Analyzing the Connections of Microglial Phenotypes in the Progression of Neurodegeneration and Tumors And The Future For Therapeutic Treatments

Sanjana Vidhyacharan

Abstract:
Immunotherapies have proven immense success in treating autoimmune diseases in the human body but researchers know little about the effectiveness of using the brain's immune cells, microglia, to treat neurodegeneration and tumors. But it can be inferred from microglia's plasticity and heterogeneity that they could play a key role in altering the future for therapeutic treatment options by targeting specific glial factors and attacking lesions in the early stage of progression. Microglia can be easily influenced by their microenvironment to progress or impede inflammation and within any given disease, there is a diverse microenvironment present full of various phenotypes. Understanding how these changes can be triggered can be invaluable in treating various forms of brain disease by creating targeted treatments. Specifically in Gliomas, microglia have shown to communicate with tumor cells to improve function so limiting the glioma cells to work in an autocrine as opposed to a paracrine manner will significantly hinder their growth and the tumor severity. In neurodegeneration (Alzheimer's and Parkinson's), TREM2 mutations have shown to be both neuroprotective and neurotoxic but using microglia as a tool to inhibit TREM2 before neurodegeneration reaches its untreatable stages could be the key towards finding a treatment for these incurable diseases. Utilizing the brain's innate negative feedback loop and the key players in this loop could be the key towards unlocking new ways to approach existing diseases and possibly treat them.

What is Microglia and What Role Does It Play in Promoting Disease?

I. Background Information

Just like the human body, the brain also has built in immune cells that are meant to fend off disease and regulate the microenvironment to prevent inflammation. But in the human brain specifically, these immune cells perform homeostatic functions and also help in rebuilding synaptic connections. These immune cells are called microglia, which originate from erythro myeloid progenitors that began in the blood islands of the yolk sac and migrate to the developing CNS to mature into microglia. Like the body's immune cells, microglia are adept at fighting and detecting inflammation in the brain and are easily triggered by their microenvironment to change phenotypes. These slight phenotypical changes can cause chaos but also growth in the brain depending on the functions they play in various forms of brain disease. Therefore, attempting to treat brain disease in a targeted way rather than using invasive and broad therapies could be the key towards stopping progression in early stages (Radin & Tsirka, 2020).

II. M1 and M2 Phenotypes

Easily influenced by their environment, microglia assume a diversity of phenotypes with the ability to shift phenotypes to keep tissue homeostasis. Widely researched microglial activation is often categorized into two opposite types: classical (M1) or alternative (M2), although further research indicates more to the picture. (Wu & Watabe, 2017)

M1 phenotype microglia exerts pro-inflammatory activities and are then polarized into M2 which is an anti-inflammatory response. M1 activation of microglia is also known as classical activation and these microglia have shown to produce specific cytokines and chemokines to

promote neurotoxicity. Chemokines are a family of small proteins known to attract immune cells, such as leukocytes (white blood cells), to sites of infection, tissue damage, or inflammation.

When talking about M1 microglia specifically, it has shown that M1 is often triggered by type 1 chemokines. Some examples of type 1 chemokines are LPS, TNF-a, and some other lipoproteins. These cytokines perform pro-inflammatory immune function by producing pro-inflammatory cytokines which eventually express signal transducer and activator of transcription 1 (STAT1). STAT 1 is a transcription factor, which is a protein that regulates gene expression by binding to specific DNA sequences in the promoter region of target genes. It is particularly important in the immune response to viral infections and has roles in cell proliferation, differentiation, and apoptosis. Dysregulation of STAT1 activity has been associated with various diseases, including immune disorders and cancer. (Wu & Watabe, 2017)

In contrast, M2 phenotype microglia have shown to exhibit functions such as phagocytosis, clearing of cell debris, and extracellular matrix reconstruction, all leading to neuron survival and neuroprotection. These anti-inflammatory activities are activated by cytokines which produce a variety of tissue growth factors, fibroblast growth (tissue repair and wound healing), and a factor shown for pro-survival: prostaglandin. Specifically for M2, these cytokines are type 2 which include IL-4, IL-10, IL-13, and transforming growth factor-β (TGF-β). They have an anti-inflammatory immune response by producing immunosuppressive factors and exhibit high levels of STAT3, another transcription factor which decreases the expression of surface molecules in microglia that are necessary for antigen presentation (Wu & Watabe, 2017). Antigen presentation is critical for the coordination and regulation of the immune response. It allows the immune system to distinguish between self and non-self and mount specific responses against invading pathogens or abnormal cells while avoiding harmful reactions against the body's own tissues. This leads to adaptive immunity and eventually, the body building up protection against infections and disease (Wang et al., 2022). Below is a figure highlighting specific markers and chemokines used to trigger M1 or M2 activation.

