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NEUROINFLAMMATION AND REGENERATION: THE DOUBLE-EDGED ROLE OF MICROGLIA

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Abstract

Neuroinflammation represents a complex defense mechanism of the central nervous system (CNS) that, when chronically activated, contributes to progressive neuronal injury. Microglia, the resident immune cells of the CNS, play a pivotal role in maintaining neural homeostasis. Depending on environmental cues, these cells can exhibit either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, which collectively determine the outcome of neural damage or repair. The dualistic nature of microglial activation has emerged as a central theme in neurodegenerative and regenerative research. In pathological conditions such as Alzheimer's disease, Parkinson's disease, stroke, and diabetic neuropathy, persistent M1 activation induces oxidative stress, cytokine release, and neuronal apoptosis. Conversely, M2 microglia promote tissue regeneration through the secretion of neurotrophic factors and anti-inflammatory mediators. Recent advances highlight the therapeutic potential of modulating microglial polarization using pharmacological agents and natural compounds to restore neuroimmune balance. Understanding the molecular mechanisms underlying microglial plasticity offers novel strategies for enhancing neuroregeneration and mitigating chronic neurodegeneration.

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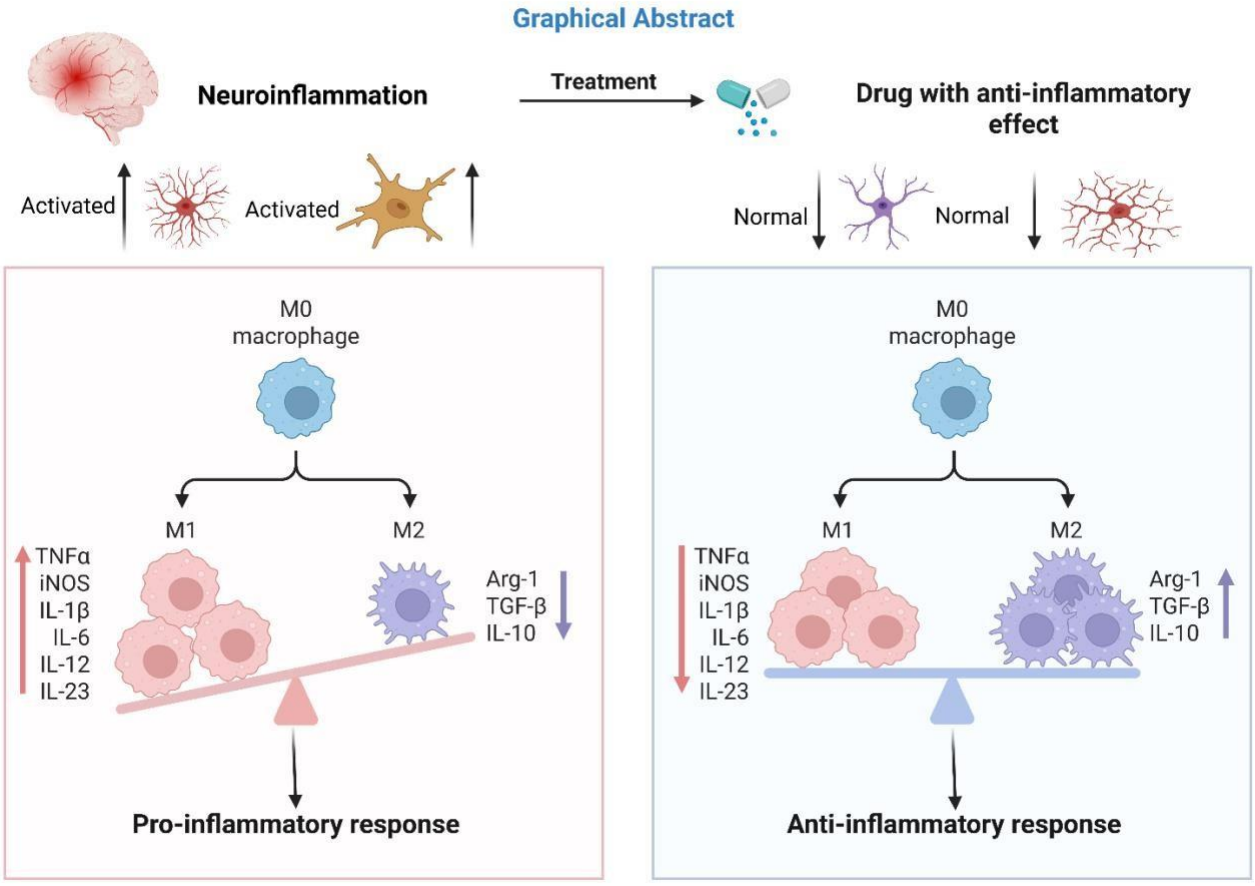

INTRODUCTION

The central nervous system (CNS) was once believed to be an immune-privileged organ, protected from inflammatory processes by the blood-brain barrier (BBB). However, extensive research over the past two decades has demonstrated that the CNS possesses an intrinsic immune system that is primarily mediated by microglia, the resident macrophages of the brain and spinal cord [1]. Under physiological conditions, microglia perform essential housekeeping roles, such as removing cellular debris, monitoring synaptic activity, and maintaining neurochemical balance [2]. Yet, when exposed to chronic stressors, infection, metabolic dysfunction, or trauma, these cells undergo morphological and functional changes, resulting in either neuroprotective or neurotoxic outcomes [3].

Neuroinflammation is a tightly regulated defense response intended to restore tissue integrity and homeostasis following injury or infection. However, prolonged or uncontrolled activation of the inflammatory machinery contributes to neurodegenerative cascades [4]. Among the various immune players in the CNS, microglia are recognized as the principal modulators of inflammation. They act as sentinels, responding rapidly to pathological stimuli by releasing cytokines, chemokines, and reactive oxygen species (ROS) [5]. Depending on the local microenvironment, microglia can polarize into distinct functional states: the pro-inflammatory M1 phenotype, which promotes cytotoxicity and neuronal death, or the anti-inflammatory M2 phenotype, which facilitates neuroprotection and tissue repair [6].

