Heterotypic phase separation in aggregation: Driver or deterrent?

Tina Jacob, Wolfgang Hoyer

Biophysical Chemistry 331 (2026) 107577

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: www.elsevier.com/locate/biophyschem

Heterotypic phase separation in aggregation: Driver or deterrent?☆

Tina Jacob [a], Wolfgang Hoyer [a,b,*]

[a] Institut für Physikalische Biologie, Faculty of Mathematics and Natural Sciences, Heinrich Heine University Düsseldorf, 40204 Düsseldorf, Germany
[b] Institute of Biological Information Processing (IBI-7: Structural Biochemistry), Forschungszentrum Jülich, 52428 Jülich, Germany

ARTICLE INFO

Keywords:
Liquid–liquid phase separation (LLPS)
Tau protein
α-Synuclein
Protein aggregation
Heterotypic condensates
Neurodegenerative diseases

ABSTRACT

Liquid–liquid phase separation (LLPS) of proteins implicated in neurodegenerative diseases has gained growing attention in recent years, due to its potential role in driving the transition from functional protein monomers to pathogenic aggregates. However, the mechanisms by which phase separation contributes to the loss of protein function and promotes aggregation remain poorly understood. Recent studies show that multiple proteins or other biomolecules can colocalize within the biomolecular condensates, creating a highly interactive microenvironment that can modulate aggregation. In this review we look into the heterotypic phase separation of tau and α-synuclein, the two key proteins responsible for critical neurodegenerative disorders. By compiling recent findings, this review highlights the modulatory role of heterotypic condensates in disease progression and aims to provide an alternative perspective on regulation of protein aggregation in neurodegeneration.

1. Introduction

1.1. Emergence and biological roles of LLPS

Liquid–liquid phase separation (LLPS) refers to the process by which distinct phases emerge from a homogeneous solution. In eukaryotic cells, phase separation serves as a crucial mechanism for the spatial organization of biomolecules into dynamic compartments to facilitate specific cellular functions [1–3]. These compartments are distinct from conventional organelles, as they lack a membrane that allows selective regulation of molecular transmission through it. Typically, they exhibit liquid-like characteristics and adopt a spherical shape, minimizing the interfacial surface energy [4]. They show rapid molecular exchange with the surrounding cytoplasm and undergo physical processes such as Ostwald ripening and fusion, further reducing system energy [5]. Strome and Wood et al. were among the pioneers who recognized P-granule as a membraneless organelle with liquid-like properties [6]. Since then, several other cellular systems, including nucleolus [7], Cajal bodies [8], stress granules [9] were found to be formed through LLPS.

Although still in the early stages of investigation, LLPS has emerged as a fundamental mechanism regulating a wide range of biological processes. LLPS plays critical roles in transcription and translation, signal transduction, stress responses, chromatin organization and DNA damage response [10,11]. Recent studies have also underscored the role of LLPS in cancer biology, suggesting its potential as a therapeutic target for modulating drug efficacy and overcome resistance in tumor cells [12–14]. LLPS is highly responsive to environmental conditions and is therefore strongly influenced by temperature, pH, post-translational modifications and interactions with small molecules [10,12,15]. To maintain focus and avoid redundancy, this review will specifically explore phase separation in the context of proteins implicated in neurodegenerative diseases.

1.2. The convergence of phase separation and protein aggregation

Protein aggregation poses a significant challenge to biological systems, often resulting in cellular dysfunction and neurodegenerative disorders [16–18]. Upon aggregation, proteins misfold and form non-native structures that contribute to cellular toxicity. Recently, phase separation has gained attention as a potential intermediate in the transition from functional protein states to pathological aggregates [19,20]. Several proteins associated with neurodegenerative diseases have been shown to undergo phase separation, particularly above a critical threshold concentration or in response to external stimuli [21].

The tendency of a protein to undergo phase separation depends significantly on its structure. Proteins with greater proportions of

☆ This article is part of a Special issue entitled: 'condensation/aggregation' published in Biophysical Chemistry.

* Corresponding author at: Institut für Physikalische Biologie, Faculty of Mathematics and Natural Sciences, Heinrich Heine University Düsseldorf, 40204 Düsseldorf, Germany.
E-mail address: wolfgang.hoyer@hhu.de (W. Hoyer).

https://doi.org/10.1016/j.bpc.2026.107577
Received 27 October 2025; Received in revised form 8 January 2026; Accepted 9 January 2026
Available online 12 January 2026

intrinsically disordered regions (IDRs) and low-complexity domains (LCDs) are more likely to phase separate. IDRs are multifunctional, highly flexible, unstructured regions of a protein that can critically contribute to the multivalent interactions during phase separation [22,23]. LCDs are compositionally biased regions of a protein, often being a subset of IDRs. However, IDRs and LCDs are not strictly required for phase separation; phase separation abilities of proteins are also strongly influenced by post-translational modifications, environmental conditions, and heterotypic interactions [22]. The saturation concentration (C_{sat}) represents the threshold concentration above which a molecule undergoes phase separation, serving as a key determinant of phase separation propensity. Several factors including temperature, pH, ionic strength, intrinsic molecular properties and interactions with other molecules can influence C_{sat}. While self-association and phase separation of proteins have been extensively studied and implicated in various neurodegenerative diseases [1,24–26], this review will now focus on heterotypic LLPS, exploring how interactions between different molecular species drive or regulate condensate formation and aggregation.

1.3. Heterotypic LLPS

Membraneless organelles can contain dozens to hundreds of components, interacting through a wide spectrum of affinities and stoichiometries. Their formation is influenced by the relative strengths of homotypic and heterotypic interactions [3,27]. When diverse biomolecules are recruited into a single condensed liquid phase, they create microenvironments that facilitate biochemical reactions and enhance cellular compartmentalization [28]. This recruitment process establishes a two-, three- or multi-component system, resulting in a heterotypic organization, commonly referred to as heterotypic LLPS or multicomponent LLPS. While homotypic LLPS involves the self-association of identical molecules, heterotypic condensates arise from multivalent interactions between different types of molecules including electrostatic, hydrophobic, π–π or cation–π interactions between distinct molecular species [29].

We consider three possible cases for heterotypic systems; other cases have been discussed elsewhere [30,31]. (i) Cooperative heterotypic phase separation; both components have strong self-interactions and phase separate. They also exhibit strong cross-interactions and efficiently form heterotypic condensates. (ii) Scaffold-client heterotypic phase separation; here the scaffold component can phase separate on its own while the client component, which does not have phase separating abilities but has strong affinity for the scaffold, gets recruited into scaffold condensates. This scaffold-client system will be elaborated in a later section. (iii) Cross-interaction driven heterotypic phase separation. In this system, neither of the components can phase separate on its own and phase separation occurs only through strong mutual cross interactions.

Recent studies have highlighted the ability of proteins implicated in neurodegenerative diseases to form heterotypic condensates with distinct biophysical properties [3,32]. This phenomenon has gained significant attention due to its potential role in synergistic toxicity in cells, *in vitro* and in animal models. The recruitment of one protein into the condensates of another might also provide the basis for synergistic aggregation of proteins. For instance, the amyloidogenic proteins, αS and tau which are known to co-aggregate in various dementias, have also been shown to form heterotypic droplets that may contribute to the pathophysiology of Alzheimer's disease (AD) and Parkinson's disease (PD) [31,33]. Furthermore, studies demonstrating that the synergistic action of multiple proteins accelerates neurotoxicity [34–39] underscore the importance of studying protein phase behaviour in a heterotypic context.

1.4. Scaffold-client heterotypic phase separation

In scaffold-client heterotypic condensation, molecules are classified into scaffolds and clients. The scaffold component plays a crucial role by driving the formation of condensates, which then recruit client partners. Scaffolds have an intrinsic trigger to form condensates, driven by multivalent interactions or the presence of LCDs. The client partners do not favor condensation independently [27], but due to their affinity for the scaffold, they are recruited into the compartments formed by scaffolds and can significantly influence the stability and structural properties of condensates [27,40–43]. Low-valency clients compete for scaffold-scaffold binding sites, reducing scaffold connectivity and condensate stability. Alternatively, high valency clients form additional client–scaffold interactions and increase condensate stability [42]. However, the recruitment of client molecules by scaffold proteins may not be essential for condensate formation itself. One of the key determinants of client partitioning is the electrostatic interaction between charged scaffold and client components. Negatively charged molecules, such as RNA, exhibit a strong propensity for partitioning into condensates due to favourable electrostatic interactions with cationic scaffold proteins and this partitioning can be therefore regulated by the presence of ions [44]. Additionally, the concentration of the components, phase separating conditions, specific amino acid composition and post-translational modifications of client proteins can modulate the partitioning into condensates [27,45]. Importantly, the distinction between scaffold and client may be blurred for several systems and could vary with cellular conditions [41]. Nevertheless, the scaffold-client distinction is useful for understanding condensate composition.

In the following sections, we aim to integrate two key areas of research: molecular interaction studies and phase separation studies. We discuss the heterotypic phase separation partners of tau and αS, analyse the driving forces underlying their interactions, their prior associations with the corresponding protein and their effects on the heterotypic condensates formed. We further classify the nature of each heterotypic system according to their effects on tau and αS aggregation.

2. Heterotypic phase separation of tau and the impact on its aggregation

2.1. Tau

Tau is a prevalent protein in the central nervous system (CNS) primarily responsible for microtubule stability and other vital cellular functions like axonal transport, synaptic plasticity, and cell signalling [46,47]. Tau is an intrinsically disordered protein (IDP) that exists in six isoforms in the human brain, generated by alternative splicing of the MAPT gene [12]. Structurally, tau can be divided into four distinct domains: an N-terminal projection domain, a proline-rich domain, a repeat region, and a C-terminal domain [48] (Fig. 1a). The repeat domain, also known as the microtubule binding domain, is critical for tubulin binding and microtubule stabilization. Under normal physiological conditions, tau is predominantly bound to microtubules and the concentration of unbound cytosolic tau remains in nanomolar range. This low abundance of free tau makes it particularly challenging to investigate the early molecular events that lead to tau pathology [49].

The abnormal aggregation of tau into large, insoluble protein assemblies is a hallmark of AD and other neurodegenerative disorders collectively known as tauopathies [50]. The pathological cascade of tau involves several intermediate species, each associated with varied neurotoxicity. Kinases and phosphatases play vital roles in regulating tau under physiological conditions. However, dysregulated kinase activity, along with inhibited phosphatase function, can lead to tau hyperphosphorylation and misfolding. In response to these pathological triggers, monomeric tau aggregates into small, soluble oligomeric species. These oligomers have been implicated in a variety of neurotoxic effects and are considered key drivers of tau mediated toxicity [51]. With time, these oligomers are replaced by higher molecular weight (HMW) species and fibrillar forms, which appear to be less toxic than the early-stage oligomers [52–54]. This is supported by studies showing that

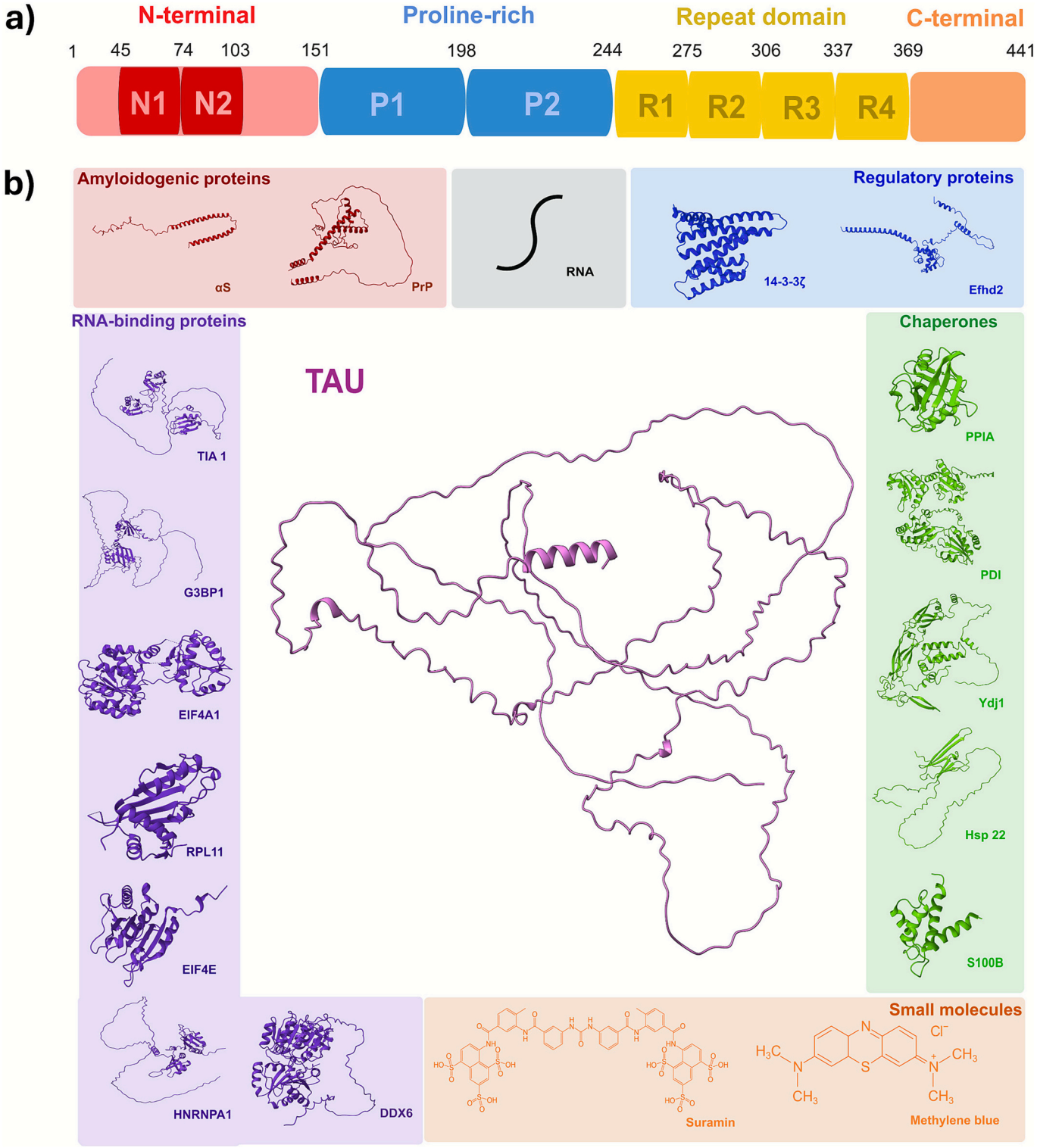

Fig. 1. a) Domains of tau. b) Structures of key heterotypic LLPS partners of tau (AF-P10636-8-F1); RNA, PrP (AF-P04156-F1), αS (PDB:1XQ8), TIA 1 (AF-P31483-F1), G3BP1 (AF-Q13283-F1), EIF4A1(PDB: 3EIQ), RPL11 (PDB: 4XXB), EIF4E, HNRNPA1(AF-Q6IPF2-F1), DDX6 (AF-P26196-F1), 14–3-3ζ (PDB: 1IB1), Efhd2 (AF-Q96C19-F1), PPIA (1AK4), PDI (AF-P07237-F1), Ydj1 (AF-A6ZS16-F1), Hsp22 (AF-Q9UJY1-F1), S100B (PDB: 1MQ1), suramin, methylene blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tau oligomers, but not fibrils, cause neurotoxicity when injected into the mouse brain, despite both species being capable of propagating tau pathology [55,56].

The process of LLPS drives the local crowding of tau, raising its concentration well above the threshold required for aggregation. As a result, LLPS has been proposed to serve as a molecular bridge between physiologically soluble, monomeric tau and its pathological, aggregated forms. The finding that tau undergoes phase separation, first demonstrated *in vitro* [57] and confirmed *in vivo* [58], was a striking addition for understanding the early steps of tau pathology. Tau condensates have been shown to gradually transition into amyloid-like aggregates, indicating LLPS as a potential intermediate step in tau aggregation

[58,59]. Although the precise contribution of LLPS in the pathology of tau still remains under active research, LLPS provides a mechanistic basis for tau accumulation.

Interestingly, tau condensates are not exclusively linked to pathology. In a physiological context, they can recruit tubulin and function as microtubule nucleation sites [60], highlighting potential functional roles of tau phase separation. However, disease-associated phosphorylation of tau has been shown to impair its microtubule-nucleating ability, even though tubulin still partitions into tau condensates [61]. These findings suggest that disease associated modifications, interactions or mutations may disrupt the balance between the functional and pathological roles of tau condensates.

As discussed generally earlier, tau LLPS is mediated by a combination of electrostatic forces, hydrophobic interactions, and thermal modulations [32,57,58,62,63]. The presence of IDRs and sequence-based charge anisotropy, confers tau with a strong propensity for phase separation [64]. High tendency for post-translational modifications and the presence of flexible IDRs, enable tau to adopt multiple conformations allowing interactions with a wide range of binding partners including proteins, nucleic acids and membranes [65]. This versatility of tau in binding diverse partners, together with its ability to undergo LLPS, facilitates its incorporation into different heterotypic systems [62,66,67]. In many of these systems, tau acts as the scaffold component, recruiting client molecules into its condensates and conferring properties distinct from homotypic tau condensates.

Here, we bring together the key systems in which tau undergoes heterotypic phase separation and summarise their effects on tau phase separation and aggregation (Fig. 1b).

2.2. Tau and RNA

The interaction between tau and RNA is among the most extensively studied heterotypic LLPS systems, explored under diverse thermodynamic conditions [32,62,63]. RNA acts as a multivalent binding partner promoting tau assembly and phase separation. Interestingly, the phase separation boundary in the phase diagram of tau:RNA LLPS lies close to physiological conditions, highlighting its potential *in vivo* relevance [68]. The net positive charge of tau at physiological pH and ionic strength facilitates its interaction with negatively charged polyanions such as RNA through long-range, weak, multivalent electrostatic interactions. Consequently, cellular ionic strength is a critical regulator of tau:RNA LLPS. The repeat domain of tau, enriched in positively-charged lysine and arginine residues, exhibits the strongest propensity for RNA association [63].

