



Review paper

Targeting Microglial Immunometabolism in Neuroinflammation: Molecular Mechanisms and Emerging Nanotherapeutic Strategies

Praveena T.^{a*}, Gopi Krishnan S.^a, Bhavithra M.^a, Ramganesha J.^a, Boopathi Raja Kumar J.^a, Shenbagavel A.^a

^a Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Krishnan Koil, Virudhunagar, Tamil Nadu, India

ARTICLE INFO	ABSTRACT
Keywords microglia immunometabolism reactive oxygen species neuroinflammation redox signaling neurodegeneration	Brain resident immune cells (microglia) have critical functions in neuro-homeostasis and inflammation. In many neurodegenerative diseases, neuroinflammation is a common pathological process that occurs as a result of the persistent activation of microglia by stimuli. Microglia were once thought to be either "pro" or "anti" inflammatory, but more recently, it has been recognized that immunometabolism is also important in the phenotypical determination of microglia, and metabolic reprogramming is a key factor in resting microglial homeostasis and the transition into a neuro-inflammatory cell state. One of the key parameters that affect the metabolic profile of microglia is oxidative signaling. Reactive oxygen species (ROS) that were previously believed to be side products of metabolism that are toxic is now recognized as important signaling molecules that can impact gene expression and activate innate immune responses. A mitochondrial dysfunction, characterized by dysfunctional metabolism, ROS generation and dynamics, in turn, exacerbates neuro-inflammation and causes microglial homeostasis destabilization. Redox regulation and mitochondrial function are important in the disease process of neuro-inflammation. Therapeutic strategies based on nanotechnology with properties directly interacting with these synergic mechanisms can be used for the treatment of neurodegenerative diseases. Nanotechnology nanocarrier systems can be used to deliver targeted therapeutics and antioxidant nanomaterials as well as mitochondria targeted drugs across the blood brain barrier. However, the diversity of microglia and the safety of nanomaterials are issues that have to be taken care of. In translational research, unifying models and combining more targeted strategies for clinical application are the new promising in this field.
  DOI 10.5281/ib-2710926 *Corresponding author Praveena T. Email praveenathangaraj28@gmail.com 	

1. Introduction

Microglia, the endogenous immune cells of the CNS, play an imperative role in neural homeostasis by constant environmental monitoring, synaptic elimination, and removal of apoptotic debris.(1–3) . In physiological settings microglia play an essential supportive role for neuronal function and tissue repair but under pathological conditions, it can become activated and these functions may be

beneficial or harmful, depending on the situation and on how long this occurs (4). There is an ever-increasing body of evidence to support the notion that activated microglia are critical participants in chronic neuroinflammation and the neurodegeneration that may arise from it. The hallmark feature of major neurodegenerative diseases such as AD and PD is now accepted to be neuroinflammation. In the case of AD, initial activation of microglia helps in removing of the amyloid- aggregates, whereas activation over

extended period results in release of pro-inflammatory mediators and oxidative stress that results in damage to neurons (4–6). Also in PD activated microglia induce dopaminergic neuronal degeneration via releasing excessive amount of inflammatory cytokines and ROS that promote disease progress (7,8). These results show that microglial functions are complicated and context-dependent in the pathology of CNS. While for a long time microglial activation has been dichotomized into the two polarized states of pro-inflammatory M1 and anti-inflammatory M2 phenotypes, it is more and more being viewed as an oversimplification to explain microglial heterogeneity and response in vivo (9,10). Advances in transcriptomic and functional profiling have revealed that microglia exhibit a spectrum of activation states influenced by environmental causes, disease stage, and intracellular signaling networks(10,11). This approach shift highlights the need for more integrative models that better reflect microglial functional diversity. In this regard, the emerging field of immunometabolism has provided new insights into how metabolic pathways regulate immune cell function. Microglia display remarkable metabolic flexibility, switching between oxidative phosphorylation and glycolysis depending on their activation state and functional requirements(12,13). This metabolic reprogramming is not only due to the activation but actively drives microglial behavior, influencing cytokine production, phagocytosis, and inflammatory signaling(13,14). Mitochondria play a central role in this process, acting as central points that integrate bioenergetic and immune signaling pathways. Redox biology further adds complexity to this regulatory network. ROS, generated from sources such as NADPH oxidase and mitochondrial respiration, function as signaling molecules under physiological conditions but become detrimental when produced in excess(14,15). Elevated ROS levels disrupt mitochondrial integrity, activate pro-inflammatory signaling pathways such as nuclear factor- κ B and mitogen-activated protein kinases, and promote sustained neuroinflammation (15,16). Importantly, recent studies indicate that redox signaling is tightly coupled with metabolic reprogramming, forming an interconnected axis that governs microglial activation and function(17). In parallel, mitochondrial dysfunction—characterized by impaired oxidative phosphorylation, increased mitochondrial ROS, and defective mitophagy—has been identified as a key driver of chronic inflammatory responses in microglia(18). Moreover, while nanotechnology-based therapeutic approaches have shown promise in targeting neuroinflammation and improving drug delivery across the blood–brain barrier, their potential to modulate microglial immunometabolism has not been comprehensively explored (19,20). This lack of integration limits the