The dualistic nature of microglial activation has given rise to the concept of a “double-edged sword” in neuroinflammation. While M1 activation serves as an essential first line of

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defense, chronic persistence of this state exacerbates oxidative damage, synaptic dysfunction, and neuronal apoptosis [7]. Conversely, the M2 phenotype plays a pivotal role in neuroregeneration through the release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1) [8]. The dynamic balance between these phenotypes determines whether the outcome of neuroinflammation will be deleterious or restorative.

Recent evidence indicates that dysregulated microglial activity contributes not only to classical neurodegenerative disorders such as Alzheimer's and Parkinson's disease but also to metabolic conditions like diabetic neuropathy and cognitive dysfunction associated with hyperglycemia [9]. Moreover, molecular pathways such as NF-κB, JAK/STAT, and Nrf2 have been identified as critical regulators of microglial polarization and oxidative signaling [10]. Understanding these mechanisms opens new therapeutic perspectives for controlling neuroinflammation and promoting regeneration.

In this review, we aim to explore the paradoxical role of microglia in both neurodegeneration and regeneration. We discuss the molecular signaling pathways that govern microglial activation, the contribution of these cells to various neurological and metabolic disorders, and the emerging potential of pharmacological and natural modulators in reprogramming microglial responses toward repair.

2. Microglia: Origin and Functions

Microglia are the resident immune cells of the central nervous system (CNS) and constitute approximately 10-15% of the total glial population. Unlike peripheral macrophages derived from circulating monocytes, microglia originate from primitive myeloid progenitors in the yolk sac during early embryogenesis [11]. These progenitors migrate into the developing neural tube before the formation of the blood–brain barrier (BBB) and differentiate into long-lived microglial populations [12]. Under physiological conditions, microglia maintain a ramified morphology characterized by highly motile processes that constantly scan the surrounding microenvironment for signs of infection, injury, or cellular distress [13].

In the healthy CNS, microglia serve as key regulators of homeostasis. They participate in **synaptic pruning,** a process essential for neural circuit refinement during development and learning [14]. Microglia also clear apoptotic cells and extracellular debris through phagocytosis, thereby preserving tissue integrity and preventing the accumulation of neurotoxic waste [15]. Additionally, they secrete a range of trophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)**,** which promote neuronal survival, axonal growth, and synaptic plasticity [16]. These neurotrophic interactions highlight the critical contribution of microglia to neurodevelopment and the maintenance of functional neuronal networks.

Microglial activity is influenced by diverse molecular cues within the CNS microenvironment. Pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) **and** nucleotide-binding oligomerization domain-like receptors (NLRs)**,** enable microglia to detect pathogen-associated and damage-associated molecular patterns (PAMPs and DAMPs) [17]. Activation of these receptors triggers intracellular signaling cascades involving nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, ultimately leading to the release of cytokines and chemokines [18]. Through these mechanisms, microglia act as the **first responders** to neural injury, coordinating immune surveillance and repair responses.

Emerging evidence suggests that microglia exhibit remarkable **plasticity,** allowing them to rapidly transition between surveillance, activation, and repair states. This plasticity is vital for balancing immune defense with tissue regeneration. However, when microglial homeostasis is disturbed by chronic metabolic stress, infection, or aging, these cells can shift toward a persistent pro-inflammatory phenotype, resulting in the overproduction of reactive oxygen species (ROS)

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and nitric oxide (NO) [19]. This excessive inflammatory state disrupts neuronal communication and contributes to synaptic dysfunction, thereby linking microglial dysregulation with neurodegenerative disorders [20].

Thus, microglia represent a dynamic cellular population that bridges the gap between the nervous and immune systems. Their ability to sense microenvironmental changes and mount appropriate responses makes them indispensable for CNS homeostasis. However, the same mechanisms that protect neurons under normal conditions can, when dysregulated, lead to chronic neuroinflammation and neuronal loss, a hallmark of many neurological and metabolic diseases.

3. Activation and Polarization Mechanisms of Microglia (M1/M2)

Microglial activation is a highly dynamic process that determines the balance between neuroprotection and neurotoxicity within the central nervous system (CNS). In response to injury, infection, or metabolic disturbance, resting microglia rapidly transform from a surveillant state into distinct functional phenotypes, broadly classified as **classically activated (M1)** and **alternatively activated (M2)** forms [21]. This polarization model, originally derived from macrophage biology, provides a conceptual framework for understanding the dual roles of microglia in neuroinflammation and regeneration [22].

The **M1 phenotype** is typically induced by pro-inflammatory stimuli such as lipopolysaccharide (LPS), interferon-gamma (IFN-γ), or tumor necrosis factor-alpha (TNF-α) [23]. Activation of pattern recognition receptors (PRRs), particularly Toll-like receptor 4 (TLR4**),** triggers intracellular signaling cascades involving nuclear factor-kappa B (NF-κB)**,** mitogen-activated protein kinases (MAPKs)**, and** Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways [24]. These signaling events lead to the transcriptional upregulation of inflammatory mediators, including TNF-α, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), which collectively contribute to neuronal damage and synaptic dysfunction [25]. Chronic persistence of the M1 phenotype has been strongly associated with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis [26].

Conversely, the **M2 phenotype** is characterized by the release of anti-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-10 (IL-10), and transforming growth factor-beta (TGF-β) [27]. M2 polarization is associated with the activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and **nuclear factor erythroid 2-related factor 2 (Nrf2)** signaling pathways, which attenuate oxidative stress and promote tissue regeneration [28]. M2 microglia also secrete neurotrophic molecules like brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and insulin-like growth factor-1 (IGF-1), which support axonal regeneration and neuronal survival [29]. Thus, the M1/M2 balance serves as a molecular switch that determines whether inflammation resolves or progresses into neurodegeneration.

However, it is now widely recognized that microglial activation exists along a **continuum** rather than a strict binary classification. Transcriptomic analyses have revealed multiple intermediate phenotypes expressing both pro- and anti-inflammatory markers, indicating that microglial states are context-dependent and highly plastic [30]. This plasticity enables microglia to respond adaptively to varying pathological environments, but it also poses a challenge for therapeutic interventions aimed at selective phenotype modulation.

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs**,** play essential roles in microglial polarization [31]. For instance, microRNA-124 (miR-124) suppresses M1-related gene expression while promoting M2-associated transcription, thereby acting as a molecular switch for anti-inflammatory signaling [32]. Similarly, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have been implicated in fine-tuning microglial responses by regulating transcription factors such as STAT3**,** IRF5**, and** PPAR-γ [33].

