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Sentinels of neuroinflammation: the crucial role of myeloid cells in the pathogenesis of gliomas and neurodegenerative diseases

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Abstract

The inflammatory processes that drive pathologies of the central nervous system (CNS) are complex and involve significant contributions from the immune system, particularly myeloid cells. Understanding the shared and distinct pathways of myeloid cell regulation in different CNS diseases may offer critical insights into therapeutic development. This review aims to elucidate the mechanisms underlying myeloid cell dysfunction and neuroinflammation in two groups of neurological pathologies with significant social impact and a limited efficacy of their treatments: the most common primary brain tumors –gliomas-, and the most prevalent neurodegenerative disorders -Alzheimer's and Parkinson's disease. Despite their distinct clinical manifestations, these diseases share key pathological features, including chronic inflammation and immune dysregulation. The role of myeloid cells in neuroinflammation has garnered special interest in recent years in both groups, as evidenced by the growing focus on therapeutic research centred on myeloid cells. By examining the cellular and molecular dynamics that govern these conditions, we hope to identify common and unique therapeutic targets that can inform the development of more effective treatments. Recent advances in single-cell technologies have revolutionized our understanding of myeloid cell heterogeneity, revealing diverse phenotypes and molecular profiles across different disease stages and microenvironments. Here, we present a comprehensive analysis of myeloid cell involvement in gliomas, Alzheimer's and Parkinson's disease, with a focus on phenotypic acquisition, molecular alterations, and therapeutic strategies targeting myeloid cells. This integrated approach not only addresses the limitations of current treatments but also suggests new avenues for therapeutic intervention, aimed at modulating the immune landscape to improve patient outcomes.

Keywords Myeloid cells, Neuroinflammation, Glioblastoma, Alzheimer disease, Clinical trials

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Introduction

Neuroinflammation, a distinct and complex inflammatory response within the brain parenchyma, serves as a defensive mechanism of the central nervous system (CNS) against infections and injuries. This process involves various cell types, including neurons, glial cells (microglia, oligodendrocytes, and astrocytes), resident non-glial myeloid cells (macrophages and dendritic cells), and peripheral leukocytes, all of which play a critical role in maintaining CNS integrity [1–4]. The primary resident immune cells in the brain, such as microglia, and peripherally infiltrating cells are essential in orchestrating the neuroinflammatory response [5]. These cells not only act as the principal defenders of the innate and adaptive immune systems but also facilitate dynamic remodeling of the cellular microenvironment, encompassing the activation of glial cells, recruitment of immune cells, release of inflammatory mediators, and tissue repair processes [5–7]. Among these immune cells, myeloid cells -particularly macrophages- play a crucial role in maintaining tissue homeostasis and represent the first line of CNS innate immune defence [8, 9].Their dual capacity to detect and respond to both pro-inflammatory and anti-inflammatory signals underscores their vital function in balancing protection and damage during CNS inflammation. While neuroinflammation initially serves a protective function, prolonged or deregulated inflammation can contribute significantly to the development or progression of various CNS diseases, including brain tumors and neurodegenerative disorders [10, 11].

The rapid advances in single-cell RNA sequencing (scRNA-seq) and other high-resolution technologies have significantly enhanced our understanding of myeloid cell diversity, revealing a range of phenotypes and activation states that differ depending on the disease stage and microenvironment. These insights allow us to revisit previously oversimplified concepts of neuroinflammation, and instead focus on the more nuanced spectrum of cellular states present in CNS disorders [12–14]. By exploring the functional and molecular heterogeneity of myeloid cells in these diseases, we can better understand how their phenotypic acquisition contributes to disease progression and therapeutic resistance.

Despite their distinct characteristics, gliomas -the most common primary brain tumors- Alzheimer's disease (AD), and Parkinson's disease (PD) -the most prevalent neurodegenerative disorders- are paradigmatic groups of age-related neurological diseases. These diseases are notably challenging due to their social impact, high healthcare-related costs, limited therapeutic approaches and unfavorable outcomes. A common feature of the three disorders is the dysregulation of the inflammatory response, with macrophages playing a pivotal role in their pathogenesis [10–13].

The role of neuroinflammation extends beyond individual disease characteristics, suggesting shared pathological mechanisms driven by chronic inflammation and immune dysregulation [1–6, 8, 10, 11, 15, 16]. This convergence highlights the importance of understanding myeloid cell function in diverse CNS disorders, as identifying distinct and common deregulated pathways could inform new therapeutic strategies that target shared molecular mechanisms. Current clinical trials targeting the immune components in glioma and neurodegenerative diseases have yielded limited success [11, 17, 18]. Thus, refining our knowledge of shared and disease-specific pathways could enhance the efficacy of immunotherapies.

This review aims to provide a comprehensive characterization of the role of myeloid cells in neuroinflammation across gliomas, AD and PD, with the objective of rethinking therapeutic targets that may improve patient outcomes. Through new knowledge based on genomic advances and the characterization of emerging cell populations, we will highlight the intricate pathways that contribute to myeloid dysfunction in these brain pathologies. By examining both the shared features and the unique aspects of these diseases, this review will also address emerging therapies aimed at targeting inflammatory pathways. Our approach aims to integrate these insights into a broader context that can inform future therapeutic strategies, potentially paving the way for novel treatments that target myeloid cells and modulate the immune microenvironment in CNS diseases.

Myeloid cells in the CNS

Myeloid cells are a heterogeneous group of immune cells crucial in mediating responses to tissue damage (Fig. 1). They play key roles in the innate immune response and the homeostasis of various tissues, including the nervous system [9]. Originating from common myeloid progenitors, these cells differentiate from hematopoietic stem cells in the bone marrow during the haematopoiesis process [19]. Myeloid cells are categorized into three main populations: granulocytes (including basophils, eosinophils, and neutrophils), mononuclear cells (such as monocytes, macrophages, and dendritic cells), and mast cells [20]. Within the CNS, myeloid cells are particularly significant due to their abundance, functional versatility, and high cellular plasticity. They contribute to both normal physiology and various pathologies [8]. The understanding of the roles played by granulocytes and dendritic cells in neuroinflammation remains incomplete, primarily due to their insufficiently characterized phenotypes and the unclear nature of their functions in homeostatic conditions [21]. Our discussion then shifts to macrophages, which are the primary myeloid cells engaged in neuroinflammation (Fig. 1).

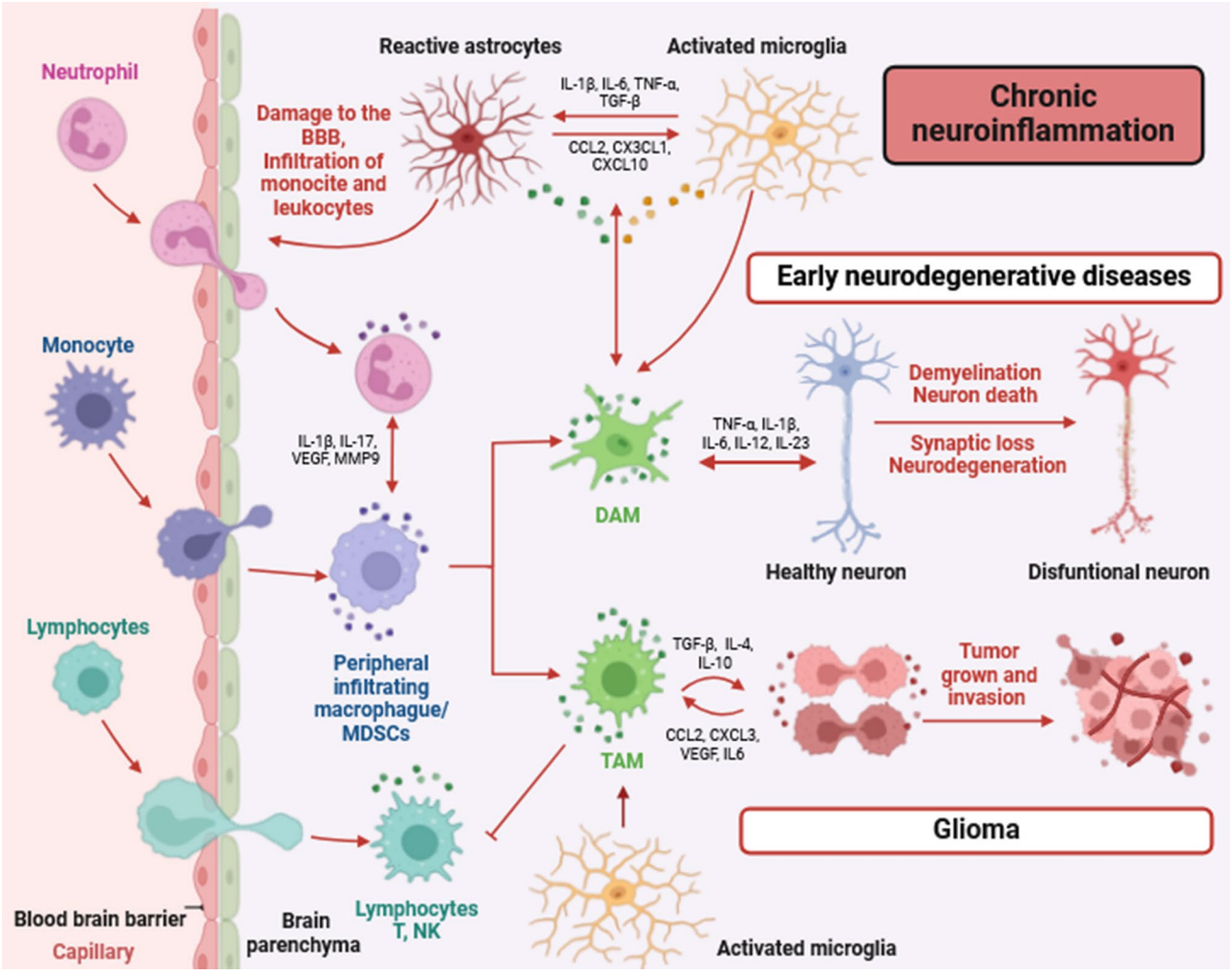

Fig. 1 Mechanisms of neuroinflammation and myeloid disfunction in neurological diseases and glioma development. This figure highlights the role of myeloid cell infiltration and chronic neuroinflammation in the pathogenesis of neurological diseases and gliomas. Blood-brain barrier (BBB) disruption allows peripheral immune cells—neutrophils, monocytes, and lymphocytes—to infiltrate the brain parenchyma. Reactive astrocytes and activated microglia damage BBB and release pro-inflammatory cytokines and chemokines (IL-1β, IL-6, TNF-α, TGF-β, CCL2…) that recruit immune cells. Disease-associated microglia (DAM) contribute to early neurodegenerative processes, leading to demyelination, synaptic loss, and neuron death, driven by cytokines (IL-1β, IL-6, IL-12, IL-23). In the glioma microenvironment, peripheral infiltrating macrophages and tumor-associated macrophages (TAMs) secrete diverse factors (IL-10, TGF-β, IL-4…) that support tumor growth and invasion through immunosuppression and angiogenesis. Tumor cells produce additional pro-tumorigenic signals (CCL2, CXCL3, VEGF, IL-6), perpetuating an inflammatory loop that enhances tumor progression and gliomagenesis. BBB: Blood-brain barrier. MDSCs: Myeloid-Derived Suppressor Cells. DAM: Disease-associated microglia. TAMs: Tumor-associated macrophages

Macrophages either reside permanently in specific organs (e.g., microglia in the brain, Kupffer cells in the liver, alveolar macrophages in the lungs) or infiltrate tissues as monocytic precursors from the bone marrow, differentiating and maturing in response to cytokines and growth factors [22]. Exhibiting various phenotypes, they are involved in tissue homeostasis and immune response under both physiological and pathological conditions [23]. Their primary functions include phagocytosis of pathogens, foreign particles, or debris from dead or damaged cells; presentation of phagocytosed fragments to T helper lymphocytes via the class II major histocompatibility complex (MHC II) system, acting as antigen-presenting cells; modulation of the immune response through cytokines and growth factors release; resolution of inflammation; and regulation of tissue remodelling and angiogenesis [22].

