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REVIEW

From nonalcoholic fatty liver disease to neuroinflammation: the role of chronic systemic inflammation

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Abstract

Neuroinflammation is a significant contributor to neurological disorders. While previous research has mainly concentrated on lesions within the brain, the potential influence of nonalcoholic fatty liver disease (NAFLD) on neuroinflammation has been largely overlooked. An increasing amount of evidence suggests that heightened chronic systemic inflammation linked to NAFLD could significantly contribute to the initiation and advancement of neuroinflammation, nonetheless, the underlying mechanisms remain unclear. This review summarizes the primary causes of chronic systemic inflammation in the context of NAFLD, delineates the mechanisms by which chronic systemic inflammation leads to neuroinflammation, analyzes the key pathways through which circulating inflammatory mediators travel from the periphery to the central nervous system and their effects on glial cells, and finally discusses the novel approaches for treating neuroinflammation via a liver-brain inflammation axis perspective. This research intends to offer an in-depth insight into how chronic systemic inflammation contributes to the connection between NAFLD and neuroinflammation.

Keywords Nonalcoholic fatty liver disease · Neuroinflammation · Chronic systemic inflammation · Liver-brain inflammation axis

Abbreviations

NAFLD	nonalcoholic fatty liver disease
CNS	central nervous system
AD	Alzheimer's disease
MASLD	metabolic dysfunction-associated steatotic liver disease
TNF-α	tumor necrosis factor-α
IL-6	interleukin-6
IL-1β	interleukin 1β
CCL2	C-C motif chemokine ligand 2
CXCL10	C-X-C motif chemokine ligand 10
BBB	blood-brain barrier
NASH	nonalcoholic steatohepatitis
FFAs	free fatty acids
ROS	reactive oxygen species
NLRP3	NACHT, LRR and PYD domains-containing protein 3
HSC	hepatic stellate cell
CCR2	chemokine receptor 2
NF-κB	nuclear factor kappa B
JNK	c-Jun N-terminal kinase
IR	insulin resistance
CHOL	cholesterol
TLR4	toll-like receptor 4
TJs	tight junctions
LPS	lipopolysaccharide
ECM	extracellular matrix
TGF-β1	transforming growth factor β1
IME	immune microenvironment
DAMPs	damage-associated molecular patterns
MS-FL	mechanical stress-induced fibrotic lesions
Aβ	amyloid β-protein
PFC	prefrontal cortex
PD	Parkinson's disease
IFN-γ	interferon gamma-γ
CECs	cerebral endothelial cells
VEGF-A	vascular endothelial growth factor-A
CVOs	circumventricular organs

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CSF	cerebrospinal fluid
CPE	choroid plexus epithelial
EVs	extracellular vesicles
Iba-1	ionized calcium-binding adapter molecule 1

Introduction

Neuroinflammation refers to the inflammatory response within the central nervous system (CNS) resulting from dysregulated cytokine synthesis and release. It constitutes a CNS immune response activated by brain-resident immune cells, such as microglia and astrocytes, as well as peripheral immune cells (Zhou et al. 2023). While neuroinflammation is initially beneficial to the nervous system, chronic or excessive inflammation serves as a key pathological factor in neuroinflammatory diseases, including Alzheimer's disease (AD) and depression (Estrada et al. 2019; Jawad et al. 2023). According to World Health Organization (WHO) statistics, the number of individuals living with AD is projected to reach approximately 152.8 million by 2050 due to persistent population growth and aging, moreover, AD ranks as the fifth leading cause of death among Americans aged 65 and older(Chen et al. 2024). Notably, recent epidemiological data indicate that approximately 322 million people globally suffer from depression, which is projected to rise to become the second leading cause of the global disease burden by 2030(Senra and McPherson 2021). Neuroinflammatory diseases represent a major contributor to human disability and mortality, with their incidence and mortality rates exhibiting a progressive annual increase. Consequently, they have emerged as key challenges and focal points in contemporary neuroscience research.

Historically, research on neuroinflammation has predominantly centered on pathologies intrinsic to the brain itself, often overlooking investigations into systems beyond the CNS. In recent years, however, a growing body of research has begun to focus on the impact of peripheral chronic systemic inflammation on central neuroinflammation. Chronic systemic inflammation has diverse etiologies, with chronic inflammatory diseases representing a primary source of its pathological drivers (Steinz et al. 2025). Furthermore, lifestyle factors such as dietary intake (Graff et al. 2023) and sedentary behavior (Vázquez-Lorente et al. 2025), as well as physiological and pathological conditions including aging (Guarner and Rubio-Ruiz 2015), overweight/obesity (Craveiro et al. 2025), and gut dysbiosis (Di Vincenzo et al. 2024), are frequently associated with a state of persistent chronic inflammation, potentially influencing neuroinflammation. Among the recognized contributors to neuroinflammation, nonalcoholic fatty liver disease (NAFLD) has garnered increasing attention. NAFLD, recently also termed metabolic-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD), refers to a hepatic disorder characterized by liver fibrosis—specifically, lipid accumulation exceeding 5% of hepatocytes—not attributable to excessive alcohol consumption or other secondary causes of liver fat accumulation. Key pathological features include hepatic lipid deposition, inflammation, and fibrosis (Milić et al. 2014). As a complex metabolic-inflammatory condition, NAFLD exhibits a close relationship with neuroinflammatory diseases. Nevertheless, research exploring the link between NAFLD and neuroinflammatory diseases has primarily focused on cross-sectional and cohort studies examining dementia and cognitive impairment (Table 1), depression (Table 2), and effects on brain structure (Table 3), with the underlying mechanisms remaining incompletely elucidated.

A complex interplay exists between the liver and the brain, with neural and humoral signaling pathways representing one of the most commonly implicated conduits for peripheral-to-brain communication. However, hepatic immune homeostasis under physiological conditions is essential for healthy brain function (Gehrke and Schattenberg 2020). Accumulating research indicates that the chronic systemic inflammation resulting from the immune-inflammatory response in NAFLD also constitutes a significant factor contributing to neuroinflammation (Dhanda et al. 2018). Within the context of chronic systemic inflammation in NAFLD, inflammatory mediators—centered on cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6(IL-6), and interleukin 1β (IL-1β), and chemokines including C-C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 10 (CXCL10)—interact synergistically, collectively refining our understanding of the intricate liver-brain connection. This mechanistic pathway involves a sequence of processes: (1) elevation of chronic systemic inflammation levels driven by hepatic immune inflammation, (2) translocation of inflammatory mediators across the blood-brain barrier (BBB) into the CNS, and (3) activation of glial cells and the ensuing neuroinflammatory response. Together, these constitute the liver-brain inflammation axis mechanism linking the liver to the brain. Clinically, the treatment of neuroinflammatory diseases presents significant challenges (see Table 4). Given that NAFLD is a key etiological factor, a deeper exploration of the mechanistic links between them is imperative. This article provides a comprehensive review of published research, aiming to offer a nuanced understanding of the complex relationship between NAFLD and neuroinflammation from the perspective of chronic systemic inflammation.

