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Mitochondria-Associated Endoplasmic Reticulum Membranes in Microglia: One Contact Site to Rule Them all

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Abstract

Microglia, the resident immune cells of the central nervous system (CNS), play a crucial role in maintaining tissue homeostasis by monitoring and responding to environmental changes through processes such as phagocytosis, cytokine production or synapse remodeling. Their dynamic nature and diverse functions are supported by the regulation of multiple metabolic pathways, enabling microglia to efficiently adapt to fluctuating signals. A key aspect of this regulation occurs at mitochondria-associated ER membranes (MAM), specialized contact sites between the ER and mitochondria. These structures facilitate the exchange of calcium, lipids, and metabolites and serve as metabolic and signaling hubs. This review synthesizes current research on how MAM influence microglial physiology, with an emphasis on their role in immunometabolism, offering new insights into the integration of metabolic and immune functions in the CNS and its impact in the context of neurodegeneration.

Keywords

mitochondria-associated ER membranes (MAM), microglia, ER-mitochondria contact sites, inflammation, metabolism, neurodegeneration

Introduction

Microglia, the immune cells of the central nervous system, protect tissue homeostasis from pathogens and environmental insults (Sierra et al., 2024). Microglia perform key functions such as inflammation control, myelin repair, and synapse remodeling through phagocytosis, surveillance, and soluble factor release. Microglia constantly monitor the brain parenchyma, and effectively integrate and respond to fluctuating environmental signals thanks to the concomitant orchestration of multiple metabolic pathways (Bernier et al., 2020). In fact, single-cell transcriptomic classifications have helped to grasp the remarkable diversity of microglia (Paolicelli et al., 2022). In recent years, genome wide association studies (GWAS) of Alzheimer's disease (AD) and Parkinson's disease (PD) patients are identifying gene variants specifically linked to myeloid cells (Raj et al., 2014). Thus, microglia are emerging as key players in the pathophysiology of neurodegenerative diseases, capturing altered transcriptomic and functional profiles (Lopes et al., 2022). Converging data points towards a chronic microglial dysfunction which ultimately leads to neuronal loss associated with neurodegenerative diseases, such as AD and PD (Bartels et al., 2020).

The compartmentalization and integration of various cellular pathways for the correct microglial functioning require the establishment of contact sites between organelles. Once thought to be mere physical appositions between membranes, these contact sites have now been recognized as dynamic functional platforms where diverse enzymes converge, enabling coordinated regulation and activity (Scorrano et al., 2019). Therefore, the mechanisms by which these active contact sites are fine-tuned can provide a new dimension to understand the highly dynamic capabilities of microglial physiology.

One such contact site occurs between the outer membrane of mitochondria and a specific subdomain of the endoplasmic reticulum (ER). This biochemically and functionally distinct domain of the ER is named MAM (mitochondria-associated

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ER membranes) and the interaction between mitochondria and MAM is collectively termed MERC (mitochondria-ER contact site) (Wu et al., 2018; Degechisa et al., 2022). These contact sites are maintained by proteins that physically tether the two organelles, with the distance typically ranging from 10 to 30 nm (Wu et al., 2018; Degechisa et al., 2022). Over a thousand proteins have been identified to be located in MAM (Zhang et al., 2011; Liu and Yang, 2022), including tethers and spacers, lipid metabolizing and calcium signaling enzymes, and proteins associated with neurodegeneration, among others. However, these structures are highly dynamic, transient, and heterogeneous, varying among different cell types and within individual cells, suggesting that the functions of MAM may be tailored to the specific metabolic and signaling needs of the cell (Simmen and Herrera-Cruz, 2018). This contact allows the ER and mitochondria to synergize, converting MAM as the platform of specialized cellular functions. This review aims to integrate current literature to explore how MAM change, coordinate, and regulate microglial biology, with a particular focus on lipid metabolism (Figure 1). Furthermore, we aim to cover how microglial dysfunction associated with MAM may be associated with the pathogenesis of neurodegenerative diseases, focusing on AD and PD.

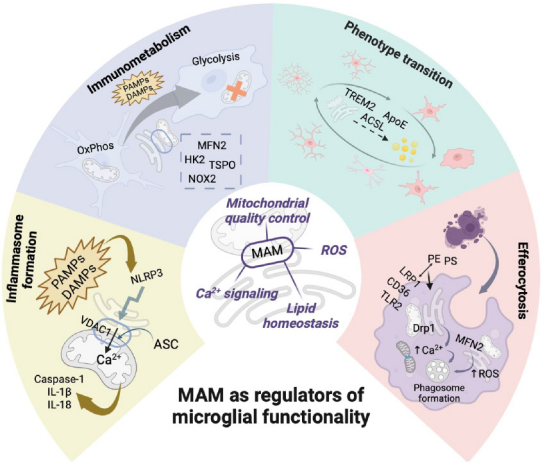

Figure 1. MAM Regulate Microglial Functionality. Graphical Abstract That Summarizes the Involvement of MAM in the Control of Lipid Homeostasis, Calcium Signaling, Mitochondrial Quality Control or Reactive Oxygen species Production (ROS) (Inner Circle). Through their involvement in these cellular processes, MAM participate in the regulation of key microglial functions such as inflammasome formation, immunometabolism, disease-associated phenotype transition or efferocytosis (outer circle). ACSL = long–chain acyl–coA synthetase; ApoE = apolipoprotein E; DAMPs = damage–associated molecular patterns; Drp1 = dynamin–related protein–1; HK = hexokinase; MFN2 = mitofusin 2; NLRP3= NOD–like receptor family protein 3; NOX2 = NADPH oxidase 2; OxPhos = oxidative phosphorylation; PAMPs = pathogen–associated molecular patterns; PE = phosphatidylethanolamine; PS = phosphatidylserine; TLR2 = Toll–like receptor 2; TREM2 = triggering receptor expressed on myeloid cells 2; TSPO = translocator protein; VDAC1 = voltage dependent anion channel 1.

Composition and Traditional Functions of MAM

MAM Regulate Calcium Signaling

MAM play a crucial role in regulating inter-organellar calcium transfer, a process vital for maintaining mitochondrial functionality in mammalian cells, as reviewed in detail elsewhere (de Ridder et al., 2023). The ER serves as the primary calcium reservoir, releasing calcium to mitochondria, where it supports key metabolic enzymes of the tricarboxylic acid cycle (TCA) and electron transport chain. The presence of high local calcium concentrations at these ER-mitochondria contact sites, known as 'calcium hotspots', highlights their importance (Szabadkai et al., 2006). Additionally, mitochondria positioned close to the ER have higher calcium concentrations than those further away, underscoring the role of MAM in this process.

