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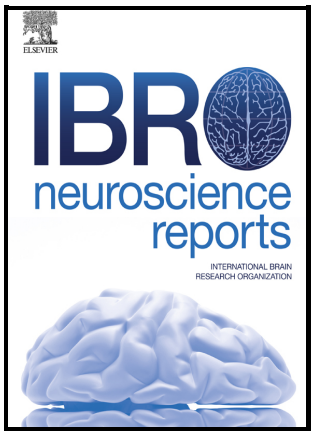

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Neurodegeneration and Inflammation Crosstalk: Therapeutic targets and perspectives

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Abstract

Glia, which was formerly considered to exist just to connect neurons, now plays a key function in a wide range of physiological events, including formation of memory, learning, neuroplasticity, synaptic plasticity, energy consumption, and homeostasis of ions. Glial cells regulate the brain's immune responses and confers nutritional and structural aid to neurons, making them an important player in a broad range of neurological disorders. Alzheimer's, ALS, Parkinson's, frontotemporal dementia (FTD), and epilepsy are a few of the neurodegenerative diseases that have been linked to microglia and astroglia cells, in particular. Synapse growth is aided by glial cell activity, and this activity has an effect on neuronal signalling. Each glial malfunction in diverse neurodegenerative diseases is distinct, and we will discuss its significance in the progression of the illness, as well as its potential for future treatment.

Keywords

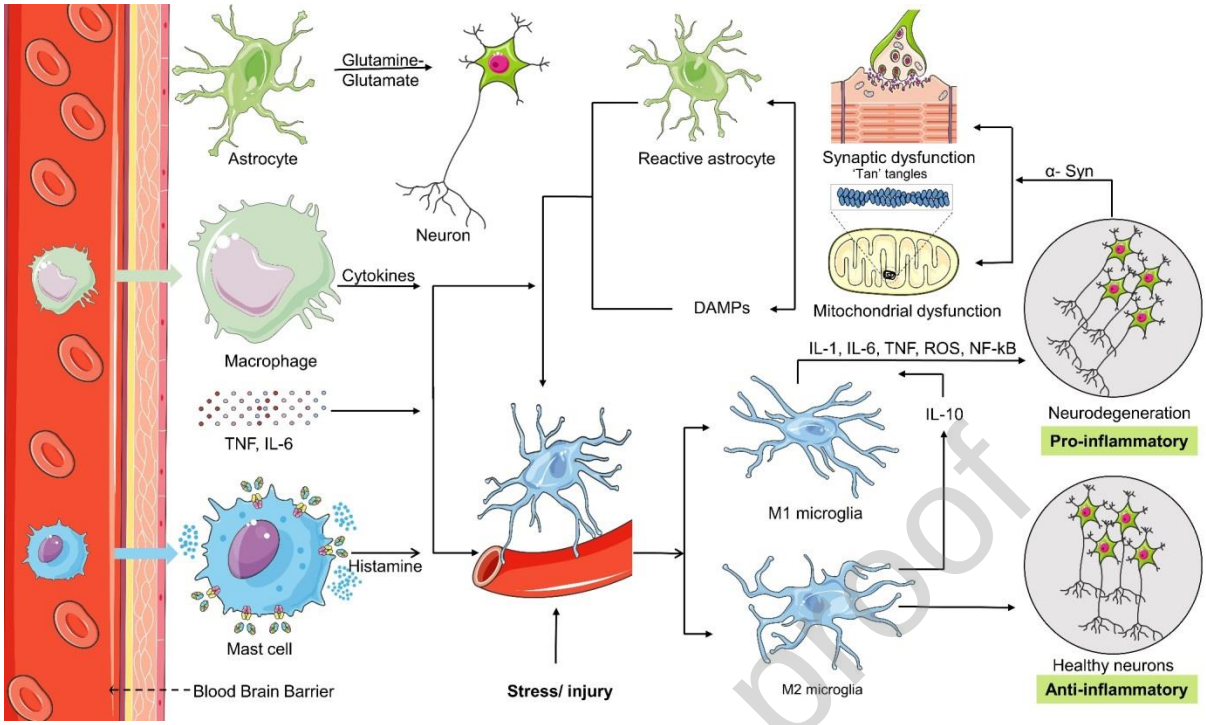
Neurons, Glial cells, Neurodegeneration, Immune system, Microglia

1- Introduction

After half a billion years of evolution, the central nervous system (CNS) evolved into highly intertwined networks of cells, consisting of neurons (the CNS's executive arm) and neuroglia (Verkhratsky and Nedergaard, 2016). Glia are non-neuronal component of the central and peripheral nervous systems that interact through non-electrical impulses, like calcium signaling. This led to the assumption that glial cells' primarily function is to act as "nerve glue" (Virchow, 1860) and perform housekeeping functions for neurons. Nevertheless, recent evidence indicates that glia play critical part in a variety of neuronal functions that extends well beyond housekeeping roles (Araque et al., 1999; Buskila et al., 2019a) Viz: CNS homoeostatic and defensive division. The coordination of the networks is required for the CNS to operate and produce cognitive functions such as behaviour, intellect, emotions, and awareness. Evolutionary specialisation resulted in a functional divide in which neurones are responsible for processing of information and the generation of circuit-mediated behaviour, whereas neuroglia are fully responsible for the nervous system's homeostatic support. Additionally, neuroglia offer protection for the nervous tissue through conserved activation programmes. These diverse roles are mirrored in the physiological differences between these

two cell types. Neuronal signalling is based on rapid synaptic transmission and voltage-gated ion channel-mediated electrical excitability with millisecond range. Glia use regulated variations in internal messengers and ions. For instance, the long-range communication in glial syncytia is due to intercellular fluxes of ions and second messengers, which occurs through the propagation of metabolic or ionic slow waves within seconds (Verkhratsky and Nedergaard, 2018). Receptors and chemical transmission mediate intercellular communication between the two networks. The glial cells' mechanism of secretion differs from synaptic exocytosis. Despite this, they can still regulate the neuronal activity through their secreted ions and signalling molecules (Verkhratsky et al., 2016).

The central nervous system is comprised of a varied population of cells with distinct characteristics that collaborate with neurons to carry out the CNS function. Neurons known as the "brain cells", are responsible for conveying, storing, and processing information. Non-neuronal cells, such as astrocytes, macroglia, and microglia serve additional essential activities in the CNS (Von Bernhardi et al., 2016). Due to their hematopoietic origin, microglia are the major immune source in the nervous system, nourishing and supporting neurons by cleaning neuronal waste and reacting to environmental cues (Rodriguez-Gomez et al., 2020; Elder et al., 2021). Trauma, neurodegenration or infection causes activation of microglia, hence the cells go through rapid reconfiguration involving alterations in function and gene expression, and are attracted to the damage site (Helmut et al., 2011; Streit et al., 2004). Here, they grow and consume injured cells and cell debris (Helmut et al., 2011). Upon activation, microglia generate pro-inflammatory mediators, such as cytokines, interferon (IFN),tumor necrosis factor (TNF), interleukin-6 (IL-6)), reactive oxygen species (ROS), nitric oxide species (NOS), and chemokines (monocyte chemoattractant protein-1-MCP-1) (Graeber et al., 2011), with cyto Anti-inflammatory cytokines (transforming growth factor beta-TGF-), IL-10, and IL-1R, inhibit activation of microglia (Figure 1) (McGeer and McGeer, 2004; Kim et al., 2005). As a result, microglia have been ascribed significant roles in survival of neurons through the control of neuroinflammation, which ultimately contributes to the homeostasis support and limiting the development of neurodegenerative events (Cartier et al., 2014). Astrocytes, like microglial cells, ensure sufficient synthesis and recycling of neurotransmitters and glutamatergic signalling by providing metabolic substrates to neurons (Fellin, 2009; Fiacco et al., 2009; Verkhratsky, 2010); In addition, the astrocytes also interacts with the blood-brain barrier endothelial cells (Yuan et al., 2021) by transporting critical substrates, including oxygen and glucose from the cerebral microvessels to the neurons (Mathiisen et al., 2010).



(Fig. 1) **Role of glial cells in neuroinflammation**: the pro-inflammatory molecules such as Il-6 and TNF can cross BBB and reach the CNS parenchymal tissue. There is a relative connection of astrocytes to the blood brain barrier. Astrocytes support neurons via glutamate-glutamine system. Mast cells secrete abundant pro-inflammatory cytokines like histamine that can induce some changes in microglia. Resting microglia can then be activated into two classical subtypes. M1 and M2 microglia transform make their action through some secretions. M1 microglia can produce pro-inflammatory cytokines that contribute to dopaminergic neurons dysfunction in the presence of INFγ and LPS. Degenerated neurons can produce α-Synuclien (α-Syn) and reactive oxygen species (ROS) cross talking with microglia and astrocytes in a non-terminating loop of neuroinflammation. α-Synuclien and ROS cause mitochondrial and synaptic dysfunction due to the accumulation of misfolded tau tangles and oligomers. Contrary, Il-4 and Il-13 induce activation of M2 microglia that downregulates M1 function by releasing Il-10 cytokines thus maintain healthy neurons and anti-inflammatory state.

2- Multifaceted Interactions Between Glial Cells and Neurodegenerative Disorders

A significant role in neuropathology is played by the homeostasis and defense capabilities of neuroglia. Each and every form of neurological disease is affected in one way or another by the presence of glia. When astrocytes are damaged, they go through a variety of changes, from pathological remodelling to atrophy/degeneration and eventually astrogliosis (Verkhratsky et al., 2013; Sofroniew, 2014b; Pekny et al., 2016; Verkhratsky and Parpura, 2016). Astrogliosis can result in a variety of reactive phenotypes with either neurotoxic or neuroprotective properties (Pekny and Pekna, 2014; Sofroniew, 2014a; Liddelow et al., 2017). Damage or pathogen-associated molecular patterns may trigger a range of neuroprotective and neurotoxic phenotypes in the microglia, which are constantly searching the brain for damage or pathogen-associated molecular patterns (Kettenmann et al., 2011; Salter and Stevens, 2017). Affectionately known as "NG2 glies," oligodendroglia and their progenitors react to illness by proliferation, Wallerian degeneration, and myelination (remyelination) (Sun et al., 2010; Catenaccio et al., 2017). These cells, collectively known as

macroglia, are made up of astrocytes and other brain-resident cells, such as oligodendrons and neurogranin-2 (NG2-glia), together with ependymal cells, whereas microglia are the brain's resident phagocytes (CNS). There are several kinds of glial cells in the central and peripheral nervous systems, each of which has a distinct role in regulating the brain's function. Astrocytes and microglia will be the focus of this review.

