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REVIEW

Genetic regulation of microglial function in Alzheimer's disease: Mechanisms and therapeutic implications

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Abstract

Alzheimer's disease (AD) is a multifaceted neurodegenerative disorder in which neuroinflammatory and immune mechanisms are increasingly recognised as central drivers of disease onset and progression. Among the brain's immune cells, microglia have emerged as critical regulators of amyloid and tau pathology, synaptic integrity, and neuronal survival. Compelling human genetic studies reveal that many AD risk loci are enriched in microglia-expressed genes, highlighting microglia not just as responders to neurodegeneration, but as active mediators of genetic susceptibility. This review explores how genetic variation shapes microglial function in AD, focusing on key pathways that govern immune sensing, phagocytosis, intracellular degradation, and inflammatory signaling. Risk-associated variants in genes such as apolipoprotein E (APOE), Triggering Receptor Expressed on Myeloid cells 2 (TREM2), and Cluster of Differentiation 33 (CD33), along with regulators of autophagy and inflammasome activity, influence the balance between protective and maladaptive microglial responses at different stages of disease. Advances in single-cell and spatial transcriptomics have revealed the remarkable heterogeneity of microglial states, challenged traditional binary models of activation, and underscored the need for gene-centered conceptual frameworks. By integrating genetics with functional and systems-level perspectives, this review emphasizes how understanding microglial genetic programs can guide precision-targeted interventions, improve risk stratification, and inspire novel disease-modifying therapies. Ultimately, a genetics-driven approach to microglial regulation provides a strategic roadmap for translating molecular insights into actionable therapeutic advances in AD.

KEYWORDS

Alzheimer's disease, Microglia, Genetic risk factors, Therapeutic Targets, Precision medicine

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease and the primary cause of dementia globally, and its prevalence is sharply increasing in older populations. AD accounts for 60-80% of all occurrences of dementia, making it the most prevalent form. According to current estimates, there are about 50 million AD patients globally; this number is anticipated to double every five years, reaching 152 million by 2050. [1,2] Though early-onset AD can also be observed in those under 30, AD predominantly impacts those over 65.[3] Progressive cognitive dysfunction and behavioural impairment are hallmarks of AD, a degenerative condition of the central nervous system that becomes apparent in old age or pre-old age. Memory loss, intellectual disability, disorientation, visual and auditory impairment, defects in critical thinking and processing information, as well as personality and behavioural abnormalities, are the main clinical indications.[4,5]

1.1 Microglia and neuroinflammation in the CNS

Microglia are brain-resident cells that regulate neural circuit maintenance, repair, and development. Although microglia function as brain macrophages, their distinctive homeostatic behaviour and rigorous oversight by the central nervous system (CNS) set them apart from other tissue macrophages.[6] As the first line of defense in the CNS, microglia play a significant role in the innate immune surveillance network. Microglia can eliminate dead cells or cellular debris via phagocytosis without provoking an inflammatory response.[7] They are responsible for eliminating bacteria, dead cells, redundant synapses, protein aggregates, and other soluble and particulate antigens that may negatively affect the CNS.[6] Moreover, microglia serve as crucial mediators of neuroinflammation and may induce or regulate a wide range of cellular responses, considering they represent the main source of proinflammatory cytokines. Microglia react to pathogen invasion with the production of complement proteins, chemokines, and cytokines that have effects that are either pro- or anti-inflammatory. Despite these responses contribute in the elimination of pathogens, they may cause a severe secondary inflammatory reaction and further worsen CNS disease.[8] Variations in microglia function have been associated with neurodegeneration, aging, and brain development.[6]

Microglia are brain-resident innate immune cells that continuously survey the CNS microenvironment and regulate tissue homeostasis.[9] They are widely distributed throughout the CNS and exhibit marked morphological diversity. They routinely evaluate the brain parenchyma and are essential to regulating CNS homeostasis under physiological conditions because of their highly dynamic and multifaceted processes.[10] Microglia also serve as important regulators of neuronal function and network stability in addition to their conventional designation as macrophages.[10] During development and adulthood, microglia shape neural circuits by modulating synaptic transmission, pruning excess synapses, and contributing to axonal remodeling and neurogenesis. Synaptic pruning is essential for proper neuronal circuit function and is mediated by highly dynamic, ramified microglial processes that contact, engulf, and remodel synapses.[11,12] Microglia also participate in axonal guidance and remodeling.[13,14] In neurogenesis, microglia balance proliferation and survival of neural progenitor cells through phagocytosis[15] and the release of trophic factors such as brain derived neurotrophic factor (BDNF), protease serine 2 (PRSS2), and cytokines.[16,17]