Table 1 Clinical studies on the association between NAFLD (encompassing liver fibrosis) and AD, dementia, and cognitive impairment

Disease	Study Type	Patient Sample	Statistical Method	Age	Findings Summary	References
NAFLD and AD	cohort study	608,994 cases	Cox proportional hazards regression model	≥60 years.	The NAFLD were associated with a risk of AD (aHR = 1.04; 95% CI: 1.01–1.07; *P* = 0.004).	https://doi.org/10.3350/cmh.2021.0332
NAFLD and AD	cross-sectional study	5129 cases	Logistic regression and mediation models	≥60 years.	The multivariable adjusted odds ratios associated with moderate-to-severe (vs. no-to-mild) NAFLD were 1.88 (95% CI = 1.01–3.50) for AD.	https://doi.org/10.1111/ene.15416
NAFLD and dementia	cohort study	656 cases and 6,436 controls	Cox proportional hazards regression model	The mean ages were 48.2 years in NAFLD and 48.4 in the matched cohort.	During a mean follow-up of 19.7 ± 8.7 years, 3.3% of the NAFLD patients and 4.9% of the controls developed dementia (*P* = 0.07). Overall, NAFLD was not significantly associated with incident dementia.	https://doi.org/10.1016/j.jhepr.2020.100218
NAFLD and dementia	cohort study	22,317 cases and 22,317 controls	Cox proportional hazards regression model	≥65 years.	There is no association between NAFLD and the incidence of all-cause dementia (HR = 0.97, 95% CI: 0.92–1.04), vascular dementia (HR = 0.89, 95% CI: 0.78–1.02).	https://doi.org/10.1007/s10620-020-06644-1
NAFLD and dementia	cross-sectional study	5129 cases	Logistic regression and mediation models	≥60 years.	The multivariable adjusted odds ratios associated with moderate-to-severe (vs. no-to-mild) NAFLD were 2.22 (95% CI: 1.41–3.49) for all - cause dementia and 2.62 (95% CI: 1.33–5.17) for VaD.	https://doi.org/10.1111/ene.15416
NAFLD and cognitive impairment	cohort study	30,239 cases and 587 controls	Weighted logistic regression models	≥45,495 years.	NAFLD was significantly associated with incident cognitive impairment (OR = 2.01; 95% CI: 1.42, 2.85).	https://doi.org/10.1371/journal.pone.0282633
NAFLD and cognitive impairment	cross-sectional study	4400 cases	Logistic regression models	50–64 years.	Participants with NAFLD showed an increased prevalence of cognitive impairment (OR = 1.26; 95% CI = 1.04–1.52).	https://doi.org/10.1038/s41598-022-16788-x
Liver fibrosis and dementia	cohort study	455,226 cases	Cox proportional hazards regression model	The mean ages were 56.5 years.	Liver fibrosis in middle age was associated with an increased risk of incident dementia (HR = 1.52, 95% CI: 1.22–1.90)	https://doi.org/10.1111/ene.15437
Liver fibrosis and cognitive impairment	cross-sectional study	3217 cases	Linear regression models	The mean ages were 69 years.	Higher liver fibrosis scores were associated with worse immediate recall (β = −0.39; 95% CI: −0.58, −0.21), language fluency (β = −0.46; 95% CI: −0.72, −0.21), and attention/concentration (β = −1.34; 95% CI: −2.25, −0.43), but not delayed recall (β = −0.10; 95% CI: −0.20, 0.01).	https://doi.org/10.1111/ene.14384

This table summarizes clinical studies on the association between NAFLD (encompassing liver fibrosis) and AD, dementia, and cognitive impairment, demonstrating the established correlation among these conditions. NAFLD, nonalcoholic fatty liver disease; AD, Alzheimer's disease; aHR, adjusted hazard ration; CI, confidence interval; HR, hazard ration; VaD, vascular dementia; RR, Relative Risk; OR, odds ratio

NAFLD as a major cause of chronic systemic inflammation

The Lipid-Inflammation crosstalk network

NAFLD is a metabolic disorder centered on lipid metabolism disorders and chronic inflammation (Fig. 1). Its pathological spectrum progressively evolves from simple steatosis to nonalcoholic steatohepatitis (NASH) and fibrosis, a process closely linked to the dissemination of systemic inflammation (Milić et al. 2014). Studies indicate an elevated risk of AD and depression in NAFLD patients (Colognesi et al. 2020; 'Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016' 2019), potentially associated with hepatic inflammatory signals triggering chronic, low-grade systemic inflammation (Gangopadhyay et al. 2022; Shang et al. 2022; Soto-Angona et al. 2020). In the early stage of simple steatosis, an overload of free fatty acids (FFAs) exceeding the β-oxidation capacity of hepatocyte mitochondria leads to toxic lipid metabolites activating the TLR4/NF-κB/MyD88 pathway, promoting the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. Concurrently, FFAs activate the JNK pathway via apoptosis signal-regulating kinase

Table 2 Clinical studies on the association between NAFLD (encompassing MASLD) and depression

Disease	Study Type	Patient Sample	Statistical Method	Age	Findings Summary	References
NAFLD and depression	cohort study	19,871 cases and 19,871 controls	Cox proportional hazards regression model	The mean age was 58.5 years.	21.2% of patients with NAFLD and 18.2% of controls were diagnosed with depression ($p<0.001$). On regression analysis, the HR for incidence of depression was 1.21 ($p<0.001$).	https://doi.org/10.1002/hep4.1541
NAFLD and depression	cross-sectional study	25,333 cases	Logistic regression model	The mean age was 47 years.	In the multivariate analysis, NAFLD showed a significant association with depression [adjusted OR = 1.43 and 95% CI: 1.14–1.80, $p=0.002$] in women.	https://doi.org/10.3389/fmed.2020.585618
MASLD and depression	cohort study	11,301 cases and 104,205 controls	Cox proportional hazards regression model	The mean age was 56 years.	Incident severe depression developed in 228 of 11 301 (2.0%) persons with MASLD and 1160 of 104 205 (1.1%) comparators (HR = 1.8, 95% CI:1.5–2.1).	https://doi.org/10.1111/liv.16019

This table summarizes clinical studies on the association between NAFLD (encompassing MASLD) and depression, demonstrating the established correlation between these two conditions. NAFLD, nonalcoholic fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HR, hazard ration; OR, odds ratio; CI, confidence interval; RR, Relative Risk

Table 3 Clinical studies on the association between NAFLD (encompassing MASLD and liver fibrosis) and brain structure

Disease	Study Type	Patient Sample	Statistical Method	Age	Findings Summary	References
NAFLD and brain structure	cross-sectional study	766 cases	Linear or logistic regression models	The mean age was 67 years.	NAFLD was significantly associated with smaller total cerebral brain volume even after adjustment for all the covariates included in the study (β [SE]= −0.26 [0.11]; $P=0.02$).	https://doi.org/10.1001/jamaneurol.2017.3229
MASLD and brain structure	cross-sectional study	70 cases	Linear regression models	The age range was 36–55 years.	Liver fibrosis development was associated with higher sCoV in the NAcc.	https://doi.org/10.1016/j.heliyon.2024.e38516
NAFLD, liver fibrosis and brain structure	cross-sectional study	5660 patients with NAFLD and 3022 patients with liver fibrosis.	Linear regression models	The age range was 53–69 years.	NAFLD was associated with smaller volumes of total brain (β = −3.5, 95% CI = −5.4 to −1.7), total gray matter (β = −1.9, 95% CI = −3.4 to −0.3), and total cortical gray matter (β = −1.9, 95% CI = −3.7 to −0.01). In addition, liver fibrosis (defined as liver stiffness measure ≥ 8.2 kPa) was related to smaller total brain volumes (β = −7.3, 95% CI = −11.1 to −3.5).	https://doi.org/10.1111/ene.16048
Liver fibrosis and brain structure	cross-sectional study	38,244 cases	Linear mixed-effect model	The mean age was 58 years.	Neuroimaging analyses revealed significant associations between liver fibrosis and reduced regional GMVs ($P_{FDR}<0.05$), primarily in the hippocampus, thalamus, ventral striatum, parahippocampal gyrus, brain stem, and cerebellum.	https://doi.org/10.1016/j.ebiom.2023.104679

This table summarizes clinical studies on the association between NAFLD (encompassing MASLD and liver fibrosis) and brain structure alterations, demonstrating established correlations between these conditions. NAFLD, nonalcoholic fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; SE, Standard Error; sCoV, spatial coefficient of variation; NAcc, nucleus accumbens; CI, confidence interval; GMVs, grey matter volumes

1 activation or endoplasmic reticulum stress, amplifying inflammatory signaling and inducing hepatocyte apoptosis (Berardo et al. 2020). During progression to NASH, toxic lipid-derived reactive oxygen species (ROS) and mitochondrial dysfunction further activate the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome, recruit neutrophils, and drive hepatic stellate cell (HSC) activation, thereby promoting fibrogenesis. At this stage, the CCL2-CCR2 chemokine axis mediates monocyte/macrophage infiltration into the liver, these cells differentiate into pro-inflammatory M1 phenotypes, releasing TNF-α and ROS, establishing a local inflammatory positive feedback loop (Mohammed et al. 2021a). TNF-α, secreted by both hepatocytes and macrophages, persistently activates the nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways by binding tumor necrosis factor receptor 1. This cytokine diffuses into the systemic circulation, elevating peripheral inflammation levels (Nagaki and Moriwaki 2008). In summary, the systemic inflammation in NAFLD results from the interplay between lipid metabolism disorders and stage-specific inflammatory pathways (TLR4/NF-κB, NLRP3, JNK). This interaction drives the sustained secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) and chemokines (e.g., CCL2, CXCL10) into the

