INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Single-Cell Multi-Omics and Cell-Type-Specific Molecular Mechanisms in Parkinson's Disease: From Human Substantia Nigra Atlas to Precision Therapeutics

Anchal*, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh, Gaurav Hastir

St.Soldier Institute of Pharmacy, Lidhran Campus behind NIT(R.E.C), Jalandhar-Amritsar Byepass , Jalandhar 14001,Punjab,India.

ARTICLE INFO

Published: 27 July 2026
Keywords:
Parkinson's disease; Single-cell RNA sequencing; Single-nucleus RNA sequencing; Multi-omics; Human substantia nigra; Dopaminergic neurons; Cell-type-specific mechanisms; Spatial transcriptomics; Biomarkers; Precision medicine; Artificial intelligence; Neurodegeneration
DOI:
10.5281/zenodo.21623249

ABSTRACT

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide and is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, resulting in both motor and non-motor impairments. Although conventional molecular studies have provided important insights into PD pathogenesis, they have been unable to resolve the extensive cellular heterogeneity of the human brain. Recent advances in single-cell and single-nucleus sequencing technologies, together with multi-omics integration, have revolutionized Parkinson's disease research by enabling high-resolution characterization of individual neuronal and glial cell populations. These approaches have uncovered distinct cell-type-specific molecular signatures, regulatory pathways, and intercellular communication networks involved in mitochondrial dysfunction, oxidative stress, α-synuclein aggregation, impaired autophagy, neuroinflammation, synaptic dysfunction, and neurovascular abnormalities. In addition, integration of transcriptomic, epigenomic, proteomic, metabolomic, and spatial omics datasets has accelerated the discovery of novel biomarkers and therapeutic targets while providing a more comprehensive understanding of disease heterogeneity. Emerging technologies, including artificial intelligence and machine learning, further enhance multi-omics data integration, facilitate biomarker identification, improve patient stratification, and support the development of precision therapeutic strategies. Furthermore, innovative approaches such as gene therapy, RNA therapeutics, stem cell transplantation, CRISPR-based genome editing, nanomedicine, and targeted drug delivery hold considerable promise for developing disease-modifying interventions tailored to individual molecular profiles. Despite significant progress, several challenges—including technical

***Corresponding Author:** Anchal
Address: *St.Soldier Institute of Pharmacy, Lidhran Campus behind NIT(R.E.C), Jalandhar-Amritsar Byepass , Jalandhar 14001, Punjab, India*
Email ✉: as1543382@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

variability, data integration, standardization, and clinical validation—must be addressed before these technologies can be fully translated into routine clinical practice. This review summarizes recent advances in single-cell multi-omics, highlights cell-type-specific molecular mechanisms underlying Parkinson's disease, and discusses their implications for biomarker discovery, precision therapeutics, and the future of personalized medicine

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and represents a growing public health concern worldwide. It is characterized by the progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta, resulting in dopamine deficiency and impairment of motor function. Although the hallmark symptoms include resting tremor, bradykinesia, rigidity, and postural instability, PD also presents with a wide range of non-motor manifestations such as cognitive impairment, depression, autonomic dysfunction, sleep disturbances, and olfactory deficits, which significantly affect patients' quality of life. Despite decades of research, the precise molecular mechanisms underlying PD remain incompletely understood due to the complex interactions among genetic susceptibility, environmental exposures, aging, mitochondrial dysfunction, protein aggregation, neuroinflammation, and oxidative stress (Bloem et al., 2021; Poewe et al., 2017).

Recent advances in high-throughput sequencing technologies have transformed our understanding of PD pathogenesis. Conventional bulk transcriptomic and proteomic analyses have provided valuable insights into disease-associated molecular pathways; however, these approaches average gene expression across heterogeneous cell populations and fail to capture cell-type-specific alterations. The emergence of single-cell and single-nucleus sequencing technologies has overcome these limitations by enabling comprehensive profiling of individual cells within the human brain. These technologies have uncovered previously unrecognized cellular heterogeneity within the substantia nigra and identified distinct molecular signatures associated with dopaminergic neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, and oligodendrocyte precursor cells. Such discoveries have opened new opportunities for biomarker identification, precision therapeutics, and personalized medicine in PD (Agarwal et al., 2020; Smajić et al., 2022).

This review summarizes current advances in single-cell multi-omics approaches and highlights how cell-type-specific molecular mechanisms contribute to Parkinson's disease. It further discusses emerging biomarkers, therapeutic targets, artificial intelligence-assisted analyses, and future perspectives for translating single-cell discoveries into precision medicine.

1.1 Parkinson's Disease: Global Burden

Epidemiology

Parkinson's disease affects more than 10 million people worldwide, and its prevalence continues to increase because of population aging and improved life expectancy. The incidence rises sharply after the age of 60 years, although approximately 5–10% of patients develop early-onset PD before the age of 50. Men are affected slightly more frequently than women. According to recent estimates from the Global Burden of Disease Study, the number of individuals living with PD has more than doubled over the past three decades, making it one of the fastest-growing neurological disorders globally (GBD 2021 Parkinson's Disease Collaborators, 2024; Bloem et al., 2021).

Economic Burden

Parkinson's disease imposes a substantial economic burden on patients, caregivers, and

healthcare systems. Direct medical costs include hospitalization, medications, rehabilitation, surgical interventions, and long-term care, while indirect costs arise from loss of productivity, disability, and caregiver support. As disease severity progresses, healthcare expenditures increase considerably due to complications and the need for continuous multidisciplinary management (Yang et al., 2020; Bloem et al., 2021).

Clinical Manifestations

The clinical presentation of PD extends beyond classical motor symptoms. Motor manifestations include resting tremor, bradykinesia, muscular rigidity, gait impairment, and postural instability. Non-motor symptoms such as depression, anxiety, cognitive decline, constipation, sleep disorders, anosmia, and autonomic dysfunction often precede motor signs by several years, indicating that neurodegeneration begins long before clinical diagnosis (Poewe et al., 2017).

Disease Progression

Parkinson's disease is a chronic progressive disorder characterized by gradual neuronal loss and increasing neurological disability. Disease progression varies considerably among individuals and is influenced by age, genetic background, environmental factors, and comorbidities. With advancing disease, patients often develop motor fluctuations, dyskinesias, cognitive impairment, and dementia, highlighting the urgent need for disease-modifying therapies (Bloem et al., 2021).

1.2 Neuropathology of Parkinson's Disease

Loss of Dopaminergic Neurons

The defining pathological feature of PD is the selective degeneration of dopaminergic neurons located in the substantia nigra pars compacta. The depletion of these neurons reduces dopamine availability within the nigrostriatal pathway, leading to impaired motor control and the characteristic movement abnormalities observed in PD. Single-cell transcriptomic studies have revealed that vulnerable dopaminergic neuron subpopulations exhibit distinct molecular signatures associated with mitochondrial dysfunction, impaired protein degradation, and metabolic stress (Agarwal et al., 2020).

α-Synuclein Aggregation

Misfolding and aggregation of α-synuclein represent central events in PD pathogenesis. Abnormal α-synuclein undergoes conformational changes, forms toxic oligomers and fibrils, and spreads between neurons in a prion-like manner. These aggregates interfere with synaptic transmission, mitochondrial function, vesicle trafficking, and intracellular protein homeostasis, ultimately promoting neuronal death (Poewe et al., 2017).

Lewy Body Formation

Lewy bodies are intracellular protein inclusions primarily composed of aggregated α-synuclein along with ubiquitin and other cellular proteins. They are considered one of the neuropathological hallmarks of PD and are widely distributed throughout the central and peripheral nervous systems. Their progressive accumulation correlates with disease severity and the emergence of cognitive dysfunction (Braak et al., 2003).

Neuroinflammation

Persistent activation of microglia and astrocytes contributes significantly to PD progression. Activated glial cells release pro-inflammatory cytokines, chemokines, reactive oxygen species, and nitric oxide, creating a neurotoxic environment that accelerates dopaminergic neuron degeneration. Single-cell analyses have demonstrated substantial heterogeneity among glial populations, suggesting that distinct

inflammatory states influence disease progression differently (Agarwal et al., 2020; Smajić et al., 2022).

Oxidative Stress

Oxidative stress plays a major role in neuronal degeneration by disrupting mitochondrial respiration and increasing reactive oxygen species production. Dopaminergic neurons are particularly susceptible because dopamine metabolism itself generates reactive intermediates. Excessive oxidative damage affects proteins, lipids, and DNA, leading to impaired cellular function and apoptosis (Dexter & Jenner, 2013).

1.3 Limitations of Conventional Molecular Studies

Traditional molecular approaches, including bulk RNA sequencing, microarray analysis, and proteomics, have substantially improved our understanding of PD biology. However, these techniques measure averaged molecular signals across mixed cell populations, masking important differences between individual cell types. Consequently, rare neuronal populations and disease-specific cellular responses often remain undetected. This limitation has hindered the identification of precise therapeutic targets and early biomarkers, particularly within the highly heterogeneous cellular environment of the substantia nigra (Agarwal et al., 2020).

1.4 Emergence of Single-Cell Technologies

The introduction of single-cell and single-nucleus sequencing technologies has revolutionized neuroscience research by enabling high-resolution analysis of individual cells. Modern platforms, including single-cell RNA sequencing (scRNA-seq), single-nucleus RNA sequencing (snRNA-seq), single-cell ATAC-seq, spatial transcriptomics, and integrated multi-omics approaches, allow researchers to characterize cellular diversity, gene regulatory networks, and intercellular communication with unprecedented precision. These technologies have identified previously unrecognized neuronal and glial subpopulations, revealed disease-associated molecular pathways, and accelerated biomarker discovery and precision therapeutic development for Parkinson's disease (Agarwal et al., 2020; Smajić et al., 2022).

1.5 Scope and Objectives of the Review

This review aims to provide a concise overview of recent advances in single-cell multi-omics technologies and their applications in Parkinson's disease research. It focuses on the cellular architecture of the human substantia nigra, cell-type-specific molecular mechanisms underlying neurodegeneration, and the integration of transcriptomic, epigenomic, proteomic, and metabolomic data. In addition, the review highlights emerging biomarkers, novel therapeutic targets, artificial intelligence-assisted analytical approaches, and future directions for translating single-cell discoveries into precision medicine.

2. HUMAN SUBSTANTIA NIGRA: CELLULAR ARCHITECTURE AND FUNCTIONAL ORGANIZATION

The substantia nigra (SN) is a highly specialized structure located in the ventral midbrain and is a central component of the basal ganglia circuitry responsible for regulating voluntary movement, motor learning, reward processing, and cognitive functions. It is anatomically divided into two major regions: the **substantia nigra pars compacta (SNpc)** and the **substantia nigra pars reticulata (SNpr)**. The SNpc contains densely packed dopaminergic neurons that project to the dorsal striatum through the nigrostriatal pathway, whereas the SNpr is primarily composed of GABAergic neurons that serve as one of the principal output nuclei of the basal ganglia. Progressive degeneration of dopaminergic

neurons within the SNpc is the pathological hallmark of Parkinson's disease (PD), leading to dopamine depletion and subsequent impairment of motor function (Poewe et al., 2017; Bloem et al., 2021).

