Latest insights into the role of astrocytes in Alzheimer's Disease and Parkinson's Disease: a Literature Review

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Abstract

Astrocytes are key players when it comes to maintaining healthy neuronal tissue. Their multitude of functions make them truly indispensable, however they have also been implicated in the pathophysiology of several neurological disorders. This review discusses the current literature and introduces the latest advancements in the role of astrocytes in (1) Alzheimer's Disease and (2) Parkinson's Disease, from a pathophysiological standpoint, as well as a therapeutic point of view. A PubMed literature search (2018-2024) using the following search strings: (astrocytes) AND (Parkinson's disease) as well as (astrocytes) AND (Alzheimer's disease) was performed. Astrocytes have been implicated in the contribution of neuroinflammation, leading to neuronal death in Alzheimer's Disease. Similarly, astrocytes may contribute to progression of Parkinson's Disease alpha-synuclein-induced neuroinflammation. Promising therapeutic interventions in this field make use of astrocytes, converting them into neurones to counteract the neurodegeneration that occurs in diseases like Parkinson's Disease.

Keywords: Alzheimer's Disease, Parkinson's Disease, Astroglia, Alzheimer's, Neuroinflammation, Neurodegeneration

Introduction

Astrocytes constitute the majority of cells in the central nervous system (CNS) and have a multitude of crucial roles in maintaining healthy neuronal tissue. From developmental to structural, as well as homeostatic functions, amongst others, these glial cells prove to be essential in the overall health and functioning of the nervous system (1–3). Indeed, astrocytes play a role in pH and ion regulation, maintenance of blood brain barrier, cerebral blood flow regulation and they also express receptors for a wide range of neurotransmitters (1,3). This makes them key players in the uptake and metabolism of neurotransmitters like noradrenaline and glutamate (2). Astroglia have also been implicated in glial scar formation, a mechanism for neuronal protection in traumatic brain injury (TBI), in order to preserve and limit the extent of damage (4). However, astrocytes have also been implicated in the pathophysiology of several neurological disorders, including Alzheimer's Disease (AD) and Parkinson's Disease (PD), just to mention a few (3,5,6). Changes in number, size and appearance of astrocytes have all been linked to pathological conditions (7,8). Astrocytic scar formation as a response to TBI can also have pathologic long-term effects (9). This review aims to discuss the latest advancements in relation to astrocytes and their relationship with (1) Alzheimer's disease and (2) Parkinson's disease.

Methods

A PubMed literature search using the following search strings: (astrocytes) AND (Parkinson's disease) as well as (astrocytes) AND (Alzheimer's disease) was performed. Case reports, clinical studies, trials as well as meta-analysis and randomised controlled trials published between 2018 and 2023 were analysed. The articles were chosen according to a relevant title and abstract, although conclusions were also taken into consideration for the selection process. Articles written in English and open access articles were analysed. The exclusion criteria included articles older than 2018, articles which were not open access as well as any articles that tackled different subject matters. Additional relevant literature was also obtained via reference snowballing.

Results/Discussion

Alzheimer's Disease

Alzheimer's Disease prevalence is on the rise worldwide, and it is the leading cause of dementia. It is an irreversible, neuropsychiatric disorder with characteristic progressive, global cognitive impairment (including memory loss, anosognosia, executive function loss) with additional non-cognitive symptoms including irritability, appetite disturbances and mood disturbances.

There is conflicting data about AD incidence and prevalence rates. On one hand, it is widely reported that AD incidence rates are decreasing in Europe (10–12) and North America (10,11). The Alzheimer Europe 2019 analysis (13) reports a decline in AD prevalence. One possible hypothesis for these observations revolves around the fact that education and health interventions are reducing risk factors predisposing to AD (10). Additionally, angiotensin-converting enzyme inhibition also slows the neurodegeneration that leads to dementia, as it indirectly influences said risk factors (eg hypertension, diabetes) (9).

On the other hand, several studies (14–16) report an increased global AD prevalence, which increases with age in view of ageing populations. In general, whilst the AD incidence may be possibly decreasing, it is still unlikely to have a significantly altered AD prevalence in the near future (17,18).

It is understood that AD causation involves both environmental and genetic factors (19,20). The pathophysiology includes extracellular toxic Beta-amyloid peptide accumulation and plaque formation, which damage neuronal cells, causing synapse loss and chronic neuroinflammation. There is also intracellular hyperphosphorylated tau neurofibrillary bundles, which are hallmark of AD (21–23). These abnormal proteins contribute the aforementioned cognitive symptoms. In addition to this, studies suggest that Beta-amyloid plaques activate astrocytes, as part of the brain's immune response, in order to clear said plaques (24,25).

In neuropathology, whether acute or chronic neurological disease, reactive astrocytes undergo prominent remodelling in a process known as 'reactive astrogliosis' (26). This astrocyte reaction is a way of responding to central nervous system (CNS) insults and disease, in order to restore homeostasis, in a process fully regulated through signalling pathways (7). The mechanism of reactive astrogliosis varies depending on the disease context and its severity.

Generally, following astrocyte activation, they undergo changes in molecular expression, hypertrophy and, at times, proliferation with scar formation. This scar physically contains any areas of tissue damage and inflammation (27). It has been proven that one cytoskeletal protein called glial fibrillary acid protein (GFAP) is essential for reactive astrogliosis, and in fact, there is GFAP upregulation during this process. GFAP is specific to astrocytes (28). The reactive astrogliosis process is hallmark of AD and it potentially contributes to the disease progression as well as severity.

In fact, the intensity of GFAP levels, and therefore of astrogliosis, were reported to increase with increasing progression of AD Braak stages, which classify the disease into different phases, from pre-clinical AD to advanced stage AD (29). Additionally, the inflammatory signals secondary to reactive astrogliosis may also have neurotoxic effects (30). However, recent evidence shows that reactive astrocytes can also be beneficial, and can be used to regenerate neuronal tissue (31,32,33).