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Targeting these epigenetic regulators represents a promising strategy to achieve controlled modulation of neuroinflammation and enhance regenerative outcomes.

Collectively, understanding the molecular determinants of microglial polarization is crucial for designing therapeutic interventions that can reprogram pathogenic M1 microglia into protective M2 phenotypes. Pharmacological or natural agents that activate the PI3K/Akt/Nrf2 axis while inhibiting NF-κB and JAK/STAT pathways hold significant potential for the treatment of neurodegenerative and metabolic neuropathies.

4. Role of Microglia in Neurodegeneration

Microglia play a central role in the initiation and progression of various neurodegenerative disorders. While transient activation of these cells is protective, persistent activation leads to a chronic inflammatory state that exacerbates neuronal injury. The imbalance between neuroprotective and neurotoxic responses determines the trajectory of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and diabetic neuropathy [34].

4.1 Alzheimer's Disease

Alzheimer's disease is characterized by the accumulation of amyloid-beta (Aβ) plaques **and** neurofibrillary tangles (NFTs)**,** which activate microglia through pattern recognition receptors such as Toll-like receptor 2 (TLR2) **and** Toll-like receptor 4 (TLR4) [35]. Activated microglia attempt to clear Aβ aggregates through phagocytosis; however, chronic stimulation leads to excessive secretion of inflammatory mediators such as TNF-α, IL-1β, and nitric oxide (NO), causing synaptic dysfunction and neuronal death [36]. This persistent inflammatory environment further amplifies amyloid pathology through a vicious cycle of oxidative stress and cytokine signaling [37]. Recent evidence indicates that microglial activation in AD is also regulated by TREM2 (Triggering Receptor Expressed on Myeloid Cells 2)**,** a receptor critical for lipid sensing and phagocytic function [38]. Mutations in TREM2 impair debris clearance and are strongly associated with late-onset AD, underscoring the role of microglial dysfunction in disease progression [39].

4.2 Parkinson's Disease

In Parkinson's disease, selective degeneration of dopaminergic neurons in the substantia nigra is accompanied by profound microglial activation [40]. Exposure to aggregated alpha-synuclein (α-syn) triggers a robust inflammatory response mediated by NF-κB **and** NLRP3 inflammasome pathways [41]. Activated microglia release neurotoxic factors, including ROS and pro-inflammatory cytokines, which accelerate neuronal apoptosis [42]. Elevated expression of microglial surface markers such as CD68 and HLA-DR **has** been observed in postmortem PD brains, confirming the involvement of chronic neuroinflammation [43]. Pharmacological inhibition of microglial activation or modulation toward the M2 phenotype has been shown to alleviate dopaminergic neuronal loss in experimental PD models [44].

4.3 Ischemic Stroke and Hypoxic Injury

Following cerebral ischemia, microglia are among the first cells to respond to hypoxic injury. During the acute phase, microglia adopt an M1-like phenotype that releases pro-inflammatory mediators to clear necrotic tissue, but prolonged activation delays recovery and worsens neuronal loss [45]. Transition to the M2 phenotype in the subacute stage supports angiogenesis, remyelination, and synaptic remodeling [46]. Therapies that accelerate this M1-to-M2 shift, such as **Nrf2 activators** and **PPAR-γ agonists**, have demonstrated significant neuroprotective effects in preclinical stroke models [47].

4.4 Diabetic Neuropathy and Cognitive Dysfunction

Microglial activation has also been implicated in diabetes-associated neurodegeneration, commonly referred to as "diabetic encephalopathy" [48]. Chronic hyperglycemia leads to excessive production of ROS, advanced glycation end products (AGEs), and inflammatory cytokines that

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activate microglia through the **RAGE–NF-κB** axis [49]. The resulting neuroinflammatory milieu contributes to neuronal apoptosis, impaired synaptic plasticity, and cognitive deficits [50]. Studies have demonstrated that targeting microglial activation using natural antioxidants such as **thymoquinone** from *Nigella sativa* or **resveratrol** can attenuate neuroinflammation and improve neuronal integrity in diabetic models [51].

Collectively, these findings emphasize that microglia act as both mediators and amplifiers of neurodegenerative processes. Their sustained activation disrupts neuronal homeostasis through cytokine release, oxidative stress, mitochondrial damage, and impaired clearance of toxic proteins. Therapeutic strategies that restore microglial balance by promoting anti-inflammatory phenotypes hold promise for preventing or slowing neurodegenerative progression across multiple disorders.

5. Role of Microglia in Neuroregeneration

Although microglial activation is often associated with neurotoxicity, increasing evidence indicates that these cells also play crucial roles in **neuroregeneration** and **tissue repair** following central nervous system (CNS) injury. Under controlled activation states, microglia facilitate the resolution of inflammation, clearance of debris, secretion of neurotrophic factors, and support for axonal and synaptic remodeling [52]. This regenerative potential largely depends on the transition of microglia from a pro-inflammatory (M1) phenotype toward an anti-inflammatory, pro-repair (M2) phenotype [53].

5.1 Microglial-Mediated Clearance and Repair Mechanisms

During acute injury, microglia initiate the **phagocytosis of apoptotic cells and damaged myelin**, thereby preventing secondary necrosis and the spread of toxic molecules [54]. This debris clearance is an essential step for the initiation of regeneration, as it provides a permissive environment for axonal sprouting and neuronal survival [55]. The M2 phenotype enhances phagocytic efficiency through the upregulation of receptors such as **Mer tyrosine** kinase (MerTK) **and** triggering receptor expressed on myeloid cells 2 (TREM2**)** [56]. In addition, M2 microglia produce anti-inflammatory cytokines such as interleukin-10 (IL-10) **and** transforming growth factor-beta (TGF-β)**,** which suppress pro-inflammatory cascades and promote tissue remodeling [57].

5.2 Promotion of Neurogenesis and Synaptic Plasticity

Microglia actively contribute to **neurogenesis** by releasing trophic molecules that stimulate neural stem cell (NSC) proliferation and differentiation [58]. In the hippocampus, M2-polarized microglia secrete brain-derived neurotrophic factor (BDNF) **and** insulin-like growth factor-1 (IGF-1**)**, which enhance neuroblast survival and facilitate the formation of new synaptic connections [59]. Similarly, glial cell-derived neurotrophic factor (GDNF) **and** nerve growth factor (NGF) released from microglia play vital roles in axonal elongation and synaptic maturation [60]. Experimental models of traumatic brain injury (TBI) and stroke have shown that promoting M2 polarization results in improved functional recovery, increased dendritic spine density, and enhanced cognitive performance [61].