Zhang et al. were the first to demonstrate that tau undergoes RNA-driven phase separation and that tau binds to RNA in cells [62]. This entropically driven heterotypic condensation maintains a dynamic and disordered structure of tau within condensates. Tau did not undergo any conformational changes upon coacervation with RNA and the resultant condensates were resistant to any change in charge distribution on RNA or disease-associated mutations [66,69]. Najafi et al. showed that tau forms reversible, RNA-mediated condensates with higher viscosity and stability compared to homotypic condensates of tau [32]. Compared to tau LLPS, tau:RNA LLPS is less influenced by hydrophobic interactions and has reduced tendency for percolation into irreversible aggregates [58]. However, other studies revealed that tau:RNA condensates, while being stable and non-percolating, show enhanced higher-order tau accumulation and elevated intracellular seeding potential compared to tau LLPS [70,71]. These observations suggest a balance between two competing forces: (i) increased local tau concentration, which promotes aggregation, and (ii) high-viscosity of the environment which restricts diffusion and slows aggregation kinetics [66]. Nonetheless, the precise behaviour of these systems in the complex cellular context remains to be fully elucidated.

RNase treatment of these heterotypic condensates leads to RNA degradation and dissolution of tau:RNA condensates, underscoring the essential role of RNA in stabilizing these condensates [72]. Tau:RNA condensates are also involved in microtubule organization. Although RNA reduces the amount of tau directly binding to microtubules, it promotes tau-mediated microtubule bundling by sequestering tubulin into tau:RNA condensates. These condensates scaffold and organize microtubule polymerization through wetting interactions [70].

Phosphorylation is a major post-translational modification for tau, regulated by over 20 different kinases [73]. With more than 80 potential phosphorylation sites, tau becomes more negatively charged and hydrophilic upon phosphorylation [70,74]. Phosphorylation attenuates the overall positive charge of tau and weakens its electrostatic interactions with RNA. But not all phosphorylation sites have the same effect; phosphorylation at serine 262 (S262) enhance coacervation with RNA, whereas phosphorylation at threonine 205 (T205) suppress it [70]. Phosphorylated tau (ptau) tends to undergo LLPS faster than unmodified tau. However in the presence of RNA, both ptau and tau show a similar delay in the formation of condensates [72]. Also, ptau:RNA condensates disassembled at lower salt concentrations and were more sensitive to ionic strength than the unmodified tau:RNA LLPS. While enhancing the stability of ptau condensates, RNA promoted their aging into gel-like states [72].

Together, studies to date indicate that tau:RNA LLPS is less associated with amyloid aggregation than tau LLPS, and both of the systems appear to follow distinct mechanistic pathways [69]. Nevertheless, under certain cellular conditions, these mechanisms may intersect or influence one another. The primary role of tau-RNA coacervation in cells may be to spatially organize tau and its cofactors, potentially facilitating aggregation under permissive conditions without necessarily being a direct driver.

2.3. Tau and amyloidogenic proteins

One of the most intriguing coacervate partners of tau is α-synuclein (αS) and several studies have reported their co-localization [75–78]. αS is an extensively studied protein due to its critical role in the development and progression of PD. The presence of tau aggregates in PD and αS aggregates in AD and other tauopathies indicate overlapping pathological mechanisms [39,79,80]. Siegert et al. were among the pioneers who study that monomeric αS is recruited as a client molecule into tau droplets, as αS showed limited homotypic LLPS under physiological conditions [78]. The recruitment of αS into tau droplets was driven primarily by electrostatic interactions, specifically between the negatively charged C-terminal domain of αS and the positively charged proline-rich P2 region of tau. Interestingly, Gracia et al. showed that αS can also act as a scaffold, forming condensates with positively charged polypeptides and subsequently recruiting tau, including non-LLPS tau mutants [75]. The heterotypic tau:αS LLPS formed dynamic, liquid-like droplets with high electrostatic surface potential due to charge imbalance. These droplets showed a high rate of coalescence into larger condensates to compensate for charge imbalance and exhibited increased resistance to high salt concentrations. Diffusion studies revealed no major effect of αS on tau dynamics upon co-localization [78], although some studies reported that the mobility of both proteins was reduced in comparison to their respective homotypic condensates [75,77]. The maturation of these heterotypic condensates involves a gradual reorganization of their complex protein network, driven by both homotypic and heterotypic interactions. Over time, some tau:αS condensates may undergo valence exhaustion, become gel-like and fusion-incompetent whereas the larger, still liquid-like droplets serve as nucleation sites for amyloid aggregation [75]. ATP acts like a protective agent on these heterotypic condensates by increasing protein dynamics, reducing both tau and αS partitioning into the condensates and solubilizing the proteins. The presence of polyamines also suppresses tau:αS condensation, but, in contrast to ATP, polyamines promote the formation of heterotypic amyloid-like aggregates. Interestingly, αS fibrils, like monomers, can also be incorporated into tau

condensates [78]. However, unlike monomers, fibrils distorted droplet morphology and destabilized the condensates. Collectively, these findings support a biophysical model in which αS accumulates inside tau condensates and forms fibrils that disrupt and deform the tau matrix, potentially leading to their release into the cellular environment.

Human prion protein (PrP) is widely expressed in various organs and tissues, particularly in the central nervous system. Misfolding of PrP leads to a group of fatal and transmissible prion diseases [81]. Elevated PrP levels in AD suggest a potential role for PrP in disease progression [82]. PrP also interacts with Aβ by acting as a receptor for Aβ oligomers, and together they synergize with tau to promote synaptic disruption [83,84]. PrP lowers the C_{sat} of tau and gets recruited into the tau condensates *via* electrostatic interactions [85]. PrP enhances the number of condensates of tau and promotes smaller, more spherical complex coacervates. Stronger tau:PrP interactions within condensates are reflected by slower tau diffusion. These tau:PrP condensates are highly sensitive to RNA concentrations. Increasing RNA levels leads to several multiphasic rearrangements in tau:PrP condensates and excess RNA ultimately cause their dissolution. PrP also accelerates the maturation into gel-like state and transition into solid-like co-aggregates and fibrils. The protective role of RNA in dissolving the heterotypic condensates into individual protein monomers warrants further investigation and could be employed to target tau:PrP interactions.

2.4. Tau and RNA binding proteins (RBPs)

RNA-binding proteins (RBPs) bind to RNA through one or multiple RNA-binding domains and play crucial roles in regulating RNA metabolism [86]. Many RBPs associate with RNA *via* LLPS, leading to the formation of ribonucleoprotein (RNP) granules such as stress granules, P-bodies, germ granules. These RNP granules are essential for various cellular functions, including RNA processing, storage of messenger RNAs (mRNAs), localization of RNAs and RNA degradation [87].

Stress granules (SGs) assemble in the cytoplasm during cellular stress to mediate a pro-survival adaptive response. The formation of SGs helps minimize cellular energy demands, and their disassembly upon stress removal is essential to restore normal cellular metabolism [5,88]. Many protein components of SGs, including TDP-43, TIA-1, PABP-1, and TTP, have been extensively studied and these proteins are often mutated or mislocalized in neurodegenerative diseases [89,90]. Several stress granule proteins exhibit unique interactions with tau and are thus closely associated with AD, with TIA-1 being a prominent example [63,91]. Colocalization of TIA-1 with tau aggregates has been observed in AD, and knockdown of TIA-1 results in suppression of TIA-1 mediated tau aggregation [92–95]. Tau supports the normal cellular functions of TIA1, including its interactions with other RBPs and stress granule formation. In contrast, overexpression of TIA1 promotes tau misfolding and neurodegeneration, while reducing TIA-1 levels mitigates tau toxicity [93].

The heterotypic coacervation of tau with RBPs is strongly influenced by several factors, including the domain structure of the RBPs, the relative concentration of RBPs to tau, electrostatic interactions, thermodynamic factors and the balance between homotypic and heterotypic interaction enthalpy. Among all RBPs studied, TIA-1 exhibits a uniquely potent influence on tau phase separation and aggregation. TIA-1 was the most effective in driving tau phase separation, even in the absence of artificial crowding [71]. TIA-1 driven condensates were smaller but higher in number. Upon heterotypic coacervation with TIA 1, tau showed a reduced mobility and accelerated maturation into a gel-like state [96]. Tau also showed multiphasic organization within the condensates. At higher TIA-1 concentration, tau formed concentrated microdomains inside TIA-1 condensates, suggesting that homotypic tau–tau interactions override heterotypic tau:TIA-1 interactions, leading to internal immiscibility. However, these condensates of tau were not toxic even at high concentrations of both proteins.

In the presence of RNA, TIA-1 selectively promoted the formation of oligomeric tau species [71]. Oligomeric tau has been studied to be more toxic than the fibrillar tau causing numerous neurotoxic effects [55]. TIA-1 together with RNA triggered the formation of oligomers of tau at a faster rate than compared to RNA alone but did not induce the formation of HMW or fibrillar tau species. Interestingly, these oligomers of tau formed in the presence of TIA-1 showed higher toxic effects than the fibrillar forms formed in the presence of RNA alone. However, a parallel study showed that TIA-1 couldn't trigger tau aggregation in the presence of artificial molecular crowders, indicating the influence of environmental factors. Overall, TIA-1 promotes tau phase separation and the formation of toxic oligomeric aggregates, but this process could be sensitive to cellular context, highlighting the need for further investigation.

Among other tested RBPs, G3BP1 was able to recruit condensates of tau in the presence of RNA, but to a lesser extent than TIA-1 [71]. Several other RBPs, including DDX6, HNRNP1, RP11, EIF4A1, and EIF4E, formed heterotypic condensates with tau only in the presence of both RNA and PEG, suggesting that they act as weaker scaffolds. DDX6 showed a concentration-dependent shift in condensate morphology, indicating a dynamic balance between homotypic and heterotypic interactions. HNRNP1 formed distinct microdomains within tau condensates. EIF4A1 exhibited pH-dependent partitioning, driven by changes in net charge and electrostatic interactions.

However, none of these RBPs other than TIA-1 triggered the formation of neurotoxic oligomers or any other accumulations of tau. Hence, the role of these RBPs which co-localize with tau condensates still needs to be explored in the context of tau aggregation.

2.5. Tau and molecular chaperones/regulatory proteins

Molecular chaperones are a diverse group of proteins that regulate essential cellular functions. They assist in protein folding under both physiological and stress conditions, and are therefore critically implicated in the context of neurodegenerative diseases [97,98]. The protective roles of several classical chaperones against neurotoxic protein deposits have been well studied [99]. Notably, Hsp70 has been shown to disaggregate tau fibrils, converting them back into monomers [100]. Recently, chaperones have been recognized for their ability to regulate phase separation, particularly in preventing the transition of protein condensates into solid-like aggregates [101,102]. Several heat shock proteins (Hsp) modulate condensation behaviour of disease-related proteins and protect them against pathological aggregation [101,103]. In this section, we explore how various chaperone and regulatory proteins interact with tau and modulate its phase separation and aggregation behaviour.

Small heat shock proteins (sHsp) are stress-induced chaperones characterized by their low molecular weight and ability to prevent protein aggregation [104]. Hsp22 is one of them and was recruited into the condensates of tau. Hsp22 significantly enhanced the number of smaller condensates [105]. Importantly, Hsp22 significantly slowed the aggregation of tau and prevented its maturation into amyloid-like aggregates.

Another key chaperone, heat shock protein 40 (Hsp40), plays a central role in regulating tau aggregation and has been linked to pathological nucleation events in AD and other neurodegenerative diseases [106]. The yeast homolog of Hsp40, Ydj1, was found to be enriched within tau condensates [107]. Ydj1 promoted tau phase separation at lower critical concentrations, and its interaction with tau is mediated by both electrostatic and hydrophobic forces and results in dense co-condensates. Ydj1 inhibited tau aggregation even at sub-stoichiometric levels. Instead of toxic amyloid fibrils, Ydj1:tau co-condensates formed non-amyloidogenic heterocomplexes. These findings highlight a condensate-mediated chaperone mechanism, in which proteins like Ydj1 enhance tau LLPS while preventing its pathological maturation, offering a promising therapeutic approach.

S100B is a Ca^{2+} binding protein known for its chaperone activity,

particularly in binding to AD proteins and preventing their misfolding [108,109]. The chaperone activity of S100B is regulated by Ca^{2+} and it binds to proteins in a Ca^{2+}-dependent manner. S100B has been shown to interact with tau *in vivo* and inhibit the seeding ability of tau oligomers [109]. Ca^{2+}-bound S100B (Ca^{2+}-S100B) was recruited into tau LLPS and slowed down tau phase separation [110]. In the presence of Ca^{2+}-S100B, a higher level of molecular crowding was required to induce tau LLPS. This inhibitory effect increased with rising concentrations of Ca^{2+}-S100B. In contrast, Ca^{2+}-free S100B had minimal impact on tau LLPS and aligned with the previous study that S100B- tau interaction is regulated by Ca^{2+} levels [109]. Importantly, excess calcium alone did not influence tau LLPS, ruling out a direct role of Ca^{2+} itself. Ca^{2+}-S100B did not alter the internal dynamics of tau after incorporation into condensates. Interestingly, although high-molecular-weight (HMW) tau oligomers formed at early stages, their levels decreased at later time points in the presence of Ca^{2+}-S100B. These findings suggest that Ca^{2+}-S100B acts as a regulator within tau condensates, dampening both condensation and subsequent aggregation processes.

14-3-3 proteins are a family of multifunctional regulatory proteins widely expressed in the central nervous system. They typically interact with target proteins at their phosphorylated sites, and these interactions are crucial in a variety of cellular processes [111]. 14-3-3 proteins have been found to associate directly with tau [112–114] and are present in neurofibrillary tangles (NFTs) in the brains of AD patients [115]. 14-3-3ζ, one of the seven isoforms, plays a particularly important role in tau regulation. Several studies have shown that 14-3-3ζ binds tau and enhances its phosphorylation and aggregation *in vitro* [116–118]. 14-3-3ζ is recruited into condensates formed by both phosphorylated and unphosphorylated tau, interacting with the proline-rich domain (PRD) and the microtubule-binding domain (MTBD) of tau. These co-condensates are stabilized by a combination of hydrophobic and electrostatic interactions [67,119]. 14-3-3ζ regulated tau LLPS in a concentration-dependent manner, where the droplet number increased initially and then dropped with increasing 14-3-3ζ concentration. In phosphorylated tau condensates, 14-3-3ζ reduced molecular mobility, while it had no significant effect on unphosphorylated tau dynamics [67,119]. However, despite being present in the droplets, 14-3-3ζ did not promote the maturation or aging of these co-condensates. The protective role of 14-3-3ζ in preventing tau aggregation is context-dependent, influenced by the phosphorylation state of tau and the cellular environment, as has been previously observed in 14-3-3ζ-mediated regulation of tau aggregation [119,120]. Hence, the exact role 14-3-3ζ in LLPS-mediated aggregation of tau is not fully understood and demands further studies.

Protein disulfide isomerase (PDI) is a multifunctional chaperone primarily located in the endoplasmic reticulum (ER), where it plays a crucial role in protein folding, particularly during ER stress [121,122]. PDI binds preferentially to misfolded proteins through hydrophobic interactions and has been implicated in various neurodegenerative diseases, especially AD [123–125]. In AD brains, PDI colocalizes with tau in NFTs and is upregulated in AD mouse models [126,127]. PDI directly interacts with tau, inhibiting its phosphorylation and aggregation [128]. PDI undergoes heterotypic condensation with tau and suppresses phase separation of tau [128]. PDI diminishes the number of condensates and in the resulting co-condensates, PDI enhanced the liquid nature of tau. PDI slows down the maturation of tau condensates into hydrogels or mature fibril filaments. However, S-nitrosylation of PDI, an aberrant modification observed in AD and PD, impairs its protective role. S-nitrosylated PDI fails to be recruited into tau condensates and does not inhibit phase separation. Instead, it is associated with increased formation of tau droplets, hydrogels, and fibrils. This highlights how post-translational modifications of PDI can convert a protective factor into a contributor to tau pathology.

EFhd2 is a highly conserved calcium-binding protein predominantly expressed in the central nervous system and implicated in various pathological conditions, including cancer and neurological disorders [129]. In AD, EFhd2 colocalizes with pathological aggregated forms of tau and is increasingly detected as neurodegeneration progresses [130,131]. Also, *in vitro* studies demonstrate that EFhd2 promotes tau amyloid formation, suggesting a critical role in AD progression [132]. EFhd2 alone exhibits phase separation in the presence of molecular crowding and in response to calcium ions (Ca^{2+}), forming dynamic liquid condensates. However, in the absence of Ca^{2+}, EFhd2 formed solid-like amorphous aggregates [133]. EFhd2 also modulates LLPS of tau at sub-molar concentrations and in a Ca^{2+}-dependent manner. In the presence of Ca^{2+}, EFhd2 forms co-condensates with tau, whereas without Ca^{2+}, EFhd2 disrupts tau phase separation and together they accumulate into solid-like structures [133]. While the solid-like accumulations of EFhd2 with tau could potentially influence tau's transition toward pathological states, the study does not directly demonstrate this, and the role of EFhd2 in neurodegeneration remains unclear [129].

Peptidyl prolyl isomerases (PPIases) or cyclophilins are a family of molecular chaperones that facilitate protein folding by catalysing the cis–trans isomerization of proline residues [134]. PPIases are essential for proper protein conformation and function, and have been implicated in a range of pathological conditions, including cancer, neurodegenerative diseases, viral infections, and psychiatric disorders [135–137]. Peptidyl prolyl isomerase A (PPIA) is vital for numerous biological processes, including those linked to neurodegenerative diseases [138,139]. PPIA has been shown to reduce tau aggregation, and high proline content of tau enhances its interaction with PPIA. PPIA is recruited into tau condensates and becomes enriched within them [140]. PPIA does not alter the liquid-like properties or dynamics of tau in co-condensates. However, when added to pre-formed tau droplets, PPIA induces their dissolution, releasing monomeric tau into solution. Although the effects of PPIA on the maturation of tau condensates remain to be fully characterized, these studies suggest a potential chaperone-like role in regulating tau LLPS and preventing pathological aggregation. Given its chaperone-like role in regulating tau aggregation [141], PPIA enzymes represent promising candidates for developing therapies for AD.

