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EDITORIAL

Targeting α-synuclein in Parkinson's disease and Lewy Body Disorders: A new era of precision medicine

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The accumulation and aggregation of the presynaptic protein α-synuclein (α-syn) represent the defining pathological hallmark of a group of neurodegenerative conditions collectively termed α-synucleinopathies. This spectrum of disorders, encompassing Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), presents formidable clinical and diagnostic challenges due to substantial symptomatic overlap and complex, multifaceted molecular etiologies. As the understanding of the molecular architecture underlying these disorders develops, α-syn has transitioned from a descriptive histological marker to the primary focal point for disease-modifying interventions. This transition marks a critical shift in the field, moving away from exclusively symptomatic management toward strategies that address the core biological drivers of neurodegeneration. The neurobiology of α-syn is remarkably complex, involving a delicate equilibrium between its physiological role in synaptic vesicle trafficking and its pathological propensity to misfold into toxic assemblies. While research has traditionally centered on its synaptic functions and the formation of Lewy body (LB) pathology, recent evidence emphasizes that α-syn is not exclusively a cytoplasmic protein. Its dynamic localization to neuronal nuclei suggests critical regulatory roles in genomic stability, the DNA damage response, and transcriptional control.[1] Recent studies demonstrate that nuclear α-syn promotes neurodegeneration through transcriptional dysregulation, DNA repair deficits, and cellular senescence, especially when present in phosphorylated or oligomeric forms.[1] Thus, α-syn can modulate nuclear import pathways and directly interact with genomic repair machinery, suggesting that the disruption of these nuclear functions is a key driver of early-stage neurodegeneration. This nuclear involvement suggests that α-syn toxicity is not merely a consequence of protein aggregation in the cytosol but involves a fundamental disruption of the cell's genetic regulatory framework.

Pathologically, α-synucleinopathies have been historically classified by the anatomical and cellular distribution of α-syn: Lewy body diseases (LBDs) featuring neuronal inclusions, and MSA defined by glial cytoplasmic inclusions. However, a significant paradigm shift is occurring as evidence indicates that visible inclusions represent only a fraction of the disease-relevant pathology. Soluble oligomeric assemblies, which are often undetectable by conventional immunohistochemistry, are increasingly implicated as the key neurotoxic species. The application of advanced methodologies, such as the proximity ligation assay (PLA), has enabled the *in situ* detection of widespread non-inclusion oligomeric pathology. Notably, PLA studies in LRRK2-associated PD demonstrate abundant oligomeric α-syn even in cases lacking

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traditional LBs, fundamentally challenging the centrality of macroscopic inclusions in defining the disease state.[2,3] This finding suggests that the process of aggregation itself, rather than the final insoluble product, is the primary mediator of neuronal dysfunction. Furthermore, the molecular composition of the LB itself is being radically re-evaluated. Rather than being simple proteinaceous deposits, new evidence suggests these inclusions consist of a dense framework of membranous organelles, including mitochondria, autophagic vesicles, and lysosomes.[3] This suggests that α-syn aggregation is inextricably linked to a profound failure of cellular proteostasis and organelle trafficking, where the "inclusion" acts as a graveyard for dysfunctional cellular machinery. The presence of these organelles within Lewy bodies implies that the pathology disrupts the entire endolysosomal and mitochondrial network, leading to a state of metabolic and energetic crisis within the neuron.

The "non-coding" revolution has further expanded our understanding of the disease's molecular regulation. Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as vital regulators of α-syn expression and mitochondrial homeostasis.[4] These molecules are not only involved in the molecular pathogenesis by targeting the 3' UTR of the α-syn gene to modulate its translation, but also serve as stable signatures that correlate with disease progression and severity.[4] The dysregulation of these ncRNAs provides a bridge between environmental triggers and genetic susceptibility, offering a more nuanced view of how α-syn levels are maintained or disrupted over time.

