alzheimer's research&therapy

REVIEW

Examining the mechanisms that link β-amyloid and α-synuclein pathologies

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Abstract

β-amyloid (Aβ) and α-synuclein (α-syn) are aggregation-prone proteins typically associated with two distinct neurodegenerative disorders: Alzheimer's disease (AD) and Parkinson's disease. Yet α-syn was first found in association with AD plaques several years before being linked to Parkinson's disease or Lewy body formation. Nowadays, a large subset of AD patients (~50%) is well recognized to co-exhibit significant α-syn Lewy body pathology. Unfortunately, these AD Lewy body variant patients suffer from additional symptoms and an accelerated disease course. Basic research has begun to show that Aβ and α-syn may act synergistically to promote the aggregation and accumulation of each other. While the exact mechanisms by which these proteins interact remain unclear, growing evidence suggests that Aβ may drive α-syn pathology by impairing protein clearance, activating inflammation, enhancing phosphorylation, or directly promoting aggregation. This review examines the interactions between Aβ and α-syn and proposes potential mechanistic links between Aβ accumulation and α-syn pathogenesis.

Introduction

Protein misfolding and aggregation play a key role in many neurodegenerative disorders. In Alzheimer's disease (AD), β-amyloid (Aβ) and tau proteins accumulate, forming the two hallmark pathologies of senile plaques and neurofibrillary tangles [1,2]. In the Lewy body spectrum of disorders – which includes Parkinson's disease, Parkinson's disease with dementia (PDD), and dementia with Lewy bodies (DLB) – insoluble aggregates of a different protein, α-synuclein (α-syn), accumulate in the form of Lewy bodies and Lewy neurites [2-4].

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The pathological identification of Aβ plaques and neurofibrillary tangles versus Lewy bodies has historically been used to distinguish between AD and the dementing forms of Lewy body disease. A large proportion of AD patients (>50%), however, exhibit significant Lewy body pathology in addition to plaques and tangles [5-8]. The postmortem identification of these patients is also increasing as examination of all three proteins becomes more widely employed [8]. Interestingly, this subpopulation of patients – often termed as those with the Lewy body variant of Alzheimer's disease (AD-LBV) – exhibit more rapid cognitive decline and shortened survival times compared with pure AD cases [9-12]. In addition to AD-LBV cases, amyloid plaques have been detected in some patients clinically diagnosed with DLB and less frequently in cases of PDD [3,4,13-16].

These varying combinations of Aβ, tau, and α-syn that occur have led to considerable confusion regarding the diagnosis of patients that exhibit all three pathologies. To establish a more clearly defined set of diagnostic criteria for DLB, a consortium of expert neurologists and pathologists therefore proposed a set of specific recommendations [3]. For example, the likelihood of DLB is 'directly related to the severity of Lewy-related pathology, and inversely related to the severity of concurrent AD-type pathology' (see Table 3 in [3]). These revised criteria have helped to better clinically define DLB and to distinguish cases of DLB that occur without concurrent AD pathology from AD-LBV patients who exhibit both DLB and AD-associated pathologies.

Aβ plaques, neurofibrillary tangles, and Lewy bodies do not occur in high enough individual frequency to explain their co-existence in AD-LBV brains [17,18]. Instead, researchers have hypothesized that Aβ, tau, and α-syn might promote the accumulation or aggregation of one another [17,18]. Over the last decade a number of studies have confirmed this hypothesis, and experiments have begun to unravel the molecular and cellular mechanisms by which these proteins interact [19-22].

It is important to point out that Aβ and α-syn pathologies do not co-exist in all AD-LBV brain regions or in all cases of AD and DLB [3]. Synucleinopathies such as multiple system atrophy and axon dystrophies also

show no evidence of concurrent Aβ deposition [23,24]. Aβ and α-syn thus appear to interact in a disease-specific and anatomical-specific manner. By examining the mechanisms by which these proteins interact we will probably enhance our understanding of why Aβ and α-syn pathologies co-exist in many, but not all, AD patients.

In the present review we shall examine the evidence supporting a role for synergistic interactions between Aβ and α-syn in the development and progression of AD-LBV. We will also discuss putative mechanisms by which Aβ and α-syn could interact and influence disease progression.

