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NEUROINFLAMMATION AND CNS DRUG TARGETS: ADVANCES IN MICROGLIAL MODULATION, NEUROIMMUNE THERAPEUTICS, AND BLOOD–BRAIN BARRIER-PENETRATING STRATEGIES

Vitthal B. Kundgir[1]*, Chandrashekhar D. Patil[1], Sharwari K. Sonawane[2], Sunil K. Mahajan[3]

[1]*Department of Pharmacology, SSS's Divine College Pharmacy, Nampur Road, Satana, Nashik, Maharashtra, India-423301.

[2]Department of Pharmaceutics, SSS's Divine College Pharmacy, Nampur Road, Satana, Nashik, Maharashtra, India-423301.

[3]Department of Chemistry, SSS's Divine College Pharmacy, Nampur Road, Satana, Nashik, Maharashtra, India-423301.

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***Corresponding Author**
Vitthal B. Kundgir
Department of Pharmacology, SSS's Divine College Pharmacy, Nampur Road, Satana, Nashik, Maharashtra, India-423301.

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ABSTRACT

Neuroinflammation is a key factor in the development and progression of various central nervous system (CNS) disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). Microglia, the brain's resident immune cells, play a crucial role in regulating innate immune responses and maintaining neuronal health. However, when microglial activation becomes dysregulated, it can lead to persistent inflammation, ultimately worsening neuronal damage. This review highlights the underlying molecular mechanisms of neuroinflammation, focusing on microglial signaling pathways, cytokine networks, and interactions between different glial cells. It also discusses recent advancements in therapeutic approaches, including monoclonal antibodies, small-molecule inhibitors, and pathway-specific modulators designed to rebalance the immune response in neurodegenerative and autoimmune diseases of the CNS. Additionally, the review emphasizes innovative drug delivery strategies that address the challenge of crossing the blood–brain

barrier (BBB). These include receptor-mediated transport, nanoparticle-based carriers, and focused ultrasound techniques. By combining precision neuroimmunology with advanced delivery systems, there is great potential to develop safer and more effective treatments for chronic neuroinflammatory disorders.

KEYWORDS: Neuroinflammation, Microglial Modulation, Neuroimmune Therapeutics, Blood–Brain Barrier, Alzheimer's disease.

1. INTRODUCTION

Neuroinflammation has emerged as a key factor in the progression of many central nervous system (CNS) disorders, including neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD), as well as autoimmune conditions such as multiple sclerosis (MS). Unlike inflammation in the rest of the body, neuroinflammation is characterized by highly specialized responses involving glial cells, neurons, immune cells, and the blood–brain barrier (BBB). While short-term neuroinflammatory responses can help protect the brain and promote repair, prolonged or uncontrolled inflammation leads to neuronal damage, synaptic dysfunction, and eventually neurodegeneration.[1]

Microglia, the brain's resident immune cells, play a central role in regulating neuroinflammatory processes. They continuously monitor the brain's environment and respond to harmful stimuli by changing their phenotype, releasing inflammatory mediators, and interacting with neurons and other glial cells. However, when microglia remain chronically activated, their protective functions can shift toward promoting neurotoxicity. In conditions such as AD and PD, overactive microglia contribute to the spread of toxic protein aggregates, oxidative stress, and persistent inflammatory signaling. In MS, both microglia and invading immune cells are involved in driving demyelination and damaging nerve fibers, worsening disease progression.[2]

Microglia and Neuroimmune Interactions in Neuroinflammation

Microglia are the main innate immune cells in the central nervous system (CNS), making up about 10–15% of total brain cells. Under normal conditions, they are essential for maintaining brain health by constantly monitoring the CNS, clearing cellular debris, and regulating synaptic connections. When exposed to harmful triggers such as injury, infections, or abnormal protein buildup, microglia change their functional state. These changes can either protect neurons and promote repair or, conversely, contribute to neuronal damage and

disease progression. Because of their pivotal role in regulating neuroimmune responses, microglia are considered an important therapeutic target for treating neuroinflammatory disorders.[3]