Calcium transfer between these two organelles is mediated by inositol-1,4,5-tris-phosphate receptors (IP3Rs), which are highly concentrated at MAM. IP3R on the ER fuels Ca^{2+} to voltage dependent anion channel 1 (VDAC1) on the outer mitochondrial membrane (OMM), forming a complex stabilized via the cytosolic chaperone GPR75 (Cárdenas et al., 2010; Wu et al., 2018). Afterwards, Ca^{2+} enters the mitochondrial matrix through the mitochondrial calcium uniporter (MCU). Further studies have shown that different proteins located within the ER, the OMM or the interorganellar space interact with the IP3R-GRP75-VDAC1 complex regulating their stability and activity, for a detailed review (Atakpa-Adaji and Ivanova, 2023).

Several protein pairs tether the ER, playing key roles in regulating Ca^{2+} transfer. For example, the ER-located protein VAPB and the mitochondrial PTPIP51 are critical for local Ca^{2+} signaling as the loss of these proteins disrupts local Ca^{2+} transfer (De Vos et al., 2012), while their overexpression or the use of synthetic linkers enhances Ca^{2+} signaling to the mitochondria (Csordás et al., 2006; Gomez-Suaga et al., 2017).

Altogether, MAM coordinate the cellular ATP demand with the ATP supply, and preventing the shuttling of Ca^{2+} from the ER to the mitochondria via MAM decreases the ATP production and the oxygen consumption rate (Cárdenas et al., 2010; Mallilankaraman et al., 2012). Nevertheless, levels of Ca^{2+} in the mitochondria need to be tightly regulated as an increase can result in changes in permeability through the permeability transition pore leading to programmed cell death through apoptosis.

MAM Regulate Lipid Metabolism

In the 1990s, studies in isolated mitochondria from rat liver revealed that a fraction enriched in ER markers was necessary

for the import of phosphatidylserine (PS) into mitochondria (Vance, 1990). This fraction, later termed MAM, is particularly enriched in PS synthases, PSS1 and PSS2, which facilitate the transport of PS to mitochondria, where it is converted into phosphatidylethanolamine (PE) by phosphatidylserine decarboxylase (PSD) (Stone and Vance, 2000). Thus, MAM are crucial for the synthesis and transfer of phospholipids between the ER and mitochondria.

Beyond phospholipid synthesis, MAM are crucial for cholesterol trafficking and metabolism. MAM contain higher cholesterol levels than other cellular membranes, including mitochondria and the bulk ER (Area-Gomez et al., 2012), supporting their characterization as lipid rafts (Simons and Vaz, 2004). The formation and function of MAM depend on the reorganization of the ER membrane into cholesterol- and sphingolipid-enriched lipid rafts, which cluster lipid-binding proteins necessary for specific metabolic activities (Vance, 2014). These transient lipid rafts are formed by local enrichment of cholesterol which, in turn, modulate MAM activities (Montesinos et al., 2020), supporting the intricate link between MAM and lipid homeostasis.

Cholesterol is either synthesized in the ER or uptaken as cholesteryl esters from lipoproteins and must be transported to the mitochondria for processes like neurosteroidogenesis (Germelli et al., 2021; Ikonen and Olkkonen, 2023). Proteins of the StAR family, such as StARD1, play a key role in facilitating cholesterol's journey across mitochondrial membranes by forming complexes, for example with TSPO, that promote its transport through the intermembrane space (Liu et al., 2006; Bose et al., 2008). It has been proposed that StARD1 interacts with MAM (Prasad et al., 2015), likely forming a complex with VDAC and TSPO, which is stabilized by the interaction of the mitochondrial ATAD3 with ER proteins (Issop et al., 2015; Brar et al., 2024). However, the precise mechanism by which cholesterol moves from the ER to the OMM and the potential involvement of MAM in this process remain areas of active research.

In addition to trafficking, MAM serve as the primary site for cholesterol esterification, a detoxification process where excess free cholesterol is converted into cholesteryl esters. This conversion is facilitated by the enzyme acyl-CoA:cholesterol acyltransferase-1 (ACAT1), which is more abundant and enzymatically active in MAM compared to other cellular regions (Rusiñol et al., 1994; Area-Gomez et al., 2012). The esterified cholesterol is then stored in lipid droplets, preventing cellular toxicity from excess cholesterol. Triacylglyceride-enriched lipid droplets can also originate from MAM through the activity of diacylglycerol acyltransferase (DGAT) and stearoyl-CoA desaturase 1 (SCD1) (Man et al., 2006).

In contrast, in its unesterified form, membrane-bound free cholesterol is shielded from the polar environment through a tight association with sphingomyelin (Endapally et al., 2019). In this way, MAM play a pivotal role in the synthesis and regulation of sphingolipids. Neutral sphingomyelinase, which breaks down sphingomyelin into ceramide and phosphocholine, is found in several cellular locations, including MAM, where its activity is significantly higher (Pera et al., 2017). Furthermore, the first and rate-limiting step in *de novo* sphingolipid synthesis, catalyzed by serine palmitoyltransferase enzymes (SPTLC1/2/3), operates within MAM. It has been shown that mitochondria-localized SPTLC2 forms a complex with ER-localized SPTLC1, further underscoring the integral role of MAM in sphingolipid metabolism (Aaltonen et al., 2022). These findings emphasize the multifaceted role of MAM in managing the balance and flow of crucial lipids within the cell and are summarized in Figure 2.

MAM Regulate Mitochondrial Quality Control

Mitochondria are highly dynamic organelles that undergo fusion and fission to meet cellular demands. Mitochondria quality control maintains their morphology, number, and activity through processes regulated by GTPases like dynamin-related protein-1 (Drp1) and mitofusins (MFN1, MFN2). These proteins are found at ER-mitochondria contact sites, implicating MAM in the regulation of these processes (Abrisch et al., 2020; Wilson and Metzakopian, 2021).

MFNs are essential for mitochondrial fusion, and also play key roles in maintaining mitochondrial morphology, calcium uptake, and mitochondrial membrane potential (Chen et al., 2003). While MFN1 is localized exclusively to mitochondria, MFN2 is present on both the OMM and MAM, with MFN2 being approximately 14 times more concentrated in MAM compared to mitochondria (de Brito and Scorrano, 2008). Silencing MFN2, but not MFN1, reduced ER-mitochondria tethering and diminished mitochondrial calcium uptake (de Brito and Scorrano, 2008), while other reports found the opposite effect (Filadi et al., 2015; Leal et al., 2016). These discrepancies might be explained by recent data showing that specific splicing variants of MFN2, named ERMIN2 and ERMIT2, are essential to shape the ER and to promote ER-mitochondria contacts, respectively (Naón et al., 2023), thus highlighting MFN2 and its splicing variants as regulators of MAM domains.

Conversely, during mitochondrial fission, the ER envelops the mitochondria provoking its constriction and recruiting the cytosolic Drp1 (Friedman et al., 2011). This further recruits Dynamin-2 (Dyn2), a GTPase which contributes to the constriction and ultimate fission of the mitochondria (Lee et al., 2016). Fissioned mitochondria have a reduced ability to tether to the ER, limiting Ca^{2+} exchange. However, Drp1 depletion does not prevent ER-mitochondria contact formation, indicating that Drp1 is not essential for tethering the organelles (Friedman et al., 2011).

