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Molecular understanding of liquid–liquid phase separation of α-synuclein for the development of novel Parkinson's disease therapies

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α-Synuclein (α-syn) exists abundantly at presynaptic terminals and plays a pivotal role in vesicle trafficking and neurotransmitter release thereafter. α-Syn exhibits structural plasticity and adopts diverse conformations such as α-helices and β-strands in response to adjacent microenvironments. These structural features facilitate the formation of aberrant α-syn condensates under specific circumstances. Aggregates and amyloid fibrils of α-syn have been observed in the brain tissue of patients with Parkinson's disease (PD) and other synucleinopathies. The nucleation of α-syn as a precursor to aggregation and amyloid formation is associated with liquid–liquid phase separation (LLPS), which forms droplets in solution. Thus, elucidating the detailed molecular formation of α-syn LLPS is necessary to understand the aberrant polymerization of α-syn, such as the formation of amyloid fibrils. In this review, we describe the formation mechanism of α-syn LLPS. In addition, we discuss several molecular strategies for targeting α-syn LLPS to block the formation of α-syn aggregates or amyloid fibrils. This review provides biophysical insights for the development of novel therapies for PD.

KEYWORDS
amyloid fibril, liquid–liquid phase separation, Parkinson's disease, protein aggregation, α-synuclein

Introduction

α-Synuclein (α-syn) is a presynaptic protein found in animals and humans (Maroteaux et al., 1988; Totterdell et al., 2004; Hoffmann et al., 2021). In humans, the *SNCA* gene encodes it (Uéda et al., 1993; Cole et al., 2021; Panicker et al., 2021; Cherian et al., 2023). α-Syn exists mainly in the axonal terminals of neurons and plays a vital role in synaptic vesicle (SV) trafficking, SV fusion, and neurotransmitter release (Iwai et al., 1995; Abeliovich et al., 2000; Chandra et al., 2004; Burré et al., 2010; Burré et al., 2014; Burré, 2015; Fusco et al., 2016; Snead and Eliezer, 2019). However, aggregation of misfolded α-syn is a histopathological hallmark of Parkinson's disease (PD) and other synucleinopathies (Sharon et al., 2003; Karpinar et al., 2009; Winner et al., 2011; Gadhe et al., 2022). Aggregated α-syn clusters in neurons constitute the dominant components of Lewy bodies and Lewy neurites, which are often found in the brain tissue of patients with PD (Spillantini et al., 1997; Spillantini et al., 1998). Therefore, much attention has been paid to the role of α-syn in PD therapy.

α-Syn plays a crucial physiological role as a monomer within presynaptic terminals, where its structural dynamics are tightly regulated by lipid membranes and protein

partners (Iwai et al., 1995; Fusco et al., 2016). In its membrane-unbound state, α-syn maintains a largely unstructured conformation (Iwai et al., 1995; Fusco et al., 2016). However, it transitions into a partially folded structure upon binding to lipid membranes and directly engaging synaptobrevin-2/vesicle-associated membrane protein (VAMP)2 (Wang et al., 2024). Within the contemporary framework of liquid–liquid phase separation (LLPS), these physiological interactions drive heterotypic co-condensation, wherein monomeric α-syn cooperatively scaffolds with VAMP2, synapsins, and anionic lipids to form multi-component liquid droplets. This heterotypic phase separation compartmentalizes and clusters SVs to facilitate orderly soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-dependent membrane fusion, neurotransmitter release, and membrane recycling (Burré et al., 2014; Burré, 2015; Panicker et al., 2021).

However, pathological conditions disrupt this equilibrium, transitioning the system from functional heterotypic assemblies toward aberrant homotypic condensation (Nemani et al., 2010; Busch et al., 2014). When localized concentrations of α-syn increase, α-syn undergoes single-component self-association driven by its intrinsically disordered regions. Unlike the multi-component heterotypic droplets that dynamically recycle SVs, these homotypic or "aged" condensates may progressively mature into fibrillar aggregates. This shift depletes the functional monomers of α-syn and decreases interactions with essential presynaptic components such as synaptobrevin-2/VAMP2 and SNARE complex formation for membrane fusion. Consequently, aberrantly homotypic or "aged" condensates of α-syn in presynaptic neurons can cause the malfunction of α-syn.