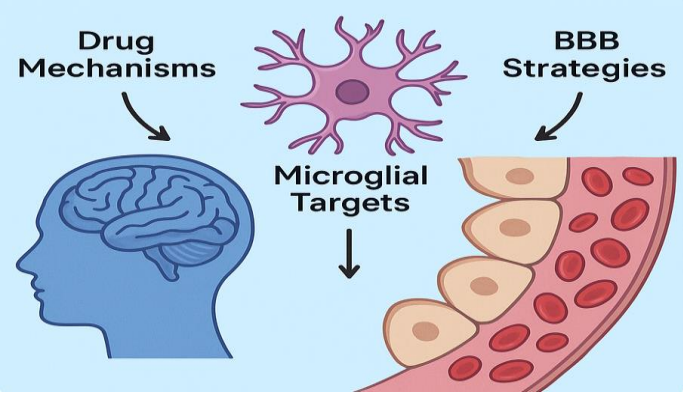

Fig. 1: Neuroinflammation and CNS Drug Targets.

Microglial Activation States and Functional Plasticity

Microglia are highly dynamic cells that can adopt a range of activation states depending on the signals they receive from their surrounding environment. Traditionally, their activation has been explained using the M1/M2 polarization model. M1, or classically activated microglia, are triggered by factors such as lipopolysaccharide (LPS) or interferon-γ (IFN-γ). These cells release pro-inflammatory molecules, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS), which can lead to neuronal damage and contribute to the progression of chronic CNS disorders. In contrast, M2, or alternatively activated microglia, are stimulated by cytokines like IL-4 and IL-13. They produce anti-inflammatory mediators such as IL-10 and transforming growth factor-β (TGF-β), which aid in tissue repair, promote debris clearance, and help resolve inflammation.

However, recent transcriptomic research has shown that microglial behavior in living systems is far more complex and cannot be fully explained by the simple M1/M2 framework. A notable example is disease-associated microglia (DAM), a specialized subtype identified in neurodegenerative diseases. These microglia exhibit unique gene expression profiles related to immune regulation, lipid metabolism, and phagocytosis, including key genes such as TREM2 and APOE, highlighting their diverse and adaptive roles in CNS pathology.[4]

Molecular Pathways Regulating Microglial Function

TREM2 Signaling

TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) is an essential receptor on microglia that plays a vital role in lipid sensing, phagocytosis, and regulating anti-inflammatory responses. Mutations that reduce or impair TREM2 function have been closely linked to a higher risk of developing Alzheimer's disease (AD). When activated, TREM2 supports microglial clustering around amyloid plaques, helping to clear toxic protein deposits while also suppressing excessive inflammatory signaling. Because of its protective role, TREM2 is being explored as a promising therapeutic target for AD and other neurodegenerative diseases.

NLRP3 Inflammasome

The NLRP3 inflammasome is a protein complex within cells that functions as a sensor for harmful stimuli. Once activated, it triggers caspase-1, which drives the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18). Overactivation of NLRP3 has been linked to several neurological disorders, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, where it contributes to persistent inflammation and neuronal damage. Current research is focused on developing NLRP3 inhibitors, such as MCC950, which are being tested in both preclinical and clinical studies to reduce neuroinflammation and protect brain health.[5]

Astrocyte–Microglia Interactions

Astrocytes, a key type of glial cell in the central nervous system (CNS), play an important role in regulating neuroinflammation through constant two-way communication with microglia. When microglia become activated, they release cytokines such as IL-1α, TNF-α, and C1q, which can trigger astrocytes to shift into a harmful A1 phenotype. These A1 astrocytes lose their normal protective and supportive roles, instead releasing toxic factors that can damage or kill neurons and oligodendrocytes. On the other hand, astrocytes also influence microglial activity by releasing signaling molecules like ATP, glutamate, and various cytokines. This reciprocal interaction between astrocytes and microglia can either amplify or reduce neuroinflammatory processes, depending on the specific disease environment, ultimately affecting the progression of neurological disorders.[6]