Recent advances in **single-cell RNA sequencing (scRNA-seq)** and **single-nucleus RNA sequencing (snRNA-seq)** have transformed our understanding of the human substantia nigra by revealing remarkable cellular diversity. Rather than consisting solely of dopaminergic neurons, the SN contains multiple neuronal and non-neuronal cell populations, including astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs), endothelial cells, and pericytes. Each cell type possesses unique transcriptional signatures and contributes differently to neuronal homeostasis, synaptic function, immune regulation, myelin maintenance, and neurovascular integrity. Single-cell transcriptomic atlases have demonstrated that these diverse cellular populations exhibit disease-specific molecular alterations in Parkinson's disease, highlighting their collective role in disease initiation and progression (Agarwal et al., 2020; Smajić et al., 2022).

2.1 Anatomy of the Substantia Nigra

The substantia nigra forms part of the extrapyramidal motor system and extends throughout the midbrain between the cerebral peduncles and the tegmentum. Anatomically, it consists of two functionally distinct subdivisions.

The **substantia nigra pars compacta (SNpc)** is characterized by pigmented dopaminergic neurons containing neuromelanin. These neurons synthesize dopamine and project extensively to the caudate nucleus and putamen, where dopamine modulates the balance between the direct and indirect motor pathways. Dopamine deficiency resulting from neuronal degeneration disrupts this balance, producing the characteristic motor symptoms of PD.

In contrast, the **substantia nigra pars reticulata (SNpr)** is composed predominantly of inhibitory GABAergic neurons. These neurons receive input from the striatum and subthalamic nucleus and transmit inhibitory signals to the thalamus and superior colliculus, thereby regulating movement initiation, eye movements, and postural control.

Besides neuronal populations, the SN contains abundant glial cells and vascular components that maintain metabolic support, immune surveillance, and blood–brain barrier integrity. Modern transcriptomic studies indicate that glial cells outnumber neurons in the adult substantia nigra, emphasizing their critical contribution to both physiological function and neurodegeneration (Agarwal et al., 2020).

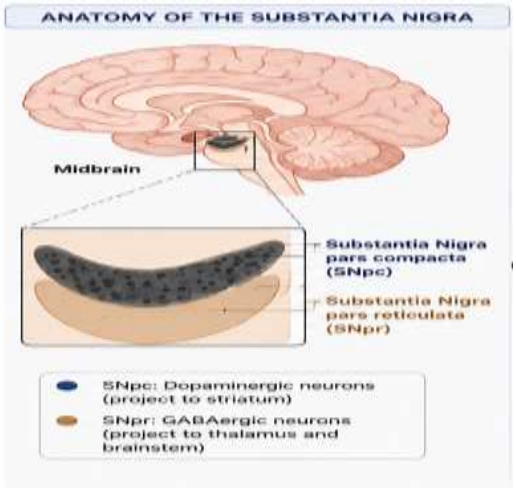

Figure 1 Anatomy of Substantia Nigra

2.2 Dopaminergic Neurons

Dopaminergic neurons are the most extensively studied cell population within the SNpc because their selective degeneration underlies Parkinson's disease. These neurons express classical molecular markers including **tyrosine hydroxylase (TH)**, **dopamine transporter (DAT/SLC6A3)**, **DOPA decarboxylase (DDC)**, **LMX1A**, **FOXA2**, and **GIRK2**.

Single-cell transcriptomic analyses have revealed substantial heterogeneity among dopaminergic neurons. Certain neuronal subpopulations exhibit increased expression of genes involved in oxidative phosphorylation, mitochondrial metabolism, calcium signaling, protein folding, and ubiquitin-mediated proteostasis, making them particularly vulnerable to degeneration. Other subpopulations display neuroprotective gene signatures associated with stress response pathways and neuronal survival.

Dopaminergic neurons possess exceptionally high metabolic demands because of their extensive axonal arborization, continuous pacemaker activity, and dopamine metabolism. Consequently, they are highly susceptible to mitochondrial dysfunction, oxidative stress, α-synuclein aggregation, impaired autophagy, and lysosomal dysfunction. Single-cell studies have identified distinct molecular pathways responsible for selective neuronal vulnerability, offering promising therapeutic targets for disease modification (Agarwal et al., 2020; Surmeier et al., 2017).

2.3 GABAergic Neurons

GABAergic neurons constitute the principal neuronal population within the substantia nigra pars reticulata and play an essential role in regulating basal ganglia output. These neurons express **GAD1**, **GAD2**, **GABRA1**, and **GABRB2**, which are involved in γ-aminobutyric acid (GABA) synthesis and receptor signaling.

Unlike dopaminergic neurons, GABAergic neurons are relatively resistant to degeneration in PD. Nevertheless, alterations in GABAergic neurotransmission contribute significantly to abnormal basal ganglia circuitry, motor dysfunction, and certain non-motor symptoms. Recent single-cell transcriptomic analyses have demonstrated disease-associated transcriptional remodeling in GABAergic neurons, including changes in synaptic signaling, neuronal development, and neurotransmitter metabolism. Emerging evidence also suggests that these neurons may contribute to psychiatric manifestations such as anxiety, depression, and cognitive impairment associated with PD (Agarwal et al., 2020).

2.4 Astrocytes

Astrocytes are the most abundant glial cells within the central nervous system and play indispensable roles in maintaining neuronal homeostasis. They regulate extracellular potassium levels, recycle neurotransmitters, provide metabolic support, maintain blood–brain barrier integrity, and modulate synaptic transmission.

Single-cell sequencing has identified multiple astrocyte subtypes within the substantia nigra. Some astrocytes exhibit inflammatory gene expression profiles characterized by increased cytokine production, whereas others demonstrate neuroprotective signatures associated with tissue repair and neuronal survival. During PD progression, reactive astrocytes undergo morphological and functional changes, producing inflammatory mediators, reactive oxygen species, and glutamate that contribute to neuronal injury. Conversely, astrocytes also secrete neurotrophic factors and antioxidants that protect surviving dopaminergic neurons, highlighting their dual role in disease progression (Agarwal et al., 2020; Liddelow & Barres, 2017).

2.5 Microglia

Microglia are the resident immune cells of the brain and serve as the primary mediators of innate immunity within the substantia nigra. Under physiological conditions, they continuously survey the neural microenvironment and eliminate cellular debris through phagocytosis.

Following neuronal injury, microglia become activated and release pro-inflammatory cytokines including **TNF-α**, **IL-1β**, and **IL-6**, together with nitric oxide and reactive oxygen species. Persistent activation results in chronic neuroinflammation that accelerates dopaminergic neuron degeneration.

Single-cell transcriptomic studies have revealed remarkable heterogeneity among microglial populations, with distinct subsets exhibiting either pro-inflammatory or neuroprotective phenotypes. Understanding these functional differences may facilitate the development of immunomodulatory therapies that selectively suppress harmful inflammatory responses while preserving neuroprotective functions (Smajić et al., 2022).

2.6 Oligodendrocytes

Oligodendrocytes are specialized glial cells responsible for myelin production and axonal metabolic support. Although historically considered less relevant to PD because dopaminergic axons are sparsely myelinated, recent single-cell studies have identified significant oligodendrocyte-specific molecular alterations associated with PD genetic risk.

Distinct oligodendrocyte subpopulations express genes involved in lipid metabolism, protein phosphorylation, mitochondrial metabolism, kinase signaling, and myelin maintenance. These findings suggest that oligodendrocytes contribute to neuronal survival beyond myelination by supporting axonal energy metabolism and maintaining white matter integrity. Consequently, oligodendrocyte dysfunction is now recognized as an emerging contributor to PD pathogenesis (Agarwal et al., 2020).

2.7 Oligodendrocyte Precursor Cells (OPCs)

OPCs are proliferative progenitor cells capable of differentiating into mature oligodendrocytes throughout adult life. Besides serving as a reservoir for myelin repair, OPCs actively communicate with neurons, astrocytes, and microglia through cytokines and growth factors.

Single-cell sequencing has demonstrated that OPCs exhibit dynamic transcriptional changes in PD, including genes associated with cellular differentiation, synaptic signaling, neurodevelopment, and metabolic regulation. Their intrinsic regenerative capacity makes OPCs promising targets for future neurorestorative therapies.

2.8 Endothelial Cells

Endothelial cells line cerebral blood vessels and form the structural basis of the blood–brain barrier (BBB). They regulate nutrient transport, immune cell trafficking, and cerebrovascular homeostasis.

In Parkinson's disease, endothelial dysfunction contributes to BBB disruption, increased vascular permeability, oxidative stress, and infiltration of peripheral immune cells into the brain. Single-cell analyses have identified altered endothelial gene expression involving angiogenesis, extracellular matrix remodeling, inflammatory signaling, and vascular integrity, suggesting that neurovascular dysfunction represents an important component of PD pathology (Agarwal et al., 2020).

2.9 Cellular Communication within the Nigrostriatal Pathway

The physiological function of the substantia nigra depends on continuous communication among neurons, glial cells, and vascular components. Dopaminergic neurons interact closely with astrocytes for metabolic support, microglia for immune surveillance, oligodendrocytes for axonal

maintenance, and endothelial cells for nutrient exchange. Single-cell multi-omics has revealed complex ligand–receptor interactions, cytokine networks, extracellular vesicle signaling, and transcriptional programs that coordinate these intercellular relationships.

Disruption of these communication networks contributes to mitochondrial dysfunction, neuroinflammation, synaptic impairment, α-synuclein propagation, and progressive neuronal loss in PD. Understanding these cell–cell interactions provides valuable insight into disease mechanisms and identifies novel opportunities for precision therapeutics targeting specific cellular populations rather than individual molecular pathways.

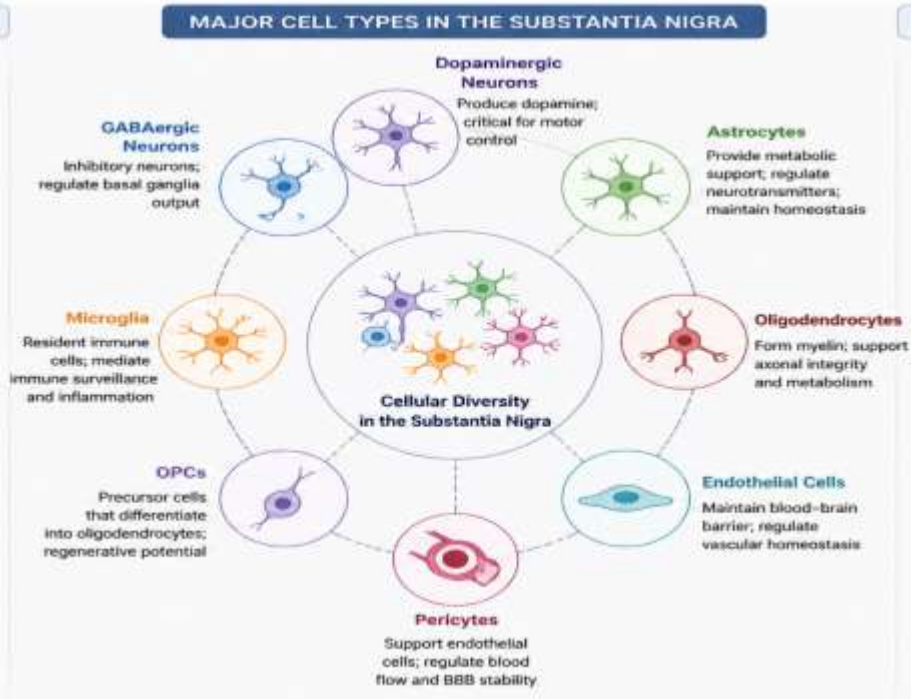

Figure 2: Cellular Architecture and Functional Organization of the Human Substantia Nigra

3. EVOLUTION OF SINGLE-CELL TECHNOLOGIES IN PARKINSON'S DISEASE

The development of single-cell technologies has revolutionized neuroscience research by enabling comprehensive characterization of individual cells within complex tissues. Unlike conventional bulk sequencing approaches, which measure average molecular signals from heterogeneous cell populations, single-cell techniques provide high-resolution insights into cellular diversity, gene expression, epigenetic regulation, and intercellular communication. These advances have significantly improved the understanding of Parkinson's disease (PD), where selective vulnerability of specific neuronal and glial cell populations plays a central role in disease progression. The integration of multiple single-cell omics platforms has uncovered previously unrecognized cellular heterogeneity within the human substantia nigra and has accelerated the discovery of disease-associated molecular pathways, biomarkers, and therapeutic targets (Tang et al., 2019; Smajić et al., 2022).