Table 4 Key molecular pathways and major pathological processes of the liver-brain inflammatory axis mechanism

NAFLD	Chronic Systemic Inflammation	Pathways for Traversing the BBB	Neuroinflammation
Metabolic dysfunction, liver fibrosis, and physiological aging activate key hepatic signaling pathways, including TLR4/NF-κB, NLRP3, and JNK, contributing to hepatic immune-inflammatory responses	Inflammatory mediators, such as pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, etc.) and chemokines (CCL2, CXCL10, etc.), are persistently secreted into the peripheral circulation, ultimately driving the initiation and progression of persistent chronic systemic inflammation	①Circulating inflammatory mediators disrupt the BBB's tight junctions. Furthermore, activated microglia phagocytose astrocytic endfeet, and the upregulation of VEGF-A in astrocytes is promoted. These mechanisms collectively cause BBB dysfunction, thus culminating in increased BBB permeability	①Circulating inflammatory mediators activate the TLR4/NF-κB/MyD88 signaling pathway, triggering microglial activation polarized to the M1 phenotype. This M1 polarization is characterized by increased expression of the marker Iba-1 and enhanced secretion of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β
		②Inflammatory mediators enter the CNS via leakage through the CVOs	
		③Circulating inflammatory mediators activate receptors such as TNF-α and IL-1β on CECs, promoting signal transduction in CECs	②Activated microglia promote the upregulation of VEGF-A expression in astrocytes. Furthermore, they stimulate the transformation of astrocytes into the A1 phenotype, which exerts neurotoxic effects and releases inflammatory cytokines
		④Peripheral inflammatory mediators can disrupt the integrity of the blood-CSF barrier and mediate signaling via EVs	

Table 4 (continued)

NAFLD	Chronic Systemic Inflammation	Pathways for Traversing the BBB	Neuroinflammation

This table delineates the key molecular pathways in the NAFLD-chronic systemic inflammation-BBB-neuroinflammation, outlining the major pathological processes of the liver-brain inflammatory axis mechanism. In this process, the hepatic immune-inflammatory response, mediated by various factors, elevates peripheral chronic systemic inflammation levels. Subsequently, inflammatory mediators cross the BBB via multiple pathways, enter the CNS, and ultimately lead to glial cell activation and neuroinflammation. NAFLD, nonalcoholic fatty liver disease; BBB, blood-brain barrier; VEGF-A, endothelial growth factor-A; CNS, central nervous system; CVOs, circumventricular organs; CECs, cerebral endothelial cells; CSF, cerebrospinal fluid; EVs, extracellular vesicles

peripheral circulation, ultimately leading to the initiation and perpetuation of persistent, low-grade chronic systemic inflammation.

Metabolic dysfunction

NAFLD, also termed MASLD, involves metabolic dysfunction characterized by the interplay of obesity, insulin resistance (IR), cholesterol (CHOL) and gut-liver axis disorder. This dysfunction drives an increase in chronic systemic inflammation levels (Fig. 1). NAFLD patients frequently present with obesity, subsequently developing dysfunctional adipose tissue. Visceral adipose tissue secretes adipokines (e.g., leptin, resistin) and chemokines (e.g., MCP-1), recruiting macrophages that infiltrate the fat, forming "adipose tissue inflammatory foci." Inflammatory signals are then transmitted to the liver via the bloodstream (Xiong et al. 2024). Furthermore, adipocyte hypertrophy in obesity leads to insufficient local microvascular density, causing tissue hypoxia and cellular necrosis. Hypoxia activates the hypoxia-inducible factor 1α signaling pathway, promoting the secretion of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and inducing adipocyte release of FFAs into the circulation (Ghanim et al. 2004). IR, a key feature of metabolic dysfunction, also increases adipose tissue lipolysis, resulting in substantial FFA release into the blood. This enhances hepatic FFA uptake. Excess FFAs accumulate within hepatocytes, triggering lipotoxicity. Toxic lipid metabolites (e.g., ceramides, diacylglycerols) further activate the immune-inflammatory response (Pararasa et al. 2015). Additionally, metabolic dysfunction is accompanied by CHOL disorder. Elevated non-high-density lipoprotein CHOL levels promote macrophage polarization towards a pro-inflammatory (M1) phenotype, while oxidized low-density lipoprotein exacerbates hepatic and vascular inflammation by activating toll-like receptor 4 (TLR4) and the NLRP3 inflammasome (Zhong et al. 2022). Metabolic dysfunction in NAFLD may also involve gut-liver axis disorder. Reduced expression of