5.3 Microglia-Astrocyte and Microglia-Neuron Crosstalk

Neuroregeneration is a highly coordinated process involving cross-talk among neurons, astrocytes, and microglia. M2 microglia communicate with astrocytes via extracellular vehicles (EVs) **and** exosome**s** that transfer microRNAs and signaling proteins to regulate astrocytic functions [62]. This intercellular exchange suppresses glial scar formation and supports axonal regeneration [63]. Microglia also form bidirectional communication loops with neurons; neuronal signals such as **fractalkine (CX3CL1)** and **colony-stimulating factor 1 (CSF1)** modulate microglial behavior toward a pro-survival phenotype [64]. In return, microglia release BDNF and other trophic factors that stabilize synaptic circuits and maintain neuronal homeostasis [65].

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5.4 Metabolic and Mitochondrial Regulation in Regenerative Microglia

The regenerative capacity of microglia is also influenced by their metabolic reprogramming. M1 microglia primarily rely on glycolysis for energy, while M2 microglia utilize oxidative phosphorylation and fatty acid oxidation pathways [66]. Activation of the AMP-activated protein kinase (AMPK) **and** peroxisome proliferator-activated receptor-gamma (PPAR-γ) pathways enhances mitochondrial efficiency and promotes M2-like polarization [67]. Therapeutic agents targeting these metabolic switches have been shown to augment neurorepair in preclinical models of spinal cord and ischemic injury [68].

Collectively, microglia function not only as immune defenders but also as architects of CNS regeneration. Their phenotypic plasticity allows them to orchestrate multiple processes from debris clearance and trophic support to cellular cross-talk and metabolic adaptation, all of which are crucial for recovery after neural injury. Harnessing the reparative potential of microglia through pharmacological or natural modulators could revolutionize therapeutic strategies for neurodegenerative and metabolic neuropathies.

6. Therapeutic Modulation of Microglial Activity

Given the dualistic role of microglia in neuroinflammation and repair, recent therapeutic efforts have focused on **reprogramming microglial phenotypes** rather than suppressing their activation altogether. The central goal is to **shift microglia from a neurotoxic M1 state to a neuroprotective M2 phenotype**, thereby promoting neuronal survival, tissue remodeling, and functional recovery [69]. Such modulation can be achieved through pharmacological agents, natural compounds, gene targeting, or nanocarrier-based delivery systems [70].

6.1 Pharmacological Modulators

Several small-molecule drugs have shown potential in modulating microglial activation through specific signaling pathways. **Minocycline**, a tetracycline derivative, is one of the most extensively studied agents for inhibiting microglial overactivation. It suppresses NF-κB signaling, reduces pro-inflammatory cytokine release, and promotes M2-like polarization [71]. **Pioglitazone**, a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist, has demonstrated similar benefits by enhancing mitochondrial metabolism and reducing oxidative stress [72]. Moreover, **dimethyl** fumarate (DMF**)**, a Nrf2 activator approved for multiple sclerosis, exerts strong antioxidant effects that shift microglial balance toward a reparative phenotype [73].

Other pharmacological interventions aim to target **purinergic signaling** via the P2X7 receptor, which regulates ATP-mediated inflammatory cascades. Antagonists of this receptor, such as **brilliant blue G**, have shown neuroprotective effects in models of spinal cord injury and diabetic neuropathy [74]. These agents collectively highlight the potential of pathway-specific microglial modulation as a strategy for treating chronic neurodegenerative and metabolic diseases.

6.2 Natural Compounds and Phytochemicals

Natural compounds have gained attention as **multi-target therapeutic agents** capable of modulating microglial functions through anti-inflammatory and antioxidant mechanisms [75]. **Curcumin**, a bioactive polyphenol from turmeric, attenuates microglial M1 activation by inhibiting NF-κB and MAPK pathways while simultaneously enhancing Nrf2-mediated antioxidant defense [76]. **Resveratrol**, a stilbene found in grapes, modulates the SIRT1/AMPK axis to suppress inflammation and promote mitochondrial biogenesis [77].

Thymoquinone, the principal active component of *Nigella sativa*, has shown promising results in reversing neuroinflammation associated with diabetes and ischemic injury. It downregulates pro-inflammatory mediators (IL-6, TNF-α) and promotes M2-like polarization via PPAR-γ activation [78]. Other compounds such as **quercetin**, **baicalein**, and **epigallocatechin gallate (EGCG)** have similarly demonstrated microglia-targeted neuroprotection through redox modulation [79].

6.3 Nanomedicine and Gene Targeting Approaches

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Emerging nanotechnology-based therapies allow **targeted delivery of microglial modulators** directly across the blood–brain barrier (BBB). Liposomal and polymeric nanoparticles encapsulating anti-inflammatory drugs or siRNAs targeting inflammatory genes (such as *NF-κB p65* or *iNOS*) have shown enhanced efficacy and reduced systemic toxicity [80]. In addition, CRISPR-Cas9-based gene editing holds potential for selectively silencing pro-inflammatory genes within microglia [81].

Table 1. Pharmacological and Natural Compounds Modulating Microglial Activation

Agent/Compound	Mechanism of Action	Effect on Microglia	Therapeutic Outcome	Reference
Minocycline	Inhibits NF-κB and MAPK signaling	Reduces M1 activation, cytokine release	Neuroprotection in AD, stroke	[71]
Pioglitazone	Activates PPAR-γ and mitochondrial metabolism	Promotes M2 polarization	Improved motor and cognitive outcomes	[72]
Dimethyl fumarate (DMF)	Activates the Nrf2 antioxidant pathway	Enhances anti-inflammatory phenotype	Used in multiple sclerosis	[73]
Brilliant Blue G	P2X7 receptor antagonist	Inhibits ATP-mediated microglial activation	Neuroprotection in diabetic neuropathy	[74]
Curcumin	Inhibits NF-κB and enhances Nrf2	Suppresses inflammation and oxidative stress	Cognitive improvement in AD	[76]
Resveratrol	Activates SIRT1/AMPK signaling	Promotes mitochondrial biogenesis	Attenuates neuroinflammation	[77]
Thymoquinone (*Nigella sativa*)	Activates PPAR-γ, suppresses IL-6 and TNF-α	Shifts M1 → M2 phenotype	Neuroprotection in diabetic models	[78]
Quercetin	Inhibits JAK/STAT and ROS production	Reduces pro-inflammatory signaling	Protective in ischemic injury	[79]
EGCG	Scavenges ROS, modulates microglial metabolism	Decreases oxidative stress	Prevents neuronal apoptosis	[79]

