Aging and Disease
www.aginganddisease.org
Early access date: February 16, 2026
http://dx.doi.org/10.14336/AD.2026.0013

Review

Aging of the Blood–Brain Barrier and Altered Permeability to Peripheral Immune Cells: Implications for Central Nervous System Disorders

Yu Gu[1,2], Liting Zhang[3], Zixin Du[3], Caiyun Wang[3], Wenyuan Deng[4], Yong U Liu[1,2,3*], Beisha Tang[1,2*]

[1]The First Affiliated Hospital, Multi-Omics Research Center for Brain Disorders, Department of Neurology, Clinical Research Center for Immune-Related Encephalopathy of Hunan Province, Hengyang Medical School, University of South China, Hengyang, Hunan, China. [2]The First Affiliated Hospital, Clinical Research Center for Immune-Related Encephalopathy of Hunan Province, Hengyang Medical School, University of South China, 421001 Hengyang, Hunan, China. [3]Laboratory for Neuroimmunology in Health and Disease, Center for Medical Research on Innovation and Translation, Institute of Clinical Medicine, School of Medicine, the Second Affiliated Hospital of South China University of Technology (Guangzhou First People's Hospital), Guangzhou, China. [4]Department of Anesthesia and Pain Medicine, The Sixth Affiliated Hospital, Sun Yat-sen University; Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

[Received January 6, 2026; Revised February 12, 2026; Accepted February 13, 2026]

ABSTRACT: The blood–brain barrier (BBB), built by endothelial tight junctions, transporters, and the endothelial–pericyte–astrocyte unit, maintains a tightly regulated the central nervous system (CNS) milieu and permits selective immune cell entry. With age, tight junction downregulation, transport and metabolic imbalance, pericyte loss, basement membrane and glycocalyx remodeling, and reactive astrocytosis erode BBB integrity. These shifts reset leukocyte-trafficking thresholds and routes, producing either excessive admission or inadequate entry of peripheral immune cells. The resulting dysregulated immune surveillance activates microglia, amplifies neuroinflammation, disrupts myelin and synaptic homeostasis, and contributes to Alzheimer's and Parkinson's diseases, vascular dementia, and other neuroinflammatory conditions. This review synthesizes cellular and molecular mechanisms of BBB aging, outlines pathways and phenotypes of immune translocation, and proposes a cascade linking permeability imbalance to immune mismatch, driving neurodegeneration and injury. We discuss interventions focused on barrier repair and immune recalibration, including the reinforcement of tight junctions, restoration of pericyte homeostasis, and modulation of endothelial transport and chemokine axes. By implementing these strategies within stage- and time-specific therapeutic windows, this framework informs earlier diagnosis, biomarker development, and disease-modifying strategies for CNS disorders.

Keywords: blood–brain barrier, aging, peripheral immune cell trafficking, neuroinflammation, neurodegeneration.

1. Introduction

The blood-brain barrier (BBB) preserves the separation and homeostatic distinction between the peripheral circulation and the central nervous system (CNS) through the neurovascular unit (NVU). This dynamic unit is architected by brain microvascular endothelial cells (BMECs), pericytes, and polarized astrocytic endfeet, with endothelial cells and pericytes embedded in a shared basement membrane and astrocytic endfeet tightly

***Correspondence should be addressed to:** Dr. Yong U Liu (Email: eyliuy@scut.edu.cn) and Dr. Beisha Tang (Email: bstang7398@163.com), Department of Neurology, Clinical Research Center for Immune-Related Encephalopathy of Hunan Province, Hengyang Medical School, University of South China, Hengyang 421001, Hunan, China

ensheathing the vessel wall. Microglia and neurons further integrate NVU function via paracrine signaling and activity-dependent regulation [1, 2]. Although endothelial cells ultimately determine barrier permeability, their transmembrane transport and tight-junction assembly are finely tuned by pericyte-derived cues, astrocytic metabolism, and neuronally driven activity, thereby sustaining a CNS steady state fundamentally distinct from that of the periphery.

Functionally, endothelial tight junctions provide the physical seal, while endothelial transporters and ion channels maintain narrow homeostatic ranges of K^+, Ca^{2+}, Mg^{2+}, and pH. Nutrient demands are met by Glucose transporter 1 (GLUT1) and dedicated amino-acid and vitamin transport systems [3, 4]. With aging and under diverse pathological conditions, weakening of tight junctions, remodeling of the glycocalyx and basement membrane, loss of pericyte support, and heightened astrocytic reactivity collectively erode BBB integrity and increase permeability. These shifts effectively reset the thresholds and routes for leukocyte trafficking across the barrier. The ensuing aberrant entry of peripheral immune cells can initiate or amplify neuroinflammation and disturb network function: peripheral monocytes are detectable within the CNS of Alzheimer's disease (AD) postmortem brains, and similar infiltration is observed in MPTP mouse models of Parkinson's disease (PD); conversely, BBB disruption may permit CNS-restricted antigens to egress into the periphery and escalate immune cascades [5–7].

To better understand the interplay between vascular dysfunction and immune susceptibility, a structured analysis of these mechanisms is essential. Therefore, this review is organized along the causal arc progressing from physiological aging to BBB functional decline, and ultimately to dysregulated immune traffic. First, we summarize the molecular, structural, and interface-cell changes of the BBB in aging and their shared mechanisms. We then distinguish physiology from pathological routes and phenotypes of peripheral immune entry. Finally, we discuss how these changes remodel the CNS microenvironment and accelerate age-related neurological diseases, concluding with intervention concepts centered on barrier repair and immune recalibration along with priorities for future research.

2. BBB alterations with aging: from molecules to cells to systems

2.1 Molecular and structural barrier alterations

Aging drives brain endothelial cells into a distinct senescence-associated secretory phenotype (SASP), fundamentally altering vascular homeostasis. At the transcriptional level, aged endothelial cells exhibit a marked upregulation of core senescence genes (e.g., *Cdkn2a*) and senescence-associated secretory phenotype (SASP) factors [8]. This senescent transition is further regulated by post-transcriptional mechanisms; for instance, the decline of *Dicer1* mRNA and protein in aged BMECs exacerbates senescent phenotypes, which can be reversed by *Dicer1* overexpression [9]. These molecular shifts have functional consequences, precipitating microvascular rarefaction and impaired vasodilation. Notably, targeting these metabolic and signaling deficits, such as through nicotinamide mononucleotide supplementation, can improve neurovascular coupling (NVC), preserve barrier integrity, and ultimately enhance cognition [10].

