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REVIEW

Lipid metabolism and neuroinflammation: What is the link?

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Lipid metabolism is central to host defense by supporting and modulating immune cell function. Immune signaling pathways control anabolic lipid processes to drive membrane synthesis and produce bioactive lipid mediators during activation. In turn, metabolic states profoundly influence immune signaling, particularly during the resolution of inflammation. Emerging evidence highlights a dynamic interplay between lipid metabolism and neuroinflammation. A striking example is the intrinsic lipoprotein system of the central nervous system, which undergoes profound changes during pathology, with lipoproteins serving not only in lipid transport but also as immune modulators and as contributors to disease tolerance. Importantly, major neurodegenerative diseases are genetically linked to disruptions in lipid metabolism. Deciphering this complex cross talk may provide opportunities for novel therapies targeting neuroinflammatory and neurodegenerative disorders.

Introduction

Inflammation plays a central role in nearly all neurological disorders, yet its definition requires clarification due to its context-dependent nature. Traditionally, inflammation is understood as an acute, protective response to harmful stimuli, such as infection or tissue injury (Medzhitov, 2008; Nathan, 2002). This acute immune response activates signaling pathways that recruit immune cells to the injury site, where they release mediators to increase vascular permeability and allow more immune effectors to enter. Subsequently, the response transitions to tissue repair and homeostasis, guided by anti-inflammatory signals, macrophages, and growth factors. In chronic disorders, however, inflammation typically lacks a resolution phase and instead persists as a continuum, from low-grade, tissue-resident immune activity to more intense responses involving infiltration by peripheral immune cells (Nathan and Ding, 2010). In the brain, this spectrum is often referred to broadly as neuroinflammation (Heneka et al., 2025; Paolicelli et al., 2022). While the underlying mechanisms of inflammation are relevant across organs, the central nervous system (CNS) possesses unique immunological features. As an immune-privileged organ, the CNS is to some extent shielded from peripheral immune surveillance. Immune cell entry is tightly regulated, resulting in a stronger reliance on CNS-intrinsic immune mechanisms (Betsholtz et al., 2024; Castellani et al., 2023; Engelhardt et al., 2017; Kim and Kipnis, 2025; Vara-Pérez and Movahedi, 2025). Furthermore, because of the limited regenerative capacity of the CNS, inflammatory responses must be finely tuned in both magnitude and duration to avoid collateral damage.

Recent studies have revealed consistent patterns of CNS-intrinsic immune activity across various neurological disorders. Glial cells, in particular, display robust and early responses to neural stress and damage. Among these, microglia, the long-lived, self-renewing innate immune cells of the CNS, are uniquely positioned to monitor and respond to changes in the CNS microenvironment. Functionally analogous to peripheral macrophages, microglia play crucial roles in tissue surveillance, phagocytosis, and immune modulation under both physiological and pathological conditions (Kettenmann et al., 2011; Lazarov et al., 2023; Prinz et al., 2019). Upon activation, they adopt a disease-associated microglia (DAM), a microglia-neurodegenerative phenotype, or an activated response phenotype (Keren-Shaul et al., 2017; Krasemann et al., 2017; Sala Frigerio et al., 2019), while astrocytes transition into a disease-associated astrocyte state (Habib et al., 2020). Similarly, oligodendrocytes can assume a disease-associated oligodendrocyte phenotype (Falcao et al., 2018; Kaya et al., 2022; Kenigsbuch et al., 2022; Kirby et al., 2019; Pandey et al., 2022; Zhou et al., 2020), activating damage-responsive molecular programs. Thus, cells like astrocytes and oligodendrocytes, not considered a cellular component of the CNS innate immune system, are also able to sense and respond to tissue dysfunction or damage. Together, these glial adaptations contribute to neuronal disease defense and tolerance, not only by providing resilience against injury and toxic insults but also by maintaining homeostasis

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during stress (Simons et al., 2023). One striking feature of disease-associated glial states is their strong link to lipid metabolic pathways. For instance, DAM show upregulation of genes involved in lipid processing, such as apolipoproteins (*Apoe*), lipases (*Lpl*), sterol-modifying enzymes (*Ch25h*), and sterol regulatory transcription factors (*Srebf2*). In disease-associated astrocyte, the most prominently upregulated genes include the apolipoproteins *Clu* and *Apoe*. In contrast, disease-associated oligodendrocytes (DAO) display marked downregulation of the cholesterol biosynthesis pathway. These patterns raise a key question: what drives the involvement of lipid metabolism across glial cell types in disease? Lipids are fundamental to cellular physiology, serving not only as structural components of biological membranes but also as signaling molecules and sources of metabolic energy (van Meer et al., 2008). Beyond these core functions, lipids are involved in cell communication, membrane trafficking, and the modulation of protein activity. In addition, when lipid homeostasis is disrupted, lipids can become cytotoxic. Lipid peroxidation, in particular, is a major trigger of ferroptosis, a regulated form of cell death marked by iron-dependent oxidative damage (Dixon and Olzmann, 2024). Thus, maintaining lipid balance is essential not only for normal cellular function but also for cell survival.

Given the diverse immune-related roles of glia, it is maybe not surprising that inflammatory activation triggers substantial reorganization of cellular processes, particularly those involving lipid metabolism. However, this relationship appears to be deeper than mere co-occurrence (Hotamisligil, 2017; Tall and Yvan-Charvet, 2015; Van den Bossche et al., 2017; Yan and Horng, 2020). This interplay can be explored from two complementary perspectives. From the immune-centric viewpoint, disease-associated glial cells actively modulate lipid metabolism to meet their functional demands for immune defense. For example, they may utilize lipids to synthesize immune mediators or shift the cell into a metabolic state favorable to specific immune responses. Conversely, from a metabolism-focused perspective, lipid metabolic pathways are crucial in regulating immune functions, ensuring that the metabolic state aligns with the immune response. In this review, we begin with a broad overview of lipid metabolism and inflammation, focusing on how sterol and fatty acid pathways intersect with immune signaling in macrophages. We then examine these interactions more specifically within the CNS, both in the context of acute and chronic injury. Particular attention is given to the roles of disease-associated glia and lipoprotein metabolism, highlighting how disruptions in lipid metabolism can drive maladaptive immune responses and contribute to disease progression.

Sterol metabolism and inflammation

Maintaining cholesterol levels within an optimal range is essential for the proper function of all mammalian cells. While excess cholesterol can be toxic, insufficient levels compromise membrane organization and integrity. To ensure cholesterol remains within a physiological range, its synthesis, uptake, storage, and efflux are tightly regulated by a homeostatic network composed of sensors, transcription factors, and downstream effector programs (Brown and Goldstein, 1997). The transcription of cholesterol biosynthetic enzymes is regulated by members of the basic helix-loop-helix-leucine zipper family of transcription factors, known as sterol regulatory element-binding proteins (SREBPs) (SREBP-1a, SREBP-1c, and SREBP-2) (Horton et al., 2002). Among these, SREBP-1a serves as an activator across all SREBP target genes, including those involved in the synthesis of cholesterol, fatty acids, and triglycerides. In contrast, SREBP-1c mainly drives the transcription of genes necessary for fatty acid synthesis, while SREBP-2 primarily promotes cholesterol biosynthesis. SREBPs are localized in the ER, where they form a complex with two other proteins, SREBP cleavage-activating protein and insulin-induced genes. This complex acts as a sterol-sensing unit that regulates the activity of SREBPs. Low sterol levels trigger their transport to the Golgi, where cleavage activates them to enter the nucleus and induce cholesterol biosynthesis genes. While sterol regulatory pathways operate in all mammalian cells, innate immune cells, including microglia in the CNS, face the distinctive challenge of integrating sterol homeostasis with immune signaling to align cholesterol levels with specific immune states (Spann and Glass, 2013). For example, immune activation triggers a proliferative response, requiring the upregulation of cholesterol biosynthesis. In macrophages, this upregulation is initiated when pattern recognition receptors (PRRs), such as TLRs, activate a myeloid differentiation primary response gene 88–dependent signaling cascade involving protein Kinase B/mammalian target of rapamycin (mTOR) and the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) (Hsieh et al., 2020). This cascade stimulates a broad increase in cholesterol production, primarily through activation of the SREBP transcriptional program (Fig. 1). Notably, NF-κB has been shown to directly activate the promoter of the gene encoding SREBP-1a, thereby promoting lipid biosynthesis during innate immune responses (Im et al., 2011). Beyond its role in lipid metabolism, SREBP-1a also upregulates *Nlrp1a*, which encodes a key component of the NLRP1 inflammasome, linking sterol metabolism to inflammasome activation (Im et al., 2011). In contrast, IFN signaling, along with PRRs that initiate IFN responses, such as TLR3-TIR-domain-containing adapter-inducing IFN-β signaling, suppresses cholesterol biosynthesis while promoting its storage as cholesterol esters (Hsieh et al., 2020). Despite this suppression, macrophages maintain their intracellular cholesterol levels in response to IFN signaling, possibly by enhancing cholesterol uptake or reducing its efflux. While the expression of most enzymes involved in cholesterol biosynthesis is downregulated by IFNs, a notable exception is the upregulation of cholesterol 25-hydroxylase (CH25H) (Cyster et al., 2014). This enzyme converts cholesterol into 25-hydroxycholesterol (25-HC), a metabolite with well-documented antiviral properties. 25-HC has been shown to alter plasma membrane lipid composition to block viral fusion and entry, inhibit viral replication, and redistribute cholesterol within internal membranes, collectively contributing to host defense against viral infection (Abrams et al., 2020; Liu et al., 2013). 25-HC also plays a role in diseases not caused by viral infections. In the CNS, microglia produce 25-HC in response to immune activation, and this metabolite has been implicated in modulating neuroinflammation (Odnoshivkina et al.,