development of targeted and effective therapeutic strategies for neurodegenerative diseases. This review aims to provide a comprehensive and integrative overview of microglial immunometabolism in neuroinflammation, focusing on the interplay between metabolic reprogramming, redox signaling, and mitochondrial dysfunction. Furthermore, it highlights emerging nano-enabled therapeutic strategies designed to modulate these interconnected pathways, with the goal of identifying novel and translational approaches for the treatment of neurodegenerative disorders.

2. Microglial Immunometabolism

Microglial metabolism is under the strict control of innate metabolic pathways within the cell that respond to stimuli and diseased environment. Rather than being epiphenomena of microglial activation, metabolic pathways are central to the regulation of microglial cell phenotype, function and inflammatory response. This has resulted in the conceptual shift towards immunometabolism as a fundamental to our understanding of microglial regulation during neuroinflammation and neurodegeneration(21,22).

2.1 Metabolic States of Microglia

Microglia have unique metabolic states that are matched to their functional needs. In fact, activated microglia have a preference for aerobic glycolysis (FG). This form of cellular respiration uses less efficient pathways of energy production for ATP manufacture but provides further biosynthesis and produces the firepower for pro-inflammatory signaling molecules – cytokines and ROS(22,23). Thus, glycolytic reprogramming is apparent in a pro-inflammatory state. On the other hand, homeostatic or reparative microglia mainly depend on mitochondrial oxidative phosphorylation (OXPHOS), which produces ATP more efficiently. The OXPHOS pathway is responsible for anti-inflammatory activities as well as for tissue repair and protection of neurons(23,24). Overall, glycolysis and OXPHOS serve as the primary regulators of the microglial phenotype. By utilizing FAO, the anti-inflammatory phenotype also benefits from a reliable energy supply and increased mitochondrial respiration. The involvement of FAO has also been associated with improvements in phagocytic function and resolution of inflammation, both of which are necessary processes to return the CNS to homeostasis after injury or stress(24,25).

2.2 Metabolic Reprogramming Triggers

Microglial metabolic states are dynamically regulated by external stimuli. Pathogen-associated molecules such as lipopolysaccharide (LPS) and disease-associated factors including amyloid- β (A β) are

potent inducers of glycolytic reprogramming, driving microglia toward a pro-inflammatory phenotype(25,26).In the same way, environmental toxins and signals from cellular stress can interfere with mitochondrial function, driving metabolic reprogramming that underpins inflammation. Metabolic regulation is also controlled by cytokine signaling. A pro-inflammatory cytokine such as tumor necrosis- α and interferon- γ increases glycolytic flux and promotes inflammation, while anti-inflammatory cytokine responses (e.g., interleukin-4 and interleukin-10) encourage oxidative metabolism and tissue-repair responses(26,27).

