Review on: The Mechanism and Function of Glia in Parkinson's Disease

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “Review on: The Mechanism and Function of Glia in Parkinson's Disease” submitted by Khondokar Mezbahul Abedin (18346064) of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

There were no unethical works involved in doing the thesis. This study does not involve any kind of human or animal trial.

Abstract

An aging population is most likely to suffer from Parkinson's disease (PD). There is currently no effective treatment for Parkinson's disease due to lack of understanding of how the disease develops and progresses. A number of studies have recently shown that glia profoundly affects the homeostasis of the brain and how the brain heals itself. A previous hypothesis regarding the cause of this condition was that the cells of the dopaminergic system in the midbrain had been damaged. An important part of the neurodegenerative process is the loss of supportive-defensive glial functions, as well as the toxic gains that result from such interventions. This article aims to provide an overview of the roles of astrocytes, oligodendrocytes, and microglia in the early development of Parkinson's disease. It also discusses the possible application of medications associated with glia in the treatment of PD.

Keywords: Parkinson; neuro-inflammation; microglia; alpha-synuclein; neuro-degeneration; oligodendrocytes; astrocytes.

Dedication

This thesis project is dedicated to my beloved parents.

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Alhamdulillah.

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List of Acronyms:

PD	Parkinson disease
CNS	Central nervous system
TLRs	Toll-like receptors
PPCs	Oligodendrocyte precursor cells
CMA	Chaperonemediated autophagy
iDANs	Induced dopamine neurons
Alpha-Syn	Alpha-synuclein
6-OHDA	6-hydroxydopamine
BBB	Blood-brain barrier
DAMPs	Damage-associated molecular patterns
LPS	Lipopolysaccharide
MPP+	1-methyl-4-phenylpyridinium
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
NLRs	Nucleotide-binding oligomerization domain-like receptors
NRF2	Nuclear factor erythroid 2-related factor 2
NURR1	Nuclear receptor related 1
PAMPs	Pathogen-associated molecular patterns
LBs	Lewy bodies

Chapter 1

Introduction

1.1 Parkinson’s disorder

In general, Parkinson's disease (PD) is considered to be one of the most common disorders in the world because it is a neurodegenerative disease characterized by both movement abnormalities as well as non-motor abnormalities. In addition to a number of motor symptoms, stiff muscles, bradykinesia, static tremors, postural dysfunction, and abnormal gait may also be observed. Some of the most common non-motor symptoms are sleep problems, fatigue, olfactory difficulties, soreness, cognitive impairments, mental disorders, and autonomic dysfunction (Devika Agarwal, 2020). In Parkinson's disorder, dopaminergic neurons start to degenerate and die. This results in downstream nerve pathways and the striate nucleus not receiving adequate levels of dopamine, which results in movement difficulties. There is an abnormal aggregation of alpha-synuclein protein in Lewy neurites and bodies characteristic of Parkinson's disease (Muqit, 2022). There are a number of factors that contribute to the etiopathogenesis of PD, including swelling, oxidative stress, and cell death (Sandeep K. Barodia, 2019).

1.2 Pathology

A key pathological characteristic of Parkinson's disorder is the degeneration of the nigrostriatal dopaminergic innervation. However, neurodegeneration doesn't just affect the neurons located predominantly in the nigral area of the brain, but also impacts cells located elsewhere within the network. There are a great deal of pathologies that affect the PD brain, which makes the condition very heterogeneous, and there is not yet a reliable diagnostic test. According to the current diagnostic criteria, the condition must have two of the following clinical features for it

to be diagnosed: resting tremor (tremor associated with movement), bradykinesia (movement associated with movement), rigidity and/or postural instability. Although clinical criteria can be used to indicate a possible diagnosis of Parkinsonism, histopathological testing is needed to confirm a definitive diagnosis. This includes identifying lewy bodies containing synuclein and lewy nerves containing synuclein.

1.3 Glia

Neuroglial cells in the cerebrospinal nervous system are typically classified into astrocytes, microglia, and oligodendrocytes, which are responsible for inflammation, myelination regeneration and metabolism. However, it is important to note that these cells do not act in isolation. A further function of microglia is to regulate myelination (Dzamko, 2017). According to recent studies, microglia and astrocytes work together to maintain the central nervous system's homeostasis (Angelique di Domenico, 2019).

Pro-inflammatory cytokines are secreted by microglia, which have an immune function. It has been shown that microglia play two distinct roles in neuroinflammation: their poisonous effects (M1-phenotype) as well as their protective effects (M2-phenotype) (Biondetti, 2021). As a result of microglia activation, IL-1a, TNF-a, and C1q (a subunit of the C1) are released, which induces astroglia to become A1s. In CNS lesions, activated microglia cause infection and pathologic changes. Microglia that are activated participate in inflammation, engage with cells, and impact one another (Choi, 2020).

Furthermore, astrocytes (A1-phenotype) contribute significantly in cytokine production and immune cell activation. In the CNS, it regulates glucose metabolism, reuptakes glutamate, grows synapses, and maintains blood-brain barrier homeostasis. Scientists have found that astrocytes can be converted into neurons. In the CNS, oligodendrocytes produce myelin to

wrap axons. In order for action potentials to propagate efficiently along axons, myelin is necessary (Damisah, 2020).

