THE FUTURE OF PARKINSON DISEASE THERAPY: EMERGING DISEASE-MODIFYING STRATEGIES

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ABSTRACT

Parkinson's disease is a progressive neurological disorder characterized by the loss of dopaminergic neurons and the accumulation of α-synuclein in the brain. These accumulations lead to both motor symptoms such as tremors, stiffness and non-motor symptoms that affect the quality of life. The current treatments mainly focus on replacing dopamine and managing symptoms,but they do not stop the disease progression. Recent research has shifted towards the emerging therapies that target the main causes of Parkinson disease. Includes α-synuclein accumulation, LRRK2 activity, and glucocerebrosidase (GCase) dysfunction. Among these, GCase-based approaches such as pharmacological chaperones, enzyme activators, and gene therapy are shown the best results in improving cellular function. Also, emerging treatments like immunotherapy and cell based treatments are used to protect and restore damaged neurons. The ongoing advances in biomarkers and targeted therapies are important for more effective treatments, which is slow or modify disease progression in the future.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized primarily by the selective loss of dopaminergic neurons in the substantia nigra pars compacta**,** resulting in reduction of dopamine levels in striatal pathways and the classical motor symptoms such as tremors, rigidity, bradykinesia and postural instability. In addition to motor symptoms, PD patients often experience a huge range of non-motor symptoms such as cognitive impairment, depression, sleep disturbances, and autonomic dysfunction which affects the quality of life.[1] The exact etiology of parkinson disease is not clear but it is believed to be a combination of genetic and environmental factors. The parkinson disease is caused either by inherited factors or non-inherited factors. Inherited factors include mutation of genes such as SNCA (produce alpha synuclein), LRRK2 (controls cell function), PARKIN (helps to clear the damaged proteins) leads to abnormal protein buildup and brain damage. In other hand, the non-inherited factor includes sporadic type which means the disease occurs randomly without inheritance. It includes pesticide exposure and aging related cellular dysfunction.[2]

fig 1: motar and non motor symptomps of parkinson's disease

This neurodegenerative process also involves protein misfolding, formation of Lewy bodies containing α-synuclein, mitochondrial dysfunction, oxidative stress and neuroinflammation. Current pharmacological treatments for PD—including levodopa and dopamine agonists—provide only symptomatic relief and do not halt or reverse the underlying dopaminergic neurodegeneration.

PATHOPHYISOLOGY

The pathophysiology of PD includes multiple interacting molecular pathways such as alpha-synuclein pathway, LRRK2 pathway and GBA1 pathway.

