International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 6, June 2026 ijppr.humanjournals.com ISSN: 2349-7203

# Microglial Immunometabolism in Neuroinflammation: Mechanisms and Nanotherapeutic Targeting

**T Praveena[*1], M Bhavithra[1], R Vanathi[1], V Sathyakala[1], K Anushiya[1]**

1. Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Virudhunagar, Tamil Nadu, India - 626 126.

Received: 07 May 2026 Revised: 30 May 2026 Accepted: 10 June 2026

**ABSTRACT:**

As the key residents immune cells of the central nervous system, microglia have an important function in the homeostasis of the brain and inflammatory processes. Chronic microglial activation under pathologic stimulus leads to neuroinflammation, a characteristic pathology in many neurodegenerative diseases. The function of microglia was classically viewed as a binary of pro-inflammatory/anti-inflammatory states, but it has become accepted that immunometabolism is a critical control factor for the functional profile of microglia, and that metabolic rewiring controls the phenotype and the inflammatory status of microglia. Redox signaling is a central regulatory mechanism that acts upon the metabolic status of microglia. While reactive oxygen species (ROS) have previously been regarded as cytotoxic cell damage products, they are now seen to act as important signaling mediators that control gene expression and innate immunity. Concomitant mitochondrial dysfunction (defined by impaired bioenergetics, excessive ROS production, and dysregulated dynamics) further exacerbates neuroinflammation and destabilizes microglial homeostasis. Interactions between redox homeostasis and mitochondrial function play a decisive role in determining neuroinflammation. Nanotechnology strategies that target these interrelated mechanisms hold promise for treatment of neurodegenerative diseases. Nanocarriers can deliver targeted antioxidants, metabolic modulators and mitochondria-targeted therapeutics across the blood-brain barrier effectively. There are, however, considerable challenges remain such as the microglial heterogeneity, safety of the nanomaterials in the long term. More effort is needed for translational research, to establish standardized models, and to develop more effective target strategies in the clinical treatment.

**Keywords:** Microglia; Immunometabolism; Reactive Oxygen Species; Mitochondria; Neuroinflammation; Nanomedicine; Redox signaling; Neurodegeneration

## INTRODUCTION:

### 1. Microglial Immunometabolism

Intracellular metabolic programs are tightly regulated by the environment and pathological cues and control the function of microglia. These metabolic programs are not mere downstream events of microglial activation but actively drive the microglial phenotype, effector functions and inflammatory responses. These views culminated in immunometabolism that has emerged as a unifying concept for microglial activities in neuroinflammation and neurodegeneration(21,22).

### 1.1 Metabolic States of Microglia

The activated states of microglia are characterized by different metabolic signatures. When activated, microglia will choose aerobic glycolysis, which is a relatively fast but low efficient pathway for ATP generation. This metabolic switch is beneficial for supporting the high biosynthetic activity required and generating pro-inflammatory molecules, such as cytokines and reactive oxygen species (ROS)(22,23).It can be seen that glycolytic reprogramming is closely correlated with a pro-inflammatory phenotype. Homeostatic/reparative microglia utilize the major energy-producing pathway which is the OXPHOS located in mitochondria generating an ample amount of ATP; this would favor the anti-inflammatory function as well as aid in repair and survival of neurons(23,24).Hence this trade off between glycolysis and OXPHOS governs activation of microglial cells. Apart from this FAO is also a source for anti inflammatory phenotype of microglia cells by providing stable energy source and by enhancing the mitochondrial respiration. FAO has also shown to increase phagocytosis and is also responsible for resolution of inflammation(24,25).

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 6, June 2026 ijppr.humanjournals.com ISSN: 2349-7203

### 1.2 Metabolic Reprogramming Triggers

The metabolic status of microglia is highly controlled and subject to the influence of their surroundings. Stimuli that are intrinsically associated with pathogens (e.g., lipopolysaccharide) and disease-associated stimuli (e.g., amyloid- [A]) are strong activators of glycolytic reprogramming and elicit a pro-inflammatory phenotype in microglia(25,26).Like those above, toxins and the stresses in the cell that they promote can affect mitochondrial respiration and further the metabolic switch toward inflammation. Cytokine signaling is also critical in metabolic processes. Pro-inflammatory cytokines TNF and interferon stimulate glycolysis and inflammatory activity while anti-inflammatory cytokinesIL-4 and IL-10 are responsible for driving oxidative respiration and tissue repair(26,27).

### 1.3 Key Regulatory Pathways

Multiple intracellular signaling pathways contribute to metabolic reprogramming in microglia. The signaling molecule HIF-1 is a key inducer of glycolysis which upregulates the transcription of enzymes associated with this metabolic pathway and shifts the cells towards a pro-inflammatory profile during hypoxia and inflammation (27,28).The activation of HIF-1 has been tightly correlated with increased ROS generation and inflammatory signaling. The mammalian target of rapamycin (mTOR) pathway is an important metabolic sensor which couples nutrient and growth factors signaling to cell metabolism. Activation of mTOR can increase glycolysis and anabolic processes and thus can promote inflammation activation of microglia(28).AMP-activated protein kinase (AMPK), in contrast, is an energy sensor which is able to stimulate both oxidative metabolism and mitochondrial biogenesis. Microglial metabolic profile changes toward OXPHOS and fatty acid oxidation when AMPK is activated and shows anti-inflammatory properties with recovery of cellular homeostasis(29).Combined, these signaling networks regulate how metabolic state influences immune function of microglia. Elucidating this network will allow targeting it with therapeutics in neuroinflammatory disease to modulate microglial function.

**Table 1. Metabolic Pathways and Functional Outcomes in Microglia**

| Metabolic Pathway | Key Characteristics | Regulatory Factors | Microglial Phenotype | Functional Outcome |
|---|---|---|---|---|
| Glycolysis | Rapid ATP production; lactate accumulation | HIF-1α, mTOR | Pro-inflammatory | Cytokine release, ROS production |
| Oxidative Phosphorylation | Efficient mitochondrial ATP generation | AMPK, PGC-1α | Homeostatic / anti-inflammatory | Tissue repair, reduced inflammation |
| Fatty Acid Oxidation | Sustained energy via lipid metabolism | AMPK, PPAR-γ | Anti-inflammatory | Resolution of inflammation, enhanced phagocytosis |
| Pentose Phosphate Pathway | NADPH production | Nrf2 | Activated microglia | Improved cellular survival and resilience |

## 2. Redox Signaling in Microglial Activation

Redox signaling is an important mechanism by which microglial activation is controlled and connects cellular metabolism to inflammation. ROS, once considered damaging side products of cellular respiration, is now understood to be a vital signal regulating the activity of immune cells. Production of ROS within microglia needs to be finely tuned for physiological signaling purposes and imbalanced redox homeostasis can mediate neuronal injury and chronic neuroinflammation Angelova PR, Abramov AY. Role of mitochondrial ROS in neurodegeneration(30,31).