Since time immemorial, glial cells have been seen as just background players to the neuronal performance. In contrast, recent studies have shown that glial cells are involved in several brain functions, both in health and disease. It was the goal of this review article to provide an overview of recent discoveries in glial biology and its connection to neurodegenerative illnesses. Neuroinflammation and degeneration of the CNS, as well as the development of these disorders, have been associated to the microglial activation. Researchers believe non-neuronal cells in the brain play a vital role when it comes to influencing the operation of neuronal networks. In the early stages of neurodegenerative diseases, the involvement of astrocytes, microglia, oligodendrocytes, and their progenitors and invading immune cells was seen as a subsequent adaptive response to the disease-specific neuronal pathology. Other non-neuronal cells and glial cells seem to be affected directly by neurodegenerative stressors, therefore increasing neuronal dysfunction (Taylor et al., 2016; De Strooper and Karran, 2016). A wide range of neurodegenerative illnesses may now be targeted by dissecting fundamental sickness from secondary processes in a number of cell types, which has opened up new avenues for treatment.

The hallmarks of alpha-synucleinopathies are the misfolding, aggregation, and accumulation of the Alpha-Syn protein generated by the Alpha-Syn gene (SNCA) (Peng et al., 2018). Alpha-Syn-related illnesses include MSA, Parkinson's disease, and dementia with Lewy bodies (DLB) (Spillantini and Goedert, 2000; Geodert et al., 2017). SNPc dopaminergic neurons in the SNPc dopaminergic neurons of PD have neuronal alpha-Syn inclusions in the form of neuronal Lewy bodies (LB), as well as Lewy neurites (LNs). In DLB, the substantia nigra and locus coeruleus, as well as the amygdala and the peripheral nervous system, are filled with LBs and LNs. Because the symptoms of PD and DLB are so similar, it may be difficult to distinguish the two conditions (Morra and Donovick, 2014, McKeith et al., 2005; Nakatsuka et al., 2013). MSA (Multiple Sclerosis Atrophy) includes argyrophilicglial cytoplasmic inclusions (GCIs) in the oligodendrocytes, which may cause symptoms such as Parkinsonism, Dysautonomia, motor dysfunction, and cerebellar ataxia. Motor symptoms in MSA are divided into two categories: the cerebellar (MSA-C) and the parkinsonian (MSA-P) variations (Wenning et al., 2008).

Atypical parkinsonian syndromes are neurodegenerative illnesses characterized by intracellular amyloidogenic protein accumulation. DLB, MSA, and PD are characterized by the abnormal deposition of the protein a-synuclein (and are therefore known as synucleinopathies); in PSP and CBD, the tau protein causes damage, and these entities are therefore known as tauopathies (Dickson, 2012; Jellinger, 2008). In PD and DLB, neurons have a-synuclein aggregates, but in MSA, oligodendrocytes are largely affected. Tau aggregates influence neurons, oligodendrocytes, and astrocytes in PSP and CBD. The morphology of astrocytic tau deposits differentiates PSP and CBD. Typically, the various disease entities affect particular regions of the brain. The misfolding and aggregation of these proteins can, on the one hand, lead to the degeneration of the affected cell populations and, on the other hand, facilitate their spread into anatomically connected regions of the brain, thereby facilitating the progression of the disease. In order to halt the progression of these

currently incurable disorders, a better understanding of the pathophysiology enables the development of new causally-oriented treatment strategies.

On the basis of neurological-psychiatric symptom constellations and MRI results, atypical parkinsonism has for a long time attempted to diagnosis molecular-neuropathologically defined disease entities. The correlation between the clinical syndromes and patterns of regional cerebral atrophy and functional impairments confirmed by nuclear medical techniques is strong. As it turns out, however, distinct molecular pathologies can cause syndromes and imaging results that overlap. CBS, for instance, may be caused by CBD, PSP, or other underlying diseases (Armstrong et al., 2013). In contrast, PSP disease may appear in a variety of symptoms (Respondek et al., 2014). Consequently, symptoms often do not permit appropriate identification to a specific disease entity. Since recognized medicines try to alleviate symptoms by modulating neurotransmitters, a syndromal categorization has been adequate for therapeutic practice. However, current treatment methods are inadequate in terms of symptom management and do not slow the progression of the illness. Fortunately, remarkable insights into illness processes have been acquired in recent years, allowing for the clinical investigation of causative treatment approaches. Modulators of pathogenic protein misfolding include Anle138b and antibodies to alpha-synuclein or tau (Wagner et al., 2013; Castillo-Carranza et al., 2015). However, interventions targeting identified molecular target structures need a molecular pathology-based diagnosis to prove the existence of the molecular target structures for causative treatment in the specific patient. Define and diagnose neurodegenerative illnesses on the basis of their molecular pathology, and not on the basis of clinical symptoms as entities. On this basis, it is to be commended that new diagnostic tools, such as tau-PET, have been developed. Thus, diagnostic use may be made of molecular processes that were previously detectable only via neuropathological investigation, such as deposits of the tau protein. We may thus be confident that significant advances will be made in the treatment of these quickly advancing, deadly illnesses in the future years.

3- Microglia in PD and DLB

Glial dysfunction, such as reactive microgliosis and astrogliosis, has been linked to alpha-synucleinopathies. Parkinson's disease (PD) pathogenic processes have been connected to microglial activation and have been demonstrated to correlate with the severity of the illness (Ouchi et al., 2005; Gerhard et al., 2003). There is an abundance of microglial activation and gliosis in the brains of people with Parkinson's disease (Imamura et al., 2003). Positron emission tomography (PET) imaging utilizing a microglia activation marker (171(R)-PK11195-PET shows that microglial activity in the brains of PD patients correlates with PD pathological processes (Ouchi et al., 2005; Gerhard et al., 2006; Iannaccone et al., 2013). Similar to wild-type alpha-Syn, animals expressing alpha-Syn exhibit early activation of microglial cells (Su et al., 2008). An investigation of DLB patients' central and peripheral inflammatory changes using 171(R)-PK11195-PET shows increased microglia activation in various brain areas, including those linked to cognition (Surendranathan et al., 2018; Kohl et al., 2017). In DLB patients, there is a strong link between cognitive scores and microglial activity (Surendranathan et al., 2018). A buildup of pathogenic alpha-Syn causes abnormal activation of microglial cells, which in turn causes neurotoxicity and neurodegeneration (Zhang et al., 2005; Bliederhaeuser et al., 2016). Injecting alpha-Syn fibrils centrally into the SNpc of rats induces microglial activation, peripheral immune cell infiltration into the SNpc, progressive dopaminergic cell death, and striatal degeneration (Bliederhaeuser et al., 2016). (Harms et al., 2017). In vitro and in vivo, microglia, monocytes, and macrophages respond to alpha-Syn fibrils with a persistent MHCII response (Harms et al., 2017). Because microglia

include TLRs (Toll-Like Receptors), neurons that release alpha-Syn may trigger inflammatory responses through the microglia, ultimately leading to neuroinflammation (Kim et al., 2013). Neuronal alpha-Syn stimulates microglial TLR4, which in turn induces transcriptional upregulation of p62/SQSTM1 (Ubiquitin-binding protein p62/Sequestosome 1) through the NF-kB signaling pathway, as shown by recent study (Choi et al., 2020).

Animals lacking TLR4 treated with human alpha-Syn did not raise p62 mRNA or protein in microglia (Choi et al., 2020). NLRP3 (LRR, pyrin domain-containing protein 3, and NOD) inflammasome complex signaling through TLR2 is also triggered by pathogenic alpha-Syn fibrils, leading to activation of caspase-1 and release of IL-1b in microglia (Codolo et al., 2013; Gordon et al., 2018). The microglial expression of ASC and cleaved caspase-1 (p20) is increased in the SN of postmortem Parkinson's disease patient brains and numerous preclinical Parkinson's disease animal models (Gordon et al., 2018). Alpha-Syn-related diseases and dopaminergic neuron loss are reduced in vitro and vivo when the NLRP3 inflammasome is inhibited (Gordon et al., 2018). Dopaminergic neuronal death is prevented by autophagic degradation of NLRP3 inflammasomes in rats injected with MPTP-PD (1-methyl 4-phenyl-1,2,3,6 tetrahydropyridine), SNpc LPS (Lipopolysaccharide), or both (Han et al., 2019). Primary microglial cells have also been shown to express the CD36 (Cluster of differentiation) scavenger receptor, which has been linked to alpha-Syn-induced microglial inflammation (Su et al., 2008). It is necessary for tissue injury and healing that CD36 belongs to the PRR family. The TLR/NF-kB/NLRP3 inflammasome signaling pathway is activated in macrophages when CD36 binds with oxLDL (Lamkanfi et al., 2012; Kunz et al., 2008). Alpha-synucleinopathies are linked to CD36 deficiency because primary microglia cultures from CD36-deficient mice show lower inflammatory response to recombinant ha-Syn compared to controls (Su et al., 2008). Accumulated alpha-Syn induces microglial activation and neurodegeneration through NADPH-oxidase-dependent oxidative stress in primary mouse and rat midbrain cultures (Zhang et al., 2005). Microglia phagocytose alpha-Syn aggregates produced by SNPc dopaminergic neurons, activating microglia, generating inflammatory mediators and neurotoxicity (Zhang et al., 2005). Matrix metalloproteinase 3 (MMP3), an ECM degradation protease that induces microglial activation, follows ROS/RNS release and neuronal death in dopaminergic (DA) neurons that are degenerating or have perished. MMP3-deficient mice' microglial activation and nigrostriatal neurodegeneration are reduced after MPTP injection (Kim et al., 2005; 2007).

Microgliosis and Parkinson's disease are linked to pathogenic alpha-Syn, a dark pigment present in neurons, as well as neuromelanin (NM). catecholaminergic neurons, such as dopaminergic and epinephrinergic neurons, are the only ones that respond to the neurotransmitter NM (Fedorow et al., 2005). In the formation of melanin, tyrosinase is the most important enzyme (Simon and Pele, 2009). Differently colored SNPc dopaminergic neurons in Parkinson's disease (PD) are vulnerable to degradation (Hirsch et al., 1988; Kastner et al.,1992). Neurons with a high concentration of melanin are more vulnerable than those with a low concentration of melanin (Hirsch et al., 1988; Kastner et al.,1992). Administration of NM particles to primary microglia causes stimulation of the cells and subsequent generation of reactive oxygen and nitrogen species (RONs) and inflammatory cytokines and (Zhang et al., 2011). NM injection into the rat SNPc causes microglial activation and dopaminergic neuron death in a similar manner (Zhang et al., 2011). Studies by Carballo-Carbajal and colleagues show that overexpression of human tyrosinase using AAV vectors produces microgliosis, proteostasis failure, and progressivenigrostriatal dementia in the SNPc of rats (AAV-hTyr) (Carballo-Carbajal et al., 2019).