The role of Astrocytes in Alzheimer's Disease

Neuroinflammation is hypothesized to play a role in the development and/or the progression of AD. Regarding the contribution of astrocyte-mediated inflammation to neuronal loss by Beta-amyloid plaques, Garwood et al. (34) conclude that reactive astrocytes are triggers for the production of Aβ-induced tau phosphorylation. This is because there is an association between the neurotoxicity caused by the plaques and the increased activity of caspase-3, a key player in the apoptotic pathway. Interestingly, astrocytes further exacerbated this increased caspase-3 activity, which leads to neuronal death in vitro. Lian et al. (35) conclude that there is increased astrocytic activation of NF-KB pathway by Aβ plaques, resulting in upregulation of C3 complement protein by astrocytes, which ultimately results in altered intraneuronal electrolyte balance and the consequent impaired synaptic transmission seen in AD. Contrasting evidence has also shown that one astrocyte phenotype also plays an active role in plaque clearance, in response to chemokines released by the Aβ plaques in AD mice models (36). These highlight the multiple roles of astrocytes in AD albeit having both detrimental and neuroprotective functions; understandably making them potential therapeutic targets in future studies.

Past human post-mortem studies have investigated the role of astrocytes in the entorhinal cortex of AD patients, responsible for memory function.

One might hypothesise that this conflicting evidence is possibly due to the age of the post-mortem patients from whom the samples were taken. The cohort contained more elderly patients in the study by Porchet et al. (37), compared to Rodríguez et al. (41), with a discrepancy of about 10 years. The studies have different sample sizes, with that of Rodríguez et al. (41) and Hsu et al. (42) being larger than that of Porchet et al. (37) and therefore more representative of the population. Additionally, the study by Rodríguez et al. (41) was performed 20 years following that of Porchet et al. (37), and therefore discrepancies due to technological advancements cannot be excluded. Therefore, enhancing our understanding of the precise functioning of astroglia in the context of neurodegenerative disease is evidently the way forward, allowing the introduction of astrocyte-targeted therapy for AD patients. Being able to perform such studies on living patients would also be revolutionary in this aspect (42).

A number of genes have also been identified as possible risk factors for AD, including amyloid precursor protein (APP) gene, presenilin-1 (PSEN1) and presenilin-2 (PSEN2) genes as well as apolipoprotein E (APOE) (43). APOE originates from astrocytes, and allelic variation in this gene is the most prevalent of all genetic risk factors identified to date. One of the functions of APOE is lipid transport throughout the body. Having investigated the effects of the different APOE isoforms with reference to AD, Simonovitch et al. (44) demonstrate that the ApoE4 allele in mice astrocytes renders them less able to clear Aβ plaques, possibly driven by impaired endocytosis, autophagy and lysosomal degradation. Interestingly, the contrary applies for the ApoE2 isoform, which is protective against AD (45). Using this information, mice models were developed in order to further understand the mechanisms underlying this neurodegenerative disorder (34,46).

The Role of Astrocyte-induced cytokines in Alzheimer's Disease Progression

Neuroinflammation involves the release of 'TIC' cytokines, ie. tumour necrosis factor (TNF), Interleukin-1α (IL-1α) together with complement protein 1q (C1q) (47). Neuroinflammation has been closely linked to AD, and it has been recently speculated to contribute majorly to the early phase of AD pathogenesis (48,49). Astrocytes play a crucial role in this neuroinflammatory process, by increasing astrocyte-derived cytokines (including Interleukin-6 [IL-6]) (5,50). This is sphingomyelinase-mediated in astrocytes (34). This neuroinflammatory response might precede Aβ plaques in AD, but it is evident that neuroinflammation becomes more severe as plaques accumulate and the disease develops. In human neurodegenerative diseases, including AD, the TIC cytokines were also found to induce A1 neurotoxic reactive astrocytes, which drive neuronal and oligodendrocyte death through unidentified neurotoxin release (51), reactive oxygen species, nitric oxide and proteolytic enzymes, amongst others (52). At present, the scope behind the production of a neurotoxic astrocyte remains unclear. However, it is evident that these processes influence later stages of the disease, driving its progression with ever-evolving complications (48).

A high level of astrocytic IL-6 secretion was observed in mild and moderate AD patients (53). A 2022 study (54) investigated the effects of astrocytic IL-6 overexpression in transgenic mice from ages 3 months to 1 year of age, in relation to neuronal degeneration. Although IL-6 is typically considered to be "neuroprotective" (5,52), it was concluded that with increased astrocytic IL-6 expression, there was a significantly decreased cerebellar volume with possible cerebellar neuronal loss for mice aged 1 year (54). This is in keeping with (47), where TIC cytokines were found to contribute to the maintenance of neuroinflammation, and in fact, this decreased when TIC cytokines were removed, in the context of a stroke, in 8-week-old mice.

On the other hand, Interleukin-4 (IL-4) plays the role of an "anti-inflammatory" cytokine in vitro, contributing to the enzymatic clearance of Aβ plaques (53). Interleukin-10, for instance, also plays an important neuroprotective role in AD (55). Therefore, one can conclude that whilst astrocytes produce a multitude of cytokines which are crucial and necessary for the host defence, it is the imbalance between the pro- and anti-inflammatory mediators that is evidently pathologic. Although the cytokines benefit the CNS to a great extent, being non-specific, the surrounding neurones confer some inevitable damage in this way.

Neuronal regeneration from astrocytes in the treatment of Alzheimer's disease

Much of the existing literature has revolved around the generation of new neurones from neuroprogenitor cell transplants (56–58). However, novel reprogramming tools using viral vectors to target astrocytes are being introduced to establish neurogenesis in vivo. The latest advancements include the work of Zhang et al. (31), who demonstrated the in vivo reactive astrocyte conversion into neurones at the injury site, in the context of TBI. This not only generates neuronal tissue, but also simultaneously decreases the amount of reactive glial cells. TBI mice models induced reactive astrogliosis at the injury site, with astrocyte proliferation and accumulation. An AAV Cre-FLEX vector system was developed, which targets astrocyte DNA, specifically at the loxP site. The aim was to integrate NeuroD1 transcription factor, which induces the change to neuronal cells. In order to monitor the expression of NeuroD1, a separate vector including a dye (mCherry) was developed, FLEX-CAG::NeuroD1-P2A-mCherry together with a control AAV mCherry, without NeuroD1. The reactive astrocytes were exposed to the virus 10 days post-injury, as well as 21 days post-injury, in separate experiments. The results show that in both cases, ie. both before and after the formation of the glial scar, reactive

astrocytes were successfully converted into functional neurones, expressing NeuroD1 and NeuN, with large sodium and potassium currents as well as repetitive action potentials. Such therapy can potentially be used for neuronal repair in the days and months following neurotrauma.

