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Comparing α-Synucleinopathy Models and Human Neuropathology: Similarities and Differences

Grech Gribee*

Department of Psychological Medicine, National University of Singapore, Queenstown, Singapore

Description

α-Synucleinopathies, including Parkinson's Disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), are characterized by the accumulation of α-synuclein aggregates in the brain. Understanding these disorders requires effective animal and cellular models that replicate human neuropathology. This review compares α -synucleinopathy models with human neuropathology to identify similarities and differences, which can guide the development of more accurate models and improve therapeutic strategies. α -Synucleinopathies represent a group of neurodegenerative diseases distinguished by the abnormal accumulation of α -synuclein protein. Despite advances in research, the complexity of α-synucleinopathy pathogenesis remains challenging. Animal models, including transgenic mice, viral vector-based models, and non-human primates, alongside cellular models derived from Induced Pluripotent Stem Cells (iPSCs), have been developed to study these diseases. However, the extent to which these models accurately reflect human disease is still under investigation. α -Synuclein is a presynaptic protein implicated in neurotransmitter release and synaptic plasticity. In α-synucleinopathies, misfolded α-synuclein aggregates into Lewy Bodies (LBs) and Lewy neurites, which are associated with neuronal dysfunction and neurodegeneration. Understanding the pathological role of α-synuclein involves examining its impact on cellular and molecular pathways, which are often replicated in animal and cellular models [1].

Models of α-synucleinopathy are essential for understanding the pathogenesis of diseases like Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), and Multiple System Atrophy (MSA). These models allow researchers to dissect the molecular mechanisms underlying α-synuclein aggregation and its consequences on neuronal function. They also provide a platform for testing potential therapeutic interventions. While various models have been developed, each has its strengths and limitations, which influence their utility in mimicking human disease. Transgenic Mouse Models are among the most widely used in α-synucleinopathy research. These models involve the genetic modification of mice to express human α -synuclein, often with specific mutations known to be associated with familial forms of Parkinson's disease, such as the A53T or A30P mutations. Transgenic mice typically exhibit motor deficits, α-synuclein aggregation, and some degree of synaptic and neuronal loss, mirroring aspects of human α-synucleinopathies.

These models often have limitations in replicating the full spectrum of human disease, particularly in terms of non-motor symptoms and disease progression. Additionally, the expression levels of α-synuclein in these models may not accurately reflect the pathological conditions observed in humans, which can impact the translation of findings to human therapies. Viral Vector-Based Models offer an alternative approach by using viral vectors to deliver α-synuclein genes directly into specific brain regions. This technique allows for localized expression of α -synuclein, which can be useful for studying regional pathology and understanding how localized α-synuclein aggregation might affect neuronal circuits. While this model provides valuable insights into the effects of α -synuclein in specific brain areas, it often lacks the chronic nature of human disease and the complexity of widespread α -synuclein pathology. Furthermore, the short-term expression and variability in viral delivery can influence the reproducibility of results [2].

Non-Human Primate Models provide a closer approximation to human neuropathology due to their anatomical and physiological similarities to humans. In these models, α -synuclein can be introduced through various methods, including genetic modification or viral vector delivery, to study disease progression and pathology in a more complex and naturalistic context. Non-human primates exhibit motor symptoms and α -synuclein aggregation patterns similar to those observed in human α -synucleinopathies, making them valuable for studying disease mechanisms and potential therapies. However, the high cost, ethical considerations, and the complexity of managing these models pose significant challenges. Cellular Models, particularly those derived from Induced Pluripotent Stem Cells (iPSCs), offer a human genetic background and can be differentiated into various neural cell types. These models are useful for studying disease mechanisms at the cellular level, including α -synuclein aggregation, mitochondrial dysfunction, and synaptic impairment. iPSC-derived models provide insights into cell-specific pathology and facilitate drug screening. Nonetheless, they have limitations in replicating the full brain architecture and systemic interactions present in human α-synucleinopathies, which can affect the broader relevance of findings [3].

Each model of α -synucleinopathy has its unique advantages and limitations. A comprehensive approach that integrates different models may offer the most complete understanding of α -synuclein-related diseases and contribute to the development of effective treatments. Continued refinement and validation of these models are crucial for bridging the gap between preclinical research and clinical application. Transgenic mouse models expressing human α -synuclein with mutations associated with familial Parkinson's disease (e.g., A53T, A30P) or overexpressing wild-type α -synuclein have been widely used. These models exhibit motor deficits, synaptic loss, and α -synuclein aggregation, resembling some features of human α -synucleinopathies. However, they often lack the full spectrum of human disease phenotypes, such as the complex neuroanatomical spread and cognitive impairments seen in DLB [2].

Differences in α -synuclein expression levels and aggregation patterns compared to humans; often do not fully replicate non-motor symptoms or the progression of disease. Viral vector-based models involve the delivery of α -synuclein genes into specific brain regions using viral vectors. This approach can induce localized expression and aggregation of α-synuclein, providing insights into regional pathology and potential therapeutic targets. Non-human primate models, such as macaques, have been used to study α-synucleinopathies due to their close evolutionary relationship to humans. These models can exhibit motor symptoms and α-synuclein aggregation patterns more similar to those observed in humans [4].

Cellular models derived from iPSCs can be differentiated into various neural cell types, including dopaminergic neurons, to study disease mechanisms and

***Address for Correspondence:** Grech Gribee, Department of Psychological Medicine, National University of Singapore, Queenstown, Singapore, E-mail: rheegrech@uchc.edu*

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screen for potential drugs. These models can capture disease-related cellular phenotypes, such as α-synuclein aggregation and neurotoxicity. In humans, α -synucleinopathies are characterized by the presence of LBs and Lewy neurites, with distinct regional patterns of α -synuclein deposition. Mouse models often show α -synuclein aggregates but may lack the characteristic spread and distribution observed in human brains. Viral vector-based models can produce localized pathology but may not fully recapitulate the global distribution seen in human disease. Non-human primates more closely mimic human pathological features but are less practical for extensive research.

Human α -synucleinopathies present with a range of symptoms including motor deficits, cognitive decline, and autonomic dysfunction. Mouse models primarily exhibit motor symptoms and may not fully capture the non-motor symptoms or cognitive impairments. Cellular models can replicate some aspects of cellular dysfunction but do not model complex behavioral and clinical symptoms. The progressive nature of α-synucleinopathies is a critical feature of human disease, involving gradual spread of pathology. Mouse models may exhibit early-stage pathology but often do not progress in a manner that fully reflects the slow and variable progression observed in humans. Non-human primates can exhibit more progressive changes, though this model is limited by its complexity [5].

Comparing α -synucleinopathy models with human neuropathology highlights both the advances and limitations of current research tools. While transgenic, viral vector-based, non-human primate, and cellular models offer valuable insights, none fully replicate the complexity of human α-synucleinopathies. Future research should focus on refining these models, combining different approaches, and integrating advanced techniques to better capture the multifaceted nature of α -synuclein-related diseases. Improved models will be essential for understanding disease mechanisms and developing effective therapies.

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Conflict of Interest

Authors declare no conflict of interest.

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