1.4 Microglia

The microglia were first identified in 1919 by Del Rio Hortega. In the late stages of embryonic development, it's a mesodermal cell type that enters the brain. He demonstrated their phagocytic capacity and reactive nature by inflicting stab wounds on them. For nearly six decades, Hortega's discovery of mesodermal cells and their phagocytic function was questioned. Recently, a number of studies have discussed the possible contribution of microglia to Parkinson's disease pathogenesis. There are about ten percent of glial cells that are microglia. There are a lot of ramified processes in the brain, but they are not closely related to each other. As a result, each cell patrols its own territory exclusively.

1.5 Astrocyte

Neurons are over five times outnumbered by astrocytes, a specialized type of glial cell. Healthy central nervous systems include a network of millions of neurons that cover a vast area of the brain and exert many complex functions. A prominent feature of structural lesions of the CNS is reactive astrogliosis, which occurs when the astrocytes of the CNS respond to insults directed toward them. There has been growing research on the role of astrocytes in diseases of the CNS as well as the function of reactive astrogliosis over the past few years. It is being established that active astrocytes possess an extensive molecular arsenal. Researchers are using transgenic mice to dissect reactivated astrocytosis and glial scars in vivo. Specifically, astrocytes play a role in clinical pathology. Now, it is clear that the process of reactive astrogliosis involves a finely gradated spectrum of changes that are regulated by specific signaling events rather than a simple all-or-nothing process. There are several types of changes that can occur, including reversible gene expression changes, cell hypertrophy that preserves tissue structure, and

chronic scarring that rearranges tissue structure permanently. During reactive astrogliosis, astrocytes may lose or gain abnormal effects, which could lead to CNS disorders as a result of their breakdown or loss. There are several theories regarding the mechanism and function of reactive astrogliosis and glial scarring. In addition, there is the possibility that these reactivated astrocytes can trigger or contribute to specific neurological disorders or lesions.

1.6 Oligodendrocytes

A central nervous system (CNS) contains myelinating cells known as oligodendrocytes. They form the insulating sheath around axons as a result of a multistep and meticulously controlled process of proliferation, migration, differentiation, and myelination. This culminates in the production of this protective sheath around axons. In addition to this complex differentiation program, oligodendrocytes are vulnerable cells in the central cerebrospinal nervous system because of their unique metabolism and physiology.

1.7 Methodology

This review research paper explains the mechanism and function of glia in Parkinson's disease. I used 20 articles sample related to the topic so that I can understand main theme of the article. After collecting study material I found out types of glial cells and its important function, then I tried to summarize it as easy possible for the reader. The study criteria I developed from previous and similar studies. I found through my research that instead of improved function and higher self-esteem, the individuals within the treatment group displayed lower levels of cognitive and emotional function and lower self-esteem. These results led my research to conclude that each glial cells roles are key to Parkinson disease, their significant roles play in regulating inflammation, metabolism, regeneration and myelination of neurons. Also, plays crucial roles in nervous system development, function and plasticity. These concepts are useful in understanding the etiology and treatment strategies for the neurodegenerative disorder.

The purpose was to determine the prevalent terminology; a process known as literary warrant. From this, common review types and their associated key attributes were identified and mapped against a search, synthesis and analysis framework. Each review type was analysed, its characteristics were described and its perceived strengths and weaknesses were outlined. An example of each type of review was identified and selected, primarily for its usefulness in illustrating review characteristics. No judgment of quality is implied by each selection.

Objective: The objective of this study is to provide a descriptive insight into the most common examples of review, illustrated by examples from health and health information domains.

Significance: These concepts are useful in understanding the etiology and treatment strategies for neurodegenerative disorder.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary Material: Refer to Web version on PubMed Central for supplementary material

Chapter 2

Mechanism

2.1 Mechanisms of glia in Parkinson’s disorder

Glial tissues play an active role in the development of Parkinson's dysfunction, which is characterized as a multifactorial disorder of the nervous system. PD is associated with neural dysfunctions as well as neural circuit malfunctions. Non-neuronal elements, such as glial cells, are also critical in the development, function, and plasticity of the nervous system (Errea, 2021). According to SemraSmajic, RNA sequencing of neuronal clusters and "pan-glial" activation are involved in idiopathic PD (Ettle, 2016). The progression of PD is influenced by the function of glial cells. Astrocytes and microglia play a dual role in the body. These roles

vary depending upon the microenvironment along with the cellular subtype, producing a variety of responses and performing different actions. The activation of microglia and astrocytes is mediated by molecules related to congenital forms of Parkinson's disease, such as parkin, a-syn, DJ-1, and ATPase 13A2 (Filippini, 2021) (Fu, 2021). It is believed that demyelination in PD is caused by oligodendrocytes.