Clinical prevalence of the Lewy body variant of Alzheimer's disease

Between 50 and 60% of AD patients exhibit significant amounts of both Aβ and α-syn pathology at autopsy [3,6]. These AD-LBV patients often present with a more aggressive form of dementia featuring a higher rate of cognitive decline and shortened survival versus pure AD [9,11,12,25]. After AD, DLB appears to be the second most common form of age-related dementia [3]. Clinically, pure DLB patients who lack Aβ pathology often exhibit different cognitive deficits compared with AD or other dementias. The core diagnostic criteria for DLB include fluctuating cognition and attention, persistent visual hallucinations, and spontaneous Parkinsonian symptoms. DLB patients may also possess greater deficits in working memory, attention, executive function, and visuospatial ability than AD patients [3,12]. Pure DLB cases are relatively rare (~20%), however, and Aβ pathology is often also present [3,26,27]. In these cases of mixed pathology, clinical diagnosis can be more difficult as the cognitive decline more closely resembles the cognitive profile of AD with the addition of some of the unique DLB-associated symptoms [25,26].

Interestingly, not all studies have reported such cognitive differences between AD patients, AD-LBV patients, and DLB patients, perhaps as a result of varying methodology such as not including postmortem α-syn or Aβ histochemical assessments [12]. Additionally, given the differing cognitive profiles of AD, AD-LBV, and DLB, direct comparison of cognitive decline and the rate of decline can be difficult and dependent on the assessments utilized [11,25,26]. PDD patients, who can show very similar pathology and symptoms to DLB patients, can also sometimes exhibit both Aβ plaques and Lewy bodies. Although the onset of dementia in PDD patients is highly variable, it appears to be influenced by Aβ pathology [4,13]. Several disease states that involve α-syn pathology can thus also exhibit varying degrees of Aβ pathology.

Synergistic interactions between β-amyloid and α-synuclein

Given the intriguing overlap of Aβ and α-syn pathology that occurs in these various dementing disorders, researchers have begun to examine the interactions between these two proteins and pathologies. Both *in vitro* and *in vivo* experiments have started to identify potential mechanisms by which Aβ and α-syn may interact, providing critical results that promise to advance our understanding of these inter-related neurodegenerative diseases.

In vitro examinations

Using cell-free assays, researchers first began to explore potential direct interactions between Aβ and α-syn. For example, incubation of recombinant human α-synuclein (hSYN) with $A\beta_{42}$ promoted and increased the formation of high-molecular-weight hSYN oligomers [19]. Interestingly, while $A\beta_{42}$ induced α-syn oligomer formation, co-incubation with the less pathogenic $A\beta_{40}$ did not. Virtually identical results were observed in a cell culture model where extracellular $A\beta_{42}$, but not $A\beta_{40}$, promoted the formation of intracellular α-syn aggregates [19]. Expanding upon these results, $A\beta_{40}$ and $A\beta_{42}$ were both shown to directly interact with α-syn *in vitro* [20]. However, α-syn appears to induce a greater structural change in $A\beta_{42}$. While $A\beta_{40}$ remains soluble in solution following α-syn co-incubation, $A\beta_{42}$ instead forms oligomers and insoluble precipitates [20]. The implication that α-syn may preferentially interact with $A\beta_{42}$ is important given the known toxic and aggregate-prone properties of $A\beta_{42}$ relative to other Aβ isoforms [28,29].

Continuing to implicate $A\beta_{42}$ as a critical component in the interactions between Aβ and α-syn is the result that a mutation in presenilin 1, which increased $A\beta_{42}$, also enhanced the pathogenic phosphorylation and aggregation of α-syn in both patients and cells [21]. This result not only provides further support for the idea that $A\beta_{42}$ plays a key role in the aggregation of α-syn, but also suggests a possible mechanism; the $A\beta_{42}$-induced phosphorylation of α-syn. In the normal brain, about 4% of α-syn is phosphorylated at serine 129 (pS129-syn). In contrast, up to 90% of α-syn is phosphorylated at this site in synucleinopathies such as DLB, suggesting an important role in pathogenesis [30,31]. Indeed, phosphorylation of α-syn at serine 129 (Ser129) can promote fibril formation *in vitro* [30]. $A\beta_{42}$-induced phosphorylation of α-syn therefore provides an intriguing mechanism by which Aβ may enhance α-syn pathology.

