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THEMED ISSUE REVIEW

Myeloid cells in vascular dementia and Alzheimer's disease: Possible therapeutic targets?

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Growing evidence supports the suggestion that the peripheral immune system plays a role in different pathologies associated with cognitive impairment, such as vascular dementia (VD) or Alzheimer's disease (AD). The aim of this review is to summarize, within the peripheral immune system, the implications of different types of myeloid cells in AD and VD, with a special focus on post-stroke cognitive impairment and dementia (PSCID). We will review the contributions of the myeloid lineage, from peripheral cells (neutrophils, platelets, monocytes and monocyte-derived macrophages) to central nervous system (CNS)-associated cells (perivascular macrophages and microglia). Finally, we will evaluate different potential strategies for pharmacological modulation of pathological processes mediated by myeloid cell subsets, with an emphasis on neutrophils, their interaction with platelets and the process of immunothrombosis that triggers neutrophil-dependent capillary stall and hypoperfusion, as possible effector mechanisms that may pave the way to novel therapeutic avenues to stop dementia, the epidemic of our time.

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; BAMs, border-associated macrophages; BM, bone marrow; CBF, cerebral blood flow; HMGB1, high mobility family protein box 1; MDMs, monocyte derive macrophages; MGnD, microglia neurodegenerative phenotype; NET, neutrophil extracellular trap; NFT, neurofibrillary tangles; NLR, neutrophil/lymphocyte ratio; PSCID, post-stroke cognitive impairment and dementia; PVMs, perivascular macrophages; scRNA-seq, single-cell RNA sequencing; snRNA-seq, single-nucleus RNA sequencing; TREM2, triggering receptor of myeloid cells 2; TRM, transiting response microglia; VCID, vascular cognitive impairment and vascular dementia; VD, vascular dementia; WAM, white matter-associated microglia.

Alicia García-Culebras and María Isabel Cuartero have contributed equally to this work and share first authorship.

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Alzheimer's disease, myeloid cells, NETs, neutrophils, PSCID

1 | INTRODUCTION

As human life expectancy increases, the impact of dementia on society has taken on dramatic importance (Kirkwood, 2008). At present, dementia affects approximately 55 million people worldwide, a figure increasing due to the lack of preventive and curative treatments and to its silent progression (Shin, 2022). In particular, there is a heterogeneous group of brain disorders where cognitive impairment is attributed to pathologies of vascular origin. These disorders, grouped under the term *vascular cognitive impairment* and *vascular dementia* (VCID), are crowned as the second most important cause of dementia after Alzheimer's disease (AD).

At the pathological level, AD is well defined by the presence of amyloid plaques formed by **amyloid-β** (Aβ) peptide, neurofibrillary tangles (NFT) formed by aggregates of hyperphosphorylated **tau**-protein and brain atrophy caused by loss of neurons and synapses in specific brain regions (Figure 1) (Bloom, 2014). In addition, proliferation and activation of glial cells, termed 'gliosis', is a well-established hallmark of this disease (Prinz et al., 2011). Of note, AD and vascular dementia (VD) frequently coexist, making differential diagnosis difficult. VD together with mixed VD/AD pathology accounts for more than 50% of dementia subjects, suggesting a synergistic effect on cognitive decline (Azarpazhooh et al., 2018; Iadecola et al., 2019). In fact, cerebrovascular dysfunction, increased blood–brain barrier (BBB) permeability and a reduction in cerebral blood flow (CBF) are also critical components of the pathophysiology of late-life dementia including AD (Iadecola et al., 2019).

The neuropathology of VD, described as a multifactorial process, is less clear, but in recent years, a variety of processes have been identified. These include chronic hypoperfusion, as well as secondary thromboembolic events or microthrombosis, small vessel disease, microbleeds and/or cerebral haemorrhages (Figure 2) (Venkat et al., 2015). Many vascular risk factors such as hypertension, atherosclerosis and cerebrovascular disease have been found to be associated with the occurrence of dementia and cognitive decline (Iadecola et al., 2019).

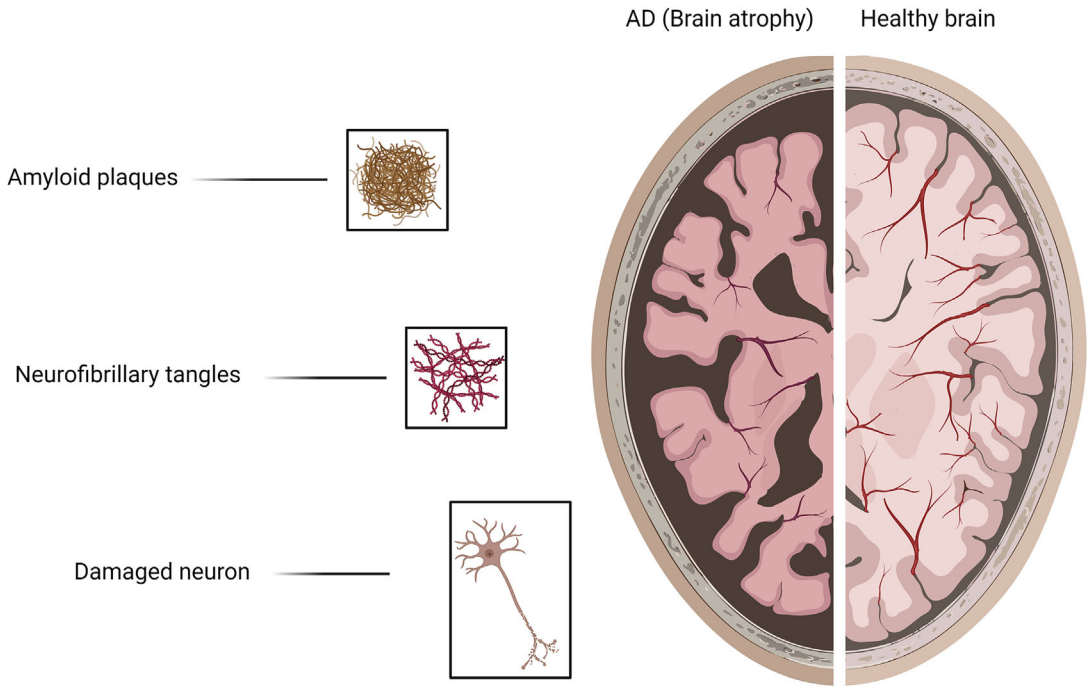

FIGURE 1 Pathophysiological processes in Alzheimer disease: amyloid plaques formed by amyloid-β (Aβ) peptide, neurofibrillary tangles (NFT) formed by aggregates of hyperphosphorylated tau-protein and brain atrophy caused by loss of neurons and synapses in specific brain regions.