1.2 Genetic and molecular features of AD

AD has been defined by specific tissue alterations, including the accumulation of extracellular amyloid-β (Aβ) peptides produced by the breakdown of amyloid precursor protein (APP) and intracellular hyperphosphorylated tau deposits. AD is a genetically diverse condition that can be generally divided into two types: familial (FAD) and sporadic. Autosomal dominant mutations in genes such as APP and presenilin-1/2 (PSEN1/2), which increase the formation or aggregation of Aβ, are the cause of familial AD[18,19], which accounts for less than 5% of cases.[20] In contrast, sporadic AD is substantially impacted by genetic risk factors, most notably the apolipoprotein E ε4 (APOE4) allele, while APOE2 confers relative protection.[21] Comprehensive genetic studies have shown other risk variations beyond these traditional amyloid-related genes, such as those in triggering receptor expressed on myeloid cells 2 (TREM2), emphasising the role of immune-related pathways in AD susceptibility and progression.[22] These findings imply that the onset, course, and heterogeneity of disease are significantly influenced by parallel or downstream processes, particularly neuroinflammatory mechanisms mediated by non-neuronal cells such as microglia.[23,24]

These functions are mediated through both direct membrane-to-membrane interactions with neurons[25,26] and indirect signaling pathways involving astrocytes,[27] cytokines, growth factors[28], and cerebrospinal fluid.[29] By eliminating cellular waste and potentially dangerous antigens and by secreting chemokines, cytokines, and neurotrophic factors that facilitate tissue maintenance and immunological regulation, microglia also contribute to the healthy functioning of the CNS.[6] Proper microglial function is therefore essential for sustaining neuronal health, synaptic plasticity, and overall brain homeostasis.

Depending on their activation state, microglia exhibit context-dependent roles ranging from neuroprotective to neurotoxic.[30] Microglial responses have historically been categorised into pro-inflammatory and anti-inflammatory phenotypes, although emerging evidence supports a more complex spectrum.[6]

1.3 Microglia in AD pathogenesis

In AD, microglia mount an acute immune response against harmful stimuli, including misfolded proteins such as Aβ. While acute activation can enhance phagocytosis and clearance of Aβ, chronic activation shifts microglia toward a pro-inflammatory state, impairing their physiological functions and contributing to synapse loss and neurotoxicity. Activated microglia, along with immunoglobulins and complement components, closely associate with Aβ plaques in AD patients (also in mouse models)[31], displaying increased proliferation [32] and upregulation of inflammatory surface receptors and inducible enzymes[33,34] characteristic of a pro-inflammatory phenotype.[31] Microglia also contribute to tau pathology, actively propagating tau aggregates via

phagocytosis and exosome-mediated secretion[35], and can indirectly induce neuronal death by promoting neurotoxic A1 astrocytes.[36]

Microglial activation is associated with dynamic cellular adaptations, including morphological remodeling (process shortening and soma enlargement), alterations in surface phenotype, changes in secretory activity, and increased proliferative responses.[37] When describing the wide spectrum of microglial cellular and biochemical changes simply as "activation," it may mask the contrasting functional consequences of these responses. In AD, microglial activity is highly context-dependent. Transient or acute activation may support Aβ removal by enhancing phagocytic capacity, whereas prolonged activation is associated with synaptic damage and neurotoxicity driven by persistent inflammatory signaling. Microglia detect Aβ and danger-associated molecular patterns via pattern recognition receptors (PRRs), which bind distinct Aβ species with varying affinities.[38] Aβ-mediated activation occurs through multiple PRRs, triggering pro-inflammatory cytokine production (interleukin (IL)-1β, tumour necrosis factor (TNF)-α) and sometimes compromising phagocytic clearance.[39,40]

Notably, variability in cytokine expression profiles influences phagocytic efficiency, highlighting the functional diversity of activated microglia.[41] Furthermore, as neurodegeneration progresses, additional endogenous danger signals may arise, further amplifying microglial activation and compromising clearance mechanisms.[42] Collectively, these processes likely contribute to the persistent neuroinflammatory environment observed in AD (Figure 1).