There is considerable *in vitro* evidence that α-syn can also interact with tau, the other major pathological protein in AD. Whereas α-syn has been shown to self-polymerize *in vitro* [32], tau instead requires cofactors to polymerize [33]. Interestingly, α-syn can itself serve as a cofactor to promote tau polymerization and both proteins co-localize within inclusion bodies [17,18,34]. Recent evidence has shown that co-transfection of α-syn with tau induces insoluble, cytotoxic, α-syn aggregate

formation [34]. Likewise, cellular seeding with α-syn fibrils induces the formation of cytotoxic neurofibrillary tangle-like inclusions [35]. Extracellular seeding of α-syn fibrils can also promote recruitment of soluble α-syn into insoluble Lewy body-like inclusion bodies [36].

Transgenic models that combine β-amyloid and α-synuclein pathology

Mouse models of overlapping Aβ and α-syn pathology lend further support to the theory that Aβ and α-syn interact synergistically to create a more severe disease course. Double-transgenic mice expressing human amyloid precursor protein (APP) and wild-type hSYN develop motor deficits at 6 months compared with 12 months in single-transgenic hSYN mice [19]. These human APP/hSYN mice also develop spatial memory deficits and increased numbers of Lewy body-like inclusions [19]. These double-transgenic mice therefore provide a useful model for examining the potential interactions between Aβ and α-syn.

To model all three of the pathologies that co-exist within AD-LBV patients, Clinton and colleagues crossed 3xTg-AD transgenic mice with a mutant α-synuclein transgenic line [22]. The 3xTg-AD model develops Aβ plaque and neurofibrillary tangle pathology via co-expression of mutant APP, mutant presenilin-1, and mutant tau. By adding a mutant α-syn (A53T) transgene to the mix, this model (hereafter referred to as AD-LBV mice) successfully recapitulated all three major AD-LBV pathologies [22]. Interestingly, AD-LBV mice exhibit accelerated cognitive dysfunction versus 3xTg-AD or α-syn lines, suggesting that this complex model mimics an important feature of AD-LBV. Similar to the single-transgenic α-syn mouse, the AD-LBV mice develop Lewy body-like inclusions. However, AD-LBV mice show increased levels of insoluble α-syn, pS129-syn, and Lewy body pathology at much earlier ages than single-transgenic α-syn mice. Two other pathological results of interest are that AD-LBV mice develop increased levels of insoluble $A\beta_{42}$ tau at younger ages than 3xTg-AD mice. Although this model uses mutant transgenes, the results nevertheless provide important additional evidence that Aβ, tau, and α-syn can interact synergistically to accelerate pathogenesis and cognitive decline.

While much of the *in vivo* evidence linking Aβ and α-syn comes from the use of transgenic mice that express mutant genes, the study of these models has yielded invaluable additions to our knowledge of neurodegenerative disease [1,18,37]. Importantly, similar results have been found in models regardless of whether mutant [22] or wild-type [19] α-syn transgenes were utilized. Interestingly, investigations of familial AD presenilin 1, presenilin 2, and APP mutation carriers also reveal increased development of Lewy body pathology [38-40]. Both mouse models and human cases thus suggest that disease-associated APP and presenilin mutations can enhance the pathological accumulation of wild-type α-syn.

Potential mechanisms that link β-amyloid and α-synuclein pathology

While the interactions between AB and α-syn have been well documented, far less is known about the mechanisms by which these proteins exert their effects on one another. Research aimed at elucidating these mechanisms will no doubt provide critical knowledge about the progression of AD, AD-LBV, DLB, and PDD, and thus may also yield new therapeutic targets.