Recent studies combining transcriptomics, epigenomics, proteomics, metabolomics, and spatial transcriptomics have demonstrated that Parkinson's disease is not solely a neuronal disorder but rather a multicellular disease

involving complex interactions among dopaminergic neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, and immune cells. Single-cell multi-omics has therefore become an indispensable tool for precision neurology, enabling researchers to investigate cellular responses at unprecedented resolution while identifying patient-specific therapeutic opportunities (Agarwal et al., 2020; Kamath et al., 2022).

3.1 Single-Cell RNA Sequencing (scRNA-seq)

Single-cell RNA sequencing (scRNA-seq) is one of the most transformative technologies in modern molecular biology. It enables genome-wide quantification of messenger RNA (mRNA) from individual cells, allowing researchers to identify distinct cell populations, characterize transcriptional heterogeneity, and reconstruct developmental trajectories.

In Parkinson's disease research, scRNA-seq has revealed that dopaminergic neurons are not a homogeneous population but consist of several molecularly distinct subtypes exhibiting different levels of vulnerability to neurodegeneration. These analyses have identified disease-associated alterations in genes regulating mitochondrial respiration, oxidative phosphorylation, calcium signaling, protein ubiquitination, lysosomal degradation, and synaptic transmission. Furthermore, scRNA-seq has demonstrated that astrocytes, microglia, and oligodendrocytes undergo substantial transcriptional remodeling during disease progression, highlighting their active participation in neurodegeneration rather than merely supporting neuronal survival (Agarwal et al., 2020; Smajić et al., 2022).

Despite its remarkable resolution, scRNA-seq requires viable single-cell suspensions, making its application to postmortem human brain tissue technically challenging because mature neurons are highly susceptible to mechanical damage during tissue dissociation.

3.2 Single-Nucleus RNA Sequencing (snRNA-seq)

Single-nucleus RNA sequencing (snRNA-seq) has emerged as a preferred alternative for studying human neurodegenerative disorders because it analyzes isolated nuclei instead of intact cells. This approach preserves nuclear RNA and enables transcriptional profiling of frozen or archived postmortem brain tissues without significant cellular damage.

The application of snRNA-seq has generated comprehensive cellular atlases of the human substantia nigra, identifying multiple neuronal and non-neuronal cell populations, including dopaminergic neurons, GABAergic neurons, astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs), endothelial cells, and pericytes. Importantly, snRNA-seq studies have demonstrated that Parkinson's disease-associated genetic risk is enriched within specific dopaminergic neuron populations and oligodendrocytes, providing novel insights into disease susceptibility and cellular vulnerability (Agarwal et al., 2020).

Because of its compatibility with human brain tissue, snRNA-seq has become the gold standard for constructing human brain cell atlases and investigating neurodegenerative diseases.

3.3 Single-Cell ATAC Sequencing (scATAC-seq)

While transcriptomic analyses reveal gene expression patterns, they do not explain how these genes are regulated. Single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) addresses this limitation by profiling chromatin accessibility at the single-cell level, thereby identifying active promoters,

enhancers, transcription factor binding sites, and regulatory DNA elements.

In Parkinson's disease, scATAC-seq has uncovered cell-specific epigenetic alterations affecting genes involved in neuronal differentiation, mitochondrial homeostasis, inflammatory signaling, lysosomal function, and α-synuclein metabolism. Integration of scATAC-seq with scRNA-seq enables simultaneous investigation of gene regulation and gene expression, providing a more comprehensive understanding of disease-associated molecular networks (Corces et al., 2020).

3.4 Single-Cell Proteomics

Proteins represent the functional products of gene expression and are directly responsible for cellular activities. Advances in mass spectrometry and antibody-based technologies have enabled quantitative analysis of protein expression at the single-cell level.

Single-cell proteomics complements transcriptomic studies by identifying post-translational modifications, protein localization, phosphorylation events, and signaling pathways that cannot be inferred solely from RNA data. In Parkinson's disease, these approaches have facilitated detailed investigation of α-synuclein aggregation, mitochondrial protein dysfunction, inflammatory mediators, and synaptic proteins involved in neuronal degeneration. Such information is essential for identifying clinically relevant biomarkers and therapeutic targets (Kelly, 2020).

3.5 Single-Cell Metabolomics

Cellular metabolism plays a crucial role in neuronal survival and neurodegeneration. Single-cell metabolomics measures metabolites within individual cells, enabling direct assessment of metabolic activity and biochemical pathways.

In Parkinson's disease, metabolomic analyses have revealed disturbances in glucose metabolism, mitochondrial respiration, lipid metabolism, amino acid synthesis, and oxidative stress pathways. Dopaminergic neurons exhibit particularly high metabolic demands, making them exceptionally susceptible to mitochondrial dysfunction and reactive oxygen species generation. Integration of metabolomics with transcriptomics and proteomics has improved understanding of disease-associated metabolic remodeling (Johnson et al., 2021).

3.6 Single-Cell Epigenomics

Epigenetic modifications regulate gene expression without altering DNA sequence. Single-cell epigenomic technologies investigate DNA methylation, histone modifications, chromatin accessibility, and three-dimensional genome organization at single-cell resolution.

Emerging evidence suggests that aging, environmental exposures, and genetic susceptibility induce cell-specific epigenetic changes that influence Parkinson's disease risk. These modifications affect neuronal differentiation, immune activation, mitochondrial function, and inflammatory signaling. Single-cell epigenomics therefore provides valuable insight into early disease mechanisms that may precede detectable neuronal degeneration (Corces et al., 2020).

3.7 Multi-Modal Single-Cell Sequencing

Recent technological advances enable simultaneous measurement of multiple molecular features from the same cell. Multi-modal platforms combine transcriptomics, chromatin accessibility, DNA methylation, protein expression, immune receptor profiling, and spatial information within a single experiment.

These integrated approaches provide a comprehensive molecular portrait of individual

cells and facilitate identification of coordinated regulatory networks underlying Parkinson's disease. Multi-modal sequencing is particularly valuable for linking genetic variants to downstream molecular consequences and understanding cellular responses to neurodegeneration (Stuart & Satija, 2019).

3.8 Spatial Transcriptomics

Although single-cell sequencing identifies cellular diversity, conventional methods lose information regarding the original spatial location of cells within tissues. Spatial transcriptomics overcomes this limitation by preserving tissue architecture while simultaneously measuring gene expression.

In Parkinson's disease, spatial transcriptomics enables visualization of dopaminergic neuron loss, neuroinflammatory responses, vascular remodeling, and glial activation directly within the substantia nigra. Combining spatial transcriptomics with single-cell sequencing has substantially improved understanding of cellular interactions and disease microenvironments (Marx, 2021).

3.9 Computational Integration and Artificial Intelligence

The enormous datasets generated by single-cell multi-omics require advanced computational approaches for data integration and interpretation. Artificial intelligence (AI), machine learning (ML), and deep learning algorithms are increasingly employed for cell-type annotation, trajectory inference, regulatory network reconstruction, biomarker discovery, and therapeutic target prediction.

AI-driven analytical pipelines can integrate transcriptomic, epigenomic, proteomic, metabolomic, imaging, and clinical datasets to identify disease-associated molecular signatures with greater accuracy than traditional statistical methods. These computational advances are accelerating biomarker discovery, precision diagnosis, and personalized therapeutic development in Parkinson's disease, marking a new era of data-driven precision neurology (Smajić et al., 2022; Kamath et al., 2022).

4. SINGLE-CELL ATLAS OF THE HUMAN SUBSTANTIA NIGRA

The human substantia nigra (SN) is one of the most complex and functionally important regions of the midbrain, serving as the principal source of dopaminergic innervation to the striatum. For many years, the cellular composition of the SN was primarily characterized using histological techniques and bulk molecular analyses. Although these approaches identified major neuronal and glial populations, they were unable to resolve the extensive cellular heterogeneity that exists within this brain region. The introduction of **single-cell RNA sequencing (scRNA-seq)** and **single-nucleus RNA sequencing (snRNA-seq)** has fundamentally transformed our understanding of the SN by enabling transcriptomic profiling at single-cell resolution. These technologies have generated detailed cellular atlases that reveal distinct neuronal and glial subpopulations, their molecular signatures, and their potential contributions to Parkinson's disease (PD) pathogenesis (Agarwal et al., 2020; Smajić et al., 2022).

Single-cell atlases have demonstrated that the SN is composed not only of dopaminergic neurons but also of GABAergic neurons, astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs), endothelial cells, pericytes, and vascular-associated cells. Each cell population exhibits unique gene expression patterns that regulate neuronal function, immune responses, metabolic support, synaptic communication, and tissue homeostasis. These discoveries have reshaped the understanding of PD by highlighting the involvement of multiple cell types rather than

selective degeneration of dopaminergic neurons alone (Kamath et al., 2022).

4.1 Development of Human Brain Cell Atlases

Comprehensive brain cell atlases have emerged through international collaborative efforts aimed at cataloguing every cellular population within the human brain. Projects such as the **Human Cell Atlas**, the **BRAIN Initiative Cell Census Network (BICCN)**, and several Parkinson's disease consortium studies have combined single-cell sequencing with advanced computational analyses to generate high-resolution maps of brain cellular diversity.

Among these efforts, the landmark study by **Agarwal et al. (2020)** provided the first detailed single-nucleus transcriptomic atlas of the human substantia nigra. By sequencing approximately **17,000 nuclei** obtained from matched substantia nigra and cortical tissues, the investigators identified multiple neuronal and glial cell populations together with their characteristic transcriptional signatures. Importantly, this atlas demonstrated that Parkinson's disease genetic risk is predominantly associated with dopaminergic neurons and oligodendrocytes, providing novel insights into disease susceptibility and molecular pathogenesis.

These reference atlases now serve as valuable resources for comparing healthy and diseased brain tissues, identifying disease-associated cellular states, and facilitating biomarker discovery.

4.2 Cellular Diversity Revealed by Single-Cell Studies

Single-cell sequencing has revealed remarkable cellular heterogeneity within the substantia nigra that was previously unrecognized. Rather than existing as homogeneous populations, individual neuronal and glial cell types comprise multiple molecularly distinct subgroups with specialized biological functions.