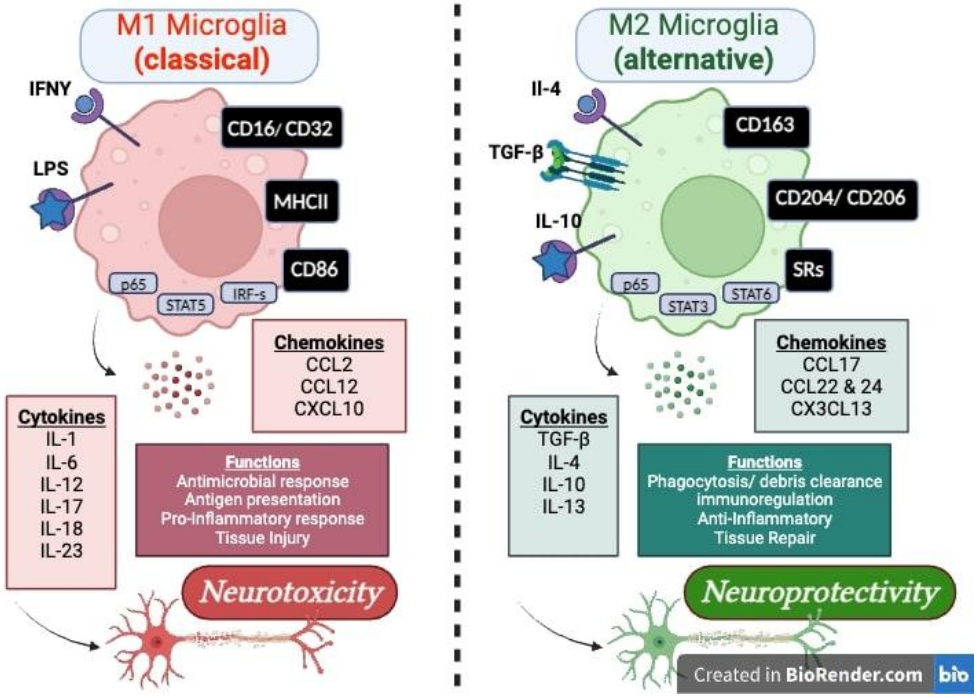

Image Description: The left column represents the M1 microglia phenotype which most commonly promotes neurotoxicity. It describes the various cytokines, chemokines, functions, and even a diagram of a classically activated microglia. The right column represents the M2 microglial phenotype which most commonly promotes neuroprotection. The figure describes various cytokines, chemokines, functions, and a diagram of an alternatively activated microglia as well as subtypes of the phenotype. However, further science has shown that microglia can be categorized into many more phenotypes that do not primarily exhibit either pro or anti-inflammatory functions (discussed later in the paper) (Created with BioRender.com).

Often, microglia can be easily influenced by their microenvironment through minute factors and understanding the process of which microglia can elicit different immune responses can be important in targeting specific pathways to stop disease progression.

III. Understanding M1 to M2 Plasticity

Delving further into this change from anti-inflammatory to pro-inflammatory microglia, it is important to discuss what factors can polarize a M1 microglia to become M2 and whether this process is reversible. Understanding the process can help with understanding neurodegeneration, such as how it originates and spreads over time.

The polarization pathway for an M1 and M2 microglial phenotype can be best described as a negative feedback loop. A negative feedback loop is important in restoring homeostasis even when situations are abnormal. It is important to understand that the polarization pathway of M1 to M2 is not a linear, one-directional pathway but rather a cycle with many branches and sub-pathways to increase heterogeneity and easy transitions between the inflammatory states. It is structured like this intentionally to find and reduce inflammation after disease strikes but can backfire if one phenotype is triggered for too long. For the purpose of this paper, we shall look at plasticity in the M1 to M2 direction just for the sake of clarity, but it is also highly viable for a microglia to polarize in the opposite direction as well.

M1 to M2 polarization first begins in the Toll-like Receptor Signal Pathways (TLR), which belong to a transmembrane pattern-recognition receptor family highly expressed in resident immune cells like microglia. The ligand of the TLR is lipopolysaccharide (LPS), which is a strong factor in regulating inflammatory mediators and M1 microglia polarization. LPS binds its binding protein which starts a pro-inflammatory cascade and eventually activates the transforming growth factor and pro-inflammatory pathways such as nuclear factor kappa-B (NF-κB) (Guo et al., 2022).

NF-κB is a key transcription factor related to M1 microglial activation since inhibiting its pathway has driven microglia to polarize to the M2 phenotype. If non-activated, NF-κB is left in the cytoplasm, but when activated by TAK1 complex, it can translocate into the nucleus, bind to target promoters, and transcribe pro-inflammatory genes. TAK-1 also triggers another signaling pathway named mitogen-activated protein kinases (MAPK). This pathway signals and exerts anti-inflammatory effects as well as M2 polarization (Guo et al., 2022).