2.3 Key Regulatory Pathways

Several intracellular signaling pathways orchestrate metabolic reprogramming in microglia. Hypoxia-inducible factor-1 α (HIF-1 α) is a central regulator of glycolysis, promoting the expression of glycolytic enzymes and facilitating the transition toward a pro-inflammatory state under hypoxic or inflammatory conditions (27,28).HIF-1 α activation is also associated

with ROS generation and inflammation. The activity of mTOR (mechanistic target of rapamycin) is an important metabolic sensor for coordinating nutrients and growth factors, which will also control cellular metabolism. MTOR promotes glycolysis and anabolic metabolism for inflammatory microglial activation(28). On the other hand, AMP-activated protein kinase (AMPK) functions as an energy sensor to favor oxidative metabolism and mitochondrial biogenesis. Microglia can induce the switch to OXPHOS and fatty acid oxidation metabolism by activating AMPK, which can have an anti-inflammatory effect and bring it back to basal level(29).Individually, these pathways comprise a coordinated neuro-immune signalling network that couples the metabolic state of the brain to microglial phenotype. Therapies designed to target neuroinflammatory and neurodegenerative conditions should focus on relevant pathways within this signalling network.

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-1 α , mTOR	Pro-inflammatory	Cytokine release, ROS production
Oxidative Phosphorylation	Efficient mitochondrial ATP generation	AMPK, PGC-1 α	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

3. Redox Signaling in Microglial Activation

Redox signaling is a key factor in the control of microglia activation, bridging metabolism with neuroinflammation. Reactive oxygen species (ROS), which were previously thought of as waste products of the cellular respiratory chain, are now appreciated as key signaling molecules that regulate immune cell function. In microglia, ROS production must be carefully regulated for physiological signaling, and alterations in redox balance can lead to sustained neuroinflammation and neuronal death Angelova PR, Abramov AY. Role of mitochondrial ROS in neurodegeneration(30,31).

3.1 Sources of ROS

ROS derived from microglia are enzymatic as well as mitochondrial. One of the most significant enzymes producing ROS in immune cells is NADPH oxidase 2 (NOX2), a ROS-producing enzyme activated upon immune cell stimulation. NOX2 mediates the transfer of electrons from NADPH to molecular oxygen, resulting in the production of superoxide radicals that

will downstream trigger redox signaling(31,32).ROS derived from NOX2 have been shown to be critical mediators of responses to inflammatory stimulus such as lipopolysaccharide and aggregated proteins. Concurrently mitochondria are another major source of ROS within cells. During oxidative phosphorylation electrons can leak from complex I and III of the electron transport chain to generate mitochondrial ROS (mtROS). MtROS generation can be tightly controlled under normal conditions, but mitochondrial dysfunction causes uncontrolled accumulation of mtROS which can significantly amplify inflammatory processes and result in cellular stress.(32,33).

3.2 ROS as Signaling Molecules

In addition to their destructive ability, ROS also serve as critical second messengers of various intracellular signaling pathways. As second messengers, ROS can regulate the activation of transcription factors and kinases that induce the transcription of inflammatory genes in microglia. Among the most prominent of these pathways is the nuclear factor-B (NF-B)

pathway, which can be activated by ROS-mediated oxidation of signaling molecules upstream of the pathway. This activates NF- κ B, which then induces the transcription of pro-inflammatory cytokines, such as tumor necrosis factor- α and interleukin-1(33,34). ROS control also mitogen-activated protein kinases (MAPK), those being ERK, JNK and p38 signalling. These kinases, once activated, stimulate the inflammatory reaction via production of cytokines and cellular stress responses(34,35). It's not that ROS-driven signaling, at the appropriate levels, is bad - it actually allows the microglia to scale their response to the environment. But sustained production results in hypersecretion of cytokines and continued propagation of the neuroinflammatory cascade (35).

3.3 Oxidative Stress versus Redox Balance

At the cellular level, the tendency for either homeostatic or inflammatory ROS production depends on the tight balance to which antioxidant mechanisms must keep ROS effects at bay. Microglia have antioxidant defenses to prevent oxidative stress, and these defenses are based on nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, which, when activated, promotes the expression of antioxidant enzymes such as heme oxygenase-1 and glutathione related factors(36). In pathological state, excessive ROS generation in excess of antioxidant defense will create oxidative stress. This oxidative stress will cause damage of mitochondria, inflammasome activation and loss of inflammatory signals that might lead to neuronal damage and neuronal cell death(37,38).