4- Specific Cytokine Signalling in Parkinson's Disease (PD)

Following the activation of microglia, the production of cytokines IL-1, IL2, IL-1, TNF-, IL-6, TGF-, and IFN has been linked to the degeneration of DA neurons in SNpc (Karpenko et al., 2018). Increased levels of pro-inflammatory cytokines are evidence of an immune system response to DA neuronal injury, as shown by their detection. Studies examining the CSF and peripheral blood of PD patients revealed higher serum IL-1 and IL-6, as well as elevated CSF TGF (Imamura et al., 2005). Moreover, the mRNA expression of IL-6 was reported to be considerably elevated in the hippocampus of PD patients who also suffered from dementia (McCoy et al., 2006). Moreover, in the case of TNF, the injection of recombinant dominant-negative TNF inhibitorXENP345 inhibits soluble TNF signalling, resulting in about 50% recovery of DA neurons in numerous animal model investigations (Elyaman and Khoury, 2017). IL9 is another major cytokine involved in the pathophysiology of Parkinson's disease. Depending on the situation in which it is generated and the type of the generating cells, IL9 is a pleiotropic cytokine having pro-inflammatory and regulatory roles. IL9 regulates the functioning of several immunological and central nervous system cell lines (CNS). Notably, neurodegeneration and autoimmune CNS disorders have been related with Th9 cells/IL9 signaling (Elyaman et al., 2009). The significant difference between IL9 and other cytokines is its neuroprotective activity and support for repair processes (Picca et al., 2020). Recent findings of lower IL9 serum concentrations in PD patients may indicate a dysregulation in IL9 signalling that leads to reduced neuroprotective ability in PD (Deleidi and Gasser, 2013). Therefore, it seems that the pattern of systemic inflammatory markers in individuals with PD (i.e., lower levels of IL9 and greater quantities of CRP, MIP-1, and TNF-) demonstrates the presence of a unique inflammatory signature (Tang et al., 2014). In addition, the levels of these markers correspond with the clinical stage of the illness, demonstrating that peripheral inflammation contributes to the development of PD (Imamura et al., 2005).

5- Astrocytes and NDG

Astrocytes are subtype of specialized glial cells in the CNS that involved in neuronal homeostasis including gliotransmission (Bezzi et al., 2004), transfer of glucose, ATP, ions, gliotransmitters, and amino acids (Orellana and Stehberg, 2014). Astrocytes also involved in other functions that are vital for the maintenance of healthy brain such as regulation of blood-brain barrier and cerebral blood flow (Abbott, 2002), modulation of neuronal communication (Halassa et al., 2010) through synaptic plasticity (Singh and Abraham, 2017), and also act as innate immune cells in the brain (Cunningham et al., 2018). The heterogeneity of astrocytes has been well indicated in different genetic compositions (Zhang et al., 2020), age groups (Mathias et al., 2019), disease conditions (Trias et al., 2018), and even significant differences are seen between the *in vivo* and *ex vivo* cultures of astrocytes (Cahoy et al., 2018). In line with this, more recent findings revealed profound differences in the electrophysiology, morphology, and cell signalling in different neuronal circuits, such as the striatum and hippocampus (Chai et al., 2017). In pathological conditions, six different forms of astrocytes have been recognized. For instance, in primary tauopathies, globular, plaques, ramified, and tufted astrocytes are abundant. Whereas, the granular fuzzy and torn-shaped astrocytes are more dominant in aging-related tau (ARTAG) tauopathies (Meldolesi, 2020). The morphological changes along with the accompanied discrepancies in the communications with neighbouring cells influence neuroinflammatory responses and pathophysiology of diseases (Meldolesi, 2020).

5.1. Countless faces of Astrocytes in Alzheimer's Disease

Over a century ago, Alois Alzheimer coined the term "Alzheimer's disease" to describe the most familiar form of dementia in the world. Alzheimer's disease affects millions of people throughout the globe and is expected to cost the health care system $500 billion a year (Takizawa et al.,2015). Today, FDA-approved treatments for Alzheimer's disease (AD) improve quality of life, however they do not stop or change AD's course (Alzheimer's Association, 2020).
AD's pathophysiology is unclear at this time, and current treatment options are ineffectual. Neurofibrillary tangles, which are made up of hyperphosphorylated tau protein, are the hallmarks of the disease's progression (Gong and Iqbal, 2008). In order to learn more about these aberrant indications, scientists have focused on neurons. A century before this, Ramon y Cajal had eloquently expressed these pathogenic traits (Garcia-Marin et al., 2007). Reactive hypertrophic astrocytes encircling blood vessels with amyloid deposits and senile plaques were also seen in deceased AD patients by Ramon y Cajal (Garcia-Marin et al., 2007). In other words, astrocytic changes in neurodegeneration are not a new phenomenon. However, the significance of astrocytes in the development of AD has yet to be fully understood. This stalemate was most likely caused by a lack of technology and processes. Because of new breakthrough technologies, there is an increased interest in describing the pathophysiological changes taking place in astrocytes throughout the development of AD. Neurotransmitter buffering and ion homeostasis are only some of the many functions they play in the central nervous system, which also includes synaptogenesis and BBB and inter/intracellular communication. Astrocytes, on the other hand, are a diverse group of cells with regionally specialized phenotypes and activities (Khakh and Deneen, 2019; Huang et al., 2020). Astrocytes' specific roles in neurodegenerative disease are being studied extensively at the time (Khakh and Denee., 2019; John et al., 2017).

Astrocytes have been investigated in the genesis and progression of AD in several studies. Understanding the evolution of astrocytes and their biomarkers in AD has been made possible by the advent of new technologies, including single-molecule imaging and single cell RNA sequencing (Bayraktar et al., 2020). We now know a lot more about how reactive astrocytes change into different molecular states as Alzheimer's disease progresses because to transcriptome studies (Escartin et al., 2021). According to our previous findings, scRNAseq investigation of AD model-derived reactive astrocytes revealed several stages-dependent conditions or subpopulations of astrocytes (Grubman et al., 2019; Mathys et al., 2019; Zhou et al., 2020). As a result of these discoveries, it is vital to describe the function and wide diversity of reactive astrocytes in each of their unique stages in order to get a knowledge of their particular involvement in developing Alzheimer's disease (AD) (Grubman et al., 2019; Mathys et al., 2019). As a consequence, it's more difficult to determine whether reactive astrocytes in Alzheimer's disease are beneficial or detrimental. By gaining a better understanding of the molecular changes occurring in individual cells, we can determine when therapeutic intervention against reactive astrocytes is most effective in slowing or stopping the progression of Alzheimer's disease (AD) and its associated symptoms. Transcriptomics in conjunction with sophisticated technologies like as viral gene transfer, electrophysiology, and optogenetics may help to uncover more about the reactive astrocyte activities in Alzheimer's disease (AD). (Escartin et al., 2021; Yang et al., 2017). Long non-coding transcripts (lncRT) are yet to be elucidated in the pathophysiology of Alzheimer's disease (AD) (Cuevas-Diaz et al., 2019; Duran et al., 2017). Currently, research shows that lncRNA regulates tau hyperphosphorylation, and it has also been reported that lncRNA might be a potential biomarker for AD (Fotuhi et al., 2019). These results show that long noncoding RNAs have significant promise as both diagnostic and therapeutic targets for Alzheimer's disease.

The utilization of suitable in vitro and in vivo experimental models is another critical part of unraveling the pathophysiological processes underlying Alzheimer's disease and discovering therapy targets that are feasible. There is a significant loss of spatial information when mRNA samples are separated (Chen et al., 2020). Similarly, the morphology and transcriptomes of human and mouse reactive astrocytes were shown to be very different (Esccartin et al., 2021). As this study shows, in vitro and animal models of AD have intrinsic limitations, and interpreting findings from studies compared to post-mortem data may be problematic. More and more scientists are turning to human induced pluripotent stem cells to fill up these research holes (Esccartin et al., 2021). Another way to keep cellular spatial information safe is to use a combination of genomic methods such as in situ sequencing and spatial transcriptomics (Chen et al., 2020). Finally, gaining agreement on important research models and combining different "omic" methodologies may lead to better diagnostic and therapeutic targets for reactive astrocytes.

5.2. Astrocytes biomarkers in AD and *PD*

Chitinase-3-like protein (YKL-40), glial fibrillary acidic protein (GFAP), and blood S100B levels were found to be significantly increased in the cerebrospinal fluid (CSF) from individuals with Alzheimer's disease (AD) (Bellaver et al., 2021). Dementia severity has long been linked to CSF GFAP levels (Fukuyama et al., 2001). Even yet, several previous studies have identified no significant change in GFAP levels between AD patients and controls (Olsson et al., 2016). Plasma GFAP has recently been linked to both long-term amyloid- PET and cognitive decline, indicating that plasma GFAP is an early indication of brain amyloid-pathology (Pereira et al., 2021). Adding credence to this, plasma GFAP levels were shown to be increased in both cognitively normal and AB-positive older persons with moderate cognitive impairment (Chatterjee et al., 2021). (Benedet et al., 2021).

Like GFAP, YKL-40 was shown to be overexpressed in Alzheimer's disease (Querol-Vilaseca, 2017), but not in dementia with Lewy bodies (DLB) (Craig-Schapiro et al., 2010). (Llorens et al., 2017). White matter and cerebral cortex in AD were discovered to have YKL-40-positive astrocytes, which were also observed in clusters, around -amyloid plaques, and in the vicinity of arteries with -amyloid angiopathy (Llorens et al., 2017). It has also been shown to be high in individuals with vascular dementia, late-onset Alzheimer's disease (Mecocci and colleagues 1995; Chaves and colleagues 2010), and non-AD people with pathological levels of P-tau (Mecocci and colleagues 1995; Chaves and colleagues 2010). (Hov et al., 2017).