2.2 Role of microglia in PD

In the cerebrospinal nervous system, macrophages are located within the microglia and are considered primary immune cells. An average number of microglia is about 10% in a healthy human brain, making them a significant cell population. In order to maintain appropriate overall densities, microglia undergo periodic renewal cycles, which may also regulate the proportion of different microglial phenotypes. In addition, microglia serve critical roles in maintaining parenchymal homeostasis by being dynamic, mobile, and vigilant surveilants of tissue damage or infection. Microglia play a crucial role in PD and other neurodegenerative diseases because they influence immunity, especially by initiating neuroinflammation when pro-inflammatory molecules are present. There is a difference between microglial phenotypes in the midbrain and elsewhere in the CNS, which may alter dopaminergic neurons in Parkinson's patients. In microglia and astrocytes. Microglia are targeted preferentially by these exosomes. This protein tyrosine kinase regulates adverse effects in T cells as well as other immune cells and relates to astrocytic movement and oligodendrocyte growth in the central nervous system (Glass, 2010). In any kind of cell, Fyn activates

the NLRP3 inflammasomes. In a genome-wide association study (GWAS), the FYN locus was recognized as a potential risk factor for Parkinson's disease.

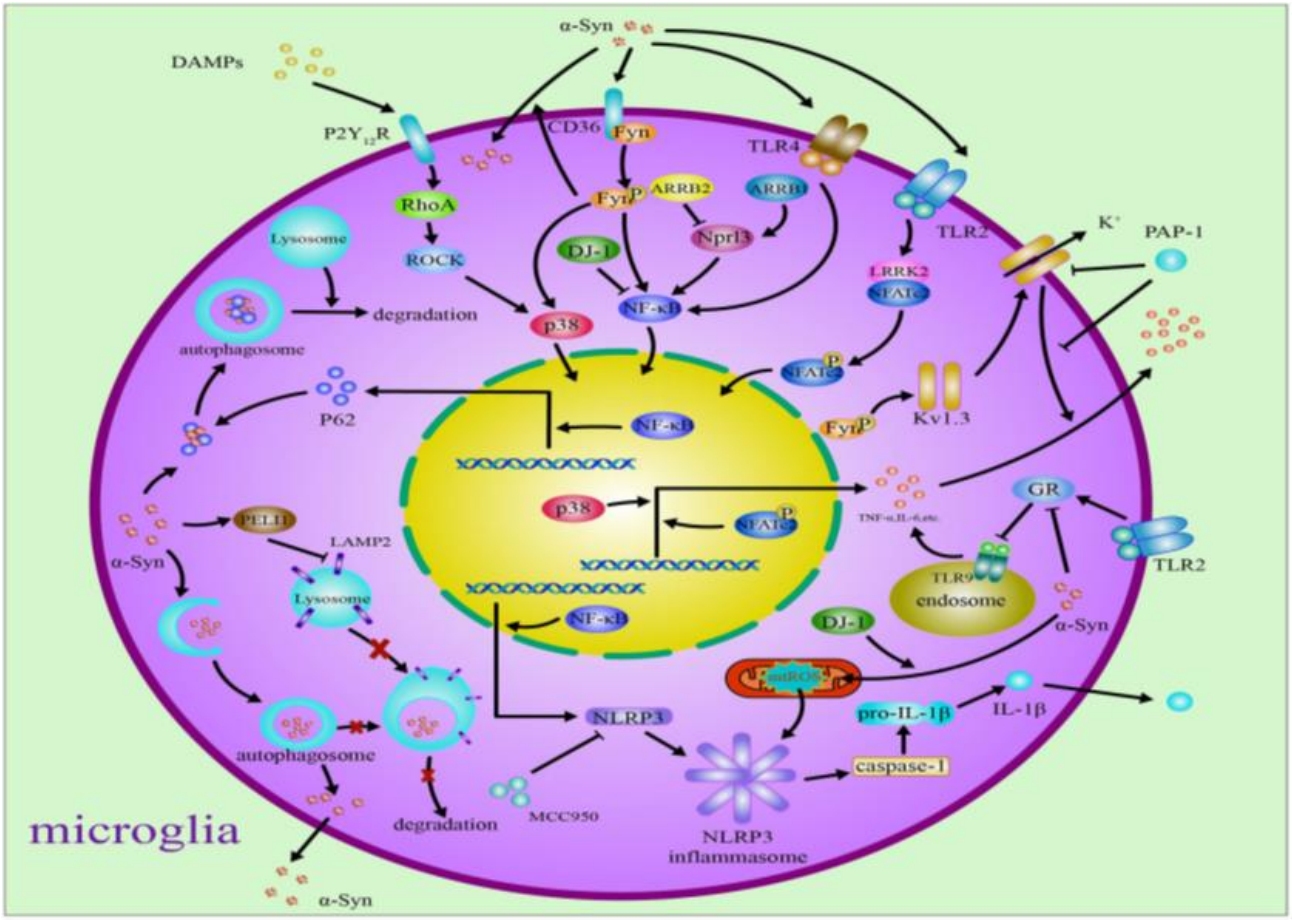

Figure 1: Microglia

As a result of its interaction with CD36, Fyn enhances a-syn import via microglia (Guo, 2020). In microglia, Fyn promotes transcriptional upregulation and post-translational modifications of Kv1.3. On the other hand, small-molecule inhibitors of Kv1.3 can block neuroinflammation activated by Kv1.3 in neurodegenerative diseases. According to the human microglial transcriptome study, P2Y12R expression is associated with Parkinson's disease. In addition to controlling cytokine production, P2Y12R controls ras homolog family member (Rho)-associated coiled coil-containing protein kinase (ROCK) (Hentrich, 2020). In the prolonged neurodegenerative process, P2Y12Rs are essential for maintaining the activation of microglia and triggering the pro-inflammatory