### 2.1 Sources of ROS

Microglial ROS originate primarily from enzymatic and mitochondrial sources. Among these, NADPH oxidase 2 (NOX2) is a major contributor to ROS generation during immune activation. Upon stimulation, NOX2 catalyzes the transfer of electrons from NADPH to molecular oxygen, leading to the formation of superoxide radicals that initiate downstream redox signaling cascades(31,32). NOX2-derived ROS are particularly important in mediating responses to inflammatory stimuli such as lipopolysaccharide and aggregated proteins. In parallel, mitochondria represent a significant intracellular source of ROS. During oxidative phosphorylation,

electron leakage from complexes I and III of the electron transport chain leads to the formation of mitochondrial ROS (mtROS). Under physiological conditions, mtROS production is tightly regulated; however, mitochondrial dysfunction results in excessive ROS accumulation, which amplifies inflammatory signaling and disrupts cellular homeostasis(32,33).

**2.2 ROS as Signaling Molecules**

Besides their harmful effects, ROS also play important roles as the second messengers in intracellular signaling pathways. In microglia, ROS regulate the activation of the kinases and transcription factors which control inflammation-associated gene expression. NF-B signaling cascade is one of the most critical pathways regulated by ROS. By oxidizing up-stream signaling elements, ROS can activate NF-B and promote the transcription of pro-inflammatory cytokines such as TNF- and IL-1(33,34).ROS additionally govern the signaling pathways of mitogen-activated protein kinases (MAPKs,ERK,JNK andp38)which then leads to further inflammation as it stimulates the cytokine and stress response in cells(34,35).Critically, ROS-driven signaling is not intrinsically problematic, and at regulated levels allows for the successful response of microglia to external stimuli. High rates of ROS production however cause a flood of cytokine release, and activation of downstream neuroinflammatory events(35).

**2.3 Oxidative Stress versus Redox Balance**

Whether redox signaling is physiological or pathological depends on the balance between ROS production and antioxidant defense. Microglia also has intrinsic antioxidant defense system, which is used to neutralize oxidative stress. Among these defenses, transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) has a critical role. Nrf2 activation results in transcription of genes encoding antioxidant enzymes such as HO-1 (heme oxygenase-1), glutathione-related protein, etc, in this way restoring redox balance(36).Pathologically, excessive amounts of ROS lead to the failure of antioxidant defenses and ultimately result in oxidative stress. Mitochondrial dysfunction, inflammasome activation, and prolonged inflammatory signaling can result from this redox imbalance, which can cause neurotoxicity and neuronal loss(37,38).

**3. Mitochondrial Dysfunction and Neuroinflammation**

In fact, mitochondria are at the heart of the control of microglial functions, serving as an interface between cellular metabolism and innate immune signals. Beyond ATP production, mitochondria represent signaling hubs which affect inflammatory pathways, and it is their dysfunction rather than being a secondary factor which becomes a major culprit of neuroinflammation during neurodegenerative disease(39).

**3.1 Mitochondrial Dynamics: Fission–Fusion Imbalance**

Structure and function of mitochondria are preserved by antagonistic fission and fusion processes to equally distribute mitochondrial constituents and to isolate compromised parts. Fusion (involves mitofusins and OPA1) maintains mitochondrial integrity while fission (regulated by dynamin-related protein 1 (Drp1)) allows segregation of damaged mitochondria(40).Fission process that occurs excessively in activated microglia results in mitochondrial fragmentation that contributes to heightened oxidative stress and impaired energy metabolism(41).Such an imbalance may result in a pro-inflammatory phenotype and was associated with pathology, like in AD, where mitochondrial dynamics impairment enhanced neuron dysfunction(42).

**3.2 mtROS and Inflammation: Link to Inflammasome Activation**

Mitochondrial reactive oxygen species (mtROS) also play important roles in microglial inflammatory signaling pathways. High mtROS is known to activate the NLRP3 inflammasome under stress(43). These complex activation induces caspase-1 maturation of IL-1, enhancing inflammation cascades. Besides, the loss of mitochondrial damages release oxdative mitochondrial DNA into the cytosol, leading to further inflammasome activation(44).

**3.3 Bioenergetic Failure: ATP Depletion and Metabolic Shift**

A breakdown in mitochondrial activity causes dysfunction in oxidative phosphorylation, thereby decreasing ATP production and causing a state of bioenergetic stress. The cell attempts to compensate by increasing the glycolytic pathway, which generates ATP more rapidly but inefficiently(45).This is not merely adoptive but rather it is operational, it is pro-inflammatory signaling, pro-cytokine signaling and in degenerative conditions, like Parkinson's disease, the continuous bioenergetic failures of the neuron will ultimately lead to cell death and degeneration(46).

### 3.4 Mitophagy Defects and Accumulation of Damaged Mitochondria

Mitophagy is a key quality control pathway, the removal of damaged mitochondria to maintain homeostasis of the cell. The principal pathway regulating mitophagic turnover is that of the PINK1-Parkin pathway, responsible for targeting malfunctioning mitochondria for autophagic breakdown(47).Faulty mitophagy results in accumulation of flawed mitochondria and generation of a large amount of ROS, triggering chronic inflammation. In Parkinsons disease, Parkin and PINK1 gene mutations contribute to mitochondrial malfunction and consequently to defective mitophagy(48).

### Integrated Disease Relevance

Together, defects in mitochondrial dynamics, uncontrolled mtROS production, bioenergetic collapse and compromised mitophagy initiate a vicious cycle of mitochondrial dysfunction and inflammation that has been identified as a key mechanism of neurodegeneration, involving mitochondrial-induced microglial activation that leads to further neuronal loss(49).Hence, intervention of mitochondrial pathways seems a good therapeutic approach in neuroinflammation and disease progression.(50).

## 4. Crosstalk: Immunometabolism–Redox–Mitochondria Axis

The activation of microglial cells is controlled by an intricately linked network of cellular metabolism, redox signaling and mitochondrial biology. These components do not function separately; they actually exist as part of a closely integrated signaling pathway where metabolic conditions influence redox balance, which, in turn, changes the mitochondrial state and mitochondrial biology exerts an influence over the metabolism and inflammatory state(51).

### 4.1 Metabolic Control of ROS Generation

Metabolism at the cellular level directly controls the amount and source of microglial ROS generation. While pro-inflammatory activation of microglial involves a shift toward increased reliance on glycolysis and away from mitochondrial oxidative phosphorylation, it actually increases ROS production, largely through the activation of NADPH oxidase and increased redox cycling(52). In contrast, oxidative metabolism maintains controlled ROS production through efficient electron transport chain function, thereby preserving redox homeostasis (53).Notably, succinate, a metabolic intermediate, has signaling functions which lead to the stabilization of hypoxia-inducible factor-1, thereby increasing ROS-dependent inflammatory responses(54).