Dopaminergic neurons exhibit considerable transcriptional diversity, with some subpopulations preferentially expressing genes involved in dopamine synthesis and neurotransmission, whereas others display enhanced mitochondrial activity, calcium regulation, oxidative phosphorylation, or stress-response pathways. These molecular differences partly explain why only specific dopaminergic neuron subsets undergo selective degeneration during Parkinson's disease.

Similarly, astrocytes demonstrate distinct inflammatory and neuroprotective phenotypes. Reactive astrocytes express genes associated with cytokine production and immune activation, whereas homeostatic astrocytes maintain neurotransmitter recycling and metabolic support. Microglia also exhibit multiple activation states ranging from immune surveillance to highly inflammatory phenotypes that contribute differently to disease progression.

Non-neuronal populations, including oligodendrocytes, OPCs, endothelial cells, and pericytes, display substantial transcriptional specialization related to myelin maintenance, vascular integrity, extracellular matrix remodeling, and neuronal metabolic support. These findings emphasize that PD involves coordinated dysfunction across multiple cellular compartments rather than isolated neuronal degeneration (Agarwal et al., 2020; Smajić et al., 2022).

4.3 Cell-Type-Specific Marker Genes

Identification of reliable molecular markers is essential for distinguishing individual cell populations and investigating their biological functions. Single-cell transcriptomic studies have identified several highly specific marker genes that

define the major cell types within the substantia nigra.

Dopaminergic neurons are characterized by expression of **TH (tyrosine hydroxylase)**, **SLC6A3 (dopamine transporter)**, **DDC**, and **GIRK2**, reflecting their role in dopamine synthesis and transport. GABAergic neurons express **GAD1**, **GAD2**, **GABRA1**, and **GABRB2**, which are involved in γ-aminobutyric acid synthesis and neurotransmission.

Astrocytes are identified by **GFAP**, **AQP4**, and **SLC1A3**, whereas activated astrocyte populations additionally express inflammatory markers such as **OLR1**. Microglia express **CSF1R**, **P2RY12**, **CX3CR1**, and **TMEM119**, indicating their immune surveillance function. Oligodendrocytes are characterized by **MOG**, **MOBP**, **MAG**, and **PLP1**, while OPCs predominantly express **VCAN**, **PDGFRA**, and **CSPG4 (NG2)**. Endothelial cells exhibit expression of **RGS5**, **CLDN5**, and **PECAM1**, reflecting their role in maintaining blood–brain barrier integrity (Agarwal et al., 2020).

These molecular markers have become fundamental tools for identifying disease-associated cellular alterations and developing targeted therapeutic strategies.

4.4 Regional Cellular Heterogeneity

Single-cell analyses have demonstrated that substantial regional differences exist between the substantia nigra and other brain regions, including the cerebral cortex. Compared with cortical tissue, the substantia nigra contains a markedly higher proportion of glial cells, particularly oligodendrocytes, reflecting its unique structural and metabolic requirements.

Furthermore, cellular composition differs between the **substantia nigra pars compacta (SNpc)** and the **pars reticulata (SNpr)**. The SNpc is enriched with dopaminergic neurons responsible for dopamine production, whereas the SNpr predominantly contains GABAergic neurons involved in basal ganglia output pathways. Even within these anatomical subdivisions, individual neuronal subtypes exhibit diverse transcriptional programs associated with neuronal survival, oxidative metabolism, synaptic signaling, and inflammatory responses.

Understanding this regional heterogeneity is essential for interpreting disease-associated molecular changes and designing therapies that selectively target vulnerable neuronal populations while preserving normal brain function (Kamath et al., 2022).

4.5 Comparison Between Healthy and Parkinsonian Brain

Comparative single-cell transcriptomic studies have revealed profound molecular alterations in Parkinsonian substantia nigra compared with healthy brain tissue. Dopaminergic neurons from PD patients exhibit reduced expression of genes involved in dopamine synthesis, mitochondrial respiration, oxidative phosphorylation, and synaptic transmission, accompanied by increased activation of inflammatory and cellular stress pathways.

Reactive astrocytes and activated microglia demonstrate enhanced expression of cytokines, chemokines, complement proteins, and immune-related signaling molecules, indicating persistent neuroinflammation. Oligodendrocytes display alterations in lipid metabolism and myelin-associated genes, whereas endothelial cells exhibit transcriptional changes associated with vascular dysfunction and blood–brain barrier disruption.

Collectively, these findings demonstrate that Parkinson's disease is characterized by widespread multicellular remodeling involving neuronal degeneration, chronic inflammation, metabolic dysfunction, and impaired neurovascular homeostasis rather than isolated loss of

dopaminergic neurons (Smajić et al., 2022; Agarwal et al., 2020).

4.6 Major Public Cell Atlas Resources

Several publicly accessible databases now provide comprehensive single-cell datasets that facilitate Parkinson's disease research and comparative analyses. These resources enable investigators to explore gene expression profiles, identify disease-associated biomarkers, and investigate cell-specific signaling pathways.

Important public resources include:

- **Human Cell Atlas (HCA)** – Comprehensive reference atlas of human cell types across tissues.
- **BRAIN Initiative Cell Census Network (BICCN)** – High-resolution atlas of neuronal and glial diversity in the human brain.
- **Allen Brain Cell Types Database** – Integrated transcriptomic, morphological, and electrophysiological data for brain cells.
- **CELLxGENE** – Interactive platform for visualization and analysis of single-cell datasets.
- **Single Cell Portal (Broad Institute)** – Repository of publicly available single-cell sequencing studies.
- **Parkinson's Progression Markers Initiative (PPMI)** – Multi-omics resource supporting biomarker discovery and precision medicine in PD.

These databases have become indispensable resources for validating experimental findings, identifying novel therapeutic targets, and accelerating translational research in neurodegenerative diseases.

5. CELL-TYPE-SPECIFIC MOLECULAR MECHANISMS IN PARKINSON'S DISEASE

Parkinson's disease (PD) is increasingly recognized as a multicellular neurodegenerative disorder involving complex interactions among neurons, glial cells, and vascular cells. Although degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) remains the defining pathological feature, growing evidence from single-cell transcriptomics indicates that astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs), GABAergic neurons, and endothelial cells also contribute significantly to disease initiation and progression. These cell populations exhibit distinct molecular signatures associated with mitochondrial dysfunction, protein misfolding, oxidative stress, neuroinflammation, impaired autophagy, and disrupted intercellular communication. Understanding these cell-type-specific mechanisms is essential for identifying novel biomarkers and developing precision therapeutics aimed at slowing or preventing neurodegeneration (Agarwal et al., 2020; Smajić et al., 2022).

Recent single-cell multi-omics studies have demonstrated that different cell populations respond uniquely to pathological stress. Dopaminergic neurons primarily exhibit defects in mitochondrial metabolism and α-synuclein homeostasis, whereas glial cells undergo inflammatory activation and metabolic remodeling. Oligodendrocytes display abnormalities in myelin maintenance and lipid metabolism, while endothelial cells contribute to blood–brain barrier dysfunction. These discoveries suggest that Parkinson's disease results from coordinated dysfunction across multiple cellular compartments rather than degeneration of a single neuronal population. Consequently, cell-type-specific molecular profiling provides a strong foundation for precision medicine by enabling targeted therapeutic interventions tailored to individual cellular mechanisms (Kamath et al., 2022; Bloem et al., 2021).

Figure 3: Pathogenesis of Parkinson's Disease

5.1 Dopaminergic Neurons

Dopaminergic neurons located in the **substantia nigra pars compacta (SNpc)** are the primary neuronal population affected in Parkinson's disease (PD). These neurons regulate voluntary movement by releasing dopamine into the striatum. Their selective degeneration results from multiple interconnected molecular abnormalities.

Mitochondrial Dysfunction

Mitochondria are responsible for ATP production and cellular energy metabolism. In PD, impaired mitochondrial respiration, particularly Complex I deficiency, reduces ATP generation and increases reactive oxygen species (ROS), making dopaminergic neurons highly susceptible to degeneration. Single-cell transcriptomic studies have identified dysregulated mitochondrial genes specifically within vulnerable dopaminergic neuron populations (Agarwal et al., 2020; Bose & Beal, 2016).

Oxidative Stress

Dopamine metabolism naturally generates free radicals. Excessive ROS production combined with reduced antioxidant defenses causes oxidative damage to proteins, lipids, and DNA, ultimately leading to neuronal apoptosis. Oxidative stress is considered one of the earliest pathological events in PD (Dexter & Jenner, 2013).

Calcium Homeostasis

Dopaminergic neurons continuously rely on calcium channels for pacemaker activity. Chronic calcium influx increases mitochondrial workload and promotes oxidative damage. Disruption of intracellular calcium regulation accelerates neuronal dysfunction and cell death (Surmeier et al., 2017).

Synaptic Dysfunction

Early synaptic impairment precedes neuronal degeneration in PD. Reduced dopamine release, defective synaptic vesicle recycling, and altered neurotransmission contribute to progressive motor impairment. Single-cell analyses have revealed altered expression of genes involved in synaptic signaling and vesicle transport (Smajić et al., 2022).

Autophagy Impairment

Autophagy removes damaged proteins and dysfunctional organelles. Defective autophagy leads to accumulation of abnormal proteins,

damaged mitochondria, and cellular waste, thereby accelerating neurodegeneration (Menzies et al., 2017).

Protein Ubiquitination

The ubiquitin–proteasome system maintains protein quality by degrading misfolded proteins. Mutations in genes such as **PARK2 (Parkin)** impair ubiquitination, resulting in toxic protein accumulation and neuronal death (Pickrell & Youle, 2015).

α-Synuclein Toxicity

Misfolding and aggregation of α-synuclein form toxic oligomers and Lewy bodies, the pathological hallmark of PD. These aggregates impair mitochondrial function, disrupt synaptic transmission, inhibit autophagy, and propagate between neurons in a prion-like manner, promoting progressive neurodegeneration (Poewe et al., 2017).

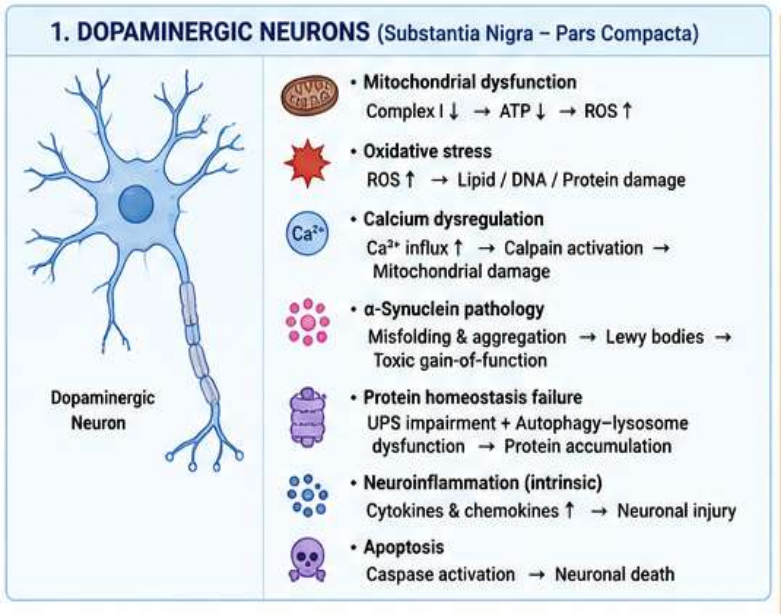

Figure 4: Dopminergic Mechanisms in Parkinson's Disease

5.2 GABAergic Neurons

GABAergic neurons are predominantly located in the **substantia nigra pars reticulata (SNpr)** and regulate inhibitory output of the basal ganglia. Although they are relatively resistant to degeneration, alterations in GABAergic signaling contribute to abnormal motor circuitry in PD. Single-cell transcriptomic studies have shown changes in genes associated with neurotransmitter release, synaptic plasticity, and neuronal communication, suggesting that GABAergic dysfunction contributes to both motor and non-motor manifestations of PD (Agarwal et al., 2020).

