicating Tau in NMDA receptor-dependent memory [81, 82]. However, silencing Tau expression in neuronal culture does not trigger neurodegeneration or prevent axon growth most likely due to functional compensation by other MAPs [83]. Hence it has been suggested that neurodegeneration in tauopathies is more strongly correlated with the gain of toxic functions rather than loss of normal functions of Tau [6].

Altered Tau interactome is likely associated with gain of toxic functions in pathological conditions. For example, Tau in AD brain showed significantly increased interactions with ribosomal RNA-binding proteins compared to Tau from healthy brain [84]. Importantly, this was associated with impaired ribosomal function and reduced translation of PSD-95, a key synaptic protein. As protein synthesis is required for consolidation of long-term memory, this likely contributes to the impairment of cognitive functions in AD and other tauopathies.

As both physiological MT-regulating functions of Tau and its aggregation propensity are regulated by the phosphorylation status of Tau [85], altered interactions with kinases and phosphatases likely play an important role in development of Tau pathology. Akt1 was suggested to serve as a major regulator of Tau biology as it regulates several Tau kinases, such as GSK3β and PAR1/MARK2, and the protein quality control and degradation machinery through the Tau ubiquitin ligase CHIP [86]. As many of the serine/threonine residues phosphorylated in Tau are proline-directed, interaction with the prolyl cis/trans isomerase Pin1 is an important regulator of Tau dephosphorylation [87]. Notably, Pin1 expression is inversely correlated with neurofibrillary degeneration in AD brain and Pin1 knockout mice show age-dependent neuropathy with hyperphosphorylated filaments of endogenous Tau [88].

Hyperphosphorylation promotes Tau interaction with c-Jun N-terminal kinase-interacting protein 1 (JIP1), a protein associated with kinesin motor protein complex, and impairs the function of kinesin complex while normal Tau does not [89]. This offers a potential mechanistic explanation for the

frequently observed axonal transport impairment in AD. Interestingly, in response to acute oxidative and heat stresses, dephosphorylated Tau accumulates in the nucleus where it binds and protects DNA from oxidative damage and possibly also enhances DNA repair [90]. Other Tau PPIs potentially altered in pathological conditions includes histone deacetylase 6, a tubulin deacetylase involved in protein sorting and transport in the autophagy pathway [91, 92] and Otub1, a Tau deubiquitinating enzyme [93].

One potential driver of altered PPIs is abnormal subcellular localization of a protein. Hyperphosphorylation results in missorting of axonal Tau to the somatodendritic compartment where Tau interacts directly, in a phosphorylation-dependent manner, with the PSD-95-NMDA receptor complex [82]. Importantly, Tau-dependent dendritic sorting of Fyn promotes Aβ-induced, NMDA receptor-mediated excitotoxicity, which constitutes an important link between neuronal dysfunction and clinical symptoms of AD [94]. Fyn also hyperphosphorylates Tau in an Aβ-dependent manner [95]. Moreover, mislocalized Tau can recruit tyrosine ligase-like enzyme 6 (TTLL6) into dendrites which triggers Spastin to sever microtubules resulting in dendritic spine degeneration [96].

Several disease-associated mutations of Tau alter its interactome. FTDP-17 related mutations, such as P301L/S, G389R, R406W, G272V, K280 and V337M, not only strongly promote Tau-Fyn interaction but also drastically reduce Tau-PP2A interaction, resulting in hyperphosphorylation and aggregation of Tau [97]. Some FTDP-17 mutations, e.g. ΔK280 and P301L, also attenuate microtubule-binding of Tau, increase cytosolic Tau and thus indirectly promote aggregation [76]. While normal Tau interacts with several chaperones and proteasomal proteins [98, 99], mutations such as P301L can disrupt these interactions, suggesting that some mutations may specifically impair mechanisms aiming to restore proteostasis in the presence of pathological Tau [100]. Moreover, as the C-terminus mediates the interactions of Tau with chaperones and proteasomal proteins, C-terminal truncations may promote accumulation of truncated forms of Tau by reducing interactions with the protein degradation machinery. Interestingly, Pin1 has opposite effects on wild-type Tau and the P301L mutant protein [101], highlighting the complexity of functional alterations of Tau interactome in various tauopathies. Under physiological conditions, Tau also interacts with membranes and this interaction can be affected by disease-associated mutations as is the case with the FTDP-17 mutation R406W, which disrupts the interaction between Tau and Annexin A2, a membrane cytoskeleton linker [102].