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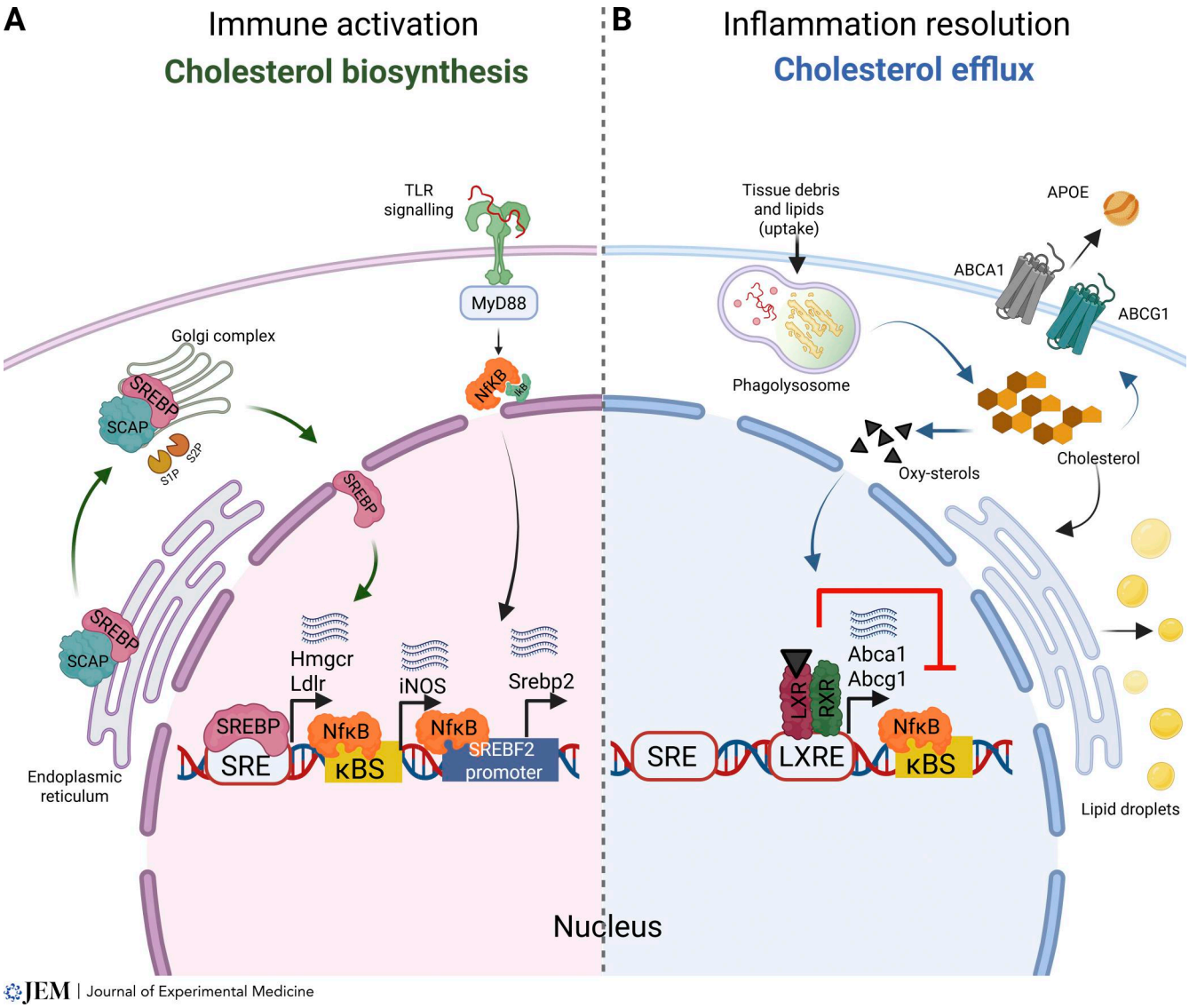

Figure 1. **Interplay between sterol metabolism and inflammation in myeloid cell activation and resolution. (A)** Upon exposure to pathogen-associated molecular patterns or DAMPs, TLR signaling activates the MyD88–NF-κB pathway, leading to the transcription of pro-inflammatory cytokines. NF-κB also binds to the *Srebf2* promoter, inducing transcription of SREBP2. After cleavage and maturation through the ER–Golgi pathway, active SREBP2 translocates to the nucleus and binds sterol regulatory elements (SREs), promoting the expression of genes involved in cholesterol biosynthesis (e.g., *Hmgcr* and *Ldlr*), which supports membrane remodelling and cell proliferation. **(B)** Following uptake of lipid-rich debris (e.g., myelin) via phagocytosis, lysosomal processing releases free cholesterol and fatty acids. Excess free cholesterol can be converted to oxysterols, which serve as endogenous ligands for LXRs. LXR activation promotes reverse cholesterol transport by upregulating cholesterol efflux genes (e.g., *ABCA1* and *ABCG1*), leading to lipidation of ApoE particles. Additionally, free cholesterol may be re-esterified in the ER and stored as lipid droplets. LXR activation also transrepresses NF-κB target genes and inhibits SREBP processing, thereby contributing to both inflammation resolution and immunometabolic reprogramming. MyD88, myeloid differentiation primary response gene 88; ABCG1, ATP-binding cassette sub-family G member 1; SCAP, SREBP cleavage-activating protein; κBS, κ-B sites.

2022). For example, deletion of CH25H, which reduces 25-HC levels, leads to markedly decreased age-related neurodegeneration and neuroinflammation in models of tauopathies (Toral-Rios et al., 2024). Thus, specific immune signaling pathways can regulate sterol biosynthesis to modulate cholesterol levels in response to immune activation or even generate sterol derivatives with immunological functions. There are also conditions in which lipid metabolic pathways must take control in shaping immune responses. One such condition arises in the resolution phase of inflammation, when macrophages have engulfed tissue debris and accumulate significant amounts of intracellular cholesterol. Since cells lack a dedicated catabolic pathway for cholesterol degradation, excess cholesterol must be either esterified and stored in cytosolic lipid droplets or exported via sterol transporters (e.g., ATP-binding cassette transporter A1 [ABCA1] and ATP-binding cassette sub-family G member 1) and apolipoproteins (e.g., apolipoprotein E [APOE]) (Groenen et al., 2021; Luo et al., 2020; Song et al., 2021). This cholesterol efflux is mainly regulated at the transcriptional level by liver X receptors (LXRs) (LXRα and LXRβ), which bind to LXR response elements

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located near their target genes as heterodimers with retinoid X receptors (RXRs) (Evans and Mangelsdorf, 2014; Hong and Tontonoz, 2014). In the absence of activating ligands, these LXR–RXR complexes recruit corepressor proteins that actively inhibit transcription. When activating ligands are present, the corepressors are replaced by coactivator complexes, resulting in the initiation of gene transcription. These ligands include 24(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S),25-epoxycholesterol, and 27-hydroxycholesterol. Remarkably, in cholesterol-laden macrophage foam cells, desmosterol emerges as the predominant endogenous LXR agonist (Muse et al., 2018; Spann et al., 2012). The accumulation of desmosterol occurs by the downregulation or inhibition of 24-dehydrocholesterol reductase, the enzyme responsible for converting desmosterol to cholesterol. In the CNS, microglia rely on a similar mechanism to regulate cholesterol efflux (Berghoff et al., 2021). In addition to promoting the expression of genes that regulate cholesterol and fatty acid homeostasis, LXRs also act by suppressing inflammation (Spann and Glass, 2013) (Fig. 1). They do this by inducing genes that encode anti-inflammatory proteins, such as those involved in the synthesis of anti-inflammatory polyunsaturated fatty acids, and by inhibiting genes controlled by pro-inflammatory transcription factors like NF-κB and activator protein-1 (AP-1) (Glass and Saijo, 2010; Schulman, 2017). Why active cholesterol efflux is associated with anti-inflammatory responses is unclear, but it is likely that cholesterol overload creates a cell state where cellular metabolic functions are prioritized and consequently pro-inflammatory responses must be downregulated.