2.6. Tau and small molecules

Suramin is a polyanionic compound with broad pharmacological activity and has been used for treating various diseases, including neurodegenerative disorders [142]. Suramin has been previously shown to inhibit the aggregation of amyloidogenic proteins, including Aβ [143,144]. Suramin strongly enhances tau LLPS, resulting in the formation of larger condensates [145]. Like RNA, suramin interacts electrostatically with tau through its multiple negative charges. Interestingly, suramin disrupts pre-formed tau condensates with RNA and heparin by outcompeting these polyanions for tau binding. Moreover, it inhibits the formation of seeding competent species from tau: suramin condensates and tau:heparin condensates. These findings suggest that suramin may serve as a therapeutic candidate to interfere with tau condensation and its pathological maturation.

Methylene Blue (MB) is a well-known redox-active dye with established clinical applications across various diseases and infections [146]. In the context of neurodegeneration, MB reduces hippocampal amyloid-β levels and inhibits tau aggregation *in vitro* [147,148]. MB directly binds to tau and enhances its phase separation, even in the absence of crowding agents [149]. MB increases droplet turbidity and size and lowers the C_{sat} for LLPS. This modulation of tau LLPS by MB is independent of its redox activity on tau cysteine residues and is instead mediated through electrostatic and hydrophobic interactions. MB significantly reduces the internal dynamics of tau within the condensates, suppresses droplet fusion, and promotes a transition from a liquid-like to a gel-like state. Importantly, MB does not interfere with tau's functional role in tubulin polymerization. While MB-induced condensates mature into non-toxic amorphous aggregates, they deviate tau from forming Thioflavin T (ThT)-positive amyloid fibrils. Thus, MB

protects against pathogenic tau aggregation by redirecting it toward alternative, less cytotoxic pathways.

Table 1 provides an overview of heterotypic LLPS partners of tau discussed in this study. Each system is classified according to the type of LLPS based on the information from original publications. Due to its strong intrinsic phase-separating propensity, tau predominantly functions as the scaffold component driving phase separation in most systems. Depending on their influence on driving tau into toxic aggregates, the interacting partners have been categorized as either drivers or deterrents of tau aggregation.

3. Heterotypic phase separation of αS and the impact on its aggregation

3.1. αS

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. The hallmark feature of PD pathology is the aggregation of alpha-synuclein (αS), a presynaptic protein, into Lewy bodies. Genetic mutations and altered expression of the *SNCA* gene, which encodes αS, are the key contributors to disease progression [150–153].

αS is a 140-amino acid protein predominantly expressed in neurons of the central and peripheral nervous system. αS plays crucial roles in synaptic function and neurotransmitter release and is predominantly localized at presynaptic terminals [154,155]. In its native state, αS is inherently disordered, which allows it to interact with various cellular membranes and proteins. However, this structural flexibility can also contribute to its pathological accumulation in neurons. The resultant toxic assemblies disrupt neuronal homeostasis and define a group of disorders known as synucleinopathies [156,157].

The structural properties of αS contribute significantly to its function and role in disease. αS is comprised of three major regions: an N-terminal region involved in membrane binding, a central hydrophobic non-Aβ component (NAC) region responsible for fibril formation and a flexible C-terminal region [158] (Fig. 2a). αS exists as an unstructured monomer, resistant to fibrillization within healthy neurons [159]. In contrast, pathological conditions induce a conformational shift toward β-sheet-rich oligomers and fibrils that accumulate into Lewy bodies. These structurally diverse species including oligomers and mature fibrils can interconvert and contribute differentially to toxicity [160]. Increasing evidence implicates prefibrillar oligomers as the primary toxic intermediates mediating pathology primarily through membrane disruption, organelle dysfunction and neuroinflammation [161,162]. Nonetheless, mature fibrils also contribute to toxicity and together with αS oligomers, they drive disease progression [163–167].

Recent studies have highlighted that αS can undergo LLPS, majorly driven by the N terminus and NAC region, to form liquid droplets that may serve as precursors to amyloid fibrils [168–170]. Although αS exhibits relatively low LLPS propensity at physiological pH, the phase separation behaviour of αS was regulated by various PD-associated factors such as local concentration of αS, pH shifts, metal exposure, lipid interactions and mutations [76,171]. Initially, αS droplets show liquid-like properties and undergo a time dependent liquid-to-solid transition, progressively forming rigid, insoluble assemblies enriched in fibrillar and oligomeric species [168]. Fibrillization of αS is accelerated when mediated through LLPS. Conditions that suppress LLPS delay or inhibit αS aggregation, suggesting a potential implications of αS condensation in PD progression [172]. However, some disease-associated αS mutants form fibrils without undergoing LLPS, and fibrils formed under LLPS conditions exhibit structural properties distinct from those formed under non-LLPS conditions [173]. Together, these findings point toward the complex nature of αS phase separation and highlights the need for further investigation within the broader landscape of neurodegenerative diseases.

The presence of large amounts of lipids in Lewy bodies indicates a close association between αS and lipids in PD pathology [174]. αS interacts with lipid membranes through a combination of electrostatic and hydrophobic interactions. The positively charged N-terminal region of αS primarily mediates binding to anionic lipid membranes, leading to partial folding of αS into an amphipathic α-helix. Hydrophobic interactions between the nonpolar face of this helix and the lipid bilayer further stabilize the membrane-bound state of αS. Under physiological conditions, these interactions are important for the normal function of

Table 1
Effect of hetero phase separation on tau aggregation.

Partner	LLPS type	Effect on LLPS	Effect on tau aggregation	Enhance (+) Suppress (−)	References
RNA	tau (scaffold) RNA (client)	Promotes heterotypic LLPS, increases droplet viscosity and stabilitv	Decreases aggregation tendency, context-dependent	+/−	[32,62,63]
αS	both tau and αS can act as scaffolds	Promotes heterotypic LLPS, retains liquid-like state, more resistant to electrostatic screening	Enables nucleation of amyloid aggregation, forms heterotypic aggregates with polyamines	+	[75,77,78]
PrP	tau (scaffold) PrP (client)	Promotes heterotypic LLPS, increases number, forms smaller and more spherical condensates	Accelerates maturation into solid-like fibrils	+	[85]
TIA 1 (RBP)	Cooperative LLPS	Forms heterotypic condensates, increases number, smaller in size	Accelerates gelation, with RNA promotes toxic tau oligomer formation	+	[71,96]
Efhd2	Cooperative LLPS	Heterotypic phase separation regulated by Ca2+, forms dynamic co-condensates with tau	Can trigger formation of solid-like co-aggregates with tau	+/−	[133]
Hsp22 (chaperone)	tau (scaffold) Hsp22 (client)	Hsp22 is recruited into tau LLPS, increases number of condensates	Prevents maturation and inhibits tau aggregation	−	[105]
PDI (chaperone)	tau (scaffold) PDI (client)	Reduce number of condensates, regulated by nitrosylation of PDI	Inhibits tau aggregation, nitrosylation impairs the neuroprotection	−	[128]
14-3-3ζ (chaperone)	tau (scaffold) 14–3-3ζ (client)	14–3-3ζ recruited into tau condensates, concentration-dependent regulation of tau LLPS	No effect on maturation or aging of co-condensates	+/−	[67]
S100B (chaperone)	tau (scaffold) S100B (client)	Slows down tau LLPS	Reduces formation of HMW tau oligomers	−	[110]
Ydj1 (chaperone)	tau (scaffold) S100B (client)	Lowers critical concentration of tau LLPS, enhances phase separation	Forms non-amyloidogenic heterocomplexes	−	[107]
PPIA	tau (scaffold) PPIA (client)	PPIA recruited into tau LLPS, maintains dynamic state of condensates	Dissolves the condensed phase into single mixed phases	−	[140]
Suramin	tau (scaffold) Suramin (client)	Enhances heterotypic LLPS, promotes bigger droplets	Inhibits formation of seed competent tau species	−	[145]
Methylene Blue	tau (scaffold) MB (client)	Binds to tau in condensates, enhances phase separation	Accelerate liquid-to-gel-like transition, redirects tau into less cytotoxic pathways	−	[149]

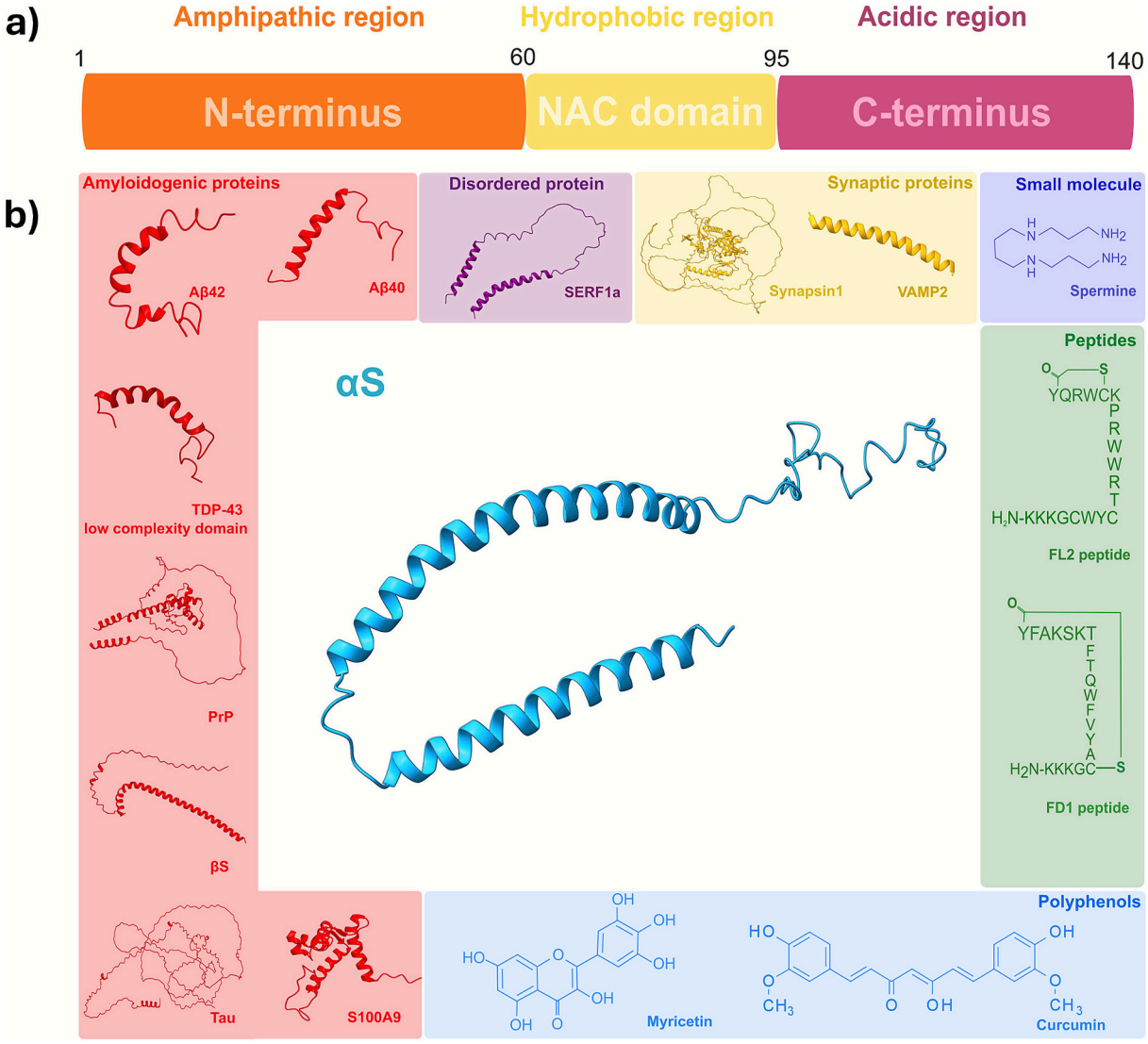

Fig. 2. a) Regions of αS. b) Structures of key heterotypic LLPS partners of αS (PDB:1XQ8); Aβ40 (PDB:1BA4), Aβ42 (PDB:1Z0Q), TDP-43 low complexity domain (PDB:2N2C), PrP (AF-P04156-F1), βS (AF-Q16143-F1), tau (AF-P10636–8-F1), S100A9 (PDB: 5I8N), SERF1a (AF-O75920-F1), synapsin1(AF-P17600-F1) VAMP2 (PDB: 3RL0), spermine, FL2 peptide, FD1 peptide, curcumin, myricetin.

αS [175]. However, under pathological conditions, the same interactions can promote αS aggregation [176]. The aggregation of αS is strongly influenced by lipid composition and by the lipid-to-αS ratio, indicating that membranes can modulate αS assembly pathways [177,178]. Lipids also modulate αS LLPS. Depending on lipid properties and the order in which components are mixed, lipid membranes can either partition into αS condensates or become recruited to their surfaces, which can accelerate αS LLPS and promote condensate maturation [168,179,180]. In contrast, other studies report that liposomes stabilize αS condensates and delay or prevent their maturation [170]. In addition, synaptic proteins such as synapsin-1 and VAMP2 can be recruited into αS condensates formed by LLPS, which may further enhance interactions between αS and lipid membranes [181–183]. Together, these findings highlight the need for further studies to better understand how lipid membranes regulate αS behaviour under LLPS conditions and how these interactions contribute to both normal function and disease.

αS interacts with a diverse array of biomolecules, including enzymes, chaperones, and cytoskeletal proteins and these interactions significantly impact its biological functions, aggregation propensity, and contributions to neurodegeneration [184]. More than 70 of these different interacting partners are identified within Lewy Bodies [185]. Moreover, other neurodegenerative disease-associated proteins such as tau, Aβ, prion proteins, TDP-43 and Huntingtin, are often found to cross-seed and co-deposit with αS aggregates [186–188]. Heterotypic interactions between these proteins may underlie the co-occurrence of multiple pathologies and their synergistic contribution to disease progression [189,190].

In the following sections, we review the interacting partners that undergo heterotypic phase separation with αS and discuss their influence on αS aggregation (Fig. 2b).

3.2. *αS and amyloidogenic proteins*

Tau is a major amyloidogenic interaction partner of αS, and their heterotypic condensation has been discussed in Section 2.3.

Transactive response DNA-binding protein 43 (TDP-43) is a critical pathological protein implicated in various neurodegenerative diseases, predominantly in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [191]. TDP-43 functions as a nuclear RNA-binding protein involved in RNA processing as well as a cytosolic regulator of stress granule dynamics. Under pathological states, TDP-43 undergoes nuclear depletion and cytoplasmic aggregation, a hallmark of

ALS and FTD pathology [192,193]. Previous studies indicate a direct interaction between TDP-43 and αS. They co-deposits in glial cytoplasmic inclusions and synergistically enhance cytotoxicity [194–196]. αS also interacts with the prion-like domain of TDP-43 (TDP-43PrLD), seeding its aggregation and forming cytotoxic heterofibrils [187]. TDP-43PrLD shows a strong propensity to undergo coacervation with RNA and form highly dynamic condensates. Although, αS alone does not phase separate under these conditions, it was readily recruited into preformed TDP-43PrLD–RNA droplets [197]. The interaction between αS and TDP-43PrLD were driven majorly by electrostatic interactions and occurred under cellular conditions as well. αS significantly reduced the liquid-like nature of TDP-43PrLD within the droplet. Together with RNA, αS localized asymmetrically to the droplet surfaces and prevented the coalescence between condensates. αS exhibited low fluorescence recovery at the condensate periphery, indicative of a more solid-like state. αS significantly accelerated fibril nucleation and aggregation within these co-condensates, producing heterotypic fibrils with morphologies resembling both αS and TDP-43PrLD control fibrils. The formation of these heterotypic aggregates suggests a mutual promotion of aggregation between αS and TDP-43, indicating that their co-pathology in neurodegeneration might be mediated by LLPS.

As discussed earlier in this review, PrP undergoes heterotypic condensation with tau. Interestingly, PrP also interacts with αS and similarly forms heterotypic condensates. Several studies have demonstrated that PrP can act as a receptor for αS aggregates, promoting their internalization and enhancing their toxicity [198,199]. The role of PrP in αS pathology appears to be complex and context dependent. While several studies support its involvement in αS propagation and toxicity, others report minimal or no contribution [200,201]. Under physiological conditions, where neither PrP nor αS phase separate on their own, their mixture leads to the spontaneous formation of co-condensates rich in both PrP and αS [202]. These PrP:αS condensates exhibit dynamic liquid-like properties and both proteins showed high mobility within the condensates. The heterotypic condensation is primarily driven by electrostatic interactions and is sensitive to higher stochiometric mixing. Spatiotemporal organization within the PrP:αS condensates was modulated by RNA, leading to the emergence of multiphasic condensates [202]. Under quiescent conditions, these droplets undergo a gradual liquid-to-solid transition; however, mechanical agitation triggers a rapid conversion into heterotypic amyloid aggregates. Notably, this conversion does not occur under non-LLPS conditions, highlighting the critical role of LLPS in facilitating aggregation. Given that the PrP:αS interaction is highly context dependent, further studies under *in vivo* contexts are needed to explore their LLPS-mediated interaction.