Although there is a confusing terminology, CNS macrophages can be broadly categorized based on origin, location, and characteristics into two groups: resident and peripheral infiltrating macrophages [24].

Resident macrophages: microglia and border-associated macrophages (BAMs)

Microglia are the principal resident macrophages of the CNS parenchyma, accounting for 10–15% of the brain

and spinal cord cellular population [25]. These cells originate from the yolk sac during embryonic development and are maintained independently of hematopoietic stem cells [26]. In a resting state, microglial cells are characterized by a branched morphology with fine cellular extensions. They perform essential functions such as continuous surveillance of the CNS, modulation of synaptic plasticity, phagocytosis of non-functional neurons and synapses, and maintenance of homeostasis [27]. Microglia express specific markers such as Iba1high, cluster of differentiation (CD)206–, CD163–, CD45low, CD11b+, MHCII+, F480+, CX3CR1high, Ly6C–, LYVE1-, distinguishing them from non-glial resident macrophages [26, 28, 29]. Other markers present on microglia surface are P2Y12, CD115, CD11b, CX3CR1, CD68 and various innate immune receptors from the pattern recognition receptor (PRR) family, including Toll-like receptors (TLR), scavenger receptors (SR), and receptors for advanced glycation end-products (RAGE) [30]. Microglial activation is triggered by damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) recognition, leading them to migrate to lesion sites and initiate an innate immune response [25]. In addition to these roles, recent studies have highlighted the intrinsic heterogeneity of microglial populations across different CNS regions. Single-cell analysis has identified region-specific gene expression profiles, indicating that microglia adapt their functions and states in response to varying environmental cues within the brain parenchyma [31]. This heterogeneity is associated with differences in microglial activity, such as neuroprotection, synaptic pruning, and immune surveillance, highlighting their adaptive potential in maintaining CNS integrity.

Border-associated Macrophages (BAMs) are categorized based on their location as perivascular, choroid plexus and meningeal macrophages. This cells express unique markers such as CD206+, which is not present in microglia or infiltrating leukocytes [26]. BAMs, along with dendritic cells, comprise the resident non-glial myeloid cells within the CNS. These cells are responsible particularly for immunological surveillance of the CNS borders and the interaction and communication with the lymphatic system [26].

Peripheral infiltrating macrophages

In stable conditions, marrow-derived monocytes are not observable in the brain parenchyma, but in pathological circumstances these cells are attracted and recruited to the CNS by cytokines released by among other cells, by resident microglia, such as C-C Motif Chemokine Ligand 2 (CCL2) [21]. These monocytes, prevalent in tissues outside the CNS, express characteristic markers such as Iba1-, CD206–, CD163+, CD45high, CD11b+, MHCIIhigh, F480+, CX3CR1low, Ly6Chigh, LYVE1+. Therefore, one of the functions of disease-associated microglia appears to be the recruitment of marrow-derived monocytes to the CNS [27]. Upon their arrival in the CNS, these monocytes can differentiate into a broad spectrum of phenotypes, some of which closely resemble CNS-resident microglia [21]. In fact, identifying peripheral myeloid cells from microglia within the inflamed CNS has been challenging in the past. However, they are now recognized as core players in neuroinflammation, although they do not integrate into the resident macrophages pool [27, 32, 33].

Myeloid-derived suppressor cells (MDSCs)

This immature population of peripheral infiltrating macrophages constitute a heterogeneous group of myeloid origin cells. MDSCs proliferate in several pathological circumstances, such as cancer and inflammation, and suppress myeloid cells and T lymphocytes functions and proliferation [20]. Its accumulation is influenced by two sets of interrelated signals. The first set, crucial for the proliferation of immature myeloid cells, is triggered by factors released by tumors or bone marrow stroma in response to chronic infection and inflammation [20, 34, 35]. Key transcriptional factors/regulators in this process are Signal Transducer and Activator of Transcription (STAT)3, STAT5, interferon regulatory factor 8 (IRF8), CCAAT/enhancer-binding protein beta (C/EBP-β), and NOTCH [20, 36, 37]. The second set of signals triggers their pathological activation. This activation is driven by inflammatory cytokines and DAMPs, including Interferon (IFN)-γ, Interleukin (IL)-1β, IL-4, IL-6, IL-13, TNF, and the TLR ligand High mobility group box 1 (HMGB1). These factors predominantly transmit signals through Nuclear Factor-Kappa B (NF-κB), STAT1, and STAT6 pathways [20, 36]. Immune suppression is the principal characteristic that distinguishes MDSCs from other disease-associated infiltrating myeloid cells. They are recognized as major negative regulators of immune responses in pathological conditions such as brain tumors and AD. However, a significant challenge remains in identifying specific markers that enable the clear phenotypical differentiation of MDSCs from neutrophils and monocytes in pathologic situations [20, 38].

The ontogeny-based classifications introduced above may serve as a useful starting point for understanding the role of myeloid cells in a healthy CNS. However, the application of single-cell technologies, particularly single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics, has dramatically advanced our understanding of myeloid cell diversity within the CNS. By allowing for high-resolution profiling of individual cells, these technologies have revealed significant heterogeneity among resident and infiltrating myeloid cells, particularly in

pathological contexts, expanding our knowledge beyond the traditional binary classifications based on origin and polarization [13, 14, 31, 39, 40].

Myeloid cells in brain diseases: novel insights from a comparative perspective

Myeloid cells, including microglia and infiltrating macrophages, are core to neuroinflammation and pathogenesis of neurodegenerative diseases and brain tumors. Despite the differences in pathology, myeloid cells exhibit both similarities and disease-specific roles. In all three diseases, myeloid cells are crucial for responding to pathological stimuli and contribute to the chronic neuroinflammatory environment characteristic of these conditions. However, the exact mechanisms and outcomes of their activation differ.

Numerous studies have highlighted the critical role of chronic neuroinflammation within tumor microenvironment (TME) as a key factor in glioma progression [41, 42]. In this context, myeloid cells are a predominant cell population within TME, constituting approximately 60% of infiltrating cells, a stark contrast to the relatively sparse presence of lymphocytic cells [11, 43]. Key myeloid cells in the glioma TME include microglia, MDSCs, and bone marrow-derived macrophages [44, 45]. Tumor-associated macrophages (TAMs) constitute about 30% of the tumor mass in gliomas (Fig. 1). Distinguishing microglia from peripheral myeloid cells in the inflamed CNS can be challenging, but it is now understood that macrophages in the TME originate from both CNS-resident microglia and bone marrow-derived cells [46, 47]. Interestingly, microglial-derived TAMs seem to be more prevalent in newly diagnosed tumors, whereas bone marrow-derived TAMs are more common in recurrent tumors, indicating a dynamic relationship between these populations [14]. These cells induce a persistent activation of inflammatory pathways, induced by the secretion of cytokines such as IL-6, IL-1β, and Tumor Necrosis Factor (TNF)-α, which are released by TAMs and neutrophils, promote an immunosuppressive and pro-tumorigenic environment, enhancing tumor cell survival, proliferation, and migration. The TME induce factors such as NF-κB and STAT3 which are upregulated, further driving transcriptional programs that support tumor growth and resistance to apoptosis. This inflammatory milieu not only sustains glioma progression but also facilitates the malignant transformation of low-grade gliomas [41, 42].

CNS inflammation is also increasingly acknowledged as a significant contributor to the progression of AD, ultimately leading to the degeneration of brain parenchyma [30, 48, 49]. In fact, neuroinflammation, rather than amyloid beta (Aβ) deposition, has been recently associated with structural and functional network disturbances in AD [50]. Reactive microglia can also influence Aβ peptide formation and aggregation modulating γ-secretase activity and iron release. Inflammatory cytokines from activated microglia upregulate β- secretase expression, contributing to pathogenic Aβ peptide generation and tau hyperphosphorylation [51, 52]. Furthermore, inflammatory cytokines released by these activated microglia, such as IL-1β, IL-6, IL-8, TNF-α, TGFβ, MCP1, nitric oxide (NO) and ROS, positively regulate β-secretase expression. Both enzymes act by cleaving the amyloid-beta precursor protein (APP) and generating pathogenic Aβ peptides through the NF-κB pathway. This, in turn, leads to hyperphosphorylation of tau and activates peripheral macrophages, resulting in the formation of characteristic neurofibrillary tangles (NFTs) [51, 52]. In this sense, Wright et al. showed in an AD mouse model that microglia were activated before the formation of Aβ plaques [53], suggesting a core role in AD pathogenesis. In fact, microglial activation has been proved to be a dynamic process in AD. Fan et al. showed that although there is a baseline microglial activation in early stages of AD, it diminishes during disease progression. After this initial drop-in microglial activity, in the follow-up of dementia stages of AD patients showed a progressive increase in microglial activation, indicating two peaks of microglial activation in AD natural history. The results suggests that early in MCI, microglia might have a protective role which shifts to a damaging pro-inflammatory role as the disease progresses [54].

Several works have also confirmed the neuroinflammation and activation of microglia in diverse PD models across different brain regions [18, 39]. In PD's pathological hallmark, α-synuclein (α-Syn) -the protein that aggregates in Lewy bodies characteristic of PD- is often phosphorylated at serine 129 (Ser129), believed to have pathological significance [55]. This phosphorylation, potentially induced by proinflammatory mediators from reactive microglia, has uncertain implications, with some studies suggesting a neuroprotective role in inhibiting further α-Syn aggregation [56]. Microglia can upregulate pro-inflammatory mediators such as TNF-α and IL-1β in response to α-synuclein aggregates, contributing to neuronal death and disease progression [57]. Subsequent clinical studies have reinforced this notion. Employing PET-TC imaging, evidence indicates the presence of cortical microglial activation in individuals with PD, both those without dementia and those with dementia [58]. This observation raises the possibility that neuroinflammation might manifest as an early event within the disease continuum, potentially preceding the onset of dementia and enduring throughout the disease's progression [59, 60]. These inflammatory responses could trigger genetic mutations and post-translational modifications, such as α-Syn phosphorylation, leading to its aggregation into insoluble oligomers. However, neuronal

degeneration in PD occurs even before the appearance of Lewy bodies, the typical abnormal deposits of α-Syn, indicating other contributing factors [61].

Historically, the binary concept of M1/M2 polarization has shaped our understanding of these cells in diverse CNS pathologies, where M1 macrophages exhibit pro-inflammatory properties and M2 macrophages display anti- inflammatory and tissue-repairing roles [8, 62, 63]. However, advancements in scRNA-seq have demonstrated that this model oversimplifies the heterogeneity of myeloid cells, especially within the CNS under pathological conditions, such as neurodegenerative diseases and gliomas [13, 14, 31, 39, 40]. Individual cells within the myeloid compartment can express a mixture of genes traditionally associated with both pro-inflammatory and anti- inflammatory functions, reflecting their highly adaptable nature where multiple myeloid cell states coexisting within the same tissue environment, suggesting that their functions are highly context-dependent [13, 40]. In these conditions, the plasticity of myeloid cells enables them to adopt a range of functional states that transcend the M1/M2 dichotomy. This plasticity is a hallmark of their role in maintaining tissue homeostasis and responding to injury or pathology [8].