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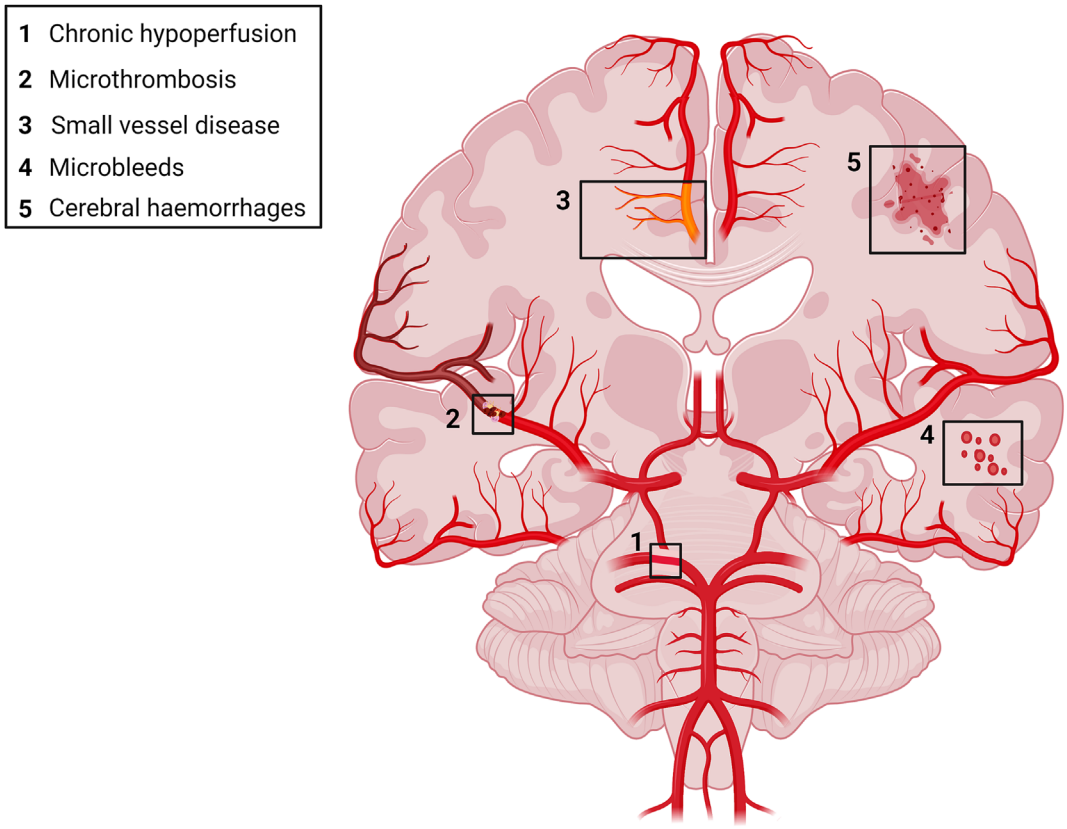

FIGURE 2 Pathophysiological processes of vascular origin that trigger vascular cognitive impairment. 1. Chronic hypoperfusion: refers to a state of reduced blood flow and oxygen supply to the brain that occurs over a long period of time. This can result from conditions such as chronic hypertension or atherosclerosis, which can lead to the narrowing or blockage of the blood vessels in the brain. 2. Microthrombosis: refers to the formation of small blood clots (thrombi) in the small blood vessels of the brain. 3. Small vessel disease: the walls of the small blood vessels are damaged, leading to a reduction in the calibre of the vessels, and ultimately, to a reduction in blood flow to the tissue. 4. Microbleeds: the rupture of small blood vessels in the brain due to a variety of causes, including hypertension or cerebral amyloid angiopathy. 5. Cerebral haemorrhages: occurs when there is bleeding in the brain due to the rupture of a blood vessel.

Notably, stroke, a leading cause of death and disability worldwide, is a major risk factor for both VD and AD (Rost et al., 2021). Cognitive alterations occur in up to 70% of stroke survivors, and up to one-third of stroke survivors can develop post-stroke cognitive impairment and dementia (PSCID) (Rost et al., 2021). PSCID is defined by the presence of cognitive impairments manifesting in 3 to 6 months after ischaemic or haemorrhagic stroke and includes deficits specific to the lesion site, those due to strategic infarcts in brain structures like the hippocampi, thalami and key cortical regions, those that may have preceded the stroke and those due to secondary process or neurodegeneration (Rost et al., 2021).

Despite the immense differences in neuropathology of AD and vascular-driven dementias, they are associated with shared and disease-specific abnormalities. Among these, neuroinflammation and immune-related mechanisms, such as the process of trained immunity, are crucially involved in the pathophysiology of the development and progression of both AD and VD. Neuroinflammation can be defined as an inflammatory response within the CNS that is caused by different pathological insults such as neurodegeneration, infection, acute injury like trauma or ischaemia and even toxins. Specifically, in the context of dementia, neuroinflammation must be considered as a chronic process that fails to resolve by itself and contributes as a key driver of the disease. Neuroinflammation is in general characterized by increased levels of different pro-inflammatory cytokines and chemokines such as **interleukin-1β (IL-1β)**, **interleukin-6 (IL-6)**, **interleukin-17 (IL-17)**, **tumour necrosis factor (TNF)**, **chemokine C-C motif ligand-1 (CCL1)** and **chemokine C-C motif ligand-5 (CCL5)**, among others, and that are produced by local activated cells such as microglia, astrocytes and macrophages but also by infiltrating leukocytes (Rauf et al., 2022). This infiltration process is likely to be enhanced when the BBB integrity is impaired. The blood–brain barrier (BBB) plays a vital role in maintaining the specialized microenvironment of the brain tissue (Zhao et al., 2015). It facilitates communication while separating the peripheral circulation from the brain parenchyma. However, normal ageing and neurodegenerative diseases can disrupt the physiological properties of the BBB (Sharma et al., 2022). In fact, BBB impairment is commonly observed as we age and is disrupted in late-cognitive impairment and dementia with the occurrence of brain capillary leakages, degeneration and the shrinkage of BBB-associated cells (including pericytes and endothelial cells). The BBB is also fundamental for clearing neurotoxic molecules from the brain parenchyma such as Aβ peptide into the blood (Zlokovic, 2011).

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Thus, the loss of BBB integrity may lead to pathogenic processes such as the invasion of peripheral immune cells (Sweeney et al., 2018) and to a defective Aβ clearance that further promotes its brain accumulation (Zlokovic, 2011).

Although the sustained inflammatory response in the brain of AD patients was first believed to be just a reaction against brain atrophy and neuronal loss in vulnerable brain regions (Murphy & LeVine, 2010), now different pieces of evidence suggest that neuroinflammation might play a critical role in the initiation and progression of AD pathology. Indeed, genome-wide association studies in AD subjects clearly show that more than 1/3 of the described susceptibility loci harbour genes that are related to the immune system and that may be expressed in myeloid cells such as **CD33** and TREM2, among others (Lewcock et al., 2020; Zhang et al., 2013) and may compromise myeloid function. As regards PSCID, both peripheral and central inflammation may contribute to long-term cognitive impairment (Stuckey et al., 2021). This process may comprise local inflammation of the brain as well as changes at a peripheral level. Supporting this in the periphery, different studies have shown that increased serum levels of pro-inflammatory markers such as TNF-α and IL-1β in stroke patients correlated with poor stroke outcomes 1 year after stroke (Stuckey et al., 2021). Moreover, stroke is also associated with a secondary immunosuppression process that exacerbates post-stroke infections and promotes a chronic inflammatory state that may lead to the development of post-stroke dementia (Endres et al., 2022).

Myeloid cells are a key component of the innate immune system and play a crucial role in neuroinflammation and maladaptive neuroimmune responses after brain injury and neurodegeneration (Doty et al., 2015). Myeloid cells include peripheral cells such as neutrophils, platelets and monocytes that either can exert their action by infiltrating into the brain or by contributing to peripheral inflammation (by secreting cytokines, for instance …). Resident brain microglia and non-parenchymal macrophages (including perivascular, meningeal and choroid plexus macrophages) are also fundamental (Herz et al., 2017).

In this review, we will explore the role of different types of myeloid cells from the periphery, perivascular space and brain parenchyma and their involvement in different types of dementia, including PSCID and AD. Finally, we will evaluate two potential strategies for pharmacological modulation of pathological processes mediated by different myeloid cell subsets that may pave the way to novel therapeutic avenues to stop dementia, the epidemic of our time.

