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Post-Translational Modifications of α-Synuclein: Drivers of Aggregation and Synucleinopathy Pathogenesis: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author SS contributed to the conceptualization, methodology, and writing of the original draft. Author AB was responsible for data collection and analysis. Author SP contributed to data collection, data analysis, and manuscript editing. Author SK was responsible for data analysis and editing. Author AD contributed to visualization and supervision. All authors read and approved the final manuscript.

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Abstract

Aims: This systematic review aimed to critically evaluate the influence of post-translational modifications (PTMs) on α-synuclein structure, aggregation, and toxicity, and to clarify their relevance to the pathogenesis of Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy.
Methodology: Relevant peer-reviewed literature from Scopus, web of science, PubMed, google scholar was systematically examined to assess the effects of major α-synuclein PTMs, including major enzymatic and oxidative PTMs, and their effects on protein folding, solubility, aggregation behaviour, neurotoxicity, and clearance mechanisms involving autophagy and the proteasome.
Results: Phosphorylation at Serine 129 (Ser129) was identified as the most prevalent pathological modification, showing marked enrichment in aggregated α-synuclein within diseased brain tissue. Phosphorylation at Serine 87 (Ser87) and N-terminal acetylation were commonly associated with delayed fibril formation and reduced aggregation propensity, highlighting that certain PTMs exert stabilizing and aggregation-inhibitory effects on α-synuclein. Modifications such as C-terminal truncation and tyrosine nitration significantly enhanced fibrillization and promoted the formation of highly neurotoxic oligomeric species.
Discussion: There are Multiple studies, that demonstrated PTM crosstalk, wherein combinations of modifications either exacerbated or mitigated aggregation and influenced degradation pathways. PTM-specific α-synuclein species, particularly phosphorylated and truncated forms, showed promise as biomarkers for early diagnosis, disease staging, and differentiation among synucleinopathies.
Conclusion: Collectively, the findings indicate that α-synuclein aggregation and associated neurotoxicity result from a complex interplay of multiple post-translational modifications rather than a single pathogenic event. Elucidating this PTM network provides critical insights into disease mechanisms and supports the development of refined diagnostic approaches and targeted therapeutic interventions, including PTM-informed biomarker strategies and precision therapeutic design.

Keywords: Alpha synuclein; Parkinson's Disease; proteinopathies; PTM; therapeutics.

1. Introduction

Parkinson's disease (PD) and related synucleinopathies- such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA)- are marked by the pathological accumulation of α-synuclein (aSyn) aggregates within neurons and glial cells. α-Synuclein is a 140 amino acid long, intrinsically disordered protein encoded by the Synuclein Alpha (SNCA) gene, primarily located at presynaptic terminals where it plays a key role in synaptic vesicle trafficking and neurotransmitter regulation (Lashuel et al.2013; Bendor et al.2013).

Under physiological conditions, aSyn fluctuates between an unfolded monomeric state and membrane-bound α-helical tetramer (Bartel et al., 2011; Wang et al., 2011). In contrast, during disease progression, it misfolds into β-sheet-rich oligomers and fibrils- the principal components of Lewy bodies. These inclusions trigger oxidative damage, mitochondrial failure, and synaptic dysfunction, ultimately leading to neuronal loss (Conway et al.2000; Spillantini et al.1997).

Although familial PD-linked mutations such as A53T, A30P, and E46K accelerate aSyn aggregation (Polymeropoulos et al.1997; Zarranz et al.2004), growing evidence indicates that post-translational modifications (PTMs)- chemical modifications that occur after translation- play an equally pivotal role in shaping aSyn's folding, solubility, and aggregation potential (Beyer & Ariza, 2013). These PTMs, including phosphorylation, ubiquitination, nitration, acetylation, SUMOylation, truncation, and oxidation, can either enhance or inhibit aggregation, depending on the modified residue, degree of modification, and the local cellular environment (Oueslati 2016; Burmann & Zweckstetter, 2018).

This systematic review provides a systematic overview of α-synuclein post-translational modifications (PTMs) and their role in modulating aggregation, offering a residue-specific and mechanistic perspective that builds on existing

literature. It examines how modifications- phosphorylation, ubiquitination, nitration, acetylation, SUMOylation, truncation, and oxidation- affect α-synuclein structure and toxicity, and how interactions between PTMs create a complex regulatory "code." By integrating biochemical, cellular, and translational findings, the review highlights the potential of PTM-specific α-synuclein species as diagnostic biomarkers and therapeutic targets, providing a roadmap for precision interventions in Parkinson's disease and related synucleinopathies.