Plasticity and polarization of myeloid cells

The plasticity of myeloid cells, particularly macrophages and microglia, is a defining feature of their role in maintaining tissue homeostasis and responding to pathological stimuli (Fig. 1). This plasticity allows them to adopt distinct functional states. Under pathological conditions, myeloid cells respond to a complex interplay of inflammatory and environmental cues, resulting in a spectrum of activation states that contribute to both disease progression and immune regulation [8, 14].

In the context of gliomas, TAMs show a high degree of plasticity. TAMs are drawn to the TME due to BBB dysfunction and the presence of chemoattractant molecules released by glioma cells, such as CCL2, CX3CL1, colony stimulating factor 1(CSF-1), SDF-1, Granulocyte-macrophage (GM)-CSF, and LOX [11, 64]. Initially, TAMs were thought to polarize strictly towards either a pro-tumorigenic M2-like phenotype or an anti-tumor M1-like state. scRNA- seq studies have revealed that TAMs in gliomas frequently co-express canonical M1 and M2 genes within the same cells, suggesting a much more fluid spectrum of activation than previously understood [13]. For example, in the glioma tumor microenvironment (TME), TAMs can simultaneously express pro-inflammatory genes such as IL-1β and anti-inflammatory markers like ARG1 or IL-10, indicating that the binary M1/M2 framework is inadequate to fully describe their functional states [13].

This complexity in polarization and plasticity is not unique to gliomas. In AD, microglial cells exhibit a similarly diverse array of phenotypes. Traditionally thought to polarize into a neurotoxic M1 phenotype in response to Aβ plaques, microglia have now been shown to adopt a range of activation states that do not neatly fit into the M1/M2 paradigm. Resting microglia detect Aβ oligomers through PRRs like TLR, CD14, and SR receptors, leading to phagocytosis of Aβ fibrils [65, 66]. The NLRP3 inflammasome in microglia recognizes Aβ aggregates as DAMPs, activating the NF-κB pathway. Many other receptors, like purinergic receptor P2×7R and RAGE also contribute to microglial activation in AD. RAGE, overexpressed in AD models, increases BBB permeability, exacerbating neuroinflammation and oxidative stress [67].This process leads to the production of proinflammatory cytokines like IL-1β and IL-18, with elevated levels of IL-1β observed in AD patients' brains, correlating with Aβ plaques, tau hyperphosphorylation, and NFTs [52, 67, 68]. Phenotypic changes are more pronounced near senile plaques and in advanced stages of the disease.

Distinct states of microglial activation have been recently described in AD. For instance, some microglial populations in AD display what has been termed a disease-associated microglia (DAM) phenotype, characterized by specific genetic and functional attributes (Fig. 1). The activation of DAM occurs in a two-phased process, starting with a triggering receptor expressed on myeloid cells 2 (TREM2)-independent phase, followed by a TREM2-dependent phase. Notably, the DAMs phenotype is associated with a reduction in the expression of key homeostatic genes and an upregulation of genes linked to neurodegenerative diseases, including ApoE, TREM2, and TYRO. In AD murine models, DAMs are predominantly found in regions with significant Aβ plaques and NFTs. When microglia become overactivated, they exhibit increased proliferation, induce chemotaxis, and upregulate inflammatory M1 markers [62]. However, the relationship between this phenotype and the degree of neuronal loss remains to be fully elucidated [69]. Other unique phenotype of senescent or dystrophic microglial cells, called dark microglia, has been associated with conditions like AD. These cells are distinguished by their darkened appearance due to an electron-dense cytoplasm and nucleoplasm. In contrast to typical microglia, dark microglia do not express the P2RY12 marker and exhibit only weak positivity for CX3CR1 and IBA1. They show signs of oxidative stress, evidenced by condensed cytoplasm and nucleoplasm, changes in mitochondrial structure, and dilated endoplasmic reticulum, indicating a level of activity that surpasses other microglial states. Dark microglia engage in close interactions with the vasculature and dystrophic synaptic components, such as axonal terminals and dendritic spines. They express CD11b and TREM2, marking

a significant immune response that may be indicative of their role in synaptic remodelling. Notably, the prevalence of dark microglia increases with age. In the context of AD, they are frequently observed near amyloid plaques and dystrophic neurites, pointing to their potential role in the typical synaptic dysfunction associated with this degenerative disorder [70].

Similarly, in PD, microglia have been shown to transition between various activation states in response to α-Syn depending on the stage of the disease and the specific microenvironmental signals they encounter. α-Syn is primarily found in the cytoplasm and may be present within microglial cells, playing a role in modulating and pre-sensitizing microglial activation [60]. Activated microglia contribute to oxidative stress and mitochondrial dysfunction, exacerbating α-Syn's pathogenicity [56]. Intriguingly, microglia loaded with α-Syn fibrils can transfer these to neighbouring cells, potentially aiding in their degradation [71] Nevertheless, microglia can adopt anti-inflammatory phenotypes, particularly in the early stages of PD, when their primary function may be to clear α-Syn aggregates through phagocytosis. Yet, as the disease progresses, microglia become chronically activated, contributing to a self-perpetuating cycle of neuroinflammation and neurodegeneration [39, 60]. However, all these interactions between α-Syn and microglia and their exact role in PD are not yet fully understood.

Response to environmental signals

One of the most striking aspects of myeloid cell plasticity in these diseases is their ability to respond to environmental cues that drive their functional diversity. In gliomas, for instance, TAMs are influenced by hypoxia, nutrient availability, and the release of tumor-derived factors such as CSF-1 and vascular endothelial growth factor (VEGF). Hypoxia, in particular, plays a central role in driving TAM polarization towards a pro-angiogenic, M2-like state, facilitating tumor vascularization and promoting immune evasion [72]. Yet, the expression of pro-inflammatory markers within the same population of TAMs, highlights the role of environmental cues in shaping their functional plasticity. The interaction between myeloid cells and tumor cells in the TME also leads to glioma cells secreting extracellular matrix proteins like tenascin-C (TNC). These molecules facilitate the remodelling of the cellular environment, stimulating TAMs to produce various proinflammatory cytokines (TGF-β, PGE2, IL-6, IL-1β, IL-10, IL-4, IL-8, MCP-1, EGF, STI-1) and matrix metalloproteases (MMPs) such as MMP9 and MMP14, which further promote neoplastic cell expansion and functional suppression of T lymphocytes [11, 33, 73, 74]. Another example is the interaction of S100 calcium-binding proteins with the receptor RAGE, leading to the upregulation of of STAT3 in TAMs. The STAT3 signalling pathway seems to play a critical role driving the adoption of a tumor-supporting TAM phenotypes [75]. A notable example of the complex interplay between myeloid cells, glioma, and tumor neovascularization is the release of hypoxia-inducible factor-1α (HIF-1α) by TAMs located in hypoxic and necrotic areas of the tumor [72, 76]. HIF-1α regulates the expression of proangiogenic factors such as VEGF-α, ANGPT2, and PIGF in both myeloid and tumor cells, as well as VEGF receptors (VEGFR) on endothelial cells [72, 77]. This VEGF-VEGFR signalling not only aids in tumor vascularization but also supports the autocrine production of immunosuppressive cytokines like TGF-β, repolarizing TAMs towards an M2-like phenotype, thereby promoting glioma angiogenesis and carcinogenesis in a positive feedback loop [72, 78].

In AD, microglia interact with various components of the degenerating brain, including Aβ plaques and NFTs. These interactions are mediated through PRRs, such as TLR and NLRP3, which initiate the inflammatory cascade by recognizing Aβ as a DAMP. This activation leads to the production of reactive oxygen species (ROS) and pro-inflammatory cytokines, but it also triggers anti-inflammatory pathways, further underscoring the complex functional states of microglia in AD [66]. Recent studies have highlighted the role of TREM2 in modulating microglial responses to Aβ. TREM2 deficiency results in a reduced microglial response to Aβ and worsened plaque pathology, suggesting that TREM2 is critical for the protective functions of microglia in AD [79]. In PD, as shown above, the aggregation of α-Syn serves as a key driver of microglial activation. α-Syn oligomers act as DAMPs, engaging TLR, NLRP3 and other PRRs, leading to the activation of pro-inflammatory signaling pathways, including NF-κB [80]. However, as with gliomas and AD, microglial responses to α-Syn are not uniformly pro-inflammatory.

Shift on metabolic pathways

Myeloid cells in gliomas, AD, and PD also share the ability to modify their metabolic pathways in response to disease-specific cues. In gliomas, TAMs often rely on oxidative phosphorylation and fatty acid oxidation to fuel their pro-tumorigenic activities. This metabolic shift supports the anti-inflammatory, tissue-remodeling functions of TAMs, which are crucial for tumor progression [72]. In contrast, TAMs that adopt a more pro- inflammatory phenotype tend to rely on glycolysis, highlighting the metabolic flexibility of these cells [81]. Similarly, in AD, microglia undergo metabolic reprogramming in response to Aβ. DAMs exhibit upregulated glycolysis and downregulated oxidative phosphorylation, which is thought to fuel their pro-inflammatory activities. This metabolic shift is linked to the increased production of

pro-inflammatory cytokines, such as IL-1β and TNF-α, which contribute to the chronic neuroinflammation observed in AD [52]. Interestingly, recent studies have also shown that metabolic reprogramming in microglia is regulated by TREM2, further underscoring the importance of this receptor in shaping microglial function in AD [82]. In PD, microglial metabolism is similarly influenced by the presence of α-Syn aggregates. Microglia exposed to α-Syn adopt a glycolytic phenotype, which is associated with the production of pro-inflammatory cytokines and ROS. This metabolic shift is thought to contribute to the chronic activation of microglia and the progressive nature of neuroinflammation in PD [80]. Moreover, the accumulation of α-Syn in mitochondria disrupts mitochondrial function in microglia, further exacerbating oxidative stress and inflammation [83].

Peripheral myeloid cell recruitment

Myeloid cell recruitment to the CNS is a hallmark of both gliomas and neurodegenerative diseases. In both groups, this recruitment is driven by local inflammatory signals and facilitated by Blood-Brain Barrier (BBB) disruption, but the functional outcomes of recruited myeloid cells vary depending on the context of the disease. Although distinct in etiology, both environments share common features that drive the recruitment and differentiation of peripheral myeloid cells.

Recruitment mechanisms and chemokine gradients

In gliomas, the recruitment of myeloid cells from the periphery is facilitated by tumor-driven chemoattractants, such as CCL2, C-X-C motif chemokine ligand 12 (CXCL12), and CSF-1 [11, 84]. These factors create a chemokine gradient that recruits circulating monocytes and promotes their differentiation into TAMs once they infiltrate the TME. In turn, TAMs play a central role in maintaining the immunosuppressive environment that allows the tumor to evade immune surveillance, releasing anti-inflammatory cytokines and inhibiting the activation of cytotoxic T cells [11, 64]. Similarly, in AD and PD, peripheral monocytes and macrophages are recruited to sites of neurodegeneration in response to inflammatory mediators. In AD, microglial activation secondary to Aβ plaques leads to the production of chemokines such as CCL5 and CXCL8 that attract peripheral myeloid cells to the CNS [54, 85]. In PD, the release of α-Syn aggregates from dying neurons triggers the release of pro- inflammatory cytokines like TNF-α and IL-1β by microglia, which recruits peripheral immune cells to the substantia nigra and other affected regions [86]. However, unlike gliomas, where the recruitment of myeloid cells supports tumor growth, in neurodegenerative diseases, the recruitment of peripheral myeloid cells has more ambiguous effects. For instance, recruited monocytes in AD and PD may either contribute to neuroinflammation and neuronal damage or promote tissue repair, depending on the context of the disease and the activation state of these cells upon entry into the CNS [57, 87].