MAM also influences mitochondrial fusion and fission by regulating the lipid composition of mitochondrial membranes. Since mitochondria rely on a continuous supply of

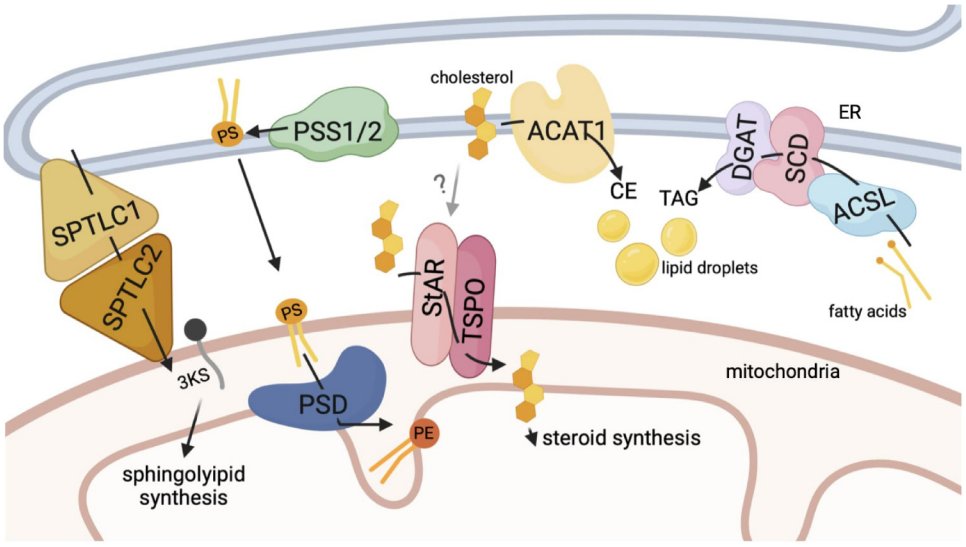

Figure 2. Lipid Pathways Located at MAM. MAM Serve as Cellular Platforms where a Number of Enzymes Implicated in Lipid Metabolism Pathways are Located. This figure summarizes the key pathways associated with lipid metabolism located at MAM, representing ER in blue and mitochondria in red. On the left, the enzymes SPTLC1/2 catalyze the formation of 3KS, a precursor of sphingolipid synthesis. On the middle left, PSS1/2 enzymes generate PS at MAM, which is then transported to the mitochondria where it is transformed into PE by PSD. On the middle of the panel, StAR and TSPO are shown, both involved in cholesterol import into the mitochondria, regulating steroid synthesis. On the middle right, cholesterol esterification by MAMlocated ACAT1 (SOAT1) is shown, which produces accumulation of CE. Finally, by the combined action of ACSL, SCD and DGAT (also located at MAM), fatty acids are incorporated into triacylglycerides. Cholesterol esters and triacylglycerides can be stored in lipid droplets. ACAT1 = acyl-CoA:cholesterol acyltransferase-1; ACSL = long-chain acyl-coA synthetase; CE = cholesterol esters; DGAT = diacylglycerol acyltransferase; 3KS = 3-keto-sphinganine; PE = phosphatidylethanolamine; PS = phosphatidylserine; PSD = phosphatidylserine decarboxylase; PSS1/2 = phosphatidylserine synthase 1/2; SCD = stearoyl-CoA desaturase; SPTLC1/2 = serine palmitoyltransferase 1/2; TAG = triacylglycerides; TSPO = translocator protein.

lipids from the ER at the MAM, disruptions in this process, such as reduction on mitochondrial PE content by a drastic reduction in PS synthesis, causes significant mitochondrial fragmentation and respiratory defects (Tasseva et al., 2013). This underscores the importance of lipid homeostasis and MAM in maintaining mitochondrial dynamics.

Proteins Associated with Neurodegenerative Diseases are Located in MAM

Given the significant pathways which can be regulated through the interaction of ER-mitochondria, it is not surprising that this association may be disrupted in pathological conditions. Indeed, neurodegenerative diseases such as AD or PD have been linked to alterations in the formation of these contact sites, as reviewed somewhere else (Paillusson et al., 2016).

AD is the most common neurodegenerative disorder in adults. Pathologically, it is characterized by progressive neuronal loss in the hippocampus and cortex, along with the buildup of extracellular neuritic plaques and intracellular neurofibrillary tangles in the brain. A number of factors have related the function of MAM with the pathophysiology of the disease. On one hand, main components in the pathophysiology, such as Presenilin 1 and 2, have been demonstrated to be located in MAM (Area-Gomez et al., 2009; Filadi et al., 2016). Indeed, the amyloid precursor protein (APP)-derived fragment C99, which γ-secretase with its catalytic components presenilins cleave into amyloid β-peptide and AICDC, accumulates at MAM in models of AD (Pera et al., 2017) leading to mitochondrial dysfunction. Presenilin 2 can also interact with MFN2 regulating ER and mitochondria distance and the efficiency of calcium transfer (Filadi et al., 2016). Besides presenilins, genetic risk factors identified through GWAS and directly linked to microglia, such as ApoE and TREM2, are also linked to MAM formation. The isoform ApoE4, which significantly increases the risk of developing AD, also upregulates the activity of MAM (Tambini et al., 2016). In the case of TREM2, its interactors have been demonstrated to be located in MAM in human microglia (Kwak et al., 2023). These observations are in line with the fact that there is an enhanced formation of these contact sites both in human samples (Area-Gomez et al., 2012) as well as in animal models of the disease (Hedskog et al., 2013). Indeed, MAM have been suggested as a convergent feature in AD where either accumulation of C99 at MAM in early-onset AD or cholesterol buildup caused by risk factors in late-onset AD lead to the

pathological upregulation of MAM activities (Area-Gomez and Schon, 2024).

PD is the most common movement disorder and the second most prevalent neurodegenerative disease after AD. Pathologically, it results from the loss of dopaminergic neurons in the substantia nigra of the midbrain and is marked by the emergence of Lewy bodies, which contain alpha-synuclein (α-syn) inclusions, impacting both cognitive function and movement. In the case of PD, key factors such as α-syn, Parkin or DJ-1 (Calì et al., 2012; Calì et al., 2013; Ottolini et al., 2013; Guardia-Laguarta et al., 2014) have been demonstrated to impact the formation of these contacts. Interestingly, α-syn has been postulated as a physical tether anchoring the ER and mitochondria (Ramezani et al., 2023). Moreover, α-syn can also interact with VDAC, regulating the opening of this calcium channel (Rajendran et al., 2022).

These observations highlight how proteins associated with neurodegenerative diseases are located at MAM and can alter, either increasing or decreasing the formation of these contacts, thus affecting the molecular pathways reviewed above.