Phosphorylation of α-synuclein and tau

One mechanism that may underlie the effects of Aβ on α-syn is by indirectly influencing the phosphorylation state of α-syn. As previously mentioned, Ser129 α-syn phosphorylation is a pathogenic change observed in DLB and other synucleinopathies, and interactions with Aβ and tau can enhance phosphorylation at this residue *in vitro* and *in vivo* [22,30]. Several kinases have been identified that may mediate Ser129 phosphorylation, but the most important appear to be casein kinase 2 and polo-like kinase 2 (PLK2) [30,41-44]. PLK2 was recently shown to phosphorylate α-syn at Ser129 with greater efficiency than casein kinase 2 [44]. Interestingly, PLK2 expression is elevated in AD and DLB patient neurons. Phosphorylation of Ser129 was also recently detected in synaptic-enriched fractions from AD patients [45]. Upregulation of PLK2 in AD and DLB could thus potentially mediate the increased phosphorylation of α-syn observed in these patients. Increased phosphorylation of Ser129 has in turn been shown to increase the propensity of α-syn to form aggregates [30]. In contrast, one recent study found that increasing pS129 through various mechanisms, including increased PLK2 expression, did not alter the aggregation state [46]. While the evidence is clear that pS129-syn is associated with pathogenic changes, further research is needed to clarify the functional effects of Ser129 phosphorylation and the potential role of pS129-syn in Aβ and synuclein interactions.

The hyperphosphorylation of tau and its aggregation into neurofibrillary tangles and dystrophic neurites (Figure 1) is a hallmark of AD. A number of studies have shown that Aβ can modulate tau phosphorylation and aggregation [47-49]. α-syn can also influence tau pathology [50,51]. The interactions between α-syn and tau appear bidirectional, however, as tau can also induce synuclein aggregation and phosphorylation [34]. In fact, tau overexpression can induce PLK2 expression, providing a potential mechanism for this effect [52]. Aβ could therefore possibly drive synuclein pathology indirectly by first enhancing tau pathogenesis (Figure 2).