Similarly, Liu et al. (32) make use of the glial scar formed during reactive astrogliosis post-TBI and reprogram it, to form neural tissue. The aim was to target astrocytes, not neurones, using modified adenoviral (AAV9P1) vectors, having an astrocyte-targeting P1 peptide on their surface. TBI was induced in mice using controlled cortical impact and immunostaining confirmed reactive astrocyte formation. AAV9P1-shPTBP1 vector was injected intra-venously, which reduced expression of polypyrimidine tract-binding protein 1 (PTBP1) and consequently astrocyte reprogramming was observed, forming neuronal cells.

This was confirmed by comparing the uptake of enhanced green fluorescent protein in mice treated with AAV9P1-shPTBP1 compared to control mice given AAV9P1-shCtrl. Although this proves that astrocyte-to-neurone conversion is possible in vivo using modified adenoviral vectors, no motor function improvement was observed in the mice, when tested on a beam walk.

The evidence reviewed here suggests a pertinent role for the therapeutic targeting of astrocytes in neural regeneration post-injury. Such approaches, however, have failed to address reactive astrogliosis secondary to neurodegenerative pathologies, including AD. There was no significant motor function amelioration seen in mice models either, indicating the need for more definitive evidence. Additionally, one must keep in mind the multitude of limitations when it comes to mouse models of human disease. The most important of which is the varying similarity to human pathology, especially when it comes to reproducing neuronal loss (59,60) as well as gene inconsistencies between mouse vs human reactive astrocytes (61).

These, together with other limiting factors, contributes to the low predictability of animal research in human clinical trials.

BACE-1 Targeted Therapy for Alzheimer's Disease Prevention

Toxic Beta-amyloid peptide accumulation and plaque formation is one of the features of AD. It is the Beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1) that contributes to the formation of Beta-amyloid peptide, and there is BACE-1 overexpression during periods of chronic stress (52,62). Animal and human studies revolving around BACE-1 targeted therapy have been ongoing for around 20 years. The advancements that have been made in the past few years have been promising. In terms of pharmaceutical developments, Neumann et al. (63) investigated the effects of BACE-1 inhibitor CNP520 for the long-term prevention of AD.

At present, approved AD medications control the symptoms, but do not prevent AD. In the previously mentioned study (63), APP-23 transgenic mice were exposed to CNP520 for over 6 months. Its effects were monitored using a Beta-amyloid specific antibody. Compared to controls, the treated mice were found to have reduced insoluble Beta-amyloid Aβ40 and Aβ42 levels. This study also concludes that CNP520 also shifts metabolism away from the amyloidogenic pathway. Additionally, plaque-associated neuroinflammation, mediated by activated astrocytes, was reduced by the BACE-1 inhibitor in the brains of mice amyloidosis models. This therefore targets the prevention of impaired neurologic function and cognitive deficits in AD.

Parkinson's Disease

PD is one of the leading progressive, neurodegenerative disorders worldwide with both physical and neuropsychiatric symptoms (64,65). There is a global rise in PD prevalence, with WHO reporting a double in PD prevalence since 1997 (66). Interestingly however, a steep rise in PD cases was reported in China (65,67,68) as well as in high-income European countries (65,69). The 2017 Global Burden of Disease Study (70) attributes the latter to their increasingly ageing population, when compared to the global population.

The pathophysiology of this movement disorder involves neuroinflammation in the substantia nigra pars compacta as well as early death of the dopaminergic nigrostriatal pathway neurones, in the midbrain (71–73). The cause of this is still not entirely clear, however, like AD, environmental factors as well as genetics seem to play a role (9,74,75). To date, several genetic mutations were found to have an association with PD. Initially, 26 years ago, it was the association of SNCA gene mutations with early-onset PD (76) that hinted to a hereditary component of PD. Indeed throughout the years to follow, the emergence of mutations in Parkin (PARK2 gene) (77), PTEN induced putative kinase 1 (PINK1 gene) (78), Daisuke-Junko-1 (DJ-1 [PARK-7 gene]) (79), Leucine-rich repeat kinase 2 (LRRK2 [PARK8 gene]) (80) and vacuolar protein sorting 35 (VPS35) (81) have further confirmed this.

Do Mutated Genes in Astrocytes Play a Role in Parkinson's Disease Pathophysiology?

In an effort to understand how mutations in these genes cause PD, several theories have emerged. Interestingly, certain PD-associated genes were found to be expressed in high levels within astrocytes of PD patients. For instance, DJ-1, which is involved in the regulation of astrocyte signal transduction (82); LRRK2 missense mutations were linked to lysosomal dysfunction and protein degradation (83); parkin mutations are hypothesized to lead to astrocytic dysfunction and therefore, neuronal death (5). This raises the question of whether having mutated genes contributes to the pathophysiology of PD, and if so, to what extent.

In 2021, Bartyl et al. (84) found no variants of glucocerebrosidase (GBA), LRRK2 and SNCA, which are risk genes for PD, within their study cohort, which included cerebrospinal fluid immunoassay analysis of 252 PD patients and 115 healthy control patients, over a timespan of 4 years. On the other hand, Di Maio et al. (85) investigated the possibility of the contribution of LRRK2 kinase gene mutation to PD. In fact, they used rodent models to show that there is an increased wildtype LRRK2 kinase activity in neurones, as well as in the nigral microglia, in idiopathic PD cases. This was causative of lysosomal dysfunction and phosphorylated alpha-synuclein protein accumulation, which are hallmarks of PD. One might attribute these conflicting results possibly due to a small sample size, patients at varied PD stages and animal model discrepancies.