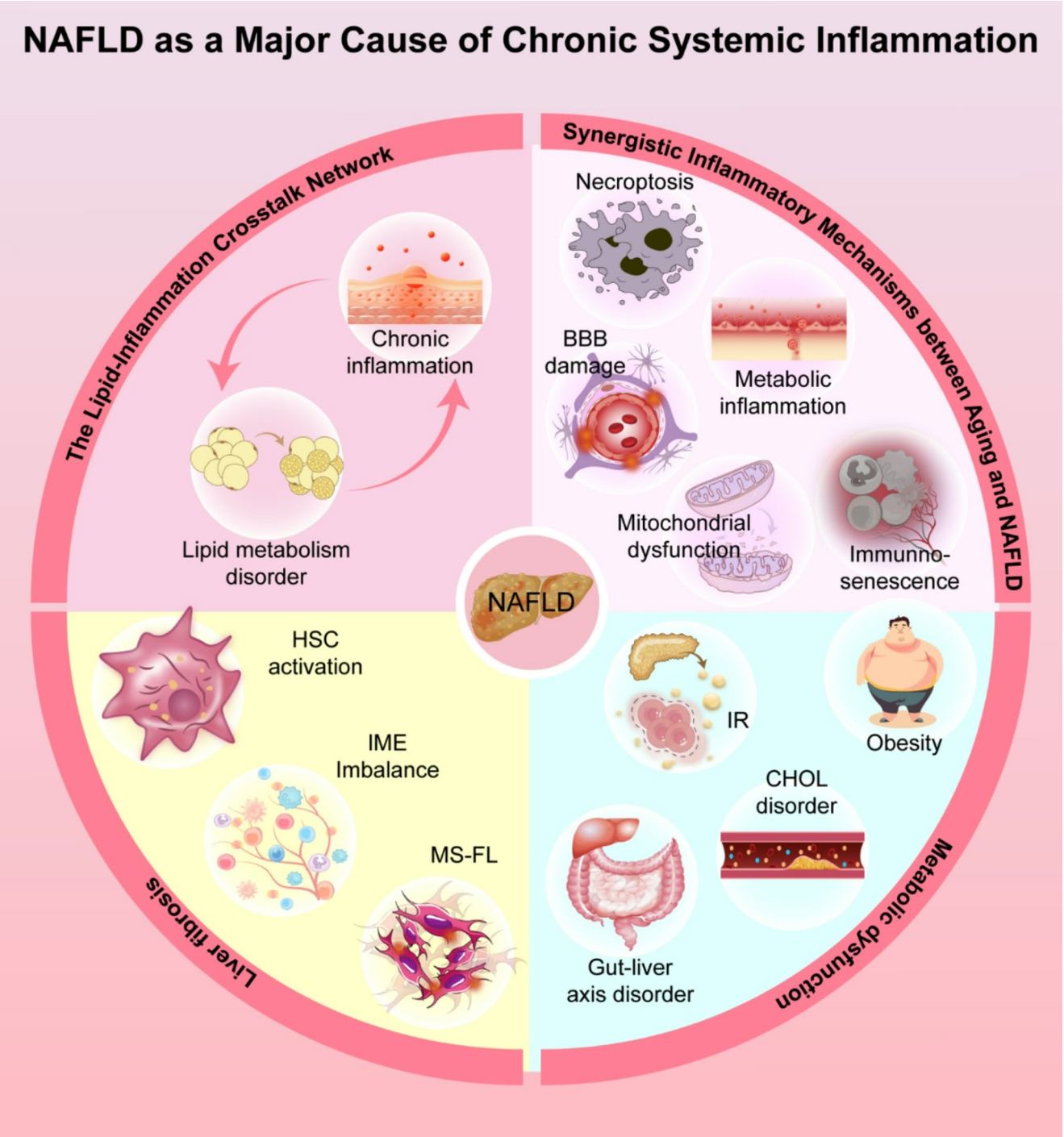

Fig. 1 This figure illustrates the diverse etiological factors contributing to chronic systemic inflammation within the context of NAFLD. Key components include: (1) The lipid-inflammation crosstalk network (encompassing lipid metabolism disorders and chronic inflammation); (2) Metabolic dysfunction (characterized by obesity, IR, CHOL disorder, and gut-liver axis disorder); (3) Liver fibrosis (driven by HSC activation, IME imbalance, and MS-FL); and (4) Synergistic inflammatory mechanisms between aging and NAFLD (involving immunosenescence, metabolic inflammation, mitochondrial dysfunction, necroptosis, and BBB damage). Collectively, these pathways potentiate NAFLD-associated inflammatory responses, facilitate the translocation of inflammatory mediators into the peripheral circulation, and ultimately propel the progression of chronic systemic inflammation. NAFLD, nonalcoholic fatty liver disease; IR, insulin resistance; CHOL, cholesterol; HSC, hepatic stellate cell; IME, immune microenvironment; MS-FL, mechanical stress-induced fibrotic lesions; BBB, blood-brain barrier

intestinal tight junctions (TJs) proteins and increased gut mucosal permeability lead to the release of bacterial metabolites and endotoxins (e.g., lipopolysaccharide, LPS) into the circulation. These activate the TLR4 signaling pathway in Kupffer cells, prompting the release of pro-inflammatory factors (e.g., IL-1β, IL-6), and recruiting neutrophils and monocytes to infiltrate the liver (Di Vincenzo et al. 2024). Gut dysbiosis further impacts bile acid deconjugation, imbalances in secondary bile acids (e.g., deoxycholic acid), which regulate hepatic inflammation and glucose/lipid metabolism via FXR/TGR5 signaling, exacerbate systemic inflammation (Yan et al. 2023). In summary, the systemic inflammation in NAFLD results from the interplay between metabolic dysfunction and immune dysregulation.

Liver fibrosis

The process by which liver fibrosis contributes to chronic systemic inflammation involves multiple mechanisms (Fig. 1). Primarily, the activation of HSCs serves as the central driver. During chronic liver injury, HSCs transition from a quiescent state to a pro-fibrogenic phenotype, releasing substantial amounts of pro-inflammatory factors (e.g., Transforming growth factor β1, TGF-β1) and extracellular matrix (ECM) components, thereby creating a pro-inflammatory microenvironment. TGF-β1 not only promotes collagen deposition via the SMAD3 pathway but also activates NF-κB signaling, inducing hepatocytes and Kupffer cells to secrete inflammatory mediators such as IL-6 and TNF-α, triggering both local and systemic inflammatory cascades (Schwabe and Brenner 2025). Secondly, an immune microenvironment (IME)- imbalance exacerbates inflammatory dissemination. In liver fibrosis, damage-associated molecular patterns (DAMPs) released from injured hepatocytes activate TLRs, promoting macrophage polarization towards the pro-inflammatory M1 phenotype and facilitating the transmission of inflammatory signals to the peripheral circulation via exosomes (Yao et al. 2025). Finally, the mechanical stress-induced fibrotic lesions (MS-FL) activates integrin signaling, prompting HSCs to secrete chemokines (e.g., CCL2, CXCL10). This recruits monocytes and neutrophils, establishing a positive feedback loop for chronic inflammation (Schwabe and Brenner 2025). Research indicates that cognitive impairment in NAFLD may be mild or absent in early stages, however, significant cognitive decline can emerge with the progression of liver fibrosis, correlating with the associated chronic systemic inflammation (Weinstein et al. 2019). Similarly, the progression of liver fibrosis potentially influences the severity of depression, particularly the chronic systemic inflammation accompanying advanced fibrosis, which may contribute to more severe depressive states (Stoenescu et al. 2024). Chronic low-grade systemic inflammation is also evident in the early stages of NAFLD fibrosis development (Haukeland et al. 2006). During liver fibrosis, the chronic inflammatory process releases core inflammatory cytokines—including TGF-β, TNF-α, IL-6, and IL-1β—and chemokines such as CCL2 and CXCL10. These factors activate HSCs, recruit immune cells, induce oxidative stress, promote ECM deposition, and enter the peripheral circulation, instigating systemic inflammation. Upon traversing the BBB, they cause endothelial dysfunction, leading to microglial activation and hippocampal atrophy (Bordet and Deplanque 2020). In summary, these findings demonstrate that liver fibrosis likely drives the dissemination of local inflammation to systemic levels through multiple mechanisms: HSC activation, IME-imbalance, and MS-FL.

Synergistic inflammatory mechanisms between aging and NAFLD

Aging represents not only a progressive decline in physiological function but also a driver of chronic systemic inflammation. Its interaction with NAFLD exacerbates hepatic and systemic inflammatory responses. Primarily, dysfunction of the immune system during aging (immunosenescence) significantly promotes the development of chronic inflammation (Guarner and Rubio-Ruiz 2015). The persistent release of senescence-associated secretory phenotype factors, such as TNF-α, IL-6, and IL-1β, not only directly promotes the upregulation of genes associated with TLR cascades (e.g., CUL1, TANK, Table 2) in hepatic Kupffer cells but also exacerbates hepatocyte lipid peroxidation and mitochondrial dysfunction via paracrine actions (Yang et al. 2024). Secondly, age-related metabolic inflammation is closely linked to NAFLD pathology. Obesity and dyslipidemia accompanying aging can induce macrophage infiltration into adipose tissue. Aberrant expression of class A scavenger receptor further activates pro-inflammatory polarization of macrophages, releasing chemokines (e.g., MCP-1) and recruiting more immune cells, thereby establishing an adipose tissue-liver inflammatory axis (Xu et al. 2015). Notably, recent research has found that abnormal accumulation of immunoglobulin G in the white adipose tissue of aged individuals activates the Ras-MEK/ERK signaling pathway in macrophages via FcγR receptors, inducing TGF-β secretion. This drives liver fibrosis and promotes the systemic dissemination of peripheral inflammatory mediators (Yu et al. 2024). Mitochondrial dysfunction constitutes another critical intersection between aging and NAFLD. With advancing age, excessive enrichment of mitochondria-associated endoplasmic reticulum membranes disrupts Ca^{2+} homeostasis and induces oxidative stress. Concurrently, diminished activity of the SIRT1 signaling pathway further impairs

cellular antioxidant capacity, leading to hepatocyte lipofuscin deposition and impaired autophagy. Autophagy impairment not only reduces the clearance of damaged organelles but also promotes IL-1β maturation by activating the NLRP3 inflammasome, creating a pro-inflammatory cycle (Walker et al. 2022). Furthermore, necroptosis increases significantly in the aged liver. The DAMPs released during this process activate immune responses via the TLR4/NF-κB pathway, accelerating liver fibrosis (Mohammed et al. 2021b). Additionally, age-related impairment of TJs in the BBB facilitates the increased permeability of peripheral inflammatory cytokines (e.g., IL-6, TNF-α) into the CNS, thereby inducing neuroinflammation (Walker et al. 2022). In summary, aging and NAFLD form a vicious cycle through multiple mechanisms—immunosenescence, metabolic inflammation, mitochondrial dysfunction, necroptosis, and BBB damage—collectively driving the progression of chronic systemic inflammation (Fig. 1).