4. Mitochondrial Dysfunction and Neuroinflammation

Mitochondria integration of cell metabolism with innate immune signaling (37, 38). Mitochondria not only produce ATP, they also serve as signaling hubs that can modulate inflammatory signaling. Dysfunction of mitochondria is not only a consequence of neuroinflammation, it can also be a major cause of neuroinflammation in neurodegenerative diseases(39).

4.1 Mitochondrial Dynamics: Fission–Fusion Imbalance

Mitochondria sustain their shape and working mode through a dynamic balance between fission and fusion processes, which are responsible for proper distribution of mitochondrial proteins and DNA, and elimination of defective mitochondrial fragments. These processes are carried out by two different groups of proteins: mitofusins and OPA1 for fusion, and dynamin-related protein 1 (Drp1) for fission(40). Overactive mitochondrial fission results in

mito-rich fragmentation, enhancing oxidative stress and energy metabolic defects in activated microglia(41). As a consequence, the cytokine production induces a pro-inflammatory profile that has been associated with dysregulated mitochondrial behaviour in pathological states such as the Alzheimer's pathology (42).

4.2 mtROS and Inflammation: Link to Inflammasome Activation

Mitochondrial reactive oxygen species (mtROS) are critical regulators of inflammatory signaling in microglia. When under stress, increases in mitochondrial ROS serve as the 'alarm' to activate the NLRP3 inflammasome, a caspase-dependent protein complex that plays a role in the inflammatory response(43). The complex activation causes caspase-1-dependent catalysis of interleukin-1, potentiating a cascade of inflammatory response. Another consequence of mitochondrial damage is the release of oxidized mitochondrial DNA into the cytoplasm, which further potentiates the activation of the inflammasome(44).

4.3 Bioenergetic Failure: ATP Depletion and Metabolic Shift

Microglia energy production and mitochondrial respiration Mitochondrial dysfunction causes an inability to perform oxidative phosphorylation and subsequent ATP generation that results in bioenergetic stress. In response, the cells flip to glycolysis, a quick but less efficient path for generating ATP (45). The switch also has functional consequences: By switching, immune cells generate pro-inflammatory cytokines and signals. In neurodegenerative diseases, like Parkinson's disease, the long-term bioenergetic deficiency that accompanies the increased autophagy is part of what makes neurons more susceptible and leads to continued cell loss(46).

4.4 Mitophagy Defects and Accumulation of Damaged Mitochondria

Most of the quality control functions of mitochondria occur through selective degradation of damaged mitochondria, a process known as mitophagy. Mitophagy is an essential process for maintaining mitochondrial homeostasis and can be modulated by pathways such as the PINK1-Parkin pathway(47). Parkin and PINK1 Regulate the Generation of Mitochondrial ROS One of the main degradative pathways for mitochondrial damage is Parkin and PINK1-mediated mitophagy, a specific type of autophagy that targets damaged mitochondria. Impairment of mitophagy leads to the accumulation of dysfunctional mitochondria, resulting

in the overproduction of ROS and prolonged inflammatory activation. These defects are strongly linked to pathogenic damage in Parkinson's disease that is related to mutations of PINK1 or Parkin(48).

4.5 Integrated Disease Relevance

Together, defective mitochondrial dynamics, mtROS overproduction, bioenergetic collapse and defective mitophagy all contribute to the formation of a self-sustaining feedback loop of mitochondrial dysfunction and inflammation. This pathogenic loop has become an important hallmark of many neurodegenerative disease states, where microglia-mediated mitochondrial activation can lead to further neuronal death(49). Targeting mitochondrial pathways therefore represents a promising strategy for modulating neuroinflammation and slowing disease progression (50).

5. Crosstalk: Immunometabolism-Redox-Mitochondria Axis

The regulation of microglia activation involves a complex interplay between cell metabolism, redox signaling, and mitochondrial regulation. These areas do not work as separate entities, but form a regulatory axis in which the redox status is controlled by the cell's state of metabolism, mitochondrial regulation influences redox signaling, and mitochondrial regulation feeds back onto the cell's metabolism and inflammatory capacity(51).