The therapeutic landscape is progressively shifting from symptomatic management toward disease-modifying therapies. While gold-standard dopamine replacement therapies effectively mitigate motor symptoms, they do not arrest the underlying neurodegenerative process. Current clinical pipelines reveal a diverse array of disease-modifying therapies designed to target the α-syn life cycle at various stages: reducing protein production, inhibiting the formation of toxic oligomers, or enhancing the clearance of existing aggregates.[5] These strategies include anti-sense oligonucleotides (ASOs) to knock down protein expression, as well as small molecules designed to stabilize the physiological monomeric form of the protein. Monoclonal antibodies targeting α-syn have been at the forefront of this effort. Although several large-scale trials have shown successful target engagement, demonstrating that these antibodies can effectively bind to and clear extracellular α-syn, they have yet to reach their primary clinical endpoints of slowing functional decline.[5] This has led to a pivot toward small-molecule inhibitors and "molecular tweezers" that can cross the blood-brain barrier more effectively to target intracellular aggregation. The field is also exploring the role of immunotherapy in preventing the cell-to-cell "prion-like" propagation of α-syn, which is thought to underlie the progressive spread of pathology through the nervous system. Secondary pathways are being targeted to bolster neuronal resilience. Glucocerebrosidase (GCase) enhancers, such as ambroxol, have shown promising results by improving lysosomal function and facilitating the degradation of α-syn.[5,6] Additionally, the repositioning of glucagon-like peptide-1 (GLP-1) receptor agonists, originally used for diabetes, is being explored for their potent anti-inflammatory and neuroprotective effects in PD and DLB models.[5,6] These agents may offer a dual benefit by addressing both the proteinopathy and the chronic neuroinflammation that characterizes these disorders.[6]

Despite these significant strides, several critical hurdles remain. The clinical and pathological heterogeneity of α-synucleinopathies suggests that a universal approach to targeting α-syn may be insufficient. Emerging evidence suggests the existence of different "strains" of α-syn, similar to prions, which may possess distinct structural properties and different levels of neurotoxicity.[2,7] This heterogeneity implies that a therapy effective against one strain of α-syn in PD might be ineffective against the strain found in MSA. Understanding the structural basis of these strains is essential for developing "strain-specific" therapies that can be tailored to the individual patient's pathology. The timing of intervention remains perhaps the most significant challenge. By the time a patient is clinically diagnosed, a substantial percentage of dopaminergic and cortical neurons have already been lost. This "ceiling effect" in clinical trials necessitates the identification of patients through specific biomarkers monitoring to capture the "prodromal" or "pre-motor" phase. Intervening at this stage offers the best chance of preserving neuronal function and altering the long-term course of the disease. Furthermore, the translation of preclinical success into clinical utility is often hindered by the limitations of current animal models, which frequently fail to capture the chronic, age-related nature of human synucleinopathies.[7] Many models rely on the overexpression of α-syn, which may not accurately reflect the slow, progressive accumulation seen in the aging human brain. Future directions must include the use of patient-derived induced pluripotent stem cells (iPSCs) to better model human-specific responses to α-syn-targeting compounds.[8] These human-cell-based models allow for the study of disease mechanisms in a way that respects the genetic background of the individual patient, paving the way for a more personalized medicine approach.

In light of these recent advances in neurodegenerative research, we recognize the importance of developing this Special Issue, entitled "Targeting α-Synuclein in Parkinson's Disease and Lewy Body Disorders," to showcase recent developments in the field, including innovative treatment, diagnosis, and pathogenesis. Its scope encompasses a broad spectrum of studies, including clinical, translational, basic science, and genomics, highlighting the multidisciplinary nature of current α-syn research. By integrating multiomic data, advanced imaging, and molecular biology, movement disorder field is entering an era where these disorders can be addressed not just through the management of their symptoms, but also through the strategic, evidence-based interruption of their underlying biological drivers.

Conflict of interest

Giorgia Sciacca serves on the Youth Editorial Board of this journal and is the sole Guest Editor of this Special Issie. She declares no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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