2 | PATHOGENIC AND NEUROPROTECTIVE MECHANISMS OF MYELOID CELLS IN AD AND VASCULAR DEMENTIA

In the last few years, different investigations have suggested the involvement of myeloid cells in the development of AD and PSCID. The mechanisms by which these cell types, with a special emphasis on neutrophils, can have a major impact on these disorders processes, are discussed below.

2.1 | Peripheral cells

2.1.1 | Neutrophils: role in neuroinflammation

Neutrophils are white blood cells that are continuously generated in the bone marrow (BM) from myeloid precursors. While in mice blood neutrophils only represent around 10%–25% of leukocytes, in humans, neutrophils are the most abundant cell representing approximately 50%–70% of circulating leukocytes (Mestas & Hughes, 2004). Although neutrophils had always been considered as a short-lived immune cell with a circulating half-life of 6–8 h in humans and mice, this concept has now changed, and several studies suggest that the lifespan of neutrophils in human circulation is around 5.4 days (18 h for mice) (Ng et al., 2019). Importantly, under inflammatory conditions, the neutrophil life span increases. This process, so-called priming, expands the half-life of neutrophils when exposed to certain cytokines or chemokines and ensures the presence of primed neutrophils at the infected or inflamed tissues (Colotta et al., 1992). As a consequence of neutrophil rapid turnover under physiological conditions, the number of circulating mature neutrophils is maintained by a fine balance between granulopoiesis, neutrophil release from BM into the blood and then their return to the BM to be cleared mainly by macrophages. Granulopoiesis is a process that includes three main stages of developmental commitment of granulocytes: (1) The stem cell pool, consisting of haematopoietic stem cells and pluripotent progenitors that are common for myeloid cells; (2) the immature neutrophils, which includes different intermediate lineage-committed proliferative cells (such as myeloblasts, promyelocytes and myelocytes) and (3) and the fully differentiated, mature neutrophils (Summers et al., 2010). The maturation process of neutrophils involves hyper-segmentation of the nucleus and also formation of cytoplasmic granules and secretory vesicles. These granules are stores of proteins that are released by neutrophils with the aim to kill microbes and digest tissues (Borregaard, 2010). The retention of neutrophils in the BM is mediated in part by the **C-X-C Motif Chemokine Receptor 4 (CXCR4)**/**C-X-C Motif Chemokine Receptor 12 (CXCL12)** axis. In this sense, neutrophils express on their surface the CXCR4 receptor that interacts with the CXCL12 ligand from stromal BM cells (Figure 3). Then, neutrophil release is promoted by the loss of CXCR4 expression that is replaced by CXCR2 during neutrophil maturation (Figure 3) (Eash et al., 2010). Although all these BM homing retention signals work properly under steady-state conditions, during infection and/or inflammation, neutrophils are rapidly mobilized from BM into the blood where they may accumulate, increasing their numbers in the circulation; from there, they may migrate towards the inflamed tissue guided by chemokines, cytokines and another chemotactic factors that are released locally at sites of inflammation (Kobayashi, 2006). The intravascular neutrophil adhesion cascade that causes neutrophils to leave the blood stream starts with the capture of neutrophils on the activated endothelium followed by their rolling and firm arrest on endothelial cells (Kolaczkowska & Kubes, 2013). Then, neutrophils may extravasate into the inflamed tissue where they trigger a variety of responses that contribute to the pathophysiology of the disease

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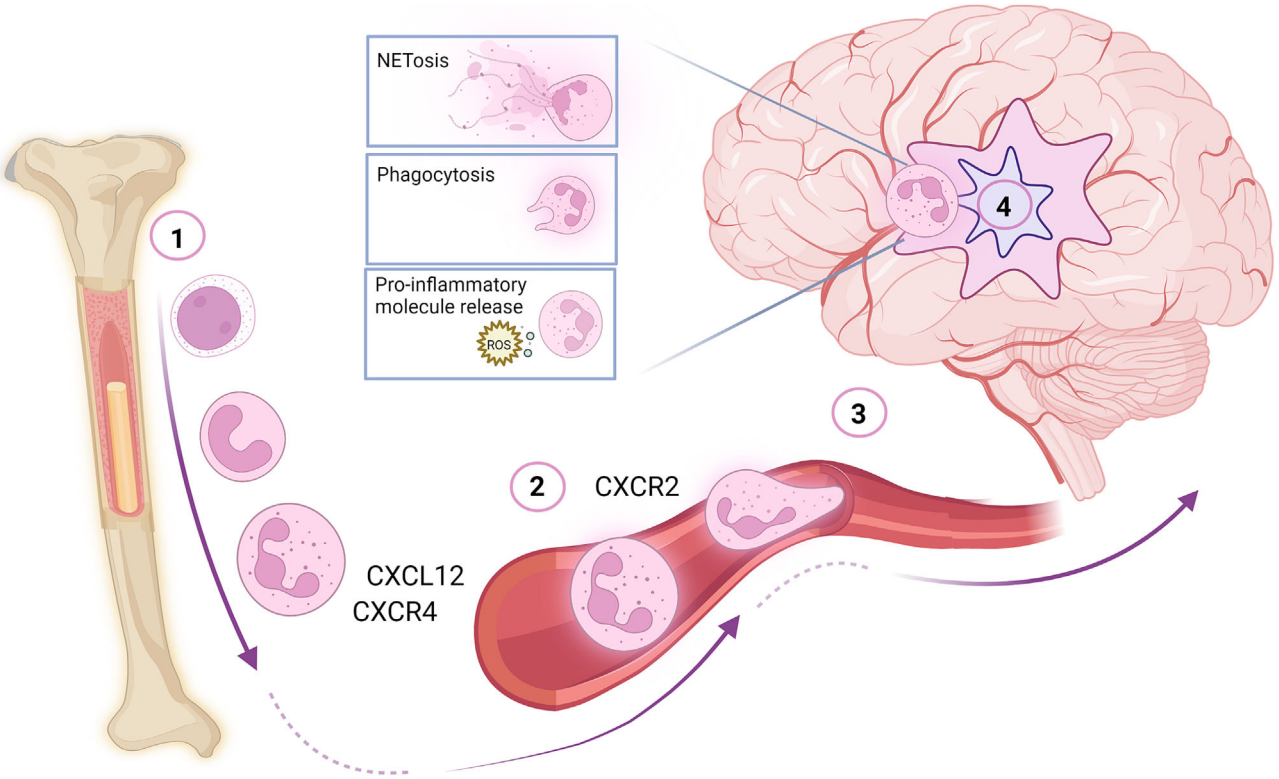

FIGURE 3 Neutrophils in neuroinflammation. 1. The maturation process of neutrophils involves hyper-segmentation of the nucleus and also the formation of cytoplasmic granules and secretory vesicles. The retention of neutrophils in the bone marrow (BM) is mediated in part by the CXCR4/CXLX12 axis. Neutrophils express on their surface the CXCR4 receptor which interacts with the CXCL12 ligand from stromal BM cells. 2. Neutrophil release is promoted by the loss of CXCR4 expression that is replaced by CXCR2 during neutrophil maturation. 3. During inflammation neutrophils are rapidly mobilized from BM into the blood wherein they may accumulate increasing their numbers in the circulation and may migrate towards the inflamed tissue. 4. Neutrophils that extravasate into the inflamed tissue where they trigger a variety of functions: neutrophils have the ability to phagocytose debris and pathogens, and to release molecules such as reactive oxygen species (ROS), cytokines, chemokines or proteases from their granules (such as MMP-9, cathepsin G, collagenase, gelatinase or heparinase) that damage the surrounding area and promote the activation of other types of immune cells. They can also release neutrophil extracellular traps (NETs), which are specific granule proteins, such as elastase and myeloperoxidase, bound to structures of filamentous DNA and histones in a single macromolecular complex.

although they may also exert beneficial and resolutive actions as observed in stroke (Figure 3) (Chen et al., 2021). When activated, neutrophils have the ability to phagocytose debris and pathogens and to release molecules such as reactive oxygen species (ROS), cytokines, chemokines or proteases from their granules (such as **MMP-9**, **cathepsin G**, collagenase, gelatinase or heparinase) that damage the surrounding area and promote the activation of other types of immune cells (Figure 3) (Kolaczkowska & Kubes, 2013), altogether contributing to the breakdown of the extracellular matrix and to vascular damage (Ruhnau et al., 2017). Importantly, apart from these actions, in response to different stimuli, neutrophils release neutrophil extracellular traps.