Fatty acid metabolism and inflammation

Fatty acid metabolism changes dramatically during the immune response following tissue injury. Inflammatory macrophages, including microglia, undergo a metabolic reprogramming characterized by a shift toward aerobic glycolysis and impaired oxidative phosphorylation (OXPHOS) (Galván-Peña and O'Neill, 2014; Pearce and Pearce, 2013). At first glance, the shift to aerobic glycolysis appears counterintuitive, as it is both inefficient and seemingly unwarranted given the presence of sufficient oxygen. However, this metabolic switch enables the production of a larger quantity of intermediates needed for anabolic growth (Vander Heiden et al., 2009). Upon activation, these cells increase glucose uptake, enhancing glycolytic flux. The resulting accumulation of glycolytic intermediates fuels the pentose phosphate pathway, which generates NADPH, crucial for fatty acid synthesis and the production of ROS. This metabolic shift also leads to elevated lactate production and increased influx of glucose-derived pyruvate into the tricarboxylic acid (TCA) cycle (Jha et al., 2015). However, the TCA cycle becomes disrupted, causing citrate to accumulate (Wculek et al., 2022). Citrate is subsequently converted into acetyl-coenzyme A (acetyl-CoA), a key precursor for the synthesis of fatty acids. Consistent with this, ATP-citrate lyase, the enzyme that converts citrate to acetyl-CoA, is upregulated in activated macrophages (Zhao et al., 2016). Inhibition or silencing of ATP-citrate lyase reduces the expression of inflammatory mediators such as nitric oxide and ROS. In addition to fueling lipid biosynthesis, acetyl-CoA also supports de novo histone acetylation, thereby promoting the expression of inflammatory genes (Dennis et al., 2010; Lauterbach et al., 2019; Wellen et al., 2009) (Fig. 2). In inflammatory macrophages, enhanced fatty acid synthesis is accompanied by widespread alterations in lipid metabolism, notably the accumulation of triglycerides and cholesterol esters within lipid droplets (Castoldi et al., 2020; Dennis et al., 2010; Hsieh et al., 2020; Huang et al., 2014). Lipid droplets serve as key energy storage organelles and play a protective role by sequestering potentially toxic lipids (Farese and Walther, 2025; Ralhan et al., 2021). However, excessive lipid droplet accumulation can induce lipotoxicity, especially in microglia under neuroinflammatory conditions. In the aging brain, microglia that accumulate lipid droplets adopt a dysfunctional, pro-inflammatory phenotype characterized by impaired phagocytosis, elevated ROS production, and increased secretion of pro-inflammatory cytokines (Marschallinger et al., 2020a). Additionally, they serve as innate immune hub for various IFN-regulated proteins and provide a functional platform for the production of inflammatory lipid mediators (Bosch et al., 2020; Melo and Weller, 2016). Thus, reprogramming lipid biosynthesis is crucial for supporting de novo lipogenesis during inflammatory responses and for the production of inflammatory mediators using enzymes such as lipoxygenases and cyclooxygenases to generate prostaglandins, leukotrienes, and eicosanoids. While the mechanisms driving this reprogramming are not yet fully understood, activation of PRRs, such as TLRs, has been implicated. One pathway involves myeloid differentiation primary response gene 88–dependent activation of TLRs and relies on the transcriptional activity of NRF2 and SREBP1c (Hsieh et al., 2020; Oishi et al., 2017). Another pathway operates through TIR-domain–containing adapter-inducing IFN-β–dependent signaling and IFN responses (Hsieh et al., 2020). Additionally, the transcription factor NF-κB has been shown to play a role by directly binding to the response element in the promoter region of SREBP-1a, thereby contributing to its regulation (Im et al., 2011).

When macrophages switch to the resolution phase, they undergo a profound lipid metabolic switch that controls inflammatory responses. During this phase, macrophages that have engulfed tissue debris exhibit an intact TCA cycle and enhanced OXPHOS, supporting sustained energy production. Fatty acids, derived from the hydrolysis of ingested lipids within lysosomes, are released into the cytosol to fuel this metabolic activity. Adenosine monophosphate (AMP)–activated protein kinase α 1 subunit, a key metabolic regulator that promotes OXPHOS, becomes rapidly activated in macrophages following tissue injury and plays a crucial role in establishing their anti-inflammatory phenotype (Mounier et al., 2013; Sag et al., 2008). Additionally, peroxisome proliferator–activated receptors (PPARs), particularly PPARγ, play a pivotal role in regulating lipid metabolism during the resolution phase of inflammation (Bensinger and Tontonoz, 2008; Chinetti et al., 2001). These nuclear receptors function as ligand-activated transcription factors, responding to a variety of endogenous lipid-derived molecules, including non-esterified fatty acids, eicosanoids, and prostaglandin derivatives (Chawla et al., 2001). Activation of PPARγ by these ligands promotes mitochondrial biogenesis and

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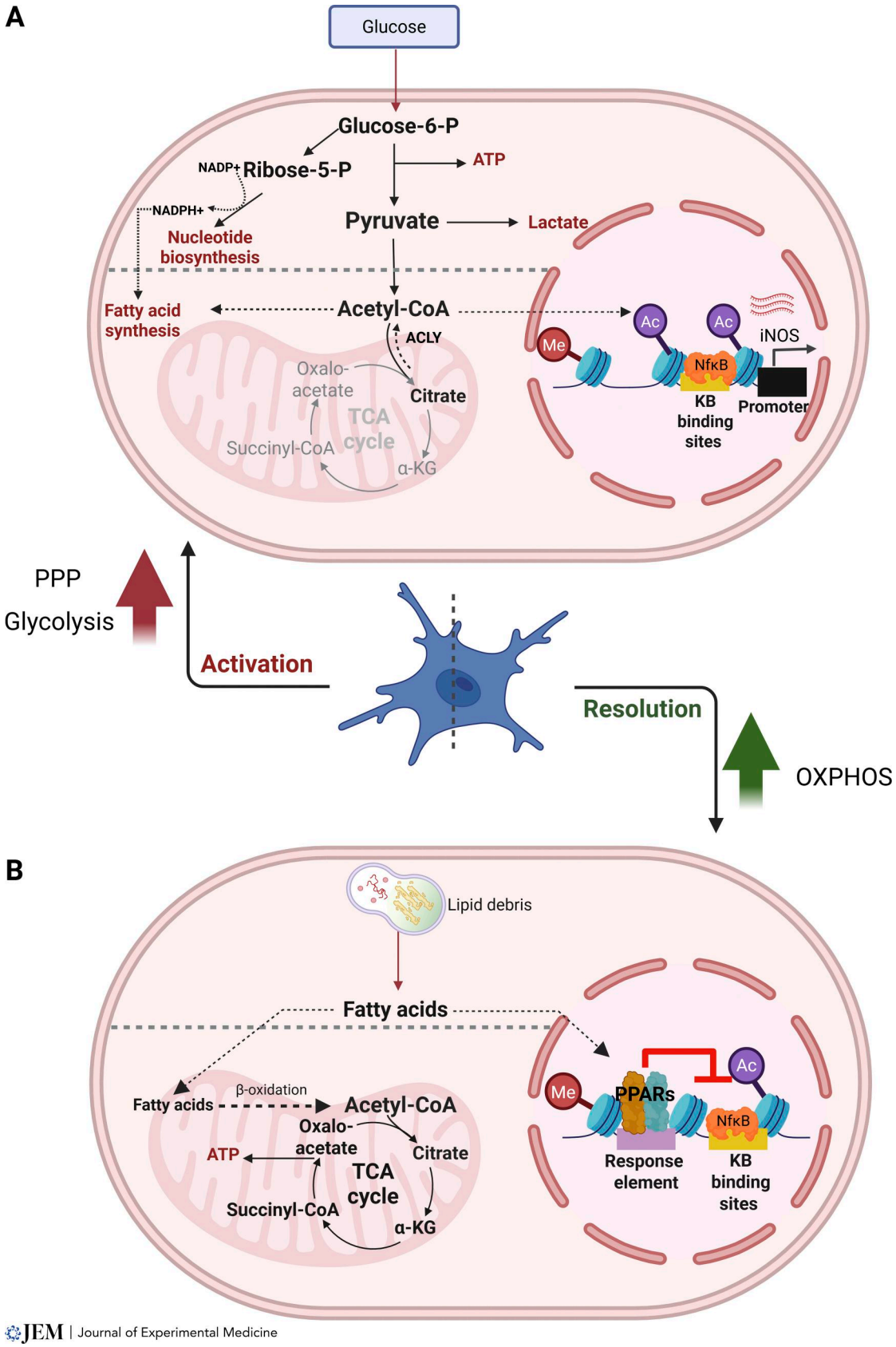

