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Telomere Shortening and Cellular Senescence in Parkinson's Disease: A Converging Axis of Aging and Neurodegeneration

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Abstract:

Parkinson's disease (PD), a progressive neurodegenerative disorder, is increasingly recognized as a disorder of accelerated cellular aging, driven by telomere shortening, cellular senescence, mitochondrial dysfunction, and chronic neuroinflammation. Central to its pathophysiology is the accumulation of α-synuclein aggregates, which trigger astrocyte and microglial senescence, leading to the secretion of pro-inflammatory SASP factors and creating a toxic neural microenvironment. These processes are tightly interwoven with mitochondrial impairment and the generation of reactive oxygen species (ROS), which accelerate telomere attrition and perpetuate neuronal loss through a self-reinforcing feedback loop. Dysregulation of key molecular regulators such as telomerase reverse transcriptase (TERT), GBA mutations, and the SATB1-miR22 axis further exacerbate lysosomal dysfunction, senescence, and α-synuclein accumulation. TERT, though neuroprotective when upregulated, is often downregulated in PD, while GBA mutations impair autophagy and contribute to a senescence-like phenotype in dopaminergic neurons. The SATB1-miR22-GBA network links epigenetic regulation to lysosomal failure and cellular aging. These interconnected mechanisms illuminate a multifactorial model of PD pathogenesis where senescence and telomere instability serve

as central hubs. Therapeutic strategies targeting telomerase activation, clearance of senescent cells via senolytics, and modulation of the GBA/SATB1-miR22 pathway represent promising avenues for mitigating neurodegeneration and improving clinical outcomes in aging-related neurodegenerative diseases such as PD.

Keywords: Parkinson's disease, Telomere shortening, Cellular senescence, α-Synuclein aggregation, GBA gene, TERT

1.Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder predominantly affecting the elderly, with an average onset age of around 60 years. Clinically, PD is marked by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to hallmark motor symptoms such as bradykinesia, rigidity, and tremor, along with various non-motor manifestations. On a molecular level, PD is closely linked with mitochondrial dysfunction, oxidative stress, and impaired protein homeostasis—features that are also associated with aging (Andersen & Chinta, 2016; Chesnokova et al., 2019; Jugal Kishore & Dunuwila, 2025). This overlap highlights aging as a significant risk factor and mechanistic contributor to PD pathogenesis.

Aging drives cellular senescence, a state of irreversible cell cycle arrest triggered by factors like telomere shortening, DNA damage, and oxidative stress (Azam et al., 2021; Kritsilis et al., 2018; Wang et al., 2024). Telomeres, the protective DNA-protein structures at chromosome ends, progressively shorten with each cell division and serve as biomarkers of cellular aging. While telomere shortening typically signifies senescence, studies in PD have shown mixed findings—including unexpectedly longer telomeres in certain tissues—suggesting a nuanced and tissue-specific relationship between telomere dynamics and disease progression (Asghar et al., 2022).

The buildup of senescent cells in the brain is believed to fuel chronic neuroinflammation and exacerbate neuronal damage, thus accelerating neurodegeneration in disorders like PD (Wissler Gerdes et al., 2020; Zhang & Sung, 2022). This review explores the intricate interplay between telomere biology, cellular senescence, and PD, with a focus on understanding mechanistic pathways and identifying therapeutic opportunities. In particular, it discusses how targeting senescence and telomere-related dysfunctions could offer promising strategies for slowing or preventing PD progression (Chesnokova et al., 2019).

2.Telomere Shortening and Aging in PD: Telomere shortening has emerged as a potential biomarker and mechanistic contributor in the aging-related pathogenesis of Parkinson's Disease (PD). While findings across studies vary, there is growing evidence that telomere attrition may be linked to disease progression and clinical outcomes in PD. Several investigations have reported significantly shorter telomeres in PD patients compared to healthy controls, particularly in buccal epithelial cells—a

difference often attributed to heightened oxidative stress in the PD population (Kolyada et al., 2016; Levstek et al., 2021).

Oxidative stress and inflammation—central features of PD pathophysiology—are known to accelerate telomere shortening, thereby promoting cellular senescence and neurodegeneration (Levstek et al., 2021; Maeda et al., 2009). This telomere attrition is further associated with aging, a major risk factor for PD, and may exacerbate neuronal vulnerability through enhanced senescence signaling pathways. However, the link between telomere length (TL) and specific PD phenotypes, such as dementia or cognitive decline, remains inconsistent, often losing statistical significance after controlling for confounding variables (Levstek et al., 2021).

Interestingly, telomere length may also influence the response to dopaminergic therapies. Shorter telomeres have been associated with earlier onset of motor complications following L-dopa treatment, although these correlations tend to weaken when adjusted for age and disease duration. Dopaminergic replacement therapy (DRT) itself appears to modulate telomere biology, with some studies showing increased telomere length and mitochondrial DNA copy number in treated patients—suggesting a possible compensatory response to mitochondrial dysfunction (Ortega-Vázquez et al., 2023).