Peripheral Immune Cell Infiltration and Microglial Crosstalk

In pathological conditions, the blood–brain barrier (BBB) becomes disrupted, allowing peripheral immune cells such as T cells, B cells, and monocytes to enter the central nervous system (CNS). Once inside, these cells interact with microglia and significantly influence the neuroimmune environment. For instance, CD8+ T cells can directly trigger neuronal cell death, while Th17 cells release IL-17, which intensifies neuroinflammation, particularly in diseases like multiple sclerosis (MS). Similarly, infiltrating monocytes can transform into macrophage-like cells within the CNS, contributing to antigen presentation and tissue damage. In response to this immune cell invasion, microglia increase the expression of MHC class II molecules, enabling them to function as antigen-presenting cells and further sustaining inflammatory responses in the brain.[7]

Microglia in CNS Disease Contexts

In Alzheimer's disease, microglia gather around amyloid plaques in an attempt to remove them through phagocytosis. However, this process is often ineffective and instead leads to persistent inflammation, worsening the disease. In Parkinson's disease, microglia become activated in response to α-synuclein aggregates, resulting in excessive production of inflammatory cytokines and oxidative stress, which further damages neurons. In multiple sclerosis, both microglia and infiltrating macrophages play a key role in the destruction of myelin and axons, while also acting as antigen-presenting cells that activate T cells, thereby driving ongoing immune attacks within the CNS.[8]

Emerging Therapeutics for Neurodegenerative Diseases

Neuroinflammation plays a central role in the development and progression of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). In recent years, there has been a significant shift in CNS drug development, moving from treatments focused only on symptom management to disease-modifying therapies aimed at addressing underlying causes like chronic inflammation, abnormal protein accumulation, and dysregulated neuroimmune interactions. This section highlights new and emerging therapeutic agents designed to regulate glial cell function, control immune signaling pathways, and slow or prevent neurodegeneration, with a focus on drugs currently in clinical trials or advanced stages of preclinical research.[9]

Alzheimer's Disease (AD)

In Alzheimer's disease (AD), chronic neuroinflammation is fueled by the buildup of amyloid-β (Aβ) plaques, tau protein hyperphosphorylation, and abnormal microglial activity. Microglia surrounding amyloid plaques often exhibit heightened expression of inflammatory genes, leading to ineffective and harmful immune responses that fail to resolve the underlying pathology. Targeting these microglial and inflammatory pathways provides promising therapeutic strategies beyond simply removing amyloid deposits.

Anti-Amyloid Monoclonal Antibodies

Drugs such as Lecanemab, Donanemab, and Aducanumab are designed to specifically bind to aggregated Aβ, promoting its clearance from the brain. These therapies may also encourage microglia to adopt a more protective, phagocytic, and anti-inflammatory state. Clinical Note: Although these treatments have demonstrated some potential in slowing cognitive decline, their overall benefits are limited and often associated with side effects like amyloid-related imaging abnormalities[10] (ARIA).

TREM2 Agonists

The TREM2 signaling pathway plays a vital role in supporting microglial functions such as survival, proliferation, and phagocytosis. Therapeutic approaches targeting this pathway are gaining attention for Alzheimer's disease (AD). For instance, AL002, a monoclonal antibody developed by Alector, is currently undergoing clinical trials aimed at activating TREM2 to promote beneficial microglial activity. Such TREM2-based therapies have the potential to regulate disease-associated microglial phenotypes and reduce neurodegeneration.

Similarly, the NLRP3 inflammasome has been identified as a key contributor to neuroinflammation in AD. Overactivation of NLRP3 triggers the release of pro-inflammatory cytokines like IL-1β, leading to neuronal damage. MCC950, a potent NLRP3 inhibitor, has shown promising results by suppressing IL-1β production, blocking microglia-induced pyroptosis, and improving cognitive function in AD animal models. Other compounds, such as OLT1177 and dapansutrile, are also under investigation as potential NLRP3-targeting agents.