Figure 2. **Metabolic reprogramming of myeloid cells during activation and inflammation resolution. (A)** Upon activation (e.g., by pathogens or DAMPs), microglia increase glucose uptake, which is metabolized through glycolysis and the pentose phosphate pathway (PPP). Glycolysis generates pyruvate and acetyl-CoA, while the PPP produces NADPH necessary for fatty acid synthesis and ROS generation. Inflammatory stimuli block the TCA cycle, diverting citrate to

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the cytosol, where ATP-citrate lyase (ACLY) converts it into acetyl-CoA. This cytosolic acetyl-CoA supports histone acetylation in the nucleus, opening chromatin and facilitating NF-κB binding, thereby promoting transcription of pro-inflammatory genes. **(B)** In the resolution state, lipid uptake (e.g., from extracellular debris) leads to intracellular fatty acid generation. These fatty acids undergo β-oxidation in mitochondria, producing acetyl-CoA that feeds into the TCA cycle, fueling OXPHOS and ATP production. Fatty acids also serve as ligands for PPARs, which inhibit NF-κB–mediated transcription, thus promoting anti-inflammatory signaling and immunometabolic homeostasis. Me, Methylation; Ac, Acetylation; a-KG, a-ketoglutarate; iNOS, nitric oxide synthase.

enhances oxidative metabolism, thereby supporting energy production and cellular repair. Concurrently, PPARγ suppresses pro-inflammatory pathways by inhibiting key transcription factors such as NF-κB and AP-1, leading to reduced cytokine production and attenuation of inflammatory signaling (Glass and Ogawa, 2006). Additionally, PPARβ/δ has been shown to attenuate macrophage-mediated inflammation, playing a key role in the resolution of inflammation and promoting the formation of benign foam cells (Bogie et al., 2013; Mukundan et al., 2009). As metabolic sensors and regulators, PPARs integrate lipid signaling with immune responses, making them essential mediators in the shift from active inflammation to resolution and the restoration of tissue homeostasis (Fig. 2). This transition is further marked by a shift in the lipid mediator profile, from pro-inflammatory lipid species, such as arachidonic acid–derived prostaglandins and leukotrienes, to pro-resolving mediators derived from omega-3 fatty acids, including eicosapentaenoic acid and docosahexaenoic acid. These and other specialized pro-resolving lipid mediators (SPMs), such as resolvins, protectins, and maresins, actively facilitate the termination of inflammation and promote tissue repair (Serhan et al., 2008). The production of SPMs is tightly regulated and temporally coordinated with transcriptional changes of genes encoding enzymes involved in their biosynthesis. Notably, SREBP1 plays a role in driving fatty acid synthesis necessary for SPM generation. While phospholipase-mediated cleavage from membrane phospholipids is the immediate step for releasing these polyunsaturated fatty acid (PUFA) precursors, SREBP1-driven synthesis is crucial for maintaining the available membrane substrate pool (Dennis et al., 2011; Serhan et al., 2008). In macrophages deficient in *Srebf1*, impaired PUFA synthesis reduces this substrate availability for phospholipase-mediated release, resulting in a failure to produce key anti-inflammatory lipid mediators (Oishi et al., 2017). This deficiency correlates with sustained NF-κB activation, impaired resolution signaling, and a prolonged inflammatory phenotype. Thus, fatty acid metabolism serves as a central hub that integrates immune signaling, energy production, and epigenetic regulation during both the initiation and resolution phases of inflammation.

Taken together, these general insights allow us to broadly categorize lipid immunometabolism in innate immune cells into two distinct metabolic states. In the initial phase, phagocytes adopt an anabolic metabolic program that supports protective immune functions, promotes cell proliferation, and facilitates the synthesis of lipid mediators critical for host defense. This anabolic state is sustained through the activation of the phosphoinositide 3-kinase–protein Kinase B–mTOR signaling axis and hypoxia-inducible factor 1 α–driven metabolic pathways, together with the suppression of AMP-activated protein kinase α 1 subunit, a key regulator of catabolic metabolism (Wang et al., 2019). Over time, a metabolic transition occurs, marked by a shift toward catabolism, enabling the degradation of internalized material and the resolution of the inflammatory response.

Lipid metabolism in acute CNS injury and inflammation

While the general conceptual framework linking lipid metabolism to innate immune responses is broadly applicable across organs, the CNS possesses several unique features that must be considered. Immune-mediated pathology in the CNS can have particularly severe consequences, requiring precise regulation of immune responses. Both the magnitude and duration of these responses must be tightly controlled to minimize collateral damage. One major regulatory mechanism is the presence of anatomical borders, such as the blood–brain barrier (BBB), which restrict the infiltration of peripheral immune cells (Betsholtz et al., 2024; Castellani et al., 2023; Engelhardt et al., 2017; Kim and Kipnis, 2025; Vara-Pérez and Movahedi, 2025). Consequently, the CNS relies heavily on intrinsic immune mechanisms to respond to injury. Given the need to prevent immune-mediated secondary damage, the brain has evolved robust adaptive strategies to cope with persistent perturbations. Among those are neuronal resilience and resistance factors and disease-associated glial states (Simons et al., 2023). In the context of lipid metabolism, the CNS again displays distinct characteristics. The brain is largely autonomous in its lipid regulation, as the BBB prevents the entry of peripheral lipoproteins (Berghoff et al., 2022; Dietschy and Turley, 2004; Schmitt et al., 2015; Vanherle et al., 2025). Instead, most lipids, including cholesterol, are synthesized locally and redistributed among cells via in situ–produced lipoproteins. To facilitate the entry of essential lipid species, such as docosahexaenoic acid, brain endothelial cells express specific transporters, such as major facilitator superfamily domain-containing protein 2a (Bazinet and Layé, 2014; Nguyen et al., 2014). One reason for the separation from systemic lipid metabolism may be that neurons rely on glucose as their primary energy source. Another reason is that this separation helps protect brain cells from lipid overload and the buildup of lipid droplets, which can lead to toxicity and, respectively, harmful tissue expansion. Despite these protective strategies, the brain remains the second most lipid-rich organ after adipose tissue, with a large fraction of its lipid content found in myelin, and with cell type– and brain region–specific lipid profiles (Fitzner et al., 2020; Osetrova et al., 2024).

When examining the interplay between lipid metabolism and neuroinflammation, it is essential to distinguish between acute and chronic forms of CNS injury. In the following section, we will begin by focusing on the responses triggered by acute CNS damage. Acute damage to the CNS, regardless of its cause, requires a tightly regulated inflammatory response tailored to the