Amyloid beta (Aβ) is a 39–43 amino acid peptide central to the AD pathogenesis [203]. In humans, Aβ is produced through sequential proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases [204], with Aβ40 and Aβ42 reposted as the most abundant isoforms. Low amounts of Aβ peptides are present in non-demented individuals and are considered part of normal physiology [205,206]. However, a net balance of Aβ production and degradation is critical and disruption of Aβ clearance mechanisms leads to its accumulation and deposition as senile plaques [207]. Under pathological conditions, Aβ aggregates extracellularly to form amyloid plaques, which, together with NFTs of tau, represent the principal neuropathological hallmarks of AD [208]. An intriguing pathological overlap has been observed between αS and Aβ. In addition to the characteristic Lewy bodies, Aβ deposits are frequently detected in PD [209,210]. Furthermore, Aβ plaques accelerates αS seeding and spreading [211]. Conversely, Lewy bodies are observed in most sporadic AD cases, and αS has been detected as a component of Aβ plaques [212]. These observations have led to several *in vitro* studies investigating the interaction between αS and Aβ, and findings show that Aβ monomers and oligomers drive αS aggregation [213,214] and also form hetero-complexes [215]. Recent studies indicate that Aβ40 and Aβ42 are recruited into αS condensates [216,217]. Although Aβ peptides have been reported to undergo LLPS previously [218–220], within the specified experimental conditions Aβ peptides did not undergo homotypic LLPS. However, αS alone underwent phase separation under similar conditions, indicating the scaffold nature of αS in driving heterotypic LLPS. While lower concentrations of Aβ40 and Aβ42 did not affect the phase separation behaviour of αS, higher concentrations inhibited LLPS. Interestingly, a different modulation behaviour for αS LLPS was observed for lower concentrations of Aβ40 and Aβ42. With αS, Aβ42 underwent aggregation and these ThT-positive aggregates promoted phase separation of αS by serving as nucleation points for αS condensates. This led to the formation of a heterotypic system, where Aβ42 existed as solid clusters while preserving the dynamic nature of the αS condensates. On the other hand, Aβ40 monomers recruited into αS remained homogenous inside αS condensates. Aβ40 promoted the number of heterotypic condensates and reduced the size of the condensates. They also showed differentiated effect on the liquid-to-solid transition of αS condensates. While Aβ42 does not significantly influence the maturation of αS condensates, increasing Aβ40 concentrations promoted the aging and solid-like properties of condensates, thereby triggering the aggregation of αS. Studies using other variants of Aβ showed that shorter variants like Aβ35–25, Aβ37 and Aβ39 showed a modulation behaviour like Aβ40, and longer variants like Aβ43 showed similar effects like Aβ42. These findings indicate that Aβ peptides undergo heterotypic LLPS with αS and that most variants promote aggregation of αS.

β-Synuclein (βS) is a member of the synuclein family, sharing 78% sequence homology with αS [221]. βS is found abundantly in the central nervous system and co-localizes with αS at the presynaptic terminals. Despite their structural similarity, βS is considerably less aggregation-prone and is generally considered neuroprotective, counteracting αS aggregation and associated toxicity. Studies have shown that βS inhibits both the initiation and amplification phases of αS aggregation by competitively binding to lipid surfaces and αS fibrils [222–224]. βS, as a client component partitions into αS condensates through electrostatic interactions and co-localizes with αS under physiological and crowded conditions [225]. Notably, αS alone undergoes phase separation under these conditions, whereas βS does not. The presence of βS enhances αS phase separation by increasing the size, number, and liquidity of the condensates. However, contrasting findings suggest that βS can also negatively regulate αS phase separation and reduce condensate fluidity [226]. Despite these opposing effects, both studies support a protective role of βS in modulating αS aggregation *via* LLPS. βS dramatically delayed the tendency of liquid-to-solid transition of the co-condensates and prevented the formation of amyloid fibrils. Yet, emerging evidence indicates that βS may gain toxic properties under pathological conditions. Altered expression levels or disease-associated mutations in βS have been shown to promote the maturation of αS condensates into gel-like, aggregation-prone states [227]. These findings highlight a delicate balance in the modulatory role of βS, which may shift from protective to pathogenic in disease contexts.

S100A9 is a pro-inflammatory protein constitutively expressed by neutrophils, dendritic cells, and monocytes and has been implicated in the pathogenesis of various types of cancer, chronic inflammation, and neurodegenerative diseases [228]. S100A9 is a potential initiator and amplifier of amyloid pathology in PD, primarily through its ability to co-aggregate with αS and significantly accelerate its fibrillation [229]. Both S100A9 and αS independently undergo LLPS under conditions of molecular crowding at physiological pH, forming homotypic condensates. In the case of S100A9, these homotypic condensates often coexist with aggregates. Upon co-incubation of S100A9 and αS, the number of condensates were enhanced and these included S100A9:αS heterotypic condensates, as well as, S100A9 and αS homotypic condensates [230]. The S100A9:αS interaction was driven by a combination of electrostatic and hydrophobic interactions. Within the mixed condensates, S100A9 aggregation is notably suppressed by αS, although it displays uneven, clumped distribution. Conversely, S100A9 strongly promotes αS aggregation, accelerating fibril formation and stabilizing a distinct αS fibril

strain with enhanced seeding capacity. The cellular abundance of S100A9, its upregulation during neuroinflammation, and its propensity to seed αS aggregation collectively suggest that S100A9 may represent a therapeutic target for Parkinson's disease.

3.3. αS and synaptic/disordered proteins

VAMP2 (vesicle-associated membrane protein 2) is a key component of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex [231]. VAMP2 mediates the fusion of synaptic vesicles (SVs) with the presynaptic membrane and facilitates exocytosis and plays a pivotal role in neurotransmitter release. αS has been shown to directly bind VAMP2 and regulate SNARE complex assembly [232]. Recent studies have demonstrated that αS undergoes heterotypic condensation with VAMP2 [183], as well as with SVs containing VAMP2 [182]. Under the corresponding experimental conditions, αS forms homotypic condensates, and the presence of VAMP2 significantly lowers the C_{sat} required for αS phase separation. VAMP2 also enhances both the size and number of αS condensates. Within these heterotypic condensates, αS retains high liquid-like mobility, indicating the preservation of a dynamic phase. Importantly, VAMP2 markedly suppresses αS oligomerization upon heterotypic condensation and also inhibits αS fibrillation, highlighting a potential protective role for VAMP2 in αS pathology [182]. Thus, beyond its established function in SV clustering and synaptic transmission [233], VAMP2 may act as a molecular modulator that mitigates the aggregation propensity of αS through LLPS.

Small EDRK-rich factor (SERF) proteins are evolutionarily conserved, highly charged and conformationally dynamic molecules that play a critical role in modulating cellular mechanisms that underpin stress granule formation and protein aggregation [234]. Their intrinsic disorder, driven by extensive intrinsically disordered regions (IDRs), enables them to engage flexibly with a wide range of interaction partners [235]. SERF proteins have been directly implicated in modulating the aggregation of amyloidogenic proteins [236–238]. Specifically, SERF binds to αS in the cytoplasm, generating SERF/αS complexes [237]. SERF competes with the protective intramolecular interactions within αS and promote the nucleation of αS aggregates [239,240]. SERF undergoes electrostatically driven homotypic LLPS forming dynamic condensates both *in vitro* and *in vivo*. Although αS alone does not phase separate under these conditions, it is readily recruited into pre-formed SERF condensates, resulting in the formation of larger and denser heterotypic droplets [241]. Interestingly, as these condensates mature, αS shows a dramatic reduction in fluorescence recovery, suggesting a transition to a solid-like state, whereas SERF retains its mobility. Over time, SERF exits the condensates, leaving behind solidified αS. This co-localization significantly accelerates the formation of ThT-positive aggregates. Notably, while SERF promotes αS fibril formation, it simultaneously suppresses the accumulation of toxic oligomeric intermediates. By redirecting aggregation toward less harmful fibrillar forms, SERF reduces αS-induced cytotoxicity, underscoring its dual role as both a pro-amyloid modulator and a mitigator of oligomer toxicity.

Synapsin proteins are integral to several functions in neuronal physiology, particularly in the assembly of SVs and regulation of neurotransmitter release [242]. Phase separation underlies SV organization, and synapsins have been shown to form liquid-like condensates *in vitro* that incorporate liposomes mimicking SVs [243]. Dysregulation of synapsin activity has been implicated in several neurological disorders [244]. In the context of PD, synapsin and αS are co-dysregulated and co-deposited, and synapsin knockout has been shown to reduce αS aggregation and toxicity [245,246]. Recent studies demonstrate that αS is recruited into synapsin1 condensates at synapses, where synapsin functions as the scaffold and αS as the dynamic client partner [181]. Importantly, excess αS disrupts synapsin condensate formation, potentially interfering with the organization of synaptic vesicles and contributing to early synaptic dysfunction. Current studies lack information on the role of synapsin in aggregation of αS *via* heterotypic LLPS. While the precise role of synapsin in modulating αS pathology remains incompletely understood, the findings point to a delicate stoichiometric balance between the two proteins that may be critical for maintaining synaptic integrity.

3.4. αS and polyphenols/small molecule modulators

Myricetin is a naturally occurring flavonoid within the broader class of polyphenolic compounds, widely distributed in fruits, vegetables, nuts, and plant-derived beverages [247]. Myricetin exhibits a broad spectrum of biological activities, including antioxidant, antiviral, anti-diabetic, anti-inflammatory, and neuroprotective effects. Notably, myricetin confers neuroprotection by mitigating oxidative stress [248] and inhibiting the aggregation of several amyloidogenic proteins implicated in neurodegenerative diseases, including Aβ [249], αS [250], insulin and superoxide dismutase 1 [251,252]. Myricetin directly binds to the N-terminal region of αS which is critical for oligomerisation and thereby suppresses oligomer formation [250,253]. Upon heterotypic condensation with αS, myricetin did not alter the morphology, number, or size of αS condensates, but slightly reduced the dynamics of αS within the co-condensates [254]. Importantly, myricetin inhibited the liquid-to-solid transition of αS condensates and blocked amyloid fibril formation in a dose-dependent manner. Moreover, it demonstrated the ability to dissolve pre-formed αS aggregates, underscoring its therapeutic potential.

Curcumin, a natural polyphenolic compound derived from the rhizome of *Curcuma longa* (turmeric), is increasingly recognized for its broad therapeutic potential, particularly in chronic inflammatory and neurodegenerative disease [255,256]. Curcumin exhibits potent antioxidant, anti-inflammatory, and neuroprotective activities [257,258]. In the context of αS pathology, curcumin enhances the solubility of αS monomers and inhibits aggregation by binding preferentially to oligomeric and fibrillar species, thereby reducing their toxicity [259–261]. αS undergoes heterotypic condensation with curcumin, where curcumin associates primarily with hydrophobic regions of αS within the condensates [262]. Curcumin does not alter the morphology, size, or number of αS condensates but reduced the initial dynamics of αS in the condensates. However, curcumin slows the liquid-to-solid maturation, and significantly inhibits fibril formation, effectively disrupting αS aggregation. Strikingly, curcumin is also capable of disassembling pre-formed αS amyloid fibrils, likely through intermediate condensate states. Furthermore, it exhibits similar inhibitory effects on PD-associated αS mutants. The effect of curcumin on αS LLPS closely mirrors that of myricetin, suggesting that small polyphenolic molecules can modulate αS phase behaviour and aggregation.

Peptide-based molecular strategies to inhibit protein misfolding, aggregation, and neurodegeneration represent a rapidly advancing frontier in therapeutic research. Owing to their structural versatility, high specificity, and potent bioactivity, peptides can be precisely engineered to target pathological protein conformations, offering innovative avenues for intervention [263,264]. The RaPID (Random Non-standard Peptides Integrated Discovery) system is a platform for identifying such therapeutic candidates, particularly against amyloidogenic targets [265,266]. Using this system, two peptides FL2 and FD1 were identified that selectively bind to fibrillar states of αS. These peptides induced LLPS with αS in the presence of molecular crowding [267]. The phase separation was concentration-dependent on both peptide and αS, and the resulting condensates displayed hallmark properties of fluid phases, including reversibility, fusion behaviour and surface wetting. Binding of the peptides to αS occurred *via* weak interactions or site-specific contacts. Interestingly, although peptide-induced LLPS facilitated nucleation by reducing the lag phase of aggregation, it concurrently promoted the formation of hydrophobic, non-amyloidogenic pre-fibrillar aggregates, inhibited seeded fibril elongation, and reduced the overall fibril load. Thus, by locally concentrating αS within condensates, these

peptides exert a dual modulatory effect enhancing early nucleation while potently blocking downstream amyloid formation and misfolding.

Spermine is a naturally occurring polyamine that plays critical roles in a wide range of biological processes, including cellular growth, differentiation, gene regulation and stress responses. Dysregulation of the polyamine metabolic pathway has been implicated in the pathogenesis of neurodegenerative disorders [268,269]. Biogenic polyamines are abundant in neurons and modulate the aggregation of amyloidogenic proteins. They exert differential effects on protein aggregation depending on their net charge, molecular length, and concentration, and have been shown to promote the aggregation of both αS [270] and Aβ [271]. Under molecular crowding conditions, spermine forms heterotypic condensates with αS *via* electrostatic interactions [76]. Notably, neither αS nor spermine alone, nor their individual combinations with PEG, underwent LLPS under these conditions. Rodríguez et al. reported that αS:spermine condensates mature into mesh-like aggregates that lack β-sheet structure [76]. This heterotypic condensation is further modulated by ATP, which promotes droplet solidification and aggregation of αS. Together, these observations indicate that upon heterotypic LLPS, spermine drives αS condensation and aggregation, with ATP further accelerating condensate maturation.

The various heterotypic LLPS partners of αS discussed above are summarized in Table 2. Each system has been classified according to the type of LLPS, based on information reported in the original publications. αS can function either as a scaffold or as a client within these condensates and this can be influenced by αS concentration and various experimental conditions used in respective studies. Furthermore, depending on their influence on the formation of toxic αS assemblies, the interacting partners have been categorized as drivers or deterrents of αS aggregation.

4. Quadrant plot summary

In this review, we brought together the heterotypic phase separation partners of tau and αS. Fig. 3(a) and (b) show the discussed phase separation partners of tau and αS in a quadrant plot. Each partner is positioned in the plot based on its effects on two aspect: (i) phase separation, as judged by the physical properties of heterotypic condensates, including number, size, and fluidity, and (ii) protein aggregation, encompassing the kinetics of maturation, progression into aggregates, and the toxicity of the resulting aggregates.

From the plots, it is evident that most amyloidogenic proteins that co-phase separate with tau or αS tend to enhance LLPS and the subsequent aggregation. This effect aligns with the observed co-pathology of these proteins in several neurodegenerative diseases**.** For tau, many molecular chaperones appear to suppress aggregation. Interestingly, this suppression does not necessarily equate to inhibition of phase separation. Rather, these chaperones often direct tau condensates toward less amyloidogenic pathways. Proteins like Efhd2 and 14-3-3ζ were not included in the tau plot due to limited data regarding their role in LLPS-mediated tau aggregation. In contrast, phase separation with molecular chaperones is less studied in the case of αS, likely due to the inherently low phase separation tendencies of both αS and chaperones. Polyphenolic compounds have shown promise in inhibiting αS aggregation *via* LLPS mechanisms. Further exploration of similar small molecules against tau could present new opportunities to slow or prevent neurodegeneration. Peptide-based therapeutic strategies have demonstrated the potential to enhance the fluid properties of αS condensates while preventing their maturation into fibrils. These approaches could serve as valuable interventions at specific intermediate stages of the aggregation process. βS, although excluded from the quadrant due to its unclear role in phase separation, effectively inhibits αS aggregation and holds promise as a therapeutic agent due to its endogenous origin and favourable cellular distribution. These findings collectively underscore the potential of targeting heterotypic phase separation as a therapeutic strategy in neurodegenerative diseases.

Table 2
Effect of hetero phase separation on αS aggregation.

Partner	LLPS type	Effect on LLPS	Effect on αS aggregation	Enhance (+) Suppress (−)	Reference
TDP- 43 (prion-like domain)	αS (client) TDP-43 (scaffold)	αS localized at droplet surfaces, reduces dynamics of TDP-43 condensates	Accelerates amyloid formation, forms heterofibrils	+	[197]
Aβ	αS (scaffold) Aβ (client)	Concentration-dependent modulation. Aβ42 aggregates acts as nucleation sites for αS LLPS, Aβ40 enhance the number of smaller αS:Aβ40 condensates	Increasing Aβ40 concentrations promoted the aging and solid-like properties of condensates	+	[216,217]
βS	αS (scaffold) βS (client)	βS is recruited into αS condensates, can enhance or suppress phase separation	Blocks aggregation of αS	−	[225,226]
PrP	Cross interaction driven LLPS	PrP formed highly dynamic heterotypic condensates with αS	Rapid formation of heterotypic aggregates under agitation	+	[202]
S100A9	Cooperative LLPS	Promote formation of heterotypic droplets	Enhances aggregation and fibril formation.	+	[230]
Synapsin	αS (client) Synapsin (scaffold)	αS recruited into synapsin condensates, αS retains mobility.	No direct aggregation effects; excess αS disrupt condensates and causes synaptic dysfunction	+/−	[181]
SERF	αS (client) SERF1 (scaffold)	Promotes heterotypic LLPS, increases droplet size and density	Reduces oligomer-mediated toxicity of αS	−	[241]
FL2/FD1 (de-novo peptides)	Cross interaction driven LLPS	Drives heterotypic LLPS, enhance fluid characteristics of condensates	Reduces the overall fibril mass	−	[267]
Myricetin	αS (scaffold) Myricetin (client)	Does not affect initial condensate formation, reduces αS dynamics	Delays liquid-to-solid phase transition, blocks αS fibril formation, disassemble pre-formed amyloids	−	[254]
Curcumin	αS (scaffold) Curcumin (client)	Recruited into αS condensates, reduces αS fluidity	Delays liquid-to-solid like transition, inhibits amyloid aggregation	−	[262]
VAMP2	αS (scaffold) VAMP2 (client)	Promotes heterotypic LLPS, increases size and number of condensates	Prevents αS aggregation	−	[183]
Spermine (Sp)	αS (client) Sp(scaffold)	Promotes heterotopic condensation with αS	Accelerates fibrillization of αS	+	[76]

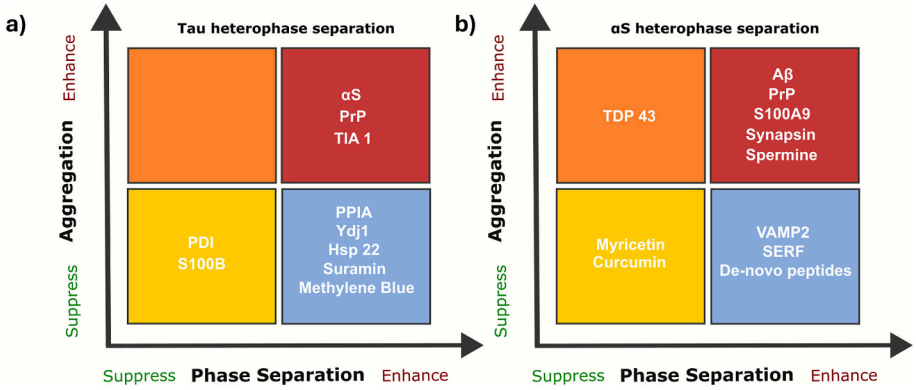

Fig. 3. Quadrant plot showing the effect of different heterotypic LLPS partners on a) tau and b) αS.