Parkinson's Disease (PD)

Neuroinflammation in PD is primarily driven by α-synuclein aggregates, which are recognized by toll-like receptors (TLRs) and internalized by microglia, triggering cytokine

production and ROS generation. Emerging therapies aim to suppress this inflammatory cascade.[11]

NLRP3 inhibitors have shown significant potential in reducing neuroinflammation associated with Parkinson's disease (PD). Dapansutrile (OLT1177) is a promising agent that blocks NLRP3 activity, offering neuroprotective benefits, particularly for dopaminergic neurons. By doing so, it helps to control excessive microglial activation while preserving normal immune functions. Another emerging therapeutic approach is α-synuclein immunotherapy. Prasinezumab, a monoclonal antibody targeting misfolded α-synuclein, is currently in clinical trials for early-stage PD. This therapy enhances the clearance of toxic α-synuclein aggregates and helps reduce inflammatory microglial responses, potentially slowing disease progression. Additionally, CSF1R inhibitors are being explored for their role in regulating microglial survival and proliferation. Compounds like PLX5622 and JNJ-40346527 are under investigation for their ability to selectively deplete harmful microglia or reprogram them into a neuroprotective phenotype, offering a novel strategy for managing neuroinflammation in PD.

Multiple Sclerosis (MS)

MS is characterized by autoimmune-driven demyelination and neuroinflammation involving both peripheral immune cells and CNS-resident microglia and astrocytes. The therapeutic landscape for MS includes agents that modulate the immune system at various levels.

In multiple sclerosis (MS), several novel therapeutic strategies are being developed to target immune-mediated neuroinflammation. Anti-CD20 monoclonal antibodies such as ocrelizumab and ofatumumab work by depleting CD20-positive B cells, which play a key role in antigen presentation and pro-inflammatory cytokine release. These therapies have shown strong efficacy in both relapsing-remitting and progressive forms of MS, helping to reduce disease activity and slow progression.

Another important class of drugs includes sphingosine-1-phosphate (S1P) receptor modulators like fingolimod, siponimod, and ozanimod. These agents prevent lymphocytes from leaving the lymph nodes, thereby limiting their infiltration into the CNS. In addition to their immune effects, they also have direct actions on CNS glial cells and may help regulate microglial activation, offering dual benefits in MS management. Bruton tyrosine kinase (BTK) inhibitors represent a promising new therapeutic avenue as they target both B cells

and myeloid cells, including microglia. Drugs such as evobrutinib, tolebrutinib, and fenebrutinib are currently in advanced clinical trials. Their goal is to reduce neuroinflammation while maintaining the protective functions of the immune system, providing a more balanced and targeted approach to MS treatment.

Table 1: Broad-Spectrum Neuroimmunomodulators Under Investigation.[12]

Drug/Target	Mechanism	Indications	Stage
MCC950	NLRP3 inflammasome inhibitor	AD, PD, MS	Preclinical
AL002	TREM2 agonist	Alzheimer's disease	Phase 2
PLX5622	CSF1R inhibitor	PD, AD	Preclinical
Evobrutinib	BTK inhibitor	Multiple sclerosis	Phase 2–3
Semaglutide	GLP-1R agonist	PD, AD	Repurposing

Blood–Brain Barrier (BBB) and Drug Delivery Challenges

The **blood–brain barrier (BBB)** serves as a specialized and highly selective boundary between the central nervous system (CNS) and the peripheral blood circulation. It plays a vital role in maintaining the brain's internal environment and protecting it from harmful substances. However, this protective feature also creates a major challenge in treating neurodegenerative and neuroinflammatory diseases, as most drugs—including large biologics and many small molecules—cannot penetrate the BBB in sufficient amounts to be therapeutically effective. As a result, the development of successful CNS-targeted treatments relies on innovative strategies to either cross or bypass the BBB while still maintaining its essential protective role.[13]