The physical barrier is compromised not only by the erosion of the luminal glycocalyx but also by the dismantling of inter-endothelial tight junctions composed of occludin, claudin-5, and Zonula occludens-1 (ZO-1). Mechanistically, aging disrupts these junctional proteins through converging pathways of oxidative stress and inflammation: MAPK activation and reduced neurotrophic support (e.g., FGF-2) drive occludin downregulation [11, 12], while senescence is associated with disrupted ZO-1 junctional continuity characterized by punctate and fragmented staining and reduced ZO-1 coverage [13]. These structural alterations are often accompanied by complex regulatory shifts, such as post-transcriptional regulation of ZO-1 suggested by increased ZO-1 mRNA without a corresponding rise in protein [14] and the release of claudin-5 into plasma, which serves as a peripheral marker of BBB injury in AD [15]. Extending beyond the junctional complex, the endothelial glycocalyx also undergoes age-related degradation. Restoring its mucin-type O-glycosylation (core-1) has been shown to improve integrity and rescue cognition [16]. Collectively, these deficits create a vicious cycle where oxidative stress suppresses barrier structures, permitting further inflammatory ingress. The data supporting these findings are summarized in Table 1.

Aging elevates inflammatory mediators and matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) activity, degrading laminins, type-IV collagen, and fibronectin. Crucially, as highlighted by Thomsen et al., the degradation of nidogen-1, the key linker between laminin and collagen IV, significantly compromises the structural stability of the vascular basement membrane scaffold [17]. Collectively, these proteolytic and cellular deficits lead to the thinning and rupturing of the basement membrane. Under inflammatory conditions, astrocyte-derived MMP-9 disrupts tight junctions and the basement membrane [18]; inhibiting MMP-2 and MMP-9 helps restore BBB structure and function [19, 20]. Chronic age-related inflammation increases Interleukin-6 (IL-6),

which may contribute to the dysregulation of tight junction proteins [21]. Basement membrane damage, especially through MMP-mediated degradation of collagen IV and laminin, weakens its structural role and facilitates leukocyte extravasation. In ischemic stroke with hemorrhagic transformation, MMP-9-positive neutrophil infiltration correlates with collagen IV degradation and BBB breakdown, increasing microbleed risk. Deficiency of key basement membrane components further enhances leukocyte migration, highlighting the importance of the extracellular matrix in limiting immune cell entry [22, 23].

Table 1. Molecular alterations of the BBB in aging and disease contexts.

Target Molecule	Expression Change	Context/Model	Functional Consequence	Ref.
Occludin	↓Protein& mRNA	hCMEC/D3cells (+Aβ1-40)	Increases permeability (MAPK-mediated)	[11]
	↓Protein levels	Aging & Dementia reviews	Compromises barrier integrity	[12]
ZO-1	Mislocalization	BubR1$^{H/H}$mice (Senescence)	Disrupts tight junction continuity	[13]
	mRNA ↑ (Protein unchanged)	Aged rats (24 months)	Suggests mRNA-protein uncoupling	[14]
Claudin-5	↑Plasma levels	Human AD patients	Peripheral marker of BBB leakage	[15]
Mucin-type O-glycans	↓Core-1 glycans	Aged mouse endothelium	Impairs luminal barrier & cognition	[16]
GLUT1	↓Global expression	Neurodegeneration reviews	Impaired cerebral glucose metabolism	[24]
	↓Protein levels	Aged C57BL/6 (Hippocampus)	Reduces hippocampal glucose supply	[25]
	↓Microvascular density	Aged & Marfan mice	Linked to microvascular rarefaction	[26]
GLUT1 / AA transporters	↑Circulating exosomes	Elders with WMH	Compensatory response to injury	[27]

Note: Arrows (↑/↓) indicate the direction of expression changes (upregulation or downregulation) compared to healthy or young controls.
Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; AA, amino acid; BubR1$^{H/H}$, BubR1 hypomorphic; hCMEC/D3, human cerebral microvascular endothelial cell line; MAPK, mitogen-activated protein kinase; WMH, white matter hyperintensities.

Metabolic dysfunction is a key feature of the aging BBB. Multiple studies confirm that GLUT1 expression and activity decline with age, compromising cerebral glucose metabolism. However, the causal direction remains uncertain, and it is unclear whether this deficit represents a primary vascular failure or a downstream consequence of broader neurovascular and metabolic changes [24, 25]. Interestingly, while Glut1-positive microvascular staining and microvascular density decline in aged mice [26], WMH in functionally normal elders is associated with increased endothelial-derived exosomal cargo levels of GLUT1 and the amino acid transporter LAT1, potentially reflecting early metabolic alterations or a reactive endothelial response [27] (Table 1). Transport dysregulation also extends to efflux pumps. For instance, P-glycoprotein (P-gp) increases in senescence-accelerated mice [28]; yet, under ischemic stress, this upregulation can paradoxically inhibit endothelial autophagy and exacerbate barrier damage [29]. These transport shifts occur alongside broader hemodynamic changes, including blunted endothelial dilation and chronic hypoperfusion [30, 31], which cumulatively drive the severe BBB disruption observed in models like SAMP8 mice [32, 33].

2.2 Phenotypic shifts in neurovascular interface cells

BBB homeostasis relies on tight coupling among endothelial cells, pericytes, and astrocytes at the NVU interface. With age, all three compartments undergo convergent shifts in energy metabolism, inflammation and oxidative stress, and structural polarity, diminishing coupling efficiency and thereby increasing permeability while reducing mechanical resilience and self-repair.

Astrocytes. Aging lowers mitofusin 2, reduces astrocyte-to-endothelium mitochondrial transfer, elevates endothelial oxidative stress, and promotes leakage; *Dmp1*$^{+}$ astrocytes lose function with downregulated angiogenic programs and vascular disruption [34]. Some datasets also suggest a compensatory astrocytic response characterized by the upregulation of protease inhibitors, heat-shock proteins, and anti-inflammatory factors, alongside the downshifting of harmful metabolic pathways, to partially buffer BBB stress [35]. In human frontotemporal dementia, loss of aquaporin-4 (AQP4) polarization at astrocytic endfeet points to impaired water flux control and barrier stability [36]. Consequently, astrocytes shift from "metabolic and structural supporters" toward a less supportive, more reactive state, weakening crosstalk with endothelium and pericytes.