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specific nature of the injury. All forms of CNS injury result in the release of tissue debris, which is typically rich in lipids. In cases involving demyelinating lesions, particularly large quantities of lipid-rich myelin debris are produced (Franklin and Ffrench-Constant, 2017; Franklin and Simons, 2022). To detect lipids, microglia are equipped with a diverse array of sensing mechanisms. Among these are PRRs, which detect endogenous molecules released from damaged or dying cells, known in this context as damage-associated molecular patterns (DAMPs) (Hickman et al., 2013; Prinz and Priller, 2014; Wolf et al., 2017; Zengeler and Lukens, 2024). These PRRs include families of transmembrane proteins, such as TLRs and C-type lectin receptors, located on the cell surface or within the endosomal system. DAMPs encompass a variety of molecules, including proteins, nucleic acids, and lipids. A shared feature of many of these signals is their hydrophobic character, and the sudden exposure of such hydrophobic domains is thought to act as an indicator of tissue damage (Seong and Matzinger, 2004). Upon recognition of these danger signals, PRRs such as TLRs trigger inflammatory signaling cascades. This includes the activation of NF-κB, which induces an anabolic lipid metabolic program essential for cell proliferation and the synthesis of lipid-derived immune mediators, for example, in microglia following demyelinating injury (Cunha et al., 2020). An additional system for sensing tissue damage in the CNS involves the triggering receptor expressed on myeloid cells 2 (TREM2) (Deczkowska et al., 2020; Lewcock et al., 2020; Morini et al., 2025; Ulland and Colonna, 2018). TREM2 interacts with anionic lipids, such as phospholipids and sulfated lipids, released by dying cells, including those present in apoptotic bodies and myelin debris (Wang et al., 2015). It also binds to lipoprotein particles, including high-density lipoproteins containing apolipoproteins such as APOE or apolipoprotein J (APOJ)/clusterin (CLU) (Atagi et al., 2015; Bailey et al., 2015; Yeh et al., 2016). Activation of TREM2 leads to phosphorylation of spleen tyrosine kinase via the adaptor protein DNAX-activating protein (DAP12), initiating an inflammatory signaling cascade that culminates in the DAM response, thereby enhancing phagocytosis and lipid metabolism pathways (Lanier, 2009). Moreover, TREM2 supports basal mTOR signaling, promoting anabolic processes required for microglial growth and proliferation (Ulland et al., 2017). Despite the similarities in damage sensing, TREM2 and TLR pathways exhibit functional differences. TREM2-mediated responses tend to be cell autonomous, whereas TLR activation promotes communication with the peripheral immune system, recruiting neutrophils and monocyte-derived macrophages to the injury site. This feed-forward inflammatory response is critical for building an effective immune defense. Thus, TLRs and TREM2 collectively contribute to the detection and response to CNS injury. However, the precise temporal and spatial coordination between these systems remains unclear. Interestingly, TLR activation suppresses TREM2 expression (and vice versa), suggesting an antagonistic relationship (Ito and Hamerman, 2012; Liu et al., 2020). It is possible that these pathways operate sequentially, with TLRs initiating the response and TREM2 sustaining it (Fig. 3). Other receptors, such as Tyro3, Axl, and MerTK are key to recognizing phosphatidylserine on the debris, facilitating the clearance process (Lemke and Rothlin, 2008; Safaiyan et al., 2021). The binding of these "eat-me" signals to bridging molecules like Gas6 and protein S helps microglia/macrophages to initiate phagocytosis. Multiple scavenger and complement receptors are also involved in debris clearance after opsonization (Grajchen et al., 2020; Husemann et al., 2002). Following the initial pro-inflammatory, anabolic phase, microglia transition to a catabolic, anti-inflammatory state. Due to the lipid-rich nature of phagocytosed tissue debris, especially from myelin, this phase requires the activation of transcriptional programs governing lipid metabolism (Bogie et al., 2012; Cantuti-Castelvetri et al., 2018; Huang et al., 2011; Mailleux et al., 2018). Key nuclear receptors involved in this process include PPARs, LXRs, and RXRs, which regulate genes responsible for cholesterol efflux, lipolysis, lipid storage, fatty acid transport, and β-oxidation (Evans and Mangelsdorf, 2014). Cholesterol metabolism is particularly critical because the brain lacks a dedicated pathway for cholesterol degradation. As a result, excess cholesterol must be tightly regulated to prevent cytotoxicity. One key protective mechanism is its efflux from cells via the APOE carrier. Another essential process involves the enzyme sterol O-acyltransferase-1/acyl-CoA: cholesterol acyltransferase, which detoxifies free cholesterol by converting it into inert cholesterol esters that are stored in lipid droplets. Following demyelinating injury, this esterification pathway becomes especially important for myeloid cells, which must manage the cholesterol overload resulting from the phagocytosis of myelin debris. When this buffering capacity is compromised, phagocytes fail to clear myelin debris from demyelinated lesions, thereby impairing tissue regeneration (Gouna et al., 2021). This dysfunction is evident in TREM2-deficient mice (Filipello et al., 2023; Gouna et al., 2021; Nugent et al., 2019). Although their phagocytes can take up myelin debris, they fail to activate the metabolic pathways required to process the excess cholesterol. As a result, free cholesterol accumulates, causing cellular toxicity, initiating cholesterol-induced ER stress response, and impeding remyelination (Bosch-Queralt et al., 2021; Cantoni et al., 2015; Gouna et al., 2021; Poliani et al., 2015). Such integrated stress response–activated microglia can have detrimental effects by secreting toxic long-chain lipids (Flury et al., 2025).

The formation of lipid droplets and increased cholesterol efflux are protective responses regulated by nuclear receptors such as PPAR and LXR/RXR, which also contribute to anti-inflammatory signaling. Under optimal conditions, the inflammatory and metabolic response of microglia is biphasic and self-resolving (Miron et al., 2013). As foam cells efficiently clear the debris and lipid burden, microglia shift toward a regenerative phenotype that supports tissue repair. An interesting aspect is that some of the pro-inflammatory microglia appear to die by necroptosis, followed by repopulation to a regenerative state (Lloyd et al., 2019). In this regenerative phase, surrounding nonimmune cells engage in anabolic processes, utilizing recycled materials from phagocytosed debris or newly synthesized components to repair damaged tissue. This supportive function by astrocytes is controlled by the suppression of the NRF2 pathway, accompanied by an increase in cholesterol biosynthesis and export in astrocytes (Molina-Gonzalez et al., 2023).

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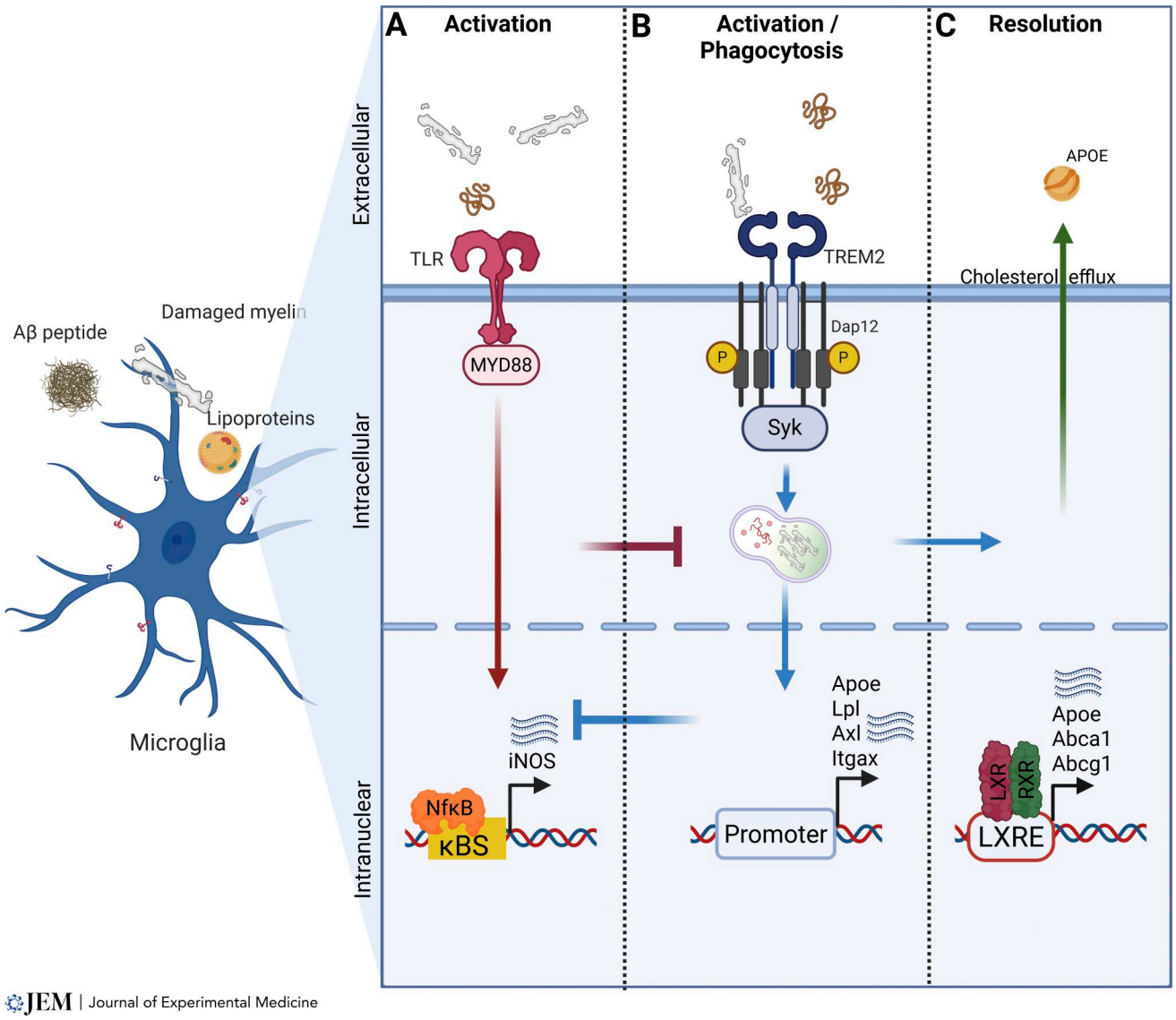

Figure 3. **TLR–TREM2-LXR signaling coordinate inflammatory activation and resolution in myeloid cells. (A)** In the pro-inflammatory state, pathogen-associated molecular patterns or DAMPs activate TLR signaling via the MyD88–NF-κB axis, inducing transcription of pro-inflammatory cytokines. This state suppresses TREM2-mediated activation/phagocytosis. **(B)** Microglia engage TREM2–DAP12–SYK signaling upon sensing lipid-rich debris. This promotes phagocytosis, lipid processing in lysosomes, transcription of genes such as *Apoe*, *Lpl*, *Axl*, and *Itgax*, and generation of oxysterols, which activate LXR. **(C)** LXR activation promotes cholesterol efflux, inhibits NF-κB, and supports inflammation resolution. This pathway enables a transition to a reparative phenotype, maintaining TREM2 function and suppressing further inflammatory activation. SYK, spleen tyrosine kinase; MyD88, myeloid differentiation primary response gene 88.