Plasma GFAP, plasma A1–42/A1–40 ratio, and generally related AD risk variables including sex, age, and APOE 4 carriage were used to identify the A and A+ people with 80% specificity and 90% sensitivity (Chatterjee et al., 2021). GFAP in CSF had lower sensitivity and specificity in the identification of amyloid-B positive, according to a second research investigation. CSF amyloid-42/40 and amyloid—PET were more reliably detected by plasma GFAP in individuals with an AUC more than 0.75 in cognitively normal, cognitively impaired, and non-AD patients compared to those with an AUC less than 0.75. (Pereira et al., 2021). In accordance with this, previous studies have shown that individuals with moderate cognitive impairment, subjective cognitive complaints, and AD-induced dementia had an AUC greater than 0.75. (Verberk et al., 2020). CSF YKL-40 AUC was different across patients with and without Alzheimer's disease (AD), with people with and without cognitive impairment registering 0.735, 0.639, and 0.585 respectively (Pereira et al., 2021). The AUC

value of YKL-40 was 0.77 in the setting of differential diagnosis in neurodegenerative dementias to distinguish between dementia and normal control groups (Llorens et al., 2017).

Switching the gear towards PD, in the past decade, the scientific community has struggled to identify appropriate biomarkers to identify people at risk for Parkinson's disease and patients in preclinical stages. Unfortunately, PD is a syndrome with multiple clinical subtypes and a highly variable disease course, necessitating the use of diverse clinical, genetic, biochemical, and imaging biomarkers (Fardell et al., 2018). Numerous promising biomarkers have been proposed thus far as a result of research into neuroinflammation and PD. Polymorphisms in genes associated with inflammation, such as LRRK2, S100B, and NURR1, were found to increase the risk of Parkinson's disease (Grime et al., 2006;Betarbet et al., 2005). Consequently, this could be utilized to develop biomarkers for the prognosis and/or diagnosis of PD by measuring the expression levels of their inflammatory proteins in CSF. Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is a deubiquitinating enzyme that regulates the metabolism of other brain proteins, primarily by removing neuronal proteins that are excessive, oxidized, or misfolded (Mondello et al., 2014). Therefore, UCH-L1 prevents the aggregation of intracellular Lewy bodies, whereas UCH-L1 deficiency or dysfunction reduces a-synuclein degradation. An apolipomorphism (S18Y) in its gene has been linked to protection against sporadic Parkinson's disease, providing a distinct antioxidant protective function (Mondello et al., 2014). Moreover, studies have demonstrated a significant decrease in UCH-L1 concentrations in the CSF of PD patients compared to normal controls and other parkinsonian syndrome patients (Brdy et al., 1965). Patients with PD had the lowest levels of CSF UCH-L1, a finding that could serve as a diagnostic marker for PD. As there is a strong positive correlation between these two proteins, the CSF a-synuclein levels could also be measured to increase the specificity of the biomarker.

Beta-Glucocerebrosidase (GCase) is a lysosomal hydrolase that plays a crucial role in alpha-synuclein breakdown (Hruska et al., 2008); it is encoded by the GBA1 gene. Loss-of-function mutations in GCase cause Gaucher disease (GD), a rare autosomal recessive lysosomal storage disorder (Tayebi et al., 2003), which is a clinical association that established the relationship between GD and parkinsonism (Sidransky, 2005). Specifically, it was shown that a subgroup of individuals with Gaucher disease acquired parkinsonian symptoms, and that the frequency of Parkinson's disease (PD) was greater among relatives of GD patients (Mazzulli et al.,2011). The development of synucleinopathies is correlated with mutations in the GCase gene (GBA1) that result in a loss of function and changes in sphingolipid metabolism. The functional loss of GCase affects lysosomal protein degradation, elevates alpha-synuclein levels in brains, and causes neurotoxicity through aggregation-dependent processes (Parnetti et al., 2014). Both dysfunctional lysosomes and alpha-synuclein aggregation seem to contribute to the etiology of Parkinson's disease (PD). Studies suggested that the combination measurement of oligomeric a-synuclein/total a-synuclein and beta-Glucocerebrosidase activity might increase the accuracy of PD diagnosis and emphasize the necessity for numerous distinct biomarkers to be successful in the early identification of PD patients (Mohan et al., 2017).

CCL28 (Mucosae-associated epithelial chemokine; MEC) is a second molecular biomarker that has shown useful for identifying neuroinflammation and for diagnosing Parkinson's disease. Chemokine CCL28 is constitutively expressed in mucosal tissue and moderately expressed in the small intestine, kidney, and brain: in neurons as opposed to glial cells (Liu et al., 2012; Santaella et al., 2020). It seems to connect the innate and adaptive immune

responses; the C-terminus is antimicrobial while the N-terminus regulates lymphocyte movement. In a recent research (Gur-Wahnon et al., 2013), CCL28 was the sole biomarker that was increased in PD patients compared to controls. The elevated levels in CSF may be consistent with the theory that viral and microbial infections as well as altered gut-microbiota increase the risk of Parkinson's disease (PD) or may even be an early trigger of the disease. The production of CCL28 by degenerating neurons is another potential cause of high levels of CCL28 in CSF.

5.3. Astrocytes transplantation as a therapeutic tool

A new therapy category, cell treatments, encourages the regeneration of damaged tissues. transplantation of GRP (glial-restricted progenitors)-derived human astrocytes improved neuronal regeneration and functional recovery in patients with dementia. Additionally, stem cells seem to be a viable option. stem cells and progenitors such as GRPs, which can differentiate into astrocytes, have been discussed in several studies as potential sources of cellular transplants or the ability of stem cells to interact with host astrocytes and enhance their own defense mechanisms (Colangelo et al., 2014; Hastings et al, 2022). (Hastings et al., 2022). These stem cells may move to the injured region, develop into astrocytes, and offer neuroprotection by lowering microglial activation levels and tolerating GLT-1 levels in the spinal cord, as previously reported.

Neurodegenerative disorders such as Parkinson's disease, ALS, and Huntington's disease have been effectively modelled using cell grafting methods. In an HD model, for example, astrocytes overexpressing BDNF with the control of the GFAP promoter were shown to be neuroprotective. Reprogramming stem cells into astrocytes has recently emerged as a novel method for replacing astrocytes that are faulty; nevertheless, more investigations are needed to determine the therapeutic and side effects of cell treatment (Colangelo et al., 2014). Transgenic mice suffering from ALS and Parkinson's disease were improved by the in-vivo implantation of precursors designed to increase the production of glial cell line-derived neurotrophic factor (GDNF) (PD). Valori et al. (2021) say this.

In addition, healthy astrocyte transplantation may decrease the progression of ALS, Parkinson's disease, Alzheimer's disease, and traumatic CNS damage in translational models (Hastings et al., 2022). Motor neurons may be preserved in many ways thanks to astrocytes, which makes them a possible therapeutic option for the treatment of neurodegenerative illnesses, since they may enhance treatments that might halt or even prevent the course of these diseases (Figure 2). As oligodendrocytes and astrocytes mature, glial-restricted progenitors are abundant in the embryonic spinal cord and may self-renew and differentiate. Neural stem cells (NSCs) are an attractive source for creating astroglial cells as well due to their multipotency and strong self-renewal capacity. In the developing and adult brains, NSCs are a naturally occurring population of cells. Their primary sources are the embryonic and adult subventricular zones of the cerebral cortex (Nicaise et al., 2015).

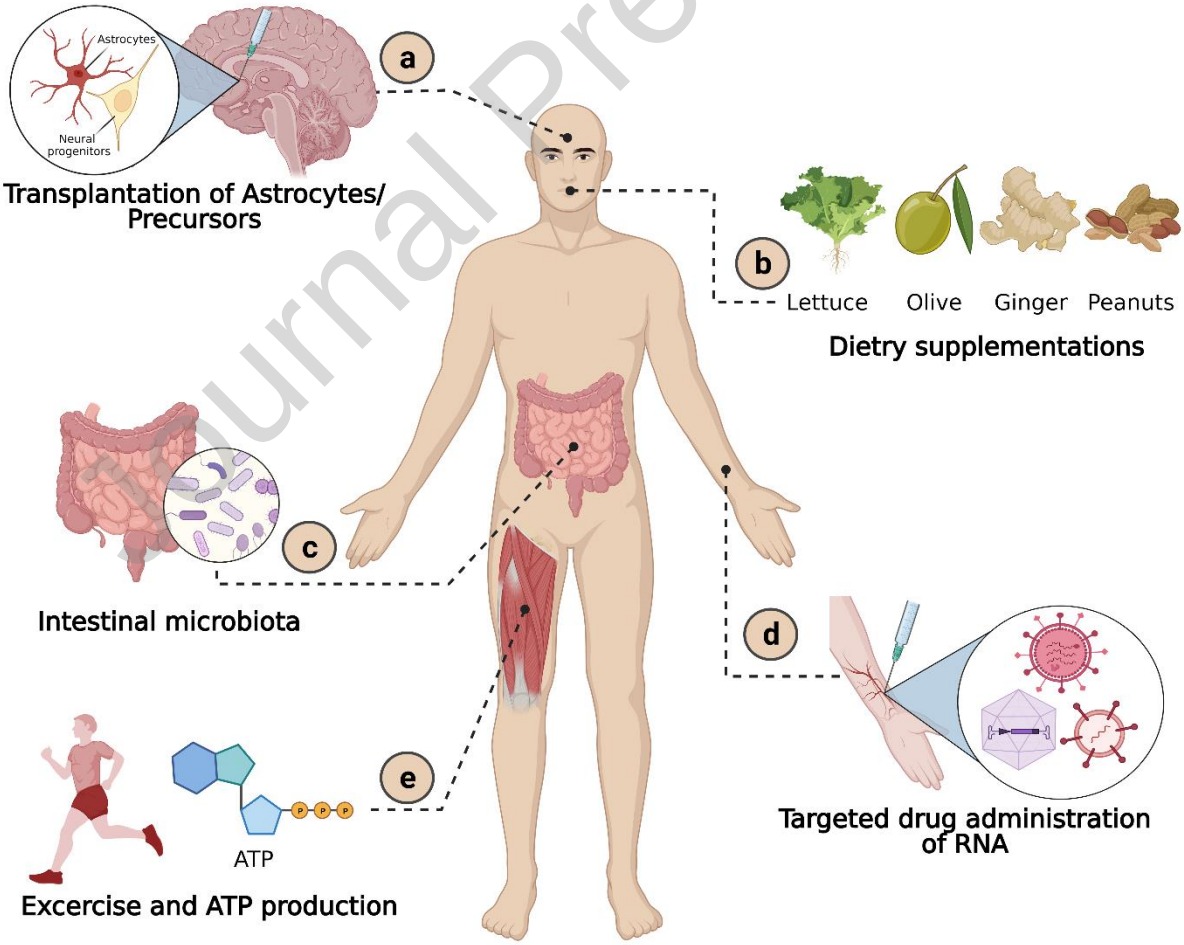
It has been shown that graft site is critical in ALS transplantation of astrocytes and their progenitors (Hastings et al., 2022). Autologous cell sources are a viable option for human astrocyte transplantation therapy because of the absence of ethical problems and the decreased risk of rejection (Hastings et al., 2022). They can replace necroptotic astrocytes, reduce inflammation and astrocytosis, produce protective secretions (such as anti-inflammatory cytokines) and membrane-bound vesicles, reduce toxic compound deposition, such as protein aggregates and elevated glutamate, potassium and calcium levels, and act as stem cell-like cells with neurogenic potential (Hastings et al., 2022). For this aim, we've identified three key cell sources that may be used:

Human embryonic astrocyte precursors are carefully sourced. For example, this source has been employed in transplantation studies for Parkinson's disease patients.