5.1 Metabolic Control of ROS Generation

Cellular Metabolism controls ROS production in microglia. The type and extent of reactive oxygen species produced by microglia depends on the cell's metabolic state. Under a pro-inflammatory stimulus, macrophage metabolism shifts away from mitochondrial oxidative phosphorylation, but ROS production is actually increased by redox cycling and activation of NADPH oxidase pathways(52). By comparison, the oxidative metabolism supports controlled ROS generation with optimal ETC function, thus normal redox state(53). Notably, some metabolic intermediates, such as succinate, serve as signaling molecules that can further stabilize hypoxia-inducible factor-1 and enhance ROS-dependent inflammation (54).

5.2 Redox Regulation of Mitochondrial Function

Once formed, ROS also have a downstream effect on mitochondria which impair mitochondrial function and morphology. The high concentrations of ROS damage mitochondrial proteins, lipids and DNA and impair electron transport chain (ETC) activity and membrane potential(55). These alterations cause a disturbance in ATP synthesis and lead to additional

leakage of electrons, thus enhancing the generation of mtROS. ROS affect also the mitochondrial process of fission by the activation of pathways involving dynamin-related proteins and the formation of fragmented, damaged mitochondria(56).

5.3 Mitochondria as Amplifiers of Inflammatory Signaling

Mitochondrial dysfunction acts as a critical amplifier of microglial inflammation. Damaged mitochondria release mitochondrial DNA and other danger-associated molecular patterns into the cytosol, which activate innate immune sensors and inflammasome pathways(57). Increased mtROS production further drives activation of redox-sensitive transcription factors, including nuclear factor- κ B, thereby enhancing cytokine expression(58).

5.4 Feedback Loops Linking Metabolism, ROS, and Mitochondria

One characteristic of the immunometabolism-redox-mitochondria axis is the existence of self-perpetuating feedback loops. ROS resulting from metabolic reprogramming damage mitochondria causing subsequent mtROS generation(59). Mitochondrial dysfunction also drives a switch to a glycolytic metabolism which in turn maintains ROS production and inflammatory signaling(60). This established crosstalk in the face of dysfunctional mitochondria provides for a chronic pro-inflammatory state, with mitochondrial damage also fueling activation of the inflammasomes and cytokine production which in turn acts back to modify metabolic and redox pathways(61). On the other hand, correcting metabolic imbalance or boosting antioxidant responses can break these feed-forward loops, thus identifying multiple points of therapeutic intervention. The crosstalk between these various pathways strongly suggests that neuroinflammation is not the consequence of independent, disconnected events but rather the consequence of network interconnectedness(62).

5.5 Implications for Neurodegenerative Diseases

Disrupted feedback loop in neurodegeneration. The axis presented above is further compromised in neurodegenerative diseases, where metabolic reprogramming, increased oxidative stress and mitochondrial dysfunction are centered on each other to ensure the continual stimulation of microglia and damage to neurons. The ongoing cycle accelerates disease progression through endless iterations, and therefore a combination approach addressing several parts of the axis, rather than only one, is worth exploring(63).

6. Implications in Neurodegenerative Diseases

The impaired crosstalk of the immunometabolism-redox-mitochondria axis is a key pathogenic driver of neurodegenerative diseases, where malfunctioning microglia play a critical role. Instead of being merely reactive cells, microglia exhibit a variety of disease-associated metabolic and redox abnormalities that directly affect neuronal viability. These abnormalities are mediated by a tight interconnected networks involving changes in cell metabolism, oxidative stress, and mitochondrial function that promote chronic neuroinflammation (64).