Blood-brain barrier dysfunction

In both AD and PD, a key mechanism underlying the recruitment of peripheral immune cells is the dysfunction of the BBB. The BBB normally restricts the entry of immune cells into the CNS, maintaining the brain's immune-privileged status. However, in the context of chronic neuroinflammation, the BBB becomes permeable, allowing circulating immune cells to infiltrate the brain parenchyma [85, 88]. In AD, BBB breakdown is closely linked to the accumulation of Aβ plaques, which disrupt endothelial cell function and induce the expression of MMPs that degrade the tight junctions of the BBB [66]. This increased permeability facilitates the entry of peripheral macrophages and monocytes, which are attracted to the brain by local chemokines and play a dual role in modulating disease progression [65, 87]. In PD, similar BBB disruptions have been observed, particularly in the substantia nigra, where α-Syn aggregates contribute to vascular dysfunction [57]. The leakage of the BBB allows the infiltration of monocytes and lymphocytes into the CNS, where they encounter the aggregated α-Syn and contribute to the inflammatory response. Peripheral monocytes recruited to the CNS in PD are often found in regions of neurodegeneration, where they produce pro-inflammatory cytokines and ROS, amplifying the neuroinflammatory cascade that drives neuronal death [80]. This recruitment is also associated with a decline in BBB function in aging, making older individuals more susceptible to neuroinflammatory diseases like PD and AD [83].

In gliomas, the disruption of the BBB is not only a consequence of tumor growth but also a driving factor in the recruitment of TAMs, which further degrade the BBB through the secretion of MMPs and other proteases [89]. This creates a vicious cycle, where BBB breakdown facilitates immune cell infiltration, which in turn exacerbates inflammation and tumor progression. Neoangiogenesis is a prominent feature of tumor progression, driven in part by TAMs and MDSCs. These cells secrete pro-angiogenic factors such as VEGF, angiopoietins, and platelet-derived growth factor (PDGF), CXCL2, placental growth factor (PIGF) and hepatocyte growth factor (HGF), which promote the formation of new blood vessels to supply the growing tumor. Angiogenesis in gliomas also contributes to the immunosuppressive environment by promoting the expression of immune checkpoint molecules and facilitating the recruitment of additional suppressive cells [72, 81]. Within the myeloid cell population, resident microglia appear to have a more significant role in regulating angiogenesis compared to monocyte-derived

macrophages [81, 90]. Additionally, TAMs independently mediate tumor neoangiogenesis through Cat Eye Syndrome Critical Region Protein 1(CECR1), a proangiogenic factor that activates PDGFβ-PDGFRβ signalling in pericytes [72, 91]. Immunosuppressive microglia also enhance tumor angiogenesis by detecting CSF-1 produced by tumor cells, activating the SYP-PI3K- NF-κB pathway [72, 92]. Besides angiogenesis, TAMs influence other forms of neovascularization, such as vasculogenesis. Endothelial progenitor cells are recruited to the tumor site in response to CXCL12 released by these myeloid cells and differentiate into mature endothelial cells that form new blood vessels [72, 93]. The parallels between BBB dysfunction in neurodegenerative diseases and gliomas underscore the importance of vascular integrity in maintaining CNS immune homeostasis.

Role of peripheral myeloid cells in CNS diseases

Peripheral myeloid cells undergo significant phenotypic changes depending on the local CNS environment. MDSCs express high levels of immunosuppressive molecules that can inhibit anti-tumor immunity [94]. Representing about 5% of the total myeloid population in gliomas, they are divided into two subtypes: monocytic-MDSCs, derived from monocytes with greater tumor immunosuppression, and polymorphonuclear (PMN)-MDSCs, of granulocytic origin and more prevalent in the TME [11, 84, 94]. The expansion and recruitment of MDSCs in this immunosuppressive environment are driven primarily by cytokines released by tumors, which can be categorized into two groups: those that attract MDSCs (CCL2, CXCL8, CXCL12, CXCL2) and those that promote their amplification/growth (IL-6, PGE2, IL-10, VEGF, GM-CSF) [11, 84, 95]. Other recruited monocytes may differentiate into TAMs under the influence of tumor-derived signals such as IL-4, IL-10, and TGF-β. These signals skew the differentiation of TAMs towards an immunosuppressive phenotype that supports tumor growth, angiogenesis, and immune evasion [11, 96]. Single- cell RNA sequencing of these TAMs has revealed that blood-derived macrophages upregulate oxidative metabolism genes and express markers linked to immunosuppression and reduced survival outcomes, including CD163 and PD-L1 [97]. Monocyte-derived TAMs can adapt to different tumor zones. They show high expression of SEPP1, GPNMB and LGALS3 in phagocytic and lipid-rich regions, aligning with enhanced phagocytic functions. In hypoxic areas, these TAMs upregulate glycolytic genes, supporting adaptation to hypoxia through anaerobic metabolism [14]. This subpopulation is prominent in recurrent tumors, where radiotherapy-induced inflammation may elevate CXCL12 levels, facilitating monocyte infiltration. These genetic alterations are associated with glioma progression, as blood-derived TAMs are preferentially located in perivascular and necrotic tumor regions where they further exacerbate the immunosuppressive microenvironment [13]. However, recent studies show that myeloid cells frequently co-express genes associated with both pro-inflammatory and anti- inflammatory states, switching between pro- and anti-tumor functions in response to local cues as shown above [13, 46]. This plasticity allows TAMs to dynamically adapt to the changing conditions of the TME.

In AD and PD, peripheral monocytes recruited to the CNS also exhibit a high degree of plasticity. However, in both neurodegenerative diseases, the recruitment of peripheral immune cells seem to have both protective and detrimental effects depending on the context and stage of the disease, and not only depending on local disease-associated microenvironment [57, 83]. Thus, in AD mouse models, bone marrow-derived cells have shown higher activity in amyloid removal compared to resident microglia [85]. A clinical study also showed how MDSCs are increased in the blood of prodromal AD patients, while the pro-inflammatory gene expression of monocytes is decreased at that stage. However, in late stages, there is a raise in pro-inflammatory gene expression at the same time that MDSC populations are reduced [87]. Specifically, PMN-MDSCs are found to be increased in blood of individuals during initial stages compared to those with moderate AD. The expansion of PMN-MDSCs and regulatory T cells does not appear to correlate with IL-10 expression; interestingly, IL- 10 levels are more pronounced in healthy individuals, even though PMN-MDSCs are known to produce IL-10 to promote regulatory T cells differentiation in blood. The M-MDSC subset, however, shows no significant changes among individuals with mild or moderate AD and healthy controls. Recruited monocytes in AD can differentiate into microglia-like cells that participate in the clearance of Aβ plaques, but they can also adopt a pro-inflammatory phenotype that exacerbates neuroinflammation [69]. Similar to TAMs in gliomas, these monocyte-derived cells often co-express genes associated with both M1 and M2 polarization [54]. The observed expansion of MDSCs during the early stages of the disease may indicate an attempt by the immune system to resolve inflammation, as MDSC occurrence is a response to initial inflammatory processes. Conversely, the reduction of MDSCs in the later stages of AD suggests the emergence of a pro-inflammatory phase that overtakes with disease progression, rendering MDSCs less effective. Recently, genetic analysis have also indicated that AD monocytes in the peripheral blood have altered expression in immune-related genes, including those coding for pro-inflammatory cytokines such as IL-1β and IL-6, as well as genes related to immune checkpoint pathways like PD-L1 [98].

Furthermore, polymorphisms in genes encoding receptors such as TREM2 and CD33 are linked to increased AD susceptibility, affecting monocyte function and reinforcing an inflammatory phenotype in peripheral immune cells [87].

PD patients display elevated levels of immunosuppressive monocytic-MDSCs, while there is no notable change in other MDSC populations [99]. Additionally, monocytes in PD patients seem to be less responsive to stimulation, particularly to LPS, and fail to respond to fibrillar α-Syn. A significant dysregulation in CD163 expression, an anti-inflammatory scavenger receptor, and turnover within PD myeloid cells suggest an impact on other immune components [88]. The transcriptome profiling of CD14+myeloid cells in PD patients have also revealed significant alterations in PD monocytes related to genes associated with mitochondrial and proteasomal functions [100]. Interestingly, the mitochondrial transcriptome signature differed between microglia and monocytes, with mitochondrial gene expression downregulated in PD microglia but upregulated in PD monocytes [100]. These results indicate the peripheral immune system is affected in PD by the alteration of the peripheral blood mononuclear cells compartment. These recruited monocytes are often found in close proximity to α-Syn aggregates, where they contribute to both the clearance of these toxic protein species and the amplification of neuroinflammatory responses [71]. As in AD and gliomas, the plasticity of recruited myeloid cells in PD is shaped by local signals, including cytokines like IL-1β and TNF-α, which promote a pro-inflammatory phenotype, and anti-inflammatory signals like TGF-β, which drive a more reparative, M2-like state [62]. The expression of immune-related hub genes such as S100A12 and CXCR4 has also been identified as central to immune infiltration and inflammation within PD, further underscoring the critical role of these immune cells in PD pathology [101].

Interaction of myeloid cells with other immune CNS cells

The interaction between resident microglia and peripheral immune cells with other immune cells is core in shaping disease progression. In gliomas, TAMs interact with various immune cells, including T cells and natural killer (NK) cells, to suppress anti-tumor immunity [43]. For instance, TAMs produce high levels of TGF-β and IL-10, which inhibit the activation of cytotoxic T cells and promote the differentiation of regulatory regulatory T cells (Tregs), thereby creating an immunosuppressive microenvironment that allows the tumor to evade immune surveillance [74, 94]. In addition to their interactions with T cells, TAMs also secrete factors that inhibit NK cell activity, further weakening the immune response against the tumor [72].

In AD, recruited peripheral monocytes and T cells can interact with activated microglia, amplifying the production of pro-inflammatory cytokines such as TNF-α and IL-1β, which contribute to neuronal death and cognitive decline [54, 62]. This interaction is particularly important in the later stages of AD, where the chronic activation of both resident and recruited immune cells leads to sustained neuroinflammation and progressive neurodegeneration. T cell infiltration into the CNS, facilitated by BBB disruption, further enhances the inflammatory milieu, as activated T cells secrete IFN-γ, which enhances the pro-inflammatory activation of microglia and recruited macrophages [52, 87]. Similarly, in PD, peripheral T cells have been shown to infiltrate the CNS and interact with microglia, leading to increased production of ROS and pro- inflammatory cytokines, which contribute to the death of dopaminergic neurons in the substantia nigra [71].

While peripheral immune cells can exacerbate inflammation and contribute to neuronal loss in neurodegenerative diseases, the recruitment of peripheral immune cells in gliomas primarily serves to support tumor growth. TAMs in gliomas interact with other immune cells, including Tregs and MDSCs, to create an immunosuppressive environment that allows the tumor to evade immune surveillance [84, 94]. In particular, MDSCs play a key role in suppressing the activation of T cells and NK cells, further weakening the anti-tumor immune response [72]. Moreover, recent studies have shown that TAMs and MDSCs in gliomas can interact with tumor cells to promote angiogenesis and tumor growth through the release of pro- angiogenic factors such as VEGF and PDGF [72, 91]. This interaction between myeloid cells and other immune cells in the TME highlights the central role of myeloid cells in shaping the immune landscape of gliomas and driving tumor progression.