cytokine response. Neurodegenerative diseases are treated by activating receptors situated on myeloid cells 2, phospholipase C G2 and PKC (Hughes, 2019).

2.3 Mechanism of the toll-like receptor

Toll-like receptor (TLR) signaling is the primary pathway that regulates inflammation. It stimulates inflammatory responses through TLR4 by reducing expression of GCR in microglia. It is revealed that TLR9 binding to endolysosomes and its cleavage is more effective in microglia without GR, leading to an increase in pro-inflammation gene expression. As a result, microglia secrete cytokines that cause neurons to die. Moreover, a-syn significantly increases the neuronal expression of TLR2, which, once activated, leads to the release of reactive oxygen species, and chemotactic mediators in macrophages.

2.4 Mechanism of LRRK2

A critical role is played by leucine-rich repeat kinase 2 (LRRK2) in inflammatory response of microglia-mediated by TLR2. By phosphorylating and activating LRRK2, a-syn stimulates the nuclear component of responding T cells, NFATc2 (cytoplasmic 2), to be translocated to the nucleus and triggers neuroinflammatory cascades. Through reducing TNF-a and IL-6 levels, the depletion of LRRK2 reduces a-syn-mediated microglial neurotoxicity. In microglia, LRRK2 affects IFN-g-stimulated cytokine synthesis independently of NFAT. As a result of increasing LRRK2 G2019S-dependent phosphorylation of PKB and activation of NFAT, INF-g enhances neuronal resistance to autoimmune damage. In the presence of a-syn binding, microglia enter a protective mode of phagocytic functions, produce exaggerated amounts of reactive oxygen species and proinflammatory molecules, and recruit other immune cells selectively. By secreting IFN-g, these immune cells create a vicious molecular spiral that induces neurons to undergo apoptosis.

In microglia, the engulfed a-syn induces the expression of E3 ubiquitin-protein ligase pellino homolog 1 (PELI1), thereby impairing autophagy flux and causing a-syn aggregation. In order to transfer a-syn from cell to cell, microglia release extracellular a-syn after exceeding its degradation capacity, and this is taken up by neurons. As a result, microglia autophagy is inhibited, resulting in neurodegeneration. Several studies have shown that microglia play a key role in PD due to the presence of a-syn. As a result of a-syn activation, microglia become activated, causing neuroinflammatory responses and inhibiting autophagy, which leads to neurotoxicity in PD. For PD, the therapy strategy is to regulate neuroinflammatory and autophagic activity in microglia.

2.5 Astrocyte mechanism

Activated brain astrocytes are able to phagocytose and degrade a-syn fibrils in vitro as well as in ex vivo brain sections (Morales, 2017). In PD animal models, 6-hydroxydopamine destroys dopaminergic neurons in the striatum. Interestingly, astrocytes were observed to phagocytose dopaminergic debris and a-syn in a rat model of 6-hydroxydopamine, suggesting they may assist in the removal of cellular components that have been damaged in Parkinson's condition (Panicker, 2019). Additionally, astrocytes prevent a-syn accumulation and spread in dopaminergic neurons. In the later stages of Parkinson's disease, it is possible for astrocytes to undergo highly reactive A1 states, which are highly toxic on oligodendrocytes as well as neurons (Cheng et al, 2021). Astrocytes also internalize a-syn at a higher rate than neurons and degrade lysosomes more rapidly than neurons (Reyes, 2019). In this case, a-syn cannot be internalized because clusterin blocks its internalization (Rivetti di Val Cervo, 2017). As a result of lysosomal degradation, it appears that neurons are capable of efficiently degrading fibrillar a-syn, thus protecting cells from being overwhelmed by fibrillar a-syn (Morales, 2017). The build-up of a-syn in astrocytes occurs as a result of dysfunctional CMA in combination with diminished macroautophagy during the pathogenesis of Parkinson's disease (Panicker, 2019).

The largest percentage of engulfed protein clumps are then secreted by astrocytes, and most are removed by microglia (Rostami, 2020). Microglia are primarily responsible for clearing a-syn.