Secreted pathological Tau conformers internalized to healthy cells may cause cellular dysfunction via acquired abnormal PPIs. We recently showed that internalized Tau oligomers display a significantly increased interaction with an RNA-binding, stress-granule protein TIA-1, which resulted in altered stress granule (SG) clearance dynamics and reduced cell viability [103]. SGs are cytoplasmic, non-membraneous RNA-containing foci that form transiently as a cellular response to various stresses. TIA-1 is one of the self-aggregating RNA-binding proteins that regulate SG formation. Interaction with TIA-1 further promotes Tau misfolding and toxicity and abnormal SGs could serve as a platform for templated seeding of protein aggregation [104].

3 Interaction between α-synuclein and Tau

3.1 Feed-forward mechanisms in aggregation and propagation of α-synuclein and Tau

Pathological misfolding of a protein elicits stress on the proteostatic machinery of cells, which in chronic conditions can affect the folding of other aggregation-prone proteins eventually resulting in

global dysregulation of protein homeostasis [105]. A recurrent theme of neurodegenerative diseases is the frequent co-occurrence of different disease protein aggregates in the same patient. For example, aSyn and Tau inclusions co-occur in multiple diseases including Lewy body variant of AD, DLB and PD with dementia [5, 106-108]. Phosphorylated forms of Tau are also found in Lewy bodies [109]. PD patients have increased risk of developing dementia, and NFTs are frequently observed at autopsy of late-stage PD patients while >50% of AD patients have Lewy bodies at autopsy, suggesting remarkable cross-talk between synucleinopathies and tauopathies [8, 110-114]. Moreover, mutations in the *SNCA* and *MAPT* genes, encoding the aSyn and Tau proteins, can both lead to disease phenotypes characterized by parkinsonism and dementia [32, 115-118].

Despite the fact that aSyn and Tau are distinct proteins that primarily contribute to different disease-specific pathologies, multiple lines of evidence suggest that aSyn and Tau interact, modulate the aggregation of each other and co-exist in pathological inclusions in human brain [5]. aSyn directly interacts with Tau [119] and can induce all six isoforms of Tau to aggregate, while neither β-synuclein nor Aβ peptide have this effect [10]. The A53T mutation enhances aSyn-induced Tau fibrillization [120]. Conversely, the presence of pathological forms of Tau can accelerate aSyn fibrillization [10]. Tau overexpression alters aSyn aggregation pattern, reducing the number but increasing the size and toxicity of aSyn aggregates [121]. aSyn may indirectly modulate Tau aggregation by promoting Tau phosphorylation changes associated with negative regulation of microtubule stability [122]. aSyn also increases GSK3β-mediated phosphorylation of Tau at AD-associated phosphoepitopes T181, S396 and S404 [123, 124], and aSyn mutations A30P, A53T and E46K enhance the interaction with GSK3β.

aSyn and Tau may influence cell-to-cell transmission of each other but the mechanisms remain poorly understood. Inoculation of pathological conformers of aSyn or Tau into healthy tissue has been shown to cross-seed aSyn or Tau aggregation in animal models (reviewed in [16]). Preformed aSyn fibrils promote intracellular aggregation of Tau in cells overexpressing both aSyn and Tau, and this effect was enhanced by P301L Tau mutation [125]. Interestingly, certain chaperone complexes may specifically regulate extracellular release of both aSyn and Tau, as was recently shown for Hsc70/DnaJC5 [126].

In PD, LBs are predominantly found in midbrain structures such as the substantia nigra and are morphologically different from those found in the cortical regions [127]. On the other hand, NFTs are more frequently detected in limbic and neocortical areas than in the midbrain [128]. Interestingly, distinct strains of aggregated aSyn were found to differentially induce Tau hyperphosphorylation and aggregation [125, 129]. As there are conformational variations in pathological aSyn species between regions in the human brain, the differential cross-seeding capacity of aSyn strains could explain the observed region-specific distribution of co-occurring LBs and NFTs [127]. Importantly, more direct in vivo evidence of cross-seeding of pathologies involving aSyn and Tau, as well as other similar pathologically misfolded proteins, is needed.

3.2 Shared interactome as a pathological point of convergence

The diversity of clinical manifestations of a disease can be related to the connectivity patterns of the associated protein interaction network. In general, there is a strong correlation between symptom similarity and shared PPIs between diseases [130]. Neurodegenerative diseases are well known to display significant overlap of symptoms and neuropathological characteristics. For example, while many tauopathies are associated with progressive cognitive impairment, tauopathies with

parkinsonism represent a spectrum of disease entities with predominant tau pathology but prominent parkinsonian symptoms [2].