In certain conditions, the resolution phase of inflammation is impaired, allowing inflammation to persist and become chronic (Franklin and Simons, 2022; Nathan and Ding, 2010). One such condition involves the failure to effectively clear and resolve lipids (Berghoff et al., 2021; Cantuti-Castelvetri et al., 2018). For example, aging impairs the ability of microglia to efficiently clear damaged myelin debris, a critical step required for effective remyelination (Huang et al., 2011; Kotter et al., 2006; Lampron et al., 2015). Moreover, increased oxidative stress in lesions can lead to the formation of oxidized phosphatidylcholines, which may drive neurodegeneration if not efficiently cleared by microglia (Dong et al., 2021). In aged microglia, internalized myelin is associated with increased lipid droplet accumulation and increased production of pro-inflammatory molecules (Arbaizar-Rovirosa et al., 2023; Cantuti-Castelvetri et al., 2018). These cells also show a diminished capacity to recycle cholesterol-rich myelin debris, accompanied by reduced activation of LXR/RXR pathway, leading to cholesterol/cholesterol-ester buildup within lysosomes and lipid droplets (Cantuti-Castelvetri et al., 2018). This accumulation can activate the NLRP3 inflammasome, further hindering remyelination. Therapeutically restoring this lipid clearance pathway has been shown to enhance debris removal, suggesting a mechanistic link between lipid metabolism, resolution of innate inflammation, and tissue repair. For example, an apolipoprotein A-I mimetic peptide, which promote activity of the lipid efflux transporter ABCA1, enhances

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remyelination (Vanherle et al., 2022). Although the precise drivers of defective microglial lipid metabolism remain unclear, emerging evidence implicates reversible epigenetic changes, potentially targetable via innate immune training (Tiwari et al., 2024). Moreover, microglia and macrophages laden with myelin-derived lipids exhibit impaired lipid droplet degradation through lipophagy and lipolysis (Haidar et al., 2022). The resulting intracellular lipid buildup increases the expression of fatty acid desaturation and elongation enzymes, particularly stearoyl-CoA desaturase-1 and elongation of very long chain fatty acids protein 6, leading to the production of fatty acids that destabilize ABCA1 and impair lipid loading onto lipoproteins (Bogie et al., 2020; Garcia Corrales et al., 2023). This dysregulated lipid metabolism promotes a pro-inflammatory microglial and macrophage phenotype, ultimately disrupting oligodendrocyte progenitor cell differentiation and impairing remyelination.

In addition, inflammatory signals may interfere with the resolution phase of the immune response, leading to retention of lipids in microglia. One may encounter such a condition in chronic active multiple sclerosis (MS) lesions, which are characterized by a demyelinated core surrounded by a rim of chronically activated microglia (Absinta et al., 2021; Alsema et al., 2024; Klotz et al., 2025; Lerma-Martin et al., 2024). Longitudinal imaging using high-resolution, ultrahigh-field magnetic resonance imaging has revealed that such chronic active lesions can remain inflamed for years and, in some cases, even expand over time. A study combining magnetic resonance imaging with single-nucleus RNA sequencing identified the transcriptional profile of cells at the edge of chronic active lesions. This study confirmed that the inflammatory front is primarily composed of reactive microglia, termed microglia inflamed in MS (MIMS) (Absinta et al., 2021). One particular cluster, named MIMS-foamy, was distinguished by an enrichment of genes involved in lipid metabolism, specifically those associated with foam cells and lipid storage, despite showing signs of immune activation. These findings suggest that the inflammatory process, once established and sequestered behind a sealed BBB, may perpetuate microglial reactivity at the lesion edge in progressive MS. The lipid-associated gene signature in the MIMS-foamy cluster raises the possibility that immune activation impairs lipid clearance, preventing these microglia from transitioning into a catabolic, inflammation-resolving state.

The link between chronic CNS injury, impaired lipid metabolism, and non-resolving inflammation

Much less is known about the immune response that develops in the context of chronic CNS pathology compared with acute injury. A defining characteristic of chronic CNS pathology is its persistence; consequently, the immune system is unable to fully eliminate the underlying cause. This raises a crucial question: how does the immune system manage such a sustained threat while minimizing harm to the brain? The immune response must strike a careful balance between controlling pathology and limiting collateral damage. If the response is too strong, immune-mediated injury may exacerbate neuronal loss. If it is too weak, pathological processes may progress unchecked. In contrast, tissues like the intestine, which contain highly proliferative cells and robust regenerative mechanisms, can tolerate greater immune-mediated damage and therefore mount more aggressive immune responses. Thus, the strength and progression of the immune response must be carefully calibrated in the CNS. Typically, the initial immune response is subtle, aimed at minimizing potential damage. If this proves insufficient, a more robust response may follow, which may be more effective at controlling pathology but comes with an increased risk of tissue injury. This graded immune response in the CNS follows a hierarchical structure.

Microglia are the first responders, initiating a stereotyped tissue injury program in response to damage (Fumagalli et al., 2025; Hammond et al., 2019). This is followed by the transformation of astrocytes and oligodendrocytes into disease-associated states (Castelo-Branco et al., 2024; Kedia and Simons, 2025; Linnerbauer et al., 2020). If this CNS-intrinsic glial response is inadequate, peripheral immune cells, including neutrophils, monocyte-derived macrophages, and lymphocytes, are recruited into the brain. Additionally, a compromised BBB exacerbates injury by allowing the leakage of blood-derived components into the CNS. As the immune response escalates, the CNS simultaneously activates protective, adaptive strategies to counterbalance both the pathology and the potential damage caused by immune activation. These include stress response pathways such as the unfolded protein response in the ER, which downregulates protein and lipid synthesis, promotes the restoration of protein folding, and reduces oxidative stress (Medzhitov et al., 2012). Cytosolic heat shock proteins also play a role by stabilizing misfolded proteins and preventing toxicity. Additionally, scavenger proteins are produced to neutralize free radicals, damaged proteins, and oxidized lipids. The brain also employs physical strategies, such as forming scar-like barriers around lesions, a process primarily mediated by astrocytes (Sofroniew, 2020). While this scarring response helps contain inflammation and prevent further damage, it also impedes tissue regeneration and may lead to functional loss. Over time, chronic immune responses in the CNS often become attenuated or exhausted. Compared with other organs, the brain tends to show a reduced magnitude of immune activity during chronic pathology, with less infiltration by peripheral immune cells and a greater reliance on intrinsic and adaptive cellular programs to manage ongoing damage. Consequently, CNS immune responses often shift from active defense to maintenance and containment. This balance is maintained through both cellular and molecular adaptations, including secreted proteins, metabolic changes, and structural containment strategies. Below, we will explore how these immune mechanisms intersect with lipid metabolism under conditions of chronic CNS injury.