6.4 Clinical Perspectives

Although most findings originate from preclinical studies, translational research is expanding rapidly. Clinical trials evaluating **curcumin** and **resveratrol** supplementation have demonstrated mild cognitive improvement and reduced inflammatory biomarkers in Alzheimer's patients [82]. Similarly, PPAR-γ agonists such as **pioglitazone** are being tested for diabetic cognitive dysfunction, reflecting growing recognition of the metabolic–neuroinflammatory interface [83]. However, further research is needed to optimize dosage, bioavailability, and BBB permeability of these compounds to ensure therapeutic efficacy in humans [84].

In summary, modulation of microglial activity using pharmacological, natural, and

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nanotechnological approaches holds promise for the treatment of neurodegenerative and metabolic disorders. By targeting the molecular switches that regulate inflammation and regeneration, these interventions can potentially restore neuroimmune balance and promote long-term neuroprotection.

7. Microglial Activation and Diabetes: A Metabolic Link to Neuroinflammation

Diabetes mellitus (DM), traditionally regarded as a metabolic disorder, has now been recognized as a significant risk factor for **neurodegeneration**. Chronic hyperglycemia, insulin resistance, and metabolic inflammation converge to induce central nervous system (CNS) dysfunction through the activation of microglia and astrocytes [85]. This condition, often termed **"diabetic encephalopathy"**, encompasses a spectrum of neuronal alterations including cognitive decline, memory impairment, and reduced synaptic plasticity [86]. Increasing evidence suggests that **microglial activation serves as the key mediator** linking metabolic dysregulation with neuroinflammatory damage.

7.1 Mechanisms of Microglial Activation in Diabetes

Persistent hyperglycemia leads to the overproduction of reactive oxygen species (ROS) and the accumulation of advanced glycation end products (AGEs)**,** which engage the receptor for advanced glycation end products (RAGE) on microglia [87]. The RAGE–NF-κB signaling axis amplifies inflammatory gene transcription, resulting in the release of TNF-α, IL-6, and IL-1β, thereby promoting oxidative and nitrosative stress [88]. In parallel, the mitochondrial dysfunction observed in diabetic states enhances ROS leakage and impairs ATP production, contributing to metabolic exhaustion of microglia [89]. This sustained stress drives the cells toward a pro-inflammatory M1 phenotype, leading to neuronal injury and synaptic loss.

Additionally, dysregulated insulin signaling in the brain directly impacts microglial physiology. Under normal conditions, insulin modulates microglial metabolism and suppresses NF-κB dependent inflammation [90]. However, insulin resistance common in both type 2 diabetes and obesity disrupts this regulation, resulting in overactivation of microglia and elevated production of inflammatory mediators [91]. These molecular changes resemble the pathophysiological features of Alzheimer's disease, leading to the conceptualization of **"type 3 diabetes"** as a state of insulin resistance in the brain [92].

7.2 Microglial Contribution to Diabetic Neuropathy

Peripheral and central neuropathies are among the most disabling complications of diabetes. Activated microglia play a critical role in the progression of **diabetic neuropathy**, particularly through their interaction with peripheral sensory neurons [93]. In experimental models, hyperglycemia-induced activation of spinal cord microglia leads to elevated expression of **ionized calcium-binding adaptor molecule 1 (Iba1)** and **CD68**, markers associated with neuroinflammation and pain hypersensitivity [94]. Pro-inflammatory cytokines released by microglia sensitize nociceptive neurons, contributing to mechanical allodynia and thermal hyperalgesia [95].

The neurotoxic environment within the diabetic CNS is further exacerbated by endoplasmic reticulum (ER) stress **and** lipid dysregulation**, which activate the** NLRP3 inflammasome in microglia [96]. This inflammasome activation triggers the release of **IL-1β** and **caspase-1-dependent pyroptosis**, leading to neuronal apoptosis and white matter degradation [97]. Targeting NLRP3-mediated microglial activation has therefore emerged as a promising therapeutic strategy in both diabetic neuropathy and cognitive dysfunction.

7.3 Therapeutic Modulation of Microglia in Diabetes

Therapeutic interventions aimed at **rebalancing microglial phenotypes** have shown notable success in experimental diabetic models. **Thymoquinone** from *Nigella sativa* exerts a protective role by suppressing NF-κB signaling,

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enhancing Nrf2-mediated antioxidant defense, and promoting M2 polarization [98]. Similarly, **resveratrol** and **metformin** modulate AMPK and SIRT1 pathways to inhibit microglial inflammation and improve synaptic integrity [99]. These compounds not only reduce inflammatory cytokine production but also restore insulin sensitivity in brain tissues, suggesting a dual benefit in metabolic and neuronal regulation [100].

Importantly, preclinical studies indicate that exercise **and** dietary interventions also modulate microglial activity by improving mitochondrial function and reducing systemic inflammation [101]. This highlights the integrative nature of metabolic and neuroimmune pathways in maintaining CNS health under diabetic conditions.

Collectively, these findings establish diabetes as a potent inducer of neuroinflammation via microglial overactivation. Therapeutic strategies that target oxidative stress, insulin resistance, and inflammasome signaling hold the potential to mitigate the cognitive and neuropathic complications associated with diabetes. The modulation of microglial activity thus represents a key bridge between metabolic control and neuroprotection.

8. Future Perspectives and Conclusion

Microglia represent one of the most versatile and influential cell populations in the central nervous system (CNS). Their dualistic nature, capable of mediating both **neuroinflammation and neuroregeneration,** underscores their pivotal role in neural health and disease. In recent years, the focus of neuroscience research has shifted from broadly suppressing inflammation to **precisely modulating microglial activity** to favor repair and recovery [102]. The complexity of microglial behavior, influenced by molecular signaling networks, metabolic cues, and environmental factors, demands an integrated therapeutic approach that addresses these multidimensional dynamics.