Neuroinflammation and immune disfunction

The neuroinflammation and immune disfunction observed in gliomas, AD and PD exhibit significant overlap, yet the nuances of these mechanisms contribute to distinct pathologic consequences. In gliomas, the TME fosters a highly immunosuppressive state driven by the infiltration of TAMs, MDSCs and other immune cells. As it was shown before, TAMs, recruited from both resident microglia and peripheral bone marrow-derived macrophages, release immunosuppressive cytokines, chemokines, and growth factors that inhibit T-cell function and promote tumor growth. The TME promotes the accumulation of MDSCs, which are potent suppressors of anti-tumor immunity, primarily through their secretion of ROS, NO and immunosuppressive cytokines such as IL-10 and TGF-β. These cells also express high levels of immune checkpoint molecules like PD-L1,

further dampening the anti-tumor immune response. This immunosuppressive environment allows gliomas to evade immune surveillance and promotes tumor progression and resistance to therapies [11, 94]. In AD and PD the immune suppression is more localized and occurs within the context of chronic neuroinflammation. In both diseases, initially the sustained activation of microglia leads to a pro-inflammatory environment characterized by the release of cytokines such as TNF-α, IL-1β, and IL-6 which contribute to neurodegeneration. However, as the diseases progress, a shift towards a more immunosuppressive microglial phenotype occurs, influenced by peripheral cells recruitment. Similar to macrophages in gliomas, these microglia adopt an anti- inflammatory profile, secreting IL-10 and TGF-β, which dampen the immune response and exacerbate the clearance of neurotoxic proteins. This transition creates a dysfunctional immune environment where inflammation persists but is insufficient to clear the pathological protein aggregates [39, 66, 102].

Shared mechanisms of immune suppression and neuroinflammation driven by myeloid cells

- **Regulators of inflammatory pathways**: A key player in this immune suppression across all three diseases is the receptor TREM2. Sun et al. have recently conducted an in- depth study on the involvement of TREM2 in glioblastoma. TREM2 was predominantly expressed in M2-like macrophages and negatively correlates with patient prognosis. Myeloid cells with a loss-of-function in TREM2 exhibited tumor-inhibitory effects in both laboratory and live animal studies. Additionally, inhibiting TREM2 was observed to shift macrophages towards a more immune-active functional state in laboratory settings [102]. Similarly, in AD, TREM2 mutations are associated with an increased risk of developing the disease, and its expression on microglia is critical for the activation of DAMs. These DAMs play a dual role in AD, where they help to contain the spread of Aβ plaques and tau tangles but also contribute to neuroinflammation and neuronal damage. In PD, TREM2 also modulates microglial responses to α-synuclein aggregates, and its deficiency has been shown to exacerbate neurodegeneration in preclinical models [69, 83]. This suggests that TREM2 plays a conserved role across CNS pathologies in regulating myeloid cell responses and highlights it as a potential therapeutic target in these diseases. Other inflammatory regulators, such as NF-κB and miRNAs, have proven crucial in neuroinflammation driven by myeloid cells [103].
- **Oxidative Stress**: The role of oxidative stress is another shared feature of immune suppression and neuroinflammation in gliomas, AD and PD. In gliomas, the rapid growth of the tumor creates hypoxic conditions that drive oxidative stress. This, in turn, promotes the recruitment and activation of MDSCs, which contribute to the immunosuppressive TME by releasing ROS and NO. These reactive molecules not only suppress T-cell function but also promote tumor growth by enhancing angiogenesis and matrix remodelling [104]. Similarly, in AD and PD, oxidative stress plays a pivotal role in the activation of microglia. The accumulation of Aβ in AD and α-Syn in PD triggers the activation of PRRs. Activation of these receptors leads to the release of ROS and pro-inflammatory cytokines, perpetuating the cycle of neuroinflammation and neuronal damage [57, 66, 105].
- **Crosstalk between Resident and Peripheral myeloid cells**: In both gliomas and neurodegenerative diseases, the recruitment of myeloid cells from the periphery plays a significant role in immune suppression and disease progression. Across PD, AD, and gliomas, there is a consistent trend in the upregulation of immunosuppressive mechanisms via MDSC expansion and increased expression of anti-inflammatory cytokines, although the functional outcomes differ by disease. Commonly dysregulated genes, such as CXCR4, S100A12, and CD163, underscore the role of immune-related pathways that are shared but are contextually adapted to disease-specific needs, such as neuroprotection in early PD and AD, versus tumor promotion in gliomas [101, 103]. The disruption of the blood-brain barrier (BBB) facilitates the infiltration of peripheral monocytes, as shown above [11, 46, 85, 87]. Blood-derived TAMs upregulate immunosuppressive cytokines and TAMs adopt predominantly an immunosuppressive phenotype, characterized by the secretion of anti-inflammatory cytokines and the expression nof immune checkpoint molecules such as PD-L1 [13, 94]. This phenotype not only suppresses anti-tumor immunity but also promotes tumor growth and resistance to therapies.

Microglia-derived TAMs are predominantly enriched in newly diagnosed tumors, displaying high expression of microglial markers and retain a transcriptional profile closer to homeostatic microglia, characterized by high levels of CX3CR1 and TREM2. In hypoxic regions of the tumor, microglial TAMs show a shift toward a DAM phenotype, marked by downregulation of homeostatic markers and upregulation of APOE, CST7, and SPP1, aligning with a phagocytic and lipid-metabolic signature [14].

In AD and PD, bone marrow-derived macrophages do infiltrate the brain in response to a previous chronic neuroinflammation, influencing distinct states of microglial activation. Peripheral cells in AD seem to contribute initially to the clearance of Aβ plaques but, like microglia, can also adopt an immunosuppressive phenotype in the later stages of disease, secreting IL-10 and TGF-β and contributing to the dysfunctional immune environment [85, 87, 88]. The initial expansion of MDSCs seen in AD is thought to be an attempt to resolve inflammation. Conversely, the reduction of MDSCs in the later stages of AD suggests the emergence of a pro-inflammatory phase that overtakes with disease progression, rendering MDSCs less effective. In these stages, DAM shows a pro-inflammatory M1-like phenotype [62]. Finally, the interaction between peripheral and resident immune cells in PD appears to involve a feedback loop, where the release of α-Syn aggregates from dying neurons not only triggers microglial activation but also stimulates the recruitment of peripheral immune cells, which further amplify the inflammatory response. This creates a vicious cycle of inflammation and neuronal damage that drives disease progression [86].

Single-cell profiling of myeloid cells: new population and markers

New high-resolution technologies such as single-cell RNA sequencing (scRNA-Seq) and spatial transcriptomics have made it possible to reveal the complexity of macrophage responses in cancer and other pathologies, going beyond the linear M1/M2 activation paradigm [13, 106]. These technologies are therefore being employed in the search for precise markers to distinguish between subpopulations and states of myeloid cells involved in the development of pathologies. Therefore, it is believed that the general treatment of tumor-associated macrophages is not a good strategy since it has not given good results at the clinical level [107, 108]. Furthermore, it seems reasonable that the precise definition of myeloid populations that cooperate with the progression of different pathologies may benefit both traditional treatments and immunotherapies.

In glioblastoma, scRNA-seq analysis performed on samples from patients with newly diagnosed and recurrent disease has identified myeloid cell subpopulations that are differentially expressed in recurrent versus newly diagnosed tumors, allowing the identification of different activation states of TAMs in tumor development. Globally, TAMs were classified into monocyte-derived macrophages (Blood-derived TAMs) and macrophages with microglial ontogeny (Mg-TAMs). Within the Blood-derived TAMs group, 6 cell subpopulations were identified. In both newly diagnosed and recurrent tumors, transitory Blood-derived TAMs (EREG, S100A6, LYZ, C1QA, IGF1), phagocytic Blood-derived TAMs (GPNMB, LGALS3, FABP5), hypoxic Blood-derived TAMs (BNIP3, ADM8, MIF and SLC2A1) and a subset of macrophages expressing interferon-induced signature were identified. In recurrent tumors, two subsets were identified according to SEPP1 levels, with $SPP1^{low}$ Blood-derived TAMs presenting microglia-like phenotype and $SPP1^{high}$ Blood-derived TAMs expressing genes associated with anti-inflammatory activation (SLC40A1, FOLR2, MRC1, RNASE1). Notably, the $SPP1^{high}$ signature was enhanced only in recurrent tumors. Differential expression analysis of Mg-TAMs, SEPP1 + Blood-derived TAMs and hypoxic Blood-derived TAMs subsets between newly diagnosed and recurrent tumors indicated that biological processes related to monocyte chemotaxis, interferon signaling, and phagocytosis are enriched in TAMs from recurrent tumors, revealing different functional states of myeloid cells during tumor progression. This study also reported an ontogeny shift in TAMs, whereas Mg-TAMs formed the largest fraction of TAMs in newly diagnosed tumors, Blood-derived TAMs were the majority myeloid population in recurrent tumors [14]. These scRNA-seq results contribute to the search for new therapeutic targets, as targeting specific subsets of TAMs may have significant therapeutic potential. In accordance with this, it has been shown that blood-derived TAMs are key in the development of glioblastoma and are associated with therapy resistance [13]. They also show an altered immunosuppressive profile and metabolism which is commonly associated with CD8 and CD4 cell dysfunction.

In Alzheimer's disease, scRNA-seq studies have focused on the characterization of the heterogeneity of microglia. In the study by Olah et al. [109], performed on patient samples, they identified 14 cell clusters, among which 9 expressed markers enriched in microglia (C1QA, C1QB, C1QC, GPR34). Thanks to this research, six functionally distinct microglial cell populations were identified: two in a homeostatic state, one enriched in genes related to antigenic presentation, two closely linked to the anti-inflammatory response, one enriched in genes of the interferon response signaling pathway, and a last one in a proliferative state, characterized by a high expression of genes associated with the cell cycle. This classification provides a more detailed view of the functional diversity of microglia under pathological conditions. Furthermore, using curated lists of genes that are up- or down-regulated in neurodegenerative diseases, they observed that microglial populations primarily responsible for antigenic presentation and anti-inflammatory response were enriched in Alzheimer's disease [109]. This and other studies [110, 111] involving scRNA-seq analysis of distinct microglial populations provides an important step toward the overall goal of characterizing

microglial diversity and function in human brain diseases, which will drive the development of targeted microglial therapies.

scRNA-seq studies have revealed distinct myeloid populations in the brain that display suppressive characteristics under pathological conditions. These populations are characterized by diminished antigen presentation capabilities and enhanced anti-inflammatory signaling, which may contribute to the progression of neuropathologies. To corroborate the relevance of these scRNA-seq-identified myeloid populations, we conducted a comprehensive analysis using both public databases and our own cohorts. Our study encompassed samples from individuals without brain pathology, serving as controls, as well as specimens from patients diagnosed with GBM and AD. Immunohistochemical analysis revealed a significant increase in the number of cells that were positive for the myeloid marker CD68 and positive for the immunosuppressive marker CD163 in glioblastoma compared to healthy brain tissue (Fig. 2A). To investigate this immunosuppression under pathological conditions, we used a panel of myeloid cell-specific markers (CD163, MS4A4A, TREM2, CSF1R, PILRA, CLEC5A) according to scRNA-seq data [112] (Fig. 2B). Among these markers are genes widely studied as therapeutic targets in GBM and AD, for example, CSF1R or TREM2. In our analysis, we also included novel markers with significant therapeutic potential, notably MS4A4A. This molecule is selectively expressed in macrophages during differentiation and polarization towards a dysfunctional myeloid phenotype in glioblastoma [113]. In Alzheimer's disease, MS4A4A has been shown to colocalize with TREM2 in human macrophages and overexpression of MS4A4A increases soluble TREM2 production [114]. Also noteworthy is CLEC5A, which has been associated with poor prognosis in glioblastoma patients through myeloid cell-mediated immunosuppressive mechanisms and may be involved in infiltrating tumor-promoting leukocytes [115]. Furthermore, in Alzheimer's disease, CLEC5A blockade has been shown to be able to enhance Aβ clearance by increasing the phagocytic capacity of microglia in a mouse model of AD [116]. Our analyses showed a significant increase in gene expression of these myeloid markers of suppressor phenotype in glioblastoma patients by both RNA-seq (Fig. 2C, D) and RT-qPCR (Fig. 2E, F) using the GTEX-TCGA database and our own glioblastoma cohort, respectively. Similar to glioblastoma, we observed an increased number of myeloid cells, especially CD163+myeloid cells (Fig. 3A) and increased myeloid suppressor gene expression in patients with AD compared to patients without brain pathology when we analyzed the cohort from the Berchtold et al. study [117, 118] (Fig. 3B, C) and our own cohort of AD patients (Fig. 3D, E). Taken together, these findings highlight novel markers such as MS4A4A and CLEC5A as a promising therapeutic targets, potentially providing a novel approach to modulate myeloid function in both glioblastoma and Alzheimer's disease.