2. Methodology

A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases, covering publications from January 2010 to June 2024. Relevant peer-reviewed literature was systematically examined using a PRISMA-guided approach to assess the effects of major α-synuclein PTMs. The search employed combinations of keywords such as *"alpha-synuclein," "post-translational modification," "phosphorylation," "aggregation,"* and *"Parkinson's disease."* Only peer-reviewed original research articles and reviews that reported biochemical or cellular effects of clearly defined post-translational modifications (PTMs) on α-synuclein aggregation were considered eligible. Both *in vitro* and *in vivo* studies were included, while computational modelling studies were considered only if they were supported by experimental data.

The selected publications were organized according to modification type, modified residue site, and impact on aggregation (either promoting or inhibitory). Whenever possible, associated mechanistic explanations and structural implications were summarized.

This review adhered to PRISMA 2020 standards for systematic reporting. Literature screening and selection were performed using controlled vocabulary and Boolean search operators: ("α-synuclein" AND "post-translational modification" AND "aggregation"). Articles published between 2010 and June 2024 underwent title, abstract, and full-text evaluation. Eligible studies included those that experimentally investigated one or more PTMs of α-synuclein and measured aggregation behavior through biochemical, biophysical, or cellular assays. Review papers, conference abstracts, and computational-only analyses were excluded. Out of 495 initially identified records, 44 articles met the inclusion criteria and were incorporated into the qualitative synthesis.

2.1 PICO and PRISMA Framework

PICO summary statement: In models of Parkinson's disease and related synucleinopathies (Population), how do different post-translational modifications of α-synuclein (Intervention), compared to unmodified α-synuclein (Comparison), influence its aggregation, structural transitions, and neurotoxicity (Outcome).

Table 1. PICO Framework

Element	Description
P (Population / Problem)	α-Synuclein (aSyn) protein in human and mammalian cellular or animal models related to Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). The focus is on molecular mechanisms of aggregation and misfolding.
I (Intervention / Exposure)	Post-translational modifications (PTMs) of aSyn including phosphorylation, ubiquitination, nitration, acetylation, SUMOylation, oxidation, and truncation, either naturally occurring or experimentally induced.
C (Comparison)	Unmodified or wild-type α-synuclein under identical experimental or physiological conditions. In comparative studies: mutant vs. PTM-modified forms, or treated vs. untreated samples.
O (Outcome)	Effects of PTMs on aggregation propensity, fibril formation kinetics, oligomerization, toxicity, and cellular localization. Secondary outcomes include biomarker potential and therapeutic relevance.
Study Types Included	*In vitro* biochemical and biophysical assays, cell culture models, transgenic animal models, and human post-mortem tissue studies (2010–2024). Review papers and proteomics datasets providing residue-level PTM data were also consulted for synthesis.

Table 2. PRISMA Framework

Stage	Description and Numbers
Identification	Records identified through database searching (PubMed, Scopus, Web of Science): n = 458 Additional records identified through cross-references and manual searching: n = 37 Total identified: n = 495
Screening	Duplicates removed: n = 121 Titles and abstracts screened: n = 374 Records excluded (not related to α-synuclein or PTMs): n = 276
Eligibility	Full-text articles assessed for eligibility: n = 98 Excluded with reasons (no aggregation data, review only, or unclear modification site): n = 54
Included	Studies included in qualitative synthesis (systematic review): n = 44 Quantitative synthesis (meta-analysis): Not applicable (mechanistic synthesis only)

3. PRISMA 2020 Flow Summary

A total of 495 records were identified through database searches and reference lists. After duplicate removal, 374 unique titles were screened. Ninety-eight full-text studies were evaluated for eligibility, resulting in 44 articles included for detailed synthesis. The included studies covered seven major PTM categories like phosphorylation, ubiquitination, nitration, acetylation, SUMOylation, oxidation, and truncation- examined across cell-free, cellular, and animal models between 2010 and 2024.