2. Genetic modulators of microglial activity

Emerging evidence highlights that genetic alterations impacting microglial function play a central role in both the initiation and progression of AD. As the resident immune cells of the CNS, microglia constantly survey the brain microenvironment, responding to tissue damage, infections, and protein aggregates.[43] Mutations in microglia-associated genes can disrupt these homeostatic functions, leading to altered cytokine secretion, impaired phagocytosis, and sustained neuroinflammation, all of which contribute to AD pathogenesis.[44]

A major consequence of microglial genetic dysfunction is the impaired clearance of Aβ peptides, a defining pathological hallmark of AD. Mutations affecting microglial genes compromise this clearance, promoting Aβ accumulation, synaptic dysfunction, and progressive cognitive decline.[43] In parallel, these genetic changes alter microglial gene expression profiles and intracellular signaling pathways,

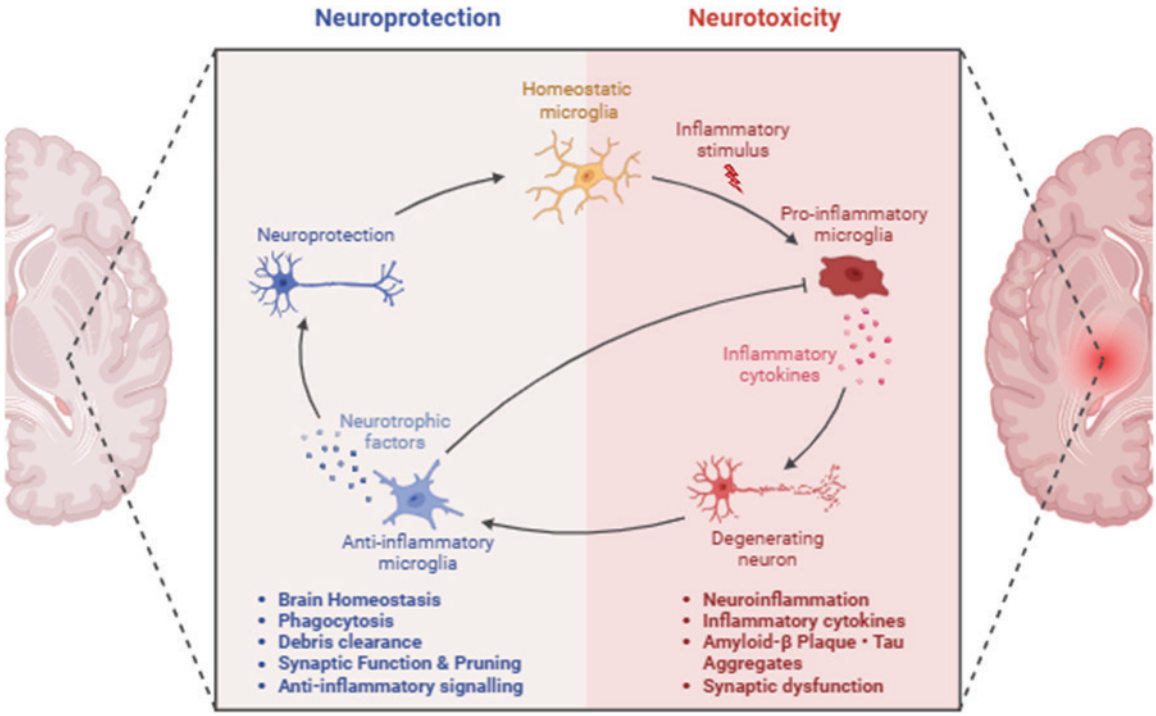

FIGURE 1 Microglial Homeostasis and Dysfunction in Alzheimer's Disease.