Targeting myeloid cells in cns diseases

The role of myeloid cells in gliomas, AD, and PD are shaped by disease-specific cues, but all three diseases share common mechanisms of immune modulation and inflammation, as it was shown above. TAMs are thought to contribute to glioma progression by promoting angiogenesis, immune suppression, and matrix remodelling, and myeloid cell response to Aβ or α-synuclein aggregates initially seem to serve a protective role but ultimately contributes to chronic neuroinflammation and neurodegeneration. Thus, given their fundamental role in pathophysiological mechanisms, myeloid cells have emerged as a promising target for innovative therapies in gliomas and neurodegenerative diseases (Supplementary Table).

Targeting myeloid cells in glioma

In glioma, current clinical trials are exploring the efficacy and effectiveness of various immunotherapeutic agents targeting the functions of myeloid cells, either directly or indirectly (Fig. 4). The principal areas of investigation include efforts to reduce myeloid cell recruitment to the TME and promote reprogramming or repolarization TAMs from an immunosuppressive to a pro-inflammatory state hold promise for enhancing anti-tumor immunity effects [108, 119–127]. Therapies focusing on enhancing myeloid phagocytic activity have also gained interest, although novel approaches targeting the myeloid population may generally affect multiple cellular functions [72, 128, 129]. The most relevant clinical trials in glioma targeting myeloid cells and their functions are shown in the Supplementary Table (Fig. 4).

Many other strategies aimed at targeting myeloid cells in glioma are currently under investigation. Innovative immune approaches, such as oncolytic viruses and chimeric antigen receptor (CAR) macrophages, are promising but still requires optimization in terms of efficiency, quality, and safety. In this context, macrophage engineering involves genetically and functionally modifying macrophages to enhance their tumor-combating capabilities. Engineered monocytes carrying NANO-DOX (nanodiamonds and doxorubicin) induced ICD and transformed M2 macrophages into M1 in vivo [130]. Further, engineered bone marrow- derived macrophages containing a photothermal nanoprobe improved photothermal therapy and inhibited glioblastoma recurrence after surgery [131]. Modified microglia transfected with rAAV2- IL-15 suppressed tumor growth by recruiting NK cells and activating resident microglia near gliomas [132]. Despite

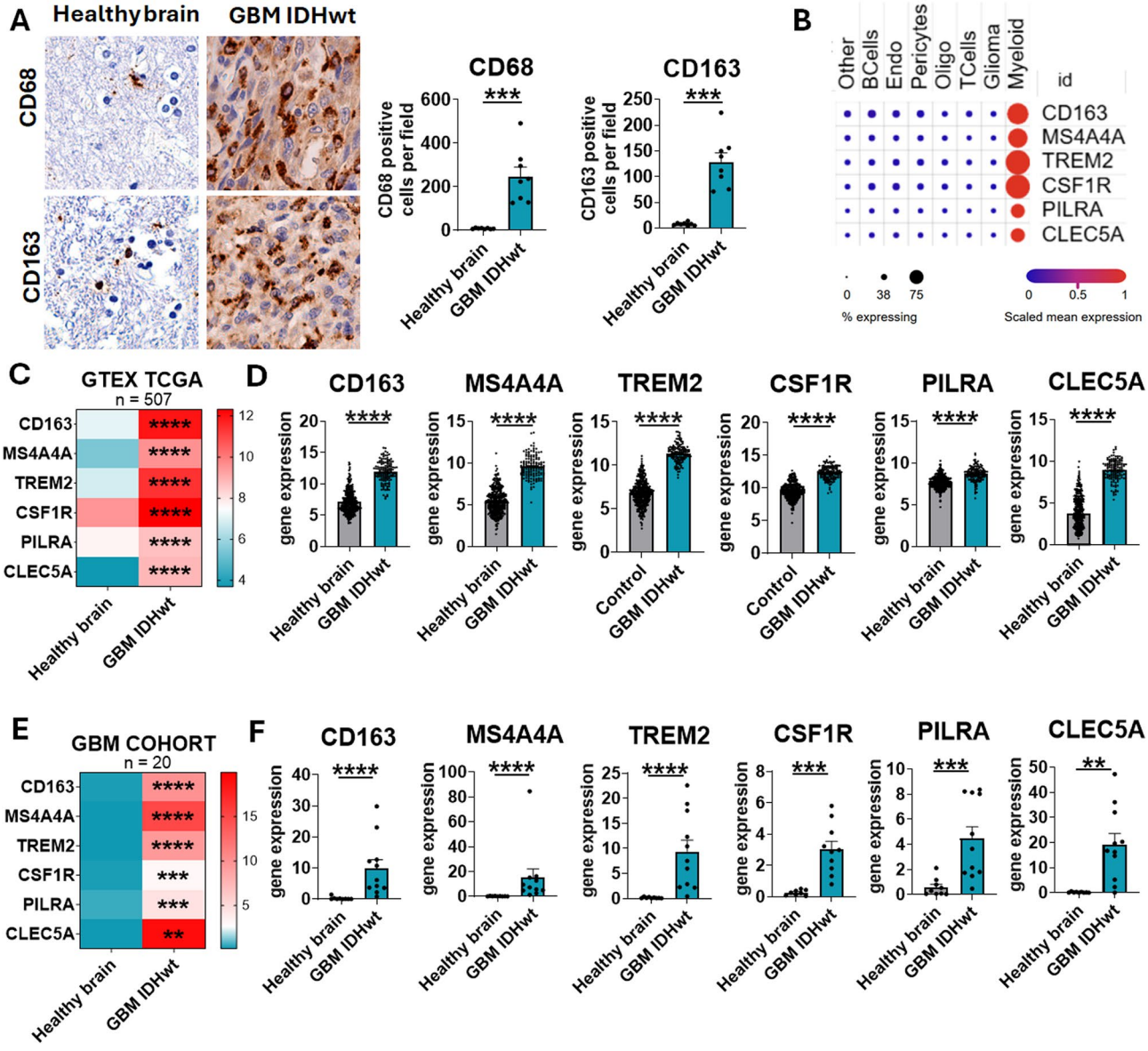

Fig. 2 Myeloid cells with immunosuppressive phenotype increase in GBM. **(A)** Representative images (left) and quantification (right) of CD68 and CD163 immunohistochemical staining in our own glioblastoma cohort ($n=8$), using healthy brain as control ($n=8$). Statistical significance was determined by unpaired Student's t-test with Welch's correction. **(B)** Dot plot of immunosuppression-associated gene expression in each cell cluster of the study of Abdelfattah et al. (GSE182109) available in Single Cell Portal. Gene expression average is color-coded, and the proportion of cells expressing the selected genes is symbolized by circle size. **(C)** Heatmap representing color-coded expression levels of immunosuppression-associated genes using RNA-seq values from GTEX-TCGA cohort ($n=507$). **(D)** Bar graphs of individual gene expression comparing healthy brain tissue versus tissue from patients diagnosed with glioblastoma in the GTEX- TCGA cohort. Significance was determined by unpaired Student's t-test with Welch's correction or Mann-Whitney test in accordance with the normality of data. **(E)** Heatmap representing color-coded expression levels immunosuppression-associated genes using our own glioblastoma cohort ($n=20$). The expression was determined by qRT-PCR analysis and HPRT was used for normalization. **(F)** Bar graphs of individual gene expression comparing healthy brain tissue versus tissue from patients diagnosed with glioblastoma in our own cohort ($n=20$). Significance was determined by unpaired Student's t-test with Welch's correction or Mann-Whitney test in accordance with the normality of data. *$p<0.05$; ** $p<0.01$,: *** $p<0.001$: **** $p<0.0001$; n.s., not significant

high therapeutic potential, macrophage engineering faces challenges like low drug loading efficiency and unstable release [129].

Ultrasound-assisted brain delivery and nanoparticles offer an interesting solution to the BBB limitation, carrying and releasing encapsulated drugs within the brain [133, 134]. Gene editing technologies and gene therapy have already become crucial in glioma immunotherapy research, the development of tumor models, and the identification of specific drugs targeting gliomas. The potential of some of these strategies lies in their ability to reprogram the TME and enhance the immune system's