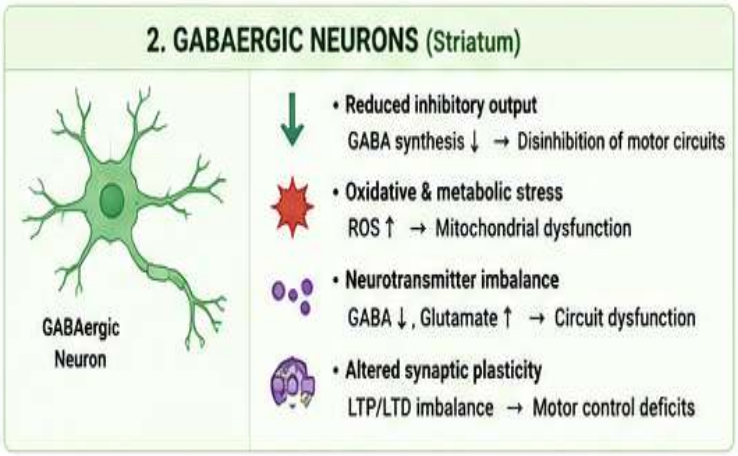

Figure 5: GABAergic Mechanisms in Parkinson's Disease

5.3 Astrocytes

Astrocytes provide structural and metabolic support to neurons while maintaining neurotransmitter balance and blood–brain barrier integrity. During PD progression, astrocytes become reactive and release inflammatory cytokines, nitric oxide, and reactive oxygen species that exacerbate neuronal injury. Conversely, they also produce neurotrophic factors and antioxidants that protect surviving neurons. Single-cell studies have identified inflammatory and neuroprotective astrocyte subpopulations, emphasizing their dual role in PD pathogenesis (Liddelow & Barres, 2017; Smajić et al., 2022).

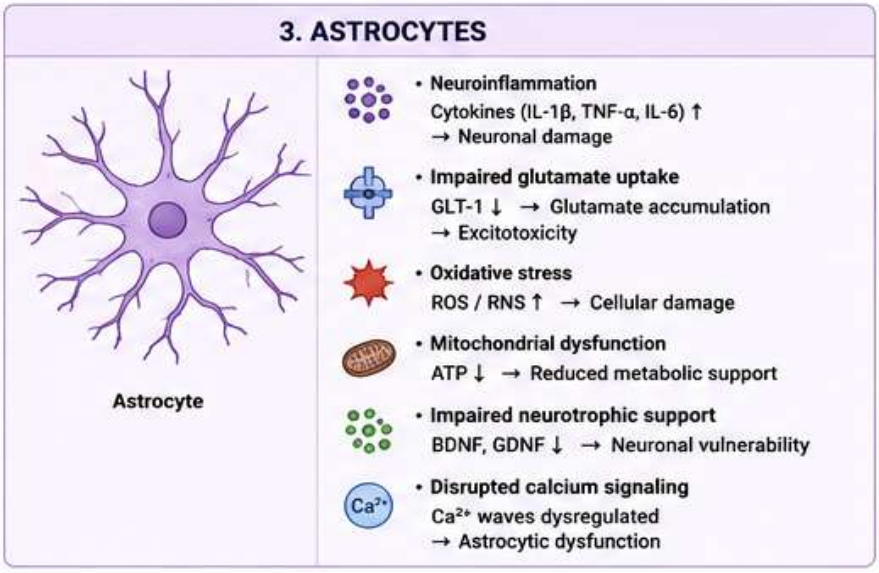

Figure 6: Astrocytic Mechanisms in Parkinson's Disease

5.4 Microglia

Microglia are the resident immune cells of the central nervous system. In Parkinson's disease, chronic activation of microglia leads to sustained release of pro-inflammatory mediators such as **TNF-α**, **IL-1β**, and **IL-6**, creating a neurotoxic environment that accelerates dopaminergic neuron degeneration. Single-cell sequencing has revealed diverse microglial activation states, indicating that some populations promote inflammation while others participate in tissue repair and

neuroprotection (Agarwal et al., 2020; Hickman et al., 2018).

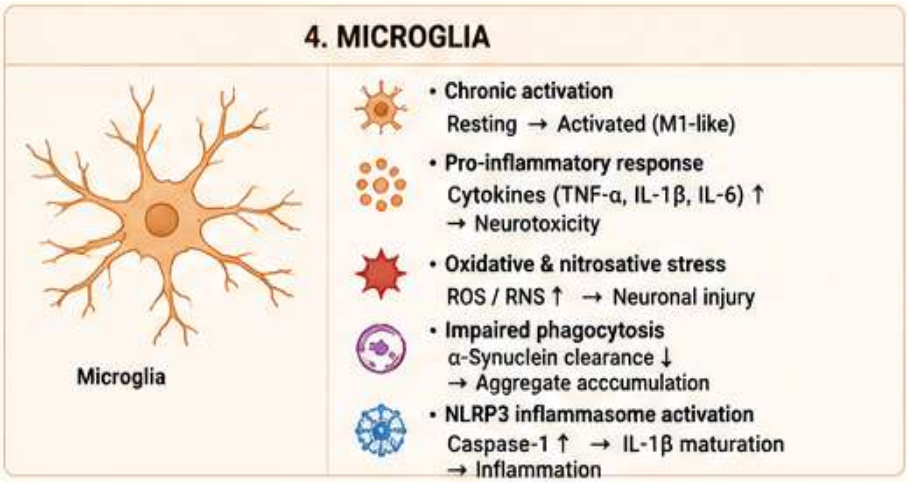

Figure 7: Microglia Mechanisms in Parkinson's Disease

5.5 Oligodendrocytes

Oligodendrocytes are responsible for myelin formation and metabolic support of axons. Although traditionally overlooked in PD, recent single-cell studies have demonstrated significant oligodendrocyte-specific gene expression changes associated with mitochondrial metabolism, lipid synthesis, and protein phosphorylation. These findings suggest that oligodendrocyte dysfunction contributes to impaired neuronal energy metabolism and white matter abnormalities observed in PD (Agarwal et al., 2020).

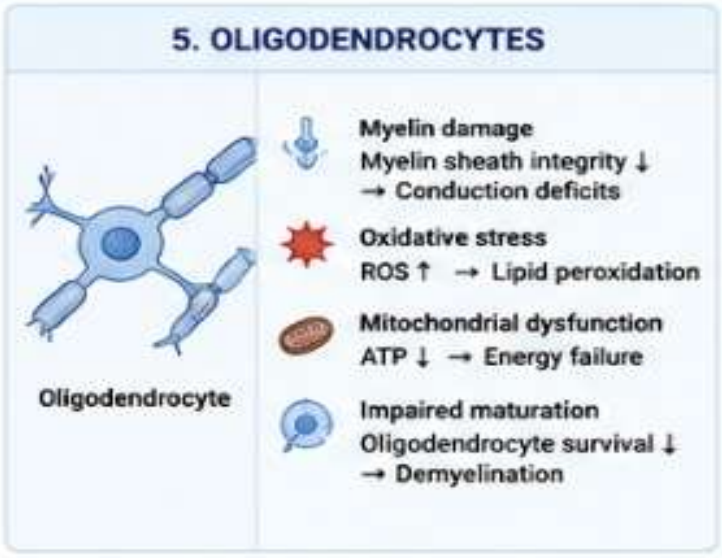

Figure 8: Oligodendrocyte Mechanisms in Parkinson's Disease

5.6 Oligodendrocyte Precursor Cells (OPCs)

OPCs are proliferative progenitor cells capable of differentiating into mature oligodendrocytes throughout adult life. Besides promoting myelin repair, OPCs regulate neuronal survival through secretion of growth factors and cytokines. Single-cell transcriptomics has demonstrated altered differentiation pathways and impaired regenerative capacity of OPCs in PD, indicating

their potential role in disease progression and neurorestoration (Kamath et al., 2022).

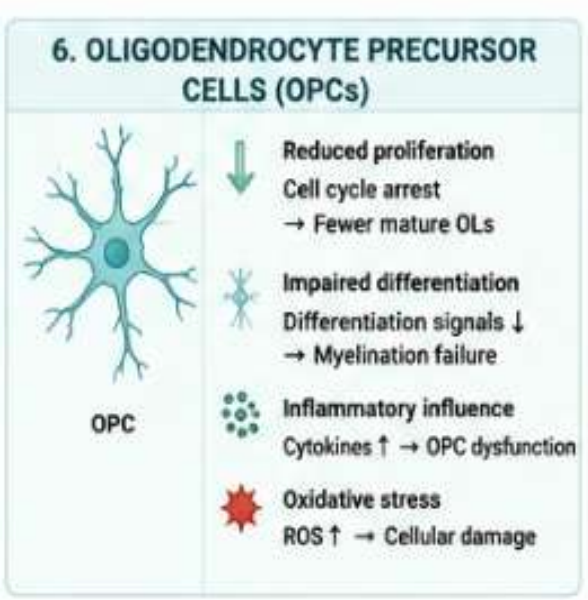

Figure 9: Oligodendrocyte Precursor Cells Mechanisms in Parkinson's Disease

5.7 Endothelial Cells

Endothelial cells form the inner lining of cerebral blood vessels and maintain the blood–brain barrier (BBB). In Parkinson's disease, endothelial dysfunction results in BBB disruption, increased vascular permeability, oxidative stress, and infiltration of peripheral immune cells into the brain. Single-cell analyses have identified altered expression of genes regulating angiogenesis, vascular inflammation, extracellular matrix remodeling, and endothelial integrity, suggesting that neurovascular dysfunction is an important contributor to PD pathology (Agarwal et al., 2020; Sweeney et al., 2019).