Microglia, the Innate Immune Cells in the CNS with Multiple Phenotypes

Given the myriad of cellular functions orchestrated by MAM, it is not surprising that these contact sites play a pivotal role in microglial functionality. Microglia, as immune cells, express a variety of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), which recognize pathogen and damage-associated molecular patterns (PAMPs and DAMPs). DAMPs are host-derived molecules released during cellular damage, while PAMPs are microbial products from bacterial, viral or fungal origin (Ma et al., 2024). Upon detection, microglia rapidly undergo cellular and metabolic changes, including morphological modifications, increased phagocytosis, inflammasome formation and the production of proinflammatory cytokines to initiate a defense response. This response is supported by metabolic reprogramming to meet the energy and biosynthetic demands of their reactive state.

In the past decade, multi-omic approaches, especially single-cell transcriptomics and proteomics, have uncovered diverse microglial phenotypes that respond to various physiological and pathological contexts (Paolicelli et al., 2022). These dynamic phenotypes allow microglia to adapt to different developmental stages and environmental changes, involving profound membrane reorganization and the formation of organelle contact sites, including MAM.

One of such phenotypes is the disease-associated microglia (DAM), first described by Keren-Shaul and collaborators in an Alzheimer's disease murine model (Keren-Shaul et al., 2017), and has since been observed in other neurodegenerative models (Paolicelli et al., 2022). The DAM phenotype is thought to arise in response to neurodegenerative signals like amyloid plaques, apoptotic bodies, or myelin debris (Deczkowska et al., 2018). These signals induce transcriptional states that include, though not limited to, the DAM signature (Dolan et al., 2023). However, the precise role of DAM remains unclear, as it may be both beneficial or harmful depending on the disease context.

Many genes associated with this phenotype, such as *APOE, APOC1*, *CH25H*, *CLU*, *ABCA7* or *LPL*, are linked to lipid metabolism, highlighting the importance of lipid modulation in this transition. Moreover, GWAS risk genes associated with AD not only affect genes highly expressed in myeloid cells, such as microglia, but also converge in pathways such as phagocytosis, cholesterol metabolism and immune response, processes tightly linked to MAM function. Furthermore, the TREM2-APOE axis is central to this process (Keren-Shaul et al., 2017; Krasemann et al., 2017), likely through its regulation of cellular metabolism. Indeed, in a model of demyelination, TREM2-deficient mice fail to upregulate lipid-associated genes, keeping microglia in a "homeostatic" state and preventing the DAM transition. This highlights the importance of metabolic reprogramming in modulating microglial phenotypes, but what role do MAM play in this process? In the following sections we will review the current knowledge on how MAM, due to their role in regulating cellular metabolism, are crucial for supporting microglial functionality and their transition between phenotypes that contribute to pathology.

MAM regulate inflammasome formation in microglia

Activation of PRRs by PAMPs or DAMPs triggers a signaling cascade that produces pro-inflammatory signals like IL-1β and IL-18, coordinated by multiprotein complexes known as inflammasomes. The NOD-like receptor family protein 3 (NLRP3) inflammasome, comprising the sensor protein NLRP3, the adaptor protein ASC, and procaspase-1, is the most studied. In stressful conditions, NLRP3 recruits ASC and procaspase-1, leading to the activation of caspase-1, which then activates pro-inflammatory mediators like IL-1β and IL-18, initiating an inflammatory response. The inflammasome activity has an important role in neurodegenerative diseases such as AD. Indeed, proteins associated to AD, such as amyloid-β aggregates or hyperphosphorylated tau (Stancu et al., 2019), or mitochondrial damage associated with PD (Sarkar et al., 2017) promote the activation of inflammasome in microglia (Friker et al., 2020), and it is considered a key factor propagating inflammation and pathophysiology. Thus, inflammasome inhibition has been proposed as a therapeutic target (Swanson et al., 2019).

The implication of MAM in inflammasome formation was first described in 2011, revealing that NLRP3 localizes to the ER under non-stimulatory conditions but relocates to MAM

upon activation (Zhou et al., 2011). In this context, the adaptor ASC is also recruited to MAM, positioning the complex strategically to sense signals that emerge from mitochondria such as reactive oxygen species (ROS), ATP, succinate, and mitochondrial DNA (mtDNA). These DAMPs increase mitochondrial ROS, triggering inflammasome formation through different molecular mechanisms still in study that seem to imply Ca^{2+} entry to the mitochondria. Indeed, inhibiting the MAM-associated VDAC1 is essential for NLRP3 inflammasome activation, as knockdown of this channel disrupts this pathway (Zhou et al., 2011). Similar results were observed when MCU was blocked, preventing Ca^{2+} entry into the mitochondria (Rimessi et al., 2020).

NLRP3 can also be recruited to MAM via the mitochondrial antiviral signaling protein (MAVS) (Subramanian et al., 2013), which links viral detection to immune response activation. Upon detecting viral RNA, the cytoplasmic RIG-I-like receptors (RLRs) interact with MAVS, which triggers a signaling cascade that activates transcription factors like interferon regulatory factors and nuclear factor-κB (NF-κB), leading to the production of type I interferons and proinflammatory cytokines. MAVS is primarily located on the OMM but also localizes to peroxisomes and MAM, facilitating the propagation of antiviral signals from RLRs to downstream effectors. A proteomic study showed that MAVS signalosome components are recruited and assembled at MAM, reinforcing their role as platforms in immune responses against viral infections (Horner et al., 2015). Notably, MFN2 knockdown reduced ER-mitochondria interactions, altered mitochondrial morphology and enhanced MAVS-dependent RIG-I activation (Horner et al., 2011).

Another sensor for cytosolic damage is cyclic GMP-AMP synthase (cGAS), which detects cytosolic double-stranded DNA (dsDNA) from viruses, bacteria, or damaged cells, including mitochondrial DNA (Dvorkin et al., 2024). Upon recognition, cGAS activates the STING pathway, triggering interferon-stimulated gene expression. Interestingly, gain-of-function mutations in cGAS specifically in microglia were sufficient to elicit reactive microglial transcriptional states, neurodegeneration and cognitive decline (Gulen et al., 2023). Mechanistically, cGAS activation promotes the dimerization of the ER-resident protein STING, which then translocates to the Golgi to activate TANK-binding kinase 1 and interferon regulatory factor 3, resulting in interferon production. STING also activates NF-κB, producing pro-inflammatory cytokines like IL-6 and TNF-α.

Under basal conditions, STING predominantly co-fractionates with MAM markers (Ishikawa et al., 2009), and increased ER-mitochondria tethering enhances STING-dependent immune activation in fibroblasts upon dsDNA virus infection (Cook et al., 2022). Additionally, STING forms a stable complex with MAVS at MAM during RNA virus infection, regulating interferon signaling and antiviral responses (Zhong et al., 2008; Ishikawa et al., 2009). In line with this, STING also promotes the ER localization of NLRP3 in THP-1 and HeLa cells, a process amplified during viral infection (Wang et al., 2020).