2. Cells that have not yet differentiated but are nonetheless very viable

Patients' own fibroblasts or mesenchymal stem cells are extracted and cultured to produce astrocyte-lineage cells ready for transplantation in an autologous cell transplant (Hastings et al., 2022).

After being transplanted into mouse spinal cords, Baloh and colleagues revealed that human iPSC-derived neural progenitors may survive and develop into a broad variety of supplemental interneurons, including astrocytes (Baloh et al., 2018). When these cells are activated with growth stimuli, they produce glial-restricted progenitor cells that can differentiate into astrocytes and oligodendrocytes (Lepore et al., 2011). Scientists have shown that transplanting healthy astrocytes into a brain damaged by illness may not only restore normal function, but it can also avoid the neuroinflammation that would otherwise result from the introduction of the new cells (Valori et al., 2021). Valori and colleagues found that either astrocytes modified to produce high levels of L-3, 4-dihydroxyphenylalanine (DOPA) or healthy glial cell progenitors in models of ALS, dementia with Lewy bodies, and subcortical white matter stroke had a favorable influence on disease progression and survival. In the work of Nicaise et al (Valori et al., 2021).



(Fig. 2) several possible strategies for increasing astrocyte protective activities toward neurons can be proposed such as: (a) the transplantation of astrocytes or their precursors can provide therapeutic benefits. (b) incorporating antioxidant-rich foods in one's diet, such as peanuts, ginger, olive, and lettuce, (c) controlling one's gut microbiota and bacterial load, (d) abnormal pathways can be precisely targeted by using advanced delivery systems, such as nanoparticles, peptides, or viruses, to deliver drugs or nucleic acids into astrocytes and correct the altered signalling cascades, and (e) engaging in regular physical activities to generate more ATP, In the case of neurodegenerative diseases, where astrocytes themselves degenerate. (Created using BioRender.com.)

6- Microglia-Astrocytes crosstalk in NDG

As we get older, our glial cells experience a great deal of change. There have been significant changes in the quantity, shape and expression of microglia, and their capacity to phagocytize (Streit et al., 2004, Hart et al., 2012; Perry et al., 1993). The buildup of lipofuscin, lipid droplets and other detritus in the glial intracellular composition has also been shown (O'Neil et al., 2018; Marschallinger et al., 2020; Tremblay et al., 2012;2016) with age. Microglial dysfunction has been connected to these phenotype abnormalities, which are characterized by a decreased ability to scan the surrounding tissue, a deficient synaptic activity, and a lack of damage recovery (Delage et al., 2021). In addition, aging astrocytes are less able to promote the delivery of metabolites to neurons, which reduces neuronal survival (Simpson et al., 2010). The glutamate-aspartate transporters and glutamine synthetase concentrations are also lower in senescent astrocytes than in young ones (Bellaver et al., 2018; Shi et al., 2017), leading to a malfunction of the glutamate regulatory system. An increase in neuroinflammation may be accompanied by the production of neurotoxic chemicals when glial function is reduced by several stressors and/or damage signals (Harry, 2021). As a result, oxidative stress and proteotoxic aggregates, which are removed under normal conditions and may induce astrocyte-mediated pro-inflammatory cytokine release (e.g., IL-6), which may activate microglia and encourage microgliosis in aging (Salminen et al., 2011) (Salminen et al., 2011) (Saijo and Glass, 2011). Chronic activation and inflammation of the microglia in the brain may cause damage and/or neurodegeneration in the context of persistent stresses. Research into the pathophysiology of neurodegeneration's age-related decline in cell quality is urgently needed, since it might lead to new therapeutic options.

Because microglia are the primary source of proinflammatory cytokines, they are thought to be key participants in astrogliosis development. Prior to the astrocyte response, the inflammatory reaction is initiated by an increase in microglia-derived mediators and activation of microglia (Quintas et al., 2018). Activation of the NF-B signaling cascade by resident microglia increases the potential to convert resting astrocytes to reactive astrocytes, which can lead to the pathophysiologic transformation of astrocytes in a variety of neurodegenerative disorders, such as PD and AD, and preventing the activation of the microglia-astrocyte activation circuit could help prevent these diseases (Park et al., 2021).

Astrocyte [Ca2+] is increased by inflammatory mediators generated by Microglia. G protein-coupled receptors are also modulated by these mediators (Quintas et al., 2018). In mouse models of acute and chronic neuroinflammation, astrocyte-derived secreted frizzled-related protein 1 (SFRP1) promotes and maintains microglial activation and, as a result, a chronic

inflammatory state. Astrocytes are thought by the authors to be activated early on by microglia, which is why they upregulate and produce SFRP1. Microglial activation is facilitated by the astrocyte-microglial signaling molecule SFRP1, which has been shown to boost microglial activation and to stimulate the expression of HIF and, to a lesser degree, downstream targets of NF-kB (Villarreal et al., 2021)

Feedback from astrocytes on microglial activity is provided by reactive microglial cells. For as long as SFRP1 levels are elevated, neuroinflammation will persist, contributing to its chronicization. Neurons and microglia are activated and killed by the release of astrocyte C3 into the extracellular environment (Villarreal et al., 2021). Microglia in other neurodegenerative disorders have a similar transcriptional profile to that of MIMS, according to Absinta and colleagues. This shows that the processes of primary and secondary neurodegeneration are comparable to those of other neurodegenerative illnesses, and that they may be treated similarly. Chronic inflammation in MS has a molecular target in C1q. In both MIMS and AIMS, researchers found parallels in the complement-gene cross-talk unique to different cell types. "(Absinta and colleagues, 2021).

7- CD38 in Neurodegeneration and Neuroinflammation

Neurodegenerative disorders are distinguished by both neuronal degeneration and neuroinflammation. Although CD38 is highly expressed in brain cells such as neurons, astrocytes, and microglial cells, its significance in neurodegeneration and neuroinflammation remains unknown. Nevertheless, CD38 expression rises as a result of aging, which is otherwise the principal risk linked with neurodegenerative illnesses, and several experimental results have revealed that CD38-deficient animals are resistant to neurodegenerative and neuroinflammatory shocks. In addition, nicotinamide adenine dinucleotide, whose levels are strictly regulated by CD38, is a well-recognized and effective neuroprotective agent, and NAD supplementation has been demonstrated to be useful against neurodegenerative disorders (Guerreiro et al., 2020).

CD38 is a 45 kDa transmembrane glycoprotein comprised of a short cytoplasmic tail (1–21 amino acids), a transmembrane domain (22–42 amino acids), and an extracellular region (43–300 amino acids) (Malavasi et al., 2008). CD38 is both receptor- and enzyme-mediated (Malavasi et al., 2008). CD38 is a multifunctional protein that catalyzes multiple reactions: (i) the conversion of NAD into adenosine diphosphate-ribose (ADPR); (ii) the conversion of NAD into cyclic ADPR (cADPR, cyclase activity); (iii) the hydrolysis of cADPR into ADPR; (iv) in the presence of nicotinic acid (NA) and under acidic conditions, the conversion (ADPRP). CD38 may also catalyze the breakdown of nicotinamide mono-nucleotide (NMN), a NAD precursor, into nicotinamide (Grozio et al., 2013). CD31 is mostly expressed by endothelial cells, where it is regarded as a constitutive marker (Kalinowska and Losy, 2006). CD38 is expressed in the brains of mice (Ceni et al., 2003), rats (Braidy et al., 2014), and humans (Mizuguchi et al., 1995). It is important to note that CD38 is expressed in practically all regions of the human brain, with statistically substantially greater levels in the caudate, pallidum, olfactory bulb, putamen, thalamus, and anterior cingulate gyrus (Quintana et al., 2019). CD38 is expressed at the cellular level in neurons (Mizuguchi et al., 1995), astrocytes (Mamik et al., 2011), and microglial cells (Ma et al., 2012). CD38 was mostly identified in neuronal perikaria but also in dendrites (Mizuguchi et al., 1995). CD38 is mostly localized at the plasma membrane but is also present intracellularly (Braidy et al., 2014) at the subcellular level in the mouse brain.

The expression of CD38 was discovered to rise after neuroinflammatory insults. Increased CD38 expression was detected in the astrocytes of the brains of HIV-1 encephalitis patients (Kou et al., 2009). The proinflammatory cytokine interleukin-1 and the HIV-1 glycoprotein 120 enhanced CD38 expression and enzymatic activity in human astrocytes dose-dependently in vitro (Banerjee et al., 2008). CD38 knockdown via particular siRNAs drastically decreased astrocyte proinflammatory cytokines and chemokines production (Kou et al., 2009), indicating that CD38 regulates neuroinflammatory processes. In addition, hydrogen peroxide (H2O2) treatment elevated CD38 expression in astrocytes, and CD38 knockdown dramatically amplified H2O2-induced astrocyte mortality, establishing a connection between oxidative stress, cell survival, and neuroinflammation (Ma et al., 2012). CD38 is also implicated in the transfer of mitochondria from astrocytes to neurons after a stroke, hence connecting CD38 to astrocyte-induced neuroprotection (Hayakawa et al., 2016). Notably, CD38 KO or suppression of its enzymatic activity slowed the evolution of glioma (Blacher et al., 2015). CD38's function in microglial cells is more uncertain. CD38 expression and enzymatic activity were elevated in primary microglial cells after treatment with lipopolysaccharide (LPS) and interferon-, just as they were in astrocytes. CD38 deletion, on the other hand, decreased activation-induced microglial cell death (Mayo et al., 2008) and regulated microglial cell survival (Ma et al., 2012). More recently, it was shown that CD38 deletion increases death in normal microglia, but protects LPS-stimulated microglia and reduces proinflammatory cytokine release (Wang et al., 2017). These findings indicate that CD38 plays a critical function in microglial cells by relating activation state to cell survival.