8.1 Emerging Therapeutic Avenues

Recent developments in multi-omics technologies**,** including single-cell RNA sequencing and spatial transcriptomics, have revolutionized the understanding of microglial heterogeneity [103]. These approaches have revealed numerous microglial subtypes with distinct transcriptional and metabolic profiles across different brain regions and disease stages. Leveraging these insights can lead to the development of precision therapies that selectively target harmful microglial subsets while preserving or enhancing beneficial ones [104].

Additionally, nanomedicine and exosome-based **delivery systems** are emerging as powerful platforms for targeted therapeutic modulation. Microglia-specific nanoparticles or engineered exosomes carrying anti-inflammatory drugs, small RNAs, or antioxidants can cross the blood-brain barrier (BBB) and achieve localized, sustained effects [105]. Similarly, **gene-editing tools** such as CRISPR/Cas9 are opening new possibilities for silencing pro-inflammatory genes or reprogramming microglial responses in situ [106]. Another promising direction involves the **gut-brain axis**, which influences microglial maturation and activation through microbial metabolites and immune signaling [107]. Modulation of gut microbiota via probiotics, prebiotics, or dietary interventions has shown potential in attenuating microglia-driven neuroinflammation and improving cognitive outcomes in animal models of diabetes and neurodegeneration.

8.2 Challenges and Knowledge Gaps

Despite substantial progress, several challenges remain. One major limitation is the **context dependency of microglial activation**, as phenotypes can vary dynamically across time and CNS regions [108]. The M1/M2 classification, while useful, oversimplifies the functional diversity of microglial states. Furthermore, differences between rodent and human microglia present a translational barrier, as human microglia exhibit distinct gene expression and metabolic responses [109]. Addressing these discrepancies will require advanced *in vitro* models such as human induced pluripotent stem cell (iPSC)-derived microglia and organoid systems.

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Conclusion

Microglia stand at the intersection of immunity, metabolism, and neural regeneration. Their ability to shift between detrimental and reparative states defines the outcome of many neurological and metabolic disorders, including Alzheimer's disease, Parkinson's disease, stroke, and diabetic neuropathy. A deeper understanding of the molecular switches that govern microglial polarization, particularly the NF-κB, JAK/STAT, Nrf2, and PPAR-γ pathways, provides an opportunity to harness these cells therapeutically. The integration of pharmacological agents, natural compounds, and nanotechnological innovations represents a forward-looking strategy to rebalance neuroimmune responses.

Ultimately, future research should emphasize **microglial reprogramming** rather than suppression, enabling the brain's intrinsic capacity for repair. The convergence of molecular neuroscience, immunology, and bioengineering will likely define the next generation of therapies aimed at restoring neural homeostasis and improving life quality for patients with neurodegenerative and metabolic diseases.

References

Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. ***Annu Rev Immunol.*** 2017; 35:441-468.

Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. ***Nat Rev Immunol.*** 2018;18(4):225-242.

Prinz M, Jung S, Priller J. Microglia biology: one century of evolving concepts. ***Cell.*** 2019;179(2):292-311.

Heneka MT et al. Neuroinflammation in Alzheimer's disease. ***Lancet Neurol.*** 2015;14(4):388-405.

Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. ***Br J Pharmacol.*** 2016;173(4):649-665.

Tang Y, Le W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. ***Mol Neurobiol.*** 2016;53(2):1181-1194.

Gaire BP, Choi JW. Pathophysiological roles of microglia in ischemic stroke. ***Brain Res Bull.*** 2021; 170:137-148.

Li J, Chen Y, Chen X. Role of microglia in neurogenesis and neuroregeneration. ***Front Cell Neurosci.*** 2022; 16:834079.

Li W, Cao T, Luo C, et al. Microglial activation in diabetic neuropathy: mechanisms and therapeutic strategies. ***Front Pharmacol.*** 2023; 14:1120058.

Liu J, Wang F, Chen J, et al. Molecular pathways regulating microglial activation in neurodegeneration. ***Trends Mol Med.*** 2024;30(2):123-139.

Ginhoux F, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. ***Science.*** 2010;330(6005):841-845.

Kierdorf K, Prinz M. Microglia in steady state. ***J Clin Invest.*** 2017;127(9):3201-3209.

Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma. ***Science.*** 2005;308(5726):1314-1318.

Paolicelli RC, et al. Synaptic pruning by microglia is necessary for normal brain development. ***Science.*** 2011;333(6048):1456-1458.

Sierra A, Tremblay MÈ, Wake H. Never-resting microglia: physiological roles in the healthy brain and pathological implications. ***Front Cell Neurosci.*** 2014; 8:240.

Parkhurst CN, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. ***Cell.*** 2013;155(7):1596-1609.

Colonna M, Butovsky O. Microglia function in the CNS during health and neurodegeneration. ***Annu Rev Immunol.*** 2017; 35:441-468.

Tang Y, Le W. Differential roles of microglia in neurodegenerative diseases. ***Mol Neurobiol.*** 2016;53(2):1181-1194.

Orihuela R, McPherson CA, Harry GJ. Microglial polarization states and metabolic control. ***Br J Pharmacol.*** 2016;173(4):649-665.

Hemonnot AL, Hua J, Ulmann L, Hirbec H. Microglia in Alzheimer's disease: a role for

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

reactive oxygen species in the inflammation. ***Front Cell Neurosci.*** 2019; 13:437.

Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization states and their relevance in neurodegeneration. ***Br J Pharmacol.*** 2016;173(4):649-665.

Franco R, Fernández-Suárez D. Alternatively activated microglia and macrophages in the central nervous system. ***Prog Neurobiol.*** 2015; 131:65-86.

Lively S, Schlichter LC. Microglia responses to pro-inflammatory stimuli (LPS, IFNγ + TNFα) and reprogramming by resolving cytokines (IL-4, IL-10). ***Front Cell Neurosci.*** 2018; 12:215.

Li J, Wang Y, Sun X, et al. NF-κB and MAPK signaling pathways in microglial activation: potential therapeutic targets for neuroinflammatory diseases. ***Front Immunol.*** 2023; 14:1123001.