MAM are Involved in the Immunometabolic Reprogramming of Microglia

Microglia exhibit metabolic flexibility, adapting to use various fuel sources (Nagy et al., 2018; Baik et al., 2019). Homeostatic microglia primarily rely on mitochondrial respiration via oxidative phosphorylation (OxPhos). However, stimulation elicits a plethora of metabolic changes that depend on the nature, concentration and duration of the stimulus, for further review (Paolicelli and Angiari, 2019; Lynch, 2020; Yang et al., 2021). These metabolic changes support essential functions like cytokine production and cytoskeleton remodeling, linking metabolism to microglial functions like morphology changes and phagocytosis (Yang et al., 2021). This section explores current understanding of microglial metabolic reprogramming under various conditions. However, much of the research has focused on traditional M1 and M2 phenotypes, highlighting the need for more comprehensive metabolomic studies to better understand how metabolism influences the transitions among the many microglial states.

The detection of PAMPs, such as LPS, triggers a shift in microglial metabolism from OxPhos to anabolic glycolysis even in the absence of hypoxia, a phenomenon known as the “Warburg effect" (Sabogal-Guáqueta et al., 2023). This process generates ATP more quickly -although less efficiently- than OxPhos and produces intermediates necessary for the synthesis of nucleotides, amino acids, and lipids. During this process, microglia increase glucose uptake and recruit glycolytic enzymes such as isoforms of hexokinase, phosphofructokinase or pyruvate kinase to the mitochondria (Wang et al., 2019; Sabogal-Guáqueta et al., 2023). Their enzymatic activation generates pyruvate, which can be further processed by lactate dehydrogenases into lactate, a hallmark of this metabolic shift (Sabogal-Guáqueta et al., 2023). Lactate production regenerates NAD + from NADH used in the previous reactions, supporting the continuous flow of glycolysis (Figure 3). Glycolysis also feeds into the pentose phosphate pathway, generating NADPH for biosynthetic reactions and maintaining redox balance for producing ROS needed for pathogen defense (Laroux et al., 2005).

However, prolonged activation or defects in this metabolic transition can lead to mitochondrial dysfunction, altering inflammation and phagocytosis (Baik et al., 2019). For example, blocking glucose uptake during PAMP challenges inhibits the glycolytic shift, suppressing phagocytosis and proinflammatory cytokine production (Wang et al., 2019), similarly to the effect of the glycolytic inhibitor 2-deoxy-D-glucose (Hu et al., 2020). Alternatively, microglia can also engage fatty acid oxidation in response to anti-inflammatory

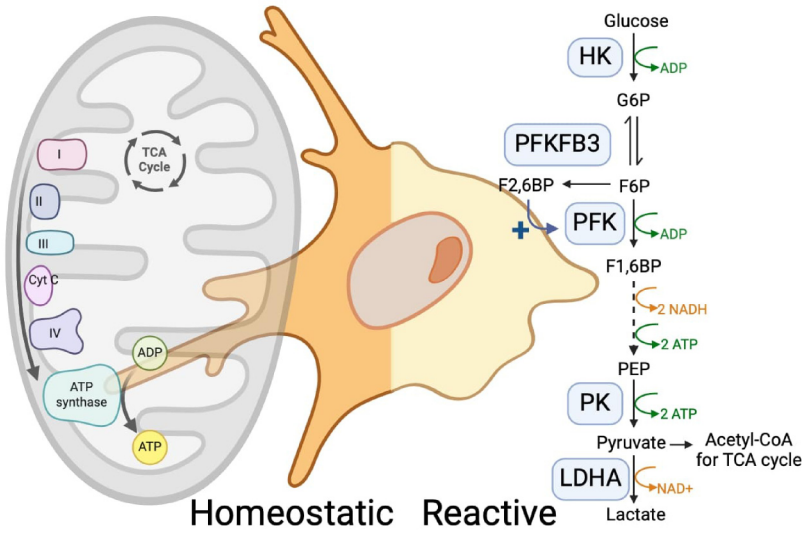

Figure 3. Summary of Energy Metabolism Pathways Involved in Microglial Reprogramming. This figure summarizes the metabolic switch of microglia in the transition from homeostatic towards reactive phenotype. Homeostatic microglia rely on the TCA cycle and oxidative phosphorylation as energetic supply while reactive microglia shift metabolism towards aerobic glycolysis. HKs, PFKs, and PKs are traditionally considered the rate-limiting steps of this metabolic pathway leading to quick production of ATP. PFKFBs are bifunctional enzymes that regulate glycolysis by controlling the levels of F2,6BP, which acts as an allosteric activator of PFKs, thereby enhancing glycolytic flux. The glycolytic end product, pyruvate, can either be processed into acetyl-CoA to enter the TCA cycle or converted into lactate to complete aerobic glycolysis. Specifically, the increased transcription and activity of HK1, 2, and 3, PFK1, PKM2 and PFKFB3 has been associated with the metabolic rewiring in microglia, though, differences between human and mouse microglia have been observed, adapted from Sabogal-Guáqueta et al. (2023). F1,6BP = fructose-1,6-bisphosphate; F2,6BP = fructose-2,6-bisphosphate; F6P = fructose-6-phosphate; G6P = glucose-6-phosphate; HK = hexokinases; LDHA = lactate dehydrogenase A; PEP = phosphoenol pyruvate; PFK = phosphofructokinases; PFKFB3 = 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PK = phosphoenolpyruvate kinases; TCA = tricarboxylic acid.

signals like IL-4 (Hu et al., 2020), in pathological conditions (Loppi et al., 2023), during ageing (Flowers et al., 2017), or following genetic disruption of glycolysis via inhibition of hexokinase 2 (Leng et al., 2022).

Hexokinase 2 (HK2), which catalyzes the first step of glycolysis, plays a pivotal role in microglia glycolytic shift. It is predominantly expressed in microglia within the CNS and significantly elevated in DAM (Hu et al., 2022). HK2 knockout impairs microglia's ability to engage glycolysis, reducing their motility, even in response to injury, and slowing their proliferation rate, likely by inducing cell cycle arrest (Hu et al., 2022). In contrast, other reports found that HK2-deficient microglia showed an enhanced pro-inflammatory and phagocytic response to PAMP challenge, effects associated with an increase in energy production via lipid metabolism (Leng et al., 2022). These studies suggest that energy provided by metabolic rewiring directly supports microglia surveillance and reactivity.

The interplay between mitochondria and MAM is crucial for regulating glucose metabolism and pyruvate oxidation. In macrophages, the dissociation of HK2 from VDAC facilitates ER-to-mitochondria Ca^{2+} transfer via IP3R, leading to VDAC oligomerization, mitochondrial DNA release into the cytosol, and NLRP3 inflammasome assembly and activation (Baik et al., 2023) (Figure 4). Similarly, in cancer cells, STING interacts with HK2 at the ER, suppressing its binding to VDAC1 and inhibiting HK enzymatic activity, thereby repressing aerobic glycolysis (Zhang et al., 2023). Not only do glycolytic enzymes like HK1/2 bind to VDAC at MAM, but several reports have also identified other rate-limiting glycolytic enzymes, such as isoforms of the pyruvate kinase (Lavik et al., 2022). Additionally, the ER-mitochondria tether MFN2 is critical for maintaining glucose homeostasis (Sebastián et al., 2012; Tubbs et al., 2014). Together, these findings suggest that glucose metabolism is regulated through the ER-mitochondria connection, though its relevance in microglia is yet to be fully explored.