The aggregation of α-syn is initiated by its nucleation (Vidović and Rikalovic, 2022; Xu et al., 2024). In this step, LLPS usually occurs (Ray et al., 2020; Mukherjee et al., 2023). LLPS is a reversible physical phenomenon that separates a macromolecular solution into two phases. LLPS is ubiquitous in various tissues, including the brain. LLPS can lead to a liquid-to-solid phase transition in response to a specific aberrant microenvironment of the liquid droplets, most of which in the nervous system are associated with neurodegenerative diseases such as PD (Elbaum-Garfinkle, 2019; Zbinden et al., 2020). This phase transition has been observed in several proteins, such as α-syn (Ray et al., 2020), Tau (Wegmann et al., 2018), TDP-43 (Conicella et al., 2016), fused in sarcoma (FUS) (Patel et al., 2015), and heterogeneous nuclear ribonucleoprotein A1 (Molliex et al., 2015). These proteins eventually form insoluble amyloid fibrils during the phase transition. As such, LLPS can be an important molecular event as a precursor to protein aggregation or the formation of amyloid fibrils. The LLPS of α-syn is triggered by differences in α-syn concentration in the microenvironment of the protein solution (Ray et al., 2020). Therefore, the α-syn LLPS phenomenon should be investigated to understand the etiological factors of PD.

In this study, we address the molecular mechanism of α-syn LLPS. Additionally, we discuss potential therapeutic strategies targeting LLPS to prevent the progression of PD. This review advances our understanding of the molecular biology of α-syn LLPS and suggests the development of new PD therapies.

Conformational states and higher-order assemblies of α-syn

α-Syn is an intrinsically disordered protein (IDP) in its unbound state (Bartels et al., 2010). However, it partially adopts α-helix or β-strand conformation upon binding to partner molecules. α-Syn consists of three domains: N-terminal, non-amyloid component (NAC), and C-terminal domains (Figure 1A). The N-terminal and NAC domains can adopt α-helices or β-strands depending on the microenvironment (Emamzadeh, 2016). Specifically, the N-terminal and NAC domains adopt α-helices when they bind to the lipid membrane (Figure 1A) (Ulmer et al., 2005) and β-strands when α-syn forms fibrils or aggregates (Figure 1A) (Tuttle et al., 2016). The fibrillar structure of decameric α-syn, elucidated by nuclear magnetic resonance (NMR), provides additional structural information on α-syn (Figure 1A) (Tuttle et al., 2016). Although this NMR structure exhibits conformational ensembles in the solution state, this *in vitro* fibrillar structure represents an artificially prepared assembly that may not fully capture the structural diversity present in the native cellular environment. To extrapolate this approach to conformations in the living system, we should consider diverse environmental factors such as intracellular macromolecular crowding, compartmentalization, and competing binding partners.

Microscopic and phase kinetic landscapes of α-syn aggregation

The aggregation mechanisms of several IDPs, including α-syn, have been extensively studied. Traditionally, the aggregation of IDPs is understood to begin with the multimerization of soluble and structurally disordered monomers (Vidović and Rikalovic, 2022). In this initial stage, conformational misfolding facilitates the self-assembly of monomers into transient oligomers (Vidović and Rikalovic, 2022). These oligomers adopt partially folded structures that constitute critical interaction regions between the monomers. The progressive accumulation and structural reorganization of these species eventually lead to the formation of insoluble amyloid fibrils exhibiting cross-β sheet structures.

Recently, the discovery of LLPS as a prominent feature of α-syn behavior has shifted the paradigm from a simple one-dimensional polymerization reaction to a multi-phase kinetic landscape (Garabedian et al., 2022; Rodríguez et al., 2024; Deka et al., 2026). Rather than functioning as a strict linear sequence where LLPS acts as an obligatory intermediate precursor to final amyloid formation, the biophysical transition of α-syn is governed by a complicated network of parallel, sequential, and competing biophysical processes (Figure 1B). To understand this intricate mechanism, it is essential to distinguish among the following seven microscopic and phase kinetic steps: 1) oligomer formation, 2) primary amyloid nucleation, 3) fibril elongation, 4) secondary nucleation, 5) LLPS, 6) condensate maturation or aging, and 7) gelation or solidification.