There is no genetic evidence directly connecting CD38 to NDDs, and CD38 levels in CSF samples from healthy and NDD patients have never been evaluated. NDDs, including Alzheimer's disease (Sonntag et al., 2017), Parkinson's disease (Wakade et al., 2014), amyotrophic lateral sclerosis (Wang et al., 2017), and multiple sclerosis (Braidy et al., 2013), are characterized by decreased NAD levels. If we take NAD levels as an inversely associated indicator of CD38 expression and activity (Camacho-Pereira,2016) this infers that NDDs express more CD38. This is the first indirect evidence of CD38's role in neurodegeneration and neuroinflammation, since NAD is a strong neuroprotective and anti-inflammatory drug (Lautrup et al., 2019). NAD levels are regulated by various additional enzymes and pathways, which may potentially play a role in NDDs. Consequently, CD38 may be one of a number of pathways contributing to the low NAD levels found in NDDs. CD38 positivity was detected in intracellular tangles and neuropil threads in Alzheimer's disease (Otsuka et al., 1994). Second, the CSF levels of mi-RNA-708 and miRNA-140-3p, which have been demonstrated to inhibit CD38 expression in vitro (Dileepan et al., 2014), are about four- and two-and-a-half-fold lower in Alzheimer's disease patients than in age-matched controls (Denk et al., 2015). GWAS research (Saad et al., 2011) found CD157 polymorphism, a paralog gene of CD38, as a risk factor related with Parkinson's disease. Several experiments with CD38 KO mice revealed that the absence of CD38 is protective against neurodegeneration and neuroinflammation. By crossing the classical Alzheimer's disease mouse model APPswePS1DE9 with CD38 KO mice, Blacher et al. (2015) discovered that CD38 deletion decreased A plaque load and soluble A levels, an effect that correlated with improved spatial learning in vivo and was mimicked by inhibitors that blocked CD38 enzyme activity in vitro. This effect seems contradictory given that CD38 KO mice had deficiencies in a variety of learning and memory tests, including the Morris water maze, contextual fear conditioning, and the object recognition test (Kim et al., 2016). In an experimental mouse model of multiple sclerosis including autoimmune encephalomyelitis, CD38 deletion improved disease severity (Herrmann et al., 2016). Note that CD38 deletion suppressed glial activation and

neuroinflammation in a mouse model of demyelination produced by cuprizone injection, an effect that was most likely attributable to an increase in NAD levels in CD38 KO animals (Roboon et al., 2019). It is intriguing to note that CD38 deletion significantly decreased neuroinflammation in all of these experiments, indicating that CD38 may play a crucial role in this process. The great majority of these investigations indicate that the positive effects reported in CD38 KO mice are due to elevated levels of NAD. Due to the insufficient characterisation of the effect of CD38 deletion in the brain, these findings must be mitigated. In fact, the effect of CD38 deletion on brain cADPR, ADPR, NAADP, and ADPRP levels is not well understood and may contribute to the favorable effects found in CD38 KO mice.

There is no direct genetic evidence linking CD38 to NDDs, and sadly, no study has directly demonstrated increased expression of CD38 in the human brain as a result of aging, or whether CD38 levels are elevated in the brains of NDDs patients compared to age-matched controls. Nevertheless, age is the principal risk factor linked with the great majority of NDDs (Hou et al., 2019), and multiple findings suggest that CD38 expression in the brain rises as a result of aging. Although Camacho-Pereira et al. established that CD38 expression rises with age in various tissues, the brain was excluded from this investigation (Camacho-Oereira et al., 2016). Braidy et al. found that as a result of aging, NADase activity increased throughout the rat brain, including the hippocampus, cortex, cerebellum, and brainstem (Braidly et al., 2014). However, the fraction of NADase activity reflected by CD38 activity was not measured. CSF and brain NAD levels decline with age in healthy adults, which may be interpreted as an increase in CD38 levels (Zhu et al., 2015).

Despite the paucity of direct evidence involving CD38 in NDDs, CD38 offers a highly potential target to combat neurodegeneration and neuroinflammation owing to its tight association with aging and experimental findings from CD38-deficient animals. Since CD38 regulates brain NAD bioavailability and the activity of NAD-dependent enzymes that are essential for neuronal survival, reduction of CD38enzyme activity resulting to higher NAD levels may be useful for the treatment of NDDs. Unfortunately, identified small molecule inhibitors of CD38 enzymatic activity either have an IC50 in the micromolar range (Blacher et al.,2015), do not cross the BBB like compound 78c (Tarrago et al., 2018), or trigger antibody-dependent cell-mediated cytotoxicity like anti-CD38 antibodies daratumumab or isatuximab (van de Donk et al., 2018). The immunosuppressive effect of anti-CD38 antibodies, such as daratumumab, on plasma cells and plasma blasts may be beneficial in the treatment of autoimmune neurological illnesses, such as multiple sclerosis (Milo, 2019). To know exactly how to modulate CD38 to maximize efficacy and reduce potential adverse events (such as the social behavior alterations observed in CD38 KO mice due to a decrease in cADPR in specific brain subparts), we still need a better understanding of the physiological role of CD38 in brain cells and, more specifically, the effect of CD38 deletion/inhibition on brain cADPR, ADPR, NAADP, and ADPRP levels.

8- Glymphatic System and NDG

Unfortunately, as we age, the health of our brains deteriorates irreversibly. Over the next several decades, the number of people 65 and older is predicted to steadily increase, reaching roughly 1.5 billion people in 2050, according to the World Health Organization (UN) (GBD, 2016). AD and PD are two of the most prevalent neurodegenerative illnesses, both connected to aging. Neurodegenerative diseases are a significant financial burden to society and one of the most pressing global health challenges of our day because of their nature and prevalence (Hou et al., 2019; Wyss-Coray, 2016).

For a long time, scientists have speculated that the brain possesses a lymphatic system for removing waste and draining fluid. It was Rudolf Virchow and Charles Robin, two anatomists working together in the 1850s, who discovered the "Virchow-Robin" gaps that surround blood vessels, including those in the brain. Many researchers use the phrase "perivascular space" to describe the region surrounding blood vessels where CSF may meet the subarachnoid space (Woollam and Millen, 1955); nevertheless, the actual contact between these two regions is still debated by other scientists (Woollam and Millen, 1955). Just a few years after Gustav Schwalbe first described the perivascular spaces in the brain, he established that dyes could enter lymphatic veins and lymph nodes in the head and neck by injecting them into the cranial subarachnoid spaces of numerous laboratory animals (Breslin et al., 2018). Experiments undertaken by Virchow and Robin revealed a clear connection between their results and the likelihood of a lymphatic drainage-like system in the brain's central nervous system (CNS). Dye injected into the CSF or directly into the subarachnoid space has been demonstrated to permeate the perivascular space in further studies, demonstrating linkage between the CSF and ISF in the brain in the CSF (Wardlaw et al., 2020; Woollam et al., 1955). All of these studies together showed that the central nervous system had a fluid-mediated clearance mechanism to be a fact. First, Maiken Nedergaard and colleagues in 2012 outlined three fundamental components of the glymphatic system: CSF inflow, ISF clearance, and trans-parenchymal exchange (Figure 3). All of which are dependent on astroglial cells (Iliff et al., 2012; Iliff and Nedergaard, 2013; Jessen et al., 2015). As the CSF made its way around their heads, the researchers used fluorescent tracer injections intracranially into brain mice. Using intravenous injection, the tracers swiftly penetrated the brain's parenchyma and spread throughout the whole brain (Iliff et al., 2012; Iliff and Nedergaard, 2013). Detection of CSF tracer in the interstitial space led researchers to conclude that an exchange route existed between CSF and ISF, allowing for communication between the two fluid systems (Iliff et al., 2012). The first description of a brain-wide fluid transport system, analogous to the peripheral lymphatic system, was established in mice by scientists. Large-calibre draining veins drained CSF from the brain into a syringe after it exchanged with ISF in the interstitial space of the brain (Figure 3). It was given the moniker "glymphatic system" due to its resemblance in function and dependency on glial cells to operate (Iliff and Nedergaard, 2013; Jessen et al., 2015).

An important link between the para-arterial CSF influx and the ISF outflow channels of the glymphatic system is thought to be astrocytes (Iliff et al., 2012). When it comes to fluid and solute transport from periarterial portions of brain parenchyma to perivenous areas, astrocytes are thought to play a key role because of their intimate physical contact with brain vasculature, according to a concept initially put up in 2012. (Iliff et al., 2012; Jessen et al., 2015). Water-specific channel aquaporin-4 (AQP4), which is expressed on the astrocytic end feet surrounding the brain's vasculature, has been identified (Jessen et al., 2015; Gleiser et al., 2016). These specialized supportive glial cells have this as a core property. Glial cells. Because AQP4 is mostly expressed in the brain, it is not thought to be involved in epithelial fast water transport like its choroid plexus-localized relative AQP1 (Gleiser et al., 2016). A network of glial projections was proposed by Iliff et al. to facilitate the pressure gradient- and convective-driven directed flow of CSF via the glymphatic system (Iliff et al., 2012). Indeed, when CSF tracer influx into brain parenchyma was observed ex vivo, tracer transport into the brain parenchyma was significantly reduced in mice defective in AQP4 (Iliff et al., 2012; Jessen et al., 2015; Plog and Nedergaard, 2018). Importantly, this work showed that the rate of fluid and solute clearance from the brain's interstitial spaces was greatly decreased in AQP4-knockout rats by injecting radiolabeled mannitol into the striatum, thus demonstrating