Pericytes. Aging elevates pericyte senescence markers and SASP output, altering functional signatures and broadly weakening mechanical and signaling support to the barrier [37]. Increased levels of circulating and cerebrospinal fluid (CSF) soluble platelet-derived growth factor receptor β (sPDGFRβ) indicates PDGF-BB axis disruption, reduced pericyte coverage, and greater BBB leakiness, correlating with hippocampal permeability [38, 39]. Pericytes also shift from Type-1 to Type-2 states, associated with fibrinogen extravasation, tight-junction loss, and barrier damage; similar patterns in simian immunodeficiency virus (SIV) models of HIV infection suggest shared disease and aging pathways [40]. Vulnerability under stress is evident: radiation-induced pericyte senescence with autophagy defects and SASP amplifies barrier injury [41]. In aged brains, coverage may appear preserved at rest yet rapidly decompensate under anesthesia and surgical stress—consistent with a "primed" state that tips into dysfunction upon challenge [42, 43].

Endothelium. As the front-line barrier, BMECs display a reactive oxygen species (ROS)–inflammation–mitochondria triad imbalance in aging. Elevated ROS activates Nuclear factor-κB (NF-κB), driving inflammatory transcription, DNA and mitochondrial damage, tight-junction loss, and microvascular rarefaction; prolonged endothelial protection reduces rarefaction and immunoglobulin G (IgG) extravasation and improves behavior [44, 45]. Under H_2O_2 load, BMECs develop a SASP-like phenotype (cell hypertrophy; increased IL-6, IL-8, MCP-1, and ICAM-1), amplifying paracrine inflammation and bystander senescence [46]. Crucially, aging concurrently disrupts specific metabolic and hemodynamic signaling pathways. The age-related decline in circulating insulin like growth factor 1 (IGF-1) impairs IGF-1 dependent endothelial protective mechanisms and leads to neurovascular uncoupling [47]. Similarly, defects in capillary inwardly rectifying potassium channels Kir2.1, critical sensors for neuronal activity evoked K^+ elevations, attenuate retrograde capillary to arteriole signaling and compromise cerebral blood flow regulation, as demonstrated in TgF344-AD rats with amyloid β induced loss of capillary endothelial Kir2.1 expression and impaired functional hyperemia [48]. Furthermore, loss of the iron exporter ferroportin (FPN1) on brain microvascular endothelial cells causes iron retention within endothelial cells and disrupts brain iron homeostasis, which is associated with cognitive impairment [49]. Endothelial mitochondria are highly sensitive to oxidative stress: AAPH and H_2O_2 depress respiration and induce organelle enlargement and fragmentation [50]; age-related ETC decline plus ROS accumulation forms a damaging feedback loop [51]. Molecularly, loss of connexin 43 (Cx43) disrupts the Cx43–poly(ADP-ribose) polymerase 1 (PARP1)–NAD^+–sirtuin 3 (SIRT3) axis, causing PARP1 hyperactivation, NAD^+depletion, defective mitophagy, and barrier failure. In humans, supplementation with GlyNAC (a combination of glycine and N-acetylcysteine) reduced oxidative stress, enhanced mitochondrial function and endothelial performance, suggesting potential benefit for the injured BBB [52, 53].

System level. Cellular shifts scale up to network-level uncoupling. Aged animals commonly exhibit reduced pericyte numbers, endothelial junctional downregulation, and heightened permeability [13, 54]. Declines in astrocytic vasoactive output, delayed neuron-evoked vasodilation, and reduced endothelial NOS activity jointly slow neurovascular coupling [55–57]. In parallel, AQP4 polarity defects weaken glymphatic clearance, fostering accumulation of metabolic by-products (e.g., Aβ) and linking to AD progression; aging markedly slows Aβ clearance via glymphatic impairment [7, 58–60]. In sum, age-related metabolic stress, heightened inflammation and oxidative stress, and loss of structural polarity across the astrocyte–pericyte–endothelium axis converge via reduced coupling to drive system-level barrier dysfunction—directly raising BBB permeability and priming the cellular context for pathological leukocyte trafficking and CNS microenvironmental remodeling.

2.3 Convergent signaling and inflammatory mechanisms

Age-related BBB damage arises from the convergence of chronic low-grade inflammation ("inflammaging"), reciprocal oxidative stress and inflammation, and the dysregulation of developmental and homeostatic signaling pathways. Inflammaging is characterized by chronic low-grade elevations of pro-inflammatory cytokines, including IL-6, tumor necrosis factor-α(TNF-α), and IL-1β, accompanied by increased innate immune responsiveness in both the periphery and the CNS [61–63]. The anti-inflammatory fractalkine (CX3CL1)–CX3CR1 signaling axis at the neuron–glia interface is compromised with age, which may attenuate neuronal inhibition of microglia and predispose to pro-inflammatory activation. Aging also induces a shift toward A1-like astrocyte reactivity, consistent with enhanced pro-inflammatory transcription in the aged CNS [64, 65]. This chronic milieu persistently activates endothelial NF-κB signaling and NLR family pyrin domain containing 3 (NLRP3) inflammasomes, generating an amplifying loop and a higher baseline propensity for barrier opening—distinct from the reversibility typical of acute inflammatory opening [66, 67].

ROS acts as a major driver under aging and disease. Mitochondrial dysfunction, NADPH oxidase activation, and reduced antioxidant defenses, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), together drive ROS accumulation [68]. Excess ROS suppresses Ten-eleven translocation 2(TET2) and lowers ZO-1 transcription, disrupting junctions, while also activating MMPs to degrade collagen and laminins, weakening the basement membrane and raising permeability [69, 70]. Notably, aging may shift oxidative modification patterns rather than simply increasing global oxidation, implying pathway specificity [71]. ROS and inflammation are mutually reinforcing: ROS activates NF-κB and cytokine release; TNF-α drives further ROS production—often via NADPH oxidase 2 (NOX2)—strengthening IL-6 and IL-1β signaling and, under metabolic dysregulation, linking systemically to cognitive decline [72, 73].