To recap, activated TLR4, a part of the Toll-Like Receptor Pathway, starts a pro-inflammatory cascade which involves tumor necrosis factors and a TAK1 complex. This TAK1 complex triggers two separate pro-inflammatory pathways: NF-κB and MAPKs. The NF-κB uses the activated TAK1 complex to catalyze the phosphorylation of proteins. This causes NF-κB to translocate into the nucleus where pro-inflammatory genes are transcribed. On the other hand, MAPK activates the protein AP-1 which exerts anti-inflammatory effects as opposed to NF-κB's pro-inflammatory cascade (Guo et al., 2022).

Separate from the above two pathways, the Janus Kinase/Signal Transducer and Activator of Transcription Signal Pathway (JAK/STAT) uses the transcription factor STAT1 covered earlier. STAT1 has shown to help with cell apoptosis and pro-inflammatory responses. Activation of the Janus Kinase induced the phosphorylation of the STAT transcription protein

family and in this process, SOCS, or suppressors of cytokine signaling, have shown to inhibit phosphorylation and attenuate inflammatory responses (Guo et al., 2022).

Other smaller signal pathways have shown to play a role in M2 polarization as well, specifically AMP-activated protein kinase. During inflammation, the intracellular Calcium increases and triggers a highly conserved cascade which phosphorylates AMPK and is a key energy sensor in many tissues. Below is a figure entailing the whole polarization process (Guo et al., 2022).

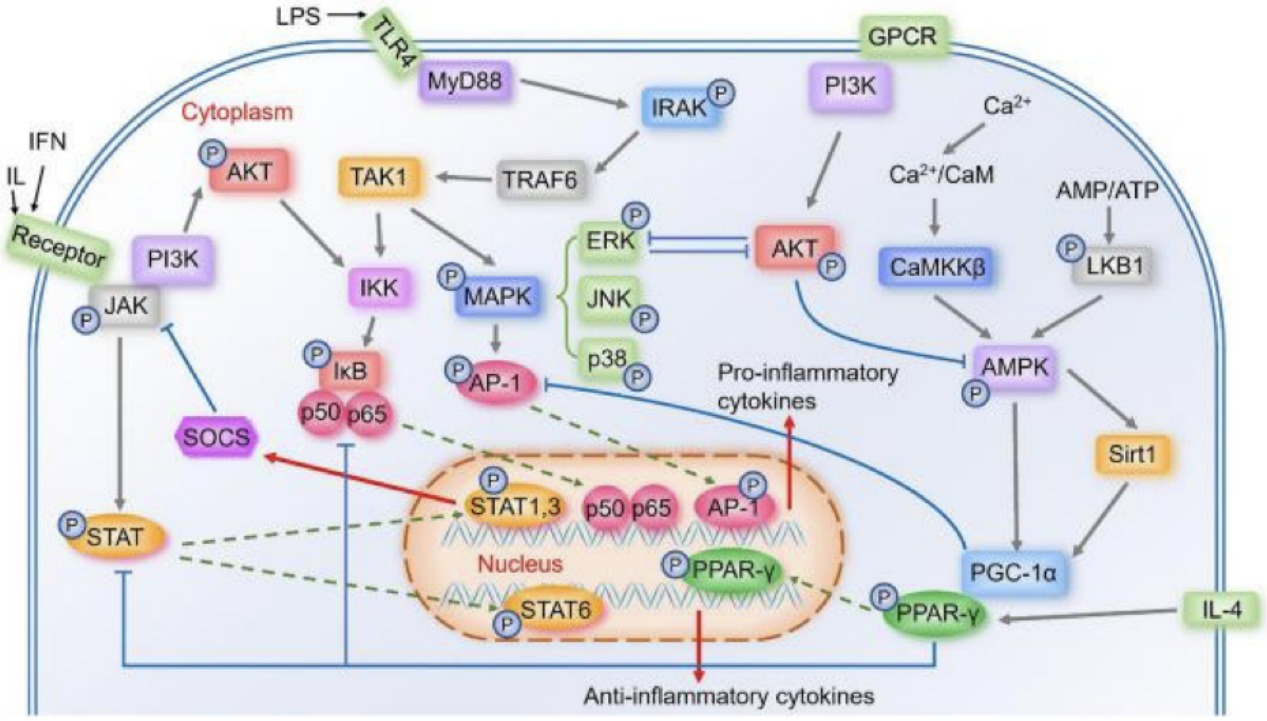

Image description: The polarization pathway begins in the TLR pathway in green on the top. Through following the arrows of that pathway, it is shown that anti-inflammatory cytokines are released via the JAK and pro-inflammatory cytokines are released through the AP-1 protein. Take note of the structure. It is branched into many subsections and many of the arrows connect to one output, indicating shared pathways.