The blood–brain barrier (BBB) is a complex structure made up of several key components, including endothelial cells tightly connected by junction proteins such as claudins and occludins, pericytes embedded within the basal lamina, and astrocytic end-feet, which play a vital role in regulating nutrient transport. Microglia and elements of the extracellular matrix further support barrier integrity and signaling. Together, these components form the neurovascular unit (NVU), which is essential for maintaining CNS homeostasis.

The BBB functions by restricting paracellular diffusion, utilizing specialized transporters like GLUT1 for glucose uptake, and employing efflux pumps such as P-glycoprotein (P-gp) to expel harmful substances and xenobiotics. In the context of neuroinflammatory diseases, the BBB often becomes compromised, resulting in increased permeability, infiltration of peripheral immune cells, and changes in drug transport dynamics. However, this disruption is

not uniform and tends to vary depending on the stage and severity of the disease, making the development of effective drug delivery strategies particularly challenging.[14]

Delivering drugs to the central nervous system (CNS) presents significant challenges due to the highly selective nature of the blood–brain barrier (BBB). One major limitation is size and polarity, as drugs larger than 400–500 Da or those that are highly polar usually cannot cross the barrier. Additionally, efflux transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance proteins (MRPs) actively pump many drugs back into the bloodstream, reducing their effectiveness. Enzymatic degradation by metabolic enzymes at the BBB can further break down certain drugs before they reach their target. Even when drugs manage to cross, limited target engagement often occurs, as their distribution within the CNS may be restricted by complex local microenvironments.[15]

To address these obstacles, several strategies have been developed to improve BBB penetration. Chemical optimization is one approach, which includes increasing drug lipophilicity to enhance passive diffusion, designing prodrugs that convert into active compounds once inside the CNS (e.g., L-DOPA converting to dopamine), and using efflux inhibitors such as elacridar to block P-gp-mediated drug removal. Another promising method is receptor-mediated transcytosis (RMT), which utilizes natural transport systems like the transferrin receptor (TfR), insulin receptor (IR), and low-density lipoprotein receptor (LDLR). A notable example is the development of Trojan horse antibodies, engineered to bind both a receptor like TfR and the therapeutic CNS target, allowing drugs to hitch a ride across the BBB.[16]

Nanoparticle-based drug delivery systems also offer significant potential. Lipid nanoparticles (LNPs), widely used in mRNA vaccines, can be adapted for CNS applications, while polymeric nanoparticles such as PLGA are designed for controlled and targeted release. Other systems, like solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), provide high biocompatibility and improved stability of drug molecules.

Lastly, exosome-mediated delivery is emerging as an innovative strategy. Exosomes are naturally occurring vesicles capable of crossing the BBB with ease. They can be bioengineered to transport drugs, small interfering RNAs (siRNAs), or CRISPR gene-editing components. Due to their low immunogenicity and high compatibility with biological

systems, exosomes are considered a highly promising platform for future CNS drug delivery solutions.[17]

Recent advances in BBB-targeting biologics have opened new possibilities for effective drug delivery to the brain. Among these innovations are bispecific antibodies, which are designed with one arm that binds to a BBB receptor, such as the transferrin receptor (TfR), and another that targets a specific disease-related antigen within the CNS. Another promising approach involves fusion proteins, where therapeutic proteins are linked to BBB-targeting ligands, improving their ability to cross the barrier and reach their site of action.

To support the development of these therapies, advanced BBB models are being utilized for drug screening. iPSC-derived BBB organoids provide a more accurate representation of the human BBB compared to traditional rodent models, enabling better prediction of human drug responses. Similarly, microfluidic BBB-on-chip systems simulate dynamic blood flow and barrier functions, allowing real-time assessment of drug transport. Humanized mouse models are also increasingly used to evaluate BBB permeability and drug distribution, offering more reliable data for clinical translation.