The role of astrocytes in Parkinson's Disease

Idiopathic PD is characterised by cytoplasmic alpha-synuclein in brainstem neurones (86). These proteins are main components of Lewy bodies, when aggregated (87) and these aggregates negatively affect astrocytes in terms of function (5,88). Research has shown that astrocytes take up alpha-synuclein released from neurones, primarily via endocytosis (87,89–92), and subsequently this causes the production of pro-inflammatory cytokines and chemokines leading to neuroinflammation in PD patients (93,94). PD development (91). Of all brain cells, it is microglia that are the most efficient in the uptake of alpha-synuclein, and not astrocytes (95). However, recently the focus has shifted towards the potential spread of toxic molecules during aggregate

clearance by astrocytes (92,94,96) in a prion-like propagation, following their internalization (88). It is the release of aggregated alpha-synuclein that exerts toxic effects, compared to the monomeric form (96). The spread has recently been hypothesized to be due to the astrocytes' inability to completely eliminate alpha-synuclein (97,98). It is therefore possible that astrocyte-mediated spread of alpha-synuclein plays a role in the pathophysiology or progression of PD (99,100). Further in-depth research about the molecular mechanisms by which astrocytes interact with alpha-synuclein in the context of PD is vital for the development of potential therapies, including vaccines to clear extracellular alpha-synuclein, alpha-synuclein gene silencing (92), reduction (101) and immunotherapy (102,103).

Targeting Astrocytes Therapeutically

In order to counteract the neuronal loss that occurs in neurodegenerative disorders, including PD, therapeutic neuronal replenishment has been attempted. A 2013 in vitro study (104) demonstrated the trans-differentiation of fibroblasts to functional neurones through repression of a single RNA binding protein (Polypyrimidine tract-binding protein). Less than a decade later, Zhou et al. (105) have demonstrated the in vivo neuronal induction, from glial cells, in PD model mice. Initially, the researchers were able to virally deliver a novel RNA-targeting CRISPR system CasRx to mice retinas, causing a Ptbp 1 knockdown. This, in turn, resulted in the conversion of Müller glia into retinal ganglion cells (RGCs) as well as amacrine cells. This led to resolution of disease symptoms associated with RGC loss, although 2022 studies (106,107) argue that this was unlikely due to Ptbp1 knockdown in Müller glial cells. This paved the way for the similar conversion of astrocytes into neuronal tissue, for the therapeutic use in neurodegenerative diseases including PD.

In a similar manner, the conversion of astrocytes to dopaminergic neurones was subsequently attempted by (105), also in vivo, in order to induce neurons in the striatum of PD model mice. The aim was to resolve disease symptoms associated with dopaminergic neuronal loss in PD, by targeting astrocytes. PD was induced in the mouse model using 6-hydroxydopamine and striatal injection with AAV-GFAP-CasRx-Ptbp1 (or AAV-GFAP-CasRx as a control) was performed 3 weeks later. The latter causes the Ptbp1 knockdown in astrocytes, and consequently, their conversion into neurones. Astrocytes were fluorescently labelled, in order to check for expression of the mature dopaminergic marker glutaminase, which, interestingly, most induced neurones expressed. The PD mice showed an improved motor function and therefore, significantly reduced motor dysfunction.

Another example of successful direct conversion of astrocytes to dopaminergic neurones is the work of Qian et al. (108). Following chemical PD-induction using 6-hydroxydopamine, astrocytes which contributed to the reactive astrocytic response were treated with AAV-shPTB (or AAV-empty as a control). The aim was to decrease PTBP1 levels, and therefore reverse the inhibition on the neural induction loop. Indeed, the percentage of cells expressing NeuN protein, ie. that were transformed neurones, was found to increase with increasing time post-infection, reaching 80% of AAV-shPTB infected cells after 10 weeks. These converted neurones were also found to express mature neurone markers, including glutamatergic or GABAergic neuronal markers. These neurones expressed DA neurone markers including DAT, and upon testing their electrical activity, it resulted in repeated action potential firing and characteristics of mature DA neurones. Mice treated with AAV-empty did not show a significant increase in nerve fibres in the striatum, on the contrary to AAV-shPTB mice, which demonstrated a 33% restoration of damaged neurones.

Activity-induced dopamine levels were also restored in 75% of mice, which also demonstrated correction of motor phenotypes post-PD induction. Similar successful results are seen in (109–111).

Although this provides a therapeutic potential for degenerative diseases including PD, additional investigations are warranted in order to comprehensively understand the therapeutic reprograming of astrocytes and the implications associated with it. In fact, many have challenged these studies, and have not observed such results (106,107,112). For instance, Wang et al. (113) hypothesise that previous studies that reported a supposed increase in astrocyte-converted neurones, were actually detecting endogenous neurones. In their experiment, brain injury was induced in adult mice and bromodeoxyuridine (BrdU) was given, which was used as a dye to label reactive astrocytes, as well as other proliferating cells. After 1 week, AAV5 viral vectors were used to induce the co-expression of NEUROD1, a transcription factor which induces neuronal development. Whilst 74% of labelled cells did express NeuN protein, only 2% of them were positive for BrdU and NeuN proteins, ie. originating from reactive astrocytes. There were no significant changes in the density of either astrocytes or neurones, in the cortex exposed to the virus. This research also challenges the shRNA-based approach seen in (108). Apart from the low percentage of converted neurones, they were also found to be non-astrocytic in origin, using astrocyte lineage reporter yellow fluorescent protein, and PTBP1 knockdown resulted in no astrocyte-neuron conversion in vivo. This highlights the importance of lineage-tracing in order to confirm the cell origin, apart from detection of immature neurones and pre-labelling of reactive cells.

Therapeutic Potential of LRRK2 Inhibition in Parkinson's Disease

Missense LRRK2 mutations are the leading cause of autosomal dominant PD (80) and LRRK2 activation is a common finding in vulnerable dopaminergic neurons in human idiopathic PD (85). This has led to investigations regarding the therapeutic targeting of LRRK2. Jennings et al. (114) have established LRRK2 inhibition using DNL201, an LRRK2 kinase inhibitor. Astrocytes from mice that were treated with DNL201 showed reduced lysosomal protein degradation, and therefore improved function, in contrast to untreated mice. Jennings et al. have subsequently performed a clinical study where this inhibitor was evaluated in both healthy and PD patients, however further clinical studies with larger sample sizes are still needed (115). Similarly, Sanyal et al. (116) investigated the lysosomal and autophagic pathways, mainly mutations in GBA1 gene (encoding for glucocerebrosidase enzyme) as well as LRRK2 gene (encoding for the leucine-rick repeat kinase 2 enzyme). Autosomal recessive mutations in the GBA1 gene cause Gaucher's disease, a lysosomal storage disorder and the heterozygous phenotype is a risk factor for PD. This study shows that inhibition of LRRK2 reversed lysosomal deficits caused by GBA1 mutations in mice astrocytes, making it a promising strategy for PD treatment.