6.1 Alzheimer's Disease

In Alzheimer's disease, amyloid- β (A β) accumulation induces significant metabolic reprogramming in microglia, shifting their energy utilization toward glycolysis while impairing mitochondrial oxidative phosphorylation (65). This change in metabolism is not just an adaptive one, but a detrimental one, by limiting phagocytosis efficiency and thus limiting A clearance via decreased generation of ATP. Exposure to A, simultaneously, increases mitochondrial dysfunction as can be seen by the increased generation of mitochondrial reactive oxygen species (mtROS) which propagates the inflammation (66). On a mechanistic level, mtROS further activate redox-sensitive transcription pathways to orchestrate the persistent secretion of cytokines and maintain the pro-inflammatory microenvironment. Moreover, abnormal mitochondrial dynamics and defective mitophagy lead to the build-up of damaged mitochondria, further aggravating oxidative stress and metabolic dysregulation (67).

6.2 Parkinson's Disease

Parkinson's disease is characterized by pronounced mitochondrial impairment, particularly involving defects in electron transport chain activity and mitochondrial quality control mechanisms (68). In microglia, these dysfunctional mitochondria produce more mitochondrial superoxide (MS) that cause inflammatory activation, and contribute to neurotoxicity. While transient ROS signaling plays a vital role in cell signaling, continuous oxidative stress disturbs cellular homeostasis and triggers additional production of pro-inflammatory cytokines (69). One of the key mechanistic aspects of PD is the failure of mitophagy and this is often linked to a dysfunction of the major regulators of mitochondrial quality control. The build-up of dysfunctional mitochondria contributes to the generation of ROS while releasing mitochondrial-derived stimuli to activate innate immune pathways (70). So, it induces a self-perpetuation loop in which mitochondrial damage triggers inflammation, which in turn causes further

mitochondrial damage. In addition, the changed metabolism to favor glycolysis contributes to the state of inflammation, as glycolysis supplies energy quickly that is needed for (71).

6.3 Other CNS Disorders

6.3.1 Stroke

In ischemic stroke, the abrupt energy failure not only causes mitochondrial dysfunction, but also generates an overproduction of ROS that induces microglia activation (72).

6.3.2 Multiple Sclerosis

Multiple sclerosis Microglia and other glial cells have been linked with a chronic neuroinflammatory response that is accompanied by sustained mitochondrial alterations and a change of metabolism in these cells (73).

6.4 Integrated Mechanistic Perspective

A shared pathogenic model in all neurodegenerative diseases: metabolic reprogramming, oxidative stress and mitochondrial dysfunction are interdependent processes along a vicious cycle of microglial dysregulation. Excess ROS further impair mitochondria, mitochondrial dysfunction perpetuates metabolic reprogramming, metabolic reprogramming is required to perpetuate and sustain mitochondrial dysfunction (74). The combined network establishes a continuous inflammatory signal that enhances damage to neurons. Addressing this activity is best achieved with a multi-pronged approach that corrects energy production, minimizes oxidative stress and enhances mitochondrial health. Treatments that do not account for this collaborative activity may not be enough to stop neurodegeneration (75).

7. Nano-Enabled Therapeutic Targeting

Nanotechnology-based strategies represent a potential platform for precise regulation of microglia via targeting of the crosstalk between the pathways of metabolism, redox homeostasis, and mitochondrial function. The specificity and versatility of nanocarriers are impossible to achieve with traditional therapeutic approaches, providing functionalities for sustained release and spatial control of drug action, improved blood-brain barrier (BBB) penetration, and marker-dependent targeting of activated microglia. These advantages are of importance for neuroinflammation where the regulation of timing and location of therapeutic action are critical (76).

7.1 Redox-Sensitive Nanocarriers

Redox-responsive nanocarriers are engineered to exploit elevated intracellular ROS levels in activated microglia. These systems incorporate oxidation-sensitive linkers that undergo structural changes in high ROS environments, enabling selective drug release at sites of inflammation(77).This approach not only minimizes the systemic effects but also enhances the effectiveness of the treatment. Indeed, in the mechanistic level this approach has the advantage of delivering the antioxidants or the anti-inflammatory agents inside the body, at the location of highest oxidative stress, by releasing them. Reduction of the level of intracellular ROS results in lower activation of redox-sensitive signaling pathways that promote cytokine synthesis and release.(78).