The initial oligomers are formed through the self-assembly of monomeric α-syn into heterogeneous and structurally dynamic multimers. This step is strongly influenced by the conformational state of the monomer. However, the physiological oligomeric state of

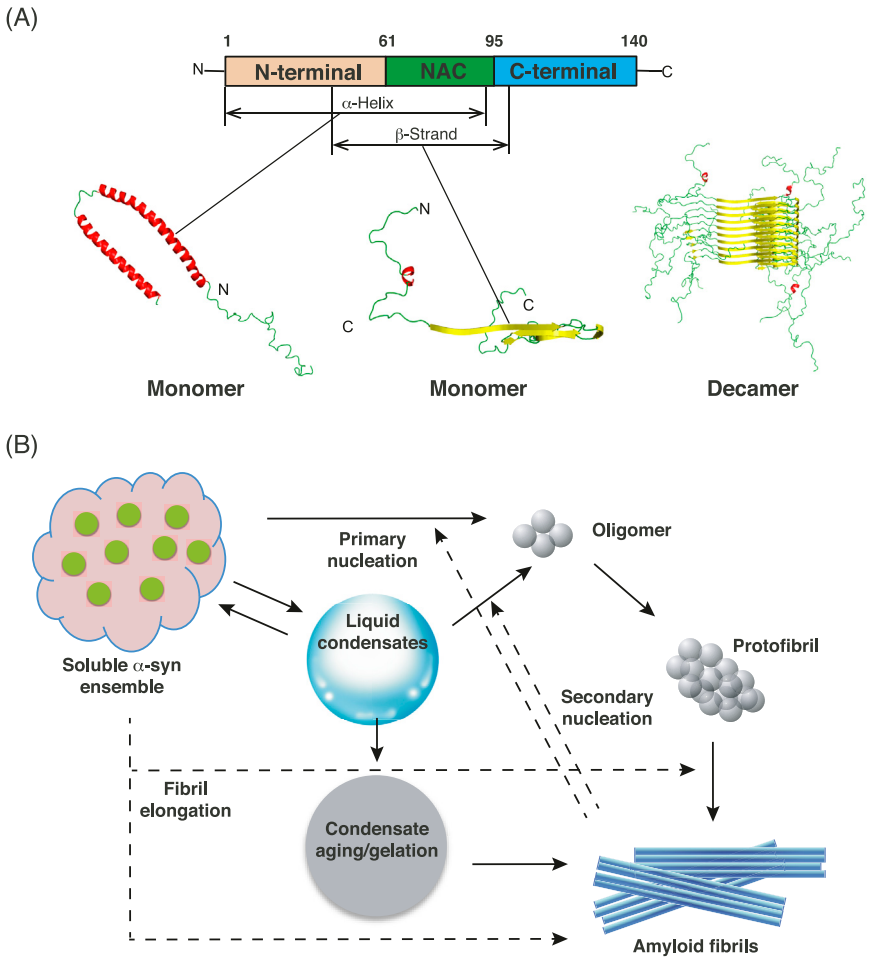


FIGURE 1
Structures of α-syn and possible mechanism of its amyloid formation. **(A)** Conformational states and assemblies of α-syn. **(B)** Potential amyloid fibrillization pathways of α-syn are schematically depicted.