The process of polarization is a cyclic process and can be done in any order. This is the reason why the brain and the body's immune system operates as a negative feedback loop since it ensures that the body returns to homeostasis. The brain, especially, has become adept through the years at looking for receptors and inflammation and triggering according pathways to process anti-inflammatory response or pro-inflammatory response. But sometimes, these immune cells work against the body.

What is the Role of Microglial Phenotypes in Stage 1-3 Gliomas and Stage 4 GBMs?

I. Tumor and Brain Cell Communication

One of the most predominant brain lesions discussed and researched are tumors, most commonly, gliomas. Understanding the role microglia can play in furthering the progression of tumors as well as stopping progression can be the future for using microglia as a strategy to attack the brain's immune system. But before understanding microglia in specificity in various

tumor types, it is important to understand how a tumor cell and a brain cell communicate to further tumor progression.

It starts when secreted soluble factors from tumor cells stimulate microglia and astrocyte activation and induces p-38 MAPK activation, up-regulation of MMP (matrix-metalloproteinases), which are enzymes that break down proteins and cause the ECM to break down and allow tumor cells to invade. Tumor cells also produce cytokines and chemokines, which makes β-catenin accumulate in the cytoplasm. Eventually, specific genes involved in cell proliferation and embryonic development are activated by these cytokines and with an accumulation of cytokines and β-catenin promoting growth, microglia create a favorable microenvironment for tumors to progress (Wu & Watabe, 2017).

II. In Gliomas (Stages I-III)

Gliomas are the most prevalent primary malignant tumor type of the central nervous system (CNS), constituting more than 80% of malignant CNS tumors in the United States. They can be separated into four total stages characterized by their degree of metastasis, with the most severe being named Glioblastoma or GBM. The standard care involves maximal safe surgical resection, followed by fractionated radiation therapy with the alkylating agent temozolomide (Radin & Tsirka, 2020). However, targeting these tumor growths early in the progression might be the key to furthering damage.

In a recent experiment testing for overlaps between cytokines found in microglia versus tumor cells, it was found that glioma cells have the ability to induce IL-10, an interleukin most prominently found in neuroprotective M2 microglia. Additionally, microglia also release IL-6 via periostin release, and this interleukin has been found in a microenvironment of high grade gliomas. Further, these microenvironments can also be tested for the lysosomal glycoprotein CD68+ which is present in a variety of cancerous and normal cells such as macrophages, microglia, and other tumor-associated glial cells.When tested for all these markers, it is clear to see that tumor cells and microglia have a great degree of overlap in their microenvironment but also a signaling pathway which is the key towards understanding the interactions between these cell types (Zhang et al., 2012). In this experiment, microglia are also co-cultured with glioma cells and it is shown that glioma cells act in a paracrine manner. In other words, they are unable to self-regulate their activity and rely on the signals transmitted by microglia to metastasize and progress. Therefore, inhibiting or blocking the communication between glioma cells and microglia could significantly hinder their growth and avoid the need for tumor resections. Additionally, targeting the CCL2/CCR2/IL-6 axis in the dialog between glioma and microglia can be a future for therapeutic treatments especially because tumor cells thrive on the communication with other cells.

III. In Glioblastomas (Stage IV)

In stage 4 gliomas or Glioblastomas, the role of microglia is similar in the sense that both pro-inflammatory and anti-inflammatory microglia are found. However as the tumor increases in malignancy, the presence of anti-inflammatory phenotypes (M2) dwindles, a recent finding in an experiment testing individuals with gliomas (Sørensen et al., 2018). In this experiment of 240 glioma patients, their cells were stained with antibodies against ionized calcium-binding adaptor molecule 1 or IBA-1 and CD204. IBA-1 and CD204 are markers specifically wired to detect anti-inflammatory microglia (Sørensen et al., 2018).

As the grade for the glioma increased from I to IV, the presence of these M2-specific markers increased. Along with some statistical analysis, it was proven that quantitative estimates of IBA-1 in total were in direct correlation with the degree of malignancy, making

IBA-1 cover as much as 30% of the whole tumor area in a grade 4 glioblastoma (GBM). In these GBM patients, CD204+ microglia correlated with poorer survival in patients receiving postsurgical treatment which could mean some form of treatment resistance but also a future for therapeutic treatment (Sørensen et al., 2018). Evidence of CD204 microglia have also been found to be associated with aggressive tumor subtypes which progress tumors, indicating that these markers contribute to a favorable microenvironment for the tumor to flourish.