### 4.2 Redox Regulation of Mitochondrial Function

Upon generation, ROS have direct impacts on mitochondrial structure and function. The increase in ROS concentration causes oxidation of mitochondrial proteins, lipids and DNA, resulting in impairment of electron transport chain and loss of membrane potential(55).Such modifications compromise the process of ATP synthesis and encourage greater electron leakage thus enhancing mtROS production. ROS in addition affect dynamics and stimulate fission by activation of dynamin-related proteins leading to fragmented mitochondria(56).

### 4.3 Mitochondria as Amplifiers of Inflammatory Signaling

The dysfunction of mitochondria serve as an important mediator ofmicroglial inflammation. Damaged mitochondria release mtDNA and other DAMPs to cytosol, triggering innate immune receptors and inflammasome signaling(57).The resulting over-production of mtROS further stimulates redox sensitive transcription factors such as the nuclear factor-B which leads to the overexpression of cytokines (58).

### 4.4 Feedback Loops Linking Metabolism, ROS, and Mitochondria

Positive feedback loops is characteristic of the immunometabolism-redox-mitochondria axis. The ROS produced during metabolic reprogramming contributes to impaired mitochondrial function which feeds back to further increase mtROS production(59).Concurrently, impaired mitochondrial function initiates a shift to glycolytic metabolism which is also dependent on ROS generation and inflammation(60). This two-way communication triggers a constitutive pro-inflammatory state in the microglia. Simultaneously, impaired mitochondria increase the activation of inflammasomes and cytokine release, which, in turn affect metabolic pathways and redox balance.(61).However, either by restoring metabolic homeostasis or by improving antioxidant defenses, this pathway is broken and shows how the therapeutic targeting of the feedback mechanism can affect this cascade. Integration of the feedback mechanism highlights that neuroinflammation is not necessarily about individual molecule processes but about network of interconnected mechanisms working with one another(62).

### 4.5 Implications for Neurodegenerative Disease

Dysregulation of this axis is also a hallmark of neurodegenerative diseases. It has been found that in both Alzheimer's and Parkinson's disease metabolic changes, overproduction of ROS, and mitochondrial dysfunction create positive feed back loops that exacerbate the chronic activation of microglia and neuronal damage. It is these ongoing loops that promote continued neurodegeneration; therefore the treatment approach needs to target the many aspects of this axis concurrently, rather than individually(63).

## 5. Implications in Neurodegenerative Diseases

An imbalance in the immunometabolism-redox-mitochondria axis has significant implication in neurodegenerative diseases as dysfunction of microglial is at its center of pathogenicity. It is no longer a passive reactive cell that takes place part in the disease but an active player which undergoes specific metabolic and redox changes, which leads to neuronal death. Microglial undergoes metabolic changes followed by oxidation state and the damage to mitochondria which are functionally connected through various feedback loops which are continuously driving neuroinflammation(64).

### 5.1 Alzheimer’s Disease

Alzheimer's Disease A aggregation triggers extensive metabolic reprogramming in microglia, driving their metabolism towards glycolysis and compromising mitochondrial oxidative phosphorylatio(65).The change in metabolism, rather than compensatory, has disruptive functional consequences-lower levels of ATP needed to achieve robust phagocytosis result in decreased clearance of A. Furthermore, the A signal stimulates more profound mitochondrial dysfunction and increased mitochondrial ROS (mtROS), promoting higher levels of inflammation(66).At the mechanistic level, mtROS initiate redox sensitive transcription pathways which trigger prolonged cytokine secretion, fueling the pro-inflammatory microenvironment. Moreover, dysfunction of mitochondrial dynamics and mitophagy contribute to the accumulation of dysfunctional mitochondria which further exacerbates oxidative stress and metabolic imbalance(67).

### 5.2 Parkinson’s Disease

Parkinson disease involves prominent mitochondrial dysfunction, specifically with abnormalities of the electron transport chain and mitochondrial quality control processes (68).This mitochondrial dysfunction causes overproduction of ROS in microglia, driving inflammation and neurotoxicity. Unlike ROS signaling, prolonged oxidative stress perturbs the cellular homeostatic equilibrium, increasing pro-inflammatory cytokine expression(69).Impaired mitophagy is another important mechanistic characteristic of Parkinson's disease and is typically related to dysfunction of key proteins controlling mitochondrial quality. Damaged mitochondria accumulate, which further increases ROS generation and also releases mitochondrial derived signals inducing innate immunity(70).This establishes a feedback loop, with mitochondrial dysfunction feeding and exacerbating inflammation, and vice versa. Metabolic reprogramming to glycolysis is also supportive of this inflammatory milieu, as it provides energy rapidly for sustained immune response(71).

### 5.3 Other CNS Disorders

#### Stroke

With the ischemia, the rapid depletion of energy causes quick mitochondria failure and overproduction of ROS, resulting in the activation of microglia(72).

#### Multiple Sclerosis

Multiple sclerosis-chronic neuroinflammation is associated with both persistent mitochondrial dysfunction and metabolic abnormalities in microglial cells(73).

#### Integrated Mechanistic Perspective

With the diverse neurodegenerative diseases, the unifying mechanism appears to be that metabolic reprograming, oxidative stress and mitochondrial failure occur in an interacting manner, rather than being separate phenomena, that leads to microglial pathogenesis. Increased ROS compromises mitochondrial integrity, and mitochondrial dysfunction exacerbates metabolic change which sustains inflammatory signaling(74).The activation of this network results in chronic inflammation, speeding up neuronal death. Hence any approach to the target of this axis must involve restoring metabolic balance, reducing oxidative stress and restoring

mitochondrial function in parallel, because only multi-dimensional treatments will be enough to stop the progression of the disease(75).

**6. Nano-Enabled Therapeutic Targeting**

Nanotechnology can be used as a tool to control microglial activity through the careful design of the intricate metabolic, redox and mitochondrial signaling network. Unlike conventional therapy, nanocarriers are a way of facilitating the regulated release of drugs, BBB crossing and targeted delivery to sites of activation of microglia. This is particularly pertinent in neuroinflammation where temporal and spatial control of therapeutic activity is key(76).

**6.1 Redox-Sensitive Nanocarriers**

In order to utilize high intra-cellular ROS concentration in activation microglia, redox responsive nanocarriers are designed with the linkage of oxidation responsive functional groups. These systems will exhibit structure transformation at high ROS concentration, so as to deliver drugs at inflammation sites (77). This can reduce the systemic toxicity and improve the therapeutic efficacy. In terms of mechanism, the ROS stimulated drug release makes sure that the antioxidants or anti-inflammatory agents are delivered to the site of high oxidative stress. It weakens the redox sensitive signal pathways which mediate the production of cytokines by decreasing the amount of intracellular ROS, thereby blocking the vicious cycle of oxidation- inflammation(78).