In summary, while telomere shortening is evident in some PD patients and may reflect underlying oxidative and inflammatory stress, its relationship with disease progression and treatment outcomes remains complex and multifactorial. Further research is needed to clarify these dynamics and to determine whether telomere-targeted interventions may offer therapeutic benefit in PD.

3.Cellular Senescence and Neuroinflammation: Cellular senescence, particularly in glial cells like astrocytes and microglia, is a key driver of chronic neuroinflammation in Parkinson's Disease (PD). Senescent glial cells are characterized by elevated expression of markers such as p16^INK4a^, p21, and senescence-associated β-galactosidase (SA-β-gal), and their accumulation contributes significantly to neurodegenerative pathology. One of the central pathological features of PD—α-synuclein aggregation—has been shown to induce senescence in glial cells. Specifically, α-synuclein preformed fibrils (PFF) decrease Lamin B1 and HMGB1 while increasing p21 in astrocytes and microglia, reflecting a shift to a senescent and reactive phenotype (Verma et al., 2021).

This senescent transformation amplifies neuroinflammatory signaling. Activated, senescent microglia and astrocytes release pro-inflammatory cytokines, creating a toxic microenvironment that promotes neuronal damage (Lee et al., 2010). Furthermore, α-synuclein-induced glial activation contributes to the disruption of the blood-brain barrier, compounding inflammation and disease progression(Harackiewicz & Grembecka, 2024).

Parallel mechanisms are observed in other neurodegenerative diseases such as multiple sclerosis (MS), where senescent cells accumulate in meningeal tissues and drive local inflammation (Manavi et al., 2024). These findings suggest a conserved role for cellular senescence in neurodegeneration. Notably, modulating microglial activation states—from pro-inflammatory (M1-like) to neuroprotective (M2-like)—is emerging as a therapeutic strategy to mitigate senescence-driven inflammation and its downstream effects (Ravenhill et al., 2023).

Targeting senescent glial cells and their inflammatory secretome offers a promising approach to slow or halt the progression of PD and other aging-related neurodegenerative disorders.

4.Mitochondrial Dysfunction, ROS, and Telomere Instability: Mitochondrial dysfunction is a central feature in the pathogenesis of Parkinson's Disease (PD), contributing to excessive production of reactive oxygen species (ROS) and initiating a cascade of cellular damage. Mitochondria are the main source of intracellular ROS, and their impairment leads to elevated oxidative stress, which is detrimental to dopaminergic neurons—the primary neuronal population affected in PD (M. Patel & McElroy, 2017; Rather et al., 2024). This oxidative stress not only exacerbates neuroinflammation but also disrupts neuronal homeostasis, accelerating neurodegeneration (Ravenhill et al., 2023).

One of the critical downstream effects of ROS overproduction is telomere instability. ROS directly damage telomeric DNA, which is particularly susceptible due to its guanine-rich sequence, leading to accelerated telomere shortening (Rather et al., 2024). This contributes to cellular senescence and functional decline, further compounding the aging phenotype observed in PD. Telomere attrition under oxidative stress conditions forms a feedback loop with mitochondrial dysfunction—ROS damage leads to telomere instability, which promotes further mitochondrial stress and ROS generation—perpetuating disease progression(Ravenhill et al., 2023).

Moreover, emerging evidence from cancer biology suggests that intercellular transfer of damaged mitochondria can amplify ROS signaling in recipient cells, enhancing proliferative and inflammatory responses. Although this has been extensively studied in cancer models, similar mechanisms may be relevant in neurodegenerative diseases like PD, where glial-neuronal interactions could propagate oxidative damage.

Together, the interplay between mitochondrial dysfunction, oxidative stress, and telomere attrition highlights a vicious cycle that drives PD pathology. Therapeutic strategies aimed at restoring mitochondrial function and reducing ROS could mitigate telomere instability and slow disease progression.

5.Regulatory Molecules TERT, GBA, SATB1-miR22 Axis: The regulatory interplay among TERT, GBA, and the SATB1-miR22 axis illustrates a multifaceted network of molecular mechanisms contributing

to the onset and progression of Parkinson's Disease (PD). These molecules influence critical cellular processes such as telomere maintenance, lysosomal function, and gene expression regulation, and their dysregulation is increasingly recognized as a hallmark of PD pathogenesis.

TERT (telomerase reverse transcriptase), the catalytic component of telomerase, is essential for maintaining telomere integrity and cellular longevity. In the central nervous system (CNS), TERT displays neuroprotective properties, but paradoxically, its dysregulation—particularly through promoter mutations—has been linked to oncogenesis in CNS malignancies (B. Patel et al., 2020). This duality reflects TERT's context-dependent role in either promoting cellular resilience or contributing to uncontrolled proliferation and degeneration, highlighting its complex involvement in neurodegenerative diseases.

In contrast, mutations in the **GBA** gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase), are among the most significant genetic risk factors for PD. GBA mutations result in decreased GCase activity, leading to lysosomal dysfunction, accumulation of glucosylceramide and α-synuclein, and impaired autophagy and calcium homeostasis in dopaminergic neurons (Schöndorf et al., 2014). These cellular impairments establish a pathogenic cascade that accelerates neurodegeneration.