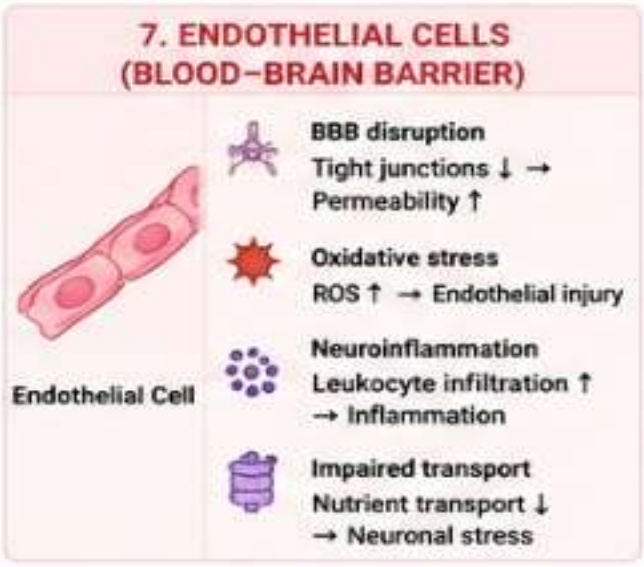

Figure 10: Endothelial Cell Mechanisms in Parkinson's Disease

6. MULTI-OMICS INTEGRATION IN PARKINSON'S DISEASE

Single-omics approaches have significantly improved our understanding of Parkinson's disease (PD), but each technique captures only one aspect of the disease process. Since PD results from complex interactions among genetic, epigenetic, transcriptomic, proteomic, and metabolic alterations, integrating multiple omics datasets provides a more comprehensive understanding of disease mechanisms. Multi-omics approaches enable researchers to identify interconnected molecular pathways, discover robust biomarkers, and develop precision therapeutic strategies. Recent advances in computational biology and artificial intelligence (AI) have further enhanced the integration of diverse omics datasets, allowing high-resolution characterization of disease-associated cellular networks and individual patient variability (Hasin et al., 2017; Smajić et al., 2022). By combining single-cell technologies with multi-omics analyses, researchers can simultaneously investigate gene expression, chromatin accessibility, protein abundance, metabolite profiles, and cellular interactions within the same tissue. This integrated strategy has revealed that Parkinson's disease is driven by coordinated dysfunction across multiple biological systems rather than alterations in a single molecular pathway. Consequently, multi-omics integration is becoming a cornerstone of precision medicine for early diagnosis, disease monitoring, and personalized treatment development (Agarwal et al., 2020).

6.1 Transcriptomics

Transcriptomics examines the complete set of RNA transcripts expressed within a cell or tissue. Single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) have identified disease-specific transcriptional changes in dopaminergic neurons, astrocytes, microglia, oligodendrocytes, and endothelial cells. These studies have highlighted dysregulated pathways involved in mitochondrial function, synaptic signaling, oxidative stress, protein degradation, and neuroinflammation, providing valuable insight into the molecular basis of PD (Agarwal et al., 2020; Smajić et al., 2022).

6.2 Epigenomics

Epigenomics investigates heritable changes in gene regulation that occur without altering the DNA sequence. DNA methylation, histone modifications, and chromatin remodeling influence neuronal survival and inflammatory responses in PD. Single-cell epigenomic studies have demonstrated cell-specific alterations in chromatin accessibility and transcription factor activity, suggesting that epigenetic dysregulation contributes to selective neuronal vulnerability and disease progression (Corces et al., 2020).

6.3 Proteomics

Proteomics provides direct information about protein expression, post-translational modifications, and signaling pathways. Since proteins perform most cellular functions, proteomic analyses complement transcriptomic data by identifying functional changes that cannot be predicted from RNA expression alone. In PD, proteomics has revealed abnormalities in α-synuclein processing, mitochondrial proteins, inflammatory mediators, and components of the ubiquitin–proteasome system, offering potential biomarkers and therapeutic targets (Kelly, 2020).

6.4 Metabolomics

Metabolomics measures small molecules produced during cellular metabolism, providing a direct indication of cellular function. Metabolic profiling in PD has identified disturbances in energy metabolism, lipid synthesis, amino acid metabolism, and oxidative stress pathways. These metabolic alterations reflect mitochondrial dysfunction and impaired neuronal bioenergetics,

which are central features of Parkinson's disease (Johnson et al., 2021).

6.5 Lipidomics

Lipidomics focuses on the comprehensive analysis of cellular lipids involved in membrane integrity, signaling, and energy storage. Altered lipid metabolism has been associated with α-synuclein aggregation, mitochondrial dysfunction, and neuroinflammation in PD. Changes in phospholipids, sphingolipids, and cholesterol metabolism may influence neuronal survival and disease progression, making lipidomic profiling a promising approach for biomarker discovery (Fanning et al., 2020).

6.6 Genomics

Genomic studies identify inherited and acquired genetic variations associated with Parkinson's disease. Mutations in genes such as **SNCA**, **LRRK2**, **PARK2**, **PINK1**, **DJ-1**, and **GBA1** increase disease susceptibility by affecting mitochondrial quality control, lysosomal degradation, and protein homeostasis. Integrating genomic information with transcriptomic and proteomic data helps establish functional relationships between genetic variants and downstream cellular alterations (Blauwendraat et al., 2020).

6.7 Integrated Multi-Omics Networks

Integrated multi-omics combines genomic, transcriptomic, epigenomic, proteomic, metabolomic, and lipidomic datasets to construct comprehensive molecular networks. Machine learning and AI-based computational models identify interactions among genes, proteins, metabolites, and signaling pathways that are not apparent when each dataset is analyzed independently. These integrated networks improve biomarker identification, patient stratification, prediction of disease progression, and discovery of personalized therapeutic targets. As single-cell multi-omics technologies continue to evolve, integrated molecular profiling is expected to play a pivotal role in translating basic research into precision medicine for Parkinson's disease (Hasin et al., 2017; Smajić et al., 2022).

7. DISEASE PATHWAYS REVEALED BY SINGLE-CELL MULTI-OMICS

Single-cell multi-omics has transformed our understanding of Parkinson's disease (PD) by identifying molecular pathways that are disrupted within specific neuronal and glial cell populations. Unlike conventional molecular studies, which provide averaged signals from mixed tissues, single-cell approaches reveal cell-type-specific alterations that contribute to disease onset and progression. These technologies have demonstrated that mitochondrial dysfunction, protein aggregation, oxidative stress, impaired autophagy, neuroinflammation, and dysregulated cell death pathways act together to drive progressive neurodegeneration. Understanding these interconnected mechanisms is essential for identifying disease biomarkers and developing targeted therapeutic strategies (Agarwal et al., 2020; Smajić et al., 2022).

7.1 Mitochondrial Dysfunction

Mitochondria are the primary source of cellular energy and play a critical role in maintaining neuronal survival. In PD, mitochondrial dysfunction results in reduced ATP production, impaired oxidative phosphorylation, and excessive generation of reactive oxygen species (ROS). Single-cell transcriptomic studies have identified altered expression of mitochondrial genes specifically within vulnerable dopaminergic neurons, indicating that impaired energy metabolism is an early event in disease progression. Mutations in genes such as **PINK1**, **PARK2**, and **DJ-1** further disrupt mitochondrial quality control, increasing neuronal susceptibility

to degeneration (Agarwal et al., 2020; Pickrell & Youle, 2015).

7.2 Protein Misfolding

Protein homeostasis is essential for normal neuronal function. In Parkinson's disease, abnormal protein folding leads to accumulation of toxic protein aggregates that interfere with intracellular signaling and organelle function. Single-cell analyses have shown that genes regulating protein folding and molecular chaperones are significantly altered in dopaminergic neurons, suggesting impaired proteostasis contributes to selective neuronal vulnerability (Smajić et al., 2022).

7.3 Ubiquitin–Proteasome System

The ubiquitin–proteasome system (UPS) is responsible for removing damaged or misfolded proteins. Dysfunction of this pathway results in intracellular accumulation of toxic proteins and accelerates neuronal degeneration. Mutations affecting **Parkin (PARK2)** and other UPS-associated proteins impair protein degradation and promote α-synuclein accumulation. Single-cell studies have demonstrated reduced expression of ubiquitination-related genes in vulnerable neuronal populations, highlighting UPS dysfunction as a major contributor to PD pathology (Pickrell & Youle, 2015).

7.4 Autophagy–Lysosomal Pathway

Autophagy is a cellular recycling process that removes damaged organelles and aggregated proteins through lysosomal degradation. Impairment of this pathway results in defective clearance of α-synuclein and dysfunctional mitochondria. Single-cell transcriptomic analyses have identified dysregulation of autophagy-associated genes in dopaminergic neurons and glial cells, suggesting impaired autophagic flux contributes to progressive neurodegeneration. Genetic variants in **GBA1**, **LRRK2**, and **ATP13A2** further support the importance of lysosomal dysfunction in PD (Menzies et al., 2017).

7.5 Oxidative Stress

Oxidative stress occurs when reactive oxygen species exceed the antioxidant capacity of the cell. Dopaminergic neurons are particularly vulnerable because dopamine metabolism itself generates free radicals. Excessive oxidative stress damages DNA, proteins, and membrane lipids, leading to mitochondrial dysfunction and neuronal apoptosis. Single-cell sequencing has identified increased oxidative stress-related gene expression in susceptible neuronal populations, indicating that oxidative injury is closely linked with disease progression (Dexter & Jenner, 2013).

7.6 Neuroinflammation

Chronic neuroinflammation is a prominent feature of Parkinson's disease. Activated microglia and reactive astrocytes release inflammatory cytokines, chemokines, nitric oxide, and reactive oxygen species that amplify neuronal injury. Single-cell studies have revealed distinct inflammatory glial subpopulations with either neurotoxic or neuroprotective functions, emphasizing the complexity of immune responses in PD. Persistent neuroinflammation contributes not only to neuronal degeneration but also to disease progression and symptom severity (Agarwal et al., 2020; Hickman et al., 2018).

7.7 Synaptic Dysfunction

Synaptic abnormalities often precede neuronal loss in Parkinson's disease. Altered dopamine release, impaired synaptic vesicle trafficking, and defective neurotransmitter recycling disrupt communication between neurons and impair motor control. Single-cell transcriptomics has demonstrated dysregulation of genes involved in synaptic organization, vesicle transport, and neurotransmitter signaling, suggesting that

synaptic dysfunction is an early pathological event (Smajić et al., 2022).

7.8 Calcium Dysregulation

Intracellular calcium plays a vital role in neuronal excitability and neurotransmitter release. Dopaminergic neurons rely on continuous calcium influx for autonomous pacemaker activity, making them particularly susceptible to calcium overload. Excess intracellular calcium increases mitochondrial stress, promotes oxidative damage, and activates apoptotic pathways. Single-cell analyses indicate altered calcium signaling genes in vulnerable neuronal populations, supporting calcium dysregulation as an important mechanism of selective neurodegeneration (Surmeier et al., 2017).

7.9 Cell Death Pathways

Progressive neuronal loss in PD results from activation of multiple programmed cell death pathways. Besides apoptosis, recent studies have identified necroptosis, ferroptosis, and pyroptosis as important contributors to dopaminergic neuron degeneration. Single-cell technologies have enabled characterization of these pathways within specific neuronal and glial populations, providing new opportunities for targeted therapeutic intervention (Kamath et al., 2022).

7.10 Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation and oxidative membrane damage. Increased iron accumulation within the substantia nigra is a well-recognized feature of Parkinson's disease. Single-cell studies suggest that dopaminergic neurons exhibit altered iron metabolism and antioxidant defense mechanisms, making them particularly vulnerable to ferroptotic cell death (Stockwell et al., 2020).

7.11 Pyroptosis

Pyroptosis is an inflammatory form of programmed cell death mediated by inflammasome activation and gasdermin pore formation. Activated microglia release inflammatory cytokines such as **IL-1β** and **IL-18**, amplifying neuroinflammation and promoting neuronal injury. Emerging evidence suggests that pyroptosis contributes to chronic inflammatory responses observed during PD progression (Cookson, 2019).