5. Concluding remarks and future perspectives

In summary, heterotypic phase separation emerges as a pivotal mechanism modulating the aggregation behaviour of key neurodegenerative proteins including tau and αS. Our review highlights that heterotypic condensates formed through interactions with diverse partners can either enhance or suppress pathological aggregation, revealing a complex regulatory network within biomolecular condensates.

The interplay between scaffolds and clients within these condensates dictates the condensate properties and aggregation propensity. Moreover, the presence of cofactors and post-translational modifications can further modulate condensate dynamics and aggregation pathways, emphasizing the multifactorial control of protein homeostasis *via* phase separation.

Looking forward, a deeper mechanistic understanding of the molecular determinants governing heterotypic phase separation will be critical. Key challenges remain in investigating how these condensates transition from functional assemblies to pathogenic aggregates *in vivo*. Advanced biophysical techniques, combined with cellular and animal models, will be essential to elucidate the temporal dynamics and structural features of heterotypic condensates.

Recent studies have advanced our understanding of the structural features that underlie LLPS in protein aggregation [272]. These structural characterizations have identified key regions and interaction motifs that contribute to phase separation. However, they do not yet provide sufficient insight to fully explain the molecular principles governing the formation and specificity of homotypic *versus* heterotypic condensates on an atomic level.

Studies have revealed that heterotypic condensation can induce structural variations in aggregates, such as the formation of heterofibrils between TDP-43PrLD and αS [197]. However, most of the studies provide limited information regarding the functional consequences of these aggregates, including their toxicity and seeding capacity. As a result, the impact of heterotypic condensation on aggregate properties and protein function remains largely unexplored.

Future research should also explore the therapeutic potential of modulating heterotypic phase separation. Targeting specific interaction interfaces or modulating condensate properties could provide novel strategies to prevent or reverse aberrant aggregation in neurodegenerative diseases. Overall, embracing the complexity of heterotypic phase separation offers promising avenues for understanding and ultimately intervening in progression of neurodegenerative diseases.

CRediT authorship contribution statement

Tina Jacob: Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Wolfgang Hoyer:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] B. Wang, L. Zhang, T. Dai, Z. Qin, H. Lu, L. Zhang, et al., Liquid–liquid phase separation in human health and diseases, Signal Transduct. Target. Ther. 6 (1) (2021 Aug 2) 1–16.
[2] S. Alberti, A. Gladfelter, T. Mittag, Considerations and challenges in studying liquid-liquid phase separation and biomolecular condensates, Cell 176 (3) (2019 Jan 24) 419–434.
[3] Y. Shin, C.P. Brangwynne, Liquid phase condensation in cell physiology and disease, Science 357 (6357) (2017 Sep 22) eaaf4382.
[4] A.M. Bergmann, J. Bauermann, G. Bartolucci, C. Donau, M. Stasi, A. L. Holtmannspötter, et al., Liquid spherical shells are a non-equilibrium steady state of active droplets, Nat. Commun. 14 (1) (2023 Oct 17) 6552.
[5] S.F. Banani, H.O. Lee, A.A. Hyman, M.K. Rosen, Biomolecular condensates: organizers of cellular biochemistry, Nat. Rev. Mol. Cell Biol. 18 (5) (2017 May) 285–298.
[6] S. Strome, W.B. Wood, Generation of asymmetry and segregation of germ-line granules in early *C. elegans* embryos, Cell 35 (1) (1983 Nov) 15–25.
[7] D.L.J. Lafontaine, J.A. Riback, R. Bascetin, C.P. Brangwynne, The nucleolus as a multiphase liquid condensate, Nat. Rev. Mol. Cell Biol. 22 (3) (2021 Mar) 165–182.
[8] D. Staněk, A.H. Fox, Nuclear bodies: news insights into structure and function, Curr. Opin. Cell Biol. 46 (2017 Jun 1) 94–101.
[9] S. Hofmann, N. Kedersha, P. Anderson, P. Ivanov, Molecular mechanisms of stress granule assembly and disassembly, Biochim. Biophys. Acta BBA Mol. Cell Res. 1868 (1) (2021 Jan 1) 118876.
[10] S. Alberti, Phase separation in biology, Curr. Biol. 27 (20) (2017 Oct 23) R1097–R1102.
[11] W.X. Xu, Q. Qu, H.H. Zhuang, X.Q. Teng, Y.W. Wei, J. Luo, et al., The burgeoning significance of liquid-liquid phase separation in the pathogenesis and therapeutics of cancers, Int. J. Biol. Sci. 20 (5) (2024 Feb 12) 1652–1668.
[12] X. Tong, R. Tang, J. Xu, W. Wang, Y. Zhao, X. Yu, et al., Liquid–liquid phase separation in tumor biology, Signal Transduct. Target. Ther. 7 (1) (2022 Jul 8) 1–22.
[13] I.A. Klein, A. Boija, L.K. Afeyan, S.W. Hawken, M. Fan, A. Dall'Agnese, et al., Partitioning of cancer therapeutics in nuclear condensates, Science 368 (6497) (2020 June 19) 1386–1392.
[14] J. Ren, Z. Zhang, Z. Zong, L. Zhang, F. Zhou, Emerging implications of phase separation in cancer, Adv. Sci. 9 (31) (2022) 2202855.
[15] Y.Y. Luo, J.J. Wu, Y.M. Li, Regulation of liquid–liquid phase separation with focus on post-translational modifications, Chem. Commun. 57 (98) (2021 Dec 9) 13275–13287.
[16] M.R. Ajmal, Protein misfolding and aggregation in proteinopathies: causes, mechanism and cellular response, Diseases 11 (1) (2023 Feb 9) 30.
[17] J.S. Fassler, S. Skuodas, D.L. Weeks, B.T. Phillips, Protein aggregation and disaggregation in cells and development, J. Mol. Biol. 433 (21) (2021 Oct 15) 167215.
[18] D. Cox, C. Raeburn, X. Sui, D.M. Hatters, Protein aggregation in cell biology: an aggregomics perspective of health and disease, Semin. Cell Dev. Biol. 99 (2020 Mar 1) 40–54.

[19] W.M. Babinchak, W.K. Surewicz, Liquid–liquid phase separation and its mechanistic role in pathological protein aggregation, J. Mol. Biol. 432 (7) (2020 Mar 27) 1910–1925.
[20] M. Li, Y. Fan, Q. Li, X. Wang, L. Zhao, M. Zhu, Liquid-liquid phase separation promotes protein aggregation and its implications in ferroptosis in Parkinson's disease dementia, Oxid. Med. Cell. Longev. 2022 (2022 Oct 6) 7165387.
[21] P. Chakraborty, M. Zweckstetter, Role of aberrant phase separation in pathological protein aggregation, Curr. Opin. Struct. Biol. 82 (2023 Oct 1) 102678.
[22] E.W. Martin, A.S. Holehouse, Intrinsically disordered protein regions and phase separation: sequence determinants of assembly or lack thereof, Emerg. Top Life Sci. 4 (3) (2020 Oct 20) 307–329.
[23] T.S. Harmon, A.S. Holehouse, M.K. Rosen, R.V. Pappu, Intrinsically disordered linkers determine the interplay between phase separation and gelation in multivalent proteins. Hyman AA, editor, eLife 6 (2017 Nov 1) e30294.
[24] A. Zbinden, M. Pérez-Berlanga, P. De Rossi, M. Polymenidou, Phase separation and neurodegenerative diseases: a disturbance in the force, Dev. Cell 55 (1) (2020 Oct 12) 45–68.
[25] S. Elbaum-Garfinkle, Matter over mind: liquid phase separation and neurodegeneration, J. Biol. Chem. 294 (18) (2019 May 1) 7160–7168.
[26] A. Naskar, A. Nayak, M.R. Salaikumaran, S.S. Vishal, P.P. Gopal, Phase separation and pathologic transitions of RNP condensates in neurons: implications for amyotrophic lateral sclerosis, frontotemporal dementia and other neurodegenerative disorders, Front. Mol. Neurosci. 16 (2023) 1242925.
[27] S.F. Banani, A.M. Rice, W.B. Peeples, Y. Lin, S. Jain, R. Parker, et al., Compositional control of phase-separated cellular bodies, Cell 166 (3) (2016 Jul 28) 651–663.
[28] J.K.A. Tom, A.A. Deniz, Complex dynamics of multicomponent biological coacervates, Curr. Opin. Colloid Interface Sci. 56 (2021 Dec 1) 101488.
[29] K. Sołtys, A. Tarczewska, D. Bystranowska, Modulation of biomolecular phase behavior by metal ions, Biochim. Biophys. Acta BBA Mol. Cell Res. 1870 (8) (2023 Dec 1) 119567.
[30] G.L. Dignon, R.B. Best, J. Mittal, Biomolecular phase separation: from molecular driving forces to macroscopic properties, Annu. Rev. Phys. Chem. 71 (2020 Apr 20) 53–75.
[31] L.C. Rodríguez, N.N. Foressi, M.S. Celej, Liquid-liquid phase separation of tau and α-synuclein: a new pathway of overlapping neuropathologies, Biochem. Biophys. Res. Commun. 741 (2024 Dec 31) 151053.
[32] S. Najafi, Y. Lin, A.P. Longhini, X. Zhang, K.T. Delaney, K.S. Kosik, et al., Liquid–liquid phase separation of tau by self and complex coacervation, Protein Sci. 30 (7) (2021) 1393–1407.
[33] N. Franzmeier, S.N. Roemer-Cassiano, A.M. Bernhardt, A. Dehsarvi, A. Dewenter, A. Steward, et al., Alpha synuclein co-pathology is associated with accelerated amyloid-driven tau accumulation in Alzheimer's disease, Mol. Neurodegener. 20 (2025 Mar 18) 31.
[34] X. Yan, R.L. Uronen, H.J. Huttunen, The interaction of α-synuclein and tau: a molecular conspiracy in neurodegeneration? Semin. Cell Dev. Biol. 99 (2020 Mar 1) 55–64.
[35] N. Badiola, R.M. de Oliveira, F. Herrera, C. Guardia-Laguarta, S.A. Gonçalves, M. Pera, et al., Tau enhances α-synuclein aggregation and toxicity in cellular models of synucleinopathy, PloS One 6 (10) (2011) e26609.
[36] J.L. Guo, D.J. Covell, J.P. Daniels, M. Iba, A. Stieber, B. Zhang, et al., Distinct α-synuclein strains differentially promote tau inclusions in neurons, Cell 154 (1) (2013 Jul 3) 103–117.
[37] B. Roy, G.R. Jackson, Interactions between tau and α-synuclein augment neurotoxicity in a Drosophila model of Parkinson's disease, Hum. Mol. Genet. 23 (11) (2014 June 1) 3008–3023.
[38] K. Bhasne, S. Sebastian, N. Jain, S. Mukhopadhyay, Synergistic amyloid switch triggered by early heterotypic oligomerization of intrinsically disordered α-synuclein and tau, J. Mol. Biol. 430 (16) (2018 Aug 3) 2508–2520.
[39] S. Moussaud, D.R. Jones, E.L. Moussaud-Lamodière, M. Delenclos, O.A. Ross, P. J. McLean, Alpha-synuclein and tau: teammates in neurodegeneration? Mol. Neurodegener. 9 (1) (2014 Oct 29) 43.
[40] S. Boeynaems, A.S. Holehouse, V. Weinhardt, D. Kovacs, J. Van Lindt, C. Larabell, et al., Spontaneous driving forces give rise to protein−RNA condensates with coexisting phases and complex material properties, Proc. Natl. Acad. Sci. 116 (16) (2019 Apr 16) 7889–7898.
[41] J.A. Ditlev, L.B. Case, M.K. Rosen, Who's in and who's out—compositional control of biomolecular condensates, J. Mol. Biol. 430 (23) (2018 Nov 2) 4666–4684.
[42] J.R. Espinosa, J.A. Joseph, I. Sanchez-Burgos, A. Garaizar, D. Frenkel, R. Collepardo-Guevara, Liquid network connectivity regulates the stability and composition of biomolecular condensates with many components, Proc. Natl. Acad. Sci. U. S. A. 117 (24) (2020 June 16) 13238–13247.
[43] I. Sanchez-Burgos, J.A. Joseph, R. Collepardo-Guevara, J.R. Espinosa, Size conservation emerges spontaneously in biomolecular condensates formed by scaffolds and surfactant clients, Sci. Rep. 11 (1) (2021 July 27) 15241.
[44] P.L. Onuchic, A.N. Milin, I. Alshareedah, A.A. Deniz, P.R. Banerjee, Divalent cations can control a switch-like behavior in heterotypic and homotypic RNA coacervates, Sci. Rep. 9 (1) (2019 Aug 21) 12161.
[45] B.K. C, T. Nii, T. Mori, Y. Katayama, A. Kishimura, Dynamic frustrated charge hotspots created by charge density modulation sequester globular proteins into complex coacervates, Chem. Sci. 14 (24) (2023 June 21) 6608–6620.
[46] L. Dehmelt, S. Halpain, The MAP2/tau family of microtubule-associated proteins, Genome Biol. 6 (1) (2004 Dec 23) 204.
[47] P. Barbier, O. Zejneli, M. Martinho, A. Lasorsa, V. Belle, C. Smet-Nocca, et al., Role of tau as a microtubule-associated protein: structural and functional aspects, Front. Aging Neurosci. 11 (2019 Aug 7) 204.
[48] M.D. Mukrasch, S. Bibow, J. Korukottu, S. Jeganathan, J. Biernat, C. Griesinger, et al., Structural polymorphism of 441-residue tau at single residue resolution, PLoS Biol. 7 (2) (2009 Feb 17) e1000034.
[49] C.A. Brunello, M. Merezhko, R.L. Uronen, H.J. Huttunen, Mechanisms of secretion and spreading of pathological tau protein, Cell. Mol. Life Sci. 77 (9) (2020 May 1) 1721–1744.
[50] H. Zheng, H. Sun, Q. Cai, H.C. Tai, The enigma of tau protein aggregation: mechanistic insights and future challenges, Int. J. Mol. Sci. 25 (9) (2024 May 2) 4969.
[51] C.A. Lasagna-Reeves, D.L. Castillo-Carranza, U. Sengupta, M.J. Guerrero-Munoz, T. Kiritoshi, V. Neugebauer, et al., Alzheimer brain-derived tau oligomers propagate pathology from endogenous tau, Sci. Rep. 2 (1) (2012 Oct 3) 700.
[52] A.B. Rocher, J.L. Crimins, J.M. Amatrudo, M.S. Kinson, M.A. Todd-Brown, J. Lewis, et al., Structural and functional changes in tau mutant mice neurons are not linked to the presence of NFTs, Exp. Neurol. 223 (2) (2010 June 1) 385–393.
[53] K. Santacruz, J. Lewis, T. Spires, J. Paulson, L. Kotilinek, M. Ingelsson, et al., Tau suppression in a neurodegenerative mouse model improves memory function, Science 309 (5733) (2005 July 15) 476–481.
[54] Y. Yoshiyama, M. Higuchi, B. Zhang, S.M. Huang, N. Iwata, T.C. Saido, et al., Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model, Neuron 53 (3) (2007 Feb 1) 337–351.
[55] C.A. Lasagna-Reeves, D.L. Castillo-Carranza, U. Sengupta, A.L. Clos, G.R. Jackson, R. Kayed, Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice, Mol. Neurodegener. 6 (1) (2011 June 6) 39.
[56] L. Jiang, P.E.A. Ash, B.F. Maziuk, H.I. Ballance, S. Boudeau, A.A. Abdullatif, et al., TIA1 regulates the generation and response to toxic tau oligomers, Acta Neuropathol. (Berl). 137 (2) (2019 Feb 1) 259–277.
[57] S. Ambadipudi, J. Biernat, D. Riedel, E. Mandelkow, M. Zweckstetter, Liquid–liquid phase separation of the microtubule-binding repeats of the Alzheimer-related protein tau, Nat. Commun. 8 (1) (2017 Aug 17) 275.
[58] S. Wegmann, B. Eftekharzadeh, K. Tepper, K.M. Zoltowska, R.E. Bennett, S. Dujardin, et al., Tau protein liquid–liquid phase separation can initiate tau aggregation, EMBO J. 37 (7) (2018 Apr 3) e98049.
[59] N.M. Kanaan, C. Hamel, T. Grabinski, B. Combs, Liquid-liquid phase separation induces pathogenic tau conformations in vitro, Nat. Commun. 11 (2020 June 4) 2809.
[60] A. Hernández-Vega, M. Braun, L. Scharrel, M. Jahnel, S. Wegmann, B.T. Hyman, et al., Local nucleation of microtubule bundles through tubulin concentration into a condensed tau phase, Cell Rep. 20 (10) (2017 Sep) 2304–2312.
[61] A. Savastano, D. Flores, H. Kadavath, J. Biernat, E. Mandelkow, M. Zweckstetter, Disease-associated tau phosphorylation hinders tubulin assembly within tau condensates, Angew. Chem. Int. Ed. 60 (2) (2021) 726–730.
[62] X. Zhang, Y. Lin, N.A. Eschmann, H. Zhou, J.N. Rauch, I. Hernandez, et al., RNA stores tau reversibly in complex coacervates, PLoS Biol. 15 (7) (2017 July 6) e2002183.
[63] T. Ukmar-Godec, S. Hutten, M.P. Grieshop, N. Rezaei-Ghaleh, M.S. Cima-Omori, J. Biernat, et al., Lysine/RNA-interactions drive and regulate biomolecular condensation, Nat. Commun. 10 (1) (2019 July 2) 2909.
[64] H. Ainani, N. Bouchmaa, R. Ben Mrid, R. El Fatimy, Liquid-liquid phase separation of protein tau: an emerging process in Alzheimer's disease pathogenesis, Neurobiol. Dis. 178 (2023 Mar 1) 106011.
[65] J. Sinsky, K. Pichlerova, J. Hanes, Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies, Int. J. Mol. Sci. 22 (17) (2021 Jan) 9207.
[66] Y. Lin, Y. Fichou, Z. Zeng, N.Y. Hu, S. Han, Electrostatically driven complex coacervation and amyloid aggregation of tau are independent processes with overlapping conditions, ACS Chem. Nerosci. 11 (4) (2020 Feb 19) 615–627.
[67] Y. Han, H. Ye, P. Li, Y. Zeng, J. Yang, M. Gao, et al., In vitro characterization and molecular dynamics simulation reveal mechanism of 14-3-3ζ regulated phase separation of the tau protein, Int. J. Biol. Macromol. 208 (2022 May 31) 1072–1081.
[68] Y. Lin, J. McCarty, J.N. Rauch, K.T. Delaney, K.S. Kosik, G.H. Fredrickson, et al., Narrow equilibrium window for complex coacervation of tau and RNA under cellular conditions. Shan Y, Barkai N, Castaneda C, editors, eLife 8 (2019 Apr 5) e42571.
[69] Y. Lin, Y. Fichou, A.P. Longhini, L.C. Llanes, P. Yin, G.C. Bazan, et al., Liquid-liquid phase separation of tau driven by hydrophobic interaction facilitates fibrillization of tau, J. Mol. Biol. 433 (2) (2021 Jan 22) 166731.
[70] J. Hochmair, C. Exner, M. Franck, A. Dominguez-Baquero, L. Diez, H. Brognaro, et al., Molecular crowding and RNA synergize to promote phase separation, microtubule interaction, and seeding of tau condensates, EMBO J. 41 (11) (2022 June) e108882.
[71] P.E.A. Ash, S. Lei, J. Shattuck, S. Boudeau, Y. Carlomagno, M. Medalla, et al., TIA1 potentiates tau phase separation and promotes generation of toxic oligomeric tau, Proc. Natl. Acad. Sci. 118 (9) (2021 Mar 2) e2014188118.
[72] M. Allahyartorkaman, T.H. Chan, E.H.L. Chen, S.T. Ng, Y.A. Chen, J.K. Wen, et al., Phosphorylation-induced self-coacervation versus RNA-assisted complex coacervation of tau proteins, J. Am. Chem. Soc. 147 (12) (2025 Mar 26) 10172–10187.
[73] L. Buée, L. Troquier, S. Burnouf, K. Belarbi, A. Van der Jeugd, T. Ahmed, et al., From tau phosphorylation to tau aggregation: what about neuronal death? Biochem. Soc. Trans. 38 (4) (2010 July 26) 967–972.