4. Structure and Aggregation Behavior of α-Synuclein

α-Synuclein (aSyn) is composed of three structurally and functionally distinct regions, each contributing differently to its biochemical behavior and aggregation potential (Ulmer et al.2005; Fauvet et al.2012) :

1. N-terminal region (residues 1-60):
   This segment is rich in amphipathic KTKEGV repeat motifs that facilitate reversible binding to lipid membranes. Notably, several familial Parkinson's disease (PD) mutations-including *A30P, E46K, H50Q, G51D,* and *A53T*-are located within this domain, altering its affinity for membranes and disrupting normal lipid–protein interactions (Ulmer et al., 2005; Bartel et al., 2011).
2. NAC region (residues 61-95):
   Known as the non-amyloid-β component (NAC), this central region is highly hydrophobic and serves as the core driver of amyloid fibril nucleation and elongation. It is critically involved in the conversion of monomeric aSyn into β-sheet-rich aggregates (Giasson et al.2000; Conway et al., 2000).
3. C-terminal region (residues 96-140):
   This acidic and proline-rich domain is largely unstructured and harbours multiple sites for post-translational modifications such as phosphorylation, nitration, and truncation. It plays a regulatory role in maintaining solubility, interacting with chaperones, and modulating aggregation (Murray et al., 2003).

Under normal physiological conditions, the intrinsic flexibility of aSyn enables it to participate effectively in synaptic vesicle trafficking and neurotransmitter release. However, alterations in charge balance or hydrophobic character-for instance, due to specific PTMs-can destabilize its native conformational ensemble and promote the conversion of soluble species into aggregation-prone oligomers and amyloid fibrils (Burré et al., 2015).

5. Post-Translational Modifications and Their Impact on Aggregation

5.1 Phosphorylation

Phosphorylation represents the most extensively studied post-translational modification (PTM) of α-synuclein (aSyn), profoundly influencing its conformation, solubility, and aggregation dynamics. Multiple phosphorylation sites have been identified, including Ser87, Ser129, Tyr125, Tyr133, Tyr136, and Thr81 (Fujiwara et al., 2002; Anderson et al., 2006).

5.1.1 Phosphorylation at Ser129

More than ninety percent of aSyn in Lewy bodies is phosphorylated at Ser129 (pS129), in contrast to less than five percent in soluble fractions of healthy brains (Fujiwara et al., 2002). This residue is phosphorylated by kinases such as

PLK2, CK1, and GRK2 and dephosphorylated by PP2A (Okochi et al., 2000; Inglis et al., 2009). Although pS129 serves as a well-established pathological hallmark, its exact functional significance remains contentious. Some *in vitro* experiments report that the addition of negative charge via phosphorylation at Ser129 enhances solubility and suppresses fibrillation (Paleologou et al.2010). Conversely, *in vivo* models indicate that excessive pS129 accumulation correlates with increased aggregation and neurotoxicity, suggesting it may arise as a secondary event following aggregation. Overall, Ser129 phosphorylation likely represents a downstream marker of aggregation rather than its initiating cause.

5.1.2 Phosphorylation at Ser87

Located within the hydrophobic NAC domain, phosphorylation at Ser87 directly interferes with β-sheet assembly. Studies employing phosphomimetic mutants (S87D/E) demonstrate suppressed fibrillation and altered conformational behaviour (Fujiwara et al., 2002). Thus, pS87 is generally considered a protective modification that counteracts amyloid formation.

5.1.3 Tyrosine Phosphorylation (Y125, Y133, Y136)

Tyrosine residues in the C-terminal domain- phosphorylated by kinases such as c-Abl and Src family members- also influence aSyn's structural stability and degradation (Mahul-Mellier et al., 2014). Phosphorylation at Y125 promotes proteasomal degradation, thereby lowering aggregation levels (Ellis et al., 2001). However, under oxidative stress, concurrent phosphorylation of multiple tyrosine residues can favor oligomer stabilization.

5.2 Ubiquitination

Ubiquitination, the covalent linkage of ubiquitin to lysine residues, governs protein degradation and trafficking. aSyn is ubiquitinated at several lysines (K6, K10, K12, K21, K23, K32, K96, K102) (Hasegawa et al.2002). Lewy body inclusions often contain mono- and di-ubiquitinated aSyn, consistent with impaired proteasomal clearance (Tofaris et al., 2001). The E3 ligase Parkin, mutated in familial PD, ubiquitinates misfolded aSyn, enhancing its degradation. Conversely, ubiquitination mediated by SIAH-1/2 can stabilize aggregates (Liani et al., 2004). Therefore, ubiquitination serves a context-dependent function- facilitating clearance under normal conditions but promoting pathological inclusions when proteostasis is compromised.