Conclusion

Astrocytes are truly indispensable cells when it comes to neuronal health and functioning, exhibiting diverse roles and contributions. This literature review discusses the complex interplay between astrocytes and the two main neurodegenerative disorders; AD and PD. In AD, Beta-amyloid peptide accumulation and plaque formation is the main pathophysiological mechanism of the disease.

As part of the brain's innate response to CNS insult, astrocytes attempt to respond through 'reactive astrogliosis' in order to restore homeostasis. However, although being inherently beneficial, this process has been linked to the neurotoxicity and impaired synaptic transmission seen in AD. Additionally, astrocyte-derived cytokines were found to contribute to the progression of AD. Similarly, in PD, astrocytes indirectly contribute to neuroinflammation and subsequent neuronal death through endocytosis of neuronal alpha-synuclein aggregates, in an effort of astrocytes to clear these aggregates. In light of this, astroglia have been largely targeted therapeutically for AD and PD, with the latest advancements revolving around the conversion of reactive astrocytes and glial scars into potential neuronal tissue. However, challenges and limitations still persist, highlighting the need for more definitive evidence surrounding astrocytic involvement in order to ultimately have improved, effective clinical strategies.

Funding

No funding was received

Conflict of Interest

The author declares no conflict of interests

List of Abbreviations

Abbreviation	Definition
AD	Alzheimer's Disease
PD	Parkinson's Disease
TBI	Traumatic Brain Injury
GFAP	Glial Fibrillary Acid Protein
APP	Amyloid Precursor protein
PSEN1	Presenilin-1
PSEN2	Presenilin-2
APOE	Apolipoprotein E
TNF	Tumour Necrosis Factor
IL-1α	Interleukin-1α
IL-6	Interleukin-6
IL-4	Interleukin-4
C1q	Complement Protein 1q
CNS	Central Nervous System
PTBP1	Polypyrimidine Tract-Binding Protein 1
BACE-1	Beta-site Amyloid Precursor Protein Cleaving Enzyme-1
RGCs	Retinal Ganglion Cells
BrdU	Bromodeoxyuridine

Bibliography

Verkhratsky A, Parpura V, Li B, Scuderi C. Astrocytes: the housekeepers and guardians of the CNS. Adv Neurobiol. 2021;26:21–53.

2. Verkhratsky A, Semyanov A, Zorec R. Physiology of astroglial excitability. Function (Oxf). 2020 Sep 4;1(2):zqaa016.

3. Wei DC, Morrison EH. Histology, Astrocytes. StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.

4. Wang H, Song G, Chuang H, Chiu C, Abdelmaksoud A, Ye Y, et al. Portrait of glial scar in neurological diseases. Int J Immunopathol Pharmacol. 2018;31:2058738418801406.

5. Phatnani H, Maniatis T. Astrocytes in neurodegenerative disease. Cold Spring Harb Perspect Biol. 2015 Apr 15;7(6).

6. Lee H-G, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases. Nat Rev Drug Discov. 2022 May;21(5):339–58.

7. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol. 2010 Jan;119(1):7–35.

8. Verkhratsky A, Butt A, Li B, Illes P, Zorec R, Semyanov A, et al. Astrocytes in human central nervous system diseases: a frontier for new therapies. Signal Transduct Target Ther. 2023 Oct 13;8(1):396.

9. Salgado A. Handbook of Innovations in Central Nervous System Regenerative Medicine. 1st ed. Amsterdam: Elsevier; 2020.

10. Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium. Neurology. 2020 Aug 4;95(5):e519–31.

11. Prof Martin Prince, Prof Anders Wimo, Dr Maëlenn Guerchet, Miss Gemma-Claire Ali, Dr Yu-Tzu Wu, Dr Matthew Prina. World Alzheimer Report 2015: The Global Impact of Dementia. 2015 Aug;

12. Wu Y-T, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time - current evidence. Nat Rev Neurol. 2017 Jun;13(6):327–39.

13. Alzheimer Europe. Dementia in Europe Yearbook 2019. Alzheimer Europe; 2019.

14. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Jan;18(1):88–106.

15. Zhang XX, Tian Y, Wang ZT, Ma YH, Tan L, Yu JT. The epidemiology of alzheimer's disease modifiable risk factors and prevention. J Prev Alzheimers Dis. 2021;8(3):313–21.

16. Monteiro AR, Barbosa DJ, Remião F, Silva R. Alzheimer's disease: Insights and new prospects in disease pathophysiology, biomarkers and disease-modifying drugs. Biochem Pharmacol. 2023 May;211:115522.

17. Prince M, Ali G-C, Guerchet M, Prina AM, Albanese E, Wu Y-T. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther. 2016 Jul 30;8(1):23.

18. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023 Apr;19(4):1598–695.

19. Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harb Perspect Med. 2012 Oct 1;2(10).

20. Eid A, Mhatre I, Richardson JR. Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. Pharmacol Ther. 2019 Jul;199:173–87.

21. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. [version 1; peer review: 2 approved]. F1000Res. 2018 Jul 31;7.