**6.2 Mitochondria-Targeted Nanoparticles**

Directly addressing the origin of oxidative stress and bioenergetic dysfunction is another logical approach that aims at mitochondria. The use of mitochondria-targeted nanoparticles often involves surface modification of the nanoparticles with lipophilic cations or peptide ligands which would enable them to target to mitochondria.(79).Upon targeting, they release therapeutic drugs that can quench the mtROS, re-establish the mitochondrial membrane potential and recover the ETC activity. The focused delivery of these drugs in the mitochondrial level can minimize the mitochondrial injury and the production of pro-inflammatory mediators. More significantly, the re-establishment of mitochondrial function helps recover the cellular energy status which results in suppression of pro-inflammatory microglial activation.(80).

**6.3 Metabolic Reprogramming via Nanomedicine**

Recent developments further demonstrated how nanomedicine can also alter microglial metabolism directly. Via targeting nanocarriers to the microglial cells that delivery the metabolic modulators,nanomedicine can induce a shift from glycolytic pathway to oxido-phos-pho-rylation (OXPHOS) to drive an anti-inflammatory phenotype of microglial cells(81).Such metabolic reprogramming decreases lactic acid accumulation and availability of metabolic intermediates that contribute to inflammation signal transduction. Meanwhile, recover mitochondrial respiration improves the production of ATP and facilitates the cellular repair process. The above measures show that targeting metabolism is not just a supplementary approach, but capable to remodel microglial cell states(82).

**6.4 Phytochemical-Based Nanoplatforms**

Phytochemical loaded nanocarriers combine two areas-the natural bioactive compounds and the novel drug delivery-that holds significant future potential. Although several naturally occurring molecules possess an inherent antioxidant and anti-inflammatory property, they often fail to exhibit therapeutic efficacy due to their low bioavailability and stability. Nano formulation helps overcome these drawbacks by improving solubility, protect bioactive molecules from degredation and target their delivery(83).Mechanism of phytochemical based nanoplatforms. The phytochemical based nanoplatforms work via various mechanism such as scavenging ROS, enhancing endogenous antioxidant response and altering inflammatory signaling pathways. Some phytochemicals work on mitochondria and other metabolic pathway, so are more likely involved in modulating immunometabolism-redox axis.(84,85).

**Integrated Therapeutic Perspective**

An important feature of nano-based strategies is their potential to address various nodes in the pathological network at the same time. Through regulation of the ROS levels, restoration of mitochondrial activity and reprogram of cell metabolism, the sustained positive feedback loop driving chronic neuroinflammation can be broken down by nanotherapeutics. Also, via surface modification, selectively targeted active microglia can be achieved thereby minimizing unwanted off-target effects(86). In addition to the above, significant issues of long-term safety, scalability and effective translation to the clinic must be solved if nanomedicine's therapeutic potential in neurodegenerative disease is to be fully exploited (87).

**Table 2. Nanoplatforms Targeting Microglial Immunometabolism**

| Nanoplatform type | Target mechanism | Mode of action | Therapeutic outcome |
|---|---|---|---|
| Redox-responsive nanoparticles | Elevated ROS | ROS-triggered drug release | Reduction of oxidative stress and inflammation |
| Mitochondria-targeted nanoparticles | mtROS, mitochondrial dysfunction | Delivery to mitochondria; restoration of function | Improved bioenergetics; decreased inflammation |
| Metabolic modulatory nanoparticles | Glycolysis/OXPHOS imbalance | Shift toward oxidative metabolism | Anti-inflammatory microglial phenotype |
| Lipid-based nanocarriers | BBB transport | Enhanced CNS delivery | Increased drug bioavailability |
| Phytochemical-loaded nanoparticles | ROS and inflammatory pathways | Antioxidant and signaling modulation | Neuroprotection and reduced cytokine release |
| Ligand-functionalized nanoparticles | Microglial receptors | Targeted cellular uptake | Increased specificity; reduced off-target effects |

## 7. Challenges and Limitations

### 7.1 Translational Gap: From Experimental Models to Clinical Reality

A key limitation in this area is the lack of translation of results from the preclinical to clinical stage. Species-specific discrepancies between rodents and human microglia mean that experimental results do not always carry over effectively. The transcriptomic and metabolic profiles of human microglia differ greatly and will consequently respond to inflammation and potential therapies in a different way(88).

### 7.2 Toxicity and Safety Concerns of Nanoparticles

While nanocarriers demonstrate the benefits of targeted delivery, the toxicity of these nanodelivery vehicles is a significant cause for concern. Nanoparticles may cause unintended cytotoxic damage, such as inducing oxidative stress, damage to membranes and disturbance of cell equilibrium(89).Certain nanomaterials have been particularly noted for their accumulation within neural tissue when exposed to these materials for extended periods, which raises concerns of potential neurotoxicity(90).Furthermore, nanoparticles may interfere with mitochondria, leading to opposite effects than those targeted.(91).Moreover, changing nanoparticle composition, size, and surface chemistry can result in unintended biological interactions, making safety evaluations and regulatory approvals more challenging.(92).

### 7.3 Targeting Specificity and Blood–Brain Barrier Limitations

The blood-brain barrier (BBB) creates a major obstacle to the effective delivery of therapeutics to microglia within the Central Nervous System (CNS). The ability of nanocarriers to deliver drugs into the CNS is limited(93). But even if the nanoparticles reach the brain, precise microglia targeting can be hard to reach without altering other cells(94).This could lower therapeutic effectiveness and raise off-target effects by way of peripheral uptake by immune cells and other resident CNS cells. In addition, diseases, like neuroinflammation, can affect BBB permeability in an unpredictable fashion and thus create delivery complications(95).

### 7.4 Lack of Standardized Experimental Models

The lack of reproducible, physiologically relevant models constitutes yet another crucial obstacle in this research area. The currently available in vitro systems primarily employ immortalized microglial cell lines, which are far removed from true human primary microglia.(96).

### Critical Perspective

Collectively, these obstacles suggest that existing treatments might be underestimating the multifaceted regulation of microglia and the feasibility of therapeutic intervention. Individual approaches to targeting specific pathways may overlook the intimate interplay between metabolism, redox signaling and mitochondrial function; consideration of these is vital for the future. Furthermore, limited understanding of long-term safety and biologic variability restricts translation of innovative treatments(97).

## 8. Future Perspectives

### 8.1 Precision Targeting of Microglial Subtypes

Microglia are remarkably heterogeneous throughout the brain and various disease states and that unique microglial subpopulations have unique functional and metabolic features. Recent transcriptomic analyses have revealed disease-associated microglial states that are distinct from homeostatic microglial populations and suggesting that singular targeting approaches may not be appropriate(98).Yet, it is difficult to attain such specificity due to the co-expression of markers and phenotypic switches over time. Temporal and spatial resolution must therefore be addressed in future studies to be able to modulate microglial response without impacting homeostatic function.(99).

### 8.2 AI-Guided Nanomedicine (Emerging Direction)

Machine learning also is being developed to improve the design of nanomedicines and predict therapeutic results. Nanoparticle composition, targeting ligands, and physical attributes (e.g., size, surface chemistry) can be refined using machine learning by training an algorithm on data of successful treatments.(100).