(NETs), which are specific granule proteins, such as elastase and myeloperoxidase, bound to structures of filamentous DNA and histones in a single macromolecular complex (Figure 3) (Brinkmann et al., 2004). NETosis includes the release of the granule components into the cytosol, modification of histones leading to chromatin decondensation, destruction of the nuclear envelope and the formation of pores in the plasma membrane (Brinkmann et al., 2004). Although NETs' primary function is to trap, restrain and neutralize invading microbes (Brinkmann et al., 2004), their role in non-infectious diseases is increasingly recognized. In this scenario, NETs may act on the intravascular compartment participating in thrombosis: Indeed, neutrophils and NETs can contribute together with platelets to immunothrombotic processes by forming heterotypic aggregates within blood vessels that impair CBF, a process that is likely to have an impact on cognitive function. Different studies have shown that neutrophil adhesion to the vessel wall without transmigration is enough to trigger endothelial injury and intravascular adhesion per se may cause NET formation and consequent endothelial injury, compromising BBB integrity (Zarbock & Ley, 2008). The adhesion-dependent production of ROS may also induce the NETosis machinery by the multienzyme complex NADPH oxidase (Stoiber et al., 2015). NADPH oxidase-deficient neutrophils of mutant mice and of humans with chronic granulomatous disease (CGD) are not able to form NETs (Bianchi et al., 2011; Fuchs et al., 2007). Also, ROS act to facilitate the citrullination of histone

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proteins by peptidyl arginine deiminase type 4 (PAD4) (Kawakami et al., 2014). In addition, NETs can also exert detrimental actions by directly acting on tissue parenchyma.

Importantly, neutrophils are phenotypically heterogeneous having the ability to switch towards a variety of phenotypes when they are activated, as they age, or when they enter into new environments. Therefore, different subpopulations of neutrophils can be distinguished by the expression of specific surface markers and differential functions. For instance, under steady-state conditions, neutrophil ageing occurs in the peripheral blood after release from bone marrow, showing increased CXCR4 and decreased CD62L expression. Neutrophil turnover is not only associated with ageing but also with changes in immune-phenotype and function (Casanova-Acebes et al., 2013). An example of this neutrophil heterogeneity comes from circulating mature neutrophils that vary their phenotype over the course of their lifespan. In fact, diurnal oscillations of CXCR4 expression have been found in the surface of circulating neutrophils from healthy subjects, which were proposed to correlate with neutrophil maturation and ageing (Ng et al., 2019). This is of special relevance since circulating aged and young neutrophils display differential properties including their granule contents and their ability for NETs formation (Adrover et al., 2019). Thus, neutrophil ageing may have important repercussions on homeostasis and inflammation (Adrover et al., 2020). More studies are needed to know why some neutrophils are more likely to produce NETs than others: Human neutrophils are faster and more efficient at releasing NETs than murine neutrophils (Ermert et al., 2009); mature (but not immature) neutrophils release NETs after stimulation with **IFNs** and **C5a** (Martinelli et al., 2004); and aged neutrophils (i.e., those primed by microbiota-derived products in the steady-state) produce NETs more readily than neutrophils newly released from the bone marrow (Zhang et al., 2015). These series of observations suggest that also heterogeneity in NET formation is established based on environmental demand and responds to defensive and physiological needs. Finally, neutrophils also may acquire a different functional phenotype under pathological situations. Studies in cancer identified N1 and N2 tumour-associated neutrophils (TAN) in mice (Fridlender et al., 2009), which, in this case, were antitumourigenic or protumourigenic, respectively. In this study, transforming growth factor beta (TGF-β) blockade resulted in an influx of TANs that were hypersegmented, more cytotoxic and with higher levels of proinflammatory cytokines that resulted in an anti-tumour phenotype (N1), whereas TGF-β favoured the TAN N2 phenotype and therefore enhanced tumour growth (Fridlender et al., 2009). Transcriptomic analysis of both populations confirmed that they were two different phenotypes (Shaul et al., 2016). This phenotypic drift has also been studied in cardiovascular diseases. In the stroke context, the expression of an "M2" marker has been described in neutrophils: Ym1+ neutrophils were detected both in blood and BM after the treatment with a **PPARγ** agonist. PPARγ activation produced neuroprotection and correlated with an increased number of N2 neutrophils in the injury site (Cuartero et al., 2013). Interestingly, this neutrophil subset was more efficiently cleared by microglial phagocytosis than the other subset. Through this pro-resolving mechanism, debris was promptly removed from the inflamed tissue by phagocytosis, contributing to the restoration of tissue homeostasis and improving the outcome (Cuartero et al., 2013). In the same way, the lack of TLR4 confers a neuroprotective effect that is concomitant to an increased density of infiltrated neutrophils into the ischaemic core (García-Culebras et al., 2019). The fact that **TLR4** drives neutrophil reprogramming was previously suggested when it was described that neutrophil ageing is driven by the microbiota via TLR (Zhang et al., 2015). Interestingly, non-aged neutrophils described by Zhang and co-workers had a transcriptional signature similar to that in TLR4-lacking neutrophils obtained 48 h after experimental stroke (García-Culebras et al., 2019; Zhang et al., 2015). Importantly TLR4-lacking neutrophils showed a higher phagocytic activity in the basal state, they were preferentially engulfed by the microglia after stroke and they produced less ROS in the first stage of the inflammatory process (Durán-Laforet et al., 2021). Finally, it is important to note a recent study in which identified a unique subset of neutrophils that can promote neuronal survival in the CNS (Sas et al., 2020). All this evidence suggests that the role of neutrophils in different pathologies may depend on their phenotype.

2.1.2 | Neutrophils as drivers of dementia

Neutrophils may play a key role in the development and progression of AD and VD, although few studies so far have directly investigated their participation.