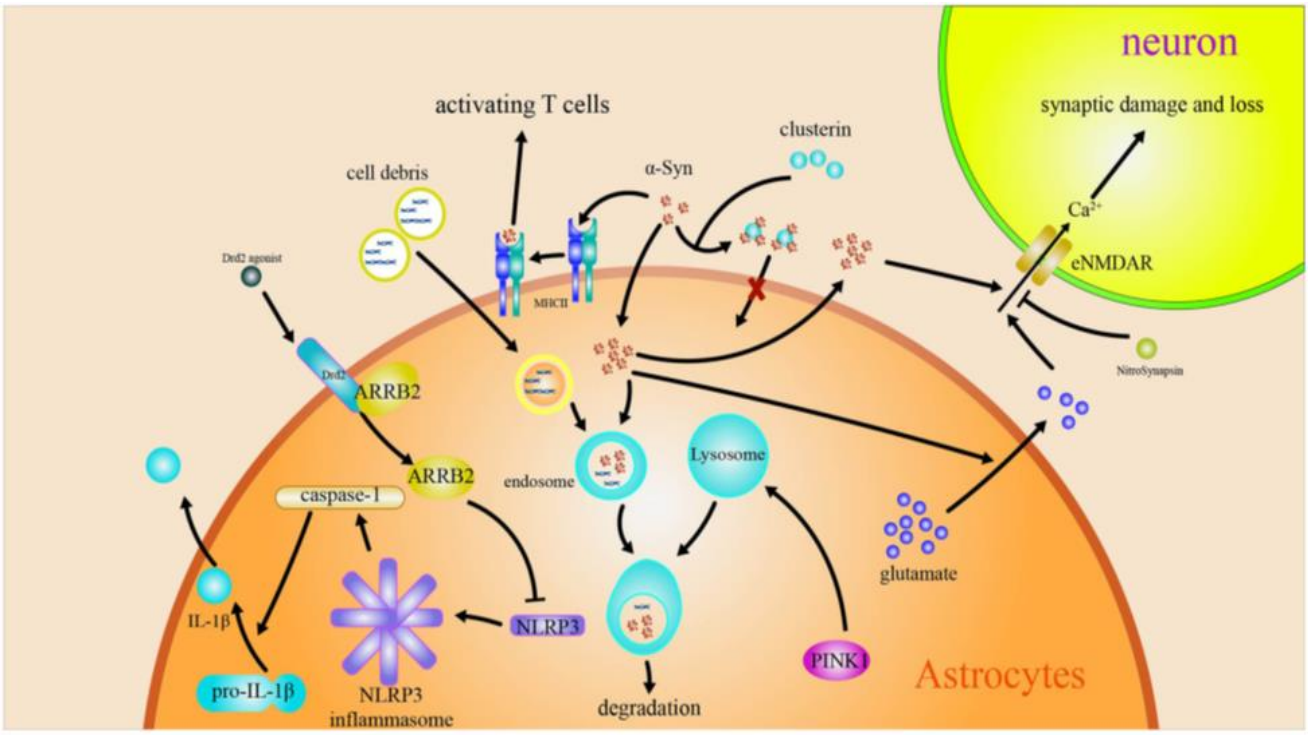

Figure 2: Astrocytes in Parkinson's disease.

2.6 Oligodendrocytes process

In the development of oligodendrocytes, oligodendrocyte precursor cells (OPCs) are differentiated. There are 5% of glial cells in the parenchyma of the central nervous system in OPCs. Neurodegenerative disorders, such as Parkinson's disease, are increasingly being linked to OPC dysfunction and insufficient differentiation (Trudler, 2021). Clinical subtypes of PD are associated with the myelin profiles in the white matter (Tsunemi, 2020). In MSA, an uncommon atypical Parkinson's disease, oligodendrocytes have been detected to deteriorate (Tu, 2021). A study of 17,000 nuclei from identical SN tissues found that dopaminergic neuron-specific transcription plays a key role in PD genetic risk which includes protein folding, ubiquitination, mitochondrial function, oligodendrocyte-specific genes, and specific cell types linked with Parkinson's disease (Vizziello, 2021). One of the risk factors for PD is myelin-

associated oligodendrocyte basic protein (MOBP) polymorphism (Williams, 2021). Moreover, myelin-associated genes are expressed more abundantly in the frontal cerebral cortex of rats overexpressing myelin synthase and patients suffering from Parkinson's disorder (Xia, 2019).