While not much has been researched regarding treatments using microglia in GBM, we have found more evidence proving that possibly repolarizing microglia to its anti-inflammatory state could stop the expression of certain markers, enhancing phagocytic activity. But it is still a field with much to explore and research.

What is the Role of Microglial Phenotypes in Neurodegeneration and What is the Current Status for Possible Treatments?

I. Caveats

Through covering microglia's role in progressing tumors, it is clear that this field is still one that requires extensive research on different facets. Some of these facets have been explored through cell typing, where scientists have uncovered various types of microglia that go beyond the widely researched M1 and M2 phenotypes. This research indicates a possibility for many more complex and undiscovered phenotypes possessing both anti- and pro-inflammatory properties. In fact, these unnamed microglia are ever present in neurodegeneration which is why it is critical to remember that microglia is a very complex immune cell with many different functions and phenotypes that cannot be narrowed down to either M1 or M2. In fact, it is possible for both to be working where neurodegeneration occurs and this section will cover two of the most widely researched neurodegenerative diseases: Alzheimer's and Parkinson's disease.

II. Alzheimer's Disease

Alzheimer's disease (AD) is a progressive and degenerative neurological disorder that primarily affects cognitive functions, memory, and behavior. It is the most common cause of dementia, accounting for about 60-80% of all dementia cases. Symptoms can show up early or later in a person's life- people are commonly diagnosed over age 65 but can be affected as young as 40 or 50. It is primarily characterized by the accumulation of abnormal protein deposits in the brain, including beta-amyloid plaques and tau tangles, which lead to the death of neurons and the subsequent shrinkage of brain tissue. However, recent research has pointed to microglia playing a major role in AD through releasing degrading enzymes and compacting amyloid deposits to create a protective barrier.

Studies have shown that having the apoE4 or apoE2 allele increases the risk for AD by threefold. When screened, apoE alleles have shown to bind to a certain TREM2 mutation which is highly expressed in microglia. While functioning individually, apoE and TREM2 have shown neuroprotective roles in microglia but their dangerous binding has shown to increase the risk for AD significantly by activating AD risk genes. These interactions work against the body and lead to loss of function and eventually, early onset neurodegeneration (Guo et al., 2022).

Regardless of its contributions to neurodegeneration, TREM2 is an important part of homeostasis in the brain. TREM2-deficient microglia have shown reduced uptake of lipoproteins which indicates reduced clearance of amyloid-beta plaques. As we had discussed before, blocking TREM2 pathways lead to neurotoxicity whereas upregulating (shown when beta

plaques start to accumulate) leads to neuroprotection Therefore, it is important to understand that TREM2 can play both roles in neurodegenerative diseases (Guo et al., 2022). Below is a figure illustrating microglial cellular activities related to the beta-amyloid pathology and the function of the TREM2 pathway.