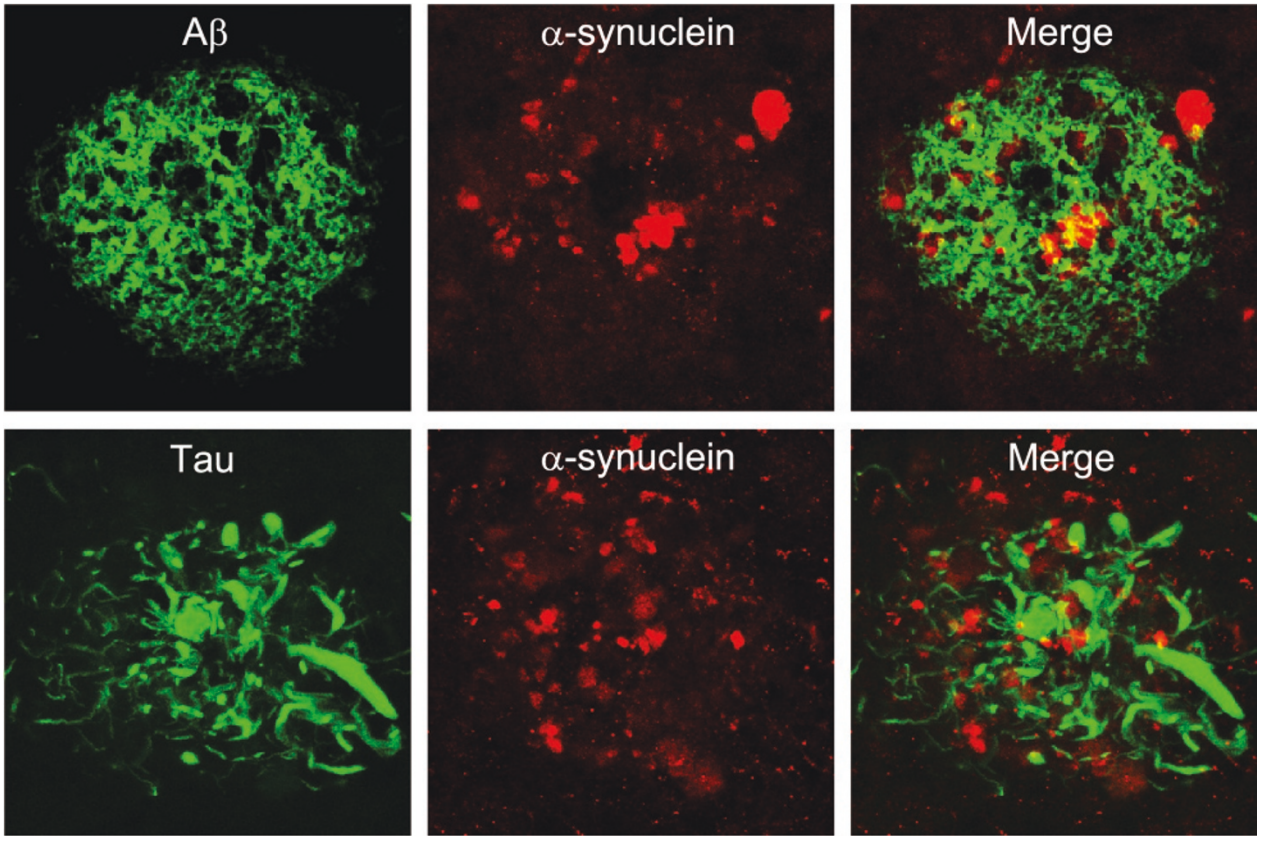

Figure 1. α-synuclein and tau immunoreactive dystrophic neurites surround β-amyloid plaques. Top panels: β-amyloid (Aβ) plaque (green) is surrounded by α-synuclein immunoreactive neurites (red) in the neocortex of a Lewy body variant of Alzheimer's disease patient. Bottom panels: Both tau immunoreactive dystrophic neurites (green) and α-synuclein (red) are detected in association with a neuritic plaque.

β-amyloid-induced inflammation

Inflammation is a critical component of AD [53] and also contributes to the pathogenesis of Lewy body disorders [54,55]. Although there is currently limited evidence connecting Aβ-induced inflammation with α-syn aggregation, we speculate that the effects of Aβ on inflammatory processes could indirectly drive the phosphorylation and aggregation of α-syn. A growing body of evidence suggests that Aβ can indeed influence tau pathology via this kind of mechanism. For example, Aβ-induced release of pro-inflammatory cytokines can in turn activate kinases such as cyclin-dependent kinase 5 that promote tau phosphorylation [37,56,57]. Interestingly, cyclin-dependent kinase 5 has also been implicated in Lewy body formation – this same kinase may therefore influence α-syn aggregation [58]. In further support of this hypothesis, age-related changes in microglial activation and cytokine release can enhance nitric oxide production, increasing α-syn nitration [59]. Nitration and oxidation of α-syn can in turn accelerate α-syn aggregation [60]. The relationship between α-syn and inflammation appears to be reciprocal, as α-syn can itself can drive astrocytic and microglia activation [61,62]. Notably, one recent report showed that tau overexpression can also drive inflammation and enhance α-syn accumulation and phosphorylation [52].

Clearly a great deal more work is needed to determine whether inflammation truly influences the interactions between Aβ and α-syn. However, inflammatory-mediated changes in cytokine expression and kinase activation probably influence α-syn in much the same way as they modulate tau.

Impaired protein degradation

Another common mechanism thought to underlie many neurodegenerative disorders is dysfunction in protein clearance mechanisms. Indeed, impairments in both the ubiquitin–proteasome system and the autophagy–lysosome pathway occur in AD and Parkinson's disease, and both pathways are important in Aβ and α-syn degradation [63-67]. Soluble oligomeric Aβ, in addition to aggregated α-syn, impairs the normal function of the proteasome [63,68]. The ubiquitin–proteasome system is also critical in the degradation of tau, and the E3 ligase (C-terminus Hsp70 interacting protein) targets both tau