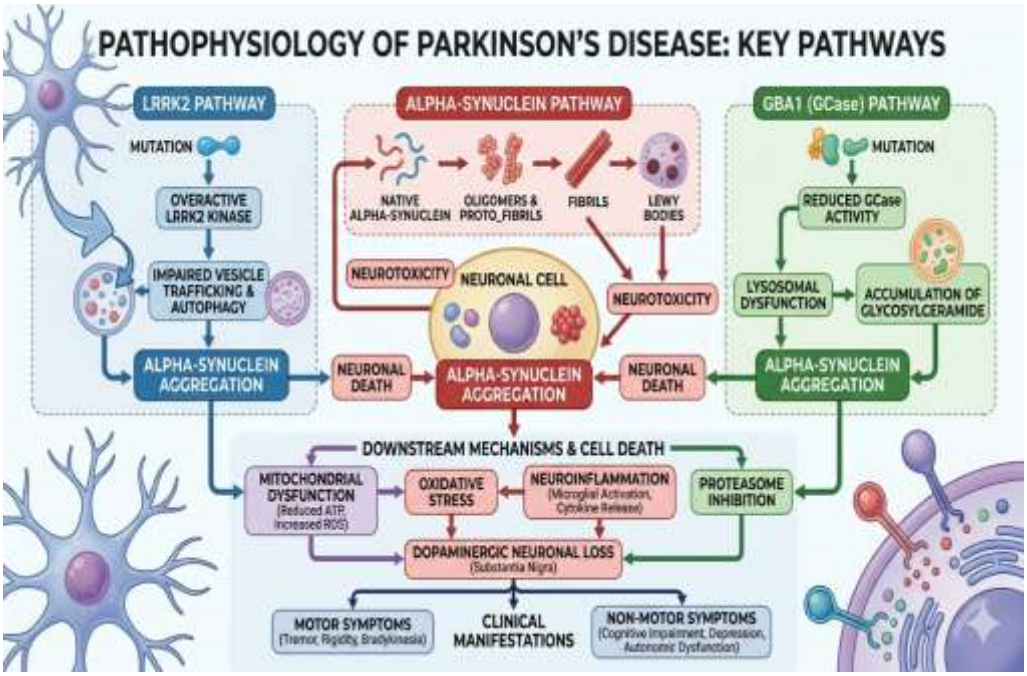

fig 2: pathophysiology of parkinson's disease

Alpha-synuclein pathway

Alpha-synuclein is a small protein which is present in presynaptic nerve terminals. It regulates the storage and release of dopamine. In Parkinson disease alpha-synuclein undergoes misfolding which may be triggered by genetic mutation, oxidative stress and environmental toxins. The normal form of alpha synuclein (monomers) which converted into small toxic clusters called oligomers and further converted into profibrils, fibrils lead to accumulation as Lewy bodies inside neurons causes neurotoxicity, mitochondrial damage and triggers neuroinflammation. These combined effects cause progressive degeneration of dopaminergic neurons. Propagation of misfolded alpha-synuclein occurs between the neurons.[3,5,14]

LRRK2 pathway

The main function of LRRK2 (Leucine-rich repeat kinase 2) gene is regulation of cell signaling which ensures proper communication between cellular components, vesicle trafficking, autophagy which regulates the removal of damaged proteins. Mutation of LRKK2 gene leads to increase the kinase activity, abnormal phosphorylation of target proteins, decreasing autophagy leads to toxic protein build up and formation of Lewy bodies.[3,5,8]

GBA1 pathway

GBA1 gene is present in lysosome which produces the gene called glucocerebrosidase (GCase). The role of GCase enzyme is to breakdown of lipid called glucocerebroside into glucose and ceramide which helps in removal of waste, maintain cell balance and prevent toxic accumulation. Mutation of GBA1 leads to misfolding of GCase enzyme, as a result lipid accumulation increases, waste clearance becomes insufficient and alpha-synuclein accumulation. These environment leads to neuroinflammation and dopaminergic neuron death. In the above three pathways accumulation of alpha-synuclein leads to mitochondrial dysfunction, oxidative stress, impaired autophagy, neuroinflammation, neuronal death. These reactions decrease the dopamine level which is a hallmark of Parkinson disease.[3,4]

CURRESNT TREATMENT

Dopamine Replacement

Levodopa

Carbidopa

Benserazide

Dopamine Agonists

Pramipexole

Ropinirole

Rotigotine

Apomorphine

MAO-B Inhibitors

Selegiline,

Rasagiline,

Safinamide

COMT Inhibitors

Entacapone,

Tolcapone,

Opicapone

Anticholinergics

Trihexyphenidyl

Benztropine

Biperiden

NMDA Receptor Antagonist

Amantadine

LIMITATIONS OF CURRENT TREATMENT

The conventional treatment of Parkinson's disease includes drugs such as levodopa, dopamine agonists, MAO-B inhibitors and COMT inhibitors to control symptoms. The levodopa is called the "gold standard" therapy. Long-term treatment has major limitations such as many patients experienced the wearing-off effect due to disease progression and involuntary movements called dyskinesia, which reduces the effectiveness of treatment and quality of life. The studies reported that nearly 50% of patients treated with levodopa for more than 5 years experience these complications. Also, conventional therapies mainly provide symptomatic relief and do not stop or slow down the neurodegeneration underlying Parkinson's disease. The other limitations

include short half-life of the drug, unpredictable response, psychiatric side effects such as hallucinations, sleep disturbances, and the need for increasing doses over time.[6,7]

EMERGING TECHNIQUES

LEUCINE-RICH REPEAT KINASE-2 (LRRK2)

Leucine-rich repeat kinase-2 (LRRK2) has emerging as an important key disease modifying therapeutic target in Parkinson's disease because currently available treatments only provide symptomatic relief without preventing the disease progression .mutation in LRRK2 gene leads to two different variant either it may be associated with alpha- syn aggregates or not associated with alpha-syn aggregates. If it is associated with alpha-syn aggregates , worsens the cognitive impartment and occur neuronal degeneration in substania nigra. If it did not associate with alpha-syn less severe motor manifestation and decline over years.[8] Experimental preclinical studies demonstrating neuroprotection and reduction of protein aggregation supports to evaluate in human trials. Clinical development of the LRRK2 inhibitor BIIB122 (DNL151) began with Phase 1 dosing initiated in 2017 and a Phase 1b study in Parkinson's disease patients in 2019 which confirmed acceptable safety brain target engagement and biomarker reduction.[9] These results enabled advancement to later-stage clinical trials initiated around 2022 with ongoing Phase 2 evaluations designed to determine whether sustained LRRK2 inhibition can slow disease progression. In addition, biomarker and clinical-phenotype investigations reported in 2025 identified LRRK2-associated Parkinson's disease as a partially distinct subtype and emphasized the importance of genetic, molecular and imaging biomarkers for precision-guided therapy. Overall, LRRK2 inhibition represents a promising emerging strategy aimed at achieving true disease modification in Parkinson's disease.[11]