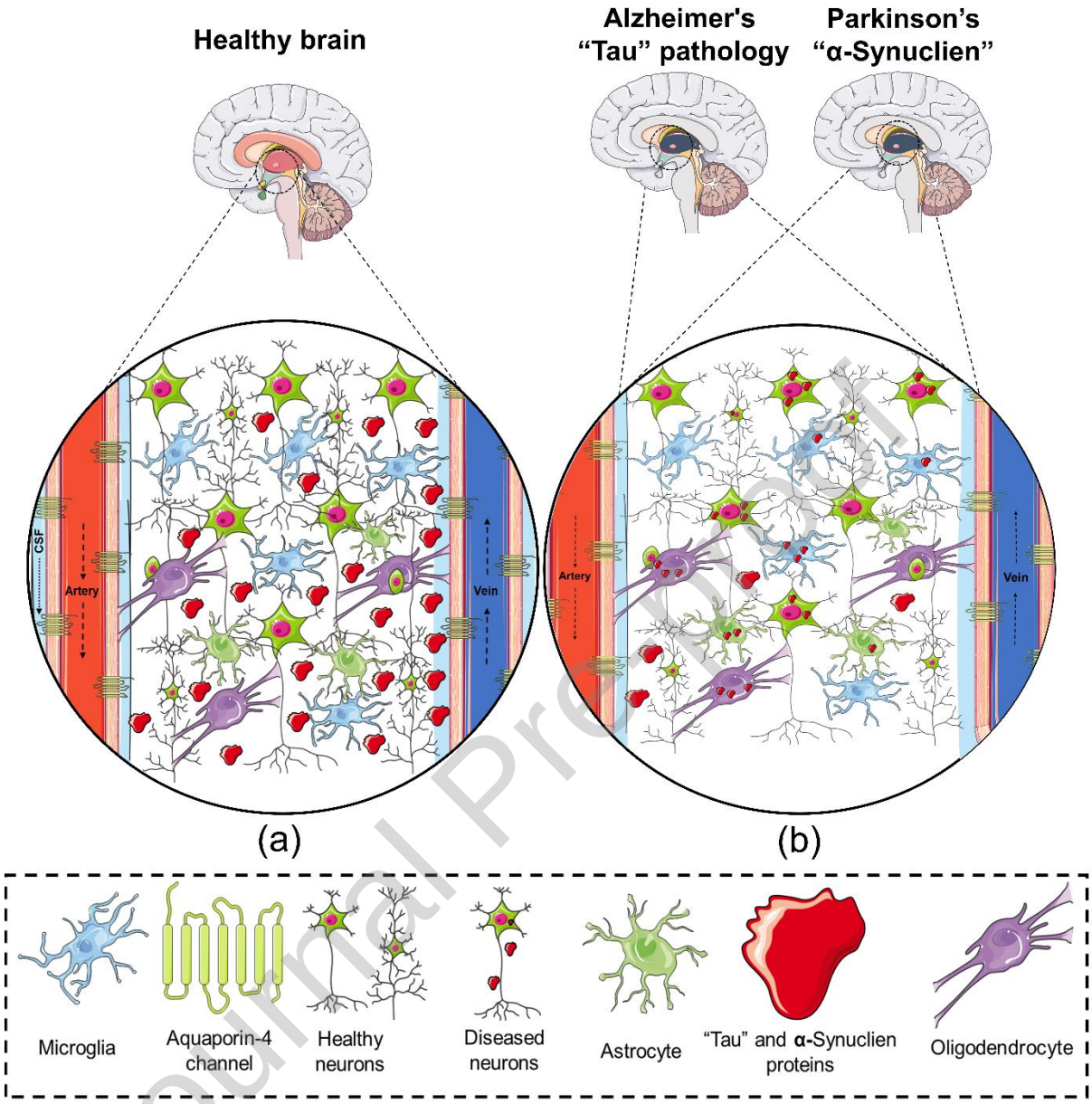
the essential function of AQP4 in the glymphatic clearance system (Iliff et al., 2012; Jessen et al., 2015; Plog and Nedergaard, 2018). Glymphatic drainage plays an important role in clearing the brain of cytotoxic waste products like as amyloid- from the brain in the context of neurodegenerative disease, according to the study (Iliff et al., 2012). As a result of these findings, future research has linked this process to the removal of tau and alpha-synuclein from the brain (Iliff et al., 2014; Harrison et al., 2020). (Zou et al., 2019; Cui et al., 2021). Further studies have shown that astrocytic AQP4 is essential for rapid glymphatic transport in a variety of systems and disease models, highlighting the fundamental role of astroglial cells in this CNS solute clearance mechanism.

It appears that glymphatic dysfunction is more common in those who are older. Astrocytic, CSF, and sleep pattern changes are common in older persons according to scientific study, which may affect the correct functioning of the glymphatic system. It was discovered that the glymphatic system in the bodies of young, middle-aged, and old animals was susceptible to age-related alterations in function (Kress et al., 2014). Fluorescent tracers were used to measure the inflow of interstitial CSF in middle-aged and elderly mice. The inflow of interstitial CSF in old mice was reduced by about 80% compared to that of young mice (Kress et al., 2014). It's unclear what's generating such a drop in CSF flow. Research has linked this shift to the loss of AQP4 end-foot polarization in astrocytic cells even while there was no overall change in AQP4 expression levels but a significant increase in brain cell numbers, particularly around the larger brain blood vessels (Kress et al., 2014). Age-related changes in the distribution of AQP4 shifted it away from end foot and toward astrocytic parenchymal processes. This resulted in abnormal water transport regulation mediated by these cells (Kress et al., 2014). It was also shown that in the striatum and hippocampus, the polarization of AQP4 was reduced more rapidly in older rats (Kress et al., 2014). Studies on a wide range of mammalian species have established a strong link between aging and a decrease in CSF production and pressure inside brains, supporting the idea that the glymphatic system becomes less active with time (Fleischman et al., 2012; Chen et al., 2009; Iliff et al., 2013).

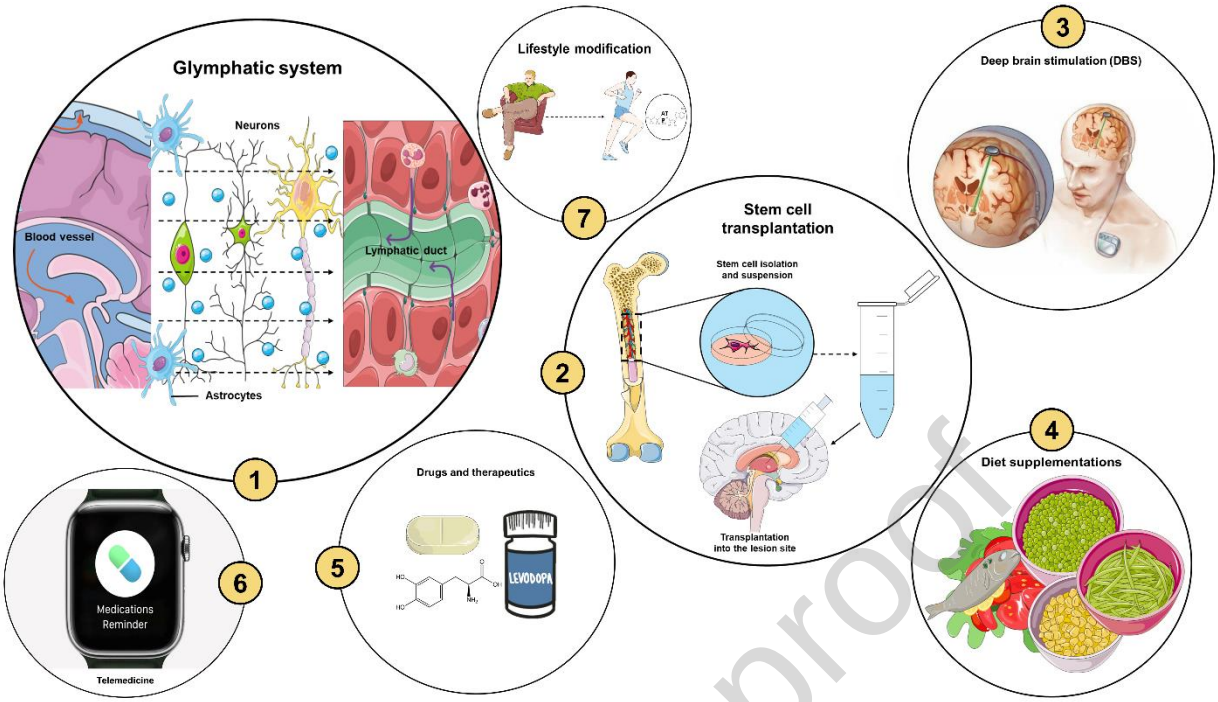
Disruption of the Glymphatic system has been linked to aging in humans, as well (Zhou et al., 2020). Glymphatic circulation and meningeal lymphatic outflow were shown to be impaired in the elderly by Zhou and colleagues using magnetic resonance imaging to study glymphatic flow (Zhou et al., 2020; Carlstrom et al., 2021). Glymphatic clearance relies on sleep, and it is well-known that sleep quality diminishes with age, resulting in insomnia, fragmented and shallow sleep, and shorter sleep duration, all of which result in a reduction in the clearance of nocturnal brain wastes (Nedergaard and Goldman, 2020). Glymphatic system failure may contribute to protein build-up in old age, but it is not yet clear if protein waste is directly responsible for the system's decline, or whether there is a contemporaneous, collaborative process at work. The glymphatic system, however, does not remove soluble waste products from the brain in isolation; there are multiple overlapping clearance processes that work together to achieve and maintain parenchymal homeostasis (for reviews, see Tarasoff-Conway et al., 2015; Rasmussen et al., 2021). A variety of convergent processes, including lymphatic clearance, may move waste solutes from the brain into the cerebrospinal fluid, including enzymatic destruction, direct clearance into the blood at the blood–brain barrier, and transfer into the cerebrospinal fluid. There has been a resurgence in study into various clearance mechanisms, CSF dynamics, and brain fluid flow thanks to the glymphatic pathway, which was first described back in 2012. Furthermore, it sparked a lot of debate (Mestre et al., 2018; 2020). There is perivascular fluid movement exclusively along the base membranes of the smooth muscle cells of cerebral arteries, and it is antiparallel to vessel blood flow rather than parallel to it. This finding was made by Carare and Weller in their

investigation of perfusion-fixed tissues (Diem et al., 2018). Mestre et al. (2018) argued that this observation was an artifact due to the collapse of the artery and the surrounding perivascular space as a result of the fixation procedure. On the basis of experiments, Smith and colleagues (2017b) challenged and contradicted Iliff and colleagues' claim that the brain parenchyma is diffusive, rather than convective, in the transport of solutes (2012). As a result, the authors of this study dismissed water channel function in solute transport inside the brain and provided evidence that AQP4 gene deletion did not affect solute transfer from subarachnoid space to parenchyma in mice and rats. Research undertaken by a global consortium of laboratories (Mestre et al., 2018) re-evaluated the role that AQP4 plays in the glymphatic clearance pathway. Research conducted in reply to Smith and colleagues used five genetically modified AQP4 mouse strains, including the Smith and colleagues strain. All of the AQP4 knockdown lines were shown to have a lower CSF influx than wild-type mice (Mestre et al., 2018). AQP4 and its membrane-binding complex played an important part in the research, which also showed that invasive procedures like intracerebral injections might disrupt and harm the glymphatic system (Mestre et al., 2018). In addition, the authors and others suggest that experimental variables such as anaesthesia, age, tracer delivery methods and perfusion-fixation could explain the discrepancy in the findings (Mestre et al., 2018a,b), reinforcing the central role of AQP4 and the perivascular space in the glymphatic system function in the rodent brain. The glymphatic system has been the subject of debate for some time, thus the pioneering lab (led by Maiken Nedergaard) has published articles outlining the current disagreements, offering evidence, and raising unsolved questions concerning the system (Mestre et al., 2020; Hablitz and Nedergaard, 2021a,b). Glymphatic fluid transport in the brain has recently been reviewed in a comprehensive Physiological review paper that provides an overview of the current state of the field, as well as a detailed discussion and point-by-point evaluation of the most contentious areas of the subject matter (Rasmussen et al., 2021).