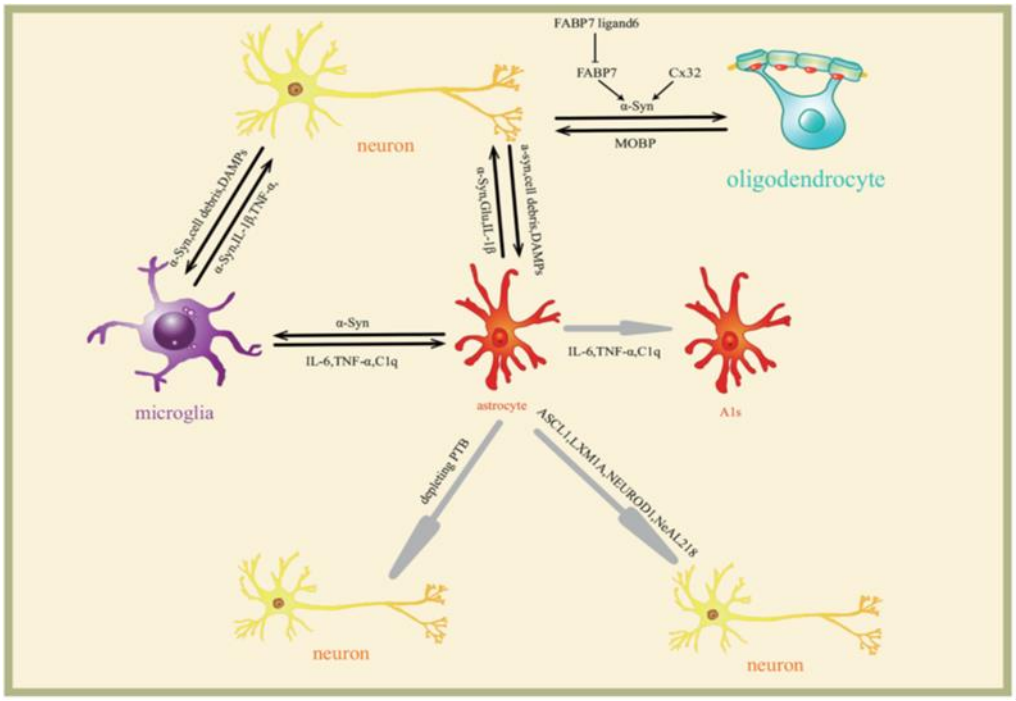

Figure 3: Neuroglial and neuronal interaction in Parkinson's.

Chapter 3

Response

3.1 Expression of risk genes in glia

Researchers have identified 90 independent genetic variants associated with Parkinson's condition risk in a recent GWAS meta-analysis. A study of expression across neurons, oligodendrocytes, fetal astrocytes, mature astrocytes, endothelial cells and microglia was conducted based on publicly available human bulk RNA sequencing data. It was found that two loci mapped to the same DNA in some cases. A total of 22 genes were most highly expressed in neurons (28.5%), and of those, only 6 genes were detected at least 50% in neurons.

In fact, it has been found that a number of genes implicated in Parkinson's degenerative disorder severity are expressed predominantly in glia or throughout the brain to some degree.

3.2 Astrocyte response in PD

Apart from activating a non-specific immune response, A-syn can also activate a specific immune response. In order to present a-syn, astrocytes have a high level of MHC-II expression. As a result, Th1/Th2 cells infiltrate the CNS, releasing Th1 cytokines, Th2 cytokines, CD8+, and CD4+ T cells that produce IFN-g. In such a reaction, dopaminergic cells are lost more rapidly. Astrocytes also contain NLRP inflammasomes, which are involved in the inflammation process. As a result of its interaction with b-arrestin2, Drd2 inhibits the activation of NLRP3 as well as interferes with the assembly of the inflammasome. By reducing caspase-1 expression in response to IL-1b release, Drd2 decreases caspase-1 expression. Scientists have shown that astrocytes can become neurons, and these strategies could be used to treat Parkinson's disorders in the future. There is evidence that ASCL1, NEUROD1, LMX1A, and NeAL218 (microRNA miR218) are capable of transforming astrocytes into induced dopamine neurons (iDANs), as well as improving their efficiency, as they promote chromatin remodeling as well as activate TGF-b, Shh, and Wnt signaling mechanisms. It appears that astrocyte functions are tightly linked to inflammation, and MHC-II-regulated Th1/Th2 cytokine production in PD. During the conversion process, astrocytes become functional neurons. Figure 2 illustrates the roles and mechanisms of astrocytes in PD. Figure 3 shows the pathways involved in the conversion of astrocytes into neurons.

3.3 Alpha-syn appliance

Alpha-syn synthesis in oligodendrocytes is associated with myelin degeneration. As a result of PD and degenerative diseases associated with Lewy bodies. There is an accumulation of MOBP in LBs that originate from the brain stem and sympathetic ganglia. There is, nevertheless,

plenty of data showing that MOBP does not appear in other neurodegenerative disorders. This includes multiple system atrophy, and Alzheimer's disease. Research has shown that MOBP is overexpressed in neurotoxicity conditions, suggesting that MOBP deposition in LBs may protect cells from damage. Despite the lack of studies on oligodendrocytes in PD, myelin-producing cells play a crucial role in PD. As it turns out, oligodendrocytes accumulate a-syn when myelin is lost. Oligodendrocytes and PD need to be studied more closely.