[74] P. Rawat, U. Sehar, J. Bisht, A. Selman, J. Culberson, P.H. Reddy, Phosphorylated tau in Alzheimer's disease and other tauopathies, Int. J. Mol. Sci. 23 (21) (2022 Oct 25) 12841.
[75] P. Gracia, D. Polanco, J. Tarancón-Díez, I. Serra, M. Bracci, J. Oroz, et al., Molecular mechanism for the synchronized electrostatic coacervation and co-aggregation of alpha-synuclein and tau, Nat. Commun. 13 (1) (2022 Aug 6) 4586.
[76] L.C. Rodríguez, N.N. Foressi, M.S. Celej, Modulation of α-synuclein phase separation by biomolecules, Biochim. Biophys. Acta BBA Proteins Proteomics. 1871 (2) (2023 Feb 1) 140885.
[77] N.N. Foressi, L.C. Rodríguez, M.S. Celej, Heterotypic liquid-liquid phase separation of tau and α-synuclein: implications for overlapping neuropathologies, Biochim. Biophys. Acta Proteins Proteomics 1871 (6) (2023 Nov 1) 140950.
[78] A. Siegert, M. Rankovic, F. Favretto, T. Ukmar-Godec, T. Strohäker, S. Becker, et al., Interplay between tau and α-synuclein liquid–liquid phase separation, Protein Sci. Publ. Protein Soc. 30 (7) (2021 July) 1326–1336.
[79] T. Ishizawa, P. Mattila, P. Davies, D. Wang, D.W. Dickson, Colocalization of tau and alpha-synuclein epitopes in Lewy bodies, J. Neuropathol. Exp. Neurol. 62 (4) (2003 Apr) 389–397.
[80] D. Twohig, H.M. Nielsen, α-synuclein in the pathophysiology of Alzheimer's disease, Mol. Neurodegener. 14 (1) (2019 June 11) 23.
[81] H. Miranzadeh Mahabadi, C. Taghibiglou, Cellular prion protein (PrPc): putative interacting partners and consequences of the interaction, Int. J. Mol. Sci. 21 (19) (2020 Sept 25) 7058.
[82] L.A. Gomes, S.A. Hipp, A. Rijal Upadhaya, K. Balakrishnan, S. Ospitalieri, M. J. Koper, et al., Aβ-induced acceleration of Alzheimer-related τ-pathology spreading and its association with prion protein, Acta Neuropathol. (Berl). 138 (6) (2019 Dec 1) 913–941.
[83] J. Laurén, D.A. Gimbel, H.B. Nygaard, J.W. Gilbert, S.M. Strittmatter, Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers, Nature 457 (7233) (2009 Feb) 1128–1132.
[84] N.W. Hu, G.T. Corbett, S. Moore, I. Klyubin, T.T. O'Malley, D.M. Walsh, et al., Extracellular forms of aβ and tau from iPSC models of Alzheimer's disease disrupt synaptic plasticity, Cell Rep. 23 (7) (2018 May 15) 1932–1938.
[85] S.K. Rai, R. Khanna, A. Avni, S. Mukhopadhyay, Heterotypic electrostatic interactions control complex phase separation of tau and prion into multiphasic condensates and co-aggregates, Proc. Natl. Acad. Sci. 120 (2) (2023 Jan 10) e2216338120.
[86] M.W. Hentze, A. Castello, T. Schwarzl, T. Preiss, A brave new world of RNA-binding proteins, Nat. Rev. Mol. Cell Biol. 19 (5) (2018 May) 327–341.
[87] N. Ripin, R. Parker, Formation, function, and pathology of RNP granules, Cell 186 (22) (2023 Oct 26) 4737–4756.
[88] N. Kedersha, P. Ivanov, P. Anderson, Stress granules and cell signaling: more than just a passing phase? Trends Biochem. Sci. 38 (10) (2013 Oct 1) 494–506.
[89] B. Wolozin, D. Apicco, RNA binding proteins and the genesis of neurodegenerative diseases, Adv. Exp. Med. Biol. 822 (2015) 11–15.
[90] M.R. Asadi, M. Sadat Moslehian, H. Sabaie, A. Jalaiei, S. Ghafouri-Fard, M. Taheri, et al., Stress granules and neurodegenerative disorders: a scoping review, Front. Aging Neurosci. 13 (2021 June 23) 650740.
[91] T. Kavanagh, A. Halder, E. Drummond, Tau interactome and RNA binding proteins in neurodegenerative diseases, Mol. Neurodegener. 17 (1) (2022 Oct 17) 66.
[92] T. Vanderweyde, H. Yu, M. Varnum, L. Liu-Yesucevitz, A. Citro, T. Ikezu, et al., Contrasting pathology of the stress granule proteins TIA-1 and G3BP in tauopathies, J. Neurosci. 32 (24) (2012 June 13) 8270–8283.
[93] T. Vanderweyde, D.J. Apicco, K. Youmans-Kidder, P.E.A. Ash, C. Cook, E. Lummertz da Rocha, et al., Interaction of tau with the RNA-binding protein TIA1 regulates tau pathophysiology and toxicity, Cell Rep. 15 (7) (2016 May 17) 1455–1466.
[94] B.F. Maziuk, D.J. Apicco, A.L. Cruz, L. Jiang, P.E.A. Ash, E.L. da Rocha, et al., RNA binding proteins co-localize with small tau inclusions in tauopathy, Acta Neuropathol. Commun. 6 (1) (2018 Aug 1) 71.
[95] D.J. Apicco, P.E.A. Ash, B. Maziuk, C. LeBlang, M. Medalla, A. Al Abdullatif, et al., Reducing the RNA binding protein TIA1 protects against tau-mediated neurodegeneration in vivo, Nat. Neurosci. 21 (1) (2018 Jan) 72–80.
[96] S.T. Kizhakkeduth, A. Abdul Vahid, M.S. Oliyantakath Hassan, A.K. Parambil, P. Jain, V. Vijayan, Molecular interactions between tau protein and TIA1: distinguishing physiological condensates from pathological fibrils, ACS Chem. Nerosci. 15 (2024) 3735–3743.
[97] M. Kosmaoglou, N. Schwarz, J.S. Bett, M.E. Cheetham, Molecular chaperones and photoreceptor function, Prog. Retin. Eye Res. 27 (4) (2008 July) 434–449.
[98] C. Hu, J. Yang, Z. Qi, H. Wu, B. Wang, F. Zou, et al., Heat shock proteins: biological functions, pathological roles, and therapeutic opportunities, MedComm 3 (3) (2022 Aug 2) e161.
[99] A. Ciechanover, Y.T. Kwon, Protein quality control by molecular chaperones in neurodegeneration, Front. Neurosci. 11 (2017) 185.
[100] E. Nachman, A.S. Wentink, K. Madiona, L. Bousset, T. Katsinelos, K. Allinson, et al., Disassembly of tau fibrils by the human Hsp70 disaggregation machinery generates small seeding-competent species, J. Biol. Chem. 295 (28) (2020 July 10) 9676–9690.
[101] Z. Liu, S. Zhang, J. Gu, Y. Tong, Y. Li, X. Gui, et al., Hsp27 chaperones FUS phase separation under the modulation of stress-induced phosphorylation, Nat. Struct. Mol. Biol. 27 (4) (2020 Apr) 363–372.
[102] C. Mörman, A. Leppert, G. Pizzirusso, Z. Zheng, X. Sun, R. Kumar, et al., Chaperone-mediated regulation of tau phase separation, fibrillation, and toxicity, J. Am. Chem. Soc. 147 (27) (2025 July 9) 23504–23518.
[103] H. Yu, S. Lu, K. Gasior, D. Singh, S. Vazquez-Sanchez, O. Tapia, et al., HSP70 chaperones RNA-free TDP-43 into anisotropic intranuclear liquid spherical shells, Science 371 (6529) (2021 Feb 5) eabb4309.
[104] Y. Sun, T.H. MacRae, Small heat shock proteins: molecular structure and chaperone function, Cell Mol. Life Sci. CMLS. 62 (21) (2005 Nov 1) 2460–2476.
[105] A.L. Darling, J. Dahrendorff, S.G. Creodore, C.A. Dickey, L.J. Blair, V.N. Uversky, Small heat shock protein 22 kDa can modulate the aggregation and liquid–liquid phase separation behavior of tau, Protein Sci. 30 (7) (2021) 1350–1359.
[106] S.A. Mok, C. Condello, R. Freilich, A. Gillies, T. Arhar, J. Oroz, et al., Mapping interactions with the chaperone network reveals factors that protect against tau aggregation, Nat. Struct. Mol. Biol. 25 (5) (2018 May) 384–393.
[107] S.K. Rai, R. Khanna, A. Sarbahi, A. Joshi, S. Mukhopadhyay, Chaperone-mediated heterotypic phase separation regulates liquid-to-solid phase transitions of tau into amyloid fibrils, Sci. Adv. 11 (23) (2025 June 6) eads1241.
[108] J.S. Cristóvão, V.K. Morris, I. Cardoso, S.S. Leal, J. Martínez, H.M. Botelho, et al., The neuronal S100B protein is a calcium-tuned suppressor of amyloid-β aggregation, Sci. Adv. 4 (6) (2018 June) eaaq1702.
[109] G.G. Moreira, F.X. Cantrelle, A. Quezada, F.S. Carvalho, J.S. Cristóvão, U. Sengupta, et al., Dynamic interactions and Ca2+−binding modulate the holdase-type chaperone activity of S100B preventing tau aggregation and seeding, Nat. Commun. 12 (1) (2021 Nov 1) 6292.
[110] G.G. Moreira, C.M. Gomes, Tau liquid–liquid phase separation is modulated by the Ca2+−switched chaperone activity of the S100B protein, J. Neurochem. 166 (1) (2023) 76–86.
[111] Cau Y, Valensin D, Mori M, Draghi S, Botta M. Structure, function, involvement in diseases and targeting of 14-3-3 proteins: an update. Curr. Med. Chem. 25(1): 5–21.
[112] Y. Chen, X. Chen, Z. Yao, Y. Shi, J. Xiong, J. Zhou, et al., 14-3-3/tau interaction and tau amyloidogenesis, J. Mol. Neurosci. MN. 68 (4) (2019 Aug) 620–630.
[113] H.Y. Qureshi, T. Li, R. MacDonald, C.M. Cho, N. Leclerc, H.K. Paudel, Interaction of 14-3-3ζ with microtubule-associated protein tau within Alzheimer's disease neurofibrillary tangles, Biochemistry 52 (37) (2013 Sept 17) 6445–6455.
[114] N.N. Sluchanko, N.B. Gusev, Probable participation of 14-3-3 in tau protein oligomerization and aggregation, J. Alzheimer's Dis 27 (3) (2011 Nov 29) 467–476.
[115] R. Layfield, J. Fergusson, A. Aitken, J. Lowe, M. Landon, R.J. Mayer, Neurofibrillary tangles of Alzheimer's disease brains contain 14-3-3 proteins, Neurosci. Lett. 209 (1) (1996 May 3) 57–60.
[116] F. Hernández, R. Cuadros, J. Avila, Zeta 14-3-3 protein favours the formation of human tau fibrillar polymers, Neurosci. Lett. 357 (2) (2004 Mar 4) 143–146.
[117] M. Hashiguchi, K. Sobue, H.K. Paudel, 14-3-3ζ is an effector of tau protein phosphorylation, J. Biol. Chem. 275 (33) (2000 Aug 18) 25247–25254.
[118] G. Sadik, T. Tanaka, K. Kato, H. Yamamori, B.N. Nessa, T. Morihara, et al., Phosphorylation of tau at Ser214 mediates its interaction with 14-3-3 protein: implications for the mechanism of tau aggregation, J. Neurochem. 108 (1) (2009) 33–43.
[119] J. Hochmair, M.C.M. van den Oetelaar, L. Ravatt, L. Diez, L.J.M. Lemmens, R. Ponce-Lina, et al., Stoichiometric 14-3-3ζ binding promotes phospho-tau microtubule dissociation and reduces aggregation and condensation, Commun. Biol. 8 (1) (2025 July 31) 1139.
[120] T. Li, H.K. Paudel, 14-3-3ζ mediates tau aggregation in human neuroblastoma M17 cells, PloS One 11 (8) (2016) e0160635.
[121] B. Wilkinson, H.F. Gilbert, Protein disulfide isomerase, Biochim. Biophys. Acta BBA Proteins Proteomics. 1699 (1) (2004 June 1) 35–44.
[122] L. Wang, X. Wang, C. Wang, chen., Protein disulfide–isomerase, a folding catalyst and a redox-regulated chaperone, Free Radic. Biol. Med. 83 (2015 June 1) 305–313.
[123] T. Uehara, T. Nakamura, D. Yao, Z.Q. Shi, Z. Gu, Y. Ma, et al., S-Nitrosylated protein-disulphide isomerase links protein misfolding to neurodegeneration, Nature 441 (7092) (2006 May) 513–517.
[124] A.K. Walker, M.A. Farg, C.R. Bye, C.A. McLean, M.K. Horne, J.D. Atkin, Protein disulphide isomerase protects against protein aggregation and is S-nitrosylated in amyotrophic lateral sclerosis, Brain 133 (1) (2010 Jan 1) 105–116.
[125] C.I. Andreu, U. Woehlbier, M. Torres, C. Hetz, Protein disulfide isomerases in neurodegeneration: from disease mechanisms to biomedical applications, FEBS Lett. 586 (18) (2012 Aug 31) 2826–2834.
[126] Y. Honjo, T. Horibe, A. Torisawa, H. Ito, A. Nakanishi, H. Mori, et al., Protein disulfide isomerase P5-immunopositive inclusions in patients with Alzheimer's disease, J. Alzheimer's Dis 38 (3) (2014 Jan 1) 601–609.
[127] J.H. Lee, S.M. Won, J. Suh, S.J. Son, G.J. Moon, U.J. Park, et al., Induction of the unfolded protein response and cell death pathway in Alzheimer's disease, but not in aged Tg2576 mice, Exp. Mol. Med. 42 (5) (2010 May) 386–394.
[128] K. Wang, J.Q. Liu, T. Zhong, X.L. Liu, Y. Zeng, X. Qiao, et al., Phase separation and cytotoxicity of tau are modulated by protein disulfide isomerase and S-nitrosylation of this molecular chaperone, J. Mol. Biol. 432 (7) (2020 Mar 27) 2141–2163.
[129] I.E. Vega, EFhd2, a protein linked to Alzheimer's disease and other neurological disorders, Front. Neurosci. 10 (2016 Mar 31) 150.
[130] Y. Ferrer-Acosta, E.N. Rodríguez-Cruz, F. Orange, H. De Jesús-Cortés, B. Madera, J. Vaquer-Alicea, et al., EFhd2 is a novel amyloid protein associated with pathological tau in Alzheimer's disease, J. Neurochem. 125 (6) (2013 June) 921–931.
[131] I.E. Vega, E.E. Traverso, Y. Ferrer-Acosta, E. Matos, M. Colon, J. Gonzalez, et al., A novel calcium-binding protein is associated with tau proteins in tauopathy, J. Neurochem. 106 (1) (2008 July) 96–106.