7.12 Necroptosis

Necroptosis is a programmed necrotic pathway regulated by receptor-interacting protein kinases (**RIPK1**, **RIPK3**) and mixed-lineage kinase domain-like protein (**MLKL**). Activation of necroptosis results in membrane rupture, inflammation, and neuronal death. Recent experimental studies indicate that inhibition of necroptotic signaling may reduce neurodegeneration and improve neuronal survival in Parkinson's disease models, highlighting this pathway as a promising therapeutic target (Venderova & Park, 2012).

8. BIOMARKER DISCOVERY THROUGH SINGLE-CELL TECHNOLOGIES

The identification of reliable biomarkers is essential for the early diagnosis, monitoring, and treatment of Parkinson's disease (PD). Traditional biomarkers often fail to detect early pathological changes because they reflect averaged molecular alterations from heterogeneous tissues. Single-cell technologies have overcome this limitation by enabling high-resolution analysis of individual cell populations, allowing researchers to identify cell-type-specific molecular signatures associated with disease onset and progression. Integration of transcriptomics, proteomics, metabolomics, and spatial multi-omics has accelerated the discovery of novel biomarkers that may improve diagnostic

accuracy and facilitate precision medicine in PD (Smajić et al., 2022; Agarwal et al., 2020).

Unlike conventional approaches, single-cell analyses can identify subtle molecular changes within vulnerable dopaminergic neurons, reactive glial cells, and vascular cells before extensive neurodegeneration occurs. These biomarkers not only improve disease detection but also provide valuable information regarding disease stage, therapeutic response, and patient-specific molecular profiles.

8.1 Blood Biomarkers

Blood-based biomarkers are attractive because sample collection is minimally invasive, inexpensive, and suitable for repeated clinical monitoring. Recent studies have identified altered levels of inflammatory cytokines, neurofilament light chain (NfL), α-synuclein species, microRNAs, and circulating immune-cell signatures in patients with Parkinson's disease. Single-cell transcriptomic analysis of peripheral blood immune cells has further revealed disease-associated alterations in monocytes, T lymphocytes, and natural killer cells, suggesting that peripheral immune responses reflect ongoing neurodegeneration (Bloem et al., 2021; Smajić et al., 2022).

8.2 Cerebrospinal Fluid (CSF) Biomarkers

Cerebrospinal fluid directly reflects biochemical changes occurring within the central nervous system and therefore represents one of the most informative sources of PD biomarkers. Reduced dopamine metabolites, abnormal α-synuclein species, neurofilament light chain, tau protein, lysosomal enzymes, and inflammatory mediators have all been investigated as potential diagnostic indicators. Single-cell and multi-omics approaches have improved the identification of CSF biomarker panels capable of distinguishing PD from other neurodegenerative disorders with greater sensitivity and specificity (Poewe et al., 2017).

8.3 Extracellular Vesicles

Extracellular vesicles (EVs), including exosomes, are membrane-bound particles released by neurons and glial cells that transport proteins, lipids, RNA, and microRNAs between cells. Because EVs cross the blood–brain barrier, they provide a non-invasive source of brain-derived molecular information. In Parkinson's disease, extracellular vesicles contain disease-associated molecules such as α-synuclein, LRRK2 protein, inflammatory mediators, and regulatory RNAs, making them promising biomarkers for early diagnosis and disease monitoring (Thompson et al., 2022).

8.4 Cell-Free RNA

Cell-free RNA (cfRNA) consists of extracellular RNA fragments circulating in blood and other body fluids. Advances in next-generation sequencing have enabled sensitive detection of disease-associated messenger RNAs, microRNAs, and long non-coding RNAs. Altered expression of several circulating microRNAs involved in mitochondrial function, inflammation, and protein degradation has been associated with Parkinson's disease, suggesting that cfRNA may serve as a minimally invasive molecular biomarker for disease progression and therapeutic response (Smajić et al., 2022).

8.5 Imaging Biomarkers

Neuroimaging complements molecular biomarkers by providing structural and functional information about the brain. Positron emission tomography (PET), dopamine transporter single-photon emission computed tomography (DAT-SPECT), magnetic resonance imaging (MRI), and neuromelanin-sensitive MRI enable visualization of dopaminergic neuron loss, nigrostriatal degeneration, and neuroinflammatory changes.

Combining imaging with single-cell molecular profiling enhances disease characterization and supports earlier diagnosis of Parkinson's disease (Bloem et al., 2021).

8.6 Multi-Omics Biomarker Panels

Individual biomarkers often lack sufficient sensitivity or specificity for clinical diagnosis. Therefore, recent research focuses on integrating genomic, transcriptomic, proteomic, metabolomic, lipidomic, and imaging data into comprehensive multi-omics biomarker panels. Artificial intelligence and machine learning algorithms further improve biomarker selection by identifying complex molecular patterns associated with disease onset and progression. Such integrated biomarker panels are expected to facilitate earlier diagnosis, patient stratification, prediction of disease progression, and personalized therapeutic decision-making in Parkinson's disease (Hasin et al., 2017; Smajić et al., 2022).

9. PRECISION THERAPEUTICS EMERGING FROM SINGLE-CELL RESEARCH

Recent advances in single-cell sequencing and multi-omics technologies have significantly influenced the development of precision therapeutics for Parkinson's disease (PD). Traditional treatments, including levodopa and dopamine agonists, primarily alleviate symptoms without preventing progressive neuronal degeneration. In contrast, single-cell analyses have identified cell-type-specific molecular alterations that enable the development of targeted therapies aimed at modifying disease progression. These technologies have facilitated the identification of vulnerable neuronal populations, disease-associated signaling pathways, and patient-specific therapeutic targets, thereby advancing the concept of personalized medicine in PD (Smajić et al., 2022; Bloem et al., 2021).

By integrating transcriptomic, epigenomic, proteomic, and metabolomic information at single-cell resolution, researchers can better understand disease heterogeneity and predict individual therapeutic responses. This precision medicine approach has accelerated the development of gene therapies, RNA-based therapeutics, stem cell transplantation, nanomedicine, genome editing, and artificial intelligence (AI)-guided drug discovery (Agarwal et al., 2020).

9.1 Gene Therapy

Gene therapy aims to correct or compensate for genetic defects associated with Parkinson's disease by delivering therapeutic genes directly into the brain. Viral vectors, particularly adeno-associated viruses (AAVs), are commonly used to deliver genes encoding neuroprotective factors, dopamine-synthesizing enzymes, or proteins involved in mitochondrial function. Therapeutic strategies targeting **GBA1**, **LRRK2**, **SNCA**, **PINK1**, and **PARK2** are currently under investigation. Single-cell transcriptomic studies help identify patients who may benefit most from gene-based interventions by revealing cell-specific gene expression patterns and molecular abnormalities (Poewe et al., 2017; Smajić et al., 2022).

9.2 RNA Therapeutics

RNA-based therapies have emerged as promising approaches for selectively regulating disease-associated gene expression. Small interfering RNA (siRNA), antisense oligonucleotides (ASOs), and microRNA-based therapies can reduce the production of toxic proteins such as α-synuclein or modulate inflammatory pathways. Single-cell sequencing enables identification of cell-type-specific RNA targets, improving therapeutic specificity while minimizing off-target effects. Several RNA-targeted therapies are currently being evaluated for their ability to slow

disease progression and preserve neuronal function (Bennett et al., 2021).

9.3 Stem Cell Therapy

Stem cell transplantation offers the potential to replace lost dopaminergic neurons and restore dopamine production within the nigrostriatal pathway. Human embryonic stem cells, induced pluripotent stem cells (iPSCs), and mesenchymal stem cells have demonstrated encouraging results in preclinical and early clinical studies. Single-cell transcriptomics plays an essential role in characterizing transplanted cells, monitoring differentiation into authentic dopaminergic neurons, and evaluating graft survival and integration within host neural circuits. These analyses improve the safety and efficacy of regenerative therapies for Parkinson's disease (Barker et al., 2020).

9.4 CRISPR-Based Genome Editing

CRISPR-Cas genome editing has emerged as a powerful tool for correcting disease-causing mutations associated with familial Parkinson's disease. Genome editing strategies targeting genes such as **SNCA**, **LRRK2**, **PINK1**, and **PARK2** have shown promising results in experimental models. Combined with single-cell sequencing, CRISPR technology enables precise evaluation of editing efficiency, gene expression changes, and potential off-target effects, thereby facilitating the development of personalized genetic therapies (Doudna, 2020).

9.5 Nanomedicine

Nanotechnology has improved targeted drug delivery by enhancing therapeutic penetration across the blood–brain barrier (BBB). Nanoparticles, liposomes, polymeric carriers, dendrimers, and lipid-based nanocarriers can deliver neuroprotective drugs, antioxidants, RNA molecules, and gene-editing components directly to affected neuronal populations. Single-cell analyses assist in evaluating nanoparticle distribution, cellular uptake, and therapeutic responses at the individual cell level, thereby optimizing nanomedicine-based treatment strategies (Saraiva et al., 2021).

9.6 Targeted Drug Delivery

Conventional pharmacological treatments often affect multiple tissues and produce systemic adverse effects. Targeted drug delivery systems aim to selectively deliver therapeutic agents to vulnerable neuronal populations while minimizing toxicity. Advances in ligand-mediated nanoparticles, antibody-conjugated drug carriers, and exosome-based delivery systems have improved therapeutic precision. Single-cell molecular profiling facilitates identification of cell-specific receptors and signaling pathways that can be exploited for targeted drug delivery (Agarwal et al., 2020).

9.7 AI-Guided Drug Discovery

Artificial intelligence (AI) and machine learning are transforming drug discovery by integrating large-scale genomic, transcriptomic, proteomic, imaging, and clinical datasets. AI algorithms can identify disease-associated molecular targets, predict drug–target interactions, prioritize candidate compounds, and accelerate drug repurposing. Combined with single-cell multi-omics, AI enables identification of patient-specific therapeutic strategies and supports precision medicine approaches for Parkinson's disease (Topol, 2019; Smajić et al., 2022).

9.8 Personalized Medicine

Personalized medicine aims to tailor therapeutic interventions according to each patient's genetic profile, molecular characteristics, disease stage, and predicted treatment response. Single-cell multi-omics provides detailed information about individual cellular composition and molecular alterations, allowing clinicians to classify patients

into biologically distinct subgroups. This approach supports individualized treatment selection, prediction of therapeutic efficacy, and optimization of long-term disease management. As multi-omics datasets continue to expand, personalized medicine is expected to become a central component of future Parkinson's disease care (Hasin et al., 2017).

10. ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN SINGLE-CELL PARKINSON'S DISEASE RESEARCH

Artificial intelligence (AI) and machine learning (ML) have become indispensable tools for analyzing the enormous datasets generated by single-cell sequencing and multi-omics technologies. These computational approaches enable rapid processing of millions of cells, identification of disease-associated molecular patterns, prediction of cellular behavior, and integration of complex biological information. In Parkinson's disease (PD), AI-driven analyses have significantly improved the understanding of cellular heterogeneity, molecular mechanisms, biomarker discovery, and therapeutic target identification. By combining AI with single-cell multi-omics, researchers can better characterize disease progression and develop personalized therapeutic strategies, making precision medicine increasingly achievable (Smajić et al., 2022; Topol, 2019).

Machine learning algorithms can analyze transcriptomic, epigenomic, proteomic, metabolomic, and clinical datasets simultaneously, identifying subtle molecular signatures that are often undetectable using conventional statistical methods. These computational advances have accelerated biomarker discovery, patient stratification, drug development, and prediction of therapeutic outcomes in Parkinson's disease (Libbrecht & Noble, 2015).

