Research Progress on the Molecular Mechanism and Regulatory Strategies of Abnormal Aggregation of α-Synuclein in Parkinson's Disease

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Abstract Parkinson's disease (PD) represents a multifaceted neurodegenerative condition, whose core pathological features include the gradual degeneration of dopaminergic neurons in the substantia nigra region, as well as the extensive deposition of aggregated alpha-synuclein (α-syn) within Lewy bodies distributed across the central nervous system[1]. Under normal physiological circumstances, α-syn belongs to the category of intrinsically disordered proteins, and it exerts indispensable regulatory functions in the processes of synaptic vesicle transport and neurotransmitter secretion[2]. Whereas in the pathological state related to PD, α-syn will experience conformational misfolding, oligomeric assembly, and eventually form insoluble amyloid fibrils that constitute the primary structural components of Lewy bodies[2]. This aggregation cascade not only serves as a core biomarker of PD pathological progression, but also has a close correlation with mitochondrial functional impairment, oxidative stress response and neuroinflammatory reaction, and these pathological events jointly drive the occurrence of neuronal injury and apoptosis[3][4][5].

Keywords Parkinson's disease; α-Synuclein protein; Aberrant aggregation; Molecular regulatory mechanism; Intervention strategies

1. Introduction

The aberrant misfolding and subsequent aggregation of α-syn are widely acknowledged as core pathogenic factors driving the initiation and advancement of Parkinson’s disease (PD)[1][6]. This aggregation process generally conforms to a nucleation-dependent polymerization paradigm: it commences with solu-

ble monomeric forms, transitions through cytotoxic oligomeric intermediate states, and ultimately terminates in the generation of insoluble amyloid fibril structures[7]. Accumulating evidence indicates that soluble oligomeric species, instead of the fully assembled fibrils, serve as the main neurotoxic agents in disease pathogenesis[3][7]. These oligomeric assemblies are capable of impairing cell membrane integrity, disturbing normal mitochondrial functionality, and hindering intracellular transport processes, which ultimately triggers cellular dysfunction and degeneration[17]. The intercellular transmission of α-syn-related pathological alterations, commonly characterized as a “prion-like” mechanistic process, is broadly accepted as a prominent hallmark of PD progression[1][8][9]. Pathological α-syn aggregates can be secreted from an affected neuron into the extracellular milieu, and then internalized by adjacent neurons through pathways including extracellular vesicles (for instance, exosomes) or tunneling nanotube structures, thereby triggering the misfolding and aggregation of endogenously expressed normal α-syn[1][10]. This propagation mechanism offers a plausible explanation for the gradual spread of PD pathology from initially affected brain regions, such as the olfactory bulb and brainstem, to other functional domains of the nervous system[1][10].

2. Molecular Mechanisms of Abnormal α-Synuclein Aggregation in Parkinson's Disease

2.1 The Relationship between α-Synuclein Aggregation and Mitochondrial Dysfunction

Aberrant α-syn aggregation and mitochondrial impairment are closely interrelated, forming a vicious positive feedback cycle. Misfolded α-syn aggregates can target and accumulate within mitochondria, disrupting their normal physiological function through suppressing the activity of electron transport chain complex I, which subsequently causes a decline in ATP synthesis and elevated production of reactive oxygen species (ROS)[1][11][12][13]. Such mitochondrial functional defects conversely further promote the misfolding and aggregation process of α-syn[1][11][12]. Emerging studies have emphasized the pivotal function of mitochondrial dynamin-related protein 1 (Drp1) in the pathological progression of Parkinson’s disease, as aberrant Drp1 activity is associated with α-syn-induced mitochondrial fission and neuronal death[14].

2.2 The Relationship between α-Synuclein Aggregation and Oxidative Stress

Oxidative stress serves as another pivotal element in the pathophysiological process of Parkinson’s disease, exhibiting a close correlation with α-synuclein aggregation and mitochondrial dysfunction[3][5]. Reactive oxygen species produced by dysfunctional mitochondria further facilitate the covalent cross-linking as well as aggregation of α-synuclein[3]. On the contrary, aggregated α-synuclein itself can trigger oxidative stress and aggravate cellular injury via suppressing antioxidant defense systems, exemplified by the

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Nrf2-Keap1 signaling pathway[3][4]. Existing research has demonstrated that nuclease-dead Staphylococcus aureus Cas9 (dCas9) is capable of reducing α-synuclein expression, and alleviating mitochondrial DNA impairment as well as oxidative stress levels in stem cell models of Parkinson's disease derived from patients[15][16].

2.3 The Relationship between α-Synuclein Aggregation and Neuroinflammation

Neuroinflammation constitutes another core dimension of Parkinson's disease progression, which is regulated by the activation of microglia and astrocytes[17][18]. Aggregated α-syn is capable of activating microglia, inducing metabolic reprogramming in these cells, initiating the activation of the NLRP3 inflammasome, and prompting the secretion of pro-inflammatory cytokines including IL-1β, thus exacerbating the neuroinflammatory response[19][20][21][22]. Reactive astrocytes, especially those with NOX4 expression, further participate in the neuroinflammatory process in the hippocampus of PD patients via mediating the generation of pro-inflammatory cytokines and osteopontin[23][24]. Such a persistent neuroinflammatory microenvironment, conversely, facilitates α-syn aggregation and neuronal loss[1].