3.4 Post-traumatic stress disorder and gut-brain axis

PD patients with Lewy bodies in their gut are being investigated further for a possible gut-brain connection. A-synuclein aggregation is probably triggered by factors, such as the bacteria in the gut. In transgenic mice, the hypothesis was confirmed. In mice, researchers found that overexpressing human a-synuclein caused Parkinsonism and aggregation of a-synuclein in the brain and gut. Alternatively, these mice do not display signs of Parkinsonism when they are raised in anti-bacterial environments or are given broad-spectrum antibiotics. The bacterial composition of the gut may influence disease pathogenesis due to the possible interaction between gut microbiota and microglia. This may even be associated with specific clinical parameters. In comparison with healthy individuals, PD patients showed persistent bowel inflammation. Initially, it was found that inflammation stimulated the central nervous system via the vagus nerve in the enteric nervous plexus. It has been investigated whether vagotomies are associated with Parkinson's disease in cohort studies of vagotomized patients. According to both studies, patients who underwent truncal vagotomy may be at reduced risk for Parkinson's disease compared with those who underwent superselective vagotomy. As a result of the compromised BBB, proinflammatory factors from the peripheral circulation as well as other types of activated immune cells were more likely to permeate the brain tissue. To be more specific, researchers examined cytokine and glial marker levels in tissue samples from colon biopsies of PD patients.

Chapter 4

Discussion

A common neurodegenerative disorder that consists of impairment in the dopaminergic synapses in the brain is Parkinson's illness. There is a degradation in motor capabilities caused by dysregulation of the dopaminergic nervous system in the brain. In particular, the loss of dopamine neurotransmission that occurs as a consequence of neurons dying in the substantia nigra pars compacta and in the caudate-putamen in the striatum results in rest tremors, rigidity, bradykinesia, and posture instability. The original description of Parkinson's disease was that it was a movement disorder unrelated to dementia. Despite this, it has since become increasingly apparent that Parkinson's disease affects other dopaminergic, serotoninrgic, and cholinergic pathways beyond the nigraarea. This results in a wide variety of nonmotor symptoms, such as anosmia, constipation, and sleep disturbances, as well as cognitive and psychiatric symptoms, including dementia and depression. It has also been shown that a-syn causes a number of cells in the central nervous system to respond.

According to recent studies, microglia cells along with astrocytes have a minor role to play in the development of Parkinson's disease (Vizziello et al., 2021). However, it appears that neurons themselves are more closely associated with the disease. In order to regulate neuroinflammatory responses triggered by alpha-syn, microglia and astrocytes possess a very significant role. Microglia are responsible for engulfing and removing the majority of the a-syn aggregates that are secreted by the astrocytes. Besides oligodendrocytes, astrocytes contribute to a large role in the formation of neurons. In order for the astrocytes to function as neurons, they must be transformed into them. According to the study reported in Figure 3, microglia, astrocytes, oligodendrocytes and neurons possess an influential effect on the development of Parkinson's disease (PD).

An attractive research direction on PD is to understand what occurs within neurons prior to their production of a-syn and to transfer neurons into a multi-cell structure. In the future, it will be critical to understand the molecular mechanisms that initiate Parkinson's disease. This will enable us to prevent and treat the disease. Research during this time period indicates that PD symptoms do not appear to be significant. Due to this, it is crucial to pay attention to the glia roles in the CNS in order to prevent the onset of PD at an early age.

Chapter 5

Conclusion

An oxidative and inflammatory attack on dopaminergic neurons of the substantia nigra, which are located within the brainstem, is particularly harmful. There are many factors that may be caused by such processes. It is likely that PD is due to a dysfunction of the glia, as they are the primary initiators of these processes. The focus of this article is on the effects of glial activity in PD. A robust inflammation is evident in the substantia nigra of Parkinson's syndrome patients with reactive astrocytes and reactive microglia. Normally, glia serves as neuro-protectors, but adverse stimulation can lead to chronic inflammation that is damaging. Since microglia produce superoxide anions and other neurotoxins in large numbers, they may be the main contributors. Multiple animal models of Parkinson's disease have shown their toxicity towards dopaminergic neurons.

References

Angelique di Domenico, G. C.-E.-P.-C. (2019). Patient-Specific iPSC-Derived Astrocytes Contribute to Non-Cell-Autonomous Neurodegeneration in Parkinson's Disease. *Stem Cell Reports*, *12*(II), 213-229. Retrieved from https://doi.org/10.1016/j.stemcr.2018.12.011

Biondetti, E. S. (2021). The spatiotemporal changes in dopamine, neuromelanin and iron characterizing Parkinson's disease. *BRAIN*, 3114-3125. doi:10.1093/brain/awab191

Choi, I. Z. (2020). PruvosMicroglia clear neuron-released alpha-synuclein via selective autophagy and prevent neurodegeneration. *nature COMMUNICATIONS*. doi:10.1038/s41467-020-15119-w

Damisah, E. C. (2020). Damisah, E. C., Hill, R. A., Rai, A., Chen, F., Rothlin Astrocytes and microglia play orchestrated roles and respect phagocytic territories during neuronal corpse removal in vivo. *Sci. Adv.* doi:10.1126/sciadv.aba3239

Devika Agarwal, C. S.-S. (2020). A single-cell atlas of the human substantia nigra reveals cell-specific pathways associated with neurological disorders. *Natural communication*, 1-11.

Dzamko, N. G. (2017). Toll-like receptor 2 is increased in neurons in Parkinson's disease brain and may contribute to alpha-synuclein pathology. *Acta neuropathologica*.