### 8.3 Strategies for Clinical Translation

If researchers are to close the gap between experiment and clinic and more rationally develop therapeutics, they need to take a more methodical approach to therapeutics development. Standardizing the preclinical models and endpoints is an essential step to make results reproducible(101).Besides, it is also necessary to have reproducible and scalable approaches of NP synthesis for predictable therapeutic effectiveness.Lastly, effective methods for crossing BBB with specificity have to be established. It seems that ligand modification and carrier designing could improve the distribution in CNS, while chronic safety profile and pharmacokinetic of CNS-targeting NP have to be determined(102).

## Conclusion

All of the above combined can define microglial immunometabolism as an understandable, applicable mechanism that provides a framework to discuss neuroinflammation in which metabolism itself would be considered to be the control center for the action of microglia. The close coordination of metabolic switching, redox state and mitochondrial function seems to have a defining role in determining the nature of beneficial or harmful microglial action in the brain. Should the redox-metabolic axis be perturbed then a positive feedback loop of ROS and mitochondrial dysfunction results in a chronically inflammatory response and neuronal death. The concept itself brings to light the inherent weaknesses in the one-target approach and favors a multi-factorial approach, a role in which nanotechnology, able to target more than one aspect of microglia more precisely simultaneously, fits nicely into the puzzle. However translating the experiments in vitro to the clinic will require enhanced accuracy in targeting, risk-benefit analysis and human based models to test hypotheses, and further research endeavors could be aimed at integrating more levels of the biological signaling cascade into one experiment using technology. This advancement could allow for interventions not only targeting inflammation but microglial behavior and neuronal well being resulting in amelioration of neurodegenerative disease states.

## REFERENCES

1. Rahimpour S, Clary BL, Nasoohi S, Berhanu YS, Brown CM. Immunometabolism In Brain Aging and Neurodegeneration: Bridging Metabolic Pathways and Immune Responses. Aging Dis. 2024 Dec 18;16(6):3361–80. doi:10.14336/AD.2024.1293 PubMed PMID: 39751865; PubMed Central PMCID: PMC12539545.
2. Microglia Function in the Central Nervous System During Health and Neurodegeneration | Annual Reviews [Internet]. [cited 2026 May 3]. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-immunol-051116-052358
3. Microglia and macrophages in brain homeostasis and disease | Nature Reviews Immunology [Internet]. [cited 2026 May 3]. Available from: https://www.nature.com/articles/nri.2017.125
4. Sadeghdoust M, Das A, Kaushik DK. Fueling neurodegeneration: metabolic insights into microglia functions. J Neuroinflammation. 2024 Nov 17;21(1):300. doi:10.1186/s12974-024-03296-0
5. Lepiarz-Raba I, Gbadamosi I, Florea R, Paolicelli RC, Jawaid A. Metabolic regulation of microglial phagocytosis: Implications for Alzheimer's disease therapeutics. Transl Neurodegener. 2023 Oct 31;12(1):48. doi:10.1186/s40035-023-00382-w
6. Neuroinflammation in Alzheimer's disease - The Lancet Neurology [Internet]. [cited 2026 May 3]. Available from: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(15)70016-5/abstract
7. Cai L, Xia M, Zhang F. Redox Regulation of Immunometabolism in Microglia Underpinning Diabetic Retinopathy. Antioxidants. 2024 Apr;13(4):423. doi:10.3390/antiox13040423

8. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007 Jan;8(1):57–69. doi:10.1038/nrn2038
9. Guo S, Wang H, Yin Y. Microglia Polarization From M1 to M2 in Neurodegenerative Diseases. Front Aging Neurosci. 2022 Feb 16;14. doi:10.3389/fnagi.2022.815347
10. A polarizing question: do M1 and M2 microglia exist? | Nature Neuroscience [Internet]. [cited 2026 May 3]. Available from: https://www.nature.com/articles/nn.4338
11. Tan YL, Yuan Y, Tian L. Microglial regional heterogeneity and its role in the brain. Mol Psychiatry. 2020 Feb;25(2):351–67. doi:10.1038/s41380-019-0609-8
12. Zhao P, Li SY, Liu Q, Peng XC, Liu L, Yang FY, et al. Reprogramming brain-resident macrophages: from disease drivers to therapeutic allies in neurological disorders. Front Cell Neurosci. 20:1726194. doi:10.3389/fncel.2026.1726194 PubMed PMID: 41737534; PubMed Central PMCID: PMC12926123.
13. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016 Sep;16(9):553–65. doi:10.1038/nri.2016.70
14. Mitochondria are the powerhouses of immunity | Nature Immunology [Internet]. [cited 2026 May 3]. Available from: https://www.nature.com/articles/ni.3704
15. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014 May 19;24(10):R453-462. doi:10.1016/j.cub.2014.03.034 PubMed PMID: 24845678; PubMed Central PMCID: PMC4055301.
16. Peruzzotti-Jametti L, Willis CM, Krzak G, Hamel R, Pirvan L, Ionescu RB, et al. Mitochondrial complex I activity in microglia sustains neuroinflammation. Nature. 2024 Apr;628(8006):195–203. doi:10.1038/s41586-024-07167-9
17. Arts RJW, Joosten LAB, Netea MG. Immunometabolic circuits in trained immunity. Seminars in Immunology. 2016 Oct 1;Immunometabolism28(5):425–30. doi:10.1016/j.smim.2016.09.002
18. Wang H, Yu SY, Nielsen S, Wang X, Zhao WW. Mitochondrial complex I: the key to sustained microglia activation and neuroinflammation maintenance. Mil Med Res. 2024 Jul 19;11(1):47. doi:10.1186/s40779-024-00554-3 PubMed PMID: 39030602; PubMed Central PMCID: PMC11264769.
19. Rajput MS, Patel V, Nirmal NP, Kumar D. Editorial: Augmented neuro-therapy with nanotechnology-based formulations: progress, opportunities and challenges. Front Pharmacol. 2024 Feb 8;15. doi:10.3389/fphar.2024.1376878
20. Silva PR da, Barbosa NMMV, Leite JM da S, Alves LP, Andrade JC de, Formiga ALD, et al. Microglia-Targeted Nanotherapeutics in Major Depressive Disorder: An Integrative Perspective on Neuroinflammation and Drug Delivery. Pharmaceutics. 2025 Dec 25;18(1):27. doi:10.3390/pharmaceutics18010027 PubMed PMID: 41599133; PubMed Central PMCID: PMC12844702.
21. Van den Bossche J, O'Neill LA, Menon D. Macrophage Immunometabolism: Where Are We (Going)? Trends Immunol. 2017 Jun;38(6):395–406. doi:10.1016/j.it.2017.03.001 PubMed PMID: 28396078.
22. Gimeno-Bayón J, López-López A, Rodríguez MJ, Mahy N. Glucose pathways adaptation supports acquisition of activated microglia phenotype. J Neurosci Res. 2014 Jun;92(6):723–31. doi:10.1002/jnr.23356 PubMed PMID: 24510633.
23. Baik SH, Kang S, Lee W, Choi H, Chung S, Kim JI, et al. A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease. Cell Metab. 2019 Sep 3;30(3):493-507.e6. doi:10.1016/j.cmet.2019.06.005 PubMed PMID: 31257151.
24. Lauro C, Limatola C. Metabolic Reprograming of Microglia in the Regulation of the Innate Inflammatory Response. Front Immunol. 2020;11:493. doi:10.3389/fimmu.2020.00493 PubMed PMID: 32265936; PubMed Central PMCID: PMC7099404.
25. Role of βarrestin1 in AT1R-mediated mitogen-activated protein kinase activation in Wistar and SHR brainstem astrocytes - Negussie - 2019 - Journal of Neurochemistry - Wiley Online Library [Internet]. [cited 2026 May 3]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jnc.14620
26. Young K, Morrison H. Quantifying Microglia Morphology from Photomicrographs of Immunohistochemistry Prepared Tissue Using ImageJ. J Vis Exp. 2018 Jun 5;(136):57648. doi:10.3791/57648 PubMed PMID: 29939190; PubMed Central PMCID: PMC6103256.
27. Moraes CA, Zaverucha-do-Valle C, Fleurance R, Sharshar T, Bozza FA, d'Avila JC. Neuroinflammation in Sepsis: Molecular Pathways of Microglia Activation. Pharmaceuticals (Basel). 2021 May 1;14(5):416. doi:10.3390/ph14050416 PubMed PMID: 34062710; PubMed Central PMCID: PMC8147235.
28. Weichhart T, Hengstschläger M, Linke M. Regulation of innate immune cell function by mTOR. Nat Rev Immunol. 2015 Oct;15(10):599–614. doi:10.1038/nri3901 PubMed PMID: 26403194; PubMed Central PMCID: PMC6095456.
29. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012 Mar 22;13(4):251–62. doi:10.1038/nrm3311 PubMed PMID: 22436748; PubMed Central PMCID: PMC5726489.
30. Angelova PR, Abramov AY. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. FEBS Letters. 2018;592(5):692–702. doi:10.1002/1873-3468.12964
31. Sorce S, Krause KH. NOX enzymes in the central nervous system: from signaling to disease. Antioxid Redox Signal. 2009 Oct;11(10):2481–504. doi:10.1089/ars.2009.2578 PubMed PMID: 19309263.