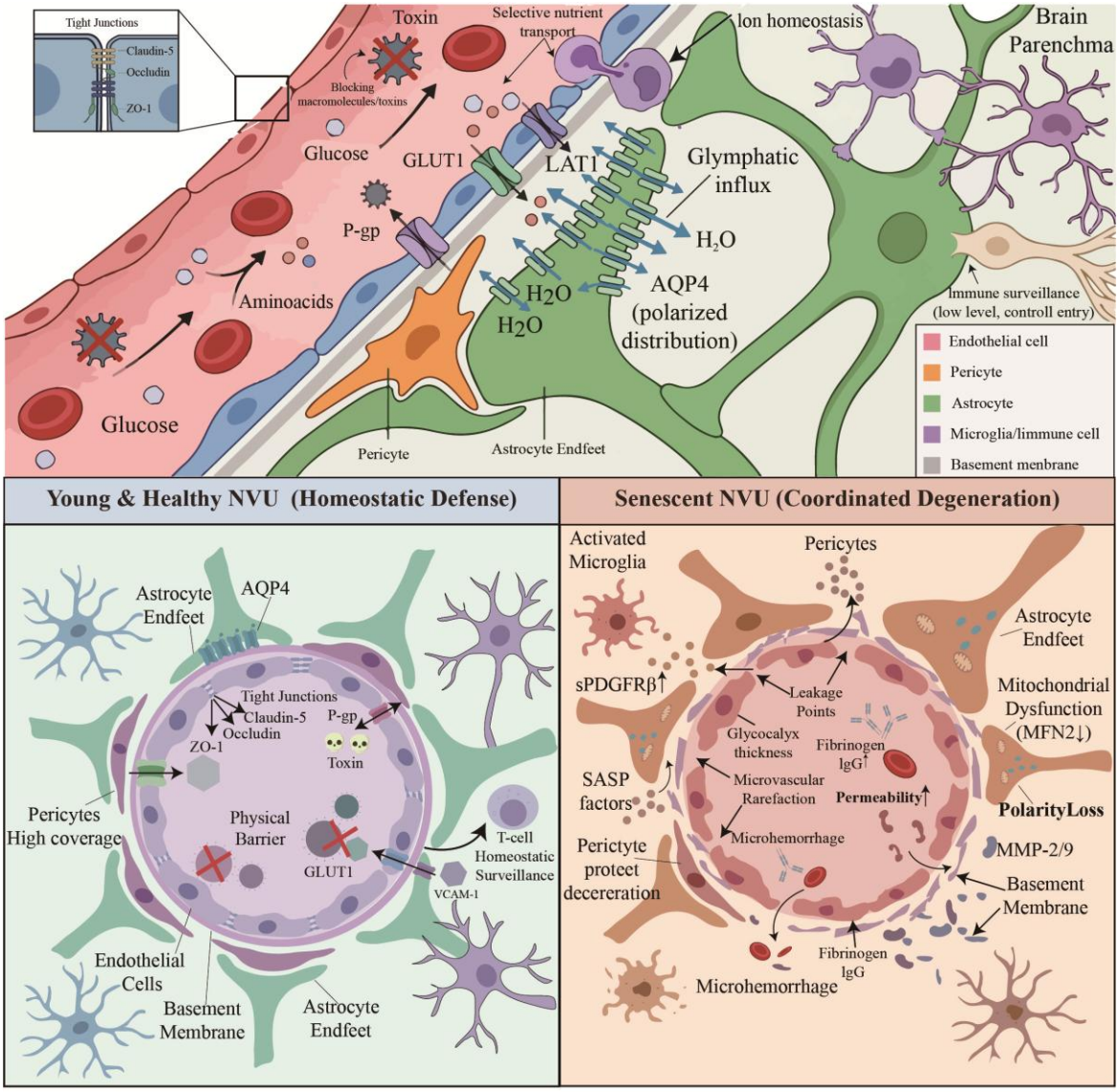

Figure 1. The transition of the neurovascular unit (NVU) from physiological homeostasis to synergistic aging. The upper panel depicts the physiological neurovascular unit (NVU) architecture composed of endothelial cells, pericytes, and astrocytic endfeet. The lower panel contrasts the homeostatic NVU (left) with the aged phenotype (right). While the healthy barrier relies on intact tight junctions and polarized astrocytes (AQP4), aging induces a synchronized collapse: endothelial degeneration, pericyte senescence (sPDGFRβ and SASP), and astrocytic uncoupling. This multidimensional breakdown, driven by MMP-mediated matrix degradation, leads to barrier leakage, plasma protein extravasation, and immune infiltration, establishing a self-amplifying neuroinflammatory loop. Abbreviations: AQP4, aquaporin-4; MMP, matrix metalloproteinase; SASP, senescence-associated secretory phenotype; sPDGFRβ, soluble platelet-derived growth factor receptor-β.

Multiple signaling pathways that sustain BBB development and homeostasis also drift with age and intersect with these inflammatory and oxidative axes. Transforming growth factor-β (TGF-β) normally restrains endothelial inflammation, promotes pericyte differentiation, and regulates extracellular matrix (ECM) synthesis; in aging, BBB leakage leads to exposure to serum albumin and subsequent TGF-β signaling hyperactivation (increased Smad2 and Smad3), which exacerbates inflammation and barrier permeability. Conversely, blocking this pathway restores BBB integrity and pericyte function, consistent with a dose- and time-dependent effect [74, 75]. The Wnt/β-catenin signaling axis, a core driver of junctional gene programs and barrier maturation—declines with reduced Wnt ligands and increased antagonists, accelerating β-catenin degradation and downregulating occludin and claudin-5, culminating in junctional collapse [76, 77]. Notch signaling modulates pericyte proliferation and migration via PDGFRβ, and its loss reduces coverage [78]; reduced Hedgehog activity limits mesenchymal ECM secretion and basement-membrane synthesis [79, 80]. Epigenetically, age-related DNA methylation and histone-modification shifts may silence key signaling genes, further uncoupling these networks and worsening barrier injury.

In aggregate, inflammaging establishes a persistent pro-inflammatory tone, ROS–inflammation coupling creates self-reinforcing damage, and age-related drift in TGF-β, Wnt, Notch, and Hedgehog signaling weakens barrier programs—spanning from gene regulation to cellular phenotypes and matrix architecture. The net result is a BBB that is easier to open and harder to close, reshaping the magnitude, timing, and lineage composition of peripheral immune trafficking, lowering CNS buffering capacity for aberrant immune flux, and laying the structural and chemotactic groundwork for pathological infiltration and neuroinflammatory amplification. This transition from a healthy barrier to a dysregulated, pro-inflammatory microenvironment is schematically summarized in Figure 1.

3. Age-related changes in peripheral immune trafficking across the BBB

3.1 Physiological immune surveillance

The classic notion of CNS "immune privilege" has been revised: even with an intact BBB, peripheral immune cells—such as monocytes and T cells—can enter the aging CNS at low, regulated levels and contribute to homeostasis [81]. This physiological ingress is largely confined to the meninges, choroid plexus, and perivascular spaces, with cell numbers far below those observed in pathological conditions; moreover, immune cell trafficking and surveillance exhibit circadian regulation [82, 83]. At the molecular level, immune cell trafficking across CNS barriers is orchestrated by adhesion and chemokine signaling axes. Aging is associated with increased expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) in the brain vasculature, which correlates with the accumulation of $CD8^+$ T cells—a process further facilitated by chemokines that drive leukocyte migration under inflammatory conditions [84, 85]. Immune cell presence in the CNS is a double-edged sword: essential for surveillance under homeostasis but pathological when dysregulated.