α-syn remains debated and depends on experimental preparation, membrane association, and analytical methodology, rather than following a fixed tetramer-versus-dimer model. Depending on initial multimerization, these assemblies may grow toward a protofibrillar state. Such disordered oligomers undergo high-barrier structural rearrangements to form highly ordered nucleus seeds containing cross-β sheets. This classical nucleation event occurs directly in the bulk aqueous solution operating at dilute micromolar regimes of 10–100 μM, neutral-to-mildly acidic pH of 6.5–7.4, physiological ionic strength of 50–150 mM NaCl, and controlled mechanical or quiescent incubation parameters (Vidović and Rikalovic, 2022; Garabedian et al., 2022), and does not inherently require a prior phase transition. The successive growth of established amyloid nuclei results in fibril elongation through the addition of incoming monomers to the exposed ends of the protofibrils and mature fibrils. The secondary nucleation is a highly non-linear process catalyzed under acidic conditions of pH 4.0–6.0 and accelerated by mechanical shearing or pre-existing fibril template seeds (Wei et al., 2025), in which the lateral surfaces of pre-existing amyloid fibrils serve as reactive templates. This molecular event accelerates the nucleation of new fibrillar species from bulk monomers.

Intriguingly, LLPS is a thermodynamic demixing phenomenon, wherein homogeneous α-syn monomers rapidly agglomerate, forming macroscopic liquid droplets, requiring threshold concentrations of 100–500 μM in the presence of macromolecular crowders or cosolute modulators (Ray et al., 2020; Ziaunys et al., 2024). This step represents a physical partitioning of the space into a dilute phase and a highly condensed phase. Crucially, spherical morphology alone is insufficient to validate LLPS. Rather, identifying genuine LLPS requires multi-parameter criteria, including concentration-dependent phase boundaries, measurable partition coefficients, wetting behavior on surfaces, active droplet fusion, and rapid internal molecular recovery via fluorescence recovery after photobleaching. Such a dense phase can undergo condensate maturation or aging governed by incubation kinetics and interfacial partitioning at anionic lipid bilayer or intracellular droplet interfaces (Hardenberg et al., 2021; Xu et al., 2022), which implies the time-dependent internal reorganization within the liquid droplets. Because the local monomeric density inside the

droplets is significantly higher than in the bulk solution, the translational mobility of trapped α-syn molecules progressively decreases. However, reduced internal mobility or arrested droplet fusion does not automatically equate to amyloid conversion. Liquid droplets, viscoelastic gels, amorphous aggregates, and cross-β amyloid fibrils are distinct physical states that are differentiated through various biophysical assays. This aging step may lead sequentially to gelation or solidification of the liquid droplets. Specifically, the aging droplets are changed into elastic gels or irreversible solids.

In crowded intracellular environments, these seven processes may occur sequentially under several specific conditions, but also proceed through parallel or competing pathways. In bulk solution, the classical cascade of oligomerization, primary nucleation, fibril elongation, and secondary nucleation may proceed efficiently under physiological conditions without requiring any liquid–droplet intermediate. However, under conditions that favor macromolecular crowding or distinct environmental triggers, α-syn may enter the LLPS pathway via homogeneous nucleation driven by 1–5 mM ATP or polyamine coacervation (Kamski-Hennekam et al., 2023; Rodríguez et al., 2023) or divalent cation Ca^{2+} and Mn^{2+} C-terminal charge neutralization at substoichiometric-to-millimolar ratios (Huang et al., 2022a; Xu et al., 2022; Wei et al., 2025). In the early stages of droplet growth, the high molecular mobility means that trapped α-syn can easily be released into the bulk aqueous solution through a fully reversible reaction. However, as the droplet matures, the high density of monomers drastically reduces the kinetic barrier for oligomerization and primary nucleation inside the condensate.