32. Ma MW, Wang J, Zhang Q, Wang R, Dhandapani KM, Vadlamudi RK, et al. NADPH oxidase in brain injury and neurodegenerative disorders. Mol Neurodegener. 2017 Jan 17;12(1):7. doi:10.1186/s13024-017-0150-7 PubMed PMID: 28095923; PubMed Central PMCID: PMC5240251.
33. Morgan MJ, Liu Z gang. Crosstalk of reactive oxygen species and NF-κB signaling. Cell Res. 2011 Jan;21(1):103–15. doi:10.1038/cr.2010.178 PubMed PMID: 21187859; PubMed Central PMCID: PMC3193400.
34. Son Y, Cheong YK, Kim NH, Chung HT, Kang DG, Pae HO. Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? J Signal Transduct. 2011;2011:792639. doi:10.1155/2011/792639 PubMed PMID: 21637379; PubMed Central PMCID: PMC3100083.
35. Kamata H, Hirata H. Redox regulation of cellular signalling. Cell Signal. 1999 Jan;11(1):1–14. doi:10.1016/s0898-6568(98)00037-0 PubMed PMID: 10206339.
36. Villavicencio Tejo F, Quintanilla RA. Contribution of the Nrf2 Pathway on Oxidative Damage and Mitochondrial Failure in Parkinson and Alzheimer's Disease. Antioxidants (Basel). 2021 Jul 2;10(7):1069. doi:10.3390/antiox10071069 PubMed PMID: 34356302; PubMed Central PMCID: PMC8301100.
37. Kaur K, Narang RK, Singh S. Role of Nrf2 in Oxidative Stress, Neuroinflammation and Autophagy in Alzheimer's Disease: Regulation of Nrf2 by Different Signaling Pathways. Curr Mol Med. 2025;25(4):372–87. doi:10.2174/1566524023666230726145447 PubMed PMID: 37493162.
38. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010 Feb;11(2):136–40. doi:10.1038/ni.1831 PubMed PMID: 20023662.
39. Mills EL, Kelly B, O'Neill LAJ. Mitochondria are the powerhouses of immunity. Nat Immunol. 2017 Apr 18;18(5):488–98. doi:10.1038/ni.3704 PubMed PMID: 28418387.
40. Chan DC. Mitochondrial Dynamics and Its Involvement in Disease. Annu Rev Pathol. 2020 Jan 24;15:235–59. doi:10.1146/annurev-pathmechdis-012419-032711 PubMed PMID: 31585519.
41. Cho B, Choi SY, Cho HM, Kim HJ, Sun W. Physiological and pathological significance of dynamin-related protein 1 (drp1)-dependent mitochondrial fission in the nervous system. Exp Neurobiol. 2013 Sep;22(3):149–57. doi:10.5607/en.2013.22.3.149 PubMed PMID: 24167410; PubMed Central PMCID: PMC3807002.
42. Amyloid Beta Mediated Mitochondrial Dysfunction in Alzheimer's disease: A Mini Review - ProQuest [Internet]. [cited 2026 May 3]. Available from: https://www.proquest.com/openview/1ea927ecdc0314ccdc7961ced08faacf/1?cbl=1936342&pq-origsite=gscholar
43. Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? Nat Rev Immunol. 2010 Mar;10(3):210–5. doi:10.1038/nri2725 PubMed PMID: 20168318.
44. West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, et al. Mitochondrial DNA Stress Primes the Antiviral Innate Immune Response. Nature. 2015 Apr 23;520(7548):553–7. doi:10.1038/nature14156 PubMed PMID: 25642965; PubMed Central PMCID: PMC4409480.
45. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. Mol Cell. 2012 Oct 26;48(2):158–67. doi:10.1016/j.molcel.2012.09.025 PubMed PMID: 23102266; PubMed Central PMCID: PMC3484374.
46. Winklhofer KF, Haass C. Mitochondrial dysfunction in Parkinson's disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2010 Jan 1;Mitochondrial Dysfunction1802(1):29–44. doi:10.1016/j.bbadis.2009.08.013
47. Narendra DP, Youle RJ. Targeting Mitochondrial Dysfunction: Role for PINK1 and Parkin in Mitochondrial Quality Control. Antioxid Redox Signal. 2011 May 15;14(10):1929–38. doi:10.1089/ars.2010.3799 PubMed PMID: 21194381; PubMed Central PMCID: PMC3078490.
48. Pickrell AM, Youle RJ. The Roles of PINK1, Parkin and Mitochondrial Fidelity in Parkinson's Disease. Neuron. 2015 Jan 21;85(2):257–73. doi:10.1016/j.neuron.2014.12.007 PubMed PMID: 25611507; PubMed Central PMCID: PMC4764997.
49. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration - Angelova - 2018 - FEBS Letters - Wiley Online Library [Internet]. [cited 2026 May 3]. Available from: https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.12964
50. Devine MJ, Kittler JT. Mitochondria at the neuronal presynapse in health and disease. Nat Rev Neurosci. 2018 Jan 19;19(2):63–80. doi:10.1038/nrn.2017.170 PubMed PMID: 29348666.
51. O'Neill LAJ, Pearce EJ. Immunometabolism governs dendritic cell and macrophage function. J Exp Med. 2016 Jan 11;213(1):15–23. doi:10.1084/jem.20151570 PubMed PMID: 26694970; PubMed Central PMCID: PMC4710204.
52. Kelly B, O'Neill LAJ. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015 Jul;25(7):771–84. doi:10.1038/cr.2015.68 PubMed PMID: 26045163; PubMed Central PMCID: PMC4493277.
53. Chandel NS. Mitochondria as signaling organelles. BMC Biol. 2014 May 27;12:34. doi:10.1186/1741-7007-12-34 PubMed PMID: 24884669; PubMed Central PMCID: PMC4035690.
54. Tannahill G, Curtis A, Adamik J, Palsson-McDermott E, McGettrick A, Goel G, et al. Succinate is a danger signal that induces IL-1β via HIF-1α. Nature. 2013 Apr 11;496(7444):238–42. doi:10.1038/nature11986 PubMed PMID: 23535595; PubMed Central PMCID: PMC4031686.
55. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009 Jan 1;417(Pt 1):1–13. doi:10.1042/BJ20081386 PubMed PMID: 19061483; PubMed Central PMCID: PMC2605959.