An important role for the brain's glymphatic system in clearing out the extracellular space and removing molecules vulnerable to aggregation in neurodegenerative illnesses like amyloid (Iliff et al., 2012) and tau has been established (Eliff et al., 2014; Harrison et al., 2020). Similarly to tau, alpha-synuclein induces neuronal cell death by intracellular aggregation, and the patterns of propagation of these proteins throughout the brain from neuron to neuron and area to region suggest that extracellular space is a crucial transport pathway for their spread (Zou et al., 2019; Cui et al., 2021). As stated before, glymphatic function is affected by aging and changes in neuroinflammation (Kress et al., 2014; Fleischman et al., 2012; Chen et al., 2009; Zhou et al., 2020); this is similar to other reports. A recent study found that variations in the AQP4 gene, which encodes the water channel essential to the glymphatic system, were linked to sleep quality (Rainey-Smith et al., 2018), amyloid buildup in the brain (Chandra et al., 2021), and varying rates of cognitive decline after an AD diagnosis (Rainey-Smith et al., 2021). (Burfeind et al., 2017). These findings indicate that the glymphatic system may be a unique treatment target for neurodegenerative illnesses (Figure 4). These two intracellular proteins have been shown to have a propagation-prone feature in the setting of neurodegeneration. For these reasons, further study into therapeutically altering the glymphatic system is needed in order to treat tauopathies and alpha-synucleinopathies, which are both caused by abnormal protein clearance in the brain.



(Figure 3) **The Glymphatic system is illustrated.** Fluid flow through Glymphatic currents of cerebrospinal fluid and interstitial spaces fluid help push neuron organic waste into the para-venous domain, where they are directed into lymphatic vessels before returning to the systemic circulation for discharging. (a) Shows healthy brain with healthy neurons that don't accumulate "tau" or "α-Synuclien" protein. Cerebrospinal fluid flows normally within the brain from arteries to veins. (b) Shows diseased neurons with "tau" or "α-Synuclien" protein accumulation in the ECM with disturbed CSF flux.



(Figure 4) Treatment modalities of Parkinson's disease (PD): (1) The Glymphatic system is illustrated. Fluid flow through Glymphatic currents of cerebrospinal fluid and interstitial spaces fluid help push neuron organic waste into the para-venous domain, where they are directed into lymphatic vessels before returning to the systemic circulation for discharging. (2) Stem cells are isolated from different tissues (i.e. bone marrow, adipose tissue, and blood) then they can be transplanted into lesion sites where they can regenerate the damaged neurons and glial cells. (3) Surgical treatment of PD using deep brain stimulation (DBS). (4) Diet supplementation can enhance PD treatment and recovery. (5) Drugs and therapeutics approved by FDA such as Levodopa (L-dopa) which supplements the brain with dopamine necessary for signal transmission. (6) Telemedicine is an effective aid that controls and notifies the patients' relatives about any emergencies the patient has. There are different smartwatches and apps approved by the FDA that help Parkinson's patients. (7) Lifestyle modification and exercises can help the patient have a high quality of life.

9- Potential Immunomodulatory Therapies

Although the role of neuroinflammation in the development and progression of Parkinson's disease is indisputable, the primary focus of this enormous study remains the potential therapeutic applications. First, experimental data and animal studies suggested that nonsteroidal anti-inflammatory medicines, notably ibuprofen and piroxicam, reduced the likelihood of developing Parkinson's disease (Poly et al., 2019). However, epidemiological studies and meta-analyses could not corroborate the favorable effects of NSAIDs in lowering the risk of Parkinson's disease (PD) or altering the course of the illness (Rees et al., 2011). Anti-TNF treatments are another possible immunomodulatory treatment based on in vitro research. TNF was reported to produce significant damage to dopaminergic neurons in vitro, and the use of nonspecific TNF inhibitors, such as thalidomide, had favorable outcomes in some MPTP mice and LPS rat model tests (Peter et al., 2018). In addition, an epidemiological investigation demonstrated a decreased incidence of PD in patients with inflammatory bowel disease who were treated with anti-TNF compared to those who were not exposed to this particular medication (Jing et al., 2017). In animal models, researchers showed that

Isobavachalcone, a major component of the Chinese herb Psoralea corylifolia, might operate as a neuroprotective and immunomodulatory agent. Isobavachalcone seems to work by inhibiting NF-KB signalling, which improves motor impairments, reduces neuronal necrosis, and simultaneously reduces the expressions of IL-6 and IL-1 (Braczynski et al., 2017). Several immunotherapies targeting a-synuclein have developed recently in the realm of immunomodulatory treatments in an effort to remove alpha-synuclein from the extracellular space and, subsequently, diminish its aggregation in the brain. Similar therapeutic immunization experiments targeting amyloid and, more recently, intracellular tau protein (Chatterjee and Kordower, 2019) being done for Alzheimer's disease. Several active and passive immunotherapies targeting alpha-synuclein have progressively evolved as immunotherapeutic techniques (Mandler et al., 2014). Active immunization is derived from anti-alpha-synuclein antibodies produced by an animal's immune system. The first vaccine produced was able to elicit large titres of antibodies against aggregated alpha-synuclein, and inoculation was successful in reducing alpha-synuclein deposition and striatal degeneration (Sanchez-Guajardo et al., 2013). The antibodies provided during passive vaccination target distinct alpha-synuclein regions (Benner et al., 2004). The purpose of these particular antibodies is to stimulate microglia, remove extracellular alpha-synuclein, and inhibit cell-to-cell transmission of alpha-synuclein.

The discovery of novel therapy strategies is the primary motivation for investigating the causes of Parkinson's disease. Unfortunately, the current treatments only address the symptoms of neurodegenerative diseases and do little to halt or reduce the progression of the illness itself. The function of neuroinflammation in the development of Parkinson's disease has grown in significance. Several therapies have been tried, each of which targets this mechanism at a different level. These treatments have grown promising, and they merit further study. Outcomes from human trials often fall short of expectations, despite promising results in animal studies. The likelihood of finding an effective immunomodulatory therapy for Parkinson's disease increases the more we learn about the involvement of the immune system in this illness.

10- Conclusions and Perspectives

Deterioration of the neural network, disruption of synaptic transmission, loss of synapses, and alterations in intracellular signalling all contribute to neuronal death in neurodegenerative illnesses (Palop and Mucke, 2010; Herms and Dorostkar, 2016; Jackson et al., 2019). There is a dearth of knowledge regarding the molecular mechanisms that underlie the evolution of most neurodegenerative disorders, making the identification of novel treatment targets exceedingly difficult (Andreone et al., 2020). Neurodegenerative disorders are one of the major unmet medical needs in the world today since there are no effective therapies for them. Therefore, it is critical and essential that novel treatment methods be developed to better understand the processes that cause and underlie these illnesses.

To understand neurodegenerative illnesses, we need to know more about the glymphatic system's involvement in clearing proteins that are prone to intracellular accumulation. Extracellular protein (amyloid-) glymphatic clearance studies seemed to affect neurodegenerative research and sparked interest in the less studied intracellular protein (tau) and alpha-synuclein. These proteins are capable of spreading from cell to cell in linked brain regions in a prion-like way. The glymphatic system's function in clearing cytotoxic proteins from the central nervous system (CNS) is now better understood in light of these results, suggesting that it may play a key role in a wide range of neurological illnesses including

NDG. New diagnostic and therapeutic prospects are emerging for disorders linked with the accumulation of aberrant proteins, such as Alzheimer's and Parkinson's, because of processes of defective brain clearance that result in the accumulation of abnormal proteins. In particular, there is growing evidence that the glymphatic function may be modified in the lab. The current investigations suggest that the glymphatic function may be regulated by repurposing previously well-described medications, although further research is needed to confirm this hypothesis. A healthy lifestyle may also have an effect on the glymphatic system in addition to its well-known advantages We still know very little about the glymphatic system and its involvement in neurodegenerative illnesses, but it is obvious that these two rapidly changing sectors play an important role.

Finally, we may say that: reviews in this issue often remind us of the many cell types involved in disease and also focus on those brain cell populations that are not inherent.. Systems biology approaches must be used to separate the initial molecular perturbations from subsequent homeostatic responses in various cell types, according to the presentations given at the symposium. Single cell or spatial transcriptomics, human stem cell-based or brain organoids, and other emerging technologies and platforms have recently shown their use in tackling the aforementioned problem (Camp et al., 2015; Giandomenico et al., 2019; Mansour et al., 2018). Data revealing human-specific variances in etiology are expected to transform translational research and personalized therapy choices in the next decade.

Cognitive decline may be treated with pharmaceuticals and nutraceuticals if the pathophysiology of neurodegeneration can be better understood. There must be a reduction in mechanisms that protect the integrity of the cell before oxidative damage and proteotoxic aggregates accumulate and cause neuroinflammation through bursting astrocyte-mediated release of pro-inflammatory cytokines. Further investigation into mitochondrial dysfunction is required in this context. A new and promising method for reducing oxidative damage, which is a primary pathophysiological process in NDG, has evolved from the study of microglia and astrocytes. However, neuroglia may be an important source of reactive oxygen species, which can cause oxidative damage as well as initiate other downstream effects including necrosis of the blood-brain barrier. To the contrary, ROS may impact glial cell phenotype by stimulating astrocytes and promoting microglial polarization, making ROS treatments a feasible, but problematic treatment for neurodegeneration.

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