[132] I.E. Vega, A. Sutter, L. Parks, A. Umstead, M.I. Ivanova, Tau's three-repeat domain and EFhd2 co-incubation leads to increased thioflavin signal, Front. Neurosci. 12 (2018) 879.
[133] I.E. Vega, A. Umstead, N.M. Kanaan, EFhd2 affects tau liquid-liquid phase separation, Front. Neurosci. 13 (2019) 845.
[134] B.M. Dunyak, J.E. Gestwicki, Peptidyl-proline isomerases (PPIases): targets for natural products and natural product-inspired compounds, J. Med. Chem. 59 (21) (2016 Nov 10) 9622–9644.
[135] P. Nigro, G. Pompilio, M.C. Capogrossi, Cyclophilin A: a key player for human disease, Cell Death Dis. 4 (10) (2013 Oct) e888.
[136] J. Koren, U.K. Jinwal, Z. Davey, J. Kiray, K. Arulselvam, C.A. Dickey, Bending tau into shape: the emerging role of peptidyl-prolyl isomerases in tauopathies, Mol. Neurobiol. 44 (1) (2011 Aug) 65–70.
[137] S.D. Frausto, E. Lee, H. Tang, Cyclophilins as modulators of viral replication, Viruses 5 (7) (2013 July) 1684–1701.
[138] L. Pasetto, M. Grassano, S. Pozzi, S. Luotti, E. Sammali, A. Migazzi, et al., Defective cyclophilin A induces TDP-43 proteinopathy: implications for amyotrophic lateral sclerosis and frontotemporal dementia, Brain J. Neurol. 144 (12) (2021 Dec 31) 3710–3726.
[139] Y. Hattori, M. Kumashiro, H. Kumeta, T. Kyo, S. Kawagoe, M. Matsusaki, et al., A disease-associated mutation impedes PPIA through allosteric dynamics modulation, Biochemistry 64 (2025) 2971–2975.
[140] M. Babu, F. Favretto, M. Rankovic, M. Zweckstetter, Peptidyl prolyl isomerase A modulates the liquid–liquid phase separation of proline-rich IDPs, J. Am. Chem. Soc. 144 (35) (2022 Sept 7) 16157–16163.
[141] S.E. Hill, A.R. Esquivel, S.R. Ospina, L.M. Rahal, C.A. Dickey, L.J. Blair, Chaperoning activity of the cyclophilin family prevents tau aggregation, Protein Sci. Publ. Protein Soc. 31 (11) (2022 Nov) e4448.
[142] R.A. Culibrk, K.A. Ebbert, D.J. Yeisley, R. Chen, F.A. Qureshi, J. Hahn, et al., Impact of suramin on key pathological features of sporadic Alzheimer's disease-derived forebrain neurons, J. Alzheimers Dis. JAD. 98 (1) (2024) 301–318.
[143] C. Exley, O.V. Korchazhkina, Promotion of formation of amyloid fibrils by aluminium adenosine triphosphate (AlATP), J. Inorg. Biochem. 84 (3–4) (2001 Apr) 215–224.
[144] P. Majumder, C.A. Trujillo, C.G. Lopes, R.R. Resende, K.N. Gomes, K.K. Yuahasi, et al., New insights into purinergic receptor signaling in neuronal differentiation, neuroprotection, and brain disorders, Purinergic Signal 3 (4) (2007 Sept) 317–331.
[145] P.R. Prince, J. Hochmair, H. Brognaro, S. Gevorgyan, M. Franck, R. Schubert, et al., Initiation and modulation of tau protein phase separation by the drug suramin, Sci. Rep. 13 (1) (2023 Mar 9) 3963.
[146] M. Oz, D.E. Lorke, M. Hasan, G.A. Petroianu, Cellular and molecular actions of Methylene Blue in the nervous system, Med. Res. Rev. 31 (1) (2011) 93–117.
[147] D.X. Medina, A. Caccamo, S. Oddo, Methylene blue reduces aβ levels and rescues early cognitive deficit by increasing proteasome activity, Brain Pathol. 21 (2) (2011 Jan 27) 140–149.
[148] C.M. Wischik, P.C. Edwards, R.Y. Lai, M. Roth, C.R. Harrington, Selective inhibition of Alzheimer disease-like tau aggregation by phenothiazines, Proc. Natl. Acad. Sci. 93 (20) (1996 Oct) 11213–11218.
[149] Y. Huang, J. Wen, L.M. Ramirez, E. Gümüşdil, P. Pokhrel, V.H. Man, et al., Methylene blue accelerates liquid-to-gel transition of tau condensates impacting tau function and pathology, Nat. Commun. 14 (1) (2023 Sept 6) 5444.
[150] M. Goedert, R. Jakes, M.G. Spillantini, The synucleinopathies: twenty years on, J. Parkinsons Dis. 7 (s1) (2017 Mar 6) S51–S69.
[151] M. Vidović, M.G. Rikalovic, Alpha-synuclein aggregation pathway in Parkinson's disease: current status and novel therapeutic approaches, Cells 11 (11) (2022 Jan) 1732.
[152] E. Srinivasan, G. Chandrasekhar, P. Chandrasekar, K. Anbarasu, A.S. Vickram, R. Karunakaran, et al., Alpha-synuclein aggregation in Parkinson's disease, Front. Med. 8 (2021) 736978.
[153] V.N. Uversky, Neuropathology, biochemistry, and biophysics of α-synuclein aggregation, J. Neurochem. 103 (1) (2007) 17–37.
[154] G. Fusco, T. Pape, A.D. Stephens, P. Mahou, A.R. Costa, C.F. Kaminski, et al., Structural basis of synaptic vesicle assembly promoted by α-synuclein, Nat. Commun. 7 (1) (2016 Sept 19) 12563.
[155] L. Maroteaux, J.T. Campanelli, R.H. Scheller, Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal, J. Neurosci. 8 (8) (1988 Aug 1) 2804–2815.
[156] P. Calabresi, A. Mechelli, G. Natale, L. Volpicelli-Daley, G. Di Lazzaro, V. Ghiglieri, Alpha-synuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction, Cell Death Dis. 14 (3) (2023 Mar 1) 176.
[157] E.M. Rocha, B. De Miranda, L.H. Sanders, Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease, Neurobiol. Dis. 109 (2018 Jan 1) 249–257.
[158] F.N. Emamzadeh, Alpha-synuclein structure, functions, and interactions, J. Res. Med. Sci. 21 (1) (2016) 29.
[159] B. Fauvet, M.K. Mbefo, M.B. Fares, C. Desobry, S. Michael, M.T. Ardah, et al., α-synuclein in central nervous system and from erythrocytes, mammalian cells, and *Escherichia coli* exists predominantly as disordered monomer, J. Biol. Chem. 287 (19) (2012 May 1) 15345–15364.
[160] P. Alam, L. Bousset, R. Melki, D.E. Otzen, α-synuclein oligomers and fibrils: a spectrum of species, a spectrum of toxicities, J. Neurochem. 150 (5) (2019) 522–534.
[161] K.M. Danzer, D. Haasen, A.R. Karow, S. Moussaud, M. Habeck, A. Giese, et al., Different species of α-synuclein oligomers induce calcium influx and seeding, J. Neurosci. 27 (34) (2007 Aug 22) 9220–9232.
[162] X. yu Du, X. xiu Xie, R. tian Liu, The role of α-synuclein oligomers in Parkinson's disease, Int. J. Mol. Sci. 21 (22) (2020 Nov 17) 8645.
[163] R. Cascella, A. Bigi, N. Cremades, C. Cecchi, Effects of oligomer toxicity, fibril toxicity and fibril spreading in synucleinopathies, Cell. Mol. Life Sci. 79 (3) (2022 Mar 4) 174.
[164] B. Winner, R. Jappelli, S.K. Maji, P.A. Desplats, L. Boyer, S. Aigner, et al., In vivo demonstration that α-synuclein oligomers are toxic, Proc. Natl. Acad. Sci. 108 (10) (2011 Mar 8) 4194–4199.
[165] L. Pieri, K. Madiona, R. Melki, Structural and functional properties of prefibrillar α-synuclein oligomers, Sci. Rep. 6 (1) (2016 Apr 14) 24526.
[166] A. Bigi, R. Cascella, C. Cecchi, α-Synuclein oligomers and fibrils: partners in crime in synucleinopathies, Neural Regen. Res. 18 (11) (2023 Nov) 2332.
[167] G. Fusco, S.W. Chen, P.T.F. Williamson, R. Cascella, M. Perni, J.A. Jarvis, et al., Structural basis of membrane disruption and cellular toxicity by α-synuclein oligomers, Science 358 (6369) (2017 Dec 15) 1440–1443.
[168] S. Ray, N. Singh, R. Kumar, K. Patel, S. Pandey, D. Datta, et al., α-Synuclein aggregation nucleates through liquid–liquid phase separation, Nat. Chem. 12 (8) (2020 Aug) 705–716.
[169] S. Mukherjee, A. Sakunthala, L. Gadhe, M. Poudyal, A.S. Sawner, P. Kadu, et al., Liquid-liquid phase separation of α-synuclein: a new mechanistic insight for α-synuclein aggregation associated with Parkinson's disease pathogenesis, J. Mol. Biol. 435 (1) (2023 Jan 15) 167713.
[170] M.C. Hardenberg, T. Sinnige, S. Casford, S.T. Dada, C. Poudel, E.A. Robinson, et al., Observation of an α-synuclein liquid droplet state and its maturation into Lewy body-like assemblies, J. Mol. Cell Biol. 13 (4) (2021 Aug 4) 282–294.
[171] A.S. Sawner, S. Ray, P. Yadav, S. Mukherjee, R. Panigrahi, M. Poudyal, et al., Modulating α-synuclein liquid–liquid phase separation, Biochemistry 60 (48) (2021 Dec 7) 3676–3696.
[172] Piroska L, Fenyi A, Thomas S, Plamont MA, Redeker V, Melki R, et al. α-synuclein liquid condensates fuel fibrillar α-synuclein growth. Sci. Adv. 9(33):eadg5663.
[173] A. Mahapatra, R.W. Newberry, Liquid–liquid phase separation of α-synuclein is highly sensitive to sequence complexity, Protein Sci. 33 (4) (2024) e4951.
[174] S.H. Shahmoradian, A.J. Lewis, C. Genoud, J. Hench, T.E. Moors, P.P. Navarro, et al., Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes, Nat. Neurosci. 22 (7) (2019 July) 1099–1109.
[175] C. Liu, Y. Zhao, H. Xi, J. Jiang, Y. Yu, W. Dong, The membrane interaction of alpha-synuclein, Front. Cell Neurosci. [Internet] (2021 Mar 4), https://doi.org/10.3389/fncel.2021.633727/full [cited 2025 Dec 19];15. Available from:.
[176] M. Kiechle, V. Grozdanov, K.M. Danzer, The role of lipids in the initiation of α-synuclein misfolding, Front Cell Dev. Biol. 8 (2020 Sept 15) 562241.
[177] C. Galvagnion, A.K. Buell, G. Meisl, T.C.T. Michaels, M. Vendruscolo, T.P. J. Knowles, et al., Lipid vesicles trigger α-synuclein aggregation by stimulating primary nucleation, Nat. Chem. Biol. 11 (3) (2015 Mar) 229–234.
[178] C. Galvagnion, J.W.P. Brown, M.M. Ouberai, P. Flagmeier, M. Vendruscolo, A. K. Buell, et al., Chemical properties of lipids strongly affect the kinetics of the membrane-induced aggregation of α-synuclein, Proc. Natl. Acad. Sci. 113 (26) (2016 June 28) 7065–7070.
[179] S. Huang, B. Xu, Y. Liu, Calcium promotes α-synuclein liquid-liquid phase separation to accelerate amyloid aggregation, Biochem. Biophys. Res. Commun. 603 (2022 May 7) 13–20.
[180] B. Xu, S. Huang, Y. Liu, C. Wan, Y. Gu, D. Wang, et al., Manganese promotes α-synuclein amyloid aggregation through the induction of protein phase transition, J. Biol. Chem. 298 (1) (2022 Jan) 101469.
[181] C. Hoffmann, R. Sansevrino, G. Morabito, C. Logan, R.M. Vabulas, A. Ulusoy, et al., Synapsin condensates recruit alpha-synuclein, J. Mol. Biol. 433 (12) (2021 June 11) 166961.
[182] C. Wang, K. Zhang, B. Cai, J.E. Haller, K.E. Carnazza, J. Hu, et al., VAMP2 chaperones α-synuclein in synaptic vesicle co-condensates, Nat. Cell Biol. 26 (8) (2024 Aug) 1287–1295.
[183] A. Agarwal, A. Chandran, F. Raza, I.M. Ungureanu, C. Hilcenko, K. Stott, et al., VAMP2 regulates phase separation of α-synuclein, Nat. Cell Biol. 26 (8) (2024 Aug) 1296–1308.
[184] S.M. Hernandez, E.B. Tikhonova, A.L. Karamyshev, Protein-protein interactions in alpha-synuclein biogenesis: new potential targets in Parkinson's disease, Front. Aging Neurosci. 12 (2020) 72.
[185] K. Wakabayashi, K. Tanji, F. Mori, H. Takahashi, The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of α-synuclein aggregates, Neuropathology 27 (5) (2007) 494–506.
[186] M.E. Chánez-Cárdenas, E. Vázquez-Contreras, The aggregation of huntingtin and α-synuclein, J. Biophys. 2012 (2012) 606172.
[187] S. Dhakal, C.E. Wyant, H.E. George, S.E. Morgan, V. Rangachari, Prion-like C-terminal domain of TDP-43 and α-synuclein interact synergistically to generate neurotoxic hybrid fibrils, J. Mol. Biol. 433 (10) (2021 May 14) 166953.
[188] D.J. Irwin, V.M.Y. Lee, J.Q. Trojanowski, Parkinson's disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies, Nat. Rev. Neurosci. 14 (9) (2013 Sept) 626–636.
[189] T.L. Spires-Jones, J. Attems, D.R. Thal, Interactions of pathological proteins in neurodegenerative diseases, Acta Neuropathol. (Berl). 134 (2) (2017 Aug 1) 187–205.
[190] L.K. Clinton, M. Blurton-Jones, K. Myczek, J.Q. Trojanowski, F.M. LaFerla, Synergistic interactions between Aβ, tau, and α-synuclein: acceleration of neuropathology and cognitive decline, J. Neurosci. 30 (21) (2010 May 26) 7281–7289.