56. Cid-Castro C, Hernández-Espinosa DR, Morán J. ROS as Regulators of Mitochondrial Dynamics in Neurons. Cell Mol Neurobiol. 2018 Apr 23;38(5):995–1007. doi:10.1007/s10571-018-0584-7 PubMed PMID: 29687234; PubMed Central PMCID: PMC11481975.
57. Deretic V, Levine B. Autophagy balances inflammation in innate immunity. Autophagy. 2018 Jan 17;14(2):243–51. doi:10.1080/15548627.2017.1402992 PubMed PMID: 29165043; PubMed Central PMCID: PMC5902214.
58. Morgan MJ, Liu Z gang. Crosstalk of reactive oxygen species and NF-κB signaling. Cell Res. 2011 Jan;21(1):103–15. doi:10.1038/cr.2010.178 PubMed PMID: 21187859; PubMed Central PMCID: PMC3193400.
59. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release. Physiol Rev. 2014 Jul;94(3):909–50. doi:10.1152/physrev.00026.2013 PubMed PMID: 24987008; PubMed Central PMCID: PMC4101632.
60. Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. Immunity. 2015 Mar 17;42(3):406–17. doi:10.1016/j.immuni.2015.02.002 PubMed PMID: 25786173; PubMed Central PMCID: PMC4365295.
61. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized Mitochondrial DNA Activates the NLRP3 Inflammasome During Apoptosis. Immunity. 2012 Mar 23;36(3):401–14. doi:10.1016/j.immuni.2012.01.009 PubMed PMID: 22342844; PubMed Central PMCID: PMC3312986.
62. Metabolic Regulation in the Induction of Trained Immunity - PMC [Internet]. [cited 2026 May 3]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11282170/
63. Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nat Immunol. 2015 Mar;16(3):229–36. doi:10.1038/ni.3102 PubMed PMID: 25689443.
64. A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease: Cell Metabolism [Internet]. [cited 2026 May 3]. Available from: https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30308-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1550413119303080%3Fshowall%3Dtrue
65. Cadonic C, Sabbir MG, Albensi BC. Mechanisms of Mitochondrial Dysfunction in Alzheimer's Disease. Mol Neurobiol. 2016 Nov;53(9):6078–90. doi:10.1007/s12035-015-9515-5 PubMed PMID: 26537901.
66. Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat Neurosci. 2019 Mar;22(3):401–12. doi:10.1038/s41593-018-0332-9 PubMed PMID: 30742114; PubMed Central PMCID: PMC6693625.
67. Schapira AHV. Mitochondrial dysfunction in Parkinson's disease. Cell Death Differ. 2007 Jul;14(7):1261–6. doi:10.1038/sj.cdd.4402160 PubMed PMID: 17464321.
68. Dorszewska J, Kowalska M, Prendecki M, Piekut T, Kozłowska J, Kozubski W. Oxidative stress factors in Parkinson's disease. Neural Regen Res. 2020 Dec 12;16(7):1383–91. doi:10.4103/1673-5374.300980 PubMed PMID: 33318422; PubMed Central PMCID: PMC8284265.
69. Pickrell AM, Youle RJ. The Roles of PINK1, Parkin, and Mitochondrial Fidelity in Parkinson's Disease. Neuron. 2015 Jan 21;85(2):257–73. doi:10.1016/j.neuron.2014.12.007 PubMed PMID: 25611507.
70. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006 Oct 19;443(7113):787–95. doi:10.1038/nature05292 PubMed PMID: 17051205.
71. Zhao SC, Ma LS, Chu ZH, Xu H, Wu WQ, Liu F. Regulation of microglial activation in stroke. Acta Pharmacol Sin. 2017 Apr;38(4):445–58. doi:10.1038/aps.2016.162 PubMed PMID: 28260801; PubMed Central PMCID: PMC5386316.
72. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015 Feb;14(2):183–93. doi:10.1016/S1474-4422(14)70256-X PubMed PMID: 25772897.
73. Angelova PR, Abramov AY. Interplay of mitochondrial calcium signalling and reactive oxygen species production in the brain. Biochem Soc Trans. 2024 Aug 28;52(4):1939–46. doi:10.1042/BST20240261 PubMed PMID: 39171662; PubMed Central PMCID: PMC11668289.
74. Peggion C, Calì T, Brini M. Mitochondria Dysfunction and Neuroinflammation in Neurodegeneration: Who Comes First? Antioxidants (Basel). 2024 Feb 16;13(2):240. doi:10.3390/antiox13020240 PubMed PMID: 38397838; PubMed Central PMCID: PMC10885966.
75. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release. 2016 Aug 10;235:34–47. doi:10.1016/j.jconrel.2016.05.044 PubMed PMID: 27208862.
76. Eleftheriadou D, Kesidou D, Moura F, Felli E, Song W. Redox-Responsive Nanobiomaterials-Based Therapeutics for Neurodegenerative Diseases. Small. 2020 Oct;16(43):e1907308. doi:10.1002/smll.201907308 PubMed PMID: 32940007.
77. Liu J, Li Y, Chen S, Lin Y, Lai H, Chen B, et al. Biomedical Application of Reactive Oxygen Species-Responsive Nanocarriers in Cancer, Inflammation, and Neurodegenerative Diseases. Front Chem. 2020;8:838. doi:10.3389/fchem.2020.00838 PubMed PMID: 33062637; PubMed Central PMCID: PMC7530259.
78. Buchke S, Sharma M, Bora A, Relekar M, Bhanu P, Kumar J. Mitochondria-Targeted, Nanoparticle-Based Drug-Delivery Systems: Therapeutics for Mitochondrial Disorders. Life (Basel). 2022 Apr 29;12(5):657. doi:10.3390/life12050657 PubMed PMID: 35629325; PubMed Central PMCID: PMC9144057.
79. Murphy MP, Hartley RC. Mitochondria as a therapeutic target for common pathologies. Nat Rev Drug Discov. 2018 Dec;17(12):865–86. doi:10.1038/nrd.2018.174 PubMed PMID: 30393373.