Importantly, this "physiological surveillance" in aging reflects a compositional shift rather than simple decline. The relative increase in memory T cells, a hallmark of T cell aging, may preserve certain recall capacities but occurs at the expense of repertoire diversity and immune flexibility [86], and circulating monocytes can be biased toward anti-inflammatory or regulatory macrophage differentiation depending on the inflammatory context [87]. Once in the CNS, these cells do not necessarily trigger inflammation; instead, they frequently cooperate with microglia to clear abnormal proteins (e.g., APP and Aβ precursors) and to secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF) that support neuronal survival [81]. Conversely, complete blockade of peripheral entry accelerates cognitive decline in aged animals, underscoring the protective value of this route.

Single-cell analyses further highlight functional specialization of immune cells that seed the aged brain: aging hematopoiesis becomes myeloid-skewed, increasing circulating myeloid populations; innate immune programs are remodeled, with tissue macrophages adopting pro-inflammatory transcriptional states that contribute to inflammaging; and natural killer (NK) cells have been shown to eliminate senescent neuroblasts, a process linked to age-associated cognitive decline [88]. More broadly, CNS immune homeostasis appears to depend on three coordinated mechanisms: (i) phagocytic clearance of aging-related debris; (ii) metabolic support via factors such as Insulin-like growth factor 1(IGF-1); and (iii) contributions to synaptic pruning that refine network efficiency. Overall, physiological surveillance requires precise control of dose and timing; once cell numbers or functions deviate, benefit can flip to injury, seeding subsequent pathologic infiltration.

3.2 Pathological infiltration and the neuroinflammatory loop

Pathological immune infiltration is initiated by inflammatory injury to the BBB. Pro-inflammatory cytokines activate endothelial NF-κB signaling, leading to phosphorylation and degradation of tight-junction proteins. In parallel, excessive MMPs activity disrupts basement-membrane integrity, creating focal breaches in the BBB. Increased permeability permits normally restricted immune cells, including T cells and monocytes, to aberrantly enter the brain parenchyma. Importantly, immune trafficking reflects a dynamic balance between adhesion and transmigration rather than a unidirectional process. Aberrant interactions between integrins such as very late antigen-4 (VLA-4) and adhesion molecules such as VCAM-1 can promote leukocyte retention within the vasculature [89], rather than intrinsic defects in chemokine receptor sensing, aberrant immune cell entry into the CNS parenchyma is driven by disruption of chemokine gradients. Specifically, loss or redistribution of abluminal C-X-C motif chemokine ligand 12 (CXCL12) removes a critical retention signal, permitting leukocyte migration into the parenchyma [90]. This migratory imbalance amplifies neuroinflammation and establishes a vicious cycle, in which infiltrating immune cells release ROS and nitric oxide (NO), further damaging the BBB and reinforcing immune entry [91].

The major driving forces of pathological immune infiltration are cytokine storms and dysregulated chemokine gradients. Cytokine storms arise during acute inflammation or infection, when excessive activation of innate and adaptive immune cells results in massive release of pro-inflammatory mediators such as IL-6, IL-17, and IFN-γ, forming self-amplifying feedback loops [92]. This systemic inflammatory state acts on BBB endothelial cells through paracrine and endocrine mechanisms, upregulating adhesion molecules and promoting peripheral immune activation. For instance, IL-17 enhances neutrophil elastase release, accelerating basement-membrane degradation [93], whereas IFN-γ induces antigen-presenting capacity in endothelial cells via STAT1 signaling, facilitating recruitment of $CD8^+$ T cells [94].

Concurrently, chemokine gradients provide directional cues for immune cell migration. Injury-induced release of chemokines such as CXCL10 and C-C motif chemokine ligand 2 (CCL2) establishes concentration gradients between the vasculature and lesion sites, guiding immune cells expressing CXCR3 or CCR2 toward areas of pathology [95]. The CCL2-CCR2 axis plays a dominant role in monocyte recruitment, as CCR2-deficient mice exhibit markedly reduced monocyte infiltration in experimental autoimmune encephalomyelitis (EAE) models [96]. Cytokines and chemokines act synergistically within this process: TNF-α enhances endothelial CXCL10 expression, while IL-1β promotes astrocytic secretion of CCL2, together forming a multilayered immune-recruitment network [97, 98].

T cells, monocytes, and macrophages represent the principal effector populations during pathological immune infiltration. $CD4^+$ T cells, particularly Th1 and Th17 subsets, secrete IFN-γ and IL-17, directly injuring oligodendrocytes and neurons. In AD models, increased proportions of Th17 cells are detected in both peripheral blood mononuclear cells and the hippocampus, accompanied by elevated amyloid-β and serum amyloid A deposition [99]. $CD8^+$ cytotoxic T cells induce neuronal apoptosis through perforin–granzyme pathways, and their activation correlates with the severity of demyelination in multiple sclerosis [100]. Monocyte-derived macrophages exhibit pronounced heterogeneity: $Ly6C^+$ inflammatory monocytes infiltrate lesions under CCR2 signaling and differentiate into M1-like macrophages that release IL-1β and TNF-α, whereas $CX3CR1^+$ resident monocytes preferentially give rise to phagocytic M2-like macrophages [101]. Disruption of this balance sustains inflammatory amplification.

Pathological activation of microglia further depends on synergistic innate and adaptive immune signals. Synergistic activation of Toll-like receptor 4 (TLR4) and IFN-γ signaling drives robust expression of inducible nitric oxide synthase (iNOS), leading to excessive NO production and subsequent neuronal toxicity [102]. Additional immune populations contribute to tissue injury: B cells exacerbate demyelination through antibody-dependent complement activation [103], while neutrophils drive early ischemic brain injury by releasing neutrophil elastase via NETosis [104]. Recent evidence suggests that insufficient infiltration of regulatory T cells (Tregs) compromises immunosuppressive control and contributes to dopaminergic neuron loss in PD [105].

In summary, pathological immune infiltration serves as a central pathogenic hub in neuroinflammatory disorders, integrating BBB disruption with cytokine–chemokine imbalances. These cascading processes not only dismantle barrier structural integrity but also fundamentally remodel the CNS microenvironment through sustained inflammation. Ultimately, the convergence of these upstream molecular drivers precipitates a drastic shift in barrier function, transforming the BBB from a regulator of homeostatic surveillance into a permissive gateway for cytotoxic infiltration, as illustrated in Figure 2.

4. Consequences of aberrant immune infiltration in aging

4.1 Microenvironmental remodeling and homeostatic disruption

With advancing age, structural and functional compromise of the BBB permits entry of peripheral T cells, monocytes, and other leukocytes that release IL-1β, TNF-α, and related mediators, directly perturbing microglial homeostasis. In health, microglia clear metabolic waste, prune synapses, and restrain excessive inflammation; under chronic, aging-associated immune cues, however, they shift from a homeostatic to a reactive and pro-inflammatory phenotype characterized by impaired clearance of Aβ and tau [106], mitochondrial dysfunction with energy imbalance [107], and hyperactivation of the NLRP3 inflammasome with sustained IL-1β release [108]. Transcriptomically, microglia show upregulation of inflammatory programs, downregulation of homeostatic genes, reduced phagocytic efficiency, and tight links to cognitive decline [109]. Thus, microglia transition from neuroprotective sentinels to pathology amplifiers, exerting upstream influence over the emergence and progression of age-related diseases such as AD and PD, and highlighting the therapeutic promise of microglial reprogramming.

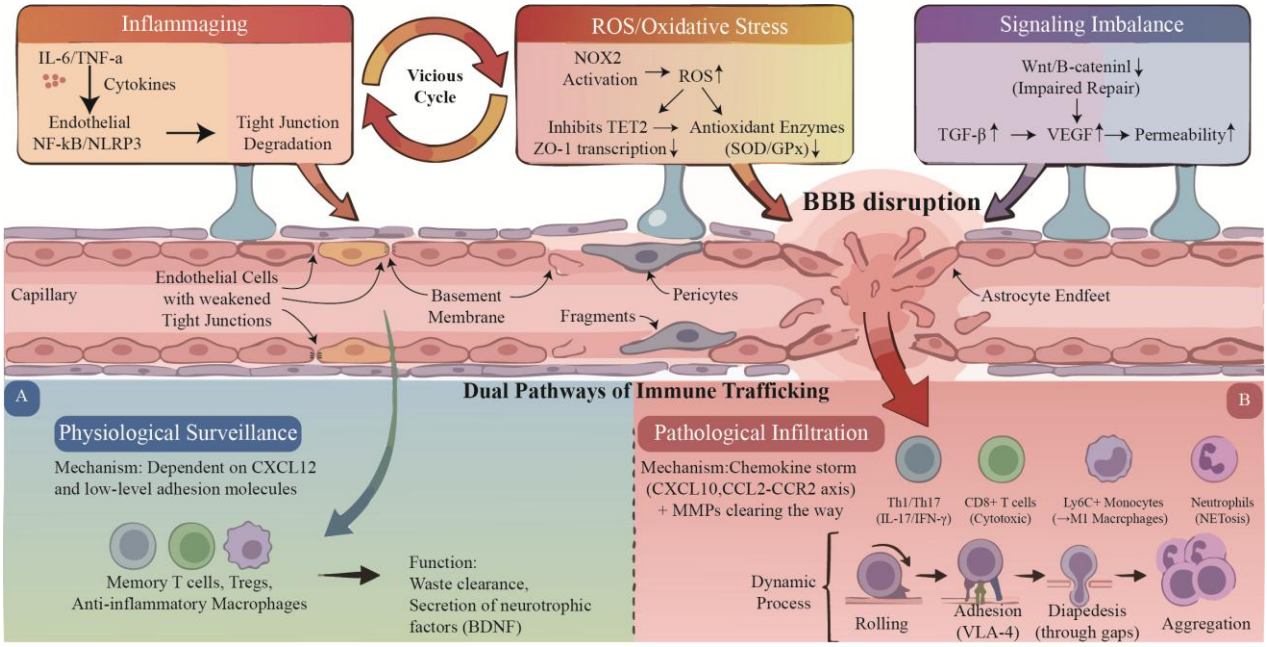

Figure 2. BBB integrity loss and associated alterations in immune infiltration profiles. The upper panel illustrates core upstream mechanisms compromising barrier integrity: (i) Inflammaging (IL-6 and TNF-α activating NF-κB); (ii) Oxidative Stress (NOX2–ROS loop and TET2 inhibition); and (iii) Signaling Imbalance (reduced Wnt and β-catenin repair vs. elevated TGF-β). The lower panel contrasts immune entry modes. Left A (Physiological): CXCL12 orchestrates controlled surveillance by neuroprotective cells (e.g., Tregs). Right B (Pathological): MMP-driven breaches and a chemokine storm (e.g., CCL2 and CXCL10) trigger massive infiltration of cytotoxic effectors (Th1, Th17, and neutrophils). This establishes a self-amplifying infiltration–damage–re-infiltration loop driving neuronal injury. Abbreviations: CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; IL-6, interleukin-6; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NOX2, NADPH oxidase 2; ROS, reactive oxygen species; TET2, ten-eleven translocation 2; TGF-β, transforming growth factor-β; Th, T helper cell; TNF-α, tumor necrosis factor-α; Tregs, regulatory T cells.

Crosstalk between infiltrating peripheral cells and microglia magnifies neuroinflammation and establishes an infiltration–barrier damage–re-infiltration loop. $CD8^+$ T cells injure neurons via granzyme B-dependent cytotoxicity [110], while monocyte-derived macrophages secrete MMPs that further erode the BBB [111]. Downstream consequences include aberrant hippocampal synapse loss, driven by complement component 1q (C1q) overactivation that promotes excessive synaptic tagging and a subsequent reduction in spine density [112]; microglia-derived ROS and cytokines triggering neuronal apoptosis [113]. Clinically, CSF from cognitively impaired individuals shows an immune "reset"—characterized by the downregulation of non-classical monocyte lipid-transport genes, such as apolipoprotein E (APOE) and apolipoprotein C1 (APOC1), and increased CXCL16 levels, which correlate with the axonal-injury marker neurofilament light chain (NfL) [84]. Experimental work further indicates that preserving the naïve T-cell pool and limiting excessive apoptosis can delay immunosenescence and ameliorate neuro-degenerative pathology [114].

At a broader microenvironmental level, aging-associated infiltration dismantles a tripartite defense—

astrocytes, endogenous antioxidant systems, and microglial surveillance. Astrocytic cholesterol metabolism and synaptic support are impaired, predisposing to complement and interferon-linked inflammation [115]. A dramatic two- to three-fold increase in malondialdehyde (MDA), coupled with diminished superoxide dismutase (SOD) activity, signals a collapse in antioxidant defenses that drives oxidative stress [116]. Microglial autophagy–lysosome dysfunction promotes protein aggregate accumulation and pyroptosis [117]. Intercellular signaling becomes biased: chronic IFN-γ elevates STAT1 in neighboring cells, while anti-aging paracrine effects mediated by neural stem-cell exosomes and lipid metabolism weaken [118]. Over time, the balance between pro-inflammatory drive and anti-aging defenses is durably shifted. This distinct microenvironmental change, when compounded by individual susceptibility, gut-brain axis interactions, and systemic metabolic shifts, transforms transient, resolvable inflammation into persistent injury, accelerating the natural history of age-related neurologic disease.

4.2 Impact on neurodegenerative disease progression

Age-elevated BBB permeability facilitates brain entry of activated T lymphocytes and monocytes whose TNF-α and IL-6–rich signals chronically polarize microglia and astrocytes toward inflammatory states. Crucially, this sustained inflammatory milieu functions as a mechanistic driver of neurodegeneration by disrupting synaptic homeostasis and inhibiting amyloid clearance pathways. Consequently, these changes result in impaired hippocampal synaptic plasticity and establish conditions that favor Aβ accumulation and tau hyper-phosphorylation, thereby accelerating AD pathology [119]. In models recapitulating the α-synuclein pathology characterizing sporadic PD, border-associated macrophages (BAMs) present antigens to peripheral $CD4^+$ T cells, amplifying neuroinflammation and aggravating dopaminergic neuron loss; BAM-derived CCL5, CXCL10, and MMP-14 further enhance leukocyte ingress and matrix remodeling [120]. Concurrently, aging reshapes the Treg compartment—fewer naïve Tregs and more memory Tregs—converging with pro-inflammatory cell accrual to disrupt the pro- and anti-inflammatory balance [121].

Immune-mediated network imbalance couples to motor and cognitive decline. Infiltrating $CD8^+$ T cells aggravate axonal degeneration via IFN-γ, impairing motor coordination and memory [122, 123]. Under inflammatory drive, microglia over-prune synapses, degrading coding capacity in motor-learning circuits [124], and—by altering AMPA receptor surface trafficking and synaptic remodeling—induce dendritic spine abnormalities and network dysfunction [125, 126]. Progressive failure of regeneration is a central barrier to reversing age-related neuropathology. The chronic inflammatory niche molded by peripheral infiltration exerts time-dependent, bidirectional effects on neural stem cells: while limited acute inflammation can transiently support plasticity, chronic microglial activation, complement-mediated synapse loss, and persistent cytokines ultimately suppress neurogenesis and drive dysfunction [127]. For example, M2a macrophages promote axon elongation via an arginase 1 (Arg1)-driven pathway involving polyamines and the Cdc42-N-WASP-Arp2/3 signaling axis. Conversely, during aging, the accumulation of myeloid cells and myeloid-derived suppressor cells secreting high levels of TGF-β inhibits oligodendrocyte precursor maturation, limiting remyelination [128, 129]. Simultaneously, thymic involution reduces generation of naïve T cells and weakens immune surveillance [130]. Notably, elevated CCL11 in aged plasma can cross the BBB, suppress hippocampal neurogenesis, and impair cognition [131]. The specific stages of this neuroinflammatory cascade and its convergence on irreversible disease outcomes are summarized in Figure 3.

5. Conclusions and Future Directions

This review highlights that aging drives the synchronized functional decline of the NVU, characterized by the synergistic deterioration of endothelial cells, pericytes, and astrocytes. Rather than isolated cellular deficits, we identify a functional breakdown driven by metabolic failure and chronic inflammation, which concurrently compromises physical barriers (tight junctions, glycocalyx) and transport homeostasis. Crucially, this collective dysfunction results in a dual pathology: the loss of barrier selectivity combined with a diminished capacity for repair. Consequently, this permissive environment facilitates aberrant immune infiltration, establishing a self-amplifying neuroinflammatory loop that accelerates synaptic loss and the progression of neurodegenerative disorders like AD and PD.

While the evidence synthesized herein offers a robust framework for understanding neurovascular dysfunction, the precise biological reality is nuanced by conflicting data and unresolved questions. Significant debate persists regarding the dominance of specific adhesion molecules (e.g., ICAM-1 vs. ALCAM) [132, 133] and the precise cellular entry routes (paracellular vs. transcellular) under varying pathological states [134]. Critically, these mechanisms are not static but exhibit significant temporal dynamics. The dominant microglial and inflammatory signatures appear to shift across aging and along the

continuum from early to late disease stages, so that immune cell profiles in early pathology can differ markedly from those in advanced degeneration [135]. This temporal heterogeneity, combined with variations in transcriptomic, proteomic, and immunophenotyping methods, contributes to the discrepancies observed across studies [136]. Moreover, the inflammatory landscape extends beyond individual cytokines, involving complex signaling hubs like the NLRP3 inflammasome, whose roles significantly impact aging-related functional decline [137]. Additionally, conflicting evidence regarding astrocytic compensatory responses and GLUT1 expression highlights the difficulty in reconciling data across diverse experimental paradigms: while endothelial GLUT1 loss is a driver of degeneration [138], astrocytes under AD-related intervention may paradoxically upregulate metabolic intake, complicating interpretation [139]. Finally, caution must be exercised when translating findings from animal models to humans, due to inherent inter-species differences in immune cell repertoires and genomic inflammatory responses [140]. Clarifying these complex interactions is critical to overcoming the translational barriers currently hindering clinical success.