Under physiological conditions (left panel), microglia preserve central nervous system homeostasis through immune surveillance, synaptic pruning, debris clearance, and neurotrophic support, thereby maintaining neuronal integrity and network stability. In Alzheimer's disease (right panel), microglia adopt disease-associated states marked by impaired clearance, enhanced pro-inflammatory cytokine signaling, and maladaptive interactions with amyloid-β plaques and tau aggregates. These alterations drive synaptic dysfunction and progressive neurodegeneration.

skewing microglia toward maladaptive activation states that exacerbate neurodegeneration.[43]

Genetic studies have identified several immunomodulatory variants associated with AD risk. In particular, late-onset Alzheimer's disease (LOAD) is strongly linked to variants in microglia-expressed genes. The APOE ε4 allele remains the most robust risk factor for LOAD[45,46], modulating microglial inflammatory responses and Aβ metabolism. Additional AD-associated variants have been reported in TREM2, phospholipase Cγ2 (PLCG2), cluster of differentiation 33 (CD33), and transient receptor potential cation channel, subfamily M, member 2 (TRPM2), which regulate microglial survival, phagocytosis, calcium signaling, and immune activation.[46,47]

Collectively, these findings underscore the central role of microglial genetics in shaping neuroinflammatory responses and disease susceptibility. The major microglia-associated risk genes, their physiological functions, mechanisms in AD, and downstream consequences are summarised in Table 1, illustrating how genetic variation orchestrates microglial phenotypes, amyloid handling, inflammatory signaling, and neurodegenerative progression.

3. Neuroinflammation and microglial activity in AD

3.1 Neuroinflammatory dynamics in AD

Neuroinflammation refers to the inflammatory responses occurring within the CNS, marked by microglial activation, recruitment of immune cells, and the release of pro-inflammatory mediators.[64] Evidence increasingly points to neuroinflammation as a key driver of AD, with inflammatory mediators rising long before clinical symptoms appear. A hallmark of AD-associated neuroinflammation is the accumulation of activated microglia at sites of neuronal injury and amyloid deposition.[65]

In AD, soluble Aβ and other damage-associated signals stimulate microglia through cell-surface receptors, triggering their migration toward amyloid plaques, morphological transformation into an amoeboid shape, and release of inflammatory mediators.[66] Microglia play a dual role as they maintain CNS homeostasis by phagocytosing Aβ through scavenger receptors, thereby limiting amyloid accumulation, yet impaired phagocytosis and chronic activation lead to excessive pro-inflammatory cytokine release, worsening neuronal injury and synaptic dysfunction.[67]

TABLE 1 **Key microglia-associated genetic risk factors in Alzheimer's disease**

Gene	Primary function	AD-associated mechanism	Microglial impact	Key pathological consequences
APOE (ε4)	Lipid transport Cholesterol homeostasis Immune modulation[48,49]	Reduced Aβ binding Impaired clearance Promotion of tau pathology[50,51]	Drives the transition to DAM phenotype;[52] Enhances pro-inflammatory signaling[53]	Increased amyloid deposition, accelerated tau pathology, enhanced neurodegeneration[50,51]
TREM2	Microglial activation, survival,[54] chemotaxis,[55] phagocytosis[56]	Disease variants impair ligand recognition and signaling[57]	Regulates plaque-associated microglial responses; supports metabolic fitness[58]	In deficiencies, Impaired Aβ clearance, dysfunctional microglial states, and exacerbated plaque expansion[59]
CD33	Inhibitory immune receptor regulating phagocytosis[60]	Risk variants favour the full-length inhibitory isoform (hCD33M)[61]	Suppresses microglial phagocytosis; isoform balance determines function[62]	Reduced Aβ uptake, impaired debris clearance, enhanced disease progression[63]

Summary of major AD susceptibility genes with established roles in microglial biology, highlighting their primary physiological functions, AD-associated mechanisms, effects on microglial phenotypes, and downstream pathological consequences. These genes illustrate how genetic variation shapes microglial responses, influencing amyloid handling, inflammatory signaling, and neurodegenerative progression. (AD – Alzheimer's disease; Aβ – amyloid beta; APOE – apolipoprotein E; DAM – disease associated microglia; TREM2 – triggering receptor expressed on myeloid cells; CD33 – cluster of differentiation 33).