22. Khakh BS, Deneen B. The emerging nature of astrocyte diversity. Annu Rev Neurosci. 2019 Jul 8;42:187–207.

23. Thakur S, Dhapola R, Sarma P, Medhi B, Reddy DH. Neuroinflammation in alzheimer's disease: current progress in molecular signaling and therapeutics. Inflammation. 2023 Feb;46(1):1–17.
24. Colton CA, Mott RT, Sharpe H, Xu Q, Van Nostrand WE, Vitek MP. Expression profiles for macrophage alternative activation genes in AD and in mouse models of AD. J Neuroinflammation. 2006 Sep 27;3:27.
25. Morgan D. Modulation of microglial activation state following passive immunization in amyloid depositing transgenic mice. Neurochem Int. 2006 Jul;49(2):190–4.
26. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions. Nat Neurosci. 2021 Mar;24(3):312–25.
27. Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci. 2009 Dec;32(12):638–47.
28. Moyse E, Krantic S, Djellouli N, Roger S, Angoulvant D, Debacq C, et al. Neuroinflammation: A possible link between chronic vascular disorders and neurodegenerative diseases. Front Aging Neurosci. 2022 May 19;14:827263.
29. Simpson JE, Ince PG, Lace G, Forster G, Shaw PJ, Matthews F, et al. Astrocyte phenotype in relation to Alzheimer-type pathology in the ageing brain. Neurobiol Aging. 2010 Apr;31(4):578–90.
30. Liddelow SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. Immunity. 2017 Jun 20;46(6):957–67.
31. Zhang L, Lei Z, Guo Z, Pei Z, Chen Y, Zhang F, et al. Development of Neuroregenerative Gene Therapy to Reverse Glial Scar Tissue Back to Neuron-Enriched Tissue. Front Cell Neurosci. 2020 Nov 5;14:594170.
32. Liu J, Xin X, Sun J, Fan Y, Zhou X, Gong W, et al. Dual-targeting AAV9P1-mediated neuronal reprogramming in a mouse model of traumatic brain injury. Neural Regen Res. 2024 Mar;19(3):629–35. .
33. Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R, et al. Astrocyte scar formation aids central nervous system axon regeneration. Nature. 2016 Apr 14;532(7598):195–200.
34. Garwood CJ, Pooler AM, Atherton J, Hanger DP, Noble W. Astrocytes are important mediators of Aβ-induced neurotoxicity and tau phosphorylation in primary culture. Cell Death Dis. 2011 Jun 2;2(6):e167.
35. Lian H, Yang L, Cole A, Sun L, Chiang AC-A, Fowler SW, et al. NFκB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. Neuron. 2015 Jan 7;85(1):101–15.
36. Ries M, Sastre M. Mechanisms of aβ clearance and degradation by glial cells. Front Aging Neurosci. 2016 Jul 5;8:160.
37. Porchet R, Probst A, Bouras C, Dráberová E, Dráber P, Riederer BM. Analysis of glial acidic fibrillary protein in the human entorhinal cortex during aging and in Alzheimer's disease. Proteomics. 2003 Aug;3(8):1476–85.
38. Vanzani MC, Iacono RF, Caccuri RL, Berria MI. Immunochemical and morphometric features of astrocyte reactivity vs. plaque location in Alzheimer's disease. Medicina (B Aires). 2005;65(3):213–8.
39. Brezovakova V, Sykova E, Jadhav S. Astrocytes Derived from Familial and Sporadic Alzheimer's Disease iPSCs Show Altered Calcium Signaling and Respond Differently to Misfolded Protein Tau. Cells. 2022 Apr 22;11(9).
40. Verkhratsky A, Zorec R, Rodríguez JJ, Parpura V. Astroglia dynamics in ageing and Alzheimer's disease. Curr Opin Pharmacol. 2016 Feb;26:74–9.
41. Rodríguez JJ, Zallo F, Gardenal E, Cabot J, Busquets X. Prominent and conspicuous astrocyte atrophy in human sporadic and familial Alzheimer's disease. Brain Struct Funct. 2023 Dec;228(9):2103–13.

42. Hsu ET, Gangolli M, Su S, Holleran L, Stein TD, Alvarez VE, et al. Astrocytic degeneration in chronic traumatic encephalopathy. Acta Neuropathol. 2018 Dec;136(6):955–72.
43. A Armstrong R. Risk factors for Alzheimer's disease. Folia Neuropathol. 2019;57(2):87–105.
44. Simonovitch S, Schmukler E, Bespalko A, Iram T, Frenkel D, Holtzman DM, et al. Impaired autophagy in APOE4 astrocytes. J Alzheimers Dis. 2016;51(3):915–27.
45. Mamun AA, Uddin MS, Bin Bashar MF, Zaman S, Begum Y, Bulbul IJ, et al. Molecular Insight into the Therapeutic Promise of Targeting APOE4 for Alzheimer's Disease. Oxid Med Cell Longev. 2020 May 15;2020:5086250.
46. Poon CH, Wang Y, Fung M-L, Zhang C, Lim LW. Rodent Models of Amyloid-Beta Feature of Alzheimer's Disease: Development and Potential Treatment Implications. Aging Dis. 2020 Oct 1;11(5):1235–59.
47. Prescott K, Münch AE, Brahms E, Weigel MM, Inoue K, Buckwalter MS, et al. Blocking formation of neurotoxic reactive astrocytes is beneficial following stroke. BioRxiv. 2023 Oct 16;
48. Kloske CM, Barnum CJ, Batista AF, Bradshaw EM, Brickman AM, Bu G, et al. APOE and immunity: Research highlights. Alzheimers Dement. 2023 Jun;19(6):2677–96.
49. Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res Rev. 2021 Dec;72:101503.
50. Viejo L, Noori A, Merrill E, Das S, Hyman BT, Serrano-Pozo A. Systematic review of human post-mortem immunohistochemical studies and bioinformatics analyses unveil the complexity of astrocyte reaction in Alzheimer's disease. Neuropathol Appl Neurobiol. 2022 Feb;48(1):e12753.
51. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017 Jan 26;541(7638):481–7.
52. Rubio-Perez JM, Morillas-Ruiz JM. A review: inflammatory process in Alzheimer's disease, role of cytokines. ScientificWorldJournal. 2012 Apr 1;2012:756357.
53. Su F, Bai F, Zhang Z. Inflammatory Cytokines and Alzheimer's Disease: A Review from the Perspective of Genetic Polymorphisms. Neurosci Bull. 2016 Oct;32(5):469–80.
54. Gyengesi E, Rangel A, Ullah F, Liang H, Niedermayer G, Asgarov R, et al. Chronic Microglial Activation in the GFAP-IL6 Mouse Contributes to Age-Dependent Cerebellar Volume Loss and Impairment in Motor Function. Front Neurosci. 2019 Apr 3;13:303.
55. Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, et al. Interleukin-10 in the brain. Crit Rev Immunol. 2001;21(5):427–49.
56. Toft A, Scott DT, Barnett SC, Riddell JS. Electrophysiological evidence that olfactory cell transplants improve function after spinal cord injury. Brain. 2007 Apr;130(Pt 4):970–84.
57. Lu P, Wang Y, Graham L, McHale K, Gao M, Wu D, et al. Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. Cell. 2012 Sep 14;150(6):1264–73.
58. Falkner S, Grade S, Dimou L, Conzelmann K-K, Bonhoeffer T, Götz M, et al. Transplanted embryonic neurons integrate into adult neocortical circuits. Nature. 2016 Nov 10;539(7628):248–53.
Nov 10;539(7628):248–53.
59. Bracken MB. Why animal studies are often poor predictors of human reactions to exposure. J R Soc Med. 2009 Mar;102(3):120–2.
60. Sanchez-Varo R, Mejias-Ortega M, Fernandez-Valenzuela JJ, Nuñez-Diaz C, Caceres-Palomo L, Vegas-Gomez L, et al. Transgenic mouse models of alzheimer's disease: an integrative analysis. Int J Mol Sci. 2022 May 12;23(10).