7.2 Mitochondria-Targeted Nanoparticles

Targeted delivery to mitochondria: A direct approach to modulate the original source of oxidative stress and bioenergetic impairments Usually targeted delivery to mitochondria is provided by functionalization of nanoparticles with lipophilic cations or peptide ligands that tend to accumulate in the mitochondrial matrix.(79).Upon targeting, therapeutics are released from these nanocarriers that directly scavenge mtROS, restore membrane potential and restore the electron transport chain. This helps to stop additional harm to the mitochondria, and to reduce the production of pro-inflammatory signals. Importantly, the nanocarriers bring about a normalization of the cellular energy levels, thus avoiding the activation of microglia to a pro-inflammatory state. (80).

7.3 Metabolic Reprogramming via Nanomedicine

The potential of using nanomedicine to directly modulate microglial metabolism is emphasized through recent advances.Nanoparticles can alter microglial metabolic functioning by increasing the proportion of energy devoted to oxidative phosphorylation (OXPHOS) instead of glycolysis, which can help induce an anti-inflammatory cell state(81).This metabolic reprogramming reduces lactate accumulation and limits the availability of

metabolic intermediates that drive inflammatory signaling. At the same time, normalised mitochondrial respiration increases ATP production and confer protection. These strategies reveal that metabolic optimization is underway and potent – rather than supportive, transformative of fire and smoke of microglial function(82).

7.4 Phytochemical-Based Nanoplatforms

The novel development is the use of bioactive natural compounds with modern drug delivery systems in the form of nanocarriers. Numerous plant-derived molecules have natural antioxidant and anti-inflammatory properties, but they have limited application due to their low bioavailability and stability. These challenges can be overcome by the use of nanoformulation to enhance the solubility of the bioactive compound, prevent degradation and promote targeted delivery(83).The mechanisms of action include ROS scavenging, activation of endogenous antioxidant systems and regulation of inflammatory signaling pathways, etc. with the use of phytochemicals-based nanoplatforms. In addition, some phytochemicals also regulate mitochondrial function and metabolic processes, which are particularly relevant for therapeutic strategies against the immunometabolism-redox axis(84,85).

7.5 Integrated Therapeutic Viewpoint

The key benefits of a nano-enabled approach is its ability to tackle multiple aspects of the pathological network simultaneously. The ROS modulation, restoration of mitochondrial function, and modulation of cell metabolism, achieved with this strategy, can effectively break these vicious cycles of the pathological network and lead to nano-formulations. These nanotherapies can also be selectively targeted via surface modification of the nanotherapies to activate microglia.(86).But, these advances are still hampered by concerns of long-term safety, scalability and clinical translation. These are still challenges to be resolved to realize the complete therapeutic potential of nanomedicine in neurodegenerative disorders.(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

8. Challenges and Limitations

8.1 Translational Gap

One of the big challenges in the field is the translation from preclinical to clinical. Comparisons of microglia across the different genomes of rodents and humans could be important for the translational relevance of experiments. Human microglia have different transcriptional and metabolic states which could influence their response to inflammatory triggers and treatment. (88).

8.2 Toxicity and Safety Concerns of Nanoparticles

Although nanocarriers offer targeted delivery advantages, their safety profile remains a major concern. Nanoparticles can induce unintended cytotoxic effects, including oxidative stress, membrane damage, and interference with cellular homeostasis (89). In particular, prolonged exposure to certain nanomaterials has been associated with accumulation in neural tissue, raising concerns about long-term neurotoxicity(90). Another critical issue is the potential for nanoparticles to disrupt mitochondrial function, paradoxically exacerbating the very pathways they are designed to target (91). Additionally, variations in nanoparticle composition, size, and surface chemistry can lead to unpredictable biological interactions, complicating safety assessment and regulatory approval (92).

8.3 Specificity in Targeting and Blood-Brain Barrier Challenges

Delivery to CNS microglia The effective delivery of therapeutics to microglial cells in the CNS can be difficult given the extremely selective permeability of the BBB. Nanocarriers have low and variable trans BBB delivery, but can help(93). Even when nanoparticles successfully enter the brain, achieving selective targeting of microglia without affecting other cell types remains difficult(94). Peripheral immune cells or CNS-resident cells may be involved in non-specific uptake and lead to side effects and/or reduced efficacy. In addition, neuroinflammation (a pathological condition) can also change the permeability of the BBB which can limit or be used to enhance delivery (95).