Chronic systemic Inflammation-Induced common neuroinflammatory diseases

Mounting evidence indicates a close association between chronic systemic inflammation and neuroinflammatory disorders. Research suggests that the impact of chronic systemic inflammation on AD may precede amyloid deposition. In the context of chronic systemic inflammation in AD patients, peripheral immune cells infiltrate the CNS and accumulate near AD lesions. These cells induce microglial activation and exacerbate amyloid β-protein (Aβ) plaque deposition (McManus et al. 2014). Microglial activation, a core component of the neuroinflammatory response in AD, synergizes with Aβ plaque deposition to drive progressive neuroinflammation and neuronal dysfunction (Schwabe et al. 2020). Chronic systemic inflammation also represents a shared risk factor for NAFLD and depression. Studies indicate that liver fibrosis, characterized by lipid accumulation within hepatocytes, can trigger a systemic inflammatory state and activate microglia. This may lead to prefrontal cortex (PFC) impairment, a common feature in depression (Ntona et al. 2023). The PFC, a brain region critical for higher cognitive functions, is also implicated in research showing that chronic systemic inflammation accompanying MASLD correlates with microglial activation and reduced synaptic density within the PFC, potentially inducing cognitive impairment (Kjærgaard et al. 2024). Beyond AD and depression, several disorders involve the core mechanism of 'chronic systemic inflammation-BBB disruption-central glial cell activation'. Research demonstrates that peripheral inflammation contributes to neuroinflammation in Parkinson's disease (PD) by compromising the BBB, promoting A1 astrocyte polarization, and increasing microglial activation, resulting in excessive production of TNF-α, IL-1β, IL-6, and interferon gamma-γ (IFN-γ) (Jurcau et al. 2023). Furthermore, peripheral monocytes from patients with prodromal PD exhibit upregulated secretion of pro-inflammatory factors upon IFNγ stimulation, this immune-activated state may exacerbate central inflammation via BBB impairment (Mark et al. 2025). Additionally, LPS released during peripheral inflammatory diseases activates the Caspase-4/11-GSDMD pathway in brain endothelial cells, causing pyroptosis and BBB integrity loss. This allows peripheral inflammatory cytokines (e.g., IL-6, TNF-α) to enter the CNS, activating microglia and astrocytes, worsening demyelinating lesions, and contributing to multiple sclerosis (Wei et al. 2024). Studies also show that peripheral inflammatory cytokines entering the brain elevate cerebral pro-inflammatory cytokine levels and exert direct and indirect neurotoxic effects, potentially promoting anxiety disorders. The PFC and limbic structures are key areas affected by neuroinflammation in anxiety (Won and Kim 2020). Previous research has also found that insomnia increases cerebral prostaglandin D2 production, which effluxes peripherally across the BBB, triggering a cytokine storm (e.g., elevated IL-1β, IL-6) that further damages BBB integrity, creating a vicious cycle. Peripheral inflammatory cytokines crossing the compromised BBB subsequently activate microglia to release neurotoxic substances (e.g., reactive oxygen species), disrupting the sleep-wake cycle and exacerbating insomnia (Huang et al. 2021). Collectively, these findings, centered on the core mechanism of 'chronic systemic inflammation - BBB disruption - central glial cell activation', deepen our understanding of the link between chronic systemic inflammation and neuroinflammation.

Mechanisms of neuroinflammation triggered by chronic systemic inflammation

The mechanisms by which chronic systemic inflammation mediates the link between NAFLD and neuroinflammation are categorized as follows (Fig. 2). Firstly, chronic systemic inflammation is intrinsically linked to the activation of circulating immune cells and cerebral endothelial cells (CECs). It enhances the secretion of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 by circulating immune cells, and promotes the synthesis of factors like GRO-α/CXCL1. These circulating inflammatory mediators can activate receptors (e.g., for TNF-α and IL-1β) on CECs, promoting CEC signal transduction, inducing the release of local inflammatory mediators, and activating microglia. This cascade stimulates the release of additional pro-inflammatory cytokines, initiating complex immune-inflammatory responses within the CNS (Abbott et al. 2010). Secondly, chronic systemic inflammation increases BBB permeability. The BBB,

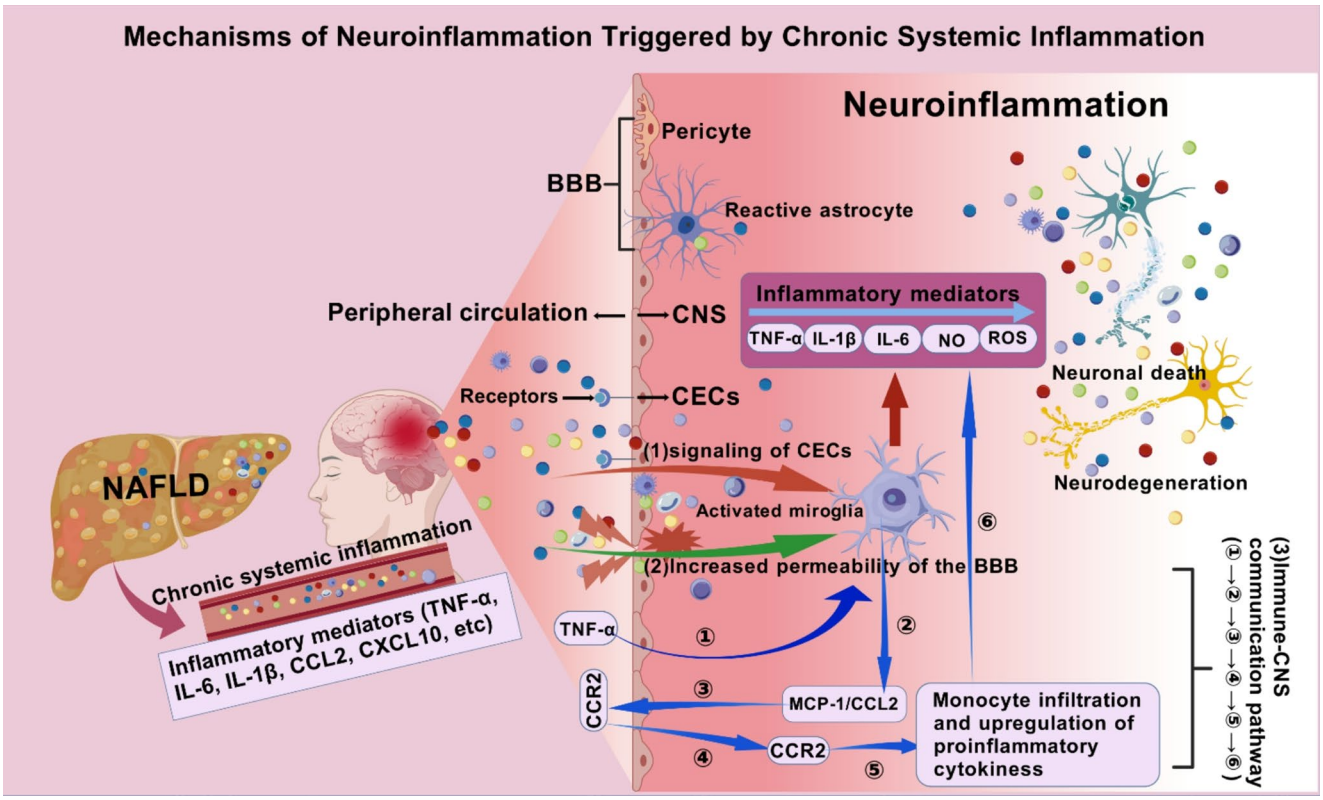

Fig. 2 This figure illustrates the primary mechanisms of neuroinflammation triggered by chronic systemic inflammation. In the context of NAFLD, inflammatory mediators, such as pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, etc.) and chemokines (CCL2, CXCL10, etc.), are persistently secreted into the peripheral circulation, ultimately driving the initiation and progression of persistent chronic systemic inflammation. Peripheral inflammatory mediators primarily trigger neuroinflammation through the following three mechanisms: (1) The signaling of CECs: Circulating inflammatory mediators can activate receptors (e.g., for TNF-α and IL-1β) located on CECs, promoting signal transduction within these cells. This activates microglia and stimulates the release of inflammatory mediators such as TNF-α, IL-1β, and IL-6, thereby initiating neuroinflammation. (2) Increased permeability of the BBB: Peripheral circulating inflammatory mediators can damage the BBB, increasing its permeability. This allows mediators like TNF-α, IL-6, IL-1β, CCL2, and CXCL10 to enter the brain, activating microglia and subsequently driving neuroinflammation within the brain parenchyma. (3) The Immune-CNS communication pathway: Peripheral TNF-α signaling first stimulates microglia to produce the monocyte chemoattractant protein MCP-1/CCL2. This subsequently drives the recruitment of peripheral immune cells, particularly monocytes expressing the chemokine receptor CCR2, into the brain. The resulting infiltration of monocytes into the brain, coupled with the upregulation of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, ultimately leads to neuroinflammation. NAFLD, nonalcoholic fatty liver disease; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin 1β; CCL2, C-C motif chemokine ligand 2; CXCL10, C-X-C motif chemokine ligand 10;CECs, cerebral endothelial cells; BBB, blood-brain barrier; CNS, central nervous system; CCR2, chemokine receptor 2; NO, nitric oxide; ROS, reactive oxygen species. Parts of the figures were drawn using materials from https://biogdp.com, accessed on 20 February 2025