Alzheimer's Disease (AD)

Either as a cause or as a consequence, neutrophil counts (Järemo et al., 2013) and neutrophil/lymphocyte ratio are higher in AD patients than in control subjects (Ramos-Cejudo et al., 2021). The accumulation of Aβ and tau in AD brain and blood vessels has been reported to impair BBB function and integrity and promote the release of pro-inflammatory mediators as well as the expression of adhesion molecules on brain endothelial cells (Sweeney et al., 2018; Zenaro et al., 2015). This process allows circulating myeloid cells such as neutrophils to invade the brain (Figure 4). In this sense, different studies in AD patients have clearly demonstrated that neutrophils infiltrate into the brain parenchyma (Baik et al., 2014; Zenaro et al., 2015). First studies in this regard found that the neutrophil-specific protease cathepsin G accumulates in the brain and blood vessels of AD patients and is commonly associated to Aβ plaques (Pietronigro et al., 2017). The presence of neutrophils in the brain of AD subjects has been further confirmed by the detection of **myeloperoxidase (MPO)**+ cells, a typical neutrophil marker. These MPO+ cells were located very close to the Aβ plaques, and their distribution was non-random, suggesting that Aβ may act as a chemoattractant by creating a favourable microenvironment for the accumulation of neutrophils inside the brain, thus promoting their pro-inflammatory activities (Zenaro et al., 2015). In agreement with the data from AD subjects, different studies in the transgenic 3xTg-AD and 5xFAD AD mouse models have also shown the presence of

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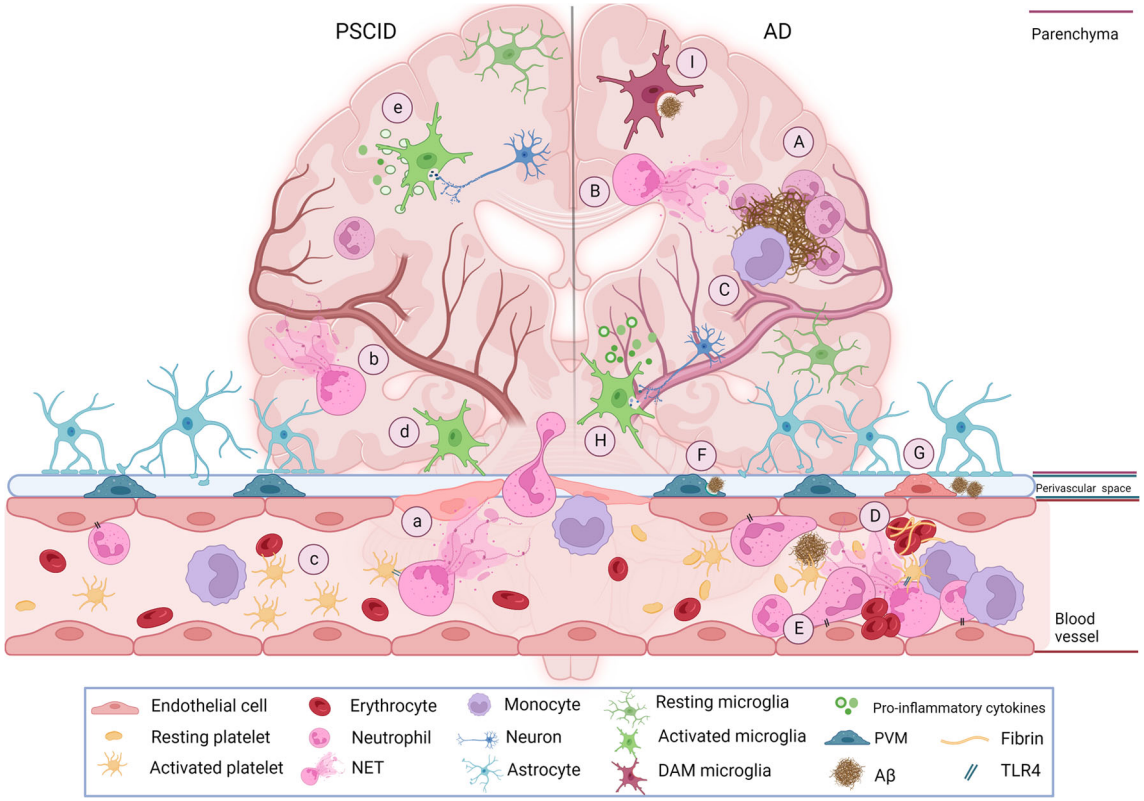

FIGURE 4 Schematic representation of main myeloid cells effects in Alzheimer's disease (AD) and post stroke cognitive impairment and dementia (PSCID). AD: (A) Neutrophils infiltrate into the brain parenchyma located very close to the amyloid-β (Aβ) plaques. (B) These infiltrating neutrophils are activated by inflammatory mediators, potentially released by microglia, and can produce neutrophil extracellular traps (NETs). (C) Presence on plaques of monocytes that could participate directly in the removal of Aß-plaque formation. (D) Neutrophils adhered to the vessel wall also produce intravascular NETs, potentially with the contribution of activated platelets via TLR4. E) Platelets may also be responsible for the accumulation of Aβ in blood clots inside and around cerebral blood vessels. (F) Aβ phagocytosis in the perivascular space by perivascular macrophages (PVMs). (G) Intravascular Aβ crosses the vascular wall, enters the perivascular space, reaches PVM, induces ROS production, and alters neurovascular function. (H) Excessive activation of microglia causes neurotoxicity and synaptic loss. (I) Disease-associated microglia (DAM) involved in Aβ clearing. PSCID: (a) NETs release in both intravascular (b) and parenchyma compartment impair vascular remodelling during stroke recovery. (c) Platelet activation is still present in the chronic phase of ischaemic stroke. (d) Vessel-attached microglia with beneficial role in maintaining the integrity of the BBB. (e) Activation of harmful microglia would lead to pro-inflammatory cytokine release, astrocytic end-feet and axons phagocytosis, aggravating BBB damage.

Gr-1+ cells infiltrated in the brain parenchyma (Baik et al., 2014; Subramanian et al., 2010). The study by Zenaro and collaborators also corroborated the presence of infiltrated neutrophils into the brain of AD mice. In the same AD mouse models, they found that neutrophils extravasated and were located in brain areas with Aβ deposition. Importantly, they also found that neutrophils released NETs that further amplified neuroinflammation, increased amyloid plaques and tau tangles and therefore worsened cognitive decline and dementia. In agreement with this, neutrophil depletion during 1 month at early stages of the disease promoted a sustained improvement in memory (Zenaro et al., 2015). Accordingly, blocking neutrophil trafficking and infiltration into the brain by inhibiting the **integrin LFA-1** also resulted in a dramatic reduction of neuropathological hallmarks of disease and memory deficits in AD mouse models, demonstrating a role for neutrophils in the development of cognitive impairment in these AD models.

Apart from the role of infiltrated neutrophils into the brain parenchyma, different studies have also demonstrated that part of the detrimental role of neutrophils in AD arise from their actions in the intravascular compartment (Figure 4). Vascular dysfunction and CBF reductions are commonly found in AD subjects (Zhang et al., 2021). Some studies have identified capillary abnormalities in AD patients (Nielsen et al., 2017) and mouse models of this pathology, showing neutrophil arrest in capillary segments (Cruz Hernández et al., 2019; Park et al., 2017), which contribute to reduced CBF. Importantly, blood neutrophils from AD patients express surface markers such as CXCR4 and CD177 that may be related to neutrophil activation, suggesting that circulating neutrophils may display a hyperactive phenotype in AD patients (Dong et al., 2018). Of note, this hyperactive phenotype is associated with an increased production of ROS and the generation of intravascular NETs (Figure 4) (Dong et al., 2018). Importantly, the balance of blood neutrophils in AD subjects also changed:

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The ratio between the harmful hyperreactive CXCR4hi/CD62Llow neutrophils and the CD16^{bright}/CD62L^{dim} immunosuppressive neutrophil subsets increased in the late phase of the AD. Of note, these alterations were higher in those patients who displayed a faster decline suggesting therefore that the neutrophil phenotype might be associated with the rate of cognitive worsening (Dong et al., 2018). Accordingly, Cruz-Hernandez et al. confirmed that neutrophils are also key mediators of AD pathology by acting inside of blood vessels in mouse models (Cruz Hernández et al., 2019). In this sense, authors found that, in both APP/PS1 and 5xFAD models of AD, neutrophils adhered in capillary segments, stalling them and blocking CBF. Then, neutrophil depletion by using an anti-Ly6G antibody reduced the number of stalled capillaries, leading to an increase in CBF and improved cognitive performance in spatial and working memory tasks, confirming therefore that reductions in the CBF are implicated in the pathogenesis of AD and importantly that it is dependent of neutrophils actions. Similar results were also found in later studies, also implicating the NOX2 pathway or VEGF signalling as mechanisms likely underlying capillary stalling and CBF reductions in AD models (Ali et al., 2022; Kang et al., 2020). In agreement with the implication of intravascular neutrophils and the generation of NETs in AD patients, the study by Zenaro and co-workers also observed the formation of intravascular NETs in AD models strongly suggesting that NETs may contribute to BBB damage and neuronal injury (Zenaro et al., 2015). In a recent study by Smyth and co-workers, the authors confirmed that neutrophils accumulate in the brain of AD subjects where they associate with blood vessels and may contribute to vascular stalling and BBB leakage. In addition, they also showed that neutrophils and NETs are the main source of MPO in the brain during AD and may represent an important mechanism through which BBB inflammation influences oxidative stress in AD (Smyth et al., 2022). Therefore, the vascular association of neutrophils observed in different studies of AD suggests an origin from the circulation, which may be associated with activated neutrophils that are more prone to form NETs.

Post-stroke cognitive impairment and dementia (PSCID)

Neutrophils are one of the first cell types to respond to an ischaemic injury. They infiltrate into the ischaemic tissue wherein they contribute to BBB disruption, cerebral oedema, and brain injury. Importantly, an increase in circulating neutrophils is associated with stroke severity, infarct volume, and worse functional outcomes (Jickling et al., 2015). The intravascular effects are mediated, at least in part, by a neutrophil contribution to the thrombosis process. Of note, the analysis of thrombi composition in stroke patients has revealed that thrombi mainly consist of red blood cells, fibrin, **von Willebrand factor**, platelets and different types of leukocytes. In this sense, monocyte and neutrophils may activate platelets to trigger thrombosis (Engelmann & Massberg, 2013). In addition, neutrophils may promote the formation of NETs that further exacerbate this immunothrombotic process (Peña-Martínez et al., 2019; Perez-de-Puig et al., 2015).

Although neutrophil participation during the acute stroke phase is well established (reviewed in Chen et al., 2021), whether they also contribute during the chronic phase and might even participate in the development of PSCI is not well defined yet. Chronic activation of innate immune responses, for instance, those from neutrophils, may trigger neurotoxic pathways leading to a secondary progressive degeneration, or can impair brain recovery mechanisms that take place after stroke. Neovascularization and vascular remodelling are functionally important for brain repair after stroke. In this sense, release of NETs in both intravascular and parenchyma compartments has been shown to impair vascular remodelling during stroke recovery (Figure 4). Thus, neutrophil blocking or NETosis inhibition improves cerebrovascular remodelling and functional recovery during the delayed phases after stroke (Kang et al., 2020). In addition, chronic hypoperfusion is one the predisposing factors to the development of PSCID (Venkat et al., 2015). Since neutrophils are key players in the chronic alterations of CBF found in both human and animal models of AD, it is also possible that neutrophils and NETs may drive a secondary immunothrombosis process after stroke. In this sense, neutrophils may stall blood flow in brain capillaries of vulnerable brain regions such as the hippocampus or the thalamus wherein a secondary BBB degeneration has been found (El Amki et al., 2020; Erdener et al., 2021). It is very interesting to note that the magnitude of the acute innate immune response after stroke onset strongly correlated with long-term cognitive trajectories of stroke subjects determined by Montreal Cognitive Assessment (MoCA) scores (Tsai et al., 2019). That basically means that elevated innate immune cell responses within the first days after stroke onset are associated with, and perhaps contribute to, poor cognitive recovery after stroke. In this sense, several recent clinical studies suggest that there may be a causal association between neutrophil response during admission and long-term outcomes. In this context, it has been shown that an increased % of neutrophils as well as an increase neutrophil/lymphocyte ratio during acute stroke phase is associated with PSCID long-term after stroke (Lee et al., 2021; Zha et al., 2021).

Involvement of neutrophil heterogeneity

High-throughput single-cell analysis in neurodegenerative diseases has currently been extended far beyond microglial cells (Zhou et al., 2022), but there is still a long way to go with this technology for other peripheral myeloid cells. Neutrophils were considered to be a homogenous population of short-lived, non-proliferative and terminally differentiated cells with reduced transcriptional capacity, producing a limited panel of cytokines, and with no ability to recirculate from tissues to blood, suggesting highly conserved specialized functions. However, more recent research based on sc/nc RNAseq and computing data analysis methods has revealed unexpected phenotypic plasticity and diversity in terms of neutrophil trafficking and functionality. Their role is now understood in homeostasis and some inflammatory pathologies (Grieshaber-Bouyer & Nigrovic, 2019), but studies are still needed to understand neutrophil heterogeneity changes that may occur in the brain microenvironment of AD and PSCID, especially after the recent identification of a subset of neutrophils that promote neuronal survival and axon regeneration in the CNS (Sas et al., 2020). Additionally, spatial single-cell omics technologies that allow the

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simultaneous collection of spatial and gene expression information (Zhang et al., 2022) can add valuable information to sc/sn transcriptomics. Furthermore, the deep immune profiling approach with mass cytometry has also proved to be a good approach for the identification of clinically relevant immune correlates of long-term cognitive trajectories in acute stroke survivors (Tsai et al., 2019).

2.1.3 | Platelets

Platelets are small anucleate cells derived from megakaryocytes. They are the most prevalent blood component after red blood cells (RBC). Platelets are mainly responsible for sealing areas of damage to the vessel wall through aggregation (Scherlinger et al., 2023). Steady-state platelets characterize by a discoidal shape; however, upon vascular injury, they interact with the endothelium by changing their discoidal shape to spherical and subsequently forming filopodia for adhesion. Although common in most of their features, mouse and human platelets show some differences that should be taken into consideration: Murine platelets are smaller (0.5 μm vs. 1–2 μm) and have a shorter lifespan compared to human platelets (2–3 days vs. 8–10 days) (Schmitt et al., 2001).

Over the last few decades, the role of platelets not only in homeostasis and thrombosis but also in inflammation has been well established. Platelets are able to interact with a large variety of cell types including monocytes and neutrophils, and these interactions have been related to the pathophysiology of vascular inflammation (Projahn & Koenen, 2012). On their surface, platelets express a wide variety of immune receptors including **toll-like receptors (TLRs)**, a family of proteins (**pattern recognition receptors or PRRs**) involved in the recognition of pathogen-associated molecular (PAMPs) and damage-associated molecular patterns (DAMPs) that activate both innate and adaptive immune responses. So far, 10 TLRs have been identified in humans and 12 in mice. However, for the purpose of this review, we will only focus on the best defined one, TLR4. For instance, TLR4 is well known to play a key role in the immune response in the context of stroke. In addition, platelets are responsible for NET formation in a TLR4-dependent manner (Clark et al., 2007).