3.2 Disease-associated microglia (DAM) states

Recent transcriptomic studies have identified disease-associated microglia (DAM) as a distinct microglial phenotype linked to AD pathology.[68] DAMs undergo extensive transcriptional reprogramming, affecting genes involved in inflammatory signaling, phagocytosis, and lipid metabolism. Importantly, DAMs are heterogeneous, with subpopulations exhibiting pro-inflammatory or anti-inflammatory profiles, reflecting diverse roles in disease progression.[52] While DAM signatures were first characterised in mouse models, human AD microglia (HAM) show only partial overlap, revealing species-specific transcriptional programs and highlighting differences in innate immune responses between humans and models.[69] Despite these differences, key regulatory pathways, particularly those involving TREM2, remain conserved, emphasising the relevance of DAM-associated mechanisms in human AD.[70]

Microglial activation is dynamic, evolving through disease progression. Evidence supports a biphasic pattern: an early anti-inflammatory response during preclinical stages followed by sustained pro-inflammatory activity as pathology advances.[71] Central to this transition are interconnected signaling pathways, notably nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the nucleotide-binding oligomerisation domain (NOD), leucine-rich repeat (LRR)- and pyrin domain containing protein 3 (NLRP3) inflammasome, and the complement cascade, which collectively orchestrate microglial responses and drive neurodegenerative processes.

3.3 Key inflammatory signaling pathways

In AD, several inflammatory signaling pathways drive microglial dysfunction and fuel the progression of neurodegeneration. Gaining a clear understanding of these pathways not only sheds light on disease mechanisms but also points toward potential therapeutic targets. The key pathways are summarised in Table 2.

TABLE 2 Major inflammatory signaling pathways contributing to microglial dysfunction in Alzheimer's disease

Pathway	Primary trigger(s)	Core molecular events	Microglial consequences	Pathological Outcome
NF-κB signaling	Aβ PRR activation, cytokines[72]	Transcription of pro-inflammatory mediators (TNF-α, cytokines);[73] inflammasome priming[74]	Sustained inflammatory activation[74]	Amplified neuroinflammation[74]
NF-κB APOE axis	NF-κB activation by $A\beta_{40}$[75]	NF-κB-dependent APOE transcription[75]	Enhanced APOE-mediated effects[75]	Increased amyloid aggregation[76]
NLRP3 inflammasome	Aggregated Aβ, cellular stress[77]	Caspase-1 activation → IL-1β / IL-18 maturation[78]	Chronic inflammatory phenotype,[79] impaired phagocytosis[80]	Accelerated Aβ/tau pathology[80]
Complement (C) system	Complement activation by Aβ/ injury	C1q[81],/C3[82] signaling via complement receptor (CR)1[81] CR3[82]	Altered phagocytosis, microglial activation[83]	Phase-dependent neurodegeneration.[84]

Overview of key pathways implicated in AD-associated neuroinflammation, summarising their primary triggers, core molecular events, effects on microglial function, and downstream pathological consequences. These pathways illustrate how dysregulated immune signaling links amyloid and stress responses to chronic inflammation and neurodegenerative progression.

(NF-βB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – the nucleotide-binding oligomerisation domain (NOD), leucine-rich repeat (LRR) – and pyrin domain containing protein 3; PRR- pattern recognition receptor; TNF-γ – tumour necrosis factor- alpha).

4. Potential therapeutic targets from genetic modulation of microglial function

Modulating microglial function at the genetic and transcriptomic level offers an exciting avenue to slow or even prevent neurodegenerative processes in AD. Several pathways ranging from receptor signaling (e.g., TREM2, CD33) and inflammatory regulators (e.g., NF-κB, NLRP3, Receptor-interacting serine/threonine-protein kinase 1 (RIPK1)) to metabolic and autophagic programs, along with key genetic risk factors such as APOE4, have emerged as promising points for intervention. By targeting these pathways through approaches like gene therapy, antisense oligonucleotides, or epigenetic modulation, it may be possible to restore protective microglial functions, improve the clearance of toxic proteins, and dampen harmful neuroinflammation. The main genetic targets, their therapeutic strategies, underlying mechanisms, and anticipated outcomes are summarised in Table 3.