Despite these advancements, several clinical and regulatory challenges remain. Ensuring safety and minimizing toxicity is critical, as manipulating the BBB must not cause long-term structural or functional damage. Additionally, scalability and reproducibility present difficulties, especially for complex technologies such as nanoparticles and exosomes. Finally, regulatory pathways for these novel delivery platforms are still evolving, which often results in longer approval timelines and added hurdles for bringing innovative CNS therapies to market.

Translational Tools and Models

The intricate nature of neuroinflammation and the difficulties associated with CNS drug delivery call for the development of advanced translational models that closely mimic human physiology. Such models are essential for accurately assessing drug efficacy, predicting pharmacokinetic and pharmacodynamic behaviors, studying microglial activity, and evaluating BBB permeability. Recent innovations in in vitro, in vivo, and ex vivo systems have significantly improved our ability to translate preclinical research into meaningful clinical outcomes, helping to bridge the gap between laboratory discoveries and real-world therapeutic applications.[18]

In Vitro Models of Neuroinflammation

Different in vitro models are being developed to study neuroinflammation and CNS drug responses with greater precision. Primary glial cell cultures, consisting of microglia and astrocytes, are valuable tools for investigating glial activation, cytokine production, and drug screening. They are especially useful for exploring specific signaling pathways, such as TLR4, NLRP3, and CX3CL1/CX3CR1.[19] Immortalized cell lines, like BV2 microglia and C8-D1A astrocytes, are commonly used for high-throughput screening and mechanistic studies, although they lack the full physiological relevance of primary cells.

Advancements in stem cell technology have introduced induced pluripotent stem cell (iPSC)-derived models, which can generate microglia, astrocytes, and neurons that replicate patient-specific disease conditions, such as TREM2 or APOE4 mutations seen in Alzheimer's disease. These models are ideal for personalized pharmacology and functional genomic studies. Additionally, 3D brain organoids and spheroids have emerged as cutting-edge systems. These miniature, self-organizing structures contain a mix of neurons, astrocytes, and microglia, providing a more realistic environment for studying neurodevelopment, protein aggregation, and glial interactions. When combined with immune cells, they offer a powerful platform for investigating neuroimmune communication and disease mechanisms in a near-native brain-like structure.

BBB Models for Drug Transport Studies

Several in vitro models have been developed to study the blood–brain barrier (BBB) and evaluate drug delivery strategies. Static Transwell BBB models involve co-culturing endothelial cells with astrocytes and/or pericytes on porous membranes. These models are commonly used to measure transendothelial electrical resistance (TEER) and assess drug permeability across the barrier.

For a more physiologically relevant approach, microfluidic BBB-on-a-chip systems have been introduced. These systems mimic dynamic blood flow, allowing real-time observation of drug transport, immune cell movement, and endothelial cell integrity. They can also be customized with human-derived cells, providing better clinical relevance and more accurate predictions of human BBB behavior.[20]

Another advanced model is **human BBB organoids**, which are three-dimensional, self-organizing structures made up of brain endothelial cells, astrocytes, and pericytes. Compared

to traditional 2D cultures, these organoids form **tighter junctions** and exhibit more realistic barrier properties, making them highly valuable for studying CNS drug delivery and BBB dysfunction in neurological diseases.