CNS damage encompasses a wide spectrum of conditions, ranging from changes associated with normal physiological aging to age-related neurodegenerative diseases, neuroinflammatory disorders affecting young adults, and severe progressive childhood brain disorders caused by genetic mutations. Rather than discussing each condition in detail, we will highlight common themes, particularly those related to lipid metabolism and inflammation. All of these conditions involve chronic, progressive tissue destruction, with aging typically

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producing the most subtle changes. Nonetheless, even during normal physiological aging, there is a reduction in both grey and white matter volume, accompanied by the deterioration of neuronal projections and myelin sheaths (Groh and Simons, 2025). This perturbation elicits a response primarily from white matter–associated microglia (Safaiyan et al., 2021), which share transcriptional features with DAM, indicating partial activation of disease-related gene expression programs. White matter–associated microglia exhibit increased expression of proteins involved in inflammation, phagocytosis, and lipid metabolism. Their transition into this aging-associated state is critically dependent on TREM2 signaling. This activation is associated with increased microglial numbers, the formation of nodules, and morphological changes, such as hypertrophy and reduced ramification (Safaiyan et al., 2021; van den Bosch et al., 2024). Within these nodules, microglia actively clear abnormal myelin, resulting in the accumulation of insoluble lipofuscin-like lysosomal inclusions, which can eventually overwhelm their phagocytic capacity (Safaiyan et al., 2016). Interestingly, unlike in acute white matter damage, microglia in chronic aging conditions form very few lipid droplets (Safaiyan et al., 2016). The reason for this remains unclear, but one hypothesis is that the slow, progressive nature of degeneration prevents microglia from transitioning into the anti-inflammatory, lipid-laden foam cell state typical of resolution phases in acute injury. Nevertheless, a subset of microglia in the aging hippocampus do accumulate small cytoplasmic lipid droplets, show impaired phagocytic function, produce elevated levels of ROS, and secrete pro-inflammatory cytokines (Marschallinger et al., 2020b). Interestingly, such cells are more frequent in Alzheimer's disease brains and in individuals with the APOE4/4 genotype (Haney et al., 2024; Prakash et al., 2025). These cells, however, are distinct from the classical foamy microglia observed during recovery from acute injury. In neurodegenerative diseases, microglial reactivity mirrors that seen in aging; however there is more robust upregulation of the DAM program in both grey and white matter (Keren-Shaul et al., 2017; Krasemann et al., 2017; Sala Frigerio et al., 2019). Similarly, astrocytes and oligodendrocytes also adopt disease-associated states, further contributing to the pathophysiology. A particularly intriguing aspect of the disease-associated glial state is its universality, appearing across multiple neurological disorders, along with its altered secretory profile. Among the most upregulated secreted proteins are apolipoproteins, notably APOE and APOJ/CLU (Habib et al., 2020; Keren-Shaul et al., 2017; Krasemann et al., 2017; Sala Frigerio et al., 2019). The reason for this upregulation is not fully understood, but one hypothesis is that these proteins serve as a first line of defense that carries minimal risk of causing immune-mediated damage. Due to their amphipathic nature, possessing both hydrophilic and hydrophobic properties, apolipoproteins are ideally suited to bind and neutralize harmful hydrophobic molecules, which are themselves recognized as ancient DAMPs capable of triggering immune responses (Chen et al., 2020). APOE, for example, is known to bind to aggregated, disease-associated peptides such as amyloid-β, facilitating their clearance (Castellano et al., 2011; Deane et al., 2008; Kanekiyo et al., 2014). Similarly, APOJ/CLU acts as an extracellular chaperone that captures misfolded proteins (Satapathy and Wilson, 2021). The increased secretion of these apolipoproteins during CNS pathology may thus represent a defense strategy to sequester and neutralize toxic hydrophobic molecules. Complement proteins, which are also upregulated in disease-associated glia, may serve a similar protective function.

Role of apolipoproteins in immune defense

Apolipoproteins may not only serve as a key component of the first-line immune defense system, but they could also play an adaptive role in promoting tolerance to disease. Under normal homeostatic conditions, astrocytes synthesize and secrete lipoprotein particles, which are believed to be taken up by neurons and oligodendrocytes (Raulin et al., 2022). These recipient cells utilize the lipid cargo in neurodevelopment and for synapse formation as well as the maintenance and generation of myelin membranes (Blanchard et al., 2022; Camargo et al., 2017; Ioannou et al., 2019; Mauch et al., 2001; Park et al., 2023; Saher et al., 2005) (Fig. 4). However, in pathological states, the direction of lipoprotein trafficking may reverse. Elevated levels of ROS can lead to the peroxidation of fatty acids, inducing cellular stress and potentially triggering ferroptosis (Dixon et al., 2012). PUFAs can also serve as "sacrificial buffers" against oxidative stress, acting as preferential targets for ROS when primary antioxidant defenses are depleted. To mitigate lipid-induced toxicity, neurons export harmful lipids in APOE-positive lipoprotein particles, which are then internalized by neighboring astrocytes via endocytosis (Ioannou et al., 2019). Within astrocytes, these fatty acids are metabolized and detoxified through enhanced mitochondrial oxidation. Overwhelming astrocytic fatty acid oxidation capacity can elevate acetyl-CoA levels and induce astrocyte-mediated neuroinflammation by enhancing signal transducer and activator of transcription 3 activation (Mi et al., 2023). Additionally, studies in *Drosophila* have shown that glial lipid droplet accumulation during disease depends on lactate transfer from glia to neurons (Liu et al., 2017; Liu et al., 2015). Under normal conditions, astrocytes take up glucose from the bloodstream, convert it to lactate, and shuttle it to neurons via monocarboxylate transporters (Funfschilling et al., 2012; Lee et al., 2012). Neurons then metabolize lactate to generate acetyl-CoA, a central substrate for both energy production and de novo fatty acid synthesis. However, when mitochondria become dysfunctional or the TCA cycle is compromised, hallmarks of many neurodegenerative diseases, the excess acetyl-CoA, appear to drive lipid synthesis in neurons. These newly synthesized lipids are then transferred to glial cells via apolipoprotein-containing particles, resulting in lipid droplet accumulation within glia. Lipid accumulation in glial cells is associated with increased inflammatory responses and may therefore contribute to the progression of CNS disorders. (Li et al., 2024; Marschallinger et al., 2020b). The various APOE isoforms exhibit distinct functions in lipid storage and transport (Lee et al., 2023; Windham et al., 2024). Notably, APOE4 appears to disrupt the coordinated lipid detoxification processes between neurons and astrocytes, partly due to impaired mitochondrial fatty acid oxidation in astrocytes (Qi et al., 2021),

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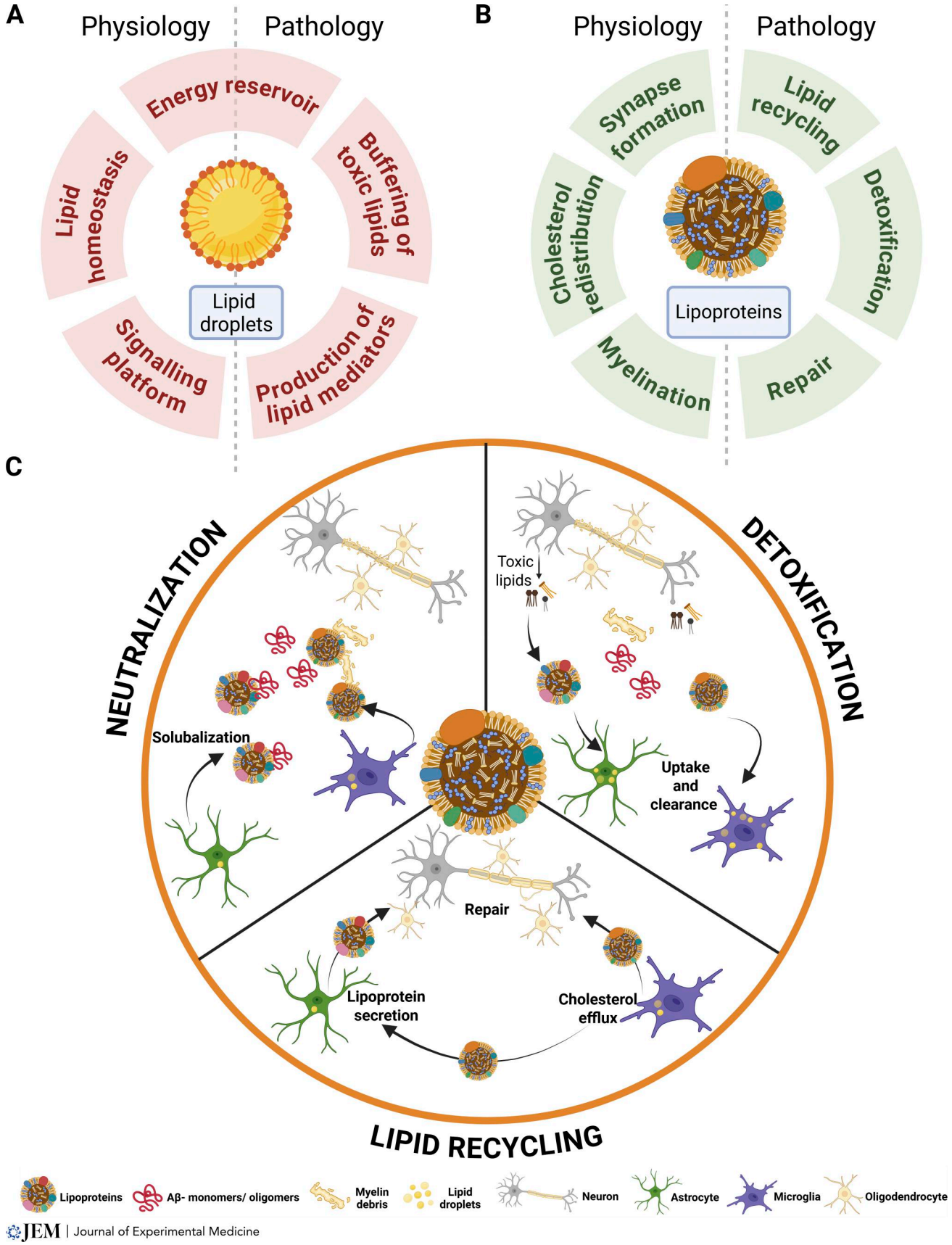