GLUCOCEREBROSIDASE (GCase)

Glucocerebrosidase (GCase) is an important enzyme found inside lysosome, responsible for the breaking down of lipid called glucosylceramide into glucose and ceramide. This enzyme is encoded by GBA1 gene. In Parkinson's disease, the activity of GCase is reduced. This can happen due to mutation in the GBA1 gene naturally decline with aging or interference from a protein called alpha synuclein. When GCase activity decrease glucoceramide and its related lipid starts accumulating inside lysosome and thus it is disturbing normal functions. This imbalance promotes the misfolding and aggregation of alpha-synuclein, which is a key feature of Parkinson's disease. In turn, the accumulated alpha-synuclein further disrupts the proper transport and function of GCase, creating a harmful cycle. Because of this strong connection, GCase has become an important target for developing disease-modifying treatments—not only for patients with *GBA1*-related Parkinson's disease but also for those with typical (idiopathic) Parkinson's disease where lysosomal dysfunction plays a role. Glucocerebrosidase targeted therapies in parkinson's disease aim to restore lysosomal function and reduce α-synuclein pathology. The main approaches include enzyme replacement therapy, substrate reduction therapy, pharmacological chaperones , allosteric GCase activators , gene theraphy targeting GBA1.[13]

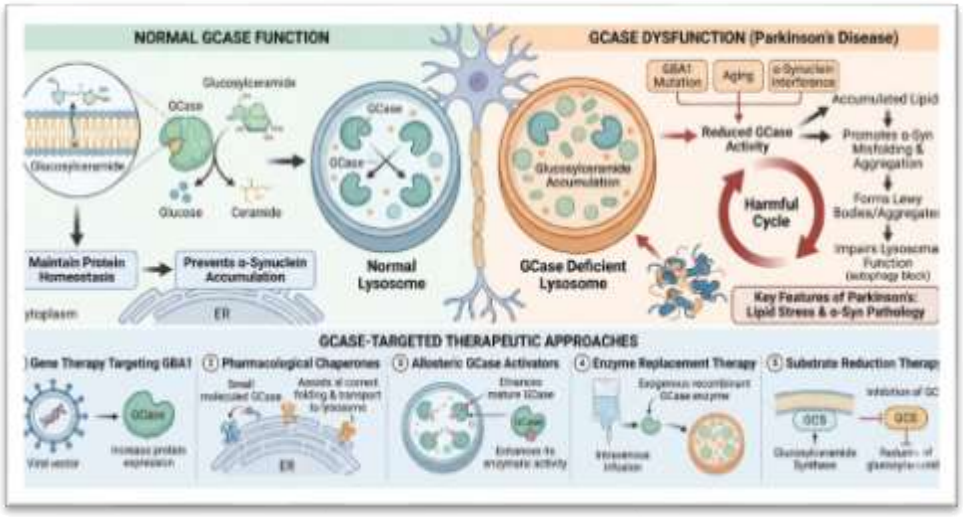

fig 3 : glucocerebrosidase pathway and it's targets

Among the GCase-targeted strategies **pharmacological chapreones, allosteric GCase activators** and **GBA1 gene therapy** have been the most actively investigated in parkinson's disease.

Pharmacological chaperones

Pharmacological chaperones are one of the most widely studied approaches for targeting GCase in parkinson's disease. These are small molecules that help the GCase enzyme fold properly and move efficiently from the endoplasmic reticulum to the lysosome and function more effectively. Among these ambroxol has received the most attention. A multicenter phase II clinical trial protocol was published in 2023 which highlight the ambroxol as disease-modifying therapy especially in patients with GBA1 associated parkinson's disease. Further clinical studies have strengthened these findings. A randomized trial reported in 2025 that the ambroxol was safe and well tolerated and successfully engaged its target in body. Even it did not show any clear improvement in cognitive symptoms in patients with PD dementia. Still several ongoing clinical trials are exploring whether ambroxol can boost GCase activity in brain and pheripheral tissue.[12]