Molecular factors for stabilizing α-syn droplets

The LLPS of α-syn is governed by a complex hierarchy of multivalent intermolecular interactions, sequence patterning, and conformational plasticity rather than its amino acid composition alone. As an IDP, α-syn utilizes its highly asymmetric charge distribution and localized hydrophobic clustering for transient intermolecular contacts, eventually causing macromolecular condensation. As mentioned in the previous section, α-syn consists of three distinct functional regions that contribute to the phase boundary, condensate dynamics, and eventual amyloid conversion. The amphipathic N-terminal domain (residues 1–60) is characterized by repeating conserved charged and apolar KTKEGV motifs. Because α-syn contains 15 Lys residues, it establishes transient intermolecular contacts that act as essential electrostatic "stickers" to anchor the protein network within the condensed phase. Conversely, the NAC domain (residues 61–95) functions as the highly hydrophobic core of α-syn and contributes to high-density homotypic multivalency, maintaining droplet stability through localized hydrophobic clustering and intramolecular cation- π, π–π stacking, aliphatic interactions at protein concentrations of 100–500 μM in the presence of macromolecular crowders like polyethylene glycol (Ray et al., 2020; Ziaunys et al., 2024). Because of its intense aggregation propensity, this NAC region serves as the critical determinant governing whether a droplet retains its fluid material properties or undergoes an aberrant liquid-to-solid phase transition. Modulating these two domains is the function of the acidic C-terminal domain (residues 96–140), which is highly disordered and heavily enriched with negative charges owing to its 6 Asp and 18 Glu residues. Under physiological baseline conditions, this C-terminal domain acts as a major electrostatic modulator, folding back onto the N terminus and NAC domains to provide an autoinhibited long-range intramolecular shield that suppresses premature self-association and droplet gelation.

Consequently, the macroscopic phase behavior of α-syn relies fundamentally on the electrostatic crosstalk and structural patterning between these three distinct domains. Rather than depending on simple monomeric concentration, droplet nucleation is dictated by transient intermolecular contacts, where weak interactions collectively yield high-affinity multivalency governed by intermediate salt concentrations where low-to-moderate NaCl screens terminal charges to favor liquid-like mobility, while excessive ionic strength alters demixing boundaries (Ray et al., 2020; Sawner et al., 2021). Disruptions in this sequence patterning release the autoinhibitory C-terminal shield. Such disruptions can result from microenvironmental factors such as localized pH changes approaching the isoelectric point near pH 4.6–4.7. Under these conditions, carboxylate protonation neutralizes C-terminal repulsion and can trigger precipitation or amyloid conversion (Uversky et al., 2001). Other relevant factors include shifts in ionic strength, crowding agents, and pathological residue mutations such as E46K or A53T. These mutations alter local electrostatic patch density or enhance LLPS propensity (Ray et al., 2020). When these long-range intramolecular interactions are attenuated, the highly amyloidogenic NAC region is exposed to the dense droplet environment. This structural deviation may accelerate a liquid-to-solid maturation process, shifting the droplet's material properties from a reversible fluid state to an irreversible gel or solid state. Within these aging condensates, the persistent and concentrated contacts among exposed NAC domains significantly lower the kinetic barrier for cross-β nucleation, eventually triggering amyloid fibril conversion and subsequent neurotoxic aggregation. The molecular determinants of α-syn LLPS, condensate maturation, and amyloid aggregation are summarized in Table 1.

Development strategies for PD therapies targeting α-syn

The therapeutic modulation of α-syn condensation requires a highly nuanced approach that targets specific states along the phase-transition landscape. Herein, emerging therapeutic strategies are categorized according to their biophysical mechanisms of action on the phase-transition landscape.

Compounds that suppress condensate formation

An immediate method to curb the amyloid cascade is blocking the initial phase transition of monomeric α-syn into liquid condensates entirely. This can be achieved by removing exogenous phase promoters or adding small molecules that disrupt early protein–protein or protein–solvent interactions. Divalent metal cations such as Ca^{2+} and Mn^{2+} readily coordinate with the negatively charged C-terminal domain of α-syn, neutralizing electrostatic repulsion and driving early droplet enlargement and maturation (Sawner et al., 2021; Huang et al.,

TABLE 1 Molecular Determinants of α-syn LLPS, Condensate Maturation, and Amyloid Aggregation.