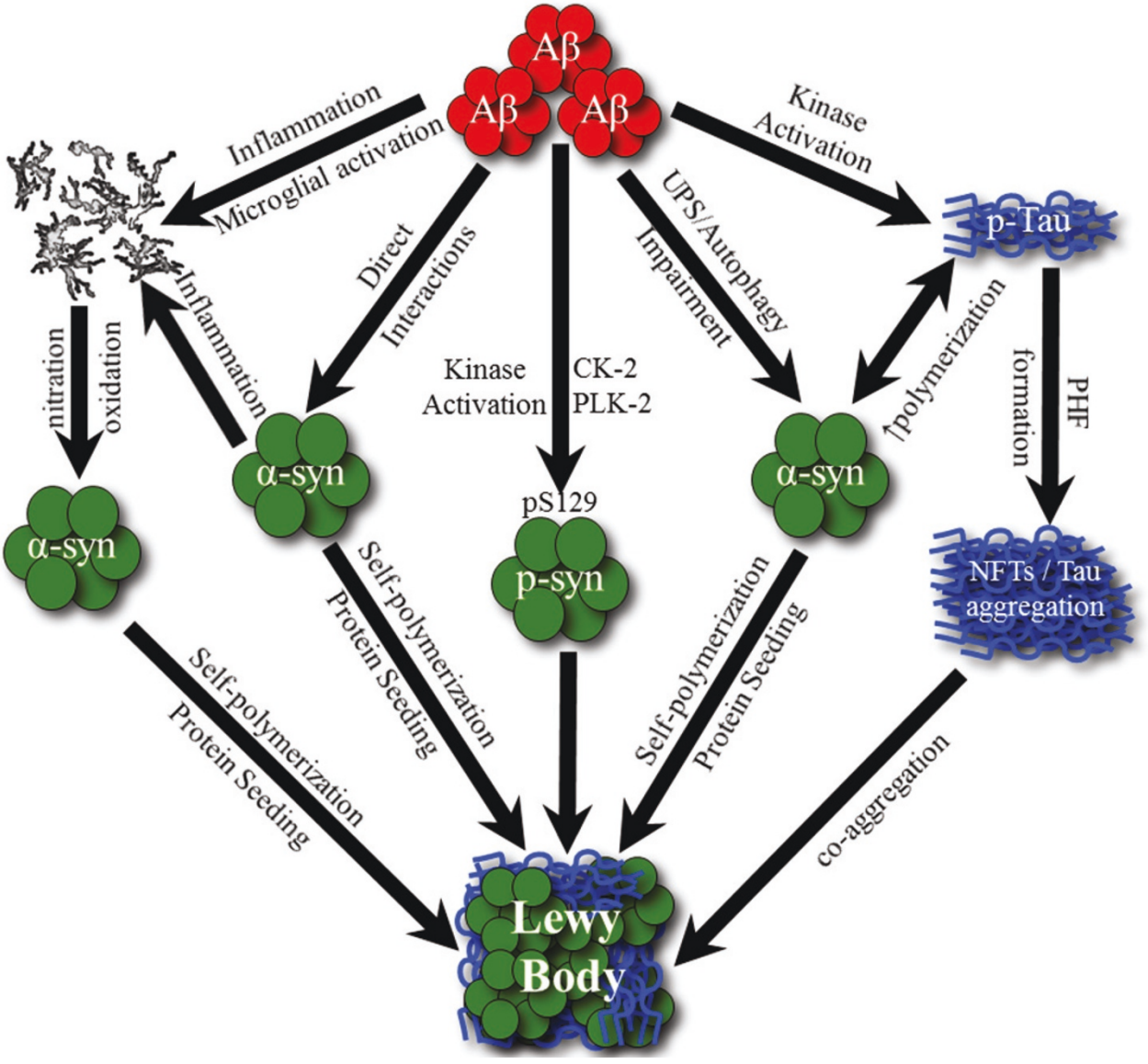

Figure 2. Potential mechanisms linking β-amyloid and α-synuclein pathology. Studies support several putative mechanisms by which β-amyloid (Aβ) and α-synuclein (α-syn) may interact to enhanced pathology and cognitive decline. Such mechanisms include (left to right): chronic inflammation and microglial activation induced by both Aβ and α-syn; direct interactions and hybrid oligomerization of Aβ and α-syn; Aβ-induced kinase activation and α-syn phosphorylation; impairment of proteasome and autophagy degradation pathways; and Aβ-induced phosphorylation of tau leading to tau-mediated enhancement of α-syn aggregation. CK-2, casein kinase 2; PLK-2, polo-like kinase 2; PHF, paired helical filaments; NFT, neurofibrillary tangle; p-Tau, phosphorylated tau; pS129, phosphorylated at serine 129; p-syn, phosphorylated α-synuclein; UPS, ubiquitin–proteasome system.

and α-syn for degradation [69-71]. Interestingly, proteasomal impairment caused by one pathogenic protein may in turn reduce degradation of other pathogenic proteins. For example, Aβ-induced proteasome dysfunction increases the accumulation of tau [64,68].