Allosteric GCase activators

Allosteric GCase activators are also one of the new treatment approaches that directly improve the activity of the GCase enzyme without binding to its active site. These drugs bind to other regions and make the enzyme work more efficiently. This helps to reduce harmful lipid buildup and indirectly decrease alpha synuclein accumulation. For example, one of the drugs was studied in this group that is LTI-291. Early phase 1 studied in healthy volunteers showed that is safe and well tolerated with no serious side effects. These early studies mainly focused on safety and biological effects not symptom improvement. Still the ability of LTI-291 to enhance enzyme activity in the brain supports its potential as a disease –modifying therapy. Larger phase II trials are now ongoing to evaluate whether long term treatment with LTI-291 can slow disease progression and improve clinical outcomes.[14]

Gene therapy targeting GBA1

Gene therapy targeting GBA1 is a promising approach that tries to fix the root cause by delivering a healthy copy of the gene into brain cells. This allows neurons to continuously produce normal GCase enzymes and improve cell function. One of the main therapies being studied is LY3884961 which uses a viral vector (AVV) to deliver the gene. In preclinical studies showed that the increased GCase activity, reduce lipid buildup and less alpha-synuclein accumulation suggesting improvement in disease-related changes. In early clinical studies have shown that this therapy is safe and delivery so clear improvement in symptoms but not confirmed yet. Even in these limitations ongoing studies are trying to see if this therapy can slow or stop the disease progression.[15]

CELL REGENERATION THERAPY

Mesenchymal stromal cells are a type of multipotent stem cells found in tissues like bone marrow and fat. They have gained attention as a treatment option for parkinson disease because of their ability to protect brain cells and regulate the immune system. MSCs mainly work by releasing helpful substance called neurotrophic factor. This substance supports the survival of dopamine producing neuron, reduce oxidative stress and control inflammation in the brain. This environment helps to slow down the disease progression. Future research is focussing on improving how long MSCs survive in the body using them along with other treatments and targetting non motor symptoms of parkinson disease. Preclinical study was conducted since 2001 demonstrated the effectiveness of bone marrow derived MSCs animal model of PD. This study shows improvement in movement and overall neurological function. Clinical trial also reported encouraging results for example 2012 study found that 3 out of 7 patient showed improved mobility after receiving bone marrow MSC injection. In another study at 2011 8 patient treated with umbilical cord derived MSCs experienced symptom relied without any major side effects. These flexible approaches, along with observed increases in dopamine levels and protection of dopaminergic neurons, contribute to better patient outcomes and quality of life. Overall, MSC therapy offers strong potential as a future treatment for parkinson's disease.[17,18]