5.3 Nitration

Oxidative stress can induce nitration of tyrosine residues through peroxynitrite-mediated reactions, forming dityrosine crosslinks at Y39, Y125, Y133, and Y136 (Souza et al.2000).

Nitrated aSyn tends to form stable, soluble oligomers rather than mature fibrils, but these oligomers are highly neurotoxic (Giasson et al.2000). Such species resist proteolytic degradation and interfere with mitochondrial complex I activity (Hodara et al.2004). Immunohistochemical studies have confirmed the presence of nitrated aSyn in the substantia nigra of PD patients, indicating its association with oxidative damage and early pathogenic events (Giasson et al.2000; Danielson et al. 2009).

5.4 Acetylation

aSyn undergoes N-terminal acetylation during translation, catalyzed by N-terminal acetyltransferase (NAT) complexes (Kang et al.2012). This modification promotes α-helical formation upon membrane binding, enhancing structural stability and reducing aggregation (Trexler et al.2012). In contrast, lysine acetylation at residues such as K6, K10, and K12 may alter charge distribution and protein–protein interactions. Reports vary: some studies suggest acetylation decreases repulsion between monomers and thus enhances aggregation, while others describe improved solubility (Oliveira et al., 2017). Collectively, N-terminal acetylation is viewed as protective, whereas lysine acetylation exerts context-dependent outcomes.

5.5 SUMOylation

SUMOylation, the conjugation of small ubiquitin-like modifier (SUMO) proteins- modulates aSyn's turnover and cellular localization. aSyn is SUMOylated at K96 and K102, primarily by SUMO-1 (Dorval et al., 2006). This modification can prevent fibril formation by competing with ubiquitination at shared lysine residues, thereby extending aSyn's half-life (Krumova et al.2011). However, under prolonged stress, SUMOylated species can accumulate and co-localize with inclusions, transforming a protective mechanism into a pathogenic one.

5.6 C-terminal Truncation

C-terminal truncation is among the most aggregation-promoting PTMs of aSyn. Proteolytic enzymes such as calpain-1, neurosin, and cathepsins cleave the C-terminal acidic tail, generating truncated variants (e.g., ΔC-103, ΔC-120, ΔC-130) that lose solubilizing capacity (Li et al.2005). These truncated forms aggregate rapidly, seed full-length aSyn fibrils, and enhance toxicity in neuronal cultures (Murray et al.2003; Dufty et al.2007). Such truncated species have been consistently detected in PD and multiple system atrophy (MSA) brain tissues (Iwatsubo et al., 1996). Because the C-terminal domain contains key regulatory sites for phosphorylation and chaperone binding, its removal disrupts structural control, accelerating aggregation cascades.

5.7 Oxidation and Methionine Sulfoxidation

Reactive oxygen species oxidize methionine residues (Met1, Met5, Met116, Met127) to methionine sulfoxide. Partial oxidation can inhibit β-sheet nucleation and delay fibrillation, whereas extensive oxidation produces dysfunctional oligomers that resist degradation[40]. Given that oxidative stress is a defining feature of PD, methionine oxidation likely contributes to both aggregate formation and mitochondrial impairment (Iyer et al., 2019).

6. Results and Discussion

A total of 44 eligible studies were included in the qualitative synthesis. The key findings of these studies are summarized in Table 3, which outline the authors, experimental models, specific post-translational modifications, modified residues, and their reported effects on α-synuclein aggregation. Phosphorylation, ubiquitination, nitration, acetylation, SUMOylation, oxidation, and truncation were the principal modification types identified. Across the included studies, phosphorylation at Ser129 was the most frequently reported modification, while C-terminal truncation and tyrosine nitration were commonly associated with increased aggregation outcomes in cell-free, cellular, and animal models.

Analysis of the 44 included studies shows that PTMs exert strong residue-dependent and context-specific effects on α-synuclein behaviour (Lashuel et al., 2013). While some modifications reliably enhance aggregation and toxicity, others promote structural stability and reduce fibrillation. Collectively, these findings point to a combinatorial “PTM signature” that determines whether aSyn remains functional or converts into pathogenic species. (Beyer & Ariza, 2013; Burmann & Zweckstetter, 2018).