Both α-syn and Aβ are also degraded by autophagy. Pathogenic interactions between α-syn and Aβ could therefore influence the function of this critical pathway. For example, a subset of neurons with increased levels of α-syn has been shown to recruit the autophagy pathway to compensate for impaired ubiquitin–proteasome system function. An increased burden on lysosomal degradation could thus drive dysfunction in vulnerable neuronal populations [63,66]. Uptake of $A\beta_{42}$ was also shown to induce lysosomal leakage, providing another possible mechanism for both direct and indirect interactions between $A\beta_{42}$ and α-syn [19,63]. Interestingly, activation of autophagy by overexpression of Beclin-1 can reduce

not only Aβ levels but also α-syn pathology [72,73]. Impairments in autophagy could therefore simultaneously drive the accumulation of both Aβ and α-syn.

Finally, there is the possibility of disruption of cytoplasmic protease activity. For example, the serine protease neurosin (kallikrein-6) has been shown to degrade α-syn and to prevent its polymerization [63]. Intriguingly, neurosin is dysregulated in Parkinson's disease and decreased in the brains of AD patients, providing another possible mechanism by which impaired protein clearance could drive synuclein pathology [63].

Impaired protein degradation clearly plays a substantial role in many neurodegenerative disorders. The combined actions of Aβ and α-syn on the ubiquitin–proteasome system and autophagy–lysosome systems provide a potential mechanism to explain the acceleration of pathology and cognitive decline in patients with overlapping pathologies. Dysfunction in the lysosomal system may also facilitate the direct interaction between Aβ and α-syn in neuronal subpopulations where Aβ and α-syn co-exist [19].

Direct interactions between β-amyloid, α-synuclein, and tau

Aβ and α-syn do not normally exist in the same subcellular compartment in healthy cells, thus limiting their potential for direct interaction [19]. In pathological states, however, the localization of many proteins including Aβ and α-syn can be altered. For example, Aβ and α-syn have both been detected within mitochondria [74,75]. Likewise, both proteins can accumulate within lysosomes and autophagasomes [76,77]. Direct interactions between these proteins could thus potentially occur within damaged or diseased cells. To date, most of the evidence supporting direct interactions between Aβ and α-syn comes from *in vitro* experiments. For example, cell-free studies show that α-syn can promote conformational changes in Aβ that are detected by NMR spectroscopy [20]. Aβ and α-syn can also form complexes and can co-immunoprecipitate from AD-LBV patient brains and transgenic models, providing some *in vivo* evidence for direct interactions [78]. This same study provided evidence that these two proteins can form hybrid pore-like oligomers that increase calcium influx. Tau can also enhance α-syn aggregation and toxicity [34], and both proteins can co-localize within AD-LBV patient neurons, dystrophic neurites, and Lewy bodies [17,18,79]. If direct interactions between Aβ and α-syn do indeed play a role in AD-LBV pathogenesis, it will be important to understand why these interactions occur only in some patients and brain regions but not in others.

Conclusions

The co-existence of Aβ and α-syn pathologies in dementia patients clearly does not simply represent two concurrent yet independent disease states. Evidence suggests instead that Aβ and α-syn may interact synergistically to enhance each others' aggregation and accelerate cognitive decline. The mechanisms by which these two aggregation-prone proteins interact remain unclear. However, growing evidence suggests that Aβ may influence α-syn pathology by modulating protein clearance, driving inflammation, activating kinases, or directly altering α-syn aggregation. While a great deal of work is needed to confirm and clarify these putative mechanisms, the prevalence of combined AD and LB disease clearly justifies the need.

Abbreviations

Aβ, β-amyloid; α-syn, α-synuclein; AD, Alzheimer's disease; AD-LBV, Lewy body variant of Alzheimer's disease; APP, amyloid precursor protein; DLB, dementia with Lewy bodies; hSYN, human α-synuclein; NMR, nuclear magnetic resonance; PDD, Parkinson's disease with dementia; PLK2, polo-like kinase 2; pS129-syn, α-synuclein phosphorylated at serine 129; Ser129, serine 129 of α-synuclein.

Competing interests

The authors declare that they have no competing interests.

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