61. Das S, Li Z, Noori A, Hyman BT, Serrano-Pozo A. Meta-analysis of mouse transcriptomic studies supports a context-dependent astrocyte reaction in acute CNS injury versus neurodegeneration. J Neuroinflammation. 2020 Jul 31;17(1):227.
62. Uddin MS, Lim LW. Glial cells in Alzheimer's disease: From neuropathological changes to therapeutic implications. Ageing Res Rev. 2022 Jun;78:101622.
63. Neumann U, Ufer M, Jacobson LH, Rouzade-Dominguez M-L, Huledal G, Kolly C, et al. The BACE-1 inhibitor CNP520 for prevention trials in Alzheimer's disease. EMBO Mol Med. 2018 Nov;10(11).
64. DeMaagd G, Philip A. Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P T. 2015 Aug;40(8):504–32.
65. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021 Jun 12;397(10291):2284–303.
66. World Health Organisation (WHO). Parkinson disease: a public health approach; Technical brief. World Health Organisation (WHO); 2022 Jun.
67. Zheng Z, Zhu Z, Zhou C, Cao L, Zhao G. Burden of Parkinson Disease in China, 1990-2019: Findings from the 2019 Global Burden of Disease Study. Neuroepidemiology. 2023;57(1):51–64.
68. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):939–53.
69. Ou Z, Pan J, Tang S, Duan D, Yu D, Nong H, et al. Global trends in the incidence, prevalence, and years lived with disability of parkinson's disease in 204 countries/territories from 1990 to 2019. Front Public Health. 2021 Dec 7;9:776847.
70. Deuschl G, Beghi E, Fazekas F, Varga T, Christoforidi KA, Sipido E, et al. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. Lancet Public Health. 2020 Oct;5(10):e551–67.
71. Kouli A, Torsney KM, Kuan W-L. Parkinson's disease: etiology, neuropathology, and pathogenesis. In: Stoker TB, Greenland JC, editors. Parkinson's disease: pathogenesis and clinical aspects. Brisbane (AU): Codon Publications; 2018.
72. Guatteo E, Berretta N, Monda V, Ledonne A, Mercuri NB. Pathophysiological features of nigral dopaminergic neurons in animal models of parkinson's disease. Int J Mol Sci. 2022 Apr 19;23(9).
73. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol. 2022 Nov;22(11):657–73.
74. Kline EM, Houser MC, Herrick MK, Seibler P, Klein C, West A, et al. Genetic and environmental factors in parkinson's disease converge on immune function and inflammation. Mov Disord. 2021 Jan;36(1):25–36.
75. Ball N, Teo W-P, Chandra S, Chapman J. Parkinson's disease and the environment. Front Neurol. 2019 Mar 19;10:218.
76. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997 Jun 27;276(5321):2045–7.
77. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998 Apr 9;392(6676):605–8.
78. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MMK, Harvey K, Gispert S, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science. 2004 May 21;304(5674):1158–60.
79. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science. 2003 Jan 10;299(5604):256–9.

80. Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron. 2004 Nov 18;44(4):601–7.
81. Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN, et al. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet. 2011 Jul 15;89(1):168–75.
82. Booth HDE, Hirst WD, Wade-Martins R. The role of astrocyte dysfunction in parkinson's disease pathogenesis. Trends Neurosci. 2017 Jun;40(6):358–70.
83. Schapansky J, Khasnavis S, DeAndrade MP, Nardozzi JD, Falkson SR, Boyd JD, et al. Familial knockin mutation of LRRK2 causes lysosomal dysfunction and accumulation of endogenous insoluble α-synuclein in neurons. Neurobiol Dis. 2018 Mar;111:26–35.
84. Bartl M, Dakna M, Galasko D, Hutten SJ, Foroud T, Quan M, et al. Biomarkers of neurodegeneration and glial activation validated in Alzheimer's disease assessed in longitudinal cerebrospinal fluid samples of Parkinson's disease. PLoS One. 2021 Oct 7;16(10):e0257372.
85. Di Maio R, Hoffman EK, Rocha EM, Keeney MT, Sanders LH, De Miranda BR, et al. LRRK2 activation in idiopathic Parkinson's disease. Sci Transl Med. 2018 Jul 25;10(451).
86. Isonaka R, Goldstein DS, Zhu W, Yoon E, Ehrlich D, Schindler AB, et al. α-Synuclein Deposition in Sympathetic Nerve Fibers in Genetic Forms of Parkinson's Disease. Mov Disord. 2021 Oct;36(10):2346–57.
87. Lee H-J, Kim C, Lee S-J. Alpha-synuclein stimulation of astrocytes: Potential role for neuroinflammation and neuroprotection. Oxid Med Cell Longev. 2010 Aug;3(4):283–7.
88. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting Alpha-Synuclein as a Therapy for Parkinson's Disease. Front Mol Neurosci. 2019 Dec 5;12:299.
89. Filippini A, Mutti V, Faustini G, Longhena F, Ramazzina I, Rizzi F, et al. Extracellular clusterin limits the uptake of α-synuclein fibrils by murine and human astrocytes. Glia. 2021 Mar;69(3):681–96.
90. Braidy N, Gai W-P, Xu YH, Sachdev P, Guillemin GJ, Jiang X-M, et al. Uptake and mitochondrial dysfunction of alpha-synuclein in human astrocytes, cortical neurons and fibroblasts. Transl Neurodegener. 2013 Oct 4;2(1):20.
91. Takahashi S, Mashima K. Neuroprotection and disease modification by astrocytes and microglia in parkinson disease. Antioxidants (Basel). 2022 Jan 17;11(1).
92. Rodriguez L, Marano MM, Tandon A. Import and Export of Misfolded α-Synuclein. Front Neurosci. 2018 May 23;12:344.
93. Lee H-J, Suk J-E, Patrick C, Bae E-J, Cho J-H, Rho S, et al. Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. J Biol Chem. 2010 Mar 19;285(12):9262–72.
94. Neupane S, De Cecco E, Aguzzi A. The Hidden Cell-to-Cell Trail of α-Synuclein Aggregates. J Mol Biol. 2023 Jun 15;435(12):167930.
95. Kim C, Kwon S, Iba M, Spencer B, Rockenstein E, Mante M, et al. Effects of innate immune receptor stimulation on extracellular α-synuclein uptake and degradation by brain resident cells. Exp Mol Med. 2021 Feb 16;53(2):281–90.
96. Choi YR, Park SJ, Park SM. Molecular events underlying the cell-to-cell transmission of α-synuclein. FEBS J. 2021 Dec;288(23):6593–602.
97. Miyazaki I, Asanuma M. Neuron-Astrocyte Interactions in Parkinson's Disease. Cells. 2020 Dec 7;9(12).
98. Choi I, Zhang Y, Seegobin SP, Pruvost M, Wang Q, Purtell K, et al. Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. Nat Commun. 2020 Mar 13;11(1):1386.