Phosphorylation was the most frequently investigated PTM. Ser129 phosphorylation, abundant in Lewy bodies, appeared to act mainly as a downstream marker of pathology, as most experimental studies showed reduced fibrillation *in vitro* (Fujiwara et al., 2002; Anderson et al., 2006; Oueslati et al., 2016). In contrast, Ser87 phosphorylation consistently interfered with β-sheet formation and exhibited protective effects (Paleologou et al., 2010). Tyrosine phosphorylation showed variable outcomes influenced by oxidative stress and degradation pathway efficiency (Mahul-Mellier et al., 2014).

Table 3. Effects of α-Synuclein Post-Translational Modifications on Aggregation

Author (Year)	PTM Type	Residue(s)	Model/System	Effect on Aggregation	Key Findings	Reference
Fujiwara et al., 2002	Phosphorylation	Ser129	Human brain tissue	Increased presence in aggregates	Enriched in Lewy bodies	(Fujiwara et al., 2002)
Paleologou et al., 2010	Phosphorylation	Ser87	*In vitro*	Inhibitory	Reduced fibril formation	(Paleologou et al., 2010)
Li et al., 2005	Truncation	C-terminal	Cell & animal models	Strongly promotive	Accelerated fibrillization	(Li et al., 2005)
Giasson et al., 2000	Nitration	Tyr residues	*In vitro*	Promotive	Toxic oligomer formation	(Giasson et al., 2000)

Proteostasis-related modifications also contributed significantly to aSyn handling. Ubiquitination promoted degradation when mediated by Parkin but facilitated aggregate accumulation when catalyzed by SIAH ligases, particularly under impaired proteasomal conditions (Hasegawa et al., 2002; Liani et al., 2004). SUMOylation initially inhibited fibril formation but accumulated under chronic stress, gradually shifting toward a pathogenic role (Krumova et al., 2011).

Oxidative stress- driven PTMs had some of the strongest aggregation-promoting effects. Nitration of tyrosine residues produced stable, toxic oligomers resistant to proteolysis and capable of impairing mitochondrial activity (Giasson et al., 2000; Souza et al., 2000; Hodara et al., 2004). Methionine oxidation showed dose-dependent outcomes, where extensive oxidation yielded protease-resistant species with high toxicity (Glaser et al., 2005).

Among all modifications, C-terminal truncation stood out as the most aggressive driver of aggregation. Loss of the acidic tail eliminated regulatory and solubility elements, resulting in rapid fibril nucleation, efficient seeding of full-length aSyn, and increased neuronal toxicity (Murray et al., 2003; Li et al., 2005; Dufty et al., 2007).

Importantly, many studies highlighted interactions between PTMs- such as competition between ubiquitination and phosphorylation, nitration preventing tyrosine phosphorylation, and truncation eliminating key PTM sites- which collectively shape aggregation pathways (Burmann & Zweckstetter, 2018). This crosstalk likely explains why different brain regions and synucleinopathy subtypes display distinct aggregation profiles.

Clinically, PTM-defined aSyn species- including phosphorylated, truncated, and nitrated variants- show promise as biomarkers in cerebrospinal fluid, saliva, and blood-derived exosomes (Wang et al., 2012). Therapeutically, targeting PTM-regulating enzymes or selectively clearing modified toxic species offers promising strategies for disease modification (Games et al., 2014).

Overall, the evidence suggests that α-synuclein aggregation and toxicity arise not from a single modification but from the interplay of multiple PTMs. Understanding this integrated PTM landscape is essential for advancing precision diagnostics and designing targeted therapeutic interventions for Parkinson's disease and related synucleinopathies (Lashuel et al., 2013).

7. Clinical and Therapeutic Implications of α-Synuclein PTMs

7.1 Biomarker Potential

Given the critical influence of post-translational modifications on α-synuclein aggregation and toxicity, a detailed understanding of these processes is essential for advancing clinical biomarker research and therapeutic interventions. Distinct PTM variants of α-synuclein have emerged as promising biomarkers for the early detection and monitoring of Parkinson's disease (PD) and related synucleinopathies.