3. Regulatory Strategies Targeting Abnormal Aggregation of α-Synuclein

3.1 Small Molecule Inhibitors

Small molecule inhibitors are designed to disrupt the α-syn aggregation cascade via diverse modes of action, including stabilizing its non-pathogenic conformations, blocking aggregation-prone interaction interfaces, or facilitating the disassembly of preformed aggregates[7]. As an example, pyrroloquinoline quinone (PQQ) has been shown to modulate intracellular α-syn aggregate formation[27]. Bis-chalcone polyphenols have likewise exhibited disaggregation efficacy against both α-syn oligomers and mature fibrils[28]. Additionally, nanomaterials such as n-MTAB gold nanoparticles have been explored for their potential to suppress α-syn aggregation[29]. Contemporary investigations prioritize the development of small molecules functioning as pharmacological chaperones, which bind to the natively folded, physiological state of α-syn to decrease its propensity to transition into misfolded conformations[7].

3.2 Gene Editing and Gene Regulation Technologies

Gene editing and gene regulation technologies aim to directly modulate the expression levels of the SNCA gene, thereby reducing α-syn production[30]. CRISPRi technology, specifically using nuclease-dead Cas9 (dCas9), has been employed to downregulate α-syn gene expression, demonstrating reduced α-

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syn levels, decreased mtDNA damage, and oxidative stress in PD patient-derived stem cell models[15][16]. Additionally, the role of non-coding RNAs (ncRNAs) in regulating the SNCA gene and α-syn aggregation is gaining attention, offering new targets for genetic modulation[30].

3.3 Targeted Protein Degradation Techniques

Targeted protein degradation techniques, such as proteolysis-targeting chimeras (PROTACs), represent an emerging paradigm in drug discovery, designed to mediate the degradation of specific proteins via the ubiquitin-proteasome system[31]. While the application of PROTACs in PD is still in its early stages, their theoretical potential lies in selectively degrading pathological α-syn while preserving physiological α-syn[31]. Beyond PROTACs, liquid-liquid phase separation (LLPS) has also been implicated in regulating α-syn aggregation and mitophagy, providing new avenues for aggregate clearance[32].

4. Key Breakthroughs and Controversies in Basic Research

4.1 Key Breakthroughs

Structural polymorphism of α-syn: Recent progress in cryo-electron microscopy techniques has made it possible to resolve the structural polymorphs of different α-syn strains, uncovering structural variations across distinct Parkinson's disease subtypes. This provides valuable insights for the development of more targeted diagnostic and therapeutic approaches[7].

Dynamics of early folding intermediates: Single-molecule Förster resonance energy transfer (FRET) approaches have clarified the kinetic behaviors of α-syn’s early folding intermediate states, offering precise molecular insights into the triggering mechanisms of aggregation[7].

Role of astrocytes in propagation: Researches integrating humanized mouse models with microfluidic chip platforms have verified the pivotal function of astrocytes in the selective internalization and transmission of α-syn, laying a foundation for targeting glial cells to block pathological dissemination[17][33].

4.2 Existing Controversies

Dominant toxic species of pathological α-syn: No unified conclusion has been reached regarding which form of α-syn (oligomers, protofibrils, or mature Lewy bodies) exerts the strongest neurotoxic effect in PD. Although existing research findings mostly support soluble oligomers as the primary toxic entities[17], further exploration of the toxicity mechanisms underlying different aggregated species remains urgently

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required.

Potential collateral damage to physiological α-syn function: A prominent hurdle for therapeutic strategies targeting α-syn lies in how to eliminate pathological aggregates while exerting no impact on the regular biological roles of endogenous α-syn, which exerts critical functions in synaptic plasticity and neurotransmitter release[10][26].

Peripheral origin hypothesis and the gut-brain axis: The "gut-first hypothesis", which puts forward that PD pathological changes might arise in the intestinal tract and transmit through the gut-brain axis, is attracting increasing focus[20]. Nevertheless, the spatiotemporal reliability of α-syn transmission in the intestinal tract and its direct association with cerebral pathological changes still need more evidence from single-cell tracking studies[20].

Clinical translation bottlenecks: While numerous small-molecule inhibitors have exhibited promising effects in cell-based assays and animal experimental models, the vast majority of such agents cannot achieve satisfactory therapeutic outcomes in clinical studies, which is primarily attributed to problems including inadequate drug concentration in human cerebrospinal fluid and unintended off-target pharmacological activities[7][26].

5. Conclusion

Taken together, the aberrant accumulation of α-syn in Parkinson’s disease constitutes a multi-stage process encompassing sophisticated molecular and cellular cascades, which is closely correlated with mitochondrial impairment, oxidative damage, and neuroinflammatory responses. Subsequent investigations will persist in centering on illuminating the exact molecular pathways underlying α-syn aggregation, formulating more selective and targeted intervention approaches, and resolving obstacles related to drug delivery and clinical transformation, in order to provide genuinely effective disease-modifying treatments for individuals suffering from PD.

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