composed of endothelial cells lining cerebral blood vessels that form TJs—its structural foundation—is surrounded by pericytes and astrocytes. Studies show that peripheral circulating inflammatory mediators can increase BBB permeability, allowing peripheral inflammatory mediators to diffuse into the brain and subsequently drive neuroinflammation within the brain parenchyma (Varatharaj and Galea 2017). Notably, immune-CNS communication pathway has garnered increasing attention. Demonstrated in murine models of inflammatory liver injury, these pathways entail peripheral TNF-α signaling, under conditions of peripheral inflammation, initially stimulating microglia to produce MCP-1/CCL2. This chemokine then drives the recruitment of peripheral immune cells, particularly those expressing the chemokine receptor CCR2, into the brain. This results in monocyte brain infiltration and upregulation of pro-inflammatory factors like TNF-α, IL-1β, and IL-6, culminating in a series of neuroinflammatory events (D'Mello et al. 2009). Peripheral TNF-α signaling is key to microglial activation and subsequent monocyte brain recruitment, this pathway operates via transvascular mechanisms involving passive or active transport of molecules and cells across the BBB (Varatharaj and Galea 2017). TNF promotes the expression of P-selectin and E-selectin on cerebral microvessels, both essential for cellular recruitment (Carvalho-Tavares et al. 2000). Clinical findings indicate that elevated CCL2 levels are a significant feature during chronic systemic inflammation in NAFLD patients (Haukeland et al. 2006). Thus,

NAFLD can increase BBB permeability and drive neuroinflammation via these immune-mediated communication pathways (Bettcher et al. 2021). Animal models further confirm the reciprocal influence between chronic systemic inflammation and neuroinflammation. Within the context of hepatic inflammation, murine models of inflammatory liver injury show increased numbers of $CCR2^{+}$ monocytes in peripheral circulation and elevated brain MCP-1 levels, accompanied by significant monocyte brain infiltration. Peripheral TNF-α signaling stimulating microglial production of CCL2 (MCP-1) plays a crucial role in this process (Baeta-Corral et al. 2023; D'Mello et al. 2009). Inhibiting this immune-mediated communication pathway and the consequent brain monocyte infiltration in mice with attenuated liver inflammation significantly improves behavioral alterations associated with liver inflammation-related neurological disorders (D'Mello and Swain 2014).

Pathways of circulating inflammatory mediators from periphery to CNS

Impairment of the BBB

The BBB is composed of endothelial cells lining the capillary walls of cerebral blood vessels, a continuous basement membrane, pericytes, microglia, astrocytes, and the enclosing glia limitans. Under physiological conditions, TJs between these endothelial cells maintain the stability of the CNS's internal environment. However, circulating inflammatory mediators such as IL-6, TNF-α, and IL-1β can impair the regulation of TJs in brain endothelial cells. This destabilizes BBB TJs, ultimately leading to BBB dysfunction characterized by increased permeability (Banks 2005), detailed mechanisms are illustrated in the Fig. 3. Furthermore, microglia play a dual role in maintaining BBB integrity during sustained inflammation. While perivascular microglia initially preserve BBB integrity by expressing Claudin-5, during persistent inflammation they can phagocytose astrocytic end-feet and compromise BBB function, resulting in BBB leakage (Haruwaka et al. 2019). Additionally, IL-1β secreted by activated microglia may promote the upregulation of vascular endothelial growth factor-A (VEGF-A) in astrocytes. This induces an endothelial nitric oxide synthase-dependent downregulation of TJ proteins—Claudin-5 and occludin—in endothelial cells, thereby disrupting TJ proteins and BBB integrity (Linnerbauer et al. 2020). The disruption of the BBB accelerates the entry of peripheral inflammatory mediators into the CNS, driving neuroinflammation.

Leakage of CVOs and signaling of CECs

Circumventricular organs (CVOs), located at the ependymal lining of junctional zones, include the area postrema of the lamina terminalis, median eminence, and organum vasculosum. They are in close proximity to immune cell reservoirs within the pia mater layer of the meninges. CVOs represent fenestrated and highly permeable regions of the brain that lack a complete BBB. This allows inflammatory mediators from the peripheral circulation direct access into the CVOs' parenchyma through these 'leaky areas' (Ransohoff et al. 2003), ultimately leading to microglial activation and alterations in neurotransmission systems (Swain and Jones 2019). CECs constitute the primary cell type forming the BBB and serve as the main interface for exchange between the peripheral circulation and the CNS. Receptors for inflammatory cytokines such as TNF-α and IL-1β are present on CECs. Circulating inflammatory mediators like peripheral TNF-α, IL-1β, and IL-6 can activate endothelial cells via their receptors, promoting CEC signal transduction, activation of perivascular cells within the brain parenchyma, and communication with microglia in the CNS. This cascade induces the release of local inflammatory mediators (Dantzer et al. 2008). Furthermore, inflammatory cytokines can upregulate adhesion molecules on CECs, facilitating leukocyte migration across the BBB and contributing to neuroinflammation. This process also increases BBB permeability (Banks 2005), detailed mechanisms are shown in Fig. 3.

Impairment of the blood-CSF barrier

Similar to the BBB, the blood-cerebrospinal fluid (CSF) barrier constitutes a crucial cerebral barrier between the peripheral circulation and the CNS, its detailed mechanisms are illustrated in Fig. 3. TJs located between the apical portions of choroid plexus epithelial (CPE) cells form the primary structural component of the blood-CSF barrier. In addition to preventing the accumulation of harmful compounds in the CSF and brain (Ghersi-Egea et al. 2018), CPE cells play a significant role in transmitting peripheral signals to the brain. In the context of chronic systemic inflammation, peripheral inflammatory mediators can disrupt the integrity of the blood-CSF barrier, allowing peripheral immune cells and inflammatory cytokines to gain access to the CNS and contribute to neuroinflammation (Gorlé et al. 2018). Furthermore, CPE cells are associated with altered expression of genes related to immune responses (Marques et al. 2009). Peripheral inflammatory mediators can also activate CPE cells, inducing the release of extracellular vesicles (EVs) containing pro-inflammatory miRNAs into the CSF and subsequently into the brain parenchyma. Cells such as