Liu J, Wang F, Chen J, et al. Molecular pathways regulating microglial activation in neurodegeneration. ***Trends Mol Med.*** 2024;30(2):123-139.

Chitnis T, Weiner HL. CNS inflammation and neurodegeneration. ***J Clin Invest.*** 2017;127(10):3577-3587.

Orihuela R, et al. Microglial polarization and anti-inflammatory responses. ***Br J Pharmacol.*** 2016;173(4):649-665.

Zhao R, Li Y, Liu J. Activation of PI3K/Akt and Nrf2 signaling in microglial polarization: implications for neuroprotection. ***Neurochem Int.*** 2022; 158:105373.

Li J, Chen Y, Chen X. Role of microglia in neurogenesis and neuroregeneration. ***Front Cell Neurosci.*** 2022; 16:834079.

Masuda T, Sankowski R, Staszewski O, Prinz M. Microglia heterogeneity in the single-cell era. ***Nat Rev Neurosci.*** 2020;21(2):88-102.

Guo L, et al. Epigenetic regulation of microglial polarization and its therapeutic potential. ***Cell Death Dis.*** 2023;14(6):410.

Ponomarev ED, et al. MicroRNA-124 promotes microglia quiescence and suppresses neuroinflammation. ***Nat Commun.*** 2011; 2:120.

Dong Y, et al. Non-coding RNA regulation of microglial polarization in CNS diseases. ***Mol Neurobiol.*** 2024;61(2):451-467.

Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer's disease: where do we go from here? ***Nat Rev Neurol.*** 2021;17(3):157-172.

Hansen DV, Hanson JE, Sheng M. Microglia in Alzheimer's disease. ***J Cell Biol.*** 2018;217(2):459-472.

Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer's disease. ***Nat Rev Neurosci.*** 2015;16(6):358-372.

Heneka MT, et al. Neuroinflammation in Alzheimer's disease. ***Lancet Neurol.*** 2015;14(4):388-405.

Ulrich JD, Holtzman DM. TREM2 function in Alzheimer's disease and neurodegeneration. ***ACS Chem Neurosci.*** 2016;7(4):420-427.

Sayed FA, et al. Microglial TREM2 regulates neuroinflammation and synaptic integrity in Alzheimer's disease. ***Cell Rep.*** 2023;42(5):112438.

Joers V, et al. Microglia in Parkinson's disease: the role of neuroinflammation. ***Front Cell Neurosci.*** 2017; 11:81.

Gordon R, et al. Inflammasome activation by α-synuclein in Parkinson's disease models. ***J Exp Med.*** 2018;215(9):2245-2259.

Gaire BP, Choi JW. Pathophysiological roles of microglia in ischemic stroke. ***Brain Res Bull.*** 2021; 170:137-148.

McGeer PL, et al. Reactive microglia in Parkinson's disease brains. ***Neurology.*** 1988;38(8):1285-1291.

Lee E, et al. Modulating microglial polarization to protect dopaminergic neurons in Parkinson's disease. ***Neurobiol Dis.*** 2023; 184:106220.

Lan X, et al. The role of microglial polarization in cerebral ischemia. ***Front Aging Neurosci.*** 2017; 9:210.

Li Z, et al. M2 microglia promote recovery after stroke by modulating neurogenesis and angiogenesis. ***Brain Behav Immun.*** 2020; 87:556-570.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Zhang L, et al. Nrf2 activation promotes microglial M2 polarization and protects against ischemic injury. ***Neurochem Int.*** 2022; 157:105364.

Li W, et al. Microglial activation in diabetic neuropathy: mechanisms and therapeutic strategies. ***Front Pharmacol.*** 2023; 14:1120058.

Wang Y, et al. RAGE–NF-κB axis in diabetes-associated neuroinflammation. ***Mol Neurobiol.*** 2024;61(3):1211-1224.

Zhao Y, et al. Diabetic cognitive impairment and microglial activation. ***Front Aging Neurosci.*** 2022; 14:909386.

Alghamdi AA. Thymoquinone and neuroinflammation: potential role in diabetic encephalopathy. ***Phytomedicine.*** 2024; 122:155023.

Cherry JD, et al. The role of microglia in neurodegenerative disease: from inflammation to regeneration. Brain. 2014;137(2):385-407.

Hu X, Leak RK, Shi Y, et al. Microglial and macrophage polarization: new prospects for brain repair. Nat Rev Neurol. 2015;11(1):56-64.

Green DR, Galluzzi L, Kroemer G. Cell death and phagocytosis: the interplay of apoptosis and clearance. Nat Rev Mol Cell Biol. 2016;17(7):487-501.

Ritzel RM, et al. Microglial clearance of debris and recovery after CNS injury. J Neurosci. 2020;40(7):1459-1472.

Hsieh CL, et al. TREM2-mediated phagocytosis in microglia: a double-edged sword in neural injury. Nat Commun. 2023;14(1):5179.

Orihuela R, McPherson CA, Harry GJ. Microglial polarization and anti-inflammatory signaling. Br J Pharmacol. 2016;173(4):649-665.

Sierra A, et al. Microglia in adult neurogenesis: friend or foe? Trends Neurosci. 2014;37(11):688-697.

Parkhurst CN, et al. Microglia promote learning-dependent synapse formation through BDNF. Cell. 2013;155(7):1596-1609.

Li J, Chen Y, Chen X. Role of neurotrophic factors in neuronal repair and regeneration. Front Cell Neurosci. 2022; 16:834079.

Wang Y, et al. Modulating microglial polarization promotes functional recovery after stroke. Front Immunol. 2023; 14:1167342.

Paolicelli RC, Bergamini G, Rajendran L. Cell-to-cell communication by extracellular vesicles: focus on microglia. Neuroscience. 2019; 405:148-157.

Chen J, et al. Microglia-derived exosomes modulate astrocytic functions to promote neuroregeneration. Brain Behav Immun. 2024; 119:98-111.

Zhan Y, Paolicelli RC, Sforazzini F, et al. Fractalkine signaling and microglial activation in synaptic maintenance. Neuron. 2014;82(2):380-397.

Park J, et al. Microglia–neuron interactions in synaptic plasticity and brain repair. Nat Rev Neurosci. 2022;23(9):568-582.

Orihuela R, McPherson CA, Harry GJ. Microglial metabolic states and activation. Br J Pharmacol. 2016;173(4):649-665.