Recent studies show that HK2 function is modulated by the mitochondrial translocator protein TSPO, commonly used as a Positron Emission Tomography probe for neuroinflammation (Zhang et al., 2021). TSPO facilitates mitochondrial cholesterol import (Liu et al., 2006) and its levels increase in microglia upon PAMP exposure (Yao et al., 2020). TSPO agonists enhance microglial phagocytosis and proliferation, while genetic ablation reduces LPS-triggered pro-inflammatory cytokine production and phagocytosis (Yao et al., 2020) though opposite results were noted in BV-2 cells (Bae et al., 2014). TSPO deficiency has been shown to impair mitochondrial function, shifting metabolism toward lipid synthesis and accumulation of lipid droplets (Fairley et al., 2023). Mechanistically, these effects are

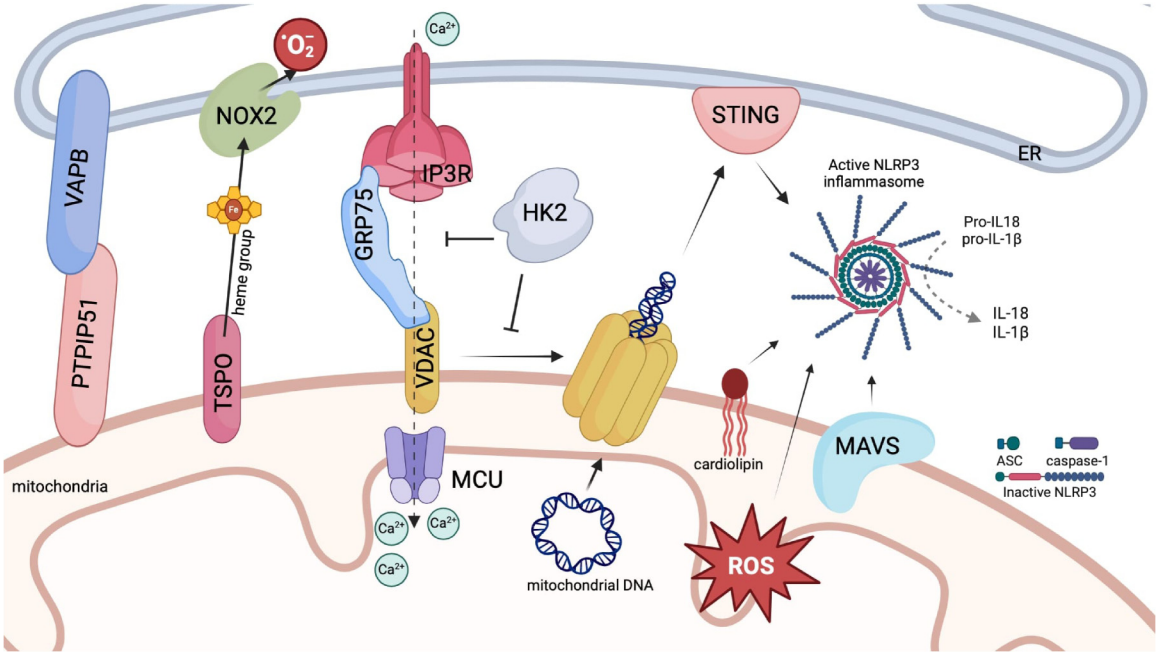

Figure 4. MAM as a signaling hub for inflammation. This figure summarizes the proteins that control inflammatory response in microglia and that are located at MAM, either in the ER (in blue) or mitochondria (in pink). It represents how (1) ER and mitochondria are stabilized by the action of different protein tethers, such as VAPB and PTPIP51. (2) The cholesterol translocator TSPO is also represented, which regulates heme group transport, for example, to NOX2 components (gp91 and p22). NOX2 generates superoxide in response to inflammatory insults which propagates the damage through oxidative stress. (3) For calcium signaling, the complex IP3R/GRP75/VDAC channels calcium from the ER into the mitochondrial matrix via the mitochondrial calcium uniporter MCU. (4) The dissociation of the enzyme HK2 from this complex triggers the oligomerization of the channel VDAC, leading to the release of mitochondrial DNA. This molecule is detected by the cGAS complex and triggers STING activation leading to interferon and proinflammatory signaling. (5) Finally, the NLRP3 inflammasome components are also strategically localized to mitochondria where different mitochondria-released danger signals, such as cardiolipin or ROS can trigger its assembly and activation. Active inflammasome amplifies inflammatory response by proteolytic maturation of several cytokines, including IL-1β and IL-18. MAVS, located in different compartments as discussed in the text, also activates the inflammasome. cGAS = GMP-AMP synthase; GRP75 = glucose related protein 75; HK2 = hexokinase 2; IP3R = Inositol-1,4,5-trisphosphate receptors; MAVS = mitochondrial antiviral signaling protein; MCU = mitochondrial calcium uniporter; NOX2 = NADPH oxidase 2; PTPIP51 = protein tyrosine phosphatase interacting protein 51; ROS = reactive oxygen species; VAPB = Vesicleassociated membrane protein-associated protein B; VDAC = voltage dependent anion channel.

linked to HK2 recruitment to mitochondria, with disruption of HK2-VDAC1 interaction restoring phagocytic activity and glycolysis in TSPO-deficient microglia (Fairley et al., 2023). Notably, a catalytically-defective HK2 mutant enhances phagocytosis, suggesting an immune signaling role independent of its metabolic function, likely via phosphorylation and degradation of the NF-kB repressor IKBα (Codocedo et al., 2024).

TSPO also interacts with the ER transmembrane components gp91 and p22 of the NADPH oxidase 2 (NOX2) complex in microglia (Loth et al., 2020), supporting the involvement of MAM (Figure 4). NOX2 produces superoxide in phagocytes to destroy microbial pathogens (Liu et al., 2024) and requires the transfer of a heme group, probably mediated by TSPO (Asagami et al., 1994; Taketani et al., 1995). Upon LPS stimulation, the association between TSPO and gp91/p22 decreases, causing their relocation to the plasma membrane, where they form an active NOX2 complex (Loth et al., 2020).