5. Current gaps, challenges, and future directions

5.1 Conceptual and biological constraints of microglial modulation

Microglia play a central role in regulating fundamental pathways in the brain, making genetic or therapeutic modulation of this cell population inherently complex and potentially associated with unintended consequences. Core microglial functions, including synaptic pruning, immune

TABLE 3 Emerging genetically informed therapeutic targets and pathways in Alzheimer's disease

Target / axis	Therapeutic strategy	Mechanistic rationale	Expected outcome
APOE4	ASOs; CRISPR editing[85]; AAV-apoE2 delivery[86]	Reduces ApoE4 toxicity[87,88] or converts to protective isoforms [85]	Broad disease modification
TREM2	Agonistic antibodies; shedding inhibition[89]; miRNA modulation[90]	Enhances protective microglial phenotype and debris clearance	Reduced neurotoxicity, improved Aβ clearance
CD33	Isoform modulation; inhibitory pathway targeting[91]	Relieves suppression of microglial phagocytosis[91]	Enhanced clearance capacity
RIPK1	RIPK1 inhibition[92,93]	Suppresses NF-κB signaling and necroptotic pathways[92,93]	Reduced maladaptive inflammation[94]
NLRP3 Inflammasome	Genetic modulation via POPs/ COPs[95]	Disrupts inflammasome & assembly priming[96]	Attenuated chronic neuroinflammation[96]
MAPT (Tau)	ASOs; gene suppression[97]	Reduces tau aggregation & propagation[98]	Mitigated tau pathology[98]
Tau Kinases (GSK-3β, CDK5)	RNA interference; kinase targeting[99,100]	Limits pathological tau modification[99,100]	Reduced neurofibrillary pathology[99,100]

Summary of key molecular targets implicated in AD pathogenesis, highlighting their biological roles, therapeutic strategies under investigation, mechanistic rationale, and anticipated functional outcomes. These approaches illustrate how modulation of genetic risk axes, inflammatory signaling, tau biology, and metabolic-autophagic pathways may enable mechanism-based disease modification. (APOE4 – apolipoprotein E 4; ASOs – antisense oligonucleotides; CRISPR – clustered regularly interspaced short palindromic repeats; AAV – adeno-associated virus; miRNA – micro ribonucleic acid; TREM2 - triggering receptor expressed on myeloid cells; CD33 – cluster of differentiation 33; RIPK1 – Receptor-interacting serine/threonine-protein kinase 1; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – the nucleotide-binding oligomerisation domain (NOD), leucine-rich repeat (LRR)- and pyrin domain containing protein 3; POPs/COPs – pyrin domain-only proteins / caspase recruitment domain-only proteins; MAPT – microtubule associated protein tau; GSK-3κ – glycogen synthase kinase-3 beta; CDK-5 – cyclin-dependent kinase 5)

surveillance, and cytokine signaling, are tightly regulated across the lifespan, and disruption of these processes may produce stage-specific effects in AD. While many developmental microglial roles occur early in life, suggesting that partial attenuation of selected pathways in LOAD may be tolerated, the long-term effects of altering genetically encoded microglial programs in the aging brain remain insufficiently understood. A major unresolved challenge is determining whether enhancing or suppressing microglial activity through genetic modulation offers therapeutic benefit. Microglial activation can be either protective or detrimental depending on disease stage, genetic background, and the local microenvironment, complicating therapeutic timing and specificity. Moreover, transitions in microglial phenotype from loss of homeostatic functions to the acquisition of neurotoxic traits are not uniform, limiting the potential effectiveness of broad activation or suppression strategies. Further complexity arises from the fact that molecular pathways governing microglial state transitions are closely intertwined with broader immune, metabolic, and developmental programs. Consequently, AD pathogenesis appears to reflect coordinated disruption of multiple genetically regulated processes, including migration, phagocytosis, cytokine signaling, and metabolic adaptation. In this context, systematic identification of microglia-enriched risk genes offers critical opportunities to refine mechanistic understanding and inform future therapeutic strategies.

5.2 Limitations of current preclinical and translational models

Many preclinical strategies continue to rely on genetic knockdown or deletion approaches that lack adequate cell-type and context specificity, thereby limiting their translational relevance. Furthermore, the age- and sex-dependent genetic regulation of microglial function remains insufficiently explored, despite its clear importance in late-onset neurodegenerative disease. Existing animal models also struggle to capture the genetic and phenotypic heterogeneity characteristic of human microglia, particularly within aging and sporadic disease contexts. Consequently, current models often fail to fully reflect the complexity of human microglial biology, constraining the broader applicability of experimental findings.