8.4 Lack of Standardized Experimental Models

Lack of standardized and biologically relevant model The lack of standard and biologically relevant models is yet another significant limitation in this field. There are microglial cell lines available that can be immortalised and used in vitro, but these may not represent the primary microglial state in humans(96).
Critical Perspective

These barriers highlight the complexity of microglial regulation and precision targeting that may be being underestimated with the approaches that have been undertaken so far. Targeting a single component of a complex pathway, such as mitochondrial health, metabolism, and redox signaling, may not be a viable approach. Inadequacies in these areas could impede the translation of the bench to bedside(97).

9. Future Perspectives

9.1 Specific targeting of microglia with precision

In the brain, microglia are highly heterogeneous in brain regions and disease states and various subpopulations exhibit distinct metabolic and functional signatures. In recent years, transcriptomic analyses have described the various microglial populations associated with disease and they differ significantly from microglial populations in the healthy brain, suggesting that there are no single approaches to target all microglial populations(98). But with such specificity has been tricky as markers are overlapping and transitional phenotypes are constantly evolving. Therefore, the temporal and spatial resolution have to be considered when targeting and modulating responses of microglia(99).

9.2 Nanomedicine with AI (Future Direction)

Cancer Nanotherapeutics: Artificial intelligence AI is being studied to speed up the design of nanomedicines, and to predict outcomes. Machine learning can, for instance, be used for the analysis of massive sets of data to help determine the most effective size, surface chemistry, targeting ligands, etc. for efficient delivery and reduced side effects of nanoparticles(100).

9.3 Clinical Translation Strategies

A more systematic approach to the development of therapy will be critical in order to more easily connect the dots between the experimental findings and the clinical context. Standardization of preclinical paradigms and benchmarks for therapy assessment will be one of the important measures(101). In addition, scalable and reproducible strategies for NP synthesis must be developed for consistent therapeutic benefits in the clinical setting. Finally, a delivery system that can cross the BBB without losing targeting specificity is needed. Although ligand engineering and carrier design could be used to enhance the delivery of the NPs into the CNS, the chronic safety and pharmacokinetic parameters of the targeted NPs for CNS delivery should be studied(102).

10. Conclusion

All the above together, make up microglial immunometabolism, which emerged as more intelligible and translatable scheme of understanding neuroinflammation by taking metabolism as the ultimate for microglial regulation. The strict linkage between the metabolic shifting, redox state and mitochondrial function seems to determine what the microglia do in the brain is beneficial or harmful. Compromised redox-metabolic axis leads to generation of positive feedback loop between ROS and mitochondrial dysfunction which results in true inflammatory cascade with adverse effects on neurons. In this new scheme, weaknesses with respect to on target approach was only revealed and preferred a multi-factorial approach. Accordingly, nanotechnology is a potential technology which can simultaneously and specifically target multiple components of microglia. However, the transfer of these studies to the clinic is not trivial and a number of additional skills, including greater precision, risk/benefit analysis and human-based model are needed. In future studies, multiple levels of signaling are being used in a single approach and may be technology supported. It will enable us to make treatments that not only will control the inflammation but restore the balance of treatment between microglial cells and neurons, thereby offering a better condition for neurodegenerative diseases.

References

- 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.
- 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>
- 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>
- 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
- Lepiarz-Raba I, Gbadamosi I, Florea R, Paolicelli RC, Jawaaid 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
- 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](https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(15)70016-5/abstract)
- 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
- 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
- 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
- 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>
- 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
- 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.
- 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
- Mitochondria are the powerhouses of immunity | Nature Immunology [Internet]. [cited 2026 May 3]. Available from: <https://www.nature.com/articles/ni.3704>
- 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.
- 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
- 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
- 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.
- 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
- 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 Reprogramming 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 *barrestin1* 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. *Pharmaceutics* (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- κ B 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-1 β via HIF-1 α . *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- κ B 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](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, Fakhruullina G, Gigli G, Leporatti S, Fakhruullin 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, Farcas 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. Stratoulis 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/emboj.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