Errea, O. a.-O. (2021). Oligodendrocytes, a new player in the etiology of Parkinson's Disease. *Mov. Disord*. doi:10.1002/mds.28393

Ettle, B. K. (2016). Ettle, B., Kerman, B. E., Valera, E., Gilalpha-Synuclein-induced myelination deficit defines a novel interventional target for multiple system atrophy. *Acta Neuropathol*, 59-75. doi:10.1007/s00401-016-1572-y

Filippini, A. M. (2021). Filippini, A., Mutti, V., Faustini, G., Longhena, F., Ramazzina, Extracellular clusterin limits the uptake of alpha-synuclein fibrils by murine and human astrocytes. *Glia 69*, 681-696. doi:10.1002/glia.23920

Fu, X. D. (2021). Fu, X., Deng, W., Cui, X., Zhou, X., STimespecific pattern of iron deposition in different regions in Parkinson's disease measured by quantitative susceptibility mapping. *Front. Neurol*. doi:Fu, X., Deng, W., Cui, X., Zhou, X., Song, W., Pan, M., et al. (2021). Timespecific pattern of iron deposition in d10.3389/fneur.2021.6311210

Glass, C. K. (2010). Mechanisms underlying inflammation in neurodegeneration. *Cell 140, 918–934.*, 918-934. doi:10.1016/j.cell.2010.02.016

Guo, M. W. (2020). Microglial exosomes facilitate alpha-synuclein transmission in Parkinson's disease. *Brain 143*, 1476–1497. doi:10.1093/brain/awaa090

Hentrich, T. W. (2020). Increased expression of myelin-associated genes in frontal cortex of SNCA overexpressing rats and Parkinson's disease patients. *Aging 12*, 18889–18906. doi:10.18632/aging.103935

Hughes, C. C. (2019). Picomolar concentrations of oligomeric alpha-synuclein sensitizes TLR4 to play an initiating role in Parkinson's disease pathogenesis. *Acta Neuropathol*, 103–120. doi:10.1007/s00401-018-1907-y

Morales, I. S.-S. (2017). Striatal astrocytes engulf dopaminergic debris in Parkinson's disease: a study in an animal model. *PLoS ONE 12:e0185989*. doi:10.1371/journal.pone.0185989

Muqit, S. A. (2022). PTEN-induced kinase 1 (PINK1) and Parkin: unlocking a mitochondrial quality control pathway linked to Parkinson's disease. *ScienceDirect*, 1-9.

Panicker, N. S. (2019). Fyn kinase regulates misfolded a-synuclein uptake and NLRP3 inflammasome activation in microglia. *Exp. Med.*, 1411–1430. doi:10.1084/jem.20182191

Reyes, J. F. (2019). Reyes, J. F., Sackmann, C., Hoffmann, A.Binding of alpha-synuclein oligomers to Cx32 facilitates protein uptake and transfer in neurons and oligodendrocytes. *Acta Neuropathol.*, 23–47. doi:10.1007/s00401-019-02007-x

Rivetti di Val Cervo, P. R.-M. (2017). Rivetti di Val Cervo, P., Romanov, R. A., Spigolon, G., Masini, D., Martin- Induction of functional dopamine neurons from human astrocytes in vitro and mouse astrocytes in a Parkinson's disease model. *Nat. Biotechnol.*, 35, 444–452. doi:10.1038/nbt.3835

Rostami, J. F. (2020). Astrocytes have the capacity to act as antigenpresenting cells in the Parkinson's disease brain. *J. Neuroinflammation*. doi:10.1186/s12974-020-01776-7

Sandeep K. Barodia, L. J. (2019). PINK1 phosphorylates ubiquitin predominantly in astrocytes. *Npj Parkinson's Disease*, 1-9.

Trudler, D. S.-B. (2021). alpha-Synuclein Oligomers induce glutamate release from astrocytes and excessive extrasynaptic NMDAR activity in neurons, thus contributing to synapse. *J. Neurosci.*, 41, 2264–2273. doi:10.1523/JNEUROSCI.1871-20.2020

Tsunemi, T. I. (2020). Astrocytes protect human dopaminergic neurons from alpha-Synuclein accumulation and propagation. *J. Neurosci.*, 40, 8618–8628. doi:10.1523/JNEUROSCI.0954-20.2020

Tu, H. Y. (2021). alpha-synuclein suppresses microglial autophagy and promotes neurodegeneration in a mouse model of Parkinson's disease. *Aging Cell 20:e13522. doi: 10.1111/acel.13522*, 20:e13522. doi:10.1111/acel.13522

Vizziello, M. B. (2021). Disruption of mitochondrial homeostasis: the role of PINK1 in Parkinson's Disease. *Cells 10:3022. doi: 10.3390/cells10113022*, 10:3022. doi:10.3390/cells10113022

Williams, G. P. (2021). CD4 T cells mediate brain inflammation and neurodegeneration in a mouse model of Parkinson's disease. *Brain*, 144, 2047–2059. doi:10.1093/brain/awab103

Xia, Y. Z. (2019). Microglia as modulators of exosomal alpha-synuclein transmission. *Cell Death Dis.*, 10:174. doi:10.1038/s41419-019-1404-9