99. Valdinocci D, Radford RAW, Siow SM, Chung RS, Pountney DL. Potential Modes of Intercellular α-Synuclein Transmission. Int J Mol Sci. 2017 Feb 22;18(2).
100. Kim YE, Lai TT, Kim YJ, Jeon B. Preferential microglial activation associated with pathological alpha synuclein transmission. J Clin Neurosci. 2020 Nov 2;81:469–76.
101. Alarcón-Arís D, Recasens A, Galofré M, Carballo-Carbajal I, Zacchi N, Ruiz-Bronchal E, et al. Selective α-Synuclein Knockdown in Monoamine Neurons by Intranasal Oligonucleotide Delivery: Potential Therapy for Parkinson's Disease. Mol Ther. 2018 Feb 7;26(2):550–67.
102. Masliah E, Rockenstein E, Mante M, Crews L, Spencer B, Adame A, et al. Passive immunization reduces behavioral and neuropathological deficits in an alpha-synuclein transgenic model of Lewy body disease. PLoS One. 2011 Apr 29;6(4):e19338.
103. Sanchez-Guajardo V, Annibali A, Jensen PH, Romero-Ramos M. α-Synuclein vaccination prevents the accumulation of parkinson disease-like pathologic inclusions in striatum in association with regulatory T cell recruitment in a rat model. J Neuropathol Exp Neurol. 2013 Jul;72(7):624–45.
104. Xue Y, Ouyang K, Huang J, Zhou Y, Ouyang H, Li H, et al. Direct conversion of fibroblasts to neurons by reprogramming PTB-regulated microRNA circuits. Cell. 2013 Jan 17;152(1–2):82–96.
105. Zhou H, Su J, Hu X, Zhou C, Li H, Chen Z, et al. Glia-to-Neuron Conversion by CRISPR-CasRx Alleviates Symptoms of Neurological Disease in Mice. Cell. 2020 Apr 30;181(3):590–603.e16.
106. Hoang T, Kim DW, Appel H, Pannullo NA, Leavey P, Ozawa M, et al. Genetic loss of function of Ptbp1 does not induce glia-to-neuron conversion in retina. Cell Rep. 2022 Jun 14;39(11):110849.
107. Xie Y, Zhou J, Chen B. Critical examination of Ptbp1-mediated glia-to-neuron conversion in the mouse retina. Cell Rep. 2022 Jun 14;39(11):110960.
108. Qian H, Kang X, Hu J, Zhang D, Liang Z, Meng F, et al. Reversing a model of Parkinson's disease with in situ converted nigral neurons. Nature. 2020 Jun 24;582(7813):550–6.
109. Maimon R, Chillon-Marinas C, Snethlage CE, Singhal SM, McAlonis-Downes M, Ling K, et al. Therapeutically viable generation of neurons with antisense oligonucleotide suppression of PTB. Nat Neurosci. 2021 Aug;24(8):1089–99.
110. Xiang Z, Xu L, Liu M, Wang Q, Li W, Lei W, et al. Lineage tracing of direct astrocyte-to-neuron conversion in the mouse cortex. Neural Regen Res. 2021 Apr;16(4):750–6.
111. Yang R-Y, Chai R, Pan J-Y, Bao J-Y, Xia P-H, Wang Y-K, et al. Knockdown of polypyrimidine tract binding protein facilitates motor function recovery after spinal cord injury. Neural Regen Res. 2023 Feb;18(2):396–403.
112. Guo T, Pan X, Jiang G, Zhang D, Qi J, Shao L, et al. Downregulating PTBP1 fails to convert astrocytes into hippocampal neurons and to alleviate symptoms in Alzheimer's mouse models. J Neurosci. 2022 Aug 9;42(38):7309–17.
113. Wang L-L, Serrano C, Zhong X, Ma S, Zou Y, Zhang C-L. Revisiting astrocyte to neuron conversion with lineage tracing in vivo. Cell. 2021 Oct 14;184(21):5465–5481.e16.
114. Jennings D, Huntwork-Rodriguez S, Henry AG, Sasaki JC, Meisner R, Diaz D, et al. Preclinical and clinical evaluation of the LRRK2 inhibitor DNL201 for Parkinson's disease. Sci Transl Med. 2022 Jun 8;14(648):eabj2658.
115. Jennings D, Huntwork-Rodriguez S, Vissers MFJM, Daryani VM, Diaz D, Goo MS, et al. LRRK2 Inhibition by BIIB122 in Healthy Participants and Patients with Parkinson's Disease. Mov Disord. 2023 Mar;38(3):386–98.
116. Sanyal A, DeAndrade MP, Novis HS, Lin S, Chang J, Lengacher N, et al. Lysosome and Inflammatory Defects in GBA1-Mutant Astrocytes Are Normalized by LRRK2 Inhibition. Mov Disord. 2020 May;35(5):760–73.