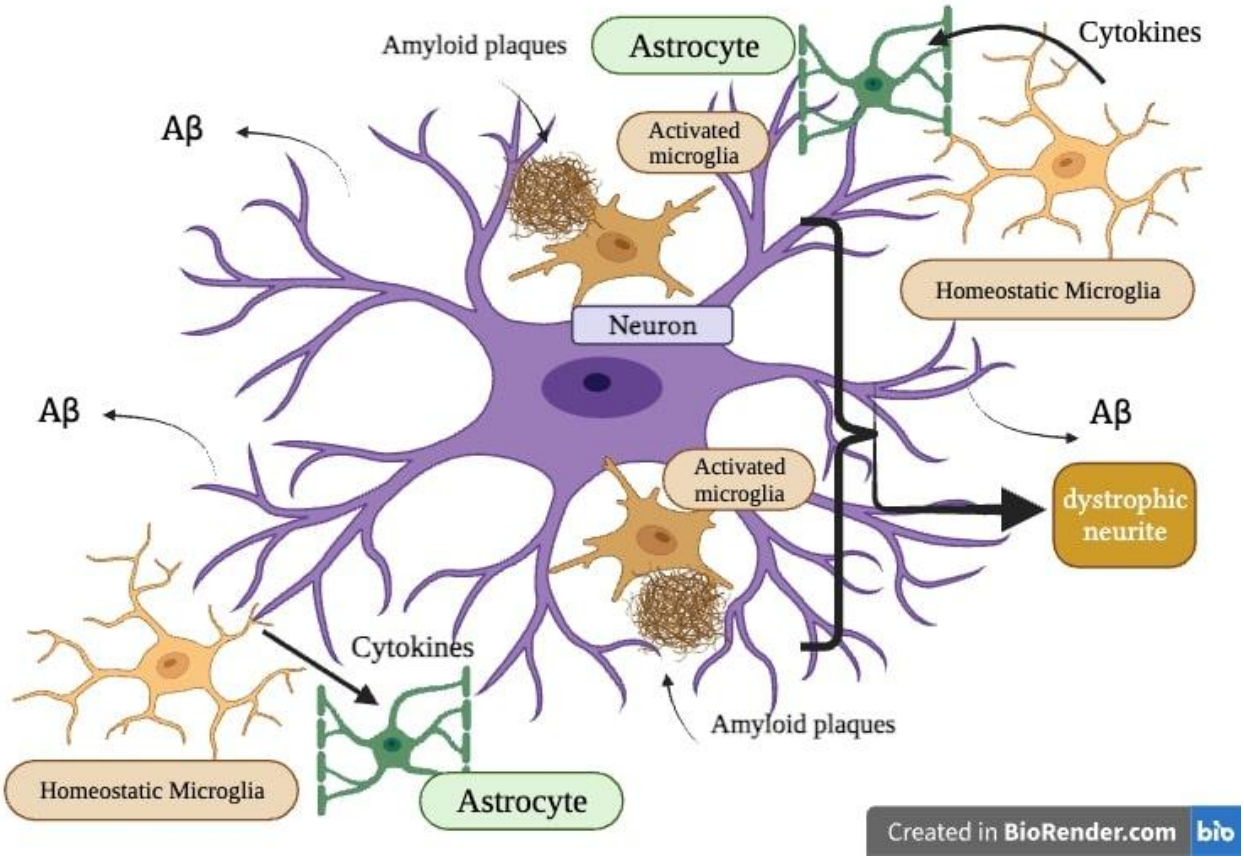

Image Description: The left side illustrates protective microglial activities that limit disease progression. Microglia may clear Aβ peptides via macropinocytosis of soluble Aβ uptake of lipoprotein-associated Aβ, or phagocytosis of fibrillar Aβ aggregates. Microglia also help corral larger deposits of Aβ in plaques, minimizing damage to the adjacent neuropil. The right side illustrates disease states when microglial containment mechanisms are defective or outstripped. Aβ fibrils on the outskirts of plaque act as substrate for additional Aβ fibrillization and a reservoir of toxic Aβ species that induce neuritic dystrophy. Microglia can secrete factors that activate astrocytes and participate in amyloid-dependent synapse loss (Created with BioRender.com).

While there are some plausible answers for how microglia can play a role in furthering neurodegeneration, there are all theories that require further research. However, the bulk of current studies support the conclusion that microglia is never just neuroprotective or neurotoxic and instead strikes a balance. Through tau pathology, microglia are introduced into an inflammatory state and overpower the neuroprotective microglia trying to clear protein debris. As the disease progresses, debris builds up faster than the cells can clean up, explaining why AD has 2 peaks of microglial activation: anti-inflammatory in the earlier preclinical stage, and pro-inflammatory in the later clinical stage (Guo et al., 2022).

While there is no working treatment for AD, targeting microglia through inhibitors that can stop AD progression like COX-2 has been proven to break the cycle of dopaminergic neuron death. COX-2 plays an important role in the secondary activation of microglia which is usually the stage associated with onset, incurable neurodegeneration in AD (*Microglia in Parkinson's Disease - IOS Press*, n.d.).

III. Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects movement control. PD is characterized by a variety of motor symptoms, including tremors, muscle rigidity, bradykinesia (slowness of movement), and postural instability. Non-motor symptoms may also occur, such as changes in mood, sleep disturbances, and cognitive impairment. Neurologically, it is known to be caused by the degeneration of dopamine-producing neurons in the substantia nigra, a region of the brain. The loss of dopamine leads to disruptions in the brain's communication pathways that regulate movement (*Microglia in Parkinson's Disease - IOS Press*, n.d.).

While the symptoms of these diseases are different, both forms of neurodegeneration have proven to involve microglia mediated inflammation as a key contributing factor in polarizing microglia into disease-promoting phenotypes. Single-cell laser microscopy studies show that neurodegeneration increases levels of Interleukin 1β (pro-inflammatory cytokine), GPNMB (transmembrane glycoprotein seen in tissue repair), and HSP90AA1 (member of the heat shock protein family which facilitate the correct protein folding) in the substantia nigra. These factors trigger activation of microglia into a disease-specific mode.

In AD, the signaling pathway in play is TREM2 whereas in PD, it is supported by the NOD-like receptor family pyrin domain which contains NLRPs inflammasomes. These receptors are an important component of the immune system which secretes proinflammatory cytokines, all triggered by α-syn. This conclusion was drawn based on a recent study highlighting that a regulator of α-syn mediates and primes the activation of NLRP3 inflammasome, releasing the Interleukin 1β. This pathway is prevalent in microglia as well as the Toll-like receptor pathways, which have shown to dual stimulate and uptake more α-syn. Seeing that the TLR pathways have reduced lysosomal activity and accelerated nigral degeneration indicates that the pathways that polarize a microglia can also cause inflammation, leading to early onset PD (*Microglia in Parkinson's Disease - IOS Press*, n.d.).