Furthermore, mitochondrial contacts with MAM influence mitochondrial respiration by affecting the assembly of respiratory complexes through changes in membrane lipid composition. For example, increased sphingolipid turnover and ceramide content in mitochondria reduce oxygen consumption and impair the assembly of respiratory supercomplexes (Pera et al., 2017). Similarly, cardiolipin, crucial for cristae structure and ATP synthase organization, is synthesized from phosphatidic acid imported from the ER/MAM, likely via the MAM-resident PTPIP51 (Yeo et al., 2021). Additionally, MAM modulates mitochondrial bioenergetics by affecting the availability of oxidative substrates. Dysfunction in MAM impairs the utilization of glucose-derived pyruvate and shifts substrate use from pyruvate to fatty acids (Larrea et al., 2022). These findings, although explored in non-immune cells, highlight the intricate link between mitochondrial function and its interaction with the ER at MAM domains, which could elucidate MAM's role in microglial immunometabolism.

This metabolic reprogramming associated with microglial activity is directly linked to pathology. This is especially relevant in the context of AD, where disease-associated mutations in *TREM2* (extensively reviewed below) have been demonstrated to block the microglial metabolic switch (Piers et al., 2020) and its loss of function is associated with metabolic compromise, including low production of ATP in microglia (Ulland et al., 2017). This metabolic compromise has also been demonstrated in a large-scale proteomic analysis from AD brains and cerebrospinal fluid which demonstrated changes in energy metabolism linked to glial cells (Johnson et al., 2020).

TREM2 and MAM: Regulators of Microglial Phenotypes Through Lipid Metabolism

TREM2 (triggering receptor expressed on myeloid cells 2) is a transmembrane surface receptor implicated in phagocytosis, proliferation and survival of myeloid cells and has also been demonstrated to regulate metabolism in microglia and macrophages (Pocock et al., 2024). Importantly, GWAS have identified TREM2 as a genetic factor for the development of AD (Guerreiro et al., 2013), specifically the loss-of-function mutation R47H significantly increases the risk of AD, at least in individuals with European ancestry. Other TREM2 coding variants have been associated with increased AD risk in African-Americans (Jin et al., 2015), although no association of TREM2 and increased AD risk has been found in Asian populations (Jiao et al., 2014; Miyashita et al., 2014; Yu et al., 2014). TREM2 binds to various lipids, particularly those with negatively charged moieties, such as phosphatidylcholine, PS and sphingomyelin (Wang et al., 2015). Ligand binding induces TREM2 phosphorylation, activating downstream signaling pathways through the recruitment of the adaptor protein DAP12. Phosphorylated DAP12 recruits and activates spleen tyrosine kinase (SYK) and phospholipase Cγ2, leading to increased intracellular calcium levels and activation of various signaling pathways (Pocock et al., 2024). Clinically, TREM2 variants are linked to a higher risk of neurodegenerative diseases, such as Alzheimer's disease, due to their impact on microglial responses. For instance, microglia derived from human induced pluripotent stem cells carrying *TREM2* R47H exhibit limited SYK signaling upon PS exposure (Cosker et al., 2021).

Importantly, TREM2 deficiency has been shown to reduce anabolic pathways and activate autophagy through AMPK (Ulland et al., 2017), suggesting that TREM2 may be regulating the transition to DAM by its role in controlling metabolism. Moreover, a recent interactome analysis revealed nearly half of TREM2 interacting protein partners are located at MAM (Kwak et al., 2023). Indeed, human microglial cells deficient in TREM2 or carrying the R47H mutation show ultrastructural alterations in contact sites and accumulation of lipid droplets (Kwak et al., 2023), probably via accumulation of cholesterol esters (Nugent et al., 2020).

Nevertheless, the precise mechanism by which TREM2 regulates MAM or cholesterol trafficking remains unclear. It has been described that elevated levels of the cholesterol transporter apolipoprotein E (ApoE) are a hallmark of DAM and ApoE has been shown to act downstream of TREM2 signaling to orchestrate the transcriptional change in neurodegenerative-associated microglia (Krasemann et al., 2017). Indeed, under oxygen-glucose deprivation (an *in vitro* model for ischemic stroke), reducing TREM2 levels in microglia decreases ApoE levels while upregulates the MAM-resident enzyme ACAT1 - responsible for cholesterol esterification - and decreases cholesterol efflux machinery (ABCA1, NECH1, NPC2) (Wei et al., 2024). These changes lead to higher levels of cholesterol and cholesterol esters, resulting in lipid droplet accumulation. Interestingly, a new microglial phenotype associated with the accumulation of these inclusions was described a few years ago and defined as lipid-droplet-accumulating microglia (LDAM) (Marschallinger et al., 2020). This phenotype seems to be common to ageing and neurodegeneration and shows defective phagocytosis and higher pro-inflammatory cytokine secretion (Marschallinger et al., 2020). However, lipidomic analysis revealed that the main component of the lipid droplets found in LDAM are glycerolipids, mainly triacylglycerides.

The inclusion of fatty acids into triacylglycerides requires the activity of long-chain acyl-coA synthetases (ACSLs), followed by the action of the MAM-located DGAT/SCD enzymes. Recently, it was found that transfer of unsaturated fatty acids from neurons was sufficient to promote LDAM emergence (Li et al., 2024) and chemical inhibition of ACSLs can prevent this transition. In fact, ACSL4 is one of the most extensively used MAM markers (Lewin et al., 2001), although the main player involved in triglyceride synthesis in LDAM was recently found to be ACSL1 (Haney et al., 2024). Interestingly, in hepatocytes, ACSL1 has been described to shuttle between mitochondria and the ER, engaging, respectively, fatty acid oxidation or fatty acid esterification to form triacylglycerides (Huh et al., 2020). Thus, either by cholesterol esters synthesis via ACAT1 or triacylglycerides formation by ACSL/DGAT/SCD, lipid droplet biogenesis is a process intrinsically linked to MAM, supporting the relevance of this ER subdomain on microglia biology.

Beyond lipid metabolism, TREM2 regulates calcium homeostasis and inflammatory responses. It suppresses NLRP3 inflammasome activation and its deficiency exacerbates inflammasome activity (Wang et al., 2022; Huang et al., 2024). Notably, human microglial cells harboring the R47H TREM2 variant exhibit disrupted NLRP3 inflammasome activation (Cosker et al., 2021), impaired motility, and phagocytosis, while being hyperresponsive to inflammatory stimuli. Additionally, in mouse brains transplanted with TREM2 R47H microglia, reduced synaptic density and upregulated complement cascade components suggest inappropriate synaptic pruning by mutant microglia (Penney et al., 2024).

Altogether, recent findings point to the interaction between TREM2 and MAM which might regulate several cellular functions, including lipid metabolism, calcium regulation, and inflammation in microglia. Nevertheless, more research is needed to fully understand the role of this interaction in mitochondrial activity.