[191] I.R.A. Mackenzie, R. Rademakers, The role of TDP-43 in amyotrophic lateral sclerosis and frontotemporal dementia, Curr. Opin. Neurol. 21 (6) (2008 Dec) 693–700.
[192] M. Štalekar, X. Yin, K. Rebolj, S. Darovic, C. Troakes, M. Mayr, et al., Proteomic analyses reveal that loss of TDP-43 affects RNA processing and intracellular transport, Neuroscience 293 (2015 May 7) 157–170.
[193] M. Jo, S. Lee, Y.M. Jeon, S. Kim, Y. Kwon, H.J. Kim, The role of TDP-43 propagation in neurodegenerative diseases: integrating insights from clinical and experimental studies, Exp. Mol. Med. 52 (10) (2020 Oct) 1652–1662.
[194] O. Yokota, Y. Davidson, T. Arai, M. Hasegawa, H. Akiyama, H. Ishizu, et al., Effect of topographical distribution of α-synuclein pathology on TDP-43 accumulation in Lewy body disease, Acta Neuropathol. (Berl). 120 (6) (2010 Dec 1) 789–801.
[195] A. Meneses, S. Koga, J. O'Leary, D.W. Dickson, G. Bu, N. Zhao, TDP-43 pathology in Alzheimer's disease, Mol. Neurodegener. 16 (1) (2021 Dec 20) 84.
[196] S. Koga, W.L. Lin, R.L. Walton, O.A. Ross, D.W. Dickson, TDP-43 pathology in multiple system atrophy: colocalization of TDP-43 and α-synuclein in glial cytoplasmic inclusions, Neuropathol. Appl. Neurobiol. 44 (7) (2018 Dec) 707–721.
[197] S. Dhakal, M. Mondal, A. Mirzazadeh, S. Banerjee, A. Ghosh, V. Rangachari, α-Synuclein emulsifies TDP-43 prion-like domain-RNA liquid droplets to promote heterotypic amyloid fibrils, Commun. Biol. 6 (1) (2023 Dec 5) 1227.
[198] T. Thom, M. Schmitz, A.L. Fischer, A. Correia, S. Correia, F. Llorens, et al., Cellular prion protein mediates α-synuclein uptake, localization, and toxicity in vitro and in vivo, Mov. Disord. 37 (1) (2022) 39–51.
[199] T.C.R.G. Vieira, C.A. Barros, R. Domingues, T.F. Outeiro, PrP meets alpha-synuclein: molecular mechanisms and implications for disease, J. Neurochem. 168 (8) (2024) 1625–1639.
[200] P. La Vitola, M. Beeg, C. Balducci, G. Santamaria, E. Restelli, L. Colombo, et al., Cellular prion protein neither binds to alpha-synuclein oligomers nor mediates their detrimental effects, Brain 142 (2) (2019 Feb 1) 249–254.
[201] R.W.L. So, G. Amano, E. Stuart, A. Ebrahim Amini, A. Aguzzi, G.L. Collingridge, et al., A-Synuclein strain propagation is independent of cellular prion protein expression in a transgenic synucleinopathy mouse model, PLoS Pathog. 20 (9) (2024 Sept 12) e1012517.
[202] A. Agarwal, L. Arora, S.K. Rai, A. Avni, S. Mukhopadhyay, Spatiotemporal modulations in heterotypic condensates of prion and α-synuclein control phase transitions and amyloid conversion, Nat. Commun. 13 (1) (2022 Mar 3) 1154.
[203] G.S. Bloom, Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis, JAMA Neurol. 71 (4) (2014 Apr) 505–508.
[204] G. fang Chen, T. hai Xu, Y. Yan, Y. ren Zhou, Y. Jiang, K. Melcher, et al., Amyloid beta: structure, biology and structure-based therapeutic development, Acta Pharmacol. Sin. 38 (9) (2017 Sept) 1205–1235.
[205] W.J. Jansen, R. Ossenkoppele, D.L. Knol, B.M. Tijms, P. Scheltens, F.R.J. Verhey, et al., Prevalence of cerebral amyloid pathology in persons without dementia, JAMA 313 (19) (2015 May 19) 1924–1938.
[206] C. Haass, M.G. Schlossmacher, A. Hung, C. Vigo-Pelfreyt, A. Mellon, B. L. Ostaszewski, et al., Amyloid p-peptide is produced by cultured cells during normal metabolism 359 (1992).
[207] A. Jan, O. Gokce, R. Luthi-Carter, H.A. Lashuel, The ratio of monomeric to aggregated forms of Aβ40 and Aβ42 is an important determinant of amyloid-β aggregation, fibrillogenesis, and toxicity, J. Biol. Chem. 283 (42) (2008 Oct 17) 28176–28189.
[208] S.V. Ovsepian, V.B. O'Leary, L. Zaborszky, V. Ntziachristos, J.O. Dolly, Amyloid plaques of Alzheimer's disease as hotspots of glutamatergic activity, Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry. 25 (4) (2019 Aug) 288–297.
[209] T. Lashley, J.L. Holton, E. Gray, K. Kirkham, S.S. O'Sullivan, A. Hilbig, et al., Cortical alpha-synuclein load is associated with amyloid-beta plaque burden in a subset of Parkinson's disease patients, Acta Neuropathol. (Berl). 115 (4) (2008 Apr) 417–425.
[210] R.A. Armstrong, N.J. Cairns, P.L. Lantos, beta-Amyloid (A beta) deposition in the medial temporal lobe of patients with dementia with Lewy bodies, Neurosci. Lett. 227 (3) (1997 May 23) 193–196.
[211] F. Bassil, H.J. Brown, S. Pattabhiraman, J.E. Iwasyk, C.M. Maghames, E. S. Meymand, et al., Amyloid-beta (Aβ) plaques promote seeding and spreading of alpha-synuclein and tau in a mouse model of Lewy body disorders with Aβ pathology, Neuron 105 (2) (2020 Jan 22) 260–275.e6.
[212] K. Uéda, H. Fukushima, E. Masliah, Y. Xia, A. Iwai, M. Yoshimoto, et al., Molecular cloning of cDNA encoding an unrecognized component of amyloid in Alzheimer disease, Proc. Natl. Acad. Sci. U. S. A. 90 (23) (1993 Dec 1) 11282–11286.
[213] J. Köppen, A. Schulze, L. Machner, M. Wermann, R. Eichentopf, M. Guthardt, et al., Amyloid-beta peptides trigger aggregation of alpha-synuclein in vitro, Molecules 25 (3) (2020 Jan) 580.
[214] D.M. Vadukul, M. Papp, R.J. Thrush, J. Wang, Y. Jin, P. Arosio, et al., α-synuclein aggregation is triggered by oligomeric amyloid-β 42 via heterogeneous primary nucleation, J. Am. Chem. Soc. 145 (33) (2023 Aug 23) 18276–18285.
[215] F. Huang, Y. Liu, Y. Wang, J. Xu, J. Lian, Y. Zou, et al., Co-aggregation of α-synuclein with amyloid-β stabilizes β-sheet-rich oligomers and enhances the formation of β-barrels, Phys. Chem. Chem. Phys. 25 (46) (2023 Nov 29) 31604–31614.
[216] A. Röntgen, Z. Toprakcioglu, O.M. Morris, M. Vendruscolo, Amyloid-β modulates the phase separation and aggregation of α-synuclein, Proc. Natl. Acad. Sci. 122 (29) (2025 July 22) e2501987122.
[217] O.M. Morris, A. Röntgen, Z. Toprakcioglu, M. Cali, S. Dada, M. Vendruscolo, Recruitment of Aβ into α-synuclein condensates catalyzes primary nucleation of α-synuclein aggregation, ACS Cent. Sci. 11 (8) (2025 Aug 27) 1481–1491.
[218] G. Šneiderienė, A. González Díaz, S.D. Adhikari, J. Wei, T. Michaels, T. Šneideris, et al., Lipid-induced condensate formation from the Alzheimer's aβ peptide triggers amyloid aggregation, Proc. Natl. Acad. Sci. 122 (4) (2025 Jan 28) e2401307122.
[219] X. Gui, S. Feng, Z. Li, Y. Li, B. Reif, B. Shi, et al., Liquid-liquid phase separation of amyloid-β oligomers modulates amyloid fibrils formation, J. Biol. Chem. 299 (3) (2023 Mar) 102926.
[220] O.M. Morris, Z. Toprakcioglu, A. Röntgen, M. Cali, T.P.J. Knowles, M. Vendruscolo, Aggregation of the amyloid-β peptide (Aβ40) within condensates generated through liquid–liquid phase separation, Sci. Rep. 14 (1) (2024 Sept 30) 22633.
[221] M.K. Jain, P. Singh, S. Roy, R. Bhat, Comparative analysis of the conformation, aggregation, interaction, and fibril morphologies of human α-, β-, and γ-synuclein proteins, Biochemistry 57 (26) (2018 July 3) 3830–3848.
[222] J.W.P. Brown, A.K. Buell, T.C.T. Michaels, G. Meisl, J. Carozza, P. Flagmeier, et al., β-synuclein suppresses both the initiation and amplification steps of α-synuclein aggregation via competitive binding to surfaces, Sci. Rep. 6 (1) (2016 Nov 3) 36010.
[223] M. Hashimoto, E. Rockenstein, M. Mante, M. Mallory, E. Masliah, β-synuclein inhibits α-synuclein aggregation: a possible role as an anti-parkinsonian factor, Neuron 32 (2) (2001 Oct 25) 213–223.
[224] M.K. Janowska, K.P. Wu, J. Baum, Unveiling transient protein-protein interactions that modulate inhibition of alpha-synuclein aggregation by beta-synuclein, a pre-synaptic protein that co-localizes with alpha-synuclein, Sci. Rep. 5 (2015 Oct 19) 15164.
[225] X. Li, L. Yu, X. Liu, T. Shi, Y. Zhang, Y. Xiao, et al., β-Synuclein regulates the phase transitions and amyloid conversion of α-synuclein, Nat. Commun. 15 (1) (2024 Oct 9) 8748.
[226] B. Xu, W. He, F. Fan, S. Chen, M. Zhu, Y. Hou, et al., β-synuclein blocks α-synuclein condensate fusion to disrupt the maturation of phase separation, Cell Rep. 44 (6) (2025 June) 115761.
[227] J. Hayashi, J.A. Carver, β-synuclein: an enigmatic protein with diverse functionality, Biomolecules 12 (1) (2022 Jan 16) 142.
[228] C. Zhang, Y. Liu, J. Gilthorpe, Maarel JRC van der, MRP14 (S100A9) protein interacts with Alzheimer beta-amyloid peptide and induces its fibrillization, PloS One 7 (3) (2012 Mar 22) e32953.
[229] I. Horvath, I.A. Iashchishyn, R.A. Moskalenko, C. Wang, S.K.T.S. Wärmländer, C. Wallin, et al., Co-aggregation of pro-inflammatory S100A9 with α-synuclein in Parkinson's disease: ex vivo and in vitro studies, J. Neuroinflammation 15 (1) (2018 June 4) 172.
[230] D. Veiveris, A. Kopustas, D. Sulskis, K. Mikalauskaite, M.N. Alsamsam, M. Tutkus, et al., Heterotypic droplet formation by pro-inflammatory S100A9 and neurodegenerative disease-related α-synuclein, Biomacromolecules 26 (6) (2025 June 9) 3525–3537.
[231] C. Yan, J. Jiang, Y. Yang, X. Geng, W. Dong, The function of VAMP2 in mediating membrane fusion: an overview, Front. Mol. Neurosci. 15 (2022) 948160.
[232] J. Burré, M. Sharma, T. Tsetsenis, V. Buchman, M. Etherton, T.C. Südhof, α-synuclein promotes SNARE-complex assembly in vivo and in vitro, Science 329 (5999) (2010 Sept 24) 1663–1667.
[233] J. Sun, L. Wang, H. Bao, S. Premi, U. Das, E.R. Chapman, et al., Functional cooperation of α-synuclein and VAMP2 in synaptic vesicle recycling, Proc. Natl. Acad. Sci. U. S. A. 116 (23) (2019 June 4) 11113–11115.
[234] B.R. Sahoo, J.C.A. Bardwell, SERF, a family of tiny highly conserved, highly charged proteins with enigmatic functions, FEBS J. 290 (17) (2023) 4150–4162.
[235] R. Mitra, E.T. Usher, S. Dedeoğlu, M.J. Crotteau, O.A. Fraser, N.H. Yennawar, et al., Molecular insights into the interaction between a disordered protein and a folded RNA, Proc. Natl. Acad. Sci. U. S. A. 121 (49) (2024 Dec 3) e2409139121.
[236] S.F. Falsone, N.H. Meyer, E. Schrank, G. Leitinger, C.L.L. Pham, M.T. Fodero-Tavoletti, et al., SERF protein is a direct modifier of amyloid fiber assembly, Cell Rep. 2 (2) (2012 Aug 30) 358–371.
[237] B.A. Meinen, V.V. Gadkari, F. Stull, B.T. Ruotolo, J.C.A. Bardwell, SERF engages in a fuzzy complex that accelerates primary nucleation of amyloid proteins, Proc. Natl. Acad. Sci. U. S. A. 116 (46) (2019 Nov 12) 23040–23049.
[238] T.Y. Tsai, W.T. Jhang, H.K. Hsu, Y.T. Chan, C.F. Chang, Y.R. Chen, Amyloid modifier SERF1a accelerates Alzheimer's amyloid-β fibrillization and exacerbates the cytotoxicity, ACS Chem. Nerosci. 15 (3) (2024 Feb 7) 479–490.
[239] Y. Yoshimura, M.A. Holmberg, P. Kukic, C.B. Andersen, A. Mata-Cabana, S. F. Falsone, et al., MOAG-4 promotes the aggregation of α-synuclein by competing with self-protective electrostatic interactions, J. Biol. Chem. 292 (20) (2017 May 19) 8269–8278.
[240] D.A. Merle, A. Witternigg, C. Tam-Amersdorfer, C. Hartlmüller, E. Spreitzer, E. Schrank, et al., Increased aggregation tendency of alpha-synuclein in a fully disordered protein complex, J. Mol. Biol. 431 (14) (2019 June 28) 2581–2598.
[241] H.N. Liu, T. Wang, J.J. Hu, L. Chen, X. Shi, Y.M. Li, et al., The disordered protein SERF promotes α-synuclein aggregation through liquid-liquid phase separation, J. Biol. Chem. 300 (3) (2024 Mar) 105667.
[242] E.F. Fornasiero, D. Bonanomi, F. Benfenati, F. Valtorta, The role of synapsins in neuronal development, Cell Mol. Life Sci. CMLS. 67 (9) (2010 May) 1383–1396.
[243] D. Milovanovic, Y. Wu, X. Bian, P. De Camilli, A liquid phase of synapsin and lipid vesicles, Science 361 (6402) (2018 Aug 10) 604–607.
[244] F.J. Mirza, S. Zahid, The role of synapsins in neurological disorders, Neurosci. Bull. 34 (2) (2018 Apr 1) 349–358.
[245] F. Longhena, G. Faustini, T. Varanita, M. Zaltieri, V. Porrini, I. Tessari, et al., Synapsin III is a key component of α-synuclein fibrils in Lewy bodies of PD brains, Brain Pathol. 28 (6) (2018 Feb 23) 875–888.

[246] M. Zaltieri, J. Grigoletto, F. Longhena, L. Navarria, G. Favero, S. Castrezzati, et al., α-synuclein and synapsin III cooperatively regulate synaptic function in dopamine neurons, J. Cell Sci. 128 (13) (2015 July 1) 2231–2243.
[247] J.A. Ross, C.M. Kasum, Dietary flavonoids: bioavailability, metabolic effects, and safety, Annu. Rev. Nutr. 22 (2002 July 1) 19–34.
[248] K. Ishige, D. Schubert, Y. Sagara, Flavonoids protect neuronal cells from oxidative stress by three distinct mechanisms, Free Radic. Biol. Med. 30 (4) (2001 Feb 15) 433–446.
[249] A.M. Kimura, M. Tsuji, T. Yasumoto, Y. Mori, T. Oguchi, Y. Tsuji, et al., Myricetin prevents high molecular weight Aβ1-42 oligomer-induced neurotoxicity through antioxidant effects in cell membranes and mitochondria, Free Radic. Biol. Med. 171 (2021 Aug 1) 232–244.
[250] R. Takahashi, K. Ono, Y. Takamura, M. Mizuguchi, T. Ikeda, H. Nishijo, et al., Phenolic compounds prevent the oligomerization of α-synuclein and reduce synaptic toxicity, J. Neurochem. 134 (5) (2015) 943–955.
[251] K.P. Prajapati, A.P. Singh, K. Dubey, M. Ansari, M. Temgire, B.G. Anand, et al., Myricetin inhibits amyloid fibril formation of globular proteins by stabilizing the native structures, Colloids Surf. B Biointerfaces 186 (2020 Feb 1) 110640.
[252] S. Sharma, V.R. Tomar, S. Deep, Myricetin: a potent anti-amyloidogenic polyphenol against superoxide dismutase 1 aggregation, ACS Chem. Nerosci. 14 (13) (2023 July 5) 2461–2475.
[253] M. Caruana, T. Högen, J. Levin, A. Hillmer, A. Giese, N. Vassallo, Inhibition and disaggregation of α-synuclein oligomers by natural polyphenolic compounds, FEBS Lett. 585 (8) (2011) 1113–1120.
[254] B. Xu, X. Mo, J. Chen, H. Yu, Y. Liu, Myricetin inhibits α-synuclein amyloid aggregation by delaying the liquid-to-solid phase transition, ChemBioChem 23 (16) (2022) e202200216.
[255] J. Zhang, R. Zhang, S. Jin, X. Feng, Curcumin, a plant polyphenol with multiple physiological functions of improving antioxidation, anti-inflammation, immunomodulation and its application in poultry production, J. Anim. Physiol. Anim. Nutr. 108 (6) (2024) 1890–1905.
[256] Y. He, Y. Yue, X. Zheng, K. Zhang, S. Chen, Z. Du, Curcumin, inflammation, and chronic diseases: how are they linked? Molecules 20 (5) (2015 May) 9183–9213.
[257] E.E. Nebrisi, Neuroprotective activities of curcumin in Parkinson's disease: a review of the literature, Int. J. Mol. Sci. 22 (20) (2021 Jan) 11248.
[258] M. Tang, C. Taghibiglou, The mechanisms of action of curcumin in Alzheimer's disease, J. Alzheimer's Dis 58 (4) (2017 June 23) 1003–1016.
[259] P.K. Singh, V. Kotia, D. Ghosh, G.M. Mohite, A. Kumar, S.K. Maji, Curcumin modulates α-synuclein aggregation and toxicity, ACS Chem. Nerosci. 4 (3) (2013 Mar 20) 393–407.
[260] N. Pandey, J. Strider, W.C. Nolan, S.X. Yan, J.E. Galvin, Curcumin inhibits aggregation of α-synuclein, Acta Neuropathol. (Berl). 115 (4) (2008 Apr 1) 479–489.
[261] K. Ono, M. Yamada, Expression of concern: antioxidant compounds have potent anti-fibrillogenic and fibril-destabilizing effects for α-synuclein fibrils in vitro, J. Neurochem. 97 (1) (2006) 105–115.
[262] B. Xu, J. Chen, Y. Liu, Curcumin interacts with α-synuclein condensates to inhibit amyloid aggregation under phase separation, ACS Omega 7 (34) (2022 Aug 30) 30281–30290.
[263] D.J. Craik, D.P. Fairlie, S. Liras, D. Price, The future of peptide-based drugs, Chem. Biol. Drug Des. 81 (1) (2013) 136–147.
[264] V. Armiento, A. Spanopoulou, A. Kapurniotu, Peptide-based molecular strategies to interfere with protein misfolding, aggregation, and cell degeneration, Angew. Chem. Int. Ed. 59 (9) (2020) 3372–3384.
[265] K. Ito, T. Passioura, H. Suga, Technologies for the synthesis of mRNA-encoding libraries and discovery of bioactive natural product-inspired non-traditional macrocyclic peptides, Molecules 18 (3) (2013 Mar) 3502–3528.
[266] T. Ikenoue, M. Oono, M. So, H. Yamakado, T. Arata, R. Takahashi, et al., A RaPID macrocyclic peptide that inhibits the formation of α-synuclein amyloid fibrils, ChemBioChem 24 (12) (2023) e202300320.
[267] T. Ikenoue, M. So, N. Terasaka, W.E. Huang, Y. Kawata, Y. Miyanoiri, et al., De novo peptides that induce the liquid-liquid phase separation of α-synuclein, J. Am. Chem. Soc. 147 (27) (2025 July 9) 24113–24126.
[268] N.M. Lewandowski, S. Ju, M. Verbitsky, B. Ross, M.L. Geddie, E. Rockenstein, et al., Polyamine pathway contributes to the pathogenesis of Parkinson disease, Proc. Natl. Acad. Sci. 107 (39) (2010 Sept 28) 16970–16975.
[269] A.K. Handa, T. Fatima, A.K. Mattoo, Polyamines: bio-molecules with diverse functions in plant and human health and disease, Front. Chem. 6 (2018) 10.
[270] T. Antony, W. Hoyer, D. Cherny, G. Heim, T.M. Jovin, V. Subramaniam, Cellular polyamines promote the aggregation of α-synuclein, J. Biol. Chem. 278 (5) (2003 Jan 31) 3235–3240.
[271] J. Luo, C.H. Yu, H. Yu, R. Borstnar, S.C.L. Kamerlin, A. Gräslund, et al., Cellular polyamines promote amyloid-beta (aβ) peptide fibrillation and modulate the aggregation pathways, ACS Chem. Nerosci. 4 (3) (2013 Mar 20) 454–462.
[272] M. Vendruscolo, M. Fuxreiter, Sequence determinants of the aggregation of proteins within condensates generated by liquid-liquid phase separation, J. Mol. Biol. 434 (1) (2022 Jan 15) 167201.