The **SATB1-miR22-GBA axis** adds another layer of regulatory complexity. SATB1 (Special AT-rich sequence-binding protein 1) normally suppresses miR-22-3p expression; however, in PD, SATB1 is often downregulated, resulting in the derepression of miR-22-3p. This microRNA subsequently suppresses GBA expression, further reducing GCase levels and promoting glucosylceramide accumulation. This biochemical imbalance induces a senescence-like phenotype in dopaminergic neurons, contributing to neuroinflammation and reactive gliosis—key features of PD and aging(Russo et al., 2024).

Moreover, the synergistic toxicity of reduced GCase activity and α-synuclein accumulation intensifies neurodegeneration. Experimental models demonstrate that co-expression of GBA mutations and α-synuclein overexpression results in pronounced nigrostriatal degeneration, reinforcing the central role of lysosomal dysfunction in PD pathogenesis (Polissidis et al., 2021).

In summary, the interconnection between TERT, GBA, and the SATB1-miR22 regulatory axis delineates a sophisticated molecular framework that modulates cellular aging, neuroinflammation, and lysosomal integrity. These pathways represent promising targets for therapeutic intervention, aiming to preserve neuronal function and mitigate disease progression in Parkinson's Disease and related neurodegenerative disorders.

6.Therapeutic Perspectives : Emerging therapeutic strategies targeting telomere dynamics, cellular senescence, and gene regulation offer promising avenues for the treatment and prevention of

neurodegenerative and age-related diseases. Among these, telomerase-based therapies, senolytic agents, and gene-modulating interventions aimed at the GBA/SATB1-miR22 axis stand out as innovative approaches with the potential to reshape clinical outcomes in conditions such as Parkinson's disease (PD).

Telomerase modulation represents a compelling strategy to combat cellular aging and its associated pathologies. Telomerase, particularly its catalytic subunit TERT, is critical for maintaining telomere length and genomic stability. Modulating telomerase activity could alter the genetic control of lifespan and address the pathological consequences of cellular senescence. By restoring telomere length and enhancing cellular repair mechanisms, telomerase therapy holds promise in delaying neurodegeneration and potentially mitigating the onset of age-associated disorders.

In parallel, **senolytic therapies**—agents designed to selectively eliminate senescent cells—have garnered attention for their capacity to attenuate the deleterious effects of the senescence-associated secretory phenotype (SASP). This phenotype, characterized by pro-inflammatory cytokine release and extracellular matrix degradation, plays a significant role in promoting chronic inflammation and tissue dysfunction in neurodegenerative diseases. Preclinical studies have demonstrated that short-term senolytic interventions can reduce neuroinflammation, improve cognitive performance, and reverse features of premature aging, particularly in radiation-induced models of frailty (Kumthekar et al., 2021). Furthermore, combining senolytics with **epigenetic modulators** offers a synergistic approach to reprogram senescent cells by targeting their unique epigenetic signatures, potentially leading to cell rejuvenation and extended healthspan.

Another promising target is the **GBA/SATB1-miR22 axis**, which influences lysosomal function and cellular homeostasis. Although clinical applications remain in early stages, gene-based modulation of this axis could restore glucocerebrosidase (GCase) activity, reduce α-synuclein accumulation, and attenuate the senescence-like phenotype in dopaminergic neurons. By re-establishing balance in these molecular pathways, such interventions may alleviate neuroinflammation and delay PD progression.

Together, these therapeutic strategies—**telomerase activation, senolytic and epigenetic therapies, and targeted gene modulation**—represent a multidimensional approach to mitigating the effects of aging and neurodegeneration. While still requiring validation through extensive clinical research, they hold transformative potential for improving the quality of life and extending functional longevity in aging populations.

7.Conclusion

Neurodegenerative diseases such as Parkinson's disease are driven by complex and interrelated mechanisms involving cellular senescence, mitochondrial dysfunction, telomere instability, and

dysregulated gene networks. The accumulation of senescent glial cells, exacerbated by α-synuclein aggregation and neuroinflammation, contributes to a self-perpetuating cycle of neural damage and cognitive decline. Mitochondrial dysfunction and reactive oxygen species further destabilize neuronal integrity through oxidative damage and telomere attrition. Additionally, emerging regulatory networks—such as the interplay between TERT, GBA mutations, and the SATB1-miR22 axis—highlight the importance of genetic and epigenetic modulators in disease progression.

Therapeutic innovations that target these core pathological processes offer new hope. Telomerase-based therapies, senolytic agents, and gene-modulating approaches not only address the root causes of cellular aging and neuroinflammation but also provide avenues to slow or reverse neurodegenerative progression. As research continues to unravel the intricate molecular underpinnings of aging and neurodegeneration, integrated strategies that combine these interventions may hold the greatest potential for improving both lifespan and healthspan in affected individuals.

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