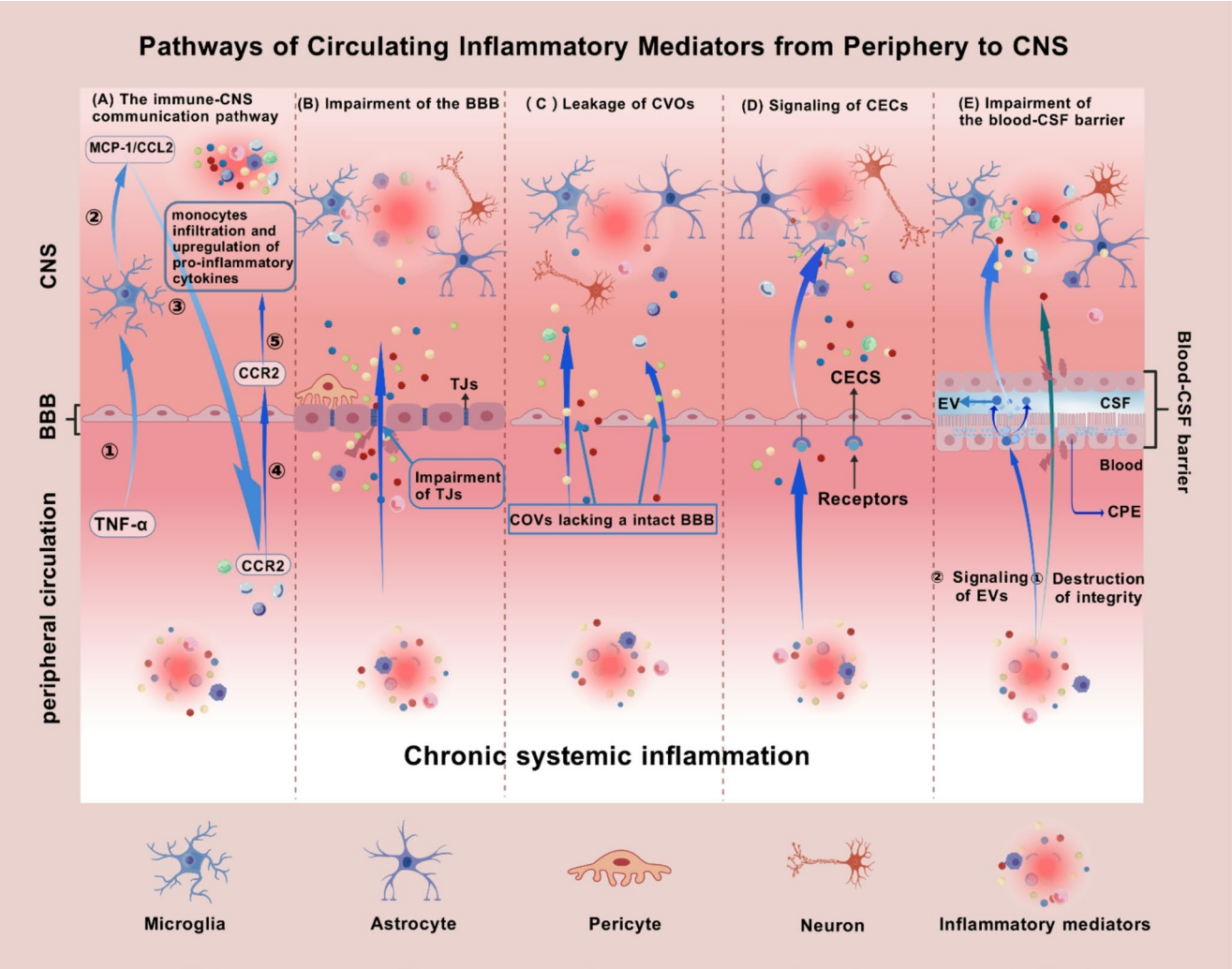

Fig. 3 This figure illustrates the pathways of circulating inflammatory mediators from periphery to CNS, primarily encompassing the following five mechanisms: (A) The immune-CNS communication pathway: Peripheral TNF-α initially stimulates microglia to produce MCP-1/CCL2, subsequently driving the recruitment of peripheral immune cells, particularly $CCR2^{+}$ monocytes, into the brain, leading to monocyte infiltration. (B) Impairment of BBB: Circulating inflammatory mediators damage the TJs of the BBB, subsequently gaining access to the CNS. (C) Leakage of CVOs: Peripheral inflammatory mediators enter the CNS through CVO regions, which lack an intact BBB. (D) Signaling of CECs: Inflammatory mediators bind to receptors on the surface of CECs; signaling through these CECs stimulates the release of local inflammatory mediators. (E) Impairment of the blood-CSF barrier: Peripheral inflammatory mediators can enter the CNS by disrupting the integrity of the blood-CSF barrier, and signal transduction from the periphery to the brain can also occur via EVs. CNS, central nervous system; TNF-α, tumor necrosis factor-α; MCP-1/CCL2, monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; CCR2, chemokine receptor 2; BBB, blood-brain barrier; TJs, tight junctions; COVs, circumventricular organs; CECs, cerebral endothelial cells; CSF, cerebrospinal fluid; EVs, extracellular vesicles; CPE, choroidal plexus epithelial. Parts of the figures were drawn using materials from https://biogdp.com, accessed on 20 February 2025

microglia and astrocytes can phagocytose these EVs and subsequently modulate gene expression, ultimately transmitting signals from the periphery to the brain (Balusu et al. 2016).

Glial cell activation in neuroinflammation

Glial cells, the most abundant and widely distributed non-neuronal cells in the CNS, include classical types such as astrocytes and microglia. These cells interact with neurons, immune cells, and other components, playing crucial roles in maintaining BBB homeostasis, protecting brain immune function, and regulating inflammatory responses (Vainchtein and Molofsky 2020). In the context of chronic systemic inflammation induced by NAFLD, circulating inflammatory mediators entering the CNS may activate microglia and astrocytes within the brain. This activation leads to sustained neuroinflammation, which subsequently causes oxidative stress damage and apoptosis in neurons (Heneka et al. 2014). Excessive inflammatory reactions can impair

neuronal regeneration and disrupt neuronal circuitry (Russo and McGavern 2016). Within neuroinflammation, inflammatory responses are particularly pronounced in the hippocampal and cortical brain regions. Pathological changes in these areas reveal impaired capillary morphology as well as reactive microgliosis and astrogliosis (Haj-Mirzaian et al. 2017).

Microglial activation

Microglia, the resident immune cells of the CNS, can be triggered by danger signals, including circulating inflammatory mediators, to transition from a resting state to an activated state (M1 phenotype) (Ransohoff and Perry 2009). M1-polarized microglia upregulate the polarization marker protein CD16/32 (Vegas-Suárez et al. 2022) and promote increased expression at the messenger ribonucleic acid or protein level of TLR (TLR-2 and TLR-4), TNF-α, and IL-1β, thereby driving neuroinflammation (Hoogland et al. 2015). Studies have found that TNF-α and IL-1β can activate microglia, leading to the release of further inflammatory cytokines and establishing a vicious cycle that causes additional neuronal damage (Shen et al. 2016). In CNS inflammatory diseases, microglial activation and immune cell infiltration represent major pathological features (Kim and Suh 2009). Ionized calcium-binding adapter molecule 1 (Iba-1) serves as a marker for M1-polarized activated microglia in the CNS, with increased Iba-1 expression indicating microglial activation (Waller et al. 2019). Recent studies utilizing autoradiography and immunohistochemical imaging methods have provided evidence of microglial activation in the prefrontal cortex of MASLD rats (Kjærgaard et al. 2024). Assessment of microglial morphology via immunohistochemical detection of the microglial marker Iba1 revealed increased microglial activation in the context of MASLD (Wittekindt et al. 2022).

Astrocyte activation

Neuroinflammation is closely associated with astrocyte activation. Astrocytes, the most abundant cells in the CNS, respond to pro-inflammatory cytokines secreted by peripherally derived immune cells recruited into the CNS, thereby modulating the responses of neighboring cells throughout the CNS (Rothhammer and Quintana 2015). In the context of neuroinflammation, astrocytes become activated and release a variety of inflammatory factors, including cytokines, inflammatory mediators, and reactive oxygen species. These factors subsequently propagate and amplify the inflammatory response, impairing neuronal function and survival (Qian et al. 2023). Nuclear translocation of NF-κB in astrocytes also elevates nitric oxide levels, accelerating inflammatory progression via the nitric oxide pathway (Linnerbauer et al. 2020). Crosstalk exists between microglia and astrocytes during neuroinflammation. IL-1β secreted by activated microglia promotes the upregulation of VEGF-A production by astrocytes (Argaw et al. 2012). This increased VEGF-A, interacting with endothelial cells, enhances BBB permeability and facilitates the infiltration of peripheral immune cells into the CNS (Sofroniew 2015). Furthermore, inflammatory mediators such as IL-1α, TNF-α, and complement component C1q, released by activated microglia, can stimulate the transformation of astrocytes into the neurotoxic A1 phenotype (Miyamoto et al. 2020). A1 astrocytes exert neurotoxic effects, release inflammatory factors, reduce phagocytic activity and neurotrophic factor expression, exacerbate neuroinflammation, and contribute to the death of neurons and oligodendrocytes (Liddelow et al. 2017). The interaction mechanisms between microglia and astrocytes play a pivotal role in regulating the progression of neuroinflammatory diseases. While current research has extensively investigated the roles of microglia and astrocytes in neuroinflammation, whether more complex interaction mechanisms exist between peripherally derived inflammatory mediators entering the CNS and these glial cells in the context of NAFLD remains to be elucidated.