5.3 Genetic risk architecture of microglia in AD

Genome-wide association studies (GWAS) have revitalised our understanding of the pivotal role microglia play in Alzheimer's disease (AD), uncovering genes that govern immune signaling, lipid metabolism, and receptor-mediated phagocytosis. Among these, TREM2, APOE, CD33, and genes within the complement pathway stand out as central regulators of microglial function. Variants in TREM2, APOE, CD33, NLRP3, and MAPT influence critical microglial processes such as survival, phagocytosis, inflammatory signaling, and interactions with pathological proteins. Of particular note, TREM2 and APOE have emerged as especially influential in shaping microglial responses to amyloid pathology, reinforcing the idea that genetically encoded immune pathways are decisive drivers of disease progression. Yet, despite compelling insights from preclinical models, the mechanisms by which genetic variation steers microglia toward protective versus maladaptive states in humans remain incompletely understood.[8]

These genetic advances collectively pave the way for a genotype-guided precision medicine approach in AD. Therapeutic strategies tailored to APOE genotype through allele-specific editing, transcript-level modulation, or pathway-focused interventions offer a rational framework to enhance efficacy while limiting unintended immune or metabolic consequences. Continued refinement of ApoE4-focused strategies will be essential to translate personalised genetic risk into durable, mechanism-driven treatments.

At the same time, microglia occupy a complex and often paradoxical position in disease pathogenesis. While genetically programmed phagocytic responses can limit amyloid and tau accumulation, maladaptive activation states may accelerate protein propagation and neurodegeneration. GWAS consistently reinforce this duality, revealing that many AD risk loci are preferentially expressed in microglia. This positions microglia not simply as reactive responders, but as central genetic effectors of disease susceptibility.

Therapeutic development is increasingly focusing on genetically informed modulation of microglial pathways, including inflammatory signaling, metabolic adaptation, phenotype switching, and TREM2-dependent responses. A key translational challenge arises from the overlap between microglial and peripheral myeloid gene programs. Many AD-associated immune genes are shared with monocytes and macrophages, raising concerns that genetic interventions could unintentionally affect systemic immunity. From a genetic standpoint, indiscriminate activation or suppression of myeloid pathways is unlikely to be beneficial: overactivation may perpetuate chronic inflammation, whereas broad immune suppression could increase susceptibility to infections, particularly in aging individuals. This underscores the need to focus on microglia-enriched genetic signatures rather than broadly conserved immune programs.

5.4 Enabling technologies and human-relevant systems

Recent technological advances provide unprecedented opportunities to tackle these gaps. Single-cell RNA sequencing and spatial transcriptomics now allow high-resolution mapping of microglial subpopulations across disease stages, revealing how genetic risk variants shape functional states within specific brain regions. Despite these advances, important questions remain regarding microglial heterogeneity and their temporal dynamics throughout disease progression. Integrative omics approaches are beginning to pinpoint key regulatory genes and pathways that govern microglial state transitions, opening doors for early, precision-targeted interventions.

Future progress will rely on unraveling gene-driven microglial crosstalk with other neural cell types and on improving human-relevant experimental systems to better capture microglial biology in the context of neurodegeneration. Clustered regularly interspaced short palindromic repeats (CRISPR)-based genome editing, antisense oligonucleotides (ASOs), and ribonucleic acid (RNA)-targeting approaches enable precise manipulation of AD-associated genes, offering platforms to validate causal mechanisms and explore allele-specific interventions. In parallel, genetically informed biomarkers that combine APOE genotype, microglial activation signatures, and imaging readouts are beginning to translate molecular insights into clinically meaningful observations.

Advancing this field will also require models that faithfully reflect human microglial genetics and aging. While animal studies have been invaluable, species-specific differences in gene expression and activation states limit translational relevance. Emerging platforms using patient-derived iPSC microglia, brain organoids, and chimeric systems offer promising avenues to study human-specific genetic effects and cell-cell interactions in disease-relevant contexts. Integrating these models with single-cell and spatial genomics will be essential to disentangle the pleiotropic effects of microglial gene regulation and guide the development of precise, stage-specific genetically driven interventions in AD. These insights underscore the multifaceted challenges and emerging opportunities that define genetically informed microglial modulation strategies in AD (Figure 2).