Apart from the gain-of-function relationship that feeds forward the aggregation of each other, aSyn and Tau may also overlap in their loss-of-function effects. Aside of the numerous specific PPIs, aSyn and Tau share a number of interacting proteins (Figure 2). These shared PPIs fall roughly in three functional categories: microtubule cytoskeleton, proteostatic machinery and protein phosphorylation/signal transduction. As protein interaction subnetworks tend to connect proteins in functional modules and pathways, it is plausible that a molecular defect in a shared network, such as extensive aggregation of one protein, either aSyn or Tau, could trigger loss-of-function effects on the other or on the cellular functions that both proteins are associated with, by spreading along the edges of the network.

Not surprisingly, aSyn and Tau share many interactions with proteins of the proteostatic machinery, including chaperones and components of the UPS and ALS systems (Figure 2). Ubiquitinated forms of aSyn and Tau, together with UPS components, are found in LBs and NFTs [131, 132]. Moreover, UPS and ALS impairments are frequently observed in synucleinopathies and tauopathies [133, 134]. In general, overloading the cellular waste management systems by one aggregating protein species can lead to accumulation of other aggregation-prone proteins. As aSyn and Tau share multiple chaperones, accumulation of aggregated aSyn may promote Tau misfolding through chaperone competition, and vice versa.

Both aSyn and Tau are expressed in neurons where they localize predominantly to the axonal/presynaptic compartment. As neurons are highly polarized cells, the structure and functionality of cytoskeleton is critical for their viability. Both Tau and aSyn interact with tubulins. While Tau serves as a microtubule stabilizer, aSyn was reported to enhance tubulin polymerization [135-137]. Altered microtubule assembly and stability is thus a possible common loss-of-function target in pathologies involving aSyn and Tau misfolding. In pathological conditions, aSyn and Tau have been reported to mislocalize to the somatodendritic compartment, which may result in changes in their respective interactomes contributing to cellular dysfunction [94, 138, 139].

One important cellular compartment for both gain- and loss-of-function effects are the membranes. Membrane turnover has a particularly important role at the presynapse and is thus tightly regulated. Membranes with altered function have been observed in AD and PD [140-142]. Lipids are also found to colocalize with aSyn and Tau in LBs and NFTs [143, 144], and lipid binding modulates aggregation properties of aSyn and Tau [145-148]. Upon binding to cell membranes, annular protofibrils of aSyn adopt an octameric structure similar to bacterial pore-forming toxins, resulting in increased permeability of membranes and influx of calcium [149-151]. Similarly, disruption of membrane integrity may partially explain the toxicity of Tau oligomers [152]. Thus, the normal function of the presynapse may be compromised by misfolded and aggregated forms of aSyn and Tau. It is currently not known if membrane-embedded annular oligomers of aSyn and Tau can exist in the form hetero-oligomers or if they interact with other membrane proteins.

Many of the kinases that interact with both aSyn and Tau are either membrane-anchored or operate at the membrane-cytoskeleton interface. 14-3-3 proteins are small ubiquitous adaptor proteins that serve as regulators in diverse cellular processes, often in phosphorylation-dependent manner and in close association with membranes. Several members of the 14-3-3 adaptor protein family bind to both aSyn and Tau, and modulate their PPIs, phosphorylation and clearance mechanisms [153, 154]. Interestingly, 14-3-3 proteins and aSyn share both physical and functional homology [155].

Certain disease-associated proteins interact with both aSyn and Tau. One interesting example is LRRK2, a kinase genetically associated with PD that phosphorylates both aSyn and Tau [156, 157]. LRRK2 specifically binds to and phosphorylates tubulin-associated Tau at Thr181, promoting its dissociation from microtubules [158]. In addition, LRRK2 can indirectly promote Tau phosphorylation at Ser396 via its interaction with GSK3β [159]. In a similar manner, aSyn can also form a heterotrimeric complex with GSK3β and Tau and promote GSK3β's kinase activity towards Tau [160]. LRRK2 G2019S, a common PD-associated missense mutation, promotes phosphorylation of both aSyn [157] and Tau [158], and is also associated with changes in Tau and aSyn expression in patient-derived stem cells [161]. Other mechanisms, such as impaired autophagy and axonal transport, may also affect aSyn and Tau and contribute to the overall pathogenic effects of LRRK2 [162].