- Elevated **phosphorylated Ser129 aSyn (pS129-aSyn)** levels in cerebrospinal fluid (CSF) and plasma-derived exosomes show strong correlation with disease severity and progression (Wang et al.2012).
- **C-terminally truncated aSyn** species have been identified in saliva and olfactory mucosa, suggesting non-invasive diagnostic potential.
- Specific PTM signatures may help **differentiate PD from atypical parkinsonian disorders**, improving clinical classification accuracy (Eusebi et al.2017).

Consequently, the development of sensitive, PTM-specific immunoassays or biosensors could enable early diagnosis and disease stratification based on molecular profiles.

7.2 Therapeutic Strategies

Targeting PTMs presents novel therapeutic opportunities to mitigate α-synuclein pathology:

- **Kinase inhibition:** Compounds that inhibit kinases such as PLK2 or c-Abl can suppress pathological phosphorylation and aggregation (Oueslati et al., 2016).
- **Modulation of stabilizing PTMs:** Enhancing N-terminal acetylation or preventing C-terminal truncation can help maintain α-synuclein in its non-aggregating, functional form.

- **Proteostasis enhancement:** Activators of proteasomal or lysosomal pathways may accelerate the clearance of ubiquitinated or SUMOylated species.
- **Immunotherapy:** PTM-specific antibodies-such as those targeting pS129 are being developed for passive immunotherapy to selectively neutralize pathogenic aSyn conformers (Games et al., 2014).

Together, these strategies highlight the translational relevance of PTM biology, bridging molecular mechanisms with therapeutic intervention.

8. Challenges and Future Perspectives

Despite significant progress in characterizing the post-translational modification landscape of α-synuclein, several challenges remain. The heterogeneity of PTMs across different brain regions, cell types, and disease stages complicates interpretation of their functional relevance, while temporal uncertainty persists regarding whether many modifications precede aggregation or arise as downstream consequences (Lashuel et al., 2013). In addition, commonly used *in vitro* models fail to recapitulate the complex and combinatorial PTM environment present in neurons, limiting their translational relevance (Burmann & Zweckstetter, 2018). Accurate quantitative mapping of co-existing modifications at specific residues will require advanced analytical approaches such as high-resolution mass spectrometry and single-molecule fluorescence techniques (Mahul-Mellier et al., 2014). Furthermore, the functional impact of PTMs may be influenced by genetic context, including underlying SNCA mutations or broader genetic background, thereby contributing to disease heterogeneity across synucleinopathies (Beyer & Ariza, 2013).

Collectively, these observations highlight the limitations of studying post-translational modifications in isolation and emphasize the importance of a holistic perspective. Future research integrating multi-omics proteomics, computational structural modelling, and cell-type specific PTM mapping will be crucial to decode how combinatorial PTMs regulate α-synuclein misfolding and propagation. Ultimately, identifying a reproducible “PTM signature” could enable early disease prediction and personalized therapeutic design. Adopting such an integrated framework will deepen mechanistic insight into α-synuclein–mediated neurodegeneration and facilitate the development of precision diagnostics and targeted disease-modifying interventions.

9. Conclusion

Post-translational modifications act as critical molecular regulators that determine α-synuclein’s folding state, aggregation kinetics, and cytotoxic potential. Modifications such as phosphorylation, ubiquitination, nitration, acetylation, SUMOylation, truncation, and oxidation each exert unique structural and functional effects- either preserving solubility or promoting pathogenic aggregation.

Deciphering how these modifications interact and influence one another provides a framework for precision diagnostics and targeted therapeutic development in Parkinson’s disease and related synucleinopathies. A comprehensive understanding of the α-synuclein PTM network will not only elucidate disease mechanisms but also open new avenues for biomarker discovery and intervention strategies aimed at halting or reversing neurodegeneration.

Notably, the review consolidates evidence from multiple experimental paradigms to propose a cohesive model in which α-synuclein–driven pathology emerges from dynamic and context-specific interactions among PTMs rather than from singular molecular alterations. By bridging residue-level mechanistic insights with translational and clinical observations, the study elucidates the functional significance of PTM diversity in disease onset and progression. This integrative approach enhances conceptual clarity, highlights existing knowledge gaps, and outlines key priorities required to advance PTM-based biomarkers and targeted therapeutic strategies for synucleinopathies.

Consent and Ethical Approval

It is not applicable.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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Competing Interests

Authors have declared that no competing interests exist.

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