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Figure 4. **Function of lipid droplets and lipoproteins in physiology and pathology of the CNS. (A and B)** Circular schematic depicting the physiological and pathological functions of lipid droplets and lipoproteins. **(C)** Tripartite circular schematic showing defense roles of CNS lipoproteins: Neutralization (left

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section): Astrocyte- and microglia-derived lipoproteins sequester and solubilize Aβ aggregates and other extracellular debris. Detoxification (right section): Neurons under stress release excess fatty acids and toxic lipids, which are captured by lipoproteins and taken up by astrocytes and microglia. These glial cells form lipid droplets to store and detoxify these lipids through distinct metabolic pathways. Lipid recycling (bottom section): Astrocytes and microglia secrete lipoproteins that deliver cholesterol and phospholipids to neurons and oligodendrocytes. This supports membrane remodelling, synapse integrity, and remyelination during recovery. Aβ, amyloid-β.

although the precise mechanisms underlying this dysfunction remain poorly understood. Cells expressing APOE4 tend to accumulate lipid droplets enriched in unsaturated triacylglycerides and show increased synthesis of both unsaturated triacylglycerides and phosphatidylcholine, suggesting that APOE4 disrupts lipogenic transcriptional programs (Lin et al., 2018; Sienski et al., 2021; Tcw et al., 2022; Victor et al., 2022). The composition of APOE4-associated lipoproteins also differs, displaying a higher triglyceride content and greater levels of polyunsaturated fatty acids (Guo et al., 2025; Lindner et al., 2022). When taken up by microglia, these fatty acids can trigger lipofuscinosis, a lysosomal pathology linked to lipid peroxidation and aging (Guo et al., 2025). These disturbances in lipid metabolism and lipoprotein assembly have profound effects in neurodegeneration models (Kaji et al., 2024; Shi et al., 2017). In particular, APOE4 has been shown to exacerbate tau pathology and promote microglia-mediated, tau-dependent neurodegeneration (Shi et al., 2017). This is accompanied by glial lipid accumulation, disrupted cholesterol metabolism, and impaired lysosomal function (Litvinchuk et al., 2024). Notably, enhancing lipid efflux in glial cells via LXR agonists or ABCA1 overexpression can mitigate tau pathology and neuronal damage, suggesting that APOE4 compromises the glial capacity for lipid clearance (Litvinchuk et al., 2024). Moreover, APOE4 has been associated with increased cholesterol deposition in oligodendrocytes, likely due to its reduced lipid efflux capacity (Blanchard et al., 2022; Cheng et al., 2022). This defect can be pharmacologically rescued, leading to enhanced myelination and improvements in learning and memory. Similarly, correcting dysregulated lipid metabolism has been shown to reverse the disease-associated oligodendrocyte state and extend lifespan in an amyotrophic lateral sclerosis model (Rezaei et al., 2025).

Thus, lipoproteins may function in various chronic neurodegenerative diseases by quenching toxic lipids and other hydrophobic molecules to provide defense and to promote tolerance to disease. However, if the concentration of these harmful molecules exceeds the neutralizing capacity of scavenger systems provided by apolipoproteins, they may activate additional innate immune receptors, escalating the immune response. At this stage, peripheral immune cells may infiltrate the CNS in limited numbers, releasing effector molecules and cytokines that drive microglia and monocyte-derived macrophages toward more activated, tissue-damaging phenotypes.

Effects of IFN pathway on lipid metabolism

IFNs, a class of cytokines produced in response to viral infections, play a central role during this phase of immune regulation (Lee and Ashkar, 2018; Platanias, 2005). Type I IFNs are particularly known for their capacity to trigger robust antiviral defenses by upregulating genes that inhibit viral replication in both infected and neighboring cells. Similarly, IFN-γ, a type II IFN, enhances antiviral immunity through its modulatory effects on the innate immune system and serves as a crucial bridge to the activation of adaptive immunity. Both type I and type II IFNs have been implicated in the pathology of nonviral, progressive CNS diseases. What drives the induction of an antiviral state in these conditions, and how is this response mechanistically connected to disruptions in lipid metabolism? Viruses reprogram host cell metabolism to optimize the production of molecular substrates required for replication (Heaton and Randall, 2011). Consequently, viral infections frequently induce the upregulation of lipid biosynthetic pathways, including fatty acid and cholesterol synthesis, to support the assembly of new virions (Heaton and Randall, 2011). A critical component of the host antiviral response involves type I IFNs, which antagonize these metabolic adaptations. Notably, type I IFNs suppress cholesterol biosynthesis by inhibiting the activity of the SREBP2 (Blanc et al., 2011; York et al., 2015). Intriguingly, inhibition of cholesterol synthesis alone is sufficient to induce type I IFN production and enhance antiviral immunity. This response is mediated via the cyclic guanosine monophosphate–AMP synthase–stimulator of IFN genes–TRAF family member–associated NF-κB activator-binding kinase 1–IFN regulatory factor 3 signaling axis (York et al., 2015). Stimulator of IFN genes, a central adaptor protein in this pathway, is localized to the ER and Golgi apparatus and contains a cholesterol-binding motif, suggesting that intracellular cholesterol levels may directly influence its activation and downstream signaling (Zhang et al., 2024). Beyond their antiviral functions, type I IFNs also modulate immune homeostasis by constraining excessive inflammation that can result in tissue damage. In the context of nonviral chronic CNS disorders, activation of type I IFN signaling may exert protective effects by promoting a catabolic immune phenotype and protecting against immune-mediated injury (Deczkowska et al., 2016). This is consistent with the established use of IFN-β as an immunomodulatory therapy in MS. It is important to note that IFNs not only transform myeloid cells into an IFN-responsive state but also affect astrocytes and oligodendrocytes (Fumagalli et al., 2025; Kaya et al., 2022). For example, activated oligodendrocytes show a significant downregulation of sterol biosynthesis, which may serve as a cytoprotective measure (Kenigsbuch et al., 2022; Pandey et al., 2022). However, dysregulated or sustained type I IFN signaling has also been implicated in driving pathology of several neurodegenerative diseases, highlighting the context-dependent effects of this pathway (Rodero and Crow, 2016; Roy et al., 2020). Moreover, IFN-γ plays a pivotal role in the innate antiviral response, with production primarily occurring in natural killer cells, innate lymphoid type 1 cells, and T cells. For example, IFN-γ secreted by cluster of differentiation 8 ($CD8^+$)

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tissue-resident memory T cells, which accumulate in the brain during aging and various chronic neurological disorders, may trigger the transformation of microglia into highly reactive effector cells (Campisi et al., 2022; Chen et al., 2023; Gate et al., 2020; Groh et al., 2025; Groh et al., 2021; Jorfi et al., 2023; Kedia et al., 2024; Merkler et al., 2022). These activated microglia then generate ROS and nitric oxide, further amplifying the immune response and fostering a more anabolic, pro-inflammatory phenotype. Consequently, IFNs may have the ability to either dampen or enhance immune reactions, depending on the type of IFN and the context.

Conclusion

Lipid metabolic reprogramming is a critical component of host defense. Immune signal transduction pathways intersect with and take control over anabolic lipid metabolism to support membrane biogenesis during cell proliferation and to produce lipid-derived immune mediators. In turn, metabolic pathways also influence immune signaling, for example, by promoting anti-inflammatory responses during the catabolic, resolution phase of immunity. We are just beginning to uncover this reciprocal relationship between lipid metabolism and neuroinflammation, a connection that will not only deepen our understanding of immune cell behavior but also reveal how nonimmune cells adapt to chronic pathological conditions. A striking example is the identification of TREM2 as a lipid-sensing receptor that modulates key aspects of innate immunity in the CNS, including immune signaling, phagocytosis, and lipid metabolism. Furthermore, the brain harbors a unique system of lipoprotein particles, which undergo reprogramming in disease states. Lipoproteins, previously recognized for their roles in lipid transport, are emerging as frontline components of immune defense. They may also contribute to disease tolerance under chronic conditions. Importantly, the most prevalent chronic neurodegenerative diseases are genetically linked to these lipid metabolic pathways. Despite this, our understanding of how lipid and lipoprotein metabolism is altered in such disorders remains limited. Advancing our knowledge of the interplay between lipid metabolism and neuroinflammation holds promise for the development of novel therapeutic strategies for both prevention and treatment.

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