In summary, the shared interactome of aSyn and Tau points to several cellular pathways known to be crucial for viability of neurons that may be affected by network perturbations initiated by pathological forms of aSyn and Tau. Nevertheless, it should be noted that both aSyn and Tau have functional homologues and thus functional compensation should be taken into account when discussing the loss-of-function effects. Although silencing Tau in neuronal culture does not trigger neurodegeneration or prevent axon growth [163], aged Tau knockout mice have dementia and parkinsonian phenotypes depending on the background strain [164]. While knockdown of aSyn results only in a modest changes presynaptic vesicles, possibly due to functional compensation by other synucleins [165, 166], triple knockout of all three synucleins triggers age-dependent neurological impairments [12].

4 Concluding remarks

aSyn and Tau proteins interact, and accumulating evidence suggests that both proteins can feed-forward misfolding and aggregation of each other. In addition, the shared interactome of aSyn and Tau may serve as a pathological point of convergence through which network perturbations, initiated by a variety of misfolding/aggregation triggers such as mutations and abnormal post-translational modifications, interfere with the physiological functions of both proteins and could facilitate development of proteotoxic stress and neurodegenerative changes in the aging brain. Similar cross-talk may occur between other disease-associated aggregating proteins, e.g. between the aSyn–TDP-43 and Tau–TDP-43. Future studies should consider the network biology perspective when investigating the pathobiology and phenotypic similarities between synucleinopathies, tauopathies and other neurodegenerative diseases.

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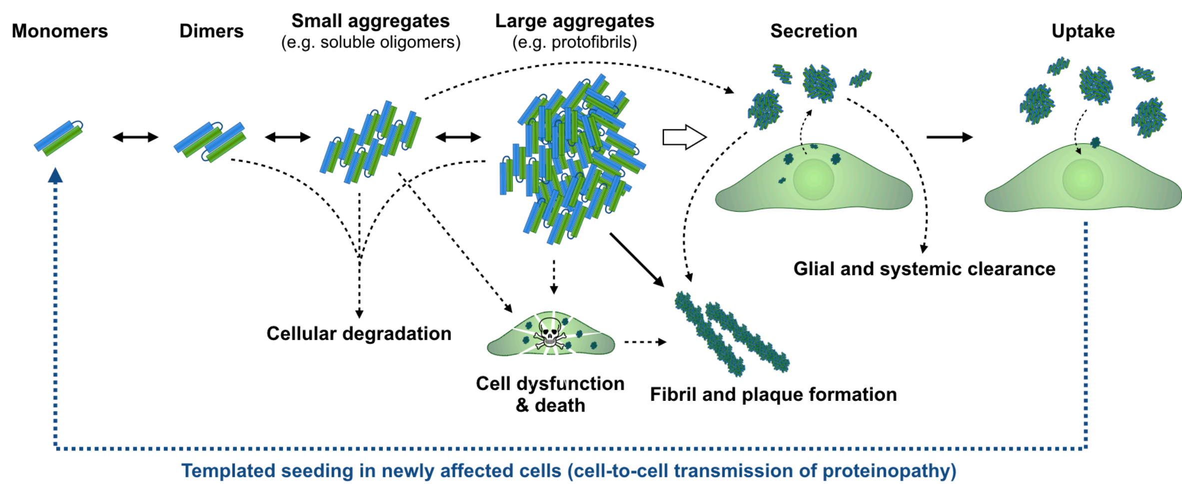
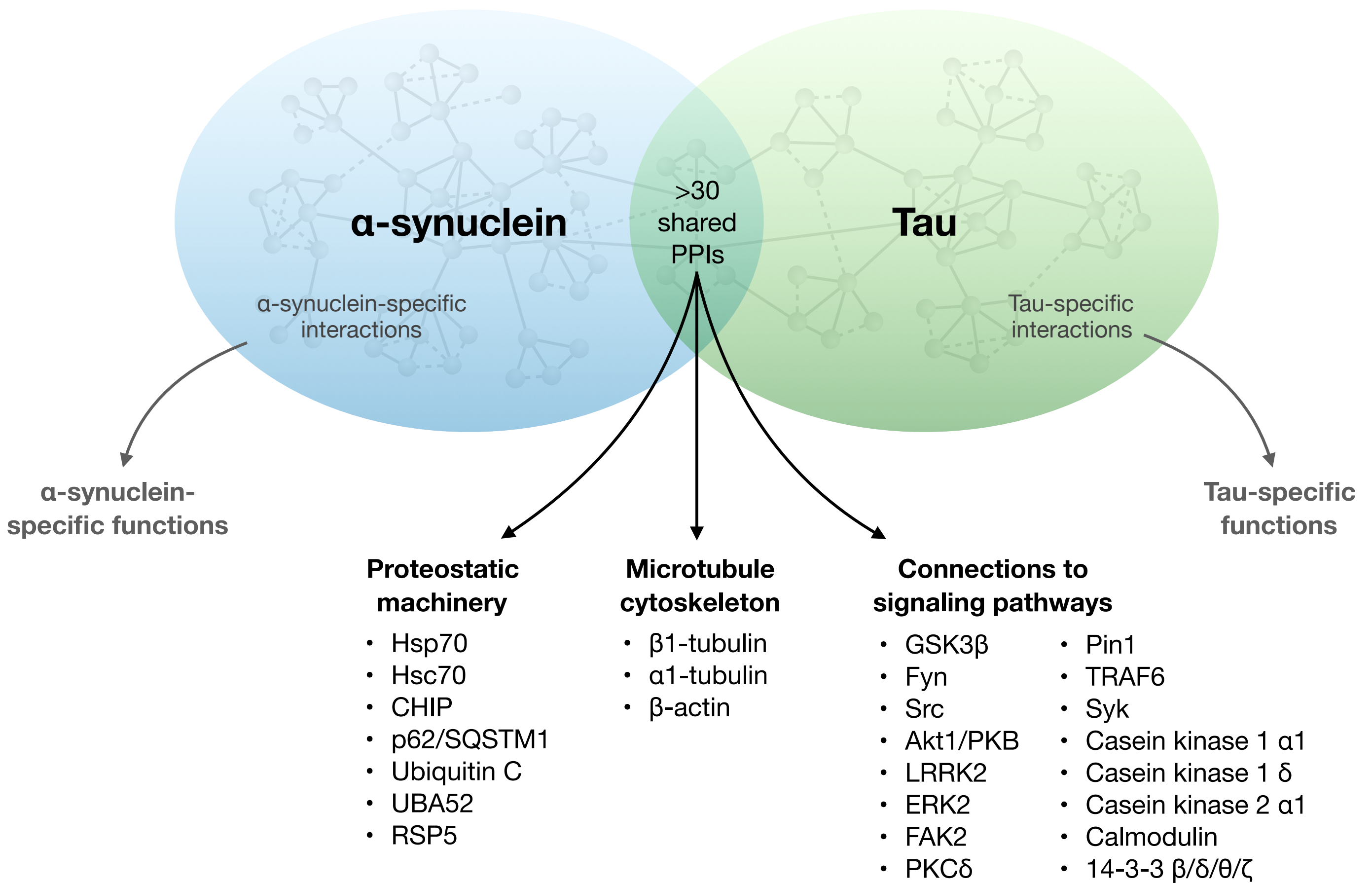
FIGURE LEGENDS