Platelet activation in dementia

In AD pathology, platelets are considered to have a key role because they represent the link between Aβ deposition, peripheral inflammation and endothelial senescence (Casoli et al., 2013). On the one hand, amyloid precursor protein (APP) is present at the platelet surface, and importantly, changes in platelet APP expression have been associated with mild cognitive impairment (MCI) and AD (Evin & Li, 2012). In fact, platelets are the main source of Aβ in blood (Kucheryavykh et al., 2017). Some studies have shown that platelets are responsible for the accumulation of Aβ in blood clots inside and around cerebral blood vessels in mouse models **(**Figure 4**)** (Kucheryavykh et al., 2017). In addition, platelets induce the conversion of soluble Aβ to toxic aggregated species (Gowert et al., 2014). Furthermore, a pre-activated state of platelets has been described in blood from AD patients, posing them as a potential biomarker for the early diagnosis of AD (Sevush et al., 1998). Accordingly, the APP23 mouse model of AD also corroborates that platelets, both in vivo and ex vivo, are in a pre-activated state showing strongly enhanced responses upon stimulation (Jarre et al., 2014). Of note, activated platelets from AD patients produce more Aβ than those from healthy individuals (Tang et al., 2006), further contributing to the pro-thrombotic milieu in AD (Cortes-Canteli et al., 2015). A recent study showed that individuals free of antiplatelet therapy with a higher platelet response were at higher risk of dementia in late life during a 20-year follow-up, reinforcing the role of platelet function in AD risk (Ramos-Cejudo et al., 2022).

On the other hand, as mentioned above, intravascular NETs may be induced by activated platelets interacting with neutrophils via TLR4 (Clark et al., 2007); in this context, it has been suggested that the release of intravascular NETs found in AD mouse models and human AD subjects could be promoted by activated platelets interacting with adherent neutrophils (Figure 4) (Pietronigro et al., 2017), supporting the role of platelets in AD pathophysiology. Interestingly, there is a similarity between the proteomic signature of the human brain with cerebral atherosclerosis, which can produce platelet activation, and AD pathology (Wingo et al., 2020).

In acute stroke, the role of platelets in immunothrombosis is supported by several pieces of evidence that suggest their potential but still quite unexplored involvement in chronic stroke and subsequent PSCID. First, platelet TLR4 has been demonstrated to play a key role in NET formation during the prothrombotic process in ischaemic stroke as well as a possible role in the extent of the ischaemic stroke lesion (Peña-Martínez et al., 2019, 2022). In addition, platelet TLR4 was sufficient to accelerate microvascular thrombosis in the cremaster venules during endotoxaemia (Stark et al., 2012). Importantly, different signs of NET formation have been described in perivascular spaces, in brain parenchyma near blood vessels and in the lumen of capillaries in the ischaemic brain in the transient middle cerebral artery occlusion (tMCAO) model (Perez-de-Puig et al., 2015), therefore suggesting that platelets, in a NET-dependent manner, could have a key role in the microvascular events responsible for the "non-reflow phenomenon" by which, despite blood flow restoration, microvessel reperfusion does not occur (El Amki et al., 2020; Erdener et al., 2021; Rolfes et al., 2021).

Although experimental stroke studies suggest that targeting activator platelet receptors might be a feasible strategy to reduce thrombo-inflammatory infarct progression following ischaemic stroke (Stegner et al., 2019), other pieces of evidence show that delayed platelet depletion does not improve functional outcome 28 days after tMCAO stroke model (Steubing et al., 2022). Furthermore, some long-term studies suggest that platelet activation is still present in the chronic phase of ischaemic stroke (Figure 4) (van Kooten et al., 1998). In the same direction, coated-platelet levels measured at the time of the ischaemic stroke were found to correlate with cognitive screening scores obtained 3 months after the initial brain infarction (Kirkpatrick et al., 2020). These data support a link between increased platelet procoagulant potential at the time of the stroke and the development of PSCID following cerebral infarction. Further studies are needed to characterize the mechanisms and determinants of platelet activation in relation to the development of PSCID.

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2.1.4 | Monocytes

Monocytes are mononuclear myeloid leukocytes born in the BM. They are the circulating precursors of macrophages and dendritic cells with functions such as phagocytosis, production of cytokines, ROS and reactive nitrogen species (RNS) and antigen presentation (Saha & Geissmann, 2011). In humans, mononuclear cells represent 5%–10% of peripheral leucocytes but only 4% in mice (Gordon & Taylor, 2005). Over 50% of monocytes are stored in the spleen as well as the lungs and accumulate rapidly in response to injury (Ginhoux & Jung, 2014). Monocytes show not only morphological heterogeneity regarding size, granularity and nuclear morphology but also immunophenotypic and functional diversity (Gordon & Taylor, 2005). In humans, three types of circulating monocytes have been identified based on the expression of **CD14**, a glycoprotein and myelomonocytic differentiation antigen that functions as an accessory protein to TLR4, and CD16, the Fcγ receptor III. They are classified as $CD14^{high}/CD16^{-}$ (also called classical monocytes), $CD14^{low}/CD16^{+}$ (also called non-classical monocytes) and $CD14^{high}/CD16^{+}$ (also called intermediate monocytes) (Saha & Geissmann, 2011). While with the advent of novel single-cell technologies higher heterogeneity has been suggested, the occurrence of the three major subsets of monocytes is still proposed (Kapellos et al., 2019). In addition, two subsets of circulating monocytes have been described in mice, $CX3CR1^{high}/CCR2^{-}/Ly6C^{low}/PD\text{-}L1^{+}$ or patrolling monocytes, because they can patrol along the blood vessels, and $CX3CR1^{low}/CCR2^{+}/Ly6C^{high}/PD\text{-}L1^{-}$ monocytes, that can be recruited to inflamed tissues (Bianchini et al., 2019). Moreover, monocytes can differentiate into tissue macrophages or dendritic cells after infiltrating into the tissue (Saha & Geissmann, 2011), but circulating monocytes cannot infiltrate into the brain under physiological conditions due to the BBB. However, $CX3CR1^{low}/CCR2^{+}/Ly6C^{high}/PD\text{-}L1^{-}$ monocytes can infiltrate into the parenchyma and become monocyte-derived macrophages (MDMs) in some disease conditions in which the BBB is compromised (Werner et al., 2020). **C-C motif chemokine receptor 2 (CCR2)** is required for extravasation from BM into blood and subsequently for transmigration into sites of inflammation in CNS (Chu et al., 2014) and **CCL2 (also known as monocyte chemoattractant protein 1, MCP-1)** is the most potent activator of CCR2 signalling in mice, leading to monocyte transmigration in brain after many neurological disorders (Ajami et al., 2011). Similar to the resident microglia, MDMs can express cellular markers, such as CD11b, Iba-1 and **CX3CR1**. However, chimeric mouse models, BM transplantation, single cell sequencing and the discovery of new microglial-specific markers have made it possible to distinguish MDMs from microglia. This is important since these cells display a remarkable plasticity and can change their phenotype (pro- versus anti-inflammatory subsets) in response to the microenvironment. Identification of these specific myeloid subsets and their functions is crucial to unravel the diversity of the myeloid compartment in CNS pathogenesis.

In addition to the typical innate immune response, the process of innate memory, also termed trained immunity, has recently been proposed as a mechanism for innate immune cells to remember an inflammatory challenge and to respond in an enhanced manner to a subsequent exposure to the same or even to an unrelated pathogen or damage-associated stimulus (Netea et al., 2016). The long-lasting effect of trained immunity is explained by the fact that training occurs within the myeloid compartment, at the level of haematopoietic stem and progenitor cells in the BM (Christ et al., 2018). As commented above, the immunological memory of the innate immune system after exposure to an inflammatory stimulus (for example, microbial components like ß-glucan, etc.) includes a boosted response upon a secondary challenge, which is reflected by increased cytokine production and metabolic and long-lasting epigenetic changes that maintain cells in a primed state (Netea et al., 2016; Saeed et al., 2014). Another question remains as to whether the immunological memory of other members of the myeloid compartment, such as macrophages residing at the borders to the CNS or CNS-invading monocytes during inflammatory conditions, could contribute to the above-described observations. Recent studies have shown that peripheral immune training can induce memory in haematopoietic precursors in the BM, leading to significant changes in myelopoiesis (reviewed by Schultze et al., 2019). Such peripheral alterations might also impact microglia activation, myeloid cell infiltration in the brain, and consequently neuropathology.