In Vivo Animal Models of Neuroinflammation

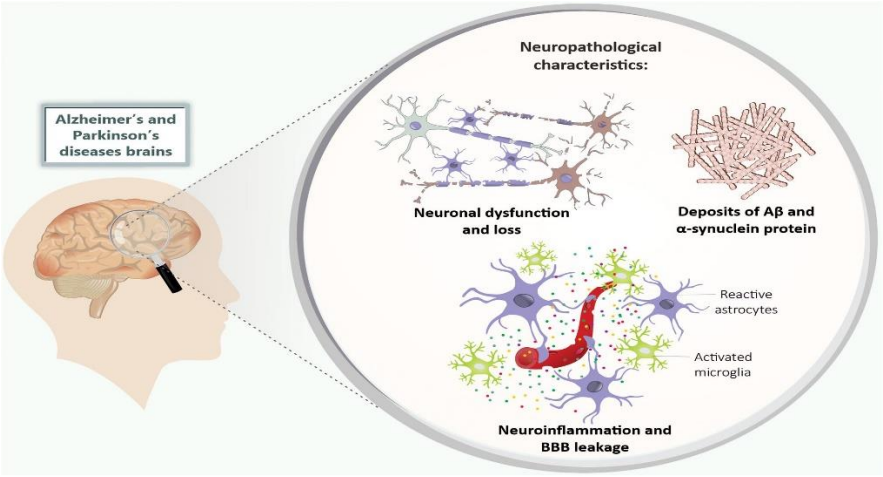

Fig. 2: Neuropathological features of Alzheimer's and Parkinson's disease.

Various animal models are widely used to study neurodegenerative and neuroinflammatory diseases and to evaluate potential therapies. In Alzheimer's disease (AD) research, models such as APP/PS1 and 5xFAD mice overexpress mutant forms of amyloid precursor protein and presenilin, leading to the formation of amyloid plaques and microglial activation. These models are particularly useful for testing anti-amyloid therapies and agents that modulate microglial function.[21]

For Parkinson's disease (PD), researchers often use α-synuclein transgenic mice or MPTP-treated mice, which replicate key features of the disease, including neuroinflammation, microglial activation, and loss of dopaminergic neurons. In the case of multiple sclerosis (MS), the experimental autoimmune encephalomyelitis (EAE) model is commonly employed. EAE is induced using myelin peptides, leading to demyelination and T cell infiltration within the CNS. This model allows for the evaluation of immunomodulatory therapies, S1P receptor modulators, and strategies aimed at preserving BBB integrity.

Advanced Imaging and Omics Tools

Several advanced tools and technologies have enhanced our understanding of neuroinflammation and CNS drug responses. In vivo imaging techniques like two-photon microscopy allow researchers to observe microglial activity in real time within living

animals, while PET tracers targeting microglial markers such as TSPO enable quantification of neuroinflammatory processes across the brain.

At the molecular level, single-cell RNA sequencing (scRNA-seq) has revealed the cellular diversity of microglia and astrocytes, identifying disease-associated subtypes such as DAM and IRM, as well as populations that respond to therapeutic interventions. Spatial transcriptomics further complements this approach by combining histological context with gene expression profiling, allowing precise mapping of neuroimmune changes within specific brain regions. Additionally, CRISPR-Cas9 and other genetic tools provide powerful methods for mechanistic studies. By enabling targeted gene knockout or activation in microglia and astrocytes, these tools help validate key drug targets like TREM2, NLRP3, and CSF1R. When coupled with iPSC-derived models, CRISPR technology facilitates patient-specific disease modeling, offering insights into personalized therapeutic strategies.[22]

Table 2: Limitations and Considerations

Tool/Model	Advantages	Limitations
iPSC-derived cells	Human-relevant, personalized	Immature phenotype, costly, time-consuming
Brain organoids	3D complexity	Lack of full vascularization or aging
Microfluidic chips	Dynamic flow, real-time analysis	Technical expertise required
Rodent models (AD/PD/MS)	Whole-organism response	Poor translatability to human diseases
scRNA-seq and omics	High-resolution insight	Data complexity, need for validation

Limitations and Challenges

Neuroinflammation is a highly complex and heterogeneous process, varying across different brain regions, cell types, disease stages, and individual patients. Microglia, for instance, exhibit region-specific phenotypes, while interactions between microglia, astrocytes, neurons, oligodendrocytes, and infiltrating immune cells are constantly evolving. Early in disease progression, inflammation may be protective, but in later stages, it often becomes neurotoxic. Genetic, epigenetic, and environmental factors further contribute to variability in disease manifestation and treatment responses. This complexity challenges the identification of universal biomarkers or therapeutic targets, emphasizing the need for precision neuroimmunology approaches.