The Emerging Role of MAM in Efferocytosis

Efferocytosis is a multi-step process comprising (i) recognition of the target ("find-me"), (ii) engulfment ("eat-me"), (iii) digestion ("digest-me") and (iv) elimination of the cargo ("pop-me") (Romero-Molina et al., 2022). Recognition involves "find-me" signals like fractalkine, sphingosine-1-phosphate, and ATP, which are detected by microglial receptors such as TREM2 and P2RY12 (Schilperoort et al., 2023) well-known to be associated with the homeostatic-DAM transition. Moreover, risk genes of AD (*APOE, TREM2, ABCA7, PLG2*) are crucial players of efficient efferocytosis, whereas in the case of PD, mutations in genes such as SNCA (coding for α-syn), GBA or LRRK2 have been associated with altered phagocytic capacity as extensively reviewed (Tremblay et al., 2019; Romero-Molina et al., 2022). During engulfment, apoptotic cells present "eat-me" signals, primarily phosphatidylserine (PS), which translocates to the cell surface during apoptosis. The oxidized form of the phospholipid phosphatidylethanolamine (PE), whose synthesis relies on MAM, also acts as an "eat-me" signal, activating TLR2 in macrophages during ferroptosis (Luo et al., 2021). Receptors such as CD36 and LRP1, key cholesterol transporters, play crucial roles in recognizing these signals. Engulfment involves actin polymerization and plasma membrane extension, enabling microglia to enclose debris. In the digestion phase, nascent phagosomes fuse with late endosomes and lysosomes to form phagolysosomes for degradation. Finally, excess cholesterol generated is eliminated in the "pop-me" step.

MAM play a crucial role in regulating lipid metabolism and calcium signaling during efferocytosis. In macrophages, exposure to apoptotic cells triggers mitochondrial fission via Drp1, which reduces mitochondrial-ER contact sites and increases cytosolic Ca^{2+} levels, facilitating vesicular trafficking and phagosome formation (Wang et al., 2017). Indeed, inhibiting the MCU impairs apoptotic cell clearance through efferocytosis (Wang et al., 2017). Additionally, MFN2, tethering ER and mitochondria, is involved in phagocytosis independent of mitochondrial fusion. Under pro-inflammatory conditions, macrophages overexpress MFN2, and its genetic ablation hinders the phagocytosis of apoptotic cells and pathogens (Tur et al., 2020). MFN1 ablation does not impact phagocytosis, and antioxidant treatment with N-acetylcysteine produces effects similar to MFN2, suggesting that mitochondrial ROS, rather than fusion, may be involved. Additionally, MFN2 appears to regulate the endolysosomal pathway, as MFN2-KO macrophages accumulate phagosomes, hindering pathogen degradation.

Lipid metabolism is critical for efferocytosis, facilitating membrane expansion, cytoskeletal reorganization, and phagolysosomal remodeling. LPS-challenged microglia exhibit changes in major lipid families, including sphingolipids, glycerophospholipids and triacylglycerides (Blank et al., 2022; Müller et al., 2023). Macrophages have high levels of phosphatidic acid in their plasma membranes, which may aid in membrane remodeling during phagocytosis (Bohdanowicz et al., 2013). Phagosome formation and maturation rely on lipid remodeling involving cholesterol, sphingolipids, and phospholipids, as reviewed in (Saharan and Kamat, 2023) and disruption of sphingolipid metabolism abolishes macrophage responses to PAMPs (Köberlin et al., 2015). Finally, ingesting apoptotic cells and myelin increases cholesterol levels in microglia [for details on cholesterol handling in microglia (Muñoz Herrera and Zivkovic, 2022), which can alter membrane lipid composition, including lysosomal membranes, thereby affecting their acidification, resulting in microglial dysfunction (Quick et al., 2023). To prevent toxicity, excess cholesterol is either esterified in lipid droplets or effluxed via proteins like ApoE or ABCA1. Thus, MAM are again involved, regulating the activity of these enzymes/transporters mediating efferocytosis.

Concluding Remarks and Future Perspectives

MAM are specialized contact sites between the ER and mitochondria that regulate crucial cellular processes. These include calcium transfer, which influences mitochondrial metabolism and energy production, and lipid exchange, essential for membrane synthesis. These platforms are becoming increasingly recognized as key regulators in microglial cells, where they manage energy demands during immune responses, control inflammation through the NLRP3 inflammasome, or participate in phagocytosis. Given the fact that these cellular pathways are disrupted in neurodegenerative diseases, there is increasing evidence demonstrating the role of MAM in controlling microglial activity. However, a microglia-specific map of the MAM proteome is still lacking, which would provide a comprehensive understanding of the MAM-resident players involved in immunometabolic regulation and their role in microglial phenotype transitions in both health and disease. Fully elucidating the role of MAM in microglial activity could open new therapeutic avenues for neuroinflammatory and neurodegenerative diseases through targeted modulation of MAM.

Abbreviations

ABCA1	ATP-binding cassette transporter A1
ACAT1	acyl-CoA:cholesterol acyltransferase 1
ACSLs	long-chain acyl-coA synthetases
AD	Alzheimer's disease

α-syn	alpha-synuclein
AMPK	5' adenosine monophosphate-activated protein kinase
ApoE	apolipoprotein E
ASC	apoptosis-associated speck-like protein
ATAD3	ATPase family AAA-domain-containing protein 3
ATP	adenosine triphosphate
cGAS	GMP-AMP synthase
CNS	central nervous system
CH25H	cholesterol hydroxylase
DAM	disease-associated microglia
DAMPs	damage-associated molecular patterns
DGAT	diacylglycerol acyltransferase
Drp1	dynamin-related protein 1
ER	endoplasmic reticulum
GRP75	glucose-regulated protein 75
GWAS	genome-wide association studies
HK	hexokinase
IP3R	Inositol-1,4,5-tris-phosphate receptors
LDAM	lipid-droplet-accumulating microglia
LPL	lipoprotein lipase
LPS	lipopolysaccharide
MAM	mitochondria-associated ER membranes
MAVS	mitochondrial antiviral signaling protein
MCU	mitochondrial calcium uniporter
MERC	mitochondria-ER contact site
MFN1,2	mitofusins 1 and 2
NOX2	NADPH oxidase 2
NLRP3	NOD-like receptor family protein 3
NF-κB	nuclear factor-κB
OMM	outer mitochondrial membrane
OxPhos	oxidative phosphorylation
PAMPs	pathogen-associated molecular patterns
PD	Parkinson's disease
PE	phosphatidylethanolamine
PRRs	pattern recognition receptors
PS	phosphatidylserine
PSD	phosphatidylserine decarboxylase
PSS	phosphatidylserine synthase
PTPIP51	protein tyrosine phosphatase interacting protein 51
RLRs	RIG-I-like receptors
ROS	reactive oxygen species
SERCA	sarco/endoplasmic reticulum Ca2+ adenosine triphosphatase
SPTLC1/2/3	serine palmitoyltransferase 1/2/3
SYK	spleen tyrosine kinase
TCA	tricarboxylic acid cycle
TLRs	Toll-like receptors
TNF-α	tumor necrosis factor α
TREM2	triggering receptor expressed on myeloid cells 2
TSPO	translocator protein
VDAC1	voltage dependent anion channel 1

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