80. Baby N, Patnala R, Ling EA, Dheen ST. Nanomedicine and its application in treatment of microglia-mediated neuroinflammation. Curr Med Chem. 2014;21(37):4215–26. doi:10.2174/0929867321666140716101258 PubMed PMID: 25039775.
81. Mulder WJM, Ochando J, Joosten LAB, Fayad ZA, Netea MG. Therapeutic targeting of trained immunity. Nat Rev Drug Discov. 2019 Jul;18(7):553–66. doi:10.1038/s41573-019-0025-4 PubMed PMID: 30967658; PubMed Central PMCID: PMC7069501.
82. Full article: Nanoparticles in Combating Neuronal Dysregulated Signaling Pathways: Recent Approaches to the Nanoformulations of Phytochemicals and Synthetic Drugs Against Neurodegenerative Diseases [Internet]. [cited 2026 May 3]. Available from: https://www.tandfonline.com/doi/full/10.2147/IJN.S347187
83. Naoi M, Wu Y, Shamoto-Nagai M, Maruyama W. Mitochondria in Neuroprotection by Phytochemicals: Bioactive Polyphenols Modulate Mitochondrial Apoptosis System, Function and Structure. International Journal of Molecular Sciences. 2019 Jan;20(10):2451. doi:10.3390/ijms20102451
84. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol. 2015 Sep;33(9):941–51. doi:10.1038/nbt.3330
85. Cerqueira SR, Ayad NG, Lee JK. Neuroinflammation Treatment via Targeted Delivery of Nanoparticles. Front Cell Neurosci. 2020 Sep 30;14. doi:10.3389/fncel.2020.576037
86. Persano F, Batasheva S, Fakhrullina G, Gigli G, Leporatti S, Fakhrullin R. Recent advances in the design of inorganic and nano-clay particles for the treatment of brain disorders. J Mater Chem B. 2021 Apr 1;9(12):2756–84. doi:10.1039/D0TB02957B
87. Gosselin D, Skola D, Coufal NG, Holtman IR, Schlachetzki JCM, Sajti E, et al. An environment-dependent transcriptional network specifies human microglia identity. Science. 2017 Jun 23;356(6344):eaal3222. doi:10.1126/science.aal3222 PubMed PMID: 28546318; PubMed Central PMCID: PMC5858585.
88. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. Science. 2006 Feb 3;311(5761):622–7. doi:10.1126/science.1114397 PubMed PMID: 16456071.
89. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles. Environ Health Perspect. 2005 Jul;113(7):823–39. doi:10.1289/ehp.7339 PubMed PMID: 16002369; PubMed Central PMCID: PMC1257642.
90. Kovacic P, Somanathan R. Nanoparticles: toxicity, radicals, electron transfer, and antioxidants. Methods Mol Biol. 2013;1028:15–35. doi:10.1007/978-1-62703-475-3_2 PubMed PMID: 23740111.
91. Fadeel B, Farcal L, Hardy B, Vázquez-Campos S, Hristozov D, Marcomini A, et al. Advanced tools for the safety assessment of nanomaterials. Nat Nanotechnol. 2018 Jul;13(7):537–43. doi:10.1038/s41565-018-0185-0 PubMed PMID: 29980781.
92. Drug Transport across the Blood–Brain Barrier [Internet]. [cited 2026 May 3]. Available from: https://journals.sagepub.com/doi/epub/10.1038/jcbfm.2012.126 doi:10.1038/jcbfm.2012.126
93. Tosi G, Duskey JT, Kreuter J. Nanoparticles as carriers for drug delivery of macromolecules across the blood-brain barrier. Expert Opinion on Drug Delivery. 2020 Jan 2;17(1):23–32. doi:10.1080/17425247.2020.1698544 PubMed PMID: 31774000.
94. Sweeney MD, Sagare AP, Zlokovic BV. Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018 Mar;14(3):133–50. doi:10.1038/nrneurol.2017.188
95. Abud EM, Ramirez RN, Martinez ES, Healy LM, Nguyen CHH, Newman SA, et al. iPSC-Derived Human Microglia-like Cells to Study Neurological Diseases. Neuron. 2017 Apr 19;94(2):278-293.e9. doi:10.1016/j.neuron.2017.03.042 PubMed PMID: 28426964.
96. Sharifi S, Mahmoud NN, Voke E, Landry MP, Mahmoudi M. Importance of Standardizing Analytical Characterization Methodology for Improved Reliability of the Nanomedicine Literature. Nano-Micro Lett. 2022 Aug 20;14(1):172. doi:10.1007/s40820-022-00922-5
97. Role of Nanotechnology in Medicine: Opportunities and Challenges | Springer Nature Link [Internet]. [cited 2026 May 3]. Available from: https://link.springer.com/chapter/10.1007/978-3-031-45956-6_14
98. Stratoulias V, Venero JL, Tremblay M, Joseph B. Microglial subtypes: diversity within the microglial community. EMBO J. 2019 Sep 2;38(17):e101997. doi:10.15252/embj.2019101997 PubMed PMID: 31373067; PubMed Central PMCID: PMC6717890.
99. B PP Ana, Alejandro PS, Washington BB. Advancing Artificial Intelligence through Biological Process Applications. IGI Global; 2008. 459 p.
100. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019 Jun;18(6):463–77. doi:10.1038/s41573-019-0024-5
101. Blood-Brain Delivery Methods Using Nanotechnology [Internet]. [cited 2026 May 3]. Available from: https://www.mdpi.com/1999-4923/10/4/269
102. Muffat J, Li Y, Yuan B, Mitalipova M, Omer A, Corcoran S, et al. Efficient derivation of microglia-like cells from human pluripotent stem cells. Nat Med. 2016 Nov;22(11):1358–67. doi:10.1038/nm.4189

**International Journal of Pharmacy and Pharmaceutical Research (IJPPR)**
Volume 32, Issue 6, June 2026 **ijppr.humanjournals.com** ISSN: 2349-7203

How to cite this article:
T Praveena et al. Ijppr.Human, 2026; Vol. 32 (6): 582-594

Conflict of Interest Statement: All authors have nothing else to disclose.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.