Monocytes: important players in dementia

In addition to the actions of microglia later described, several authors have proposed that monocytes may infiltrate the AD brain and have effects on the pathology (Figure 4) (Simard & Rivest, 2006). This is the case in a study carried out on the mouse model of AD (Tg2576) in which Ccr2 deficiency accelerated early disease progression and markedly impaired microglial downstream accumulation, suggesting that BM-derived monocytes enter the brain through the vasculature, migrate and associate with amyloid plaques (El Khoury et al., 2007). In line with this, inhibiting the infiltration of monocytes (CCR2 KO) aggravated the progression of AD (Naert & Rivest, 2011). Moreover, transplantation of wild-type BM cells expressing CCR2 decreased Aβ accumulation and prevented cognitive decline in the CCR2 KO AD mouse model (Naert & Rivest, 2012). In later studies, the authors showed that the plaque-associated myeloid cells were likely derived from infiltrating peripheral "inflammatory" monocytes, based on cellular markers (Jay et al., 2015) although another study using genetic mouse models labelling different myeloid populations found that plaque-associated myeloid cells in the AD brain were derived exclusively from resident microglia (Reed-Geaghan et al., 2020). However, recent studies indicate that peripherally derived monocytes invade the brain parenchyma, targeting amyloid plaques to reduce plaque load (Figure 4) (Yan et al., 2022). Lastly, the systematic administration of macrophage colony-stimulating factor increased the number of MDMs in the brain, thus decreasing the Aβ deposition and further rescuing social deficits and cognitive decline (Boissonneault et al., 2009). Taken together, these findings suggest that promoting MDMs can be an effective treatment for the early stages of AD (Zhou et al., 2022).

Regarding PSCID, a recent study has demonstrated that the severity and progression in PSCID patients were associated with the

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trained immunity characteristics of circulating monocytes (Noz et al., 2018). One of the most remarkable findings of this study is that there was a significant correlation between monocyte cytokine production capacity and PSD progression. Some of the earliest studies of trained immunity were conducted in patients with atherosclerosis, a disease that shares risk factors with PSCID, such as hypertension, smoking or diabetes mellitus, suggesting a common pathophysiological mechanism (Iadecola et al., 2019). Another study showed that those patients with greater peripheral monocytic activation 48 h after stroke are more likely to have cognitive decline between 90 and 365 days after the insult (Tsai et al., 2019).

Overall, genetic and functional data confirm the driving role of the innate immune component in the trajectory of the disease. For instance, infections, a common and severe post-stroke (e.g., pneumonia) (Emsley & Hopkins, 2008) but also AD complication in patients (Morton et al., 2020), are associated with worsened cognitive decline in both pathological scenarios.

The activation of inflammatory characteristics in their innate immune cells, such as a primed state of myeloid phagocytic cells like monocytes, resembles conditions of trained immunity. Therefore, it is plausible that myeloid cells in individuals with AD and PSCID initially attempt to resolve recurrent or persistent inflammation but eventually acquire a trained phenotype that lacks sufficient immune regulation. This can lead to uncontrolled progression of neurodegeneration or even support its advancement. Salani et al. (2019) have extensively reviewed this phenomenon. A deeper comprehension of these mechanisms will pave the way for the development of innovative diagnostic and therapeutic approaches for the treatment of AD and PSCID.

2.2 | Perivascular space cells

2.2.1 | Perivascular macrophages in the CNS

In the brain, non-parenchymal border-associated macrophages (BAMs) such as perivascular macrophages (PVMs) are resident macrophages located in the boundary regions, more specifically, meninges (dura mater, arachnoid mater, pia mater), perivascular spaces that are sandwiched with two basal laminas (one from the endothelial cells or basement membranes of mural cells, such as vascular smooth muscle cells [VSMC] and pericytes, and the other from the astrocytic endfeet) (Figure 4) and the choroid plexus of the CNS (Yang et al., 2019). These CNS BAMs are located surrounding vessels in both cortical and subcortical regions of the brain (Yang et al., 2019) allowing them contact with the parenchyma, cerebral spinal fluid (CSF) and blood vessels, and therefore providing structural and functional support for the BBB (Park et al., 2017). Specifically, PVMs are also essential in maintaining brain homeostasis. In recent years, increasing evidence suggests that PVMs are key components of the brain resident immune system and are also involved in a number of pathological processes, including neurodegeneration and ischaemic stroke (Zheng et al., 2022). Regarding their origin, PVMs, as well as microglia, proceed from early erythro-myeloid progenitors in the yolk sac, which migrate into the brain in the early stage of the embryo and undergo early separation into two different populations (Yang et al., 2019). Also, the development of PVMs is independent of TGF-β, unlike microglia (Utz et al., 2020). In homeostasis, PVMs are a stable cell population with a long lifespan and self-renewal ability after birth. Some PVM molecular markers are negative for microglial-specific markers such as transmembrane protein 119 (TMEM119), sialic acid-binding immunoglobulin-like lectin H (Siglec-H), **$P2Y_{12}$ purinoceptor**, Sal-like protein 1 (Sall1), Sal-like protein3 (Sall3) or ANXA3.5 (Zheng et al., 2022). Others are unique to this cell type such as Siglec1 (CD169), absent in microglia (Zheng et al., 2022). Single-cell RNA-seq confirmed that PVM can be distinguished from microglia by the respective expression of CD206 and **CD36** and of the lymphatic vessel endothelial hyaluronan receptor-1 (Lyve1) (Goldmann et al., 2016). The most studied functions of PVMs are to (1) provide structural and functional support for the BBB and lymphatic clearance, (2) carry out phagocytic function and clear metabolic waste, (3) directly contact blood, CSF, and brain parenchyma and (4) act as antigen presenting cells to recruit circulating immune cells into the CNS. All these functions are important for the maintenance of brain homeostasis (Yang et al., 2019). Furthermore, the role of PVMs in BBB permeability has been widely discussed, in which it is possible that PVMs facilitate BBB integrity under physiological conditions, and participate in BBB disruption under diseased status, as in ischaemia (Li et al., 2018).

At this point, it is important to mention the recent knowledge of the existence of complementary systems for CNS clearance. Indeed, increasing evidence suggests that the glymphatic system is functionally involved in the removal of waste products and protein aggregates, including Aβ and tau, pathological markers of AD, in regions involved in cognition (Nedergaard & Goldman, 2020). Therefore, its dysfunction would lead to a failure of clearance, with accumulation and aggregation of these harmful products eventually resulting in neurodegenerative diseases (Da Mesquita et al., 2018) with impairment of cognitive function. Glymphatic dysfunction has also been observed in ageing (Da Mesquita et al., 2018), one of the main risk factors for the pathologies here reviewed. Structures involved in brain clearance including meninges, perivascular spaces and dural venous sinuses are sites of immune cell surveillance and are considered interfaces between the brain and the immune system (Shimada & Hasegawa-Ishii, 2017). The fact that immune cell surveillance occurs at the sites of clearance suggests that a neuroimmune crosstalk initiated by patrolling immune myeloid cells, after sensing damage could ultimