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REVIEW

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Neuroinflammation across neurodegenerative diseases: an aging-conditioned convergence–divergence framework for precision neuroimmunology

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Abstract

Neuroinflammation is increasingly recognized as a disease-shaping component of neurodegeneration rather than a secondary response to neuronal injury. This review integrates mechanistic and translational evidence across Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis/frontotemporal dementia, Huntington's disease, and progressive multiple sclerosis to advance an aging-conditioned convergence–divergence framework. In this model, aging and inflammaging establish a susceptible neuroimmune ground state through microglial priming, cellular senescence, mitochondrial and lysosomal dysfunction, impaired inflammatory resolution, blood–brain barrier deterioration, and increased peripheral–central immune coupling. Distinct initiating lesions subsequently converge on a restricted immune–glial architecture involving NLRP3 inflammasome activation, cGAS–STING and interferon signaling, NF-κB/JAK–STAT/MAPK networks, complement-mediated synaptic vulnerability, TREM2-dependent microglial programs, and immunometabolic dysfunction. However, the cellular source, anatomical distribution, timing, intensity, and functional consequences of these shared pathways diverge according to disease type, stage, genotype, regional vulnerability, and systemic context. Convergence therefore defines the common mechanistic architecture, whereas conditional divergence explains disease-specific inflammatory signatures and supports precision neuroimmunology. Therapeutic evidence further indicates that molecular selectivity alone is insufficient; effective intervention requires confirmation of causal pathway activity, central nervous system exposure, target engagement, appropriate timing, and biomarker-defined patient selection. Neuroimmune therapies should therefore prioritize restoration of homeostatic and pro-resolving functions over indiscriminate suppression and be evaluated within defined inflammatory endotypes using mechanistically aligned biomarkers and testable hypotheses.

Keywords: Neuroinflammation, neurodegenerative diseases, microglia, astrocyte reactivity, inflammasome signaling, precision neuroimmunology

Introduction

Neurodegenerative diseases have traditionally been understood through a neuron-centered framework in which selective neuronal vulnerability, protein misfolding, synaptic failure, and circuit collapse drive clinical decline [1]. Although this model remains essential, it does not fully explain the biological complexity, regional variability, or heterogeneous progression of Alzheimer's disease (AD),

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Parkinson's disease (PD), amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), Huntington's disease (HD), and progressive multiple sclerosis (MS) [2, 3]. These disorders are increasingly understood as multicellular failure of central nervous system (CNS) homeostasis in which immune–glial signaling shapes disease initiation, amplification, and progression [4]. Genetic evidence further supports this view by linking neurodegenerative risk to microglial activation, macrophage biology, endocytosis, lipid handling, and inflammatory signaling, indicating that immune mechanisms are embedded in disease susceptibility rather than merely secondary to neuronal injury [5].

Aging and inflammaging provide the biological background against which these mechanisms converge. Age-related microglial priming, cellular senescence, mitochondrial and lysosomal dysfunction, impaired proteostasis, blood–brain barrier (BBB) deterioration, systemic inflammatory exposure, and reduced immune-resolution capacity lower the threshold for persistent neuroinflammatory responses [6-12]. Disease-specific insults (including amyloid-β and tau, α-synuclein, TAR DNA-binding protein 43 (TDP-43), mutant huntingtin, damaged mitochondria, and myelin debris) then recruit a restricted immune–glial architecture involving microglial and astrocytic state transitions, inflammasome activation, cGAS–STING and interferon signaling, NF-κB/JAK–STAT/MAPK networks, complement-mediated synaptic vulnerability, triggering receptor expressed on myeloid cells 2 (TREM2)-dependent programs, and immunometabolic stress [13-31].

Convergence, however, does not imply biological uniformity [14]. The cellular source, anatomical distribution, intensity, timing, and functional consequences of a shared pathway vary according to disease type, stage, genotype, regional vulnerability, vascular integrity, and systemic context [15]. The same immune response may therefore support containment and repair at one stage but promote maladaptive inflammation, synaptic elimination, or tissue injury at another [32]. The term conditional divergence is used here to describe how a common neuroimmune architecture acquires disease-specific configurations [6]. Convergence defines the shared mechanistic framework, whereas conditional divergence explains heterogeneous inflammatory signatures and provides the basis for precision neuroimmunology [33]. Synaptic remodeling, glial crosstalk, and neurovascular dysfunction illustrate this relationship by linking different molecular lesions to common circuit-level consequences while retaining disease- and stage-dependent features [16].

Accordingly, this review advances an aging-conditioned convergence–divergence framework for neuroinflammation across neurodegenerative diseases. The framework distinguishes disease-specific initiating lesions from shared cellular and molecular hubs, identifies the biological conditions that redirect protective responses toward chronic injury, and evaluates how these distinctions affect therapeutic translation. Precision neuroimmunology is treated not as an alternative to convergence but as its translational consequence: shared pathways reveal candidate targets, whereas cellular state, anatomical compartment, disease stage, inflammatory endotype, CNS accessibility, and target engagement determine when, where, and in whom those targets should be modified. This approach moves beyond descriptive cataloguing and provides a testable basis for restoring neuroimmune homeostasis while preserving surveillance, clearance, repair, and inflammatory resolution.

Aging-conditioned convergence–divergence model

Neurodegenerative diseases arise from distinct initiating lesions but repeatedly engage a restricted set of immune–glial, metabolic, and neurovascular mechanisms. The proposed aging-conditioned convergence–divergence model organizes this process into five interacting levels. First, aging and inflammaging establish a susceptible neuroimmune ground state. Aging-dependent white-matter-associated microglial states demonstrate how increasing myelin and lipid-processing demands reshape microglial function before overt neurodegenerative pathology develops [7]. Mitochondrial DNA leakage and sustained cGAS–STING activation provide a direct mechanistic link between aging, reactive microglial states, chronic inflammation, neurodegeneration, and cognitive decline [8]. Single-cell analysis of the human cerebrovasculature further shows that endothelial, pericyte, and perivascular-cell alterations contribute to BBB and vascular dysfunction, indicating that aging-related neuroimmune susceptibility extends beyond the brain parenchyma [6].

Second, disease-specific lesions—including amyloid-β and tau, α-synuclein, TDP-43, mutant huntingtin, damaged mitochondria, and autoimmune demyelination—provide different entry points into this susceptible system. TREM2-dependent microglial recognition and clearance of pathological TDP-43 illustrate how a disease-specific proteinopathy can engage a shared immune-clearance mechanism [13]. In PD models, loss of parkin activity permits neuronal NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome assembly, linking mitochondrial stress and genetic dysfunction to inflammatory neurodegeneration [17]. In HD, complement-dependent microglial elimination of corticostriatal synapses demonstrates that a genetically distinct disorder can recruit an immune-mediated pathway also implicated in other neurodegenerative conditions [18]. Human microglial xenotransplantation experiments further show that amyloid pathology induces multiple phagocytic, inflammatory, interferon-responsive, and antigen-presenting states whose expression is modified by *TREM2* and *APOE* variation [19].

Third, these initiating lesions converge on shared hubs involving glial state transitions, inflammasome and interferon signaling, inflammatory transcriptional networks, complement-mediated synaptic vulnerability, immunometabolic dysfunction, and neurovascular–immune coupling. Their effects nevertheless diverge according to cell type, anatomical region, genotype, disease stage, vascular integrity, metabolic status, and systemic inflammatory burden. Perivascular secreted phosphoprotein 1 (SPP1)-

mediated induction of phagocytic microglia shows how vascular context can redirect a shared immune response toward synaptic engulfment [15]. Human biomarker evidence similarly indicates that astrocyte reactivity conditions the relationship between amyloid-β and subsequent tau pathology [4], whereas APOE4-associated lipid-droplet accumulation shifts microglia toward a metabolically dysfunctional and neurotoxic state [20]. Fourth, context-dependent branch points—including cell type, anatomical region, genotype, disease stage, vascular or metabolic status, and systemic inflammatory burden–determine whether these shared hubs support containment and repair, become chronically maladaptive, or fail to resolve injury. Fifth, these configurations reconverge on defective clearance, synaptic and circuit loss, metabolic insufficiency, barrier failure, demyelination or failed remyelination, and neuronal or axonal degeneration. Precision neuroimmunology therefore requires identification of the pathway configuration that is active, causal, accessible, and modifiable in a defined disease stage and patient subgroup. Figure 1 summarizes the proposed aging-conditioned convergence–divergence model and illustrates the progression from aging-related susceptibility and disease-specific initiating lesions to shared neuroimmune hubs, context-dependent branch points, and common degenerative outcomes.

Aging-conditioned cellular and molecular convergence

Aging alters the baseline state of glial, vascular, and peripheral immune compartments by impairing mitochondrial and lysosomal function, lipid handling, antioxidant support, BBB integrity, and inflammatory resolution. Disease-specific lesions therefore act on an already sensitized multicellular system. Cellular convergence is expressed through recurrent phagocytic, inflammatory, complement-active, interferon-responsive, and metabolically stressed states, whereas conditional divergence reflects genotype, anatomical region, disease stage, vascular integrity, and systemic inflammatory burden.

Aging-conditioned glial state transitions

Microglia normally maintain surveillance, debris clearance, synaptic refinement, lipid balance, and immune restraint [34]. Aging increases myelin and lipid-processing demands while weakening mitochondrial, lysosomal, and resolution capacity [35]. Disease-associated states consequently combine loss of homeostatic features with phagocytic, complement, interferon, antigen-presentation, and lipid-stress programs. Aging-related white-matter microglia demonstrate that such changes can arise before

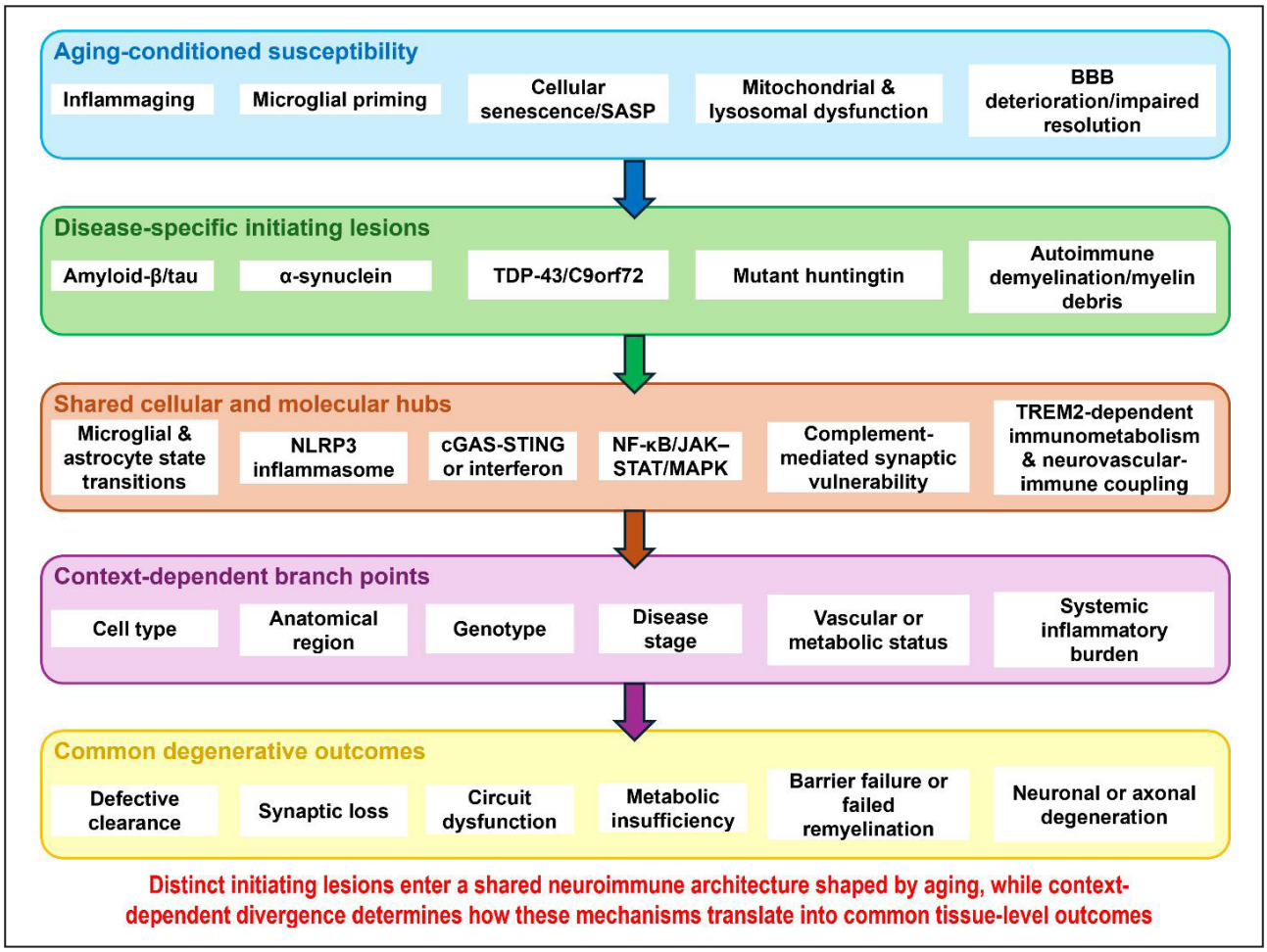


Figure 1. Aging-conditioned convergence–divergence model of neuroinflammation across neurodegenerative diseases. Individual cellular and molecular components are supported by the cited experimental and human evidence, whereas their five-level hierarchical integration, directional ordering, and predicted transitions constitute the proposed framework and require prospective validation.

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overt proteinopathy [7]. Their consequences remain context dependent: TREM2 restrained amyloid-driven tau accumulation but promoted pathological TDP-43 clearance in a different disease setting [13, 21], while human xenotransplantation studies showed that amyloid-responsive states vary with *TREM2* and *APOE* background [19]. *APOE4*-associated lipid accumulation further illustrates how impaired metabolic adaptation can redirect microglia toward neurotoxicity [20].

Astrocytes undergo parallel but distinct state transitions [4, 22, 23]. Aging weakens glutamate uptake, antioxidant buffering, metabolic support, and neurovascular regulation, increasing susceptibility to maladaptive reactivity. Microglia-driven astrocyte changes can amplify neuronal injury [32], whereas astrocyte-derived interleukin-3 (IL-3) can promote protective plaque-associated microglial activity [36]. Human biomarker evidence also indicates that astrocyte reactivity conditions the relationship between amyloid-β and subsequent tau pathology [4]. Microglia and astrocytes therefore converge on altered clearance, metabolic support, inflammatory signaling, and complement-dependent synapse remodeling [14], but the balance between protection and injury depends on pathological burden, genotype, region, and stage. Figure 2 illustrates the diverse human microglial states in response to AD-related amyloid pathology.

Aging-conditioned neurovascular and peripheral–central immune coupling

Aging-related endothelial activation, pericyte dysfunction, astrocyte-endfoot disruption, and weakened barrier regulation increase the influence of circulating and border-associated immune signals on the CNS [6, 33, 37, 38]. This coupling is stage and compartment dependent. In

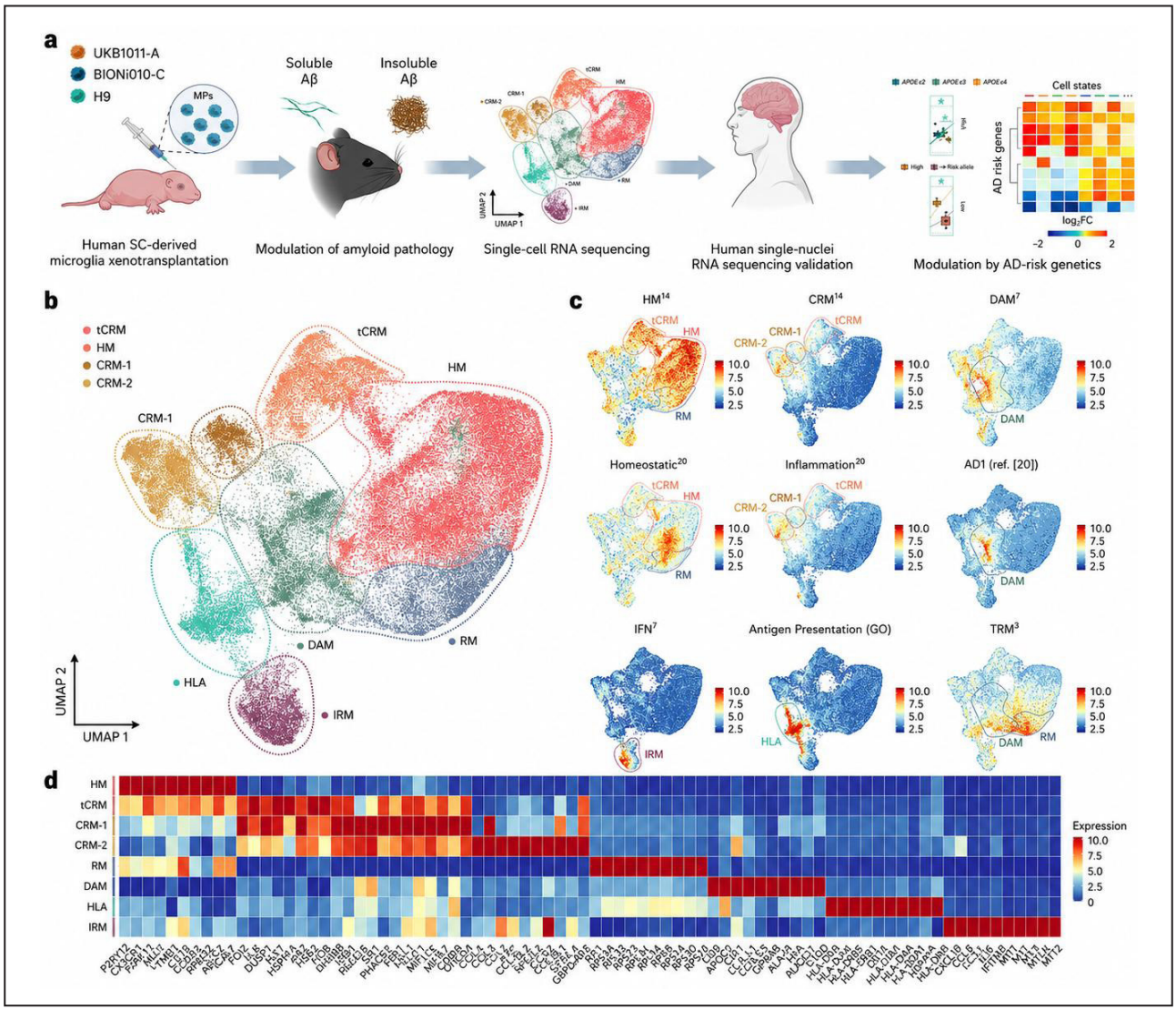


Figure 2. **Diverse human microglial states in response to AD-related amyloid pathology**. The figure summarizes the experimental strategy in which stem cell-derived human microglia were xenotransplanted into mouse models with AD-related amyloid-β pathology and analyzed by single-cell RNA sequencing. Uniform manifold approximation and projection (UMAP) clustering revealed multiple human microglial states, including homeostatic microglia (HM), ribosomal microglia (RM), disease-associated microglia (DAM), interferon-response microglia (IRM), cytokine–chemokine response microglia (CRM-1 and CRM-2), transitional CRM (tCRM), and HLA-enriched antigen-presenting microglia. Marker-gene expression patterns distinguish phagocytic/DAM-associated programs, cytokine–chemokine inflammatory programs, and antigen-presentation programs, supporting the concept that human microglial responses to AD pathology are diverse rather than uniform. The figure has been reproduced with permission from [19]. Copyright 2024 by Authors, published by Springer Nature under license CC BY 4.0.

Table 1. Aging-conditioned cellular convergence and context-dependent divergence in neuroinflammation.

Cellular compartment	Homeostatic role and aging-related change	Convergent neuroinflammatory response	Major determinants of conditional divergence	Reference
Microglia	Maintain surveillance, debris clearance, synaptic refinement, lipid balance, and immune restraint. Aging impairs lysosomal, mitochondrial, and lipid-processing capacity and lowers the activation threshold.	Recurrently acquire phagocytic, inflammatory, complement-active, interferon-responsive, antigen-presenting, and lipid-stressed states.	Genotype, anatomical region, disease stage, initiating lesion, metabolic state, and systemic inflammatory exposure.	[7, 9, 19-21]
Astrocytes	Support glutamate uptake, antioxidant defense, metabolism, synaptic function, blood–brain barrier (BBB) stability, and neurovascular coupling. Aging weakens metabolic, mitochondrial, and antioxidant support.	Develop reactive states associated with inflammatory amplification, impaired neuronal support, complement activity, synaptic dysfunction, and neurovascular disturbance.	Brain region, disease stage, microglial state, amyloid/tau burden, vascular integrity, and metabolic stress.	[4, 6, 14, 22, 32, 33, 36]
Endothelial cells and pericytes	Regulate BBB selectivity, vascular tone, nutrient transport, immune restriction, and neurovascular coupling. Aging promotes endothelial activation, pericyte stress, and barrier deterioration.	Develop inflammatory and senescence-associated states that increase barrier permeability and peripheral–central immune communication.	*APOE* genotype, vascular disease, systemic inflammation, anatomical compartment, and disease stage.	[6, 33, 37, 38, 41]
Border-associated macrophages and monocyte-derived cells	Provide immune surveillance and waste clearance at vascular, meningeal, and perivascular interfaces.	Acquire inflammatory or phagocytic programs and influence plaque-associated, vascular, and glial microenvironments.	Barrier integrity, disease severity, recruitment route, immune-cell phenotype, and systemic inflammatory burden.	[15, 37-39]
T cells	Provide adaptive immune surveillance and immune regulation at central nervous system (CNS) borders.	Pathogenic subsets may infiltrate vulnerable regions, interact with activated microglia, and contribute to cytotoxic or interferon-associated injury.	T-cell subtype, antigenic context, chemokine signaling, aging, anatomical compartment, and disease stage.	[9, 40]

human AD tissue, CD163-positive monocyte-derived cells were mainly vessel-associated in non-demented amyloid-positive individuals but entered the hippocampal parenchyma in advanced disease [39]. Aging-related microglial signaling also promoted CXCL10-dependent CD8 T-cell recruitment in white matter [9], while microglia-mediated T-cell entry contributed to neurodegeneration in tauopathy [40]. Convergence therefore occurs through vascular activation, border-interface signaling, and peripheral–glial communication; divergence depends on barrier integrity, recruitment route, immune-cell phenotype, systemic inflammatory burden, and disease stage [37, 38]. Table 1 summarizes the aging-related changes, convergent responses, and principal determinants of divergence across these cellular compartments.

Aging-conditioned NLRP3 inflammasome signaling

Aging-related mitochondrial dysfunction, lysosomal impairment, oxidative stress, and reduced autophagic clearance lower the threshold for persistent NLRP3 activation. Protein aggregates, extracellular ATP, damaged organelles, and membrane injury can thereby trigger NLRP3–ASC–caspase-1 assembly, IL-1β/IL-18 maturation, gasdermin D cleavage, and pyroptotic amplification. In AD-related microglia, GPCR19 regulated P2X7R-dependent NLRP3 activation, whereas loss of parkin permitted neuronal inflammasome assembly in a PD model [17, 23]. NLRP3 inhibition reduced demyelination, oligodendrocyte loss, and neurological impairment in experimental autoimmune encephalomyelitis, while inflammasome and pyroptosis-associated changes were detected in an ALS-like motor-neuron model [24, 25]. These findings identify NLRP3 as a shared amplifier of sterile injury, although its therapeutic relevance depends on the activating lesion, cellular source, anatomical compartment, and disease stage.

Aging-conditioned cGAS–STING and interferon signaling

Genomic instability, mitochondrial DNA leakage, senescence, and defective organelle clearance increase cytosolic DNA exposure during aging. Persistent cGAS–STING activation can consequently sustain TBK1–IRF3, NF-κB, type I interferon, and chemokine programs beyond their physiological roles in antiviral defense and genomic surveillance. Mitochondrial DNA-driven cGAS–STING activity promoted reactive microglial states, neurodegeneration, and cognitive decline during aging [8]. STING inhibition reduced glial activation and inflammatory transcription in an amyloid–tau model, while IL-6–STAT3 signaling reinforced this pathway in another AD model [26, 27]. Neuronal STING activation in ALS/FTD-related settings further demonstrates that the relevant source is

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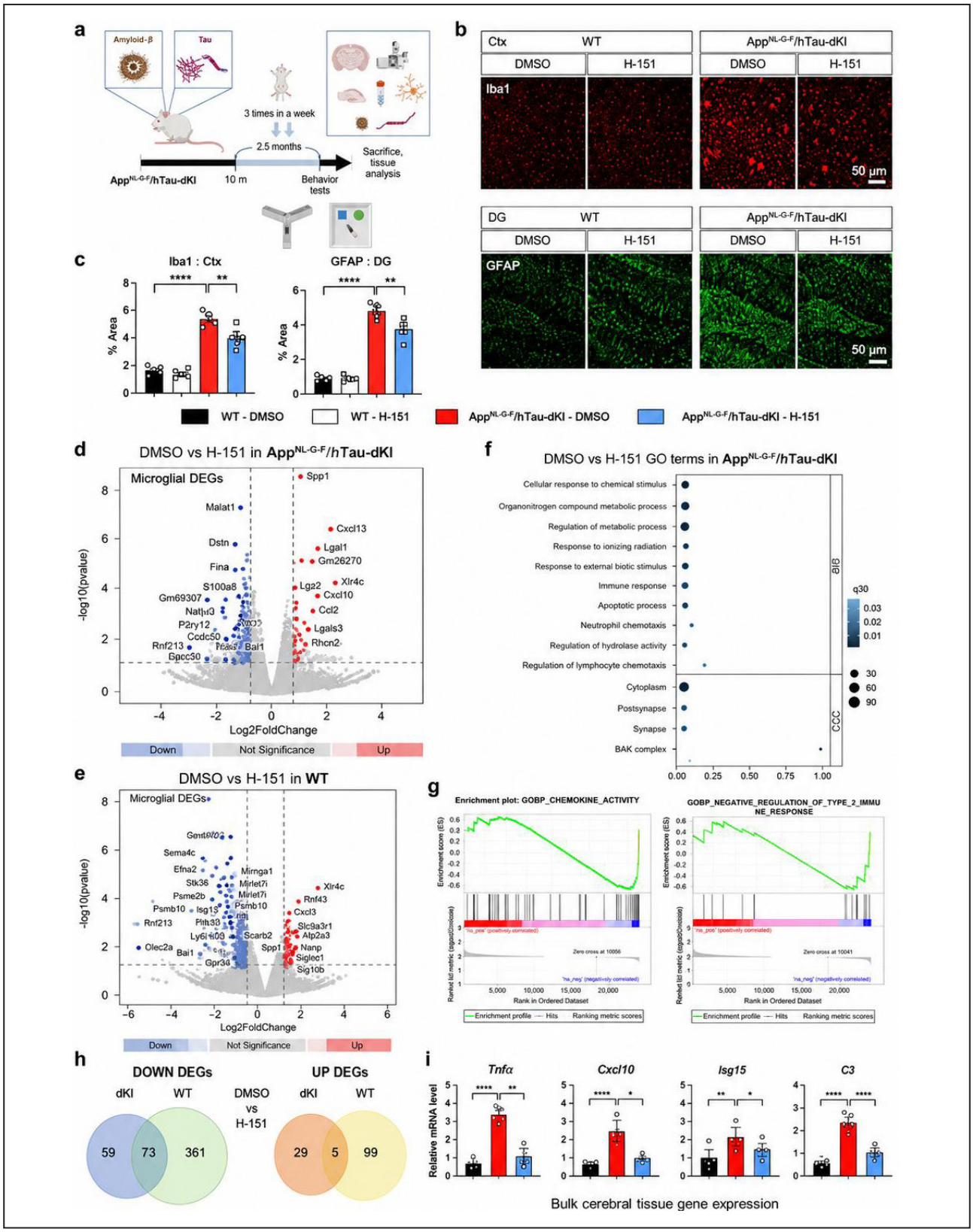


Figure 3. **Pharmacological STING inhibition attenuates glial reactivity and inflammatory transcriptional programs in an AD model**. **(a)** Experimental design showing H-151 treatment of *App*$^{NL-G-F}$/hTau double-knock-in mice followed by behavioral testing and tissue analysis. **(b–c)** Representative immunostaining and quantification demonstrate reduced cortical Iba1 (ionized calcium-binding adapter molecule 1)-positive microgliosis and dentate-gyrus GFAP-positive astrogliosis after STING inhibition. **(d–e)** Volcano plots show treatment-associated changes in microglial gene expression in double-knock-in and wild-type mice. **(f–g)** Gene ontology and gene-set enrichment analyses identify modulation of pathways related to chemokine activity, interferon responses, lymphocyte chemotaxis, synaptic organization, and postsynaptic specialization. **(h)** Venn diagrams summarize shared and distinct differentially expressed genes. **(i)** Bulk cerebral-tissue analysis shows reduced expression of *Tnfa*, *Cxcl10*, *Isg15*, and *C3* following H-151 treatment. Together, these data support STING as a modifiable inflammatory hub linking glial activation, interferon-associated signaling, and synaptic dysfunction. The figure has been reproduced with permission from [26]. Copyright 2024 by Authors, published by Springer Nature under license CC BY 4.0.

not restricted to glia [28]. Translation therefore requires identification of the DNA source, responding cell, duration of activation, and disease-relevant CNS compartment. The experimental evidence summarized in Figure 3 provides direct support for the disease-amplifying role of persistent STING activation. In *App*$^{NL-G-F}$/hTau double-knock-in mice, pharmacological STING inhibition with H-151 reduced cortical Iba1-positive microgliosis and dentate-gyrus GFAP-positive astrogliosis. Transcriptomic analyses further showed broad changes in microglial differentially expressed genes and enrichment of pathways related to chemokine activity, interferon responses, lymphocyte recruitment, synaptic organization, and postsynaptic specialization. Bulk cerebral-tissue analysis also demonstrated reduced expression of inflammatory mediators, including *Tnfa*, *Cxcl10*, *Isg15*, and *C3*. These findings indicate that cGAS–STING signaling is not merely associated with neurodegenerative stress but can function as a modifiable inflammatory hub linking glial reactivity, interferon-associated transcription, and synaptic vulnerability.

Aging-conditioned inflammatory transcriptional networks

NF-κB, JAK/STAT, and MAPK pathways integrate cytokine, Toll-like receptor, purinergic, complement, proteotoxic, and cellular-stress signals. Aging-related cytokine exposure, oxidative stress, and impaired resolution favor recurrent activation, leading to inflammatory transcription, chemokine production, antigen presentation, reactive gliosis, and inflammasome priming. Their functions are nevertheless context dependent: astrocytic NF-κB and disease-associated astrocyte programs can support either protective or damaging responses [22, 27], while p38–TFEB signaling sustained microglial NLRP3 activity in a PD model [29]. Considerable upstream and downstream overlap also permits compensation when one node is inhibited. Therapeutic development should therefore assess network-level change rather than assume that suppression of an individual signaling component will correct the broader inflammatory state.

Aging-conditioned complement-mediated synaptic vulnerability

Aging reduces synaptic resilience and alters complement regulation, increasing the likelihood that stressed but viable synapses will be tagged for elimination. In AD models, C1q-dependent mechanisms promoted astrocytic and microglial removal of excitatory and inhibitory synapses [14]. Complement proteins similarly marked vulnerable corticostriatal synapses for early microglial engulfment in HD [18]. Perivascular SPP1 further linked vascular-associated immune signaling to phagocytic microglial states and synaptic loss [15]. Complement therefore provides a direct route from distinct initiating lesions to circuit dysfunction. However, physiological remodeling, debris clearance, synapse tagging, glial engulfment, and terminal complement injury represent different functions and therapeutic levels. Their consequences depend on the synapse type, anatomical region, glial state, vascular environment, and disease stage.

Aging-conditioned TREM2-dependent clearance and immunometabolism

Aging increases the burden of lipid-rich debris, damaged membranes, dysfunctional organelles, myelin fragments, and protein aggregates. TREM2 couples recognition of these substrates to microglial survival, chemotaxis, phagocytosis, lysosomal processing, lipid handling, and metabolic adaptation. TREM2 restrained amyloid-associated tau accumulation and promoted pathological TDP-43 clearance in experimental models [13, 21]. However, *APOE4/4* microglia accumulated lipid droplets and released neurotoxic factors, while human xenotransplantation studies showed that amyloid-responsive states vary with *TREM2* and *APOE* genotype [19, 20]. The critical issue is therefore not phagocytic initiation alone but whether internalized material is successfully degraded without metabolic exhaustion or damage to surrounding tissue. Substrate type, genotype, anatomical region, disease stage, and residual lysosomal capacity determine whether TREM2-associated responses remain protective or become insufficient.

Aging-conditioned senescence and impaired resolution

Persistent DNA damage, mitochondrial dysfunction, oxidative stress, chromatin disturbance, and proteostatic failure promote senescence-associated states in glial, vascular, and neural cells. Senescent cells can lose homeostatic functions while releasing cytokines, chemokines, complement-related mediators, oxidative signals, and tissue-remodeling factors. Experimental evidence links RE1-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) deficiency to impaired autophagy and neuronal senescence [10], while cytosolic release of mitochondrial double-stranded RNA can drive the inflammatory phenotype of senescent cells [12]. Mitochondrial DNA-driven cGAS–STING activity provides an additional link between aging, cellular damage, and chronic neuroinflammation [8], and senescence-associated vascular states may reinforce barrier dysfunction and peripheral–central immune coupling [6, 33]. The biological consequences depend on cell type, location, secretory program, and persistence: transient senescence may constrain acute damage, whereas unresolved senescent states can sustain chronic inflammation and impair repair.

Table 2 summarizes how aging modifies the major molecular hubs through which distinct neurodegenerative insults converge, while cell type, genotype, anatomical context, and disease stage determine their divergent expression and consequences.

Disease-specific expression of a convergent neuroimmune architecture

Having defined the shared aging-conditioned neuroimmune architecture, the following sections examine how it

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Table 2. Aging-conditioned molecular convergence and context-dependent divergence across neurodegenerative diseases.

Molecular hub	Aging-related susceptibility	Convergent neuroinflammatory mechanism	Major determinants of conditional divergence	Reference
NLRP3 inflammasome–IL-1β/IL-18 axis	Mitochondrial dysfunction, lysosomal impairment, oxidative stress, and reduced autophagic clearance lower the threshold for inflammasome activation.	Converts protein aggregates, ATP, damaged organelles, ionic imbalance, and membrane injury into caspase-1 activation, IL-1β/IL-18 maturation, gasdermin D cleavage, and pyroptotic amplification.	Activating lesion, cellular source, anatomical compartment, disease stage, and duration of activation.	[17, 23, 25]
cGAS–STING and type I interferon programs	Genomic instability, mitochondrial DNA leakage, cellular senescence, and impaired organelle clearance increase cytosolic DNA exposure.	Activates TBK1–IRF3, NF-κB, interferon-associated transcription, chemokine production, glial reactivity, and neuronal or vascular inflammatory responses.	DNA source, responding cell type, genotype, anatomical location, disease stage, and persistence of signaling.	[8, 26-28]
NF-κB/JAK–STAT/MAPK inflammatory networks	Increased basal cytokine exposure, oxidative stress, and impaired inflammatory resolution favour sustained or recurrent signaling.	Integrates cytokine, receptor, complement, proteotoxic, and cellular-stress signals into inflammatory transcription, reactive gliosis, antigen presentation, and inflammasome priming.	Cell type, upstream stimulus, pathway redundancy, anatomical region, disease stage, and signal duration.	[22, 27, 29]
Complement-mediated synaptic vulnerability	Reduced synaptic resilience, altered complement regulation, and primed glial phagocytosis increase inappropriate synapse tagging.	Promotes C1q/C3-dependent synapse marking and astrocytic or microglial engulfment, linking inflammation to circuit dysfunction.	Initiating lesion, synapse type, anatomical region, glial state, vascular context, and disease stage.	[14, 15, 18]
TREM2-dependent immunometabolism and clearance	Lipid-rich debris, damaged membranes, protein aggregates, and lysosomal burden increase the metabolic demands placed on microglia.	Couples damage recognition to phagocytosis, lysosomal processing, lipid handling, survival, and metabolic adaptation.	*TREM2* and *APOE* genotype, pathological substrate, metabolic demand, anatomical region, and disease stage.	[13, 19-21]
Cellular senescence and impaired inflammatory resolution	Persistent DNA damage, mitochondrial dysfunction, oxidative stress, chromatin disturbance, and proteostatic failure promote senescence-associated states.	Sustains cytokine, chemokine, complement-related, oxidative, and tissue-remodeling signals while reducing repair and inflammatory resolution.	Senescent cell type, secretory programme, anatomical location, vascular environment, and persistence of the senescent state.	[6, 8, 10, 11, 33]

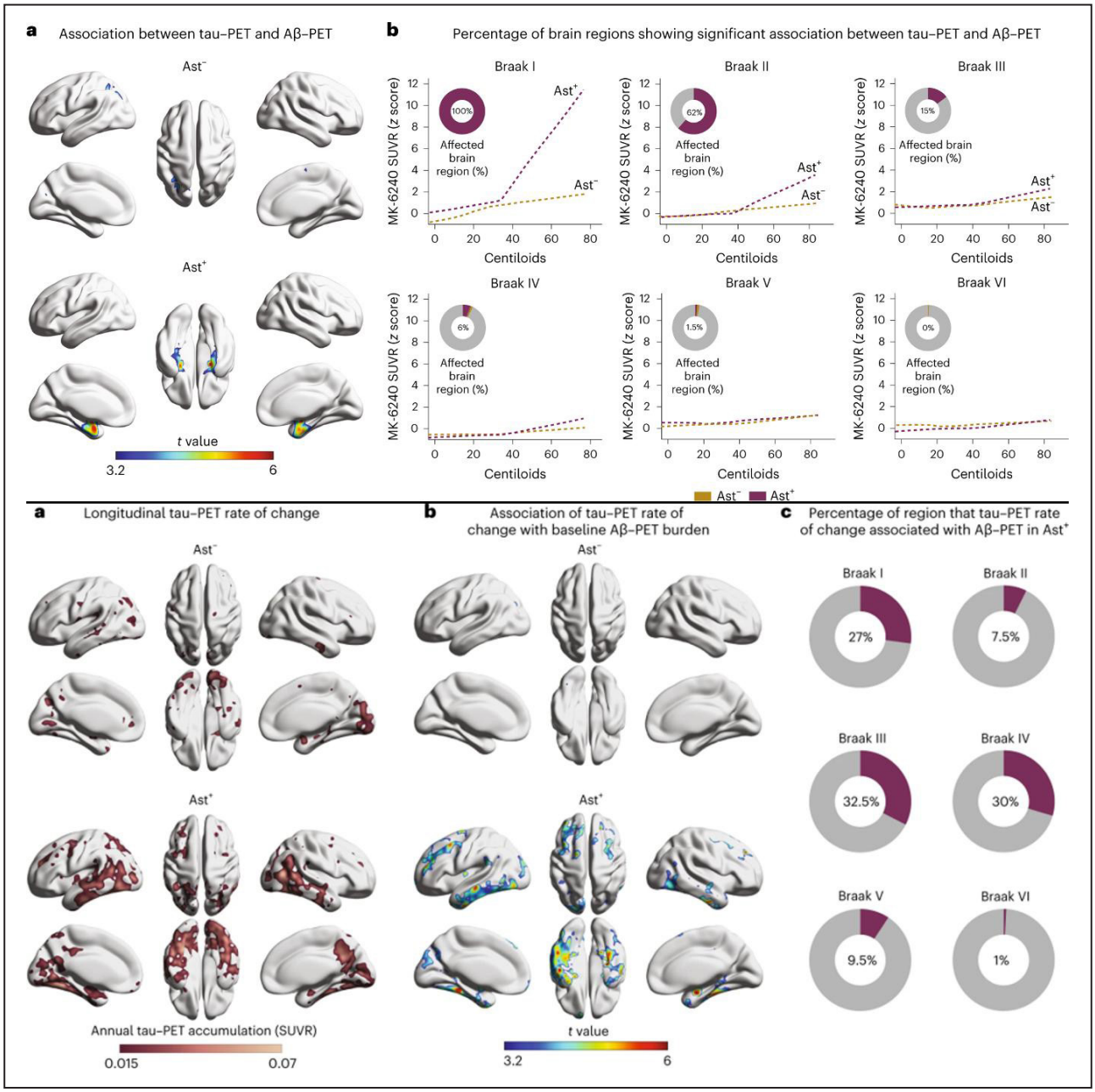


Figure 4. **Astrocyte reactivity conditions amyloid-associated tau deposition and longitudinal tau propagation in preclinical AD**. The upper panels show that the association between amyloid-β PET burden and tau-PET deposition is substantially stronger in individuals with positive astrocyte reactivity, particularly in early Braak regions. The lower panels show greater longitudinal tau accumulation and a stronger association between baseline amyloid-β burden and subsequent tau-PET increase in astrocyte-reactive individuals. Together, these findings support astrocyte reactivity as a biological modifier of amyloid–tau coupling and disease progression. The figure has been adapted from [4]. Copyright 2023 by Authors, published by Springer Nature under license CC BY 3.0.

is expressed in individual diseases. Each disorder is considered through four linked elements: the disease-specific initiating lesion, the shared cellular and molecular hubs it recruits, the contextual factors that produce conditional divergence, and the dominant tissue-level outcomes. The purpose is therefore not to repeat the mechanisms described above, but to show how a common neuroimmune architecture acquires distinct disease-, region-, genotype-, and stage-dependent configurations.

AD: amyloid–tau pathology within an aging-conditioned glial network

In AD, amyloid-β deposition and tau pathology provide the principal initiating lesions within an aging-conditioned environment characterized by impaired clearance, glial priming, vascular dysfunction, and reduced synaptic resilience. Amyloid pathology recruits heterogeneous microglial and astrocytic states rather than a single uniform inflammatory response. Human microglial xenotransplantation models showed that amyloid-responsive states were modified by *TREM2* and *APOE* variation [19], whereas APOE4-associated lipid-droplet accumulation shifted microglia toward metabolic dysfunction and the release of factors that increased tau phosphorylation and neuronal injury [20]. Astrocyte reactivity also conditioned the relationship between amyloid-β burden and subsequent tau

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pathology, indicating that protein deposition alone may be insufficient to determine downstream degeneration [4].

This relationship is illustrated in Figure 4. Cross-sectional tau-PET analyses showed that the association between amyloid-β burden and tau deposition was substantially stronger in individuals with positive astrocyte reactivity, particularly within early Braak regions. Longitudinal analyses further demonstrated greater tau accumulation and a stronger association between baseline amyloid-β burden and subsequent tau-PET increase in the astrocyte-reactive group. These findings provide empirical support for the convergence–divergence framework by showing that a shared initiating lesion does not produce a uniform downstream trajectory; instead, astrocytic state acts as a context-dependent modifier of amyloid–tau coupling and disease progression.

The shared hubs recruited in AD include TREM2-dependent clearance and immunometabolism, inflammasome and interferon-associated signaling, inflammatory transcriptional networks, and complement-mediated synaptic vulnerability. Their consequences diverge according to *APOE* and *TREM2* genotype, amyloid and tau burden, anatomical region, vascular integrity, glial state, and disease stage. TREM2-dependent responses can restrain amyloid-driven tau accumulation and neurodegeneration [21], whereas C1q-dependent astrocytic and microglial engulfment can eliminate excitatory and inhibitory synapses [14]. AD therefore illustrates how a shared neuroimmune architecture may support plaque containment and clearance in one context but promote tau amplification, synaptic loss, circuit dysfunction, and cognitive decline in another.

PD: α-synuclein and mitochondrial stress within a vulnerable nigrostriatal immune environment

In PD, α-synuclein aggregation and mitochondrial dysfunction provide the principal initiating lesions within an aging-conditioned environment characterized by impaired proteostasis, lysosomal strain, oxidative stress, defective mitochondrial quality control, and microglial priming. Extracellular or aggregated α-synuclein can be internalized by microglia and astrocytes, stimulating pattern-recognition signaling, cytokine production, and altered neuron–glia communication. In a PD mouse model, microglial inhibition reduced α-synuclein propagation and associated inflammatory responses, indicating that microglia can influence pathological spread rather than merely respond to neuronal damage [42]. Tunnelling nanotubes also enabled bidirectional transfer of α-synuclein and mitochondria be-

Disease	Initiating lesion	NLRP3	cGAS-STING	Inflammatory transcriptional networks	Complement or synaptic vulnerability	Microglial clearance or immunometabolism	Neurovascular-immune coupling	Dominant tissue outcome
AD	Amyloid-β / tau	■	■	■	■	■	■	tau amplification, synaptic loss, cognitive decline
PD	α-Synuclein / mitochondrial stress	■		■		■		Aggregate-handling failure, synaptic dysfunction dopaminergic loss
ALS/FTD	TDP-43 / C9orf72 dysfunction	■	■	■		■		Impaired protein clearance, persistent interferon signalling, selective neuronal loss
HD	Mutant huntingtin			■	■	■		Early corticostriatal synapse loss, circuit dysfunction, striatal degeneration
Progressive MS	Autoimmune demyelination / chronic active lesions	■	□	■		■	■	Chronic lesion expansion, failed remyelination, axonal loss, progressive disability

■ Prominent mechanism in the reviewed evidence (represents a qualitative synthesis of the evidence reviewed in this article and does not indicate comparative effect size or evidence certainty)

□ Limited, indirect, or context-dependent evidence

Figure 5. **Disease-specific expression of shared neuroimmune hubs across major neurodegenerative diseases**. The matrix qualitatively compares disease-specific initiating lesions or contexts, shared neuroimmune mechanisms, and dominant tissue-level outcomes in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), Huntington's disease (HD), and progressive multiple sclerosis (MS). Filled squares indicate mechanisms prominently supported by the evidence reviewed in this article, whereas open squares indicate limited, indirect, or context-dependent evidence. The overall pattern illustrates convergence on a restricted neuroimmune architecture together with disease-, region-, genotype-, and stage-dependent variation in pathway prominence. Symbol fill represents a qualitative synthesis and does not indicate comparative effect size, statistical significance, or certainty of evidence.

tween neurons and microglia, illustrating how aggregate handling and organelle stress become coupled within the local cellular environment [43].

The shared neuroimmune hubs recruited in PD include inflammasome activation, inflammatory transcriptional networks, mitochondrial danger signaling, lysosomal dysfunction, and microglial immunometabolic stress. Pathological α-synuclein conversion at mitochondria induced neuronal toxicity, while loss of parkin permitted NLRP3 inflammasome assembly within dopaminergic neurons, linking genetic and mitochondrial dysfunction to cell-autonomous inflammatory injury [17]. Microglial p38–TFEB signaling further sustained NLRP3 activity by impairing its chaperone-mediated degradation [29]. The consequences of these shared pathways diverge according to their neuronal or glial source, nigrostriatal localization, parkin and mitochondrial status, aggregate burden, and disease stage. PD therefore illustrates how neuroimmune responses may initially support aggregate handling and tissue containment but become associated with persistent inflammasome activity, oxidative injury, synaptic dysfunction, and dopaminergic degeneration when mitochondrial and lysosomal resilience is exceeded.

ALS/FTD: TDP-43 and *C9orf72* pathology within regionally vulnerable glial networks

In ALS and FTD, TDP-43 mislocalization, *C9orf72*-associated dysfunction, RNA-processing defects, and impaired proteostasis provide the principal initiating lesions within an aging-conditioned environment of reduced lysosomal capacity, mitochondrial stress, cellular senescence, and impaired inflammatory resolution. These lesions are expressed within selectively vulnerable motor, corticospinal, and frontotemporal networks. Human ALS/FTD organoid slice cultures identified early astrocytic pathology and neuronal dysfunction, demonstrating that glial abnormalities can emerge before extensive neuronal loss [44]. Patient-derived microglia-like cells similarly showed cytoplasmic TDP-43 accumulation, DNA damage, impaired phagocytosis, and associations with disease progression [45].

The shared neuroimmune hubs recruited across the ALS/

Table 3. Disease-specific expression of the aging-conditioned convergent neuroimmune architecture.

Disease	Disease-specific initiating lesion or context	Principal shared neuroimmune hubs recruited	Major determinants of conditional divergence	Dominant tissue-level outcomes	Reference
AD	Amyloid-β deposition, tau pathology, impaired proteostasis, and aging-related vascular and synaptic vulnerability.	Microglial and astrocytic state transitions, TREM2-dependent clearance, inflammasome and interferon signaling, complement-mediated synaptic vulnerability, and neurovascular dysfunction.	*APOE* and *TREM2* genotype, amyloid and tau burden, glial state, anatomical region, vascular integrity, and disease stage.	Impaired clearance, tau amplification, synaptic elimination, circuit dysfunction, and cognitive decline.	[4, 14, 19-21]
PD	α-Synuclein aggregation, mitochondrial dysfunction, impaired lysosomal processing, and selective nigrostriatal vulnerability.	NLRP3 inflammasome activity, inflammatory transcriptional networks, mitochondrial danger signaling, microglial immunometabolic stress, and altered neuron–glia communication.	Neuronal versus glial pathway activation, parkin status, aggregate burden, mitochondrial fitness, nigrostriatal localization, and disease stage.	Oxidative injury, impaired aggregate handling, synaptic dysfunction, and dopaminergic neuronal degeneration.	[11, 17, 26, 42, 43]
ALS/FTD spectrum	TDP-43 or tau pathology, *C9orf72*-associated dysfunction, RNA-processing defects, and impaired proteostasis.	Microglial and astrocytic state transitions, TREM2-dependent clearance, cGAS–STING/interferon signaling, inflammasome activity, and lysosomal dysfunction.	TDP-43 versus tau pathology, *C9orf72* genotype, neuronal versus glial pathway activation, affected anatomical network, and residual clearance capacity.	Loss of trophic support, impaired pathological-protein clearance, persistent interferon signaling, and selective motor or frontotemporal neuronal degeneration.	[13, 28, 44, 45]
HD	Mutant huntingtin, corticostriatal dysfunction, mitochondrial and metabolic stress, and reduced synaptic resilience.	Microglial state transitions, complement-mediated synaptic vulnerability, inflammatory transcriptional programs, and immunometabolic dysfunction.	CAG-repeat burden, corticostriatal localization, synapse type, disease stage, metabolic stress, and capacity to develop inflammatory tolerance.	Early corticostriatal synapse loss, circuit dysfunction, and progressive striatal degeneration.	[18, 46]
Progressive MS	Adaptive autoimmunity, inflammatory demyelination, chronic active lesions, oxidative lipid injury, and failed remyelination.	Microglial and astrocytic state transitions, TREM2-dependent lipid clearance, inflammasome activity, interferon-associated programs, metabolic stress, and neurovascular dysfunction.	Lesion type, anatomical compartment, blood–brain barrier integrity, peripheral immune activity, remyelination capacity, and transition to progressive disease.	Chronic lesion expansion, failed remyelination, oligodendrocyte loss, axonal degeneration, and progressive disability.	[24, 30, 31]

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FTD spectrum include microglial and astrocytic state transitions, impaired lysosomal clearance, cGAS–STING and interferon signaling, inflammasome activity, and inflammatory transcriptional programs. TREM2 recognized pathological TDP-43 and promoted its microglial clearance, whereas *TREM2* deficiency increased neuronal damage and motor impairment [13]. Neuronal STING activation in vulnerable cortical and spinal motor neurons further indicates that inflammatory DNA sensing may originate within neurons as well as glia [28]. Conditional divergence is shaped by TDP-43 or tau pathology, *C9orf72* genotype, affected anatomical network, neuronal versus glial pathway activation, disease stage, and residual clearance capacity. ALS/FTD therefore illustrates how shared immune-clearance and danger-sensing mechanisms may initially support disposal of pathological material but contribute to persistent interferon signaling, loss of trophic support, and selective neuronal degeneration when proteostatic and endolysosomal capacity becomes insufficient.

HD: mutant huntingtin within a vulnerable corticostriatal immune network

In HD, mutant huntingtin and progressive corticostriatal dysfunction provide the principal initiating context within an aging-conditioned environment characterized by impaired proteostasis, mitochondrial stress, altered lipid handling, reduced synaptic resilience, and microglial priming. The neuroimmune response is expressed particularly within corticostriatal circuits, where neuronal stress and glial phagocytic activity can precede extensive neuronal loss. In HD models, complement proteins marked vulnerable corticostriatal synapses for early microglial engulfment, directly linking mutant huntingtin-associated pathology to complement-mediated circuit disruption [18].

The shared hubs recruited in HD include microglial state transitions, complement-mediated synaptic vulnerability, inflammatory transcriptional programs, and immunometabolic stress. However, these responses are not uniformly exaggerated. HD microglia mounted an initial response to inflammatory stimulation but showed partially impaired development of innate immune tolerance, indicating that repeated inflammatory challenges may produce abnormal persistence rather than simple baseline hyperactivation [46]. Conditional divergence is therefore shaped by CAG-repeat burden, corticostriatal localization, synapse type, disease stage, metabolic stress, and the capacity of microglia to acquire inflammatory tolerance. HD thus illustrates how a genetically defined initiating lesion can recruit shared immune mechanisms while producing a regionally selective pattern of early synaptic loss and progressive circuit dysfunction.

Progressive MS: autoimmune demyelination within a compartmentalized neuroimmune environment

In MS, adaptive autoimmunity and inflammatory demyelination provide the principal initiating context, distinguishing the disease from primary proteinopathies. However, progressive MS increasingly recruits the same aging-conditioned mechanisms observed across neurodegenerative disorders, including microglial and astrocytic state transitions, mitochondrial stress, impaired lipid handling, inflammasome activity, neurovascular dysfunction, and reduced capacity for remyelination. Oxidized phosphatidylcholines within multiple-sclerosis lesions promoted demyelination and axonal injury, whereas TREM2-dependent microglial phagocytosis supported their removal, illustrating how the same glial response may be protective but become insufficient when oxidative and lipid burden exceeds clearance capacity [30].

The shared neuroimmune hubs are expressed within a disease-specific environment of adaptive immune recruitment, myelin injury, chronic active lesions, meningeal inflammation, and oligodendrocyte vulnerability. Microglial nodules associated with severe pathology showed enrichment of interferon-related signaling, phagocytic programs, lipid metabolism, inflammatory activation, and metabolic stress [31]. Experimental NLRP3 inhibition also reduced demyelination, oligodendrocyte loss, neuronal injury, and neurological impairment, linking inflammasome activity to tissue degeneration beyond peripheral autoimmune attack [24]. Conditional divergence is determined by lesion type, anatomical compartment, BBB integrity, peripheral immune activity, remyelination capacity, and transition from relapsing to progressive disease. Progressive MS therefore demonstrates how peripheral immune control may reduce acute inflammatory activity without fully resolving compartmentalized glial inflammation, chronic lesion expansion, failed remyelination, and axonal degeneration.

Across AD, PD, ALS/FTD, HD, and progressive MS, distinct initiating lesions repeatedly recruit a restricted set of neuroimmune mechanisms. Their disease-specific expression is determined not by the presence or absence of inflammation alone, but by the affected cell type, anatomical compartment, genetic background, pathological substrate, disease stage, vascular environment, and capacity for clearance and resolution. The cross-disease comparison therefore supports convergence at the level of shared cellular and molecular architecture while preserving conditional divergence in its spatial, temporal, and functional consequences.

Figure 5 provides a qualitative cross-disease comparison of the principal neuroimmune hubs discussed in this section. The matrix illustrates that distinct initiating lesions recruit overlapping inflammatory, glial, metabolic, complement, and neurovascular mechanisms, while the prominence of individual hubs varies across diseases. Within the evidence evaluated in this review, AD is represented across the widest range of neuroimmune hubs, whereas PD, ALS/FTD, HD, and progressive MS show more selective configurations shaped by pathological substrate, anatomical vulnerability, and disease stage. The figure therefore complements Table 3 by visually distinguishing shared mechanistic convergence from disease-specific patterns of conditional divergence.

Table 3 compares how disease-specific initiating lesions recruit the shared aging-conditioned neuroimmune architecture, while genotype, anatomical compartment, disease stage, pathological burden, and clearance capacity deter-

mine conditional divergence and dominant tissue-level outcomes.

Therapeutic translations: from target selectivity to mechanistic precision

What broad and targeted therapeutic failures reveal

Early therapeutic strategies often assumed that reducing inflammatory activity would be sufficient to slow neurodegeneration. Experience with nonsteroidal anti-inflammatory drugs illustrates the limitations of this approach. Although long-term nonsteroidal anti-inflammatory drug (NSAID) exposure has been associated with altered dementia risk in observational studies, such associations have not translated consistently into disease modification after neurodegenerative pathology is established [47]. This discrepancy likely reflects more than inadequate anti-inflammatory potency. NSAIDs do not identify the responsible immune cell, anatomical compartment, disease stage, or inflammatory endotype, and they cannot distinguish protective clearance and repair from maladaptive inflammatory amplification. Their limited success therefore challenges the assumption that neuroinflammation can be treated as a single, uniformly harmful process.

More selective interventions show that molecular specificity alone does not resolve this problem. Evobrutinib had a strong mechanistic rationale because Bruton's tyrosine kinase (BTK) regulates B-cell and myeloid signaling, yet it did not outperform teriflunomide in relapsing MS [48]. This result should not be interpreted simply as evidence that BTK biology is irrelevant. Rather, it exposes several possible translational gaps: systemic inhibition may not sufficiently modify compartmentalized CNS inflammation; the active comparator may already suppress the dominant peripheral inflammatory component; target engagement may not have been demonstrated within the relevant CNS cells; and the enrolled population may not have been enriched for a BTK-dependent inflammatory endotype. Pathway redundancy and outcome measures dominated by relapse biology may also obscure effects on slower microglial or lesion-associated processes. The trial therefore questions the assumption that a biologically plausible target will produce clinical benefit without confirming where, when, and in whom that target is causally active.

Low-dose IL-2 in ALS provides a complementary lesson. The strategy was designed to expand or restore regulatory T-cell activity and showed biologically plausible immune modulation, but benefit was not uniform across patients [49, 50]. This separation between pharmacodynamic activity and clinical effect is important. Expansion of a regulatory immune population does not establish that the modified immune state is sufficiently durable, reaches the relevant neuroanatomical compartment, occurs before irreversible motor-neuron loss, or addresses the dominant mechanism in every patient. ALS includes genetically, anatomically, and immunologically distinct subgroups; consequently, a treatment that corrects one peripheral immune abnormality may be ineffective when neuronal proteostasis failure, glial dysfunction, or endolysosomal impairment has become the principal driver.

Together, these examples show that negative or inconsistent trials should be interpreted mechanistically rather than classified only as target failures. A trial may fail because the pathway was not active, was not causal, was targeted in the wrong cellular or anatomical compartment, was insufficiently engaged, was modified outside the appropriate therapeutic window, or was evaluated using outcomes poorly aligned with its expected biological effect. Precision neuroimmunology therefore requires more than a selective molecule. It requires evidence of pathway activity, causal relevance, CNS accessibility, target engagement, appropriate timing, biomarker-defined patient selection, and outcome measures that reflect the mechanism being tested.

Target-selective molecular strategies: evidence maturity and translational constraints

Shared inflammatory hubs offer plausible therapeutic targets, but their translational maturity is uneven. Most evidence for NLRP3, cGAS–STING, and complement modulation remains preclinical, and activity of a pathway in an experimental model does not by itself establish that the pathway is causal, accessible, or therapeutically dominant in human disease. Evaluation should therefore distinguish biological proof of mechanism from clinical readiness and determine the relevant cellular source, anatomical compartment, disease stage, and measurable pharmacodynamic response.

NLRP3 inhibition has the broadest cross-disease experimental rationale within this group. Amyloid-β and ATP activated P2X7R-dependent NLRP3 signaling in AD-related microglia [23], loss of parkin permitted neuronal inflammasome assembly in PD models [17], and NLRP3-associated changes were observed in experimental demyelination and ALS-like motor-neuron disease [24, 25]. These findings support NLRP3 as a recurrent amplifier of sterile injury, but they also reveal a translational complication: the relevant inflammasome may arise in microglia, neurons, vascular cells, or infiltrating myeloid populations. A clinically useful inhibitor would therefore require adequate CNS exposure, evidence of target engagement in the disease-relevant compartment, and biomarkers distinguishing persistent pathological activation from transient inflammasome functions involved in host defense and tissue repair. Reduction of inflammatory markers alone would not establish disease modification unless accompanied by preservation of synapses, myelin, axons, or neuronal function.

cGAS–STING modulation presents a similar balance between mechanistic convergence and physiological risk. Persistent DNA sensing links mitochondrial damage, senescence, interferon-associated signaling, and neurodegeneration during aging [8]. STING inhibition reduced inflammatory and pathological features in AD models [26], while neuronal STING activation was identified in ALS/FTD-related settings [28]. However, these observations involve different cellular sources and pathological con-

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texts, and suppression of upstream IL-6–STAT3 signaling [27] is not biologically equivalent to direct STING inhibition. Because STING contributes to antiviral defense and genomic surveillance, continuous systemic blockade may create risks disproportionate to benefit. Translation therefore requires clarification of whether the therapeutic objective is to suppress microglial, neuronal, vascular, or senescence-associated STING activity, together with CNS pharmacokinetic evidence, interferon-linked pharmacodynamic markers, and justification for treatment duration.

Complement modulation is supported by a more direct connection between immune activation and structural synaptic injury. C1q-dependent pathways promoted astrocytic and microglial elimination of excitatory and inhibitory synapses in AD models [14], and complement-tagged corticostriatal synapses underwent early microglial engulfment in HD [18]. Terminal complement inhibition also reduced synaptic damage in experimental AD-related settings [51]. Nevertheless, C1q-mediated tagging, C3-dependent opsonization, and terminal membrane-attack-complex formation represent different biological levels and should not be treated as interchangeable targets. The appropriate intervention may depend on whether the dominant abnormality is inappropriate synapse tagging, excessive glial engulfment, terminal complement injury, or systemic complement activation. Clinical development would therefore require synaptic or complement-fragment biomarkers, confirmation that the targeted step is active within the CNS, and safeguards against disrupting antimicrobial defense, debris clearance, and physiological tissue remodeling.

Cytokine-directed therapies should likewise be evaluated as pathway- and endotype-specific interventions rather than as a single therapeutic class. IL-1β, IL-6, TNF-α, interferons, and regulatory cytokines have distinct cellular sources and may exert protective or damaging effects according to timing and tissue context. The low-dose IL-2 experience discussed above demonstrates that pharmacodynamic immune modulation may occur without uniform clinical benefit. Across these molecular strategies, advancement should therefore depend on a consistent sequence of evidence: confirmation of pathway activity in human disease, demonstration of causal relevance, adequate CNS exposure, measurable target engagement, selection of an appropriate disease stage and inflammatory endotype, and outcomes aligned with the expected mechanism.

Cell-state reprogramming and restoration of neuroimmune resolution

The therapeutic objective in neurodegenerative disease should be neither indiscriminate immune suppression nor generalized microglial activation. A more defensible goal is to redirect disease-associated immune states toward effective debris clearance, metabolic competence, synaptic preservation, tissue repair, and inflammatory resolution. This distinction is important because conventional markers of microglial or astrocytic activation do not reveal whether a response is protective, ineffective, or damaging. Therapeutic evaluation should therefore prioritize functional changes—including phagocytic completion, lysosomal processing, lipid handling, mitochondrial fitness, cytokine balance, synaptic integrity, and neuronal survival—rather than relying solely on reductions or increases in generic inflammatory markers.

TREM2-directed approaches illustrate both the potential and the limitations of cell-state reprogramming. A TREM2-activating antibody linked to a BBB transport vehicle improved CNS exposure and enhanced microglial metabolic activity in AD models [16]. TREM2 also supported microglial recognition and clearance of pathological TDP-43 [13]. These findings suggest that strengthening substrate recognition and metabolic adaptation may restore protective microglial functions. However, increased TREM2 signaling should not be assumed to be beneficial in every context. Microglia may recognize and internalize pathological material yet remain unable to complete lysosomal degradation when lipid stress, organelle dysfunction, or aggregate burden exceeds their metabolic capacity. The effect may also vary with *TREM2* and *APOE* genotype, pathological substrate, anatomical region, and disease stage. Evidence of increased microglial recruitment or phagocytosis must therefore be accompanied by confirmation of successful cargo processing and preservation of surrounding tissue.

Immunometabolic interventions provide a complementary strategy. Reversal of age-related PGE2–EP2-driven myeloid metabolic dysfunction restored cognitive performance in aged mice, indicating that inflammatory behavior can be altered by correcting cellular energy metabolism rather than directly suppressing cytokine production [52]. BTK inhibition has likewise modified microglial, macrophage, and B-cell inflammatory responses in experimental and human cell-based systems [53, 54]. However, the failure of evobrutinib to outperform an active comparator in relapsing MS [48] demonstrates that pathway modulation does not necessarily produce a clinically meaningful shift in the relevant CNS immune state. Future studies should therefore establish whether treatment changes disease-associated microglial metabolism and function within the CNS, rather than inferring benefit from peripheral target engagement alone.

Glial communication further shows why immune-state modulation must be spatially and functionally defined. Astrocyte-derived IL-3 promoted protective plaque-associated microglial activity in AD models [36], whereas perivascular SPP1 induced phagocytic microglial states associated with increased synaptic engulfment [15]. Both responses involve altered microglial activity, but their tissue consequences are different. A candidate immunomodulatory therapy should therefore advance only when it demonstrates a disease-relevant maladaptive state in human tissue or biomarkers, adequate CNS delivery, cell- and compartment-specific target engagement, functional correction of that state, preservation of host defense and repair, and improvement in mechanistically aligned neuronal, synaptic, myelin, or axonal outcomes. Cell-state reprogramming becomes precision neuroimmunology only when the desired biological transition and its tissue-level consequence are explicitly defined.

Table 4. Evidence maturity and translational requirements for neuroimmune therapeutic strategies.

Therapeutic strategy	Current evidence maturity	Intended neuroimmune effect	Principal translational uncertainty	Minimum evidence required for advancement	References
Broad anti-inflammatory approaches	Observational and clinically inconclusive	Reduce generalized cyclooxygenase- and prostaglandin-associated inflammatory activity.	Lack of inflammatory-endotype selection, uncertain timing, and inability to distinguish protective from maladaptive inflammation.	Demonstration of an active inflammatory endotype, appropriate therapeutic window, and mechanism-aligned clinical outcomes.	[47]
NLRP3 and cGAS–STING modulation	Predominantly preclinical	Reduce inflammasome, pyroptotic, interferon-associated, and DNA-sensing inflammatory amplification.	Relevant cellular source, CNS exposure, pathway redundancy, host-defense impairment, and uncertain chronic-dosing safety.	Human pathway-activity biomarkers, CNS pharmacokinetics, cell- or compartment-specific target engagement, and evidence of neural protection.	[8, 23-26, 28]
Complement and cytokine modulation	Preclinical to early clinical	Limit pathological synapse tagging, terminal complement injury, or maladaptive cytokine signaling.	Protective roles in host defense, clearance, repair, and immune regulation; different complement levels are not interchangeable.	Identification of the active complement or cytokine component, CNS target engagement, synaptic or tissue-level biomarkers, and stage-specific dosing.	[14, 18, 27, 49-51]
TREM2 and immunometabolic reprogramming	Predominantly preclinical	Improve substrate recognition, lysosomal processing, lipid handling, mitochondrial fitness, and microglial resolution.	Genotype-, substrate-, region-, and stage-dependent effects; increased uptake may not produce completed clearance.	Evidence of successful cargo processing, metabolic correction, preserved surrounding tissue, and CNS cell-state modification.	[13, 16, 20, 52]
BTK and immune-cell-state modulation	Preclinical and clinical, with mixed efficacy	Modify B-cell, macrophage, and microglial inflammatory programs.	Peripheral target engagement may not alter compartmentalized CNS inflammation; comparator effects and patient heterogeneity.	CNS target engagement, enrichment for a BTK-dependent endotype, compartment-relevant biomarkers, and mechanism-aligned outcomes.	[48, 53, 54]
Glial-communication and neurovascular targeting	Predominantly preclinical	Redirect astrocyte–microglia signaling, preserve barrier integrity, and reduce maladaptive synaptic engulfment.	Protective and harmful glial responses may share activation markers and vary spatially.	Spatially resolved biomarkers, defined cellular target, BBB or synaptic endpoints, and confirmation of functional rather than generic activation changes.	[15, 33, 36]
Cell-based therapies	Early clinical feasibility with limited efficacy evidence	Deliver trophic, immunoregulatory, and pro-resolving signals.	Product heterogeneity, uncertain persistence, delivery risks, variable secretory profiles, and unclear mechanism.	Defined cell product, reproducible potency, biodistribution, dose–response, safety, target engagement, and durable biological effect.	[55-57]
EV therapies	Preclinical	Deliver regulatory proteins, lipids, RNAs, and mechanism-linked cargo.	Batch variability, uncertain active cargo, contamination, storage instability, biodistribution, and lack of validated potency assays.	Standardized manufacturing, multidimensional release criteria, mechanism-linked potency assay, storage stability, CNS delivery, and batch comparability.	[59-62]

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Cell- and extracellular-vesicle (EV) therapies: product definition, potency, and manufacturing control

Cell-based interventions are proposed primarily as sources of trophic, immunoregulatory, anti-inflammatory, and pro-resolving signals rather than as direct replacements for widely distributed neuronal populations. This distinction should guide interpretation of the clinical evidence. Repeated intracerebroventricular administration of human umbilical cord blood-derived mesenchymal stromal cells in mild-to-moderate AD provided feasibility and safety information [55], while mesenchymal stromal cells engineered to secrete neurotrophic factors were generally tolerated in ALS but did not meet the primary efficacy endpoint in a phase 3 trial [56]. Umbilical cord-derived mesenchymal stromal cells and their secretome have also undergone early dose-finding evaluation in MS [57]. These studies show that administration is possible, but feasibility and biological plausibility do not establish durable neuroimmune reprogramming or disease modification.

The principal translational problem is that a cell therapy is not defined only by its tissue of origin. Donor characteristics, cell passage, culture conditions, expansion method, differentiation status, viability, secretory profile, cryopreservation, delivery route, dose, and host immune environment can alter the final biological product. Apparent similarity between two mesenchymal or neural progenitor preparations therefore does not guarantee comparable potency. Trials should establish whether the administered cells reach the intended compartment, persist for an appropriate period, release the expected mediators, and produce measurable changes in glial state, inflammatory resolution, synaptic or axonal preservation, or neuronal function. Safety assessment must also address immune incompatibility, microvascular obstruction, ectopic differentiation, inappropriate trophic signaling, and host responses to intracerebral or intraventricular delivery [58].

EVs offer a cell-free strategy for delivering proteins, lipids, messenger RNAs, microRNAs, and other regulatory cargo. Neural stem cell- and induced pluripotent stem cell-derived vesicles improved pathological or cognitive outcomes in AD-related models, entered neurons and microglia after intranasal administration, and modified inflammatory programs involving interferon, IL-6, NLRP3, p38 MAPK, and cGAS–STING signaling [59-61]. Mesenchymal stromal cell-derived vesicles also reduced inflammatory cytokines and leukocyte infiltration in experimental demyelination [62]. These findings support biological activity, but they do not establish that EVs constitute a uniform therapeutic class. Their effects depend on the donor cell, culture environment, isolation and purification method, particle composition, active cargo, dose, route, biodistribution, tissue retention, and disease context.

Batch variability is a mechanistic and regulatory concern because EV preparations with similar particle counts can differ in identity, purity, cargo, contaminants, and biological activity. EV products from iPSC-mesenchymal stromal cells showed variable immunomodulatory potency, while two- and three-dimensional culture conditions produced vesicles with similar sizes but different proteomes and functions [63, 64]. Isolation method also altered marker recovery and non-vesicular contamination [65]. Reproducible products therefore require release criteria covering source-cell identity, vesicle size and markers, purity, sterility, endotoxin, active-cargo or mechanism-linked signatures, storage stability, and batch comparability [66, 67]. Storage and functional-integrity studies show that formulation and freeze–thaw exposure can alter EV recovery and activity [68, 69]. Studies should distinguish systemic exposure, CNS entry, regional localization, cellular uptake, pharmacodynamic response, and tissue-level benefit.

Clinical advancement should depend on a defined product–mechanism relationship. Before efficacy trials, developers should establish manufacturing reproducibility, active component or potency signature, dose–response behavior, storage stability, CNS biodistribution, and batch-release thresholds. Without these controls, inconsistent products can obscure positive and negative findings. EV therapies become credible precision-neuroimmunology strategies only when product identity, intended immune-state transition, target engagement, and neural outcome are reproducibly linked.

Table 4 compares neuroimmune therapeutic strategies according to their intended mechanism, current level of evidence, principal translational uncertainty, and requirements for mechanistically interpretable clinical development.

Mechanism-aligned biomarkers, patient stratification, and endotype-guided trial design

Neuroinflammatory biomarkers should not be treated as interchangeable indicators of a single inflammatory process. Within the aging-conditioned convergence–divergence framework, they serve distinct purposes: identifying an active pathway, locating the relevant cellular or anatomical compartment, distinguishing modifiable immune activity from accumulated tissue injury, defining the therapeutic window, and confirming target engagement. No individual marker can reliably fulfill all these functions. Biomarker interpretation should therefore be organized around the biological question being tested rather than around sample availability alone.

Cerebrospinal fluid (CSF) provides relatively direct access to CNS-associated immune, glial, neuronal, and barrier-related signals. CSF sTREM2 reflects TREM2-associated myeloid activity and differs from plasma sTREM2, indicating that central and peripheral measurements are not interchangeable [70]. Plasma glial fibrillary acidic protein (GFAP) offers a scalable measure of astrocyte-associated pathology and is strongly related to amyloid burden, whereas CSF YKL-40 may capture a partly different stage of glial response [71, 72]. Translocator protein positron emission tomography adds regional information but remains limited by tracer characteristics, genotype, and incomplete cellular specificity [73]. Peripheral cytokines

Table 5. Mechanism-aligned biomarkers for endotype-guided neuroimmune trials.

Biomarker class	Sample or modality	Principal biological interpretation	Primary trial function	Main limitation	References
CSF glial-state panel: sTREM2, YKL-40/ CHI3L1, and GFAP	CSF	Microglial and astrocytic activity associated with TREM2 signaling, tissue remodeling, and glial reactivity	Endotype enrichment and pharmacodynamic assessment when interpreted longitudinally	Requires lumbar puncture; limited pathway specificity; stage-dependent interpretation	[70, 72, 77]
Plasma GFAP	Blood/plasma	Scalable indicator of astrocyte-associated pathology, particularly in amyloid-positive states	Early-stage enrichment and longitudinal tissue-response monitoring	Not disease-specific and influenced by aging, vascular injury, and other neurological disorders	[71, 75]
TSPO PET	Molecular imaging	Regional glial-associated inflammatory signal	Anatomical localization, patient enrichment, and regional inflammatory-state and pharmacodynamic assessment	Limited cellular specificity; influenced by tracer properties and TSPO genotype	[73]
Peripheral cytokine panels	Blood/serum	Systemic inflammatory context and possible immune-active endotypes	Stratification for systemic immune activity and monitoring of peripheral pharmacodynamic effects	Strongly affected by infection, medication, metabolic disease, age, and comorbidity	[74, 79]
GFAP–neurofilament injury panels	CSF and/or blood	Combination of glial response with downstream axonal injury	Distinguishing modifiable inflammatory activity from accumulated tissue damage and monitoring tissue response	Neurofilaments indicate injury but not its inflammatory cause	[76, 78]
MRI markers of chronic active lesions	MRI, including susceptibility-sensitive and lesion-expansion measures	Compartmentalized inflammation, iron-associated lesion rims, and smouldering tissue injury	Disease staging, anatomical enrichment, and monitoring of progressive lesion activity	Acquisition and interpretation require harmonization; not a molecular target-engagement marker	[80]

are accessible but are strongly influenced by infection, metabolic disease, medication, and other systemic conditions; serum IL-6 and TNF-α in PD should therefore be interpreted as measures of systemic inflammatory context rather than direct evidence of CNS target activity [74].

Disease stage and aging-related baseline changes must also be incorporated. Plasma GFAP may identify early amyloid-associated astrocytic responses before substantial clinical impairment, but it does not directly establish tau aggregation or irreversible neuronal loss [75]. Conversely, neurofilament light and heavy chains primarily indicate axonal injury rather than its inflammatory cause. In MS, CSF GFAP and neurofilament heavy chain were associated with non-relapsing progression, whereas lymphocyte measures reflected relapsing inflammatory activity [76]. Therapeutic windows should therefore be defined using longitudinal, age- and comorbidity-adjusted panels that distinguish pathway activity and glial state from downstream synaptic, axonal, or neuronal injury and overall disease progression.

Endotype-guided trials should use biomarkers at four linked stages: enrichment, to select patients with the proposed active mechanism; target engagement, to demonstrate that treatment modifies that mechanism in the relevant compartment; tissue response, to assess effects on glial, vascular, synaptic, myelin, or axonal biology; and clinical consequence, to determine whether biological modification preserves function. Combined CSF sTREM2, YKL-40, and GFAP measurements have shown associations with cognitive vulnerability [77], while integrated neurofilament and inflammatory-marker panels improved ALS differential classification [78]. Such panels should complement, rather than replace, mechanistic validation. A clinical result remains difficult to interpret when pathway activity or target engagement has not been demonstrated, even when downstream injury markers or functional outcomes are unchanged.

Table 5 summarizes the principal biomarker classes according to their biological interpretation, trial function, and major interpretive limitation.

Future directions: testable hypotheses and a translational roadmap

Single-cell, spatial, and multimodal approaches should now be used to test the aging-conditioned convergence–divergence model in human tissue and longitudinal cohorts. Multiregion studies in AD have identified inflammatory microglial states, reactive astrocyte programs, regional neuronal vulnerability, and cellular signatures associated with resilience [81, 82]. Spatial analysis of multiple-sclerosis lesions has likewise revealed distinct myeloid, endothelial, and glial niches at chronically inflamed lesion borders [83]. These technologies can determine whether shared neuroimmune hubs occupy comparable cellular

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states across diseases or whether their expression is redirected by anatomy, genotype, pathological substrate, and disease stage.

Translation should follow a staged decision pathway. Candidate interventions should advance only after demonstrating: (1) pathway activity in human disease; (2) causal relevance to tissue injury; (3) access to the relevant CNS compartment; (4) cell- and pathway-specific target engagement; (5) an appropriate disease stage and inflammatory endotype; and (6) improvement in outcomes aligned with the proposed mechanism. Failure at any step should function as a prespecified go/no-go criterion. Combination therapy should be considered only when two or more independently validated mechanisms remain active in the same patient subgroup, rather than being adopted simply because neurodegeneration is biologically complex.

The proposed framework generates four testable hypotheses. First, the aging-threshold hypothesis predicts that age-related mitochondrial, lysosomal, vascular, and resolution deficits precede and amplify disease-specific inflammatory responses. Second, the conditional-convergence hypothesis predicts that different initiating lesions recruit a restricted set of molecular hubs, but their cellular source and tissue consequences vary by genotype, anatomical compartment, and disease stage. Third, the temporal-switch hypothesis predicts that clearance- or containment-associated immune states become damaging when substrate burden exceeds metabolic and lysosomal capacity or when inflammatory resolution fails. Fourth, the compartment-engagement hypothesis predicts that therapeutic benefit requires modification of the relevant pathway within the disease-driving CNS cell population and cannot be inferred from peripheral target engagement alone. These hypotheses can be evaluated through longitudinal biomarker panels, spatially resolved human tissue, perturbation studies, and mechanism-enriched clinical trials.

Combination and immune-modulating therapies must also preserve physiological surveillance, repair, antimicrobial defense, and debris clearance. The modest benefits and safety burdens observed with anti-amyloid therapies [84, 85], together with pharmacodynamic but variable clinical responses to low-dose IL-2 strategies [49, 50, 86], reinforce the need for stage-specific selection, target-engagement measures, and explicit stopping rules. The next phase of neuroinflammation research should therefore prioritize falsifiable mechanisms and interpretable trials over increasingly broad therapeutic combinations.

Conclusions

Neurodegenerative disorders differ in their initiating lesions, yet repeatedly recruit a restricted, aging-conditioned neuroimmune architecture. Microglial and astrocytic state transitions, NLRP3 and cGAS–STING signaling, inflammatory transcriptional networks, complement-mediated synaptic vulnerability, TREM2-dependent clearance, immunometabolic dysfunction, and neurovascular–immune coupling constitute the principal points of convergence. Their effects are not uniform. Aging lowers the threshold for persistent activation, while genotype, anatomical compartment, pathological substrate, vascular integrity, disease stage, and systemic inflammatory burden determine conditional divergence and the balance between clearance, repair, failed resolution, and tissue injury.

This framework explains why molecular selectivity alone has not ensured therapeutic success. Precision neuroimmunology requires evidence that a pathway is active and causal in the relevant patient subgroup, accessible within the disease-driving CNS compartment, engaged by treatment, and modified during a reversible disease window. Biomarkers should therefore support endotype enrichment, target-engagement assessment, tissue-response monitoring, and interpretation of clinical outcomes rather than serve as nonspecific indicators of inflammation.

The model generates four falsifiable predictions. Aging-related mitochondrial, lysosomal, vascular, and resolution deficits should precede and amplify disease-specific inflammatory responses. Distinct initiating lesions should recruit a limited set of shared hubs whose cellular sources and consequences vary by context. Protective clearance states should become maladaptive when pathological burden exceeds metabolic or lysosomal capacity or when inflammatory resolution fails. Finally, therapeutic benefit should require engagement of the relevant pathway within the disease-driving CNS cell population and should not be inferred from peripheral pharmacodynamic effects alone. Testing these predictions in longitudinal cohorts, spatially resolved human tissue, perturbation models, and mechanism-enriched trials will determine whether restoring neuroimmune homeostasis can modify disease progression while preserving surveillance, clearance, repair, and host defense.

Declarations

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