Microglia have also been considered a putative biomarker for the progression and diagnosis of PD which can be assessed by positron emission tomography (PET) imaging. Earlier studies have shown a new ligand ([11C]-PK11195) binding to a translocator protein which is upregulated in activated microglia and astrocytes. This binding is especially increased in the midbrain and basal ganglia which is disadvantageous since this ligand has also been associated with low blood brain permeability, non-specific binding, and a short lifespan.

Fortunately, treatments with antibiotics like minocycline and verdi perstat on microglia in PD patients have shown to reduce the binding of [11C]-PK11195 to TSPO (*Minocycline Counter-Regulates pro-Inflammatory Microglia Responses in the Retina and Protects from Degeneration | Journal of Neuroinflammation*, n.d.). Through using microglia as a biomarker, there is a chance for future development of selective microglia sub-type specific ligands which can hopefully help us understand the progression of PD. While TREM2 has shown to play a part in both AD and PD, the best option for PD specifically is to therapeutically target α-syn,

eliminating the possibility of a signaling cascade being triggered to worsen progression. The major limitation we face is the lack of knowledge around microglial heterogeneity and its dual roles. Starting their first might be the best mode towards addressing the dynamic shift between healthy brain activity and neurodegeneration.

What is the Future for Disease-Associated Microglia and is There a Possibility to Use its Functions to Create Therapeutic Treatments?

I. Single Cell RNA Sequencing

From what we have covered, a common issue we fail to address is the study of microglial heterogeneity. Through various sequencing methods, we can hope to address these questions in the future.

Generally, RNA sequencing has proven to provide aspects to study microglial activity in healthy and pathogenic CNS and for developing appropriate therapeutic strategies for these cells. There might be a possibility for microglial cell typing (characterization of microglia into resting and activated states) to expand further as there are many more different states involved in neuroinflammation, neural development, synaptic pruning, and other functions. As of now, we characterize microglia into a neurotoxic or neuroprotective state but with the help of RNA transcriptomics and computational biology investigating the CNS from the embryonic developmental stage to the aging stage, we can shine more light on microglia. (Gerrits et al., 2020)

In an experiment involving 5XFAD mice, an amyloid AD mouse model, a cluster of disease associated microglia was identified and characterized by the upregulation of genes such as Apoe, Trem2, and Tyrobp through single cell RNA sequencing. These genes are associated with lipid metabolism and phagocytosis and were already previously identified in a meta-analysis of microglia gene expression changes in relation to aging and CNS disease. (Gerrits et al., 2020)

If researched, these microglia subtypes might be promising targets for treatment of neurological diseases through their receptors and chemokines which trigger their polarization. More importantly, they can provide new modes of treatment besides the ones existing like harsh radiation or chemotherapy or ineffective medications.

II. Sex Differences

Besides microglial heterogeneity, there has also been evidence pointing to sex being a factor in microglia functions like cell density, size, and phagocytic function.

We can see this simply from addressing the morphology in a female and male mouse, with the male mouse showing more complex morphology. This could help describe AD and how female mice could have a more profound metabolic shift towards deterioration of phagocytic activity rather than males. With enough research, there is a possibility of treatments catering to a specific sex, keeping in account their morphology. (Guillot-Sestier et al., 2021)

III. Age-Associated Risk Factors

Like sex-associated risk factors, age has also exhibited distinctive phenotypic alterations, including the upregulation of pathways associated with DNA damage, telomere maintenance and phagocytosis. Telomeres are essential structures located at the ends of chromosomes, which are the thread-like structures that carry genetic information within cells. They play a crucial role in maintaining the stability and integrity of the genome. They have shown to shorten

with each round of cell division over time, increasing the cell's risk for disease, cognitive decline, and mortality.

Specifically to the brain, microglia from post-mortem elderly individuals showed a loss of ramifications, the appearance of cytoplasmic fragmentation and shortening of cellular processes without alterations in cell density. This just proves the increase of risk factors as a person ages which is why maintaining diet and health are essential in avoiding future disease. (Zabransky et al., 2022)

IV. Limitations and Future Needs

This paper has already addressed many limitations regarding the need for research in this field as well as how little we truly know about microglia. But looking at the brain microscopically and possibly using its own immune cells for treatments rather than drugs is the future for microglia in disease and treatment. Besides these limitations, the study of microglia itself is immensely difficult and sometimes not feasible.

In order to truly study microglia, researchers must use human brain tissue without altered cell properties to resemble microglia in its natural microenvironment. Currently, extraction of brain tissue has proven to alter properties, making the study of microglia a little inaccurate. Fortunately, there has been prospect of human-induced pluripotent stem cell models and monocyte-derived microglia which can paint a more relevant picture for microglia in neurodegenerative diseases. Some drawbacks are its long incubation time in culture but even these methods don't always preserve the innate characteristics of microglia in-vivo.