CONCLUSION

AD is a genetically complex disorder in which microglia sit at the crossroads of immune regulation, lipid metabolism, and protein homeostasis. Human genetic studies have firmly established microglia-enriched risk genes, most notably APOE, TREM2, CD33, and associated pathways, as critical determinants of disease susceptibility and progression. These genes do not act in isolation; rather, they shape microglial phenotypes that influence amyloid and tau handling, inflammatory signaling, metabolic adaptation, and

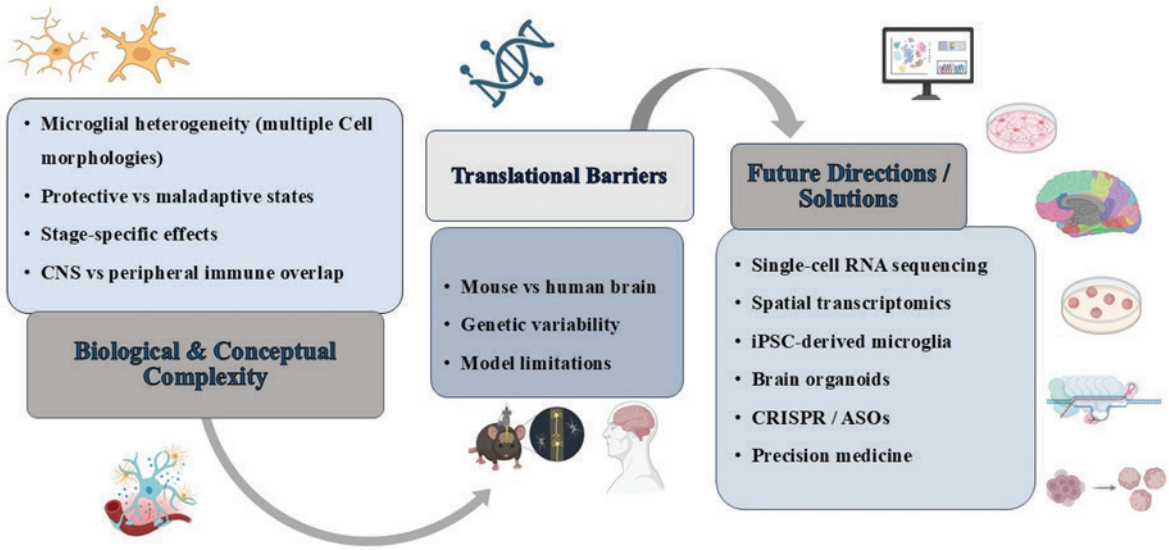

FIGURE 2 Challenges and future directions in genetically driven microglial modulation in AD.

Genetically guided modulation of microglial pathways is complicated by biological heterogeneity, context-dependent functional states, stage-specific effects, and overlap with peripheral immune programs. Limitations of current experimental models, species differences, and human genetic variability further constrain translational progress. Emerging technologies, including single-cell and spatial transcriptomics, induced pluripotent stem cell (iPSC)-derived microglia, brain organoid systems, and precision genome/ ribonucleic acid (RNA)-targeting approaches, offer promising strategies to resolve these challenges and enable stage-appropriate, mechanism-based therapeutic interventions.

neuronal integrity in a context- and stage-dependent manner.

Recent advances in single-cell and systems-level genomics have revolutionised our understanding of microglial heterogeneity, uncovering dynamic, genetically regulated states that traditional activation frameworks cannot capture. These insights highlight the importance of moving beyond broad immunomodulation toward precision strategies that selectively correct pathogenic microglial programs while preserving protective functions. Emerging genetic and genomic tools now offer unprecedented opportunities to link risk variants with causal mechanisms and to identify actionable, cell-type-specific therapeutic targets.

Translational progress will require integrating human genetics with refined experimental systems and genotype-informed patient stratification. By aligning genetic risk architecture with microglial state dynamics and immune regulatory pathways, future therapies may move AD management from merely alleviating symptoms toward durable, mechanism-based disease modification, offering hope for interventions that address the disease at its root.

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Competing interests

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Ethics statement

Ethical approval was not required for this study as it is a review article based on previously published literature.

Author contribution

Dinul Wijesinha conceived the article, performed the literature review, and wrote the manuscript.

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