Morphological phenomena Molecular determinants	Phase separation	Condensate material properties	Amyloid aggregation	Experimental system	Strength of evidence	References
Protein concentration	Promote	Accelerate maturation	Accelerate	In physiological buffers	High	Ray et al. (2020)
pH	Strongly promote	Accelerate gelation	Accelerate	At pH 5.5	High	Ray et al. (2020)
Ion strength	Promote at low-to-mid range	Accelerate hardening	Promote aggregation	Varying NaCl concentrations (50 mM to over 500 mM)	High	Sternke-Hoffmann et al. (2024)
Molecular crowding	Strongly promote	Accelerate aging	Accelerate	With 10%–15% PEG-8000, Ficoll, or Dextran	High	Ray et al. (2020)
Metal ions	Promote	Accelerate rigidification	Strongly accelerate	Micromolar additions of divalent/trivalent ions	Moderate	Xu et al. (2022)
Post-translational modifications	Promote	Accelerate maturation	Accelerate	S129E/S129D mutants	Moderate	Mukherjee et al. (2023)
Sequence truncations	Delay (N-term truncation); strongly promote (N-term truncation)	Accelerate gelation (C-term deletion)	Accelerate	Purified N/C-term deletion variants	High	Ray et al. (2026)
Familial mutations	Reduce	Variable	Accelerate	Hereditary familial Parkinson's disease mutant lines	High	Ray et al. (2026)
Membrane surfaces	Promote	Modulate wetting	Biphasic	POPC/POPS liposomes and artificial lipid bilayers	Moderate	Shaikh et al. (2026)
Heterotypic protein partners	Promote	Restrict dynamics	Accelerate cross-seeding	Co-incubation of α-syn with tau, prion protein, or viral nucleocapsid proteins	Moderate	Agarwal et al. (2022)

2022; Xu et al., 2022). Eliminating these metal ions from the presynaptic environment may represent a key suppressive strategy. The Ca^{2+}-specific chelator ethylene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA) efficiently disrupts Ca^{2+}-induced α-syn LLPS at the initial boundary (Huang et al., 2022b).

Compounds that preserve or stabilize the liquid state

Preventing droplet formation is not always the therapeutically desired intervention, as functional heterotypic co-condensation plays a crucial role in compartmentalizing synaptic vesicles and organizing presynaptic machinery. Thus, an alternative strategy can target the phase landscape by maintaining the highly fluid liquid state and preventing droplets from undergoing an aberrant liquid-to-solid phase transition. The aminosterol claramine exemplifies this approach. Rather than inhibiting LLPS itself, claramine physically stabilizes α-syn liquid condensates and shifts the phase boundary, maintaining aggregate liquidity and preventing the droplets from hardening into a viscoelastic matrix (Dada et al., 2024). Chemical osmolytes, which regulate homeostatic osmotic pressure by modifying protein folding landscapes via preferential hydration, can also modulate these states (Street et al., 2006; Hosseiniyan Khatibi et al., 2019; Pepelnjak et al., 2024).

Compounds that inhibit amyloid nucleation within condensates

When α-syn condensates are allowed to form or persist, they often accelerate the rate of primary nucleation into toxic β-sheet amyloid structures due to localized crowding. Intervening within the condensate core to obstruct fibril nucleation without altering the surrounding droplet architecture constitutes a distinct therapeutic strategy. In a *Caenorhabditis elegans* model of PD, it was demonstrated that claramine suppresses primary amyloid nucleation pathways specifically within preformed liquid droplets through its chemical kinetics profile (Dada et al., 2024). Furthermore, adenosine triphosphate (ATP) acts as a highly specialized endogenous hydrotrope with a concentration-dependent effect (Shuto et al., 2026). At low physiological levels (1–5 mM), its triphosphate moiety interacts with N-terminal residues to disrupt long-range electrostatic contacts, which can promote initial condensation (Kamski-Hennekam et al., 2023).

Compounds that reverse or dissolve mature assemblies

The final and most clinically challenging therapeutic mechanism involves deploying agents capable of entering mature, aged, or rigidified solid coacervates to reverse or dissolve them back into dynamic fluid states. The aliphatic diol 1,6-hexanediol has been widely utilized to probe this reversibility by disrupting the weak hydrophobic interactions sustaining early assemblies (Hardenberg et al., 2021). *In vivo* assays in *C. elegans* showed that 1,6-hexanediol successfully dissolves early-stage α-syn inclusion matrices in young nematodes, though its dissolving capacity drops sharply in aged cohorts due to the maturation of droplets into dense amyloid fibrils (Hardenberg et al., 2021). On the metal coordination axis, Mn^{2+} ions frequently cause accelerated maturation, forcing soluble monomers directly into solid-phase-like condensates and completely bypassing the stable fluid LLPS window (Xu et al., 2022). Remarkably, treatment with broad metal chelators such as EGTA and ethylenediaminetetraacetic acid has been shown to successfully reverse these preformed solid-like matrices, returning them to dynamic and reversible liquid droplets (Xu et al., 2022). Similarly, clinical-grade metal chelators including deferoxamine, deferasirox, deferiprone, trientine, and others are actively being evaluated for their capacity to reverse mature assemblies (Moons et al., 2020; Atarod et al., 2022).