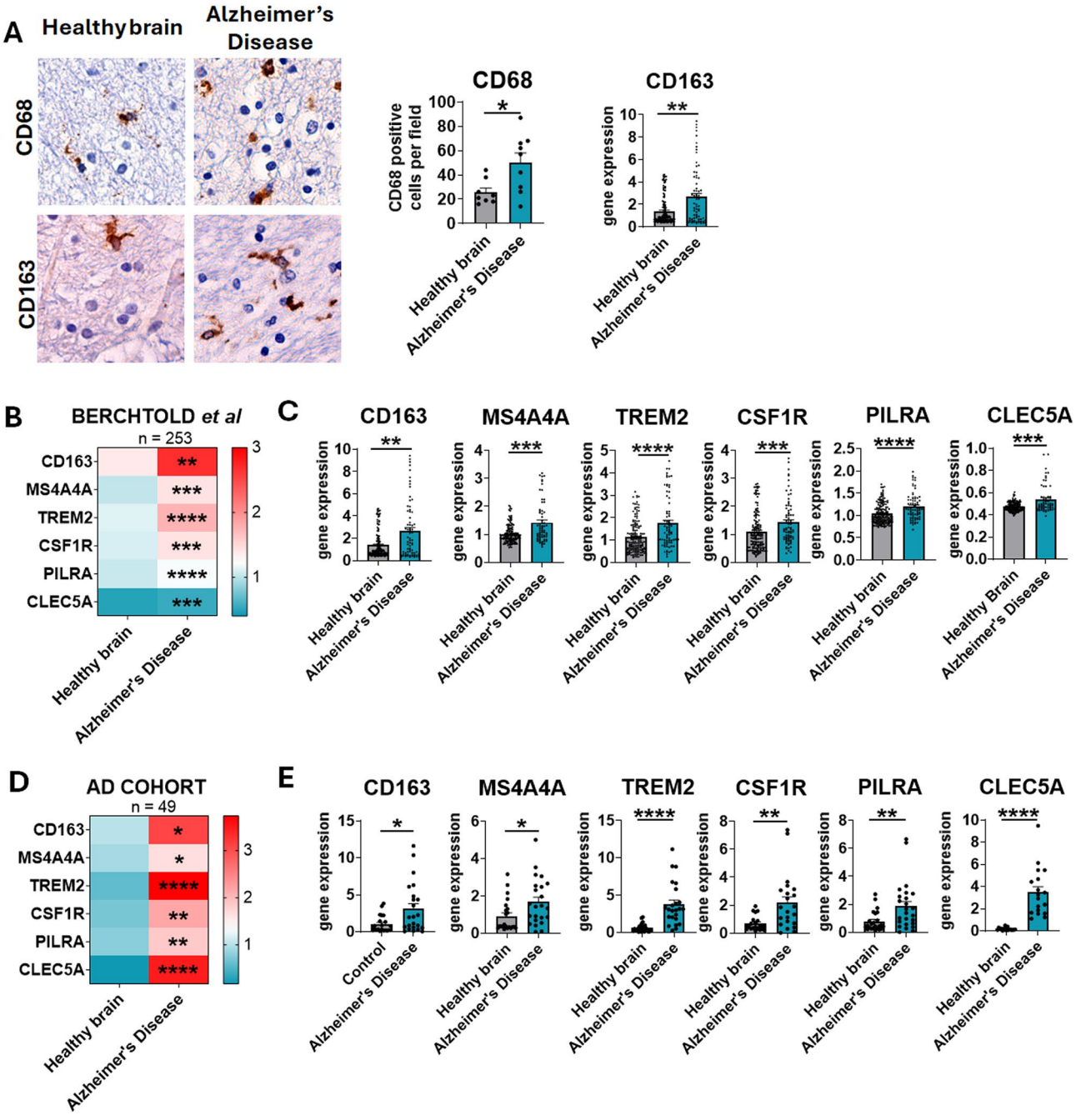

Fig. 3 Myeloid cells with immunosuppressive phenotype increase in AD. **(A)** Representative images (left) and quantification (right) of CD68 and CD163 immunohistochemical staining in our own Alzheimer's Disease cohort ($n = 9$), using healthy brain as control ($n = 9$). Statistical significance was determined by unpaired Student's t-test with Welch's correction. **(B)** Heatmap representing color-coded expression levels of immunosuppression-associated genes using microarray values from Berchtold et al. study ($n = 253$) (GSE48350). **(C)** Bar graphs of individual gene expression comparing healthy brain tissue versus tissue from patients diagnosed with Alzheimer's Disease from Berchtold et al. study. Statistical significance was determined by the Mann-Whitney test. **(D)** Heatmap representing color-coded expression levels immunosuppression-associated genes using our own Alzheimer's Disease cohort ($n = 49$). The expression was determined by qRT-PCR analysis and HPRT was used for normalization. **(E)** Bar graphs of individual gene expression comparing healthy brain tissue versus tissue from patients diagnosed with Alzheimer's Disease in our own cohort ($n = 49$). Significance was determined by unpaired Student's t-test with Welch's correction or Mann-Whitney test in accordance with the normality of data. *$p < 0.05$; ** $p < 0.01$,: *** $p < 0.001$: **** $p < 0.0001$; n.s., not significant

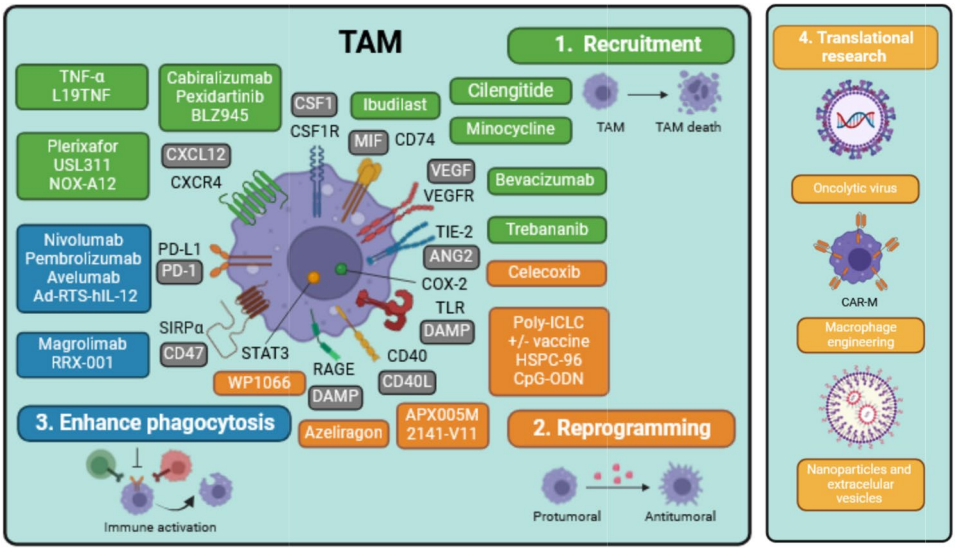

Fig. 4 Therapeutic Strategies Targeting Myeloid Cells in Glioblastoma. Various therapeutic strategies involving myeloid cells have been explored in Glioblastoma. Some of these approaches have focused on targeting mechanisms responsible for macrophage recruitment to the tumor microenvironment, but with little/no effect in clinical trials. There are promising efforts aimed at reprogramming macrophage phenotypes towards a pro-inflammatory/anti-tumoral phenotype. Immunotherapy in glioblastoma enhance macrophagic phagocytic activity as part of the anti-tumoral response. Furthermore, several promising therapeutic strategies involving myeloid cells are currently in the pre-clinical research phase. TAMs: Tumor-associated macrophages. CAR-M: Chimeric Antigen Receptor Macrophages

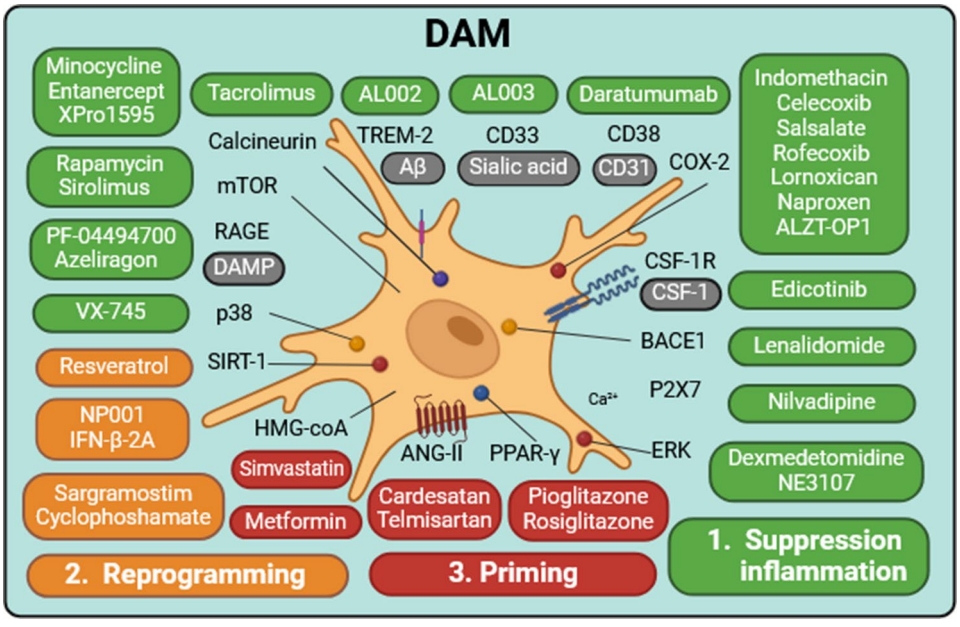

Fig. 5 Therapeutic strategies targeting myeloid cells in Alzheimer's disease (DAM). The involvement of myeloid cells in the processes led to the development of several therapeutic strategies involving myeloid cells in glioblastoma. Many of these approaches have focused on reducing or eliminating inflammatory processes or immune cell function. There are also promising strategies aimed at generating improved M1/M2 balance. Even pre-clinical data on immunotherapy against PD-1/PD-L1 pathway could have an effect in reducing cognitive impairment. DAM: disease-associated microglia. Aβ: amyloid beta

response to glioma. However, these novel therapies face important challenges in clinical application, including complex design, nonspecific toxicity, and potential long-term resistance [131].

Targeting myeloid cells in AD

The recent positive results of anti-amyloid therapies in AD have encouraged the research of targeted therapies in AD. Several clinical trials have tried to target myeloid cell function in AD (Fig. 5) (Supplementary Table). The

majority of them seek to suppress the pro-inflammatory characteristics of microglia to limit the effect of the neurotoxic microenvironment [17, 67, 135–144]. Others try to model the phenotypic plasticity of microglia to favor the anti-inflammatory response and microglial preparation in the early stages of the disease, targeting key molecules in the polarization pathway [52, 54, 145–147]. However, these approaches have failed to date.

Other promising therapeutic strategies in AD targeting myeloid cells are being explored. CAR-Tregs specific to Aβ are undergoing pre-clinical trials in AD. These have demonstrated stability and functionality in vitro [148, 149]. Interestingly, CAR- macrophages (CAR-M), engineered to secrete Macrophage-CSF and sustain themselves without external cytokines, exhibit enhanced survival in brain environments. These CAR-Ms significantly diminish plaque burden Aβ locally in vivo [150]. This successful example of CAR therapy in AD reinforces the potential of this treatment, previously exclusive to cancer treatment. Macrophage membrane engineering is also under investigation in AD, and a novel nanoantidote, Oxytocin-Lipo@M, based on macrophage membrane engineering, has been successfully developed, showing beneficial outcomes in AD mice [151]. Additionally, transcranial focused ultrasound has been validated as a method to acutely activate microglia and reduce Aβ load in mouse models [152, 153]. Ultrasounds are also being investigated as novel delivery methods in AD, like nanoparticles.

Targeting myeloid cells in PD

Following the trail of AD research several anti-inflammatory drugs have been explored in PD [60, 154]. While some of these immunomodulating mechanisms have exhibited promising preliminary results in animal models, clinical studies have yet to demonstrate robust positive results to date in PD patients. These results suggest that a broad, non-specific approach to inhibiting inflammation may not offer significant benefits for treating the disease. Instead, focusing on modulating microglial activation for neuroprotection may hold greater promise compared to completely blocking microglial activation with anti-inflammatory drugs [60, 154, 155]. Other drugs aiming to reduce the pro- inflammatory activation in microglia, such as cannabinoids and flavonoids have also been tested pre-clinically (Fig. 6) (Supplementary Table) [60 60]. However, to date there are no successful disease modifying therapies in PD.

Among the few strategies targeting myeloid cells that are currently under clinical research in PD, the most promising ones are focussed on facilitating α-Syn clearance. This could be accomplished by immunotherapies that might be used to clear extracellular α-Syn [156]. Active and passive immunotherapies have been explored to target and degrade extracellular α-Syn. These approaches have demonstrated efficacy in reducing α-Syn aggregation and averting behavioral deficits in transgenic mouse models [157]. Some of these treatments have progressed to clinical trials, where they have shown promising safety profiles and preliminary results [158]. Two vaccines have successfully completed their phase I clinical trial [159, 160].