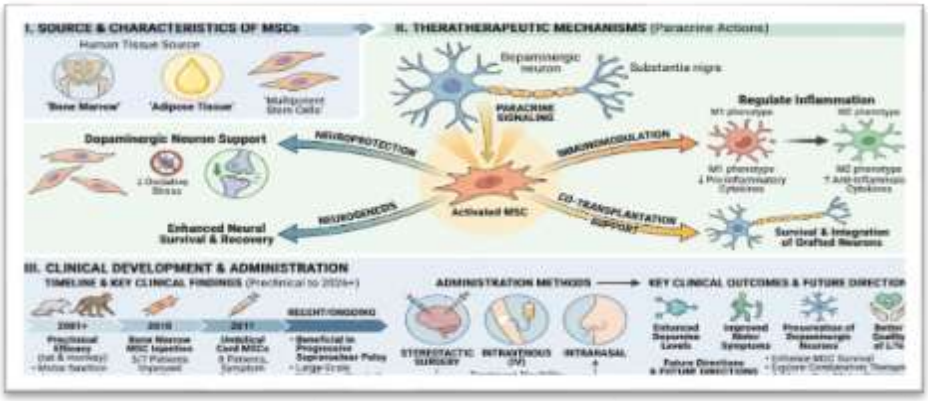

Fig 4 : Mechanism of cell regeneration therapy

ALPHA-SYNUCLEIN TARGETING THERAPY

Alpha-synuclein is a small presynaptic protein encoded by the SNCA gene that plays an important role in synaptic vesicle trafficking and neurotransmitter release in normal physiological condition.In parkinson condition it becomes misfolded and distrupts the normal function.so it is a key targeting method for parkinson's disease in disease modifynig therapy. In preclinical studies novel peptides,small molecules and lipid metabolism inhibitors have been studied for the ability to reduce aplha-synuclein aggregation,prevent mitochandrial dysfunction so that increase in neuronal survive. In clinical study immunotherapy strategy is developed with monoclonal antibodies such as prasinezumab and MEDI1342 designed to neutalize the extracellular alpha-syn and inhibits the cell-to-cell transmission. The outcome of this study is favarouble to safety profile.In other hand active immunization strategies also developed vaccines like UB-321 and AFFITOPE derivatives aim to induce endogeneous antibody production and it shown promising early phase results in reducing the PD burden. In parallel integration of biomarker-guided approaches such as alpha-synuclein seed amplification assays have improved diagnostic precision and patient stratification in clinical trials. Despite these advances challenges remain because of the structural heterogenicity of alpha-synuclein species,low blood brain barrier penetration, and the chances that therapeutic intervention occurs at early stage of disease for maximal efficacy. Overall current evidence suggests that alpha synuclein targeted therapies do not achieve better clinical success. When combined with multi-target or early-intervention strategies, it produces advancing and promising action towards disease modification.[19]

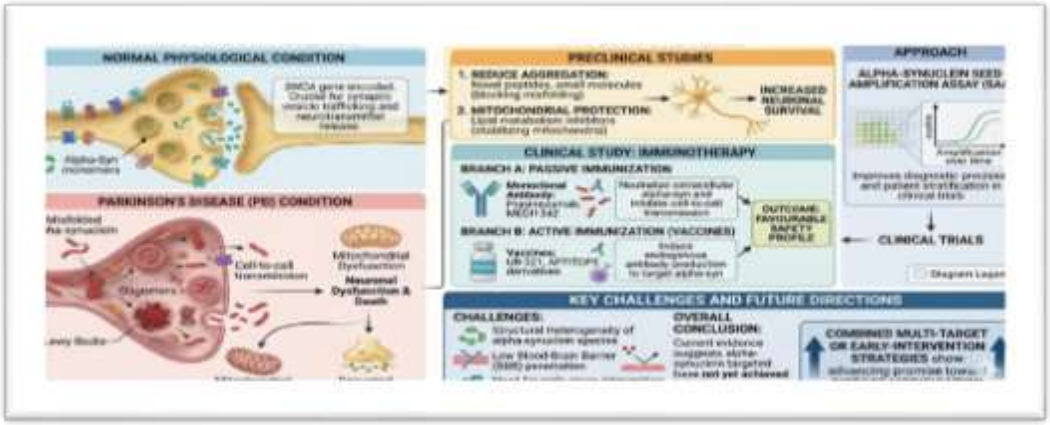

fig 5 : role of alpha synuclein and its clinical development

FUTURE PROSPECTIVE

The future of Parkinson disease (PD) therapy moves towards the true disease modification than symptomatic relief. In disease modification therapy, they highly focused on molecular mechanisms which includes alpha-synuclein aggregation, lysosomal dysfunction and genetic factors such as GBA1 and LRRK2. Precision medicine is one of the most important future direction which helps to produce promising results. The another important direction is to optimization of GCase-targeted therapies. In this therapy, pharmacological chaperones such as ambroxol produces safety and target engagement so the future research must focus on improving brain penetration, long term efficacy and clinical outcomes. Allosteric activators and gene therapies also requires large scale clinical validation to confirm their potential in disease modification. The combination therapy approaches plays a crucial role in future because instead of focusing single target, the multi targeting therapies gives better results in controlling disease progression. The multi targeting therapies includes combination of alpha synuclein aggregation inhibitors, lysosomal enhancers such as GCase activators, neuroprotective agents, dopamine replacement therapies. Additionally the cell replacement therapy have higher potential for neuroregeneration and neuroprotection. The another emerging technique is introducing artificial intelligence (AI) and digital health technologies in the management of PD. The AI can help with early disease detection, predicting disease progression, identifying novel drug targets and optimizing clinical trial design. The future advancements in coming years will be identification and validation of biomarkers such as alpha-synuclein seeding assays, neurofilament light chain and lysosomal enzyme activity.

CONCLUSION

Parkinson disease (PD) is a complex neurodegenerative disorder and current treatment only offers symptomatic relief. Emerging therapies targeting key pathways such as α-synuclein, LRRK2 and GBA1, mostly GCase-based approaches, show promise for disease modification. Immunotherapy, gene therapy and cell based therapies are all showing progress and indicative of the changing treatment landscape. However, there are still challenges such as limited clinical efficacy, blood–brain barrier issues and lack of early biomarkers, the future management will rely on personalized, multi-target strategies to slow or stop disease progression and improve patient outcomes.

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