There is an ever present need to examine microglia in its natural form through extracted brain tissue. Once we discover working solutions, we can begin to uncover the unsolved mystery of microglia.

Conclusion

This paper discussed the origins of microglia, the resident brain immune cells, its role in neurodegeneration and tumors, as well as the future for it in neuroscience. While we initially dissected microglia into two main phenotypes: M1 (pro-inflammatory), M2 (anti-inflammatory), we evolved to discuss the heterogeneity and complexity of microglia in neurodegeneration and tumors, highlighting predominant signaling pathways leading to inflammation as well as ways to target these pathways in microglia. We saw many similarities and drew many conclusions about the main factors at play in microglia, with the TREM2 signaling pathway being a common denominator amongst neurodegenerative diseases (Alzheimer's and Parkinson's). We also uncovered various receptors like CD204 and various interleukins secreted neurotoxic cytokines, furthering inflammation. Finally, we speculated the future of microglia in neuroscience, limitations in researching microglia, and areas requiring further research to possibly create a new way to approach disease in the brain. Using our own immune weapons, the future for microglia in treatment is vast.

Works Cited

Gerrits, E., Heng, Y., Boddeke, E. W. G. M., & Eggen, B. J. L. (2020). Transcriptional profiling of microglia; current state of the art and future perspectives. *Glia*, *68*(4), 740–755. https://doi.org/10.1002/glia.23767

Guillot-Sestier, M.-V., Araiz, A. R., Mela, V., Gaban, A. S., O'Neill, E., Joshi, L., Chouchani, E. T., Mills, E. L., & Lynch, M. A. (2021). Microglial metabolism is a pivotal factor in sexual dimorphism in Alzheimer's disease. *Communications Biology*, *4*, 711. https://doi.org/10.1038/s42003-021-02259-y

Guo, S., Wang, H., & Yin, Y. (2022). Microglia Polarization From M1 to M2 in Neurodegenerative Diseases. *Frontiers in Aging Neuroscience*, *14*, 815347. https://doi.org/10.3389/fnagi.2022.815347

Microglia in Parkinson's Disease—IOS Press. (n.d.). Retrieved September 3, 2023, from https://content.iospress.com/articles/journal-of-parkinsons-disease/jpd223237

Minocycline counter-regulates pro-inflammatory microglia responses in the retina and protects from degeneration | Journal of Neuroinflammation. (n.d.). Retrieved September 3, 2023, from https://link.springer.com/article/10.1186/s12974-015-0431-4

Radin, D. P., & Tsirka, S. E. (2020). Interactions between Tumor Cells, Neurons, and Microglia in the Glioma Microenvironment. *International Journal of Molecular Sciences*, *21*(22), Article 22. https://doi.org/10.3390/ijms21228476

Sørensen, M. D., Dahlrot, R. H., Boldt, H. B., Hansen, S., & Kristensen, B. W. (2018). Tumor-associated microglia/macrophages predict poor prognosis in high-grade gliomas and correlate with an aggressive tumor subtype. *Neuropathology and Applied Neurobiology*, *44*(2), 185–206. https://doi.org/10.1111/nan.12428

Wang, G., Zhong, K., Wang, Z., Zhang, Z., Tang, X., Tong, A., & Zhou, L. (2022). Tumor-associated microglia and macrophages in glioblastoma: From basic insights to therapeutic opportunities. *Frontiers in Immunology*, *13*. https://www.frontiersin.org/articles/10.3389/fimmu.2022.964898

Wendimu, M. Y., & Hooks, S. B. (2022). Microglia Phenotypes in Aging and Neurodegenerative Diseases. *Cells*, *11*(13), Article 13. https://doi.org/10.3390/cells11132091

Wu, S.-Y., & Watabe, K. (2017). The roles of microglia/macrophages in tumor progression of brain cancer and metastatic disease. *Frontiers in Bioscience (Landmark Edition)*, *22*, 1805–1829.

Zabransky, D. J., Jaffee, E. M., & Weeraratna, A. T. (2022). Shared genetic and epigenetic changes link aging and cancer. *Trends in Cell Biology*, *32*(4), 338–350. https://doi.org/10.1016/j.tcb.2022.01.004

Zhang, J., Sarkar, S., Cua, R., Zhou, Y., Hader, W., & Yong, V. W. (2012). A dialog between glioma and microglia that promotes tumor invasiveness through the CCL2/CCR2/interleukin-6 axis. *Carcinogenesis*, *33*(2), 312–319. https://doi.org/10.1093/carcin/bgr289