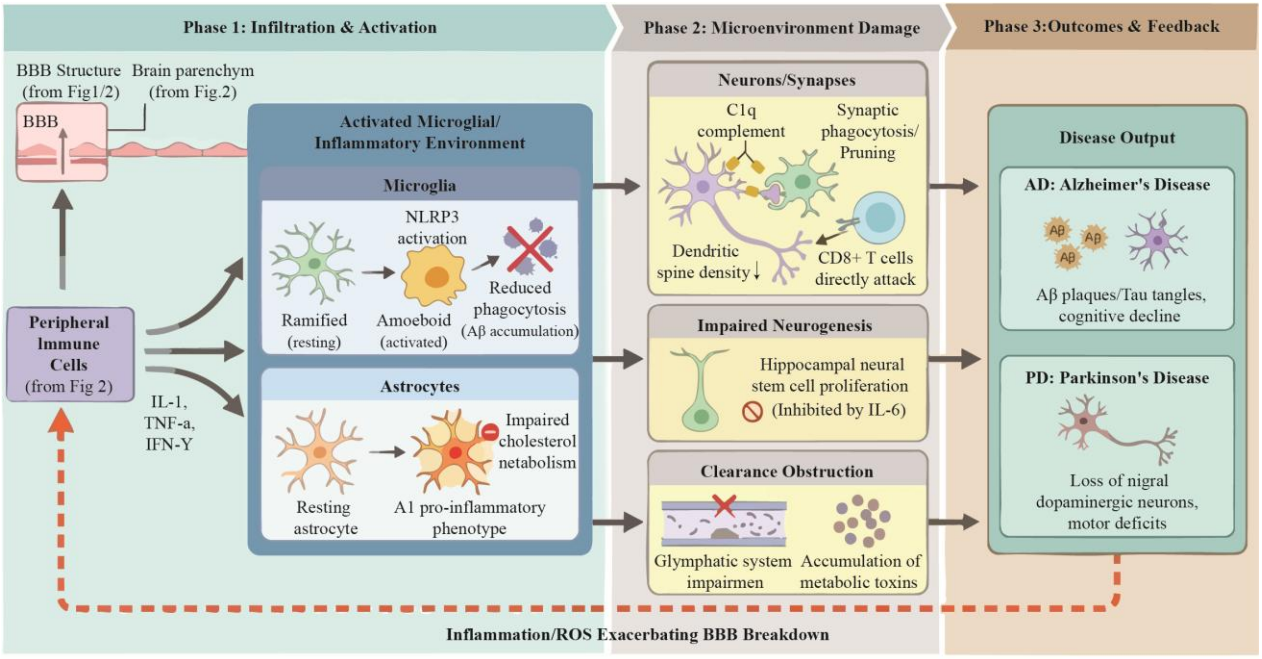

Figure 3. The neuroinflammatory cascade and resulting disease outcomes. Phase 1 (Initiation): Infiltrating immune cells release cytokines (e.g., IL-1β and TNF-α), inducing glial remodeling: NLRP3-hyperactivated microglia (amoeboid shift) and metabolically compromised astrocytes (antioxidant collapse). Phase 2 (Microenvironmental Collapse): Sustained inflammation precipitates (i) synaptic loss via C1q-mediated pruning, (ii) CD8+ T cell cytotoxicity, and (iii) regeneration failure. Phase 3 (Outcomes & Feedback): These alterations accelerate AD (amyloid and Tau) and PD progression. Crucially, central "inflammatory noise" and ROS exert negative feedback that further exacerbates BBB breakdown. This closes the infiltration–damage–re-infiltration vicious cycle, transforming reversible pathology into progressive neurodegeneration. Abbreviations: AD, Alzheimer's disease; BBB, blood-brain barrier; C1q, complement component 1q; IL-1β, interleukin-1β; NLRP3, NLR family pyrin domain containing 3; PD, Parkinson's disease; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

Future research should evolve from single-target approaches to multi-modal interventions aimed at restoring neurovascular integrity. A primary objective is to develop a combinatorial strategy that synchronizes barrier reinforcement with immune modulation. Specifically, reactivating endothelial Wnt and β-catenin signaling to suppress endothelial activation programs (e.g., VCAM-1 upregulation) and caveolae-mediated transcytosis—for example, via pharmacological β-catenin agonism—together with MMP inhibition and chemokine axis regulation (e.g., CCR2 and CXCR3), may help break the self-perpetuating cycle of leukocyte infiltration and vascular injury [141]. Furthermore, restoring the metabolic resilience of the aging NVU is equally critical. This includes enhancing transcellular metabolic crosstalk (e.g., astrocyte-to-endothelial mitochondrial transfer) and boosting NAD^+-dependent stress resistance via activation of the NAD^+ and SIRT axis (e.g., nicotinamide mononucleotide supplementation) to reduce endothelial mitochondrial ROS and improve neurovascular function [10]. To overcome bioavailability hurdles, future trials should leverage BBB-compatible delivery platforms that preferentially home to inflamed brain endothelium, such as VCAM-1–targeted nanocarriers, to increase

endothelial cargo accumulation in inflammatory lesions [142]. Finally, therapeutic precision remains paramount. Given the pleiotropic nature of pathways like TGF-β and Wnt, interventions must be temporally optimized and dose-specific. Emerging epigenetic tools also offer the potential to restore the transcriptional profiles of junctional proteins and pericytes, effectively reversing age-associated maladaptive phenotypic alterations without the need for broad systemic manipulation.

To facilitate precise intervention, a multi-dimensional diagnostic framework must be established. This system should integrate plasma and cerebrospinal fluid proteomics, single-cell transcriptomics, and advanced imaging metrics of barrier function (such as dynamic permeability and glymphatic clearance). Such an approach will enable early screening and patient stratification based on specific profiles of vascular permeability and immune dysregulation. Building on these biomarkers, clinical trial designs must transition toward a stratified, precision-medicine approach. For instance, adaptive randomized studies could employ comprehensive evaluation criteria—combining senescence markers, immunological profiling, and clinical endpoints—to validate combinatorial therapies. These therapies should target barrier reinforcement, immune modulation, and the promotion of neuroplasticity (including complement regulation and synaptic remodeling). Finally, elucidating the bidirectional gut-brain axis is crucial for understanding the causal links between the microbiome, peripheral metabolic inflammation, and neurovascular health. This research will reveal how systemic inflammatory mediators compromise BBB integrity via the NOX2–ROS and chemokine signaling pathways, providing a mechanistic rationale for synergizing lifestyle interventions with pharmacological treatments.

In conclusion, the transition from single-target approaches to the restoration of network homeostasis represents a fundamental paradigm shift. By employing time-resolved and combinatorial interventions, clinical strategies can effectively mitigate the dysregulated immune surveillance driven by BBB aging. Ultimately, this systems-level framework offers a tangible path to modify disease trajectories, slowing the pace of brain aging and improving outcomes in neurodegenerative disorders.

Acknowledgements

This work was supported by the National Key R&D Program of China (Grant No. 2023YFA1800100 to Y.U.L.), the National Natural Science Foundation of China (Grant No. 82071188 to Y.U.L.), the Science and Technology Projects in Guangzhou (Grant No. 2024A03J1256 to Y.U.L.), and foundation from University of South China (Grant No. 4310 to B.T.).

Authors' contributions

Y.G. prepared the manuscript with help from other authors. Y.G, Y.U.L. and B.T. designed this review. Y.G., L.Z., Z.D., C.W., W.D., Y.U.L. and B.T. contributed to the discussion. Y.G., Y.U.L. and B.T. are the guarantors of this work.

Conflict of interest

The authors have declared that no conflict of interest exists.

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