Discussion

The unique biophysical characteristics of α-syn suggest a complicated regulatory landscape governing its phase behavior. Its highly acidic C-terminal domain retains key residues that can be phosphorylated, notably Tyr125, Ser129, Tyr133, and Tyr136 (Xu et al., 2015; Parra-Rivas et al., 2023). Specifically, Tyr125 interacts primarily with Fe^{2+}, Cu^{+}, Cu^{2+}, and Ca^{2+}, while Ser129, Tyr133, and Tyr136 are associated with Ca^{2+} binding (Liu and Franz, 2007; Farzadfard et al., 2022). In normal intracellular milieus, these residues exhibit relatively low affinity for specific metal ions. However, if these residues are phosphorylated, their binding affinities drastically increase.

We hypothesize a potential crosstalk model wherein such C-terminal phosphorylation modifies local electrostatic landscapes to influence subsequent metal coordination and phase transitions. In this proposed mechanism, the introduction of highly charged phosphate groups at positions like Ser129 could increase the local negative charge density, theoretically elevating the binding affinity for ambient divalent or transition metal cations. The subsequent binding of these metal ions is proposed to partially neutralize the net negative charge of the C-terminal region.

Biophysically, such a neutralization event might disrupt the long-range intramolecular electrostatic interactions that typically shield the NAC domain. By exposing this amyloidogenic core, the resulting conformation is hypothesized to lower the thermodynamic barrier for intermolecular self-association, potentially predisposing the protein to phase separation and fibrillization. However, these sequential molecular events remain a speculative multi-step hypothesis. Because individual stages of this model are based on results measured under disparate experimental conditions, the complete causal linkages from phosphorylation to metal-induced LLPS and amyloid maturation remain to be experimentally validated.

α-syn LLPS is considered a critical molecular event because the droplets are products of the early stage of the aggregation pathway and can revert to a single liquid phase. Thus, metal-chelation strategies for inhibiting droplet formation can be effective at an early stage. Cationic polymers need to be investigated as another approach to masking the negatively charged C-terminal region. Traditionally, natural and synthetic polymers with positive charges have been used for charge screening on protein surfaces (Kim et al., 2020). These include chitosan, poly-*L*-lysine, polyarginine, polyamines, and poly(amidoamine) dendrimers. Therefore, it is necessary to investigate the binding affinities and therapeutic effects of these polymers for α-syn.

The LLPS phenomenon of α-syn was first observed relatively recently. The current structural information is insufficient to comprehensively understand the mechanism of α-syn LLPS. LLPS occurs in dynamic cellular environments. Therefore, future studies should address the dynamic behavior of α-syn, such as its conformational changes and stoichiometric properties, in the formation of oligomers. Cryogenic electron microscopy provides structural information on the diverse conformations of α-syn in different environments (Zhao et al., 2026; do Carmo Gonçalves et al., 2026; Yang et al., 2026). High-speed atomic force microscopy (HS-AFM) is another effective analytical tool for observing α-syn LLPS. HS-AFM has been used in recent studies on α-syn (Zhang et al., 2018; Watanabe-Nakayama and Ono, 2022). In addition, considering that α-syn has a disordered C-terminal domain, molecular dynamics simulations are another powerful method for analyzing the dynamics of the C-terminal domain (Jin et al., 2026; Chen et al., 2026; Akkum et al., 2026). Consequently, a comprehensive understanding of α-syn LLPS will represent a new paradigm for PD therapy development.

Author contributions

SK conceived this study, performed literature search, and wrote the manuscript.

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Conflict of interest

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