Therapeutic strategies for neuroinflammatory diseases

Targeted therapy for neuroinflammation

Targeted therapy for neuroinflammation constitutes a core strategy for treating neuroinflammatory diseases. For conditions such as AD and depression, the primary therapeutic approaches involve synergistic treatments targeting amyloid proteins, depression itself, and neuroinflammation. Research in neuroinflammatory pharmacology primarily focuses on inhibiting microglial activation and modulating the balance of inflammatory cytokines. However, there is currently a lack of Food and Drug Administration (FDA)-approved drugs that directly target microglial activation for treating neuroinflammation, although several agents show increasing therapeutic promise (Wei et al. 2025). TNF-α inhibitors suppress microglial activation by targeting TNF-α, thereby regulating the NF-κB pathway and balancing inflammatory cytokines. Anti-TNF-α agents like Etanercept have demonstrated improved cognitive function in AD patients, nevertheless, clinical trials of TNF-α inhibitors continue to face challenges with limited BBB penetration (Torres-Acosta et al. 2020). Furthermore, IL-1β inhibitors, such as minocycline, reduce neuroinflammation by inhibiting IL-1β secretion from microglia. Studies indicate their potential to prevent the development of depression-like

behaviors and hippocampal inflammation in AD model rats (Amani et al. 2019). IL-6 inhibitors, including tocilizumab, suppress microglia-mediated neuroinflammation by targeting the IL-6 receptor, exhibiting combined anti-inflammatory and antidepressant effects in depression models (Knight et al. 2021). NLRP3 inflammasome inhibitors (e.g., CY-09, MCC950, OLT1177) alleviate microglia-driven neuroinflammation by inhibiting NLRP3 inflammasome activation and blocking the release of IL-1β and IL-18, demonstrating beneficial therapeutic outcomes in PD models (Chen et al. 2021). 64Zn-aspartate improves cognitive function by suppressing neuroinflammation and systemic inflammation. It exhibits protective effects on dopaminergic neurons in animal models, indicating significant potential for AD treatment (Temnik et al. 2025).

Targeted therapy for NAFLD

NAFLD represents an underlying etiology of neuroinflammatory diseases, making targeted therapy for NAFLD to reduce chronic systemic inflammation a pivotal strategy for preventing or mitigating these neurological conditions. Current pharmacotherapies for NAFLD primarily encompass direct anti-inflammatory agents and metabolic modulators. Hepatoprotective anti-inflammatory compounds like silibinin inhibit hepatic pro-inflammatory cytokine release while crossing the BBB to suppress microglial TLR4 signaling (Cui et al. 2025). Vitamin E attenuates hepatic lipid peroxidation and inflammatory mediators (e.g., TGF-β), concurrently reducing cerebral microglial activation and mitigating neurodegenerative progression (Atiq et al. 2023). GLP-1 receptor agonists (e.g., semaglutide) alleviate central neuroinflammation indirectly by reducing hepatic fibrosis and inflammation, thereby lowering systemic IL-6 and TNF-α levels (Anderer 2025). Emerging strategies targeting inflammatory pathways include ASK1 inhibitors (e.g., selonsertib), which suppress hepatic inflammation and fibrosis by inhibiting ASK1 signaling while modulating gut microbiota to ameliorate liver inflammation and systemic inflammation, these agents are currently under clinical investigation (Loomba et al. 2018). Liver-targeted drug delivery systems also demonstrate growing therapeutic promise—nanocarrier-encapsulated anti-inflammatory agents (e.g., curcumin) designed for hepatic targeting show potential to reduce systemic drug exposure and BBB penetration-related adverse effects while improving central neuroinflammation (Hoti et al. 2022).

Synergistic therapy for the Liver-Brain inflammation Axis

The liver-brain axis represents a bidirectional communication pathway between the liver and brain, with circulating inflammatory mediators serving as one underlying mechanism of this crosstalk. The progression from NAFLD-induced chronic systemic inflammation to central neuroinflammation constitutes the 'liver-brain inflammation axis' system (D'Mello and Swain 2011). A growing number of agents demonstrate potential for synergistic neuroinflammatory therapy by targeting this axis. Studies indicate that gossypetin simultaneously ameliorates liver fibrosis and hippocampal neuroinflammation in mice through liver-brain inflammation axis targeting (Xu et al. 2024). Systemic administration of β-chitosan improves macrophage-driven hepatic inflammation, reduces peripheral accumulation of TNF-α and IL-1β, and attenuates central neuroinflammation via downregulation of circulating pro-inflammatory cytokines (Zou et al. 2024). Furthermore, berberine and curcumin—when combined with NAFLD treatment—show promise in mitigating central neuroinflammation. Berberine activates the AMPK pathway to reduce hepatic lipid deposition (Yu et al. 2021) while suppressing microglial activation and downregulating pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) (Lu et al. 2010). Curcumin inhibits hepatic NLRP3 inflammasome and caspase-1 activation, concurrently penetrating the BBB to improve neuroinflammation, demonstrating synergistic therapeutic effects targeting the liver-brain inflammation axis (Wei et al. 2025). Nonetheless, further experimental and clinical validation is required to confirm these synergistic outcomes.

Conclusions and future perspectives

This review synthesizes evidence from extensive literature to delineate the mediating role of chronic systemic inflammation in linking NAFLD with neuroinflammation. Within the context of chronic systemic inflammation in NAFLD, peripheral inflammatory mediators—including cytokines (TNF-α, IL-6, IL-1β) and chemokines (CCL2, CXCL10)—act upon the CNS through multiple pathways to elicit neuroinflammation. Immune-CNS communication pathway represents the principal mechanism bridging chronic systemic inflammation and neuroinflammation, involving processes such as peripheral TNF-α signaling, microglial activation, and monocyte recruitment to the brain. While growing research has progressively clarified the contributions of hepatic inflammatory mediators to neuroinflammation, it must be emphasized that more complex mechanisms may remain undiscovered within metabolic dysregulation contexts. Current investigations into the liver-brain inflammation axis predominantly focus on immune-CNS communication pathway, consequently, future studies should prioritize elucidating the distinct functions of diverse

inflammatory mediators within this axis and their intricate crosstalk mechanisms.

The BBB exhibits high selectivity toward drug permeation, historically directing therapeutic innovation for central neuroinflammatory diseases toward BBB-penetrating delivery technologies. These include novel carrier-mediated transport, targeted receptor-mediated translocation, physical assistance for trans-barrier delivery, and multimodal synergistic delivery strategies. Targeted nanotechnology demonstrates superior therapeutic potential by enhancing CNS drug permeability, showing particular promise in overcoming BBB limitations. For instance, transferrin-modified extracellular vesicles delivering berberine and palmatine achieve precise microglial targeting after crossing the BBB. This system effectively clears amyloid aggregates and significantly modulates neuroinflammatory milieus both in vitro and in vivo, demonstrating enhanced therapeutic efficacy against AD. Consequently, targeted nanotechnology warrants increased future attention. However, as all such techniques require BBB traversal, they inherently carry risks of pharmacologic or physical barrier damage. Our study offers novel insights by exploring NAFLD treatment's potential to ameliorate neuroinflammation, proposing a paradigm shift: optimizing BBB delivery technologies while concurrently developing NAFLD-neuroinflammation combination therapies. Particular emphasis should be placed on mitigating NAFLD-associated chronic systemic inflammation, as its concurrent management with neuroinflammatory therapeutics may potentiate treatment efficacy. Within this combinatorial strategy, dual-targeting nanocarriers delivering payloads simultaneously to hepatic and cerebral sites hold transformative potential. By coordinately improving peripheral and central inflammatory environments, these systems could substantially advance neuroinflammatory disease management. Collectively, our findings provide new perspectives for preventing and treating neuroinflammation.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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