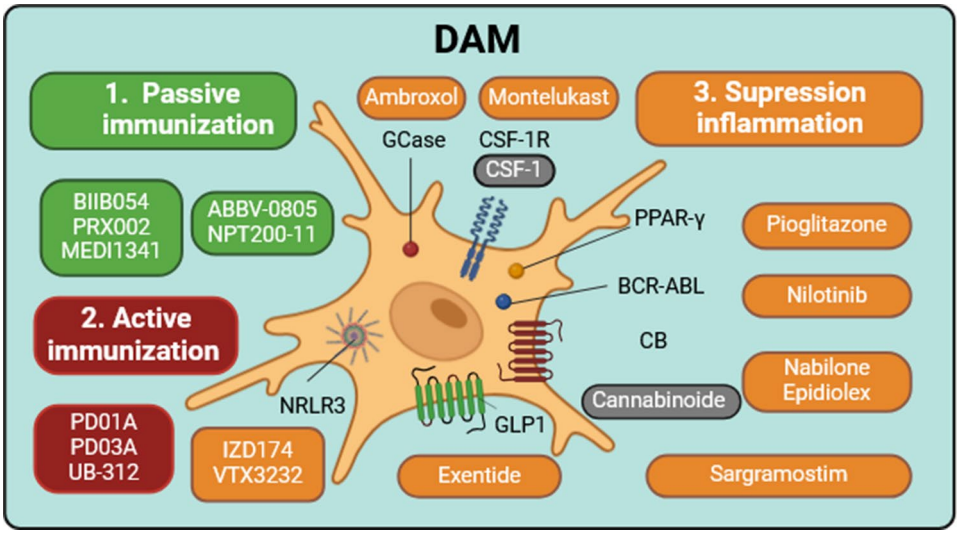

Fig. 6 Therapeutic strategies targeting myeloid cells in Parkinson's disease (DAM). Like what occurs in AD, multiple strategies have been evaluated to inhibit or reduce the inflammatory process by generic inhibitors poorly linked to the myeloid effect. Others are more specific in attempting to regulate the inflammatory process. It should be noted that more pre-clinical research is needed to encourage the incorporation of new myeloid targets that may have a strong clinical impact. DAM: disease-associated microglia

UB-312 is another α-Syn vaccine currently in a phase II clinical trial (NCT05634876) [161]. Additionally, anti-α-Syn antibodies have been tried in clinical trials, most of them failing in early phases. However, there is currently recruiting a phase IIb clinical trial to evaluate the efficacy of the anti-α-Syn antibody PRX002 (NCT04777331) [18, 162].

Discussion

Glioblastoma IDH wild-type and neurodegenerative diseases such as AD and PD are significant neurological age-related diseases, notably challenging due to their social impact, high healthcare-related costs, limited therapeutic approaches and unfavorable outcomes. Some studies have suggested an inverse relationship between glioblastoma and neurodegenerative diseases, showing opposite results [163]. Although these diseases differ clinically, they share common features, particularly in the alterations of the vasculature and myeloid cells that drives to neuroinflammation in their pathogenesis (Fig. 7).

Thus, a relevant aspect to study in both brain diseases is the deregulated, incomplete or frustrated resolution of ongoing inflammatory processes. In this context, a promising therapeutic approach to address these pathologies would involve a therapy based on pro- resolution of inflammation. Modulating the myeloid response may help in this sense. For instance, reprogramming TAMs in gliomas to transition toward a more pro- inflammatory, anti-tumor phenotype, while in AD and PD, inhibiting neuroinflammation to prevent further degeneration. The development of therapies aimed at correcting and rectifying these deficiencies will assist in directing developing inflammation toward a trajectory of termination and resolution. However, clinical trials have failed to date [11, 17, 18]. Common molecular pathways among gliomas, AD, and PD also highlight potential shared therapeutic targets. Key pathways, such as TREM2, oxidative stress, NF-κB and miRNA signaling drive myeloid activation in all three diseases, suggesting they may be modulated to attenuate chronic inflammation [103]. Targeting these pathways, among others, could modulate myeloid cell activity across different CNS diseases, presenting an opportunity for broad-spectrum interventions with targeted effects.

Addressing this objective pharmacologically poses a significant challenge due to the high heterogeneity in the mechanisms for the resolution of inflammation, which appear to be specific to each tissue and stimulus. Distinct

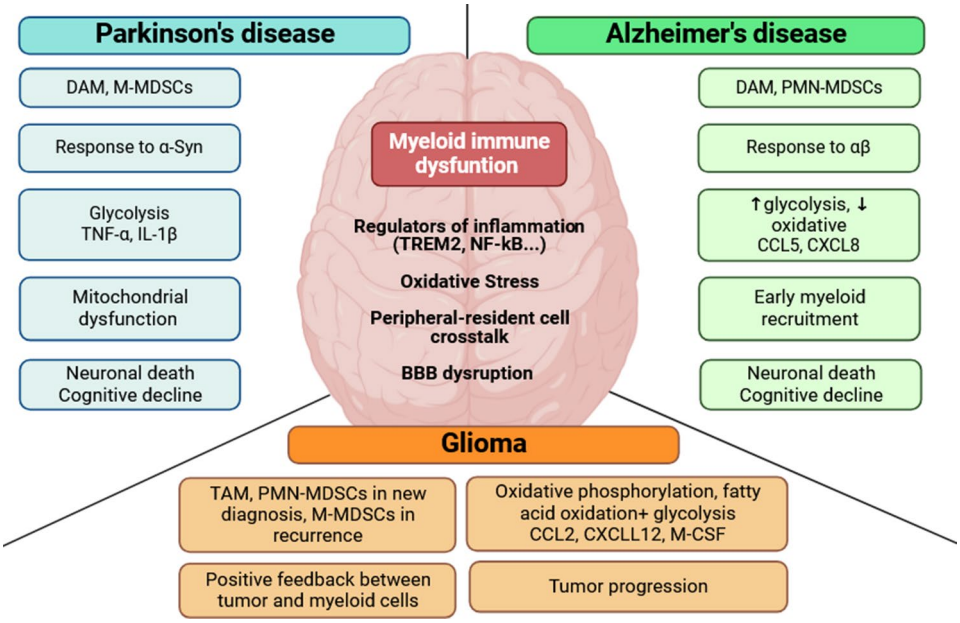

Fig. 7 Shared and distinct roles of myeloid immune dysfunction and neuroinflammation in Parkinson's disease, Alzheimer's disease, and gliomas. At the centre, the key mediators—regulators of neuroinflammation, oxidative stress, crosstalk among peripheral and resident myeloid cells, BBB disruption—drive myeloid immune dysregulation across these conditions, leading to chronic neuroinflammation. In Parkinson's disease, reactive microglia and mitochondrial dysfunction, alongside M-MDSCs in early stages and mediators such as TNF-α and IL-1β, contribute to blood-brain barrier (BBB) disruption, neuronal death, and cognitive decline. Alzheimer's disease features similar immune dysregulation with increased glycolysis and decreased oxidative metabolism in myeloid cells, recruitment of peripheral immune cells (especially PMN-MDSCs in early stages) via chemokines (CCL5, CXCL8), and early T cell inhibition, ultimately leading to neurodegeneration. In gliomas, TAMs and MDSCs promote tumor growth through oxidative phosphorylation and fatty acid oxidation, aided by a feedback loop of tumor-promoting cytokines (CCL2, CXCL12) that reinforce immune suppression and enable tumor metastasis. This visual highlight the interplay between metabolic reprogramming, immune evasion, and neuroinflammatory pathways shared among neurodegenerative diseases and brain tumors, underscoring potential therapeutic targets within these common pathways. BBB: Blood-brain barrier. MDSCs: Myeloid-Derived Suppressor Cells. DAM: Disease-associated microglia. TAMs: Tumor-associated macrophages. Aβ: amyloid beta. α-Syn: α-synuclein

myeloid populations are evident in each pathology: in gliomas, MDSCs and TAMs dominate with immunosuppressive, pro-tumoral effects; in AD, DAMs express inflammatory genes like ApoE and TYROBP, promoting chronic inflammation; in PD, microglial engagement with α-Syn perpetuates inflammation and cell death through intercellular transfer of pathogenic aggregates [44, 45, 62, 71]. Understanding these mechanisms may inform therapies that selectively enhance myeloid cell clearance functions in neurodegeneration while promoting anti-tumoral responses in gliomas.

However, the complexity of myeloid cell activation in the CNS suggests that targeting specific subsets of myeloid cells that show distinct phenotypes and distinct localizations in diverse stages of the CNS diseases, may be a more effective therapeutic strategy than attempting to modulate the entire population. Thus, promising therapies targeting myeloid cells in glioma focus primarily on blocking immune checkpoints and enhancing phagocytic reprogramming, while AD and PD strategies tend to combine immunomodulation with aggregation clearance mechanisms [11, 49]. However, if we can restore part of the immune system linked to the influx of blood-derived myeloid cells, we may have a common strategy for a wide range of central nervous system pathologies. To achieve this more studies are needed to shed light and show specific myeloid populations as described by Muller et al. 2017, for glioma pathology [13, 164]. This type of abortion can also be extended to degenerative diseases where markers of immunosuppression such as CLEC5A can aid in the clearance of the Aβ peptide in the case of Alzheimer's disease [116].

Other significant aspect of advancing therapeutic effectiveness is the early identification of stage- specific biomarkers to guide interventions. As shown in neurodegenerative disease models, detecting disease early in the degenerative process—when plaques or aggregates are still forming and neuroinflammation is not yet widespread—offers a critical window for intervention. Biomarkers that indicate not only the presence of disease, but also specific stages of disease progression could revolutionize the success of therapeutic strategies, particularly in AD and PD, where inflammation often precedes significant neurodegeneration [51, 52]. Early-stage biomarkers can improve therapeutic timing, maximizing efficacy by intervening before neuroinflammatory cycles become chronic and self-sustaining. For example, the presence of amyloid plaques in AD or misfolded α-Syn in PD correlates with increased microglial activation, suggesting these markers could help define the best timeframe for anti-inflammatory therapies.

The importance of disease and stage-specific markers also highlights why therapeutic resistance remains a recurrent challenge, particularly in broad-spectrum interventions. Widespread use of these therapies, while promising, can inadvertently lead to acquired resistance in myeloid populations. For example, glioblastoma cells often adapt to immune-based therapies by altering their own cytokine and chemokine profiles, recruiting immunosuppressive cell populations like MDSCs and TAMs, which then adapt to sustain tumor growth despite treatment efforts [72]. Similarly, in AD and PD, neuroinflammatory responses driven by DAMs and microglia can become resistant to immune-modulatory therapies, either by downregulating critical receptors or altering signaling pathways that modulate inflammation. The selective targeting of specific immune cell subtypes may mitigate these resistance mechanisms, ensuring that therapeutic effects are sustained over time.

In summary, understanding the interplay between neuroinflammation, myeloid cell function, and CNS pathology offers promising avenues for therapeutic innovation (Fig. 7). By targeting the dynamic roles of myeloid cells, strategies can be developed to address the shared immune dysfunction that characterizes gliomas, AD, and PD. Emerging insights into myeloid cell heterogeneity underscore the need for disease-specific therapeutic approaches that leverage these shared immune mechanisms to enhance treatment efficacy across multiple CNS disorders. Advances in scRNA-seq and imaging technologies continue to provide new insights into these cellular interactions, allowing for the identification of novel biomarkers that could ultimately guide early- stage interventions [103, 163].

Supplementary Information

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Supplementary Material 1

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Author contributions

Designing research studies: BCM, GVA, BSC and RG; Acquiring information: BCM, LRM and GVA,; Writing-Original Draft: BCM, GVA; LRM and RG; Writing-Review & Editing: BCM, GVA, BSC, JMSS and RG; Funding Acquisition: BSC, JMSS and RG; Supervision: JMSS and RG.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Human tissues were obtained from surgical specimens obtained from patients undergoing treatment at the "Hospital 12 de Octubre" in Madrid, Spain (CEIm: 21/551 and 24/084).

Competing interests
The authors declare no competing interests.

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