Zhang D, et al. AMPK activation promotes microglial M2 polarization and neural repair. Mol Neurobiol. 2022;59(6):3770-3785.

Wang H, et al. PPAR-γ activation enhances neuroregeneration by modulating microglial metabolism. Front Pharmacol. 2024; 15:1184009.

Tang Y, Le W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. Mol Neurobiol. 2016;53(2):1181-1194.

Liu J, Wang F, Chen J, et al. Molecular pathways regulating microglial activation in neurodegeneration. Trends Mol Med. 2024;30(2):123-139.

Plane JM, Shen Y, Pleasure DE, Deng W. Prospects for minocycline neuroprotection. Arch Neurol. 2010;67(12):1442-1448.

Wang H, et al. PPAR-γ activation enhances neuroregeneration by modulating microglial metabolism. Front Pharmacol. 2024; 15:1184009.

Peng Y, et al. Dimethyl fumarate modulates microglial activation and protects against

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

oxidative stress. Neurobiol Dis. 2023; 185:106243.

Burnstock G, Knight GE. The potential of P2X7 receptor antagonists for neuroprotection. Purinergic Signal. 2020;16(1):1-25.

Li W, et al. Natural products targeting microglial activation in neurodegeneration. Front Pharmacol. 2023; 14:1100459.

Yang F, et al. Curcumin inhibits microglial activation and promotes neuroprotection. Neurochem Int. 2023; 159:105382.

Hou Y, et al. Resveratrol suppresses neuroinflammation via the SIRT1/AMPK pathway. Brain Behav Immun. 2022; 102:223-235.

Alghamdi AA. Thymoquinone and neuroinflammation: potential role in diabetic encephalopathy. Phytomedicine. 2024; 122:155023.

Xu L, et al. Flavonoid-mediated modulation of microglial activation: therapeutic insights. Front Cell Neurosci. 2024; 18:1340594.

Blanco E, et al. Nanoparticle strategies for microglial-targeted drug delivery. Adv Drug Deliv Rev. 2022; 188:114451.

Liu Y, et al. CRISPR-based modulation of microglial inflammatory genes. Nat Neurosci. 2024;27(5):749-762.

Small GW, et al. Randomized clinical trial of curcumin on cognitive function and amyloid imaging. Am J Geriatr Psychiatry. 2021;29(3):266-277.

Chen L, et al. Pioglitazone ameliorates cognitive dysfunction in type 2 diabetes through PPAR-γ activation. Neuropharmacology. 2023; 229:109515.

Prasad KN, Bondy SC. Dietary phytochemicals as modulators of microglial activity: translational challenges. Free Radic Biol Med. 2025; 211:78-95.

Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. ***Nat Rev Endocrinol.*** 2018;14(10):591-604.

Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. ***Endocr Rev.*** 2008;29(4):494-511.

Wang Y, et al. RAGE–NF-κB axis in diabetes-associated neuroinflammation. ***Mol Neurobiol.*** 2024;61(3):1211-1224.

Sharma P, et al. Microglial activation and oxidative stress in diabetic encephalopathy. ***Front Aging Neurosci.*** 2023; 15:1122440.

Zhang X, et al. Mitochondrial dysfunction in diabetic microglia: a driver of neurodegeneration. ***Free Radic Biol Med.*** 2023; 208:132-144.

S. Insulin resistance and Alzheimer's disease: the role of microglia. ***Trends Endocrinol Metab.*** 2022;33(9):659-672.

Duarte AI, et al. Insulin signaling in the brain and its role in neurodegenerative disease. ***Front Neurosci.*** 2023; 17:1120045.

De la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes–evidence reviewed. ***J Diabetes Sci Technol.*** 2008;2(6):1101-1113.

Li W, et al. Microglial activation in diabetic neuropathy: mechanisms and therapeutic strategies. ***Front Pharmacol.*** 2023; 14:1120058.

Cheng KI, et al. Microglial activation in diabetic pain hypersensitivity. ***Pain.*** 2021;162(5):1358-1368.

Ji RR, et al. Central mechanisms of pain hypersensitivity in diabetes: the role of microglia. ***Nat Rev Neurol.*** 2022;18(7):413-428.

Chen J, et al. ER stress and NLRP3 inflammasome activation in diabetic neuroinflammation. ***Brain Behav Immun.*** 2024; 119:150-162.

Zhu Y, et al. Microglial pyroptosis contributes to cognitive impairment in diabetes. ***Front Immunol.*** 2023; 14:1160289.

Alghamdi AA. Thymoquinone and neuroinflammation: potential role in diabetic encephalopathy. ***Phytomedicine.*** 2024; 122:155023.

Hou Y, et al. Resveratrol suppresses neuroinflammation via the SIRT1/AMPK pathway. ***Brain Behav Immun.*** 2022; 102:223-235.

Zhang Y, et al. Metformin modulates microglial activation through AMPK signaling in

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

diabetic models. ***Front Pharmacol.*** 2023; 14:1159654.

Erickson KI, et al. Physical activity, microglia, and brain health: metabolic and inflammatory links. ***Nat Rev Neurosci.*** 2023;24(6):381-397.

Liu J, Wang F, Chen J, et al. Molecular pathways regulating microglial activation in neurodegeneration. ***Trends Mol Med.*** 2024;30(2):123-139.

Masuda T, Sankowski R, Staszewski O, Prinz M. Microglia heterogeneity in the single-cell era. ***Nat Rev Neurosci.*** 2020;21(2):88-102.

Sankowski R, et al. Mapping microglial diversity and function in human brain disease. ***Nature.*** 2019;566(7744):388-392.

Blanco E, et al. Nanoparticle strategies for microglial-targeted drug delivery. ***Adv Drug Deliv Rev.*** 2022; 188:114451.

Liu Y, et al. CRISPR-based modulation of microglial inflammatory genes. ***Nat Neurosci.*** 2024;27(5):749-762.

Zheng D, et al. Gut microbiota–microglia interactions in neurological disorders. ***Trends Neurosci.*** 2023;46(1):33-48.

Stratoulias V, et al. Microglial subtypes and their roles in neurodegeneration. ***Front Immunol.*** 2019; 10:1909.

Gosselin D, et al. Environment drives microglial identity and function in the CNS. ***Science.*** 2017;356(6344):1248-1252.