Figure 1. Templated seeding of protein aggregation and cell-to-cell transmission of proteinopathies.

Figure 2. The shared interactome of aSyn and Tau. PPIs for aSyn and Tau were retrieved from the PINA database (accessed on June 2nd, 2017). Comparison of interactomes using the Cytoscape plugin PINA4MS identified 33 shared PPIs (approximately 7% of all retrieved PPIs).


Monomers
Dimers
Small aggregates
(e.g. soluble oligomers)
Large aggregates
(e.g. protofibrils)
Secretion
Uptake
Glial and systemic clearance
Cellular degradation
Cell dysfunction
& death
Fibril and plaque formation
Templated seeding in newly affected cells (cell-to-cell transmission of proteinopathy)
Loss of normal functions via lost interactions
Gain of toxic functions via acquired or abnormal interactions


α-synuclein
Tau
>30
shared
PPIs
α-synuclein-specific
interactions
Tau-specific
interactions
α-synuclein-
specific functions
Tau-specific
functions
Proteostatic
machinery
• Hsp70
• Hsc70
• CHIP
• p62/SQSTM1
• Ubiquitin C
• UBA52
• RSP5
Microtubule
cytoskeleton
• β1-tubulin
• α1-tubulin
• β-actin
Connections to
signaling pathways
• GSK3β
• Fyn
• Src
• Akt1/PKB
• LRRK2
• ERK2
• FAK2
• PKCδ
• Pin1
• TRAF6
• Syk
• Casein kinase 1 α1
• Casein kinase 1 δ
• Casein kinase 2 α1
• Calmodulin
• 14-3-3 β/δ/θ/ζ