Preclinical models also have significant limitations. Animal models frequently fail to capture the full spectrum of human neurodegenerative diseases, particularly in Alzheimer's and

Parkinson's disease. Rodent microglia differ markedly from human microglia in both transcriptional profiles and functional behavior. While the EAE model for multiple sclerosis demonstrates robust demyelination and immune cell infiltration, its relevance to progressive MS is limited. iPSC-derived and organoid models provide valuable human-specific insights but often lack mature vasculature and full immune system interactions, making long-term studies challenging. Consequently, many therapeutics that show promise preclinically fail in phase II/III clinical trials, highlighting the need for more predictive models.[23] Blood–brain barrier (BBB) drug delivery remains another critical challenge. The BBB restricts access of large or hydrophilic molecules, and although technologies like nanoparticles, exosomes, and focused ultrasound offer potential solutions, they face hurdles related to scalability, cost, safety, and regulatory approval. Moreover, BBB permeability varies temporally and spatially during disease progression, complicating optimal therapeutic timing and targeting.

Targeting neuroimmune pathways also poses difficulties. Broad suppression of inflammation can interfere with protective immune functions, potentially worsening disease outcomes. Pathways such as NLRP3 inflammasome, TNF-α, and TREM2 may have dual roles depending on the disease stage and cellular context. Off-target effects and limited selectivity remain major concerns, particularly for small-molecule inhibitors and kinase blockers[24]. Finally, biomarker and diagnostic limitations hinder the development and monitoring of neuroinflammatory therapies. Reliable indicators of CNS inflammation are scarce. PET ligands like TSPO are non-specific and can be influenced by genetic variations, while cytokine levels in CSF or blood do not always accurately reflect CNS activity. This lack of robust biomarkers complicates patient stratification and the assessment of therapeutic response in clinical trials.[25]

Future Directions in Neuroinflammation and CNS Drug Development

Advances in treating neuroinflammatory and neurodegenerative disorders are focusing on precise modulation of microglia and innovative strategies to cross the blood–brain barrier (BBB). Therapies that target specific microglial subtypes, such as DAMs and IRMs, using gene-editing tools, monoclonal antibodies, or small molecules, aim to reduce harmful inflammation while supporting neuroprotection. Methods to improve drug delivery across the BBB include receptor-mediated transport, nanoparticles, exosomes, and focused ultrasound, enhancing the ability of therapeutics to reach the CNS effectively. The use of iPSC-derived cells, brain organoids, advanced imaging techniques, and omics approaches enables

personalized disease modeling and helps identify microglial populations that respond to treatments. Additionally, artificial intelligence is aiding the design of targeted CNS drugs.

Despite these advances, challenges such as safety, large-scale production, and regulatory hurdles remain. Nonetheless, these innovations are paving the way for more precise and effective therapies for neuroinflammatory and neurodegenerative diseases.

CONCLUSION

Neuroinflammation has emerged as a central hallmark and therapeutic target in a wide spectrum of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Microglia, astrocytes, peripheral immune cells, and their complex interactions with neurons orchestrate a dynamic immune environment within the CNS. While inflammation can be initially protective, its chronic or dysregulated activation drives neuronal injury and disease progression. Recent advances in our understanding of neuroimmune signaling pathways—such as TREM2, NLRP3, CX3CR1, and CSF1R—have led to the development of targeted therapeutic agents aimed at modulating glial phenotypes, promoting resolution of inflammation, and restoring CNS homeostasis. Simultaneously, the persistent challenge of delivering drugs across the blood–brain barrier has catalyzed innovations in nanoparticle-based delivery systems, focused ultrasound, and receptor-mediated transcytosis.

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