10.1 Cell Annotation

One of the primary applications of AI in single-cell research is automated cell annotation. Machine learning algorithms classify individual cells according to their gene expression profiles, enabling rapid identification of dopaminergic neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, and other brain cell populations. Automated annotation reduces manual bias and improves the accuracy of large-scale cellular atlases, facilitating comparison between healthy and Parkinsonian brain tissues (Agarwal et al., 2020).

10.2 Disease Prediction

Artificial intelligence can identify molecular signatures associated with early Parkinson's disease before the appearance of clinical symptoms. By integrating genetic, transcriptomic, imaging, and clinical information, predictive models estimate disease susceptibility, progression rate, and patient prognosis. These predictive systems may support earlier diagnosis and timely therapeutic intervention, ultimately improving patient outcomes (Topol, 2019).

10.3 Drug Repurposing

Developing new drugs for neurodegenerative diseases is time-consuming and expensive. AI-based drug repurposing accelerates this process by identifying approved drugs that may target disease-associated molecular pathways. Machine learning algorithms analyze large pharmacological databases together with single-cell transcriptomic data to predict compounds capable of restoring normal cellular function. This strategy shortens drug development timelines while reducing research costs and clinical risk (Pushpakom et al., 2019).

10.4 Multi-Omics Integration

Single-cell multi-omics generates diverse datasets that require sophisticated computational analysis.

AI integrates genomic, transcriptomic, epigenomic, proteomic, metabolomic, and imaging information into unified molecular networks. This comprehensive approach enables researchers to identify regulatory pathways, discover biomarkers, understand cell–cell interactions, and reveal mechanisms underlying selective neuronal vulnerability in Parkinson's disease. Integrated analyses also improve patient stratification and facilitate personalized therapeutic decision-making (Hasin et al., 2017; Smajić et al., 2022).

10.5 Digital Twin Models

Digital twin technology is an emerging concept that combines AI with patient-specific biological data to generate a virtual representation of an individual patient. By integrating clinical information with single-cell multi-omics data, digital twins can simulate disease progression, predict therapeutic responses, and evaluate personalized treatment strategies before clinical implementation. Although still in its early stages, this technology has considerable potential to support individualized management of Parkinson's disease and optimize precision medicine approaches (Björnsson et al., 2020).

CONCLUSION

Parkinson's disease (PD) is a complex and progressive neurodegenerative disorder characterized by selective degeneration of dopaminergic neurons and widespread dysfunction of multiple neuronal and non-neuronal cell populations. Traditional molecular approaches have provided valuable insights into disease biology; however, they have been limited in their ability to resolve the extensive cellular heterogeneity of the human substantia nigra. The emergence of **single-cell and single-nucleus sequencing technologies**, together with **multi-omics integration**, has fundamentally transformed the understanding of PD by revealing cell-type-specific molecular signatures, regulatory networks, and intercellular interactions that drive disease initiation and progression (Agarwal et al., 2020; Smajić et al., 2022).

Single-cell analyses have demonstrated that Parkinson's disease extends beyond the degeneration of dopaminergic neurons and involves coordinated dysfunction of astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells, endothelial cells, and other supporting cell populations. These studies have identified key pathogenic mechanisms, including mitochondrial dysfunction, oxidative stress, α-synuclein aggregation, impaired autophagy, neuroinflammation, synaptic dysfunction, calcium dysregulation, and abnormal protein degradation. The integration of transcriptomic, epigenomic, proteomic, metabolomic, and spatial omics data has further improved our understanding of these interconnected pathways and highlighted novel biomarkers and therapeutic targets that were previously unrecognized (Bloem et al., 2021; Kamath et al., 2022).

Importantly, advances in **single-cell multi-omics**, **artificial intelligence**, and **machine learning** are accelerating biomarker discovery, improving patient stratification, and enabling the development of precision therapeutic strategies. Emerging approaches, including gene therapy, RNA therapeutics, stem cell transplantation, CRISPR-based genome editing, nanomedicine, and AI-assisted drug discovery, have the potential to move beyond symptomatic management toward disease-modifying interventions. Although many of these strategies remain in the preclinical or early clinical stages, they represent promising avenues for personalized treatment based on the molecular characteristics of individual patients.

Despite these remarkable advances, several challenges remain before single-cell technologies can be routinely implemented in clinical practice.

Technical variability, limited availability of high-quality human brain tissue, high analytical costs, batch effects, data standardization, and the integration of large multi-omics datasets continue to limit widespread clinical translation. Future research should focus on developing standardized analytical pipelines, expanding longitudinal patient cohorts, improving spatial and temporal resolution of single-cell analyses, and validating candidate biomarkers and therapeutic targets through multicenter clinical studies.

In summary, single-cell multi-omics has ushered in a new era of Parkinson's disease research by providing an unprecedented understanding of the cellular and molecular mechanisms underlying neurodegeneration. Continued integration of advanced sequencing technologies, computational biology, and precision medicine approaches is expected to facilitate earlier diagnosis, identify robust biomarkers, and accelerate the development of personalized disease-modifying therapies. These advances hold significant promise for improving clinical outcomes and enhancing the quality of life of individuals living with Parkinson's disease.

REFERENCES

1. Agarwal D, Sandor C, Volpato V, Caffrey TM, Monzón-Sandoval J, Bowden R, et al. A single-cell atlas of the human substantia nigra reveals cell-specific pathways associated with neurological disorders. Nat Commun. 2020;11:4183.
2. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021;397(10291):2284–2303.
3. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3:17013.
4. Smajić S, Prada-Medina CA, Landoulsi Z, Dietrich C, Jarazo J, Henck J, et al. Single-cell technologies in Parkinson's disease research. Nat Rev Neurol. 2022;18:423–436.
5. Kamath T, Abdulraouf A, Kostas JC, et al. Single-cell genomic profiling of the human brain in health and disease. Nature. 2022;604:509–520.
6. GBD 2021 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2021. Lancet Neurol. 2024;23:112–128.
7. Dexter DT, Jenner P. Parkinson disease: from pathology to molecular disease mechanisms. Free Radic Biol Med. 2013;62:132–144.
8. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci. 2017;18:101–113.
9. Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24:197–211.
10. Pickrell AM, Youle RJ. The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease. Neuron. 2015;85:257–273.
11. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. J Neurochem. 2016;139(Suppl 1):216–231.
12. Menzies FM, Fleming A, Rubinsztein DC. Compromised autophagy and neurodegenerative diseases. Nat Rev Neurosci. 2017;18:345–361.
13. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. Nat Neurosci. 2018;21:1359–1369.
14. Liddelow SA, Barres BA. Reactive astrocytes: production, function and therapeutic potential. Immunity. 2017;46:957–967.
15. Sweeney MD, Kisler K, Montagne A, Toga AW, Zlokovic BV. The role of brain vasculature in neurodegenerative disorders. Nat Neurosci. 2019;22:1573–1583.

16. Corces MR, Shcherbina A, Kundu S, et al. Single-cell epigenomic analyses implicate candidate causal variants in Alzheimer's and Parkinson's diseases. Nat Genet. 2020;52:1158–1168.
17. Stuart T, Satija R. Integrative single-cell analysis. Nat Rev Genet. 2019;20:257–272.
18. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017;18:83.
19. Kelly RT. Single-cell proteomics: progress and prospects. Mol Cell Proteomics. 2020;19:1739–1748.
20. Johnson ECB, et al. Multi-omics approaches in neurodegenerative diseases. Nat Rev Neurol. 2021;17:451–465.
21. Fanning S, Selkoe D, Dettmer U. Parkinson's disease: proteinopathy or lipidopathy? NPJ Parkinsons Dis. 2020;6:3.
22. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol. 2020;19:170–178.
23. Marx V. Method of the Year: Spatially resolved transcriptomics. Nat Methods. 2021;18:9–14.
24. Regev A, Teichmann SA, Lander ES, et al. The Human Cell Atlas. eLife. 2017;6:e27041.
25. Yao Z, van Velthoven CTJ, Nguyen TN, et al. A transcriptomic and epigenomic cell atlas of the mouse primary motor cortex. Nature. 2021;598:103–110.
26. Bennett CF, Krainer AR, Cleveland DW. Antisense oligonucleotide therapies for neurodegenerative diseases. Nat Rev Drug Discov. 2021;20:783–802.
27. Barker RA, Drouin-Ouellet J, Parmar M. Cell-based therapies for Parkinson disease—past insights and future potential. Nat Rev Neurol. 2020;16:343–356.
28. Doudna JA. The promise and challenge of therapeutic genome editing. Nature. 2020;578:229–236.
29. Saraiva C, Praça C, Ferreira R, et al. Nanoparticle-mediated brain drug delivery: overcoming blood–brain barrier. J Control Release. 2021;330:394–413.
30. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25:44–56.
31. Libbrecht MW, Noble WS. Machine learning applications in genetics and genomics. Nat Rev Genet. 2015;16:321–332.
32. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18:41–58.
33. Björnsson B, Borrebaeck C, Elander N, et al. Digital twins to personalize medicine. Genome Med. 2020;12:4.
34. Thompson AG, Gray E, Heman-Ackah SM, et al. Extracellular vesicles in neurodegenerative disease. Nat Rev Neurol. 2022;18:499–513.
35. Stockwell BR, Jiang X, Gu W. Emerging mechanisms and disease relevance of ferroptosis. Cell. 2020;181:448–464.
36. Cookson MR. The role of inflammation in Parkinson's disease. Nat Rev Neurosci. 2019;20:205–218.
37. Tang F, Barbacioru C, Wang Y, et al. Advances in single-cell sequencing technologies. Nat Rev Genet. 2019;20:631–656.
38. Yang W, Hamilton JL, Kopil C, et al. Current and projected future economic burden of Parkinson's disease in the United States. NPJ Parkinsons Dis. 2020;6:15.
39. Obeso JA, Stamelou M, Goetz CG, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th anniversary of the Shaking Palsy. Mov Disord. 2017;32:1264–1310.
40. Brundin P, Dave KD, Kordower JH. Therapeutic approaches to target alpha-

synuclein pathology. Exp Neurol. 2017;298:225–235.
41. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017;18:435–450.
42. Singleton AB, Farrer MJ, Bonifati V. The genetics of Parkinson's disease: progress and therapeutic implications. Neuron. 2013;77:8–27.
43. Sulzer D, Surmeier DJ. Neuronal vulnerability and Parkinson's disease. Mov Disord. 2013;28:715–724.
44. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386:896–912.
45. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci for Parkinson's disease. Lancet Neurol. 2019;18:1091–1102.
46. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79:368–376.
47. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011;12:723–738.
48. Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 7th ed. New York: Garland Science; 2022.
49. Lodish H, Berk A, Kaiser CA, et al. Molecular Cell Biology. 9th ed. New York: W.H. Freeman; 2021.
50. Nelson DL, Cox MM. Lehninger Principles of Biochemistry. 8th ed. New York: W.H. Freeman; 2021.

HOW TO CITE: Anchal, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh, Gaurav Hastir, Emerging Single-Cell Multi-Omics and Cell-Type-Specific Molecular Mechanisms in Parkinson's Disease: From Human Substantia Nigra Atlas to Precision Therapeutics, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 5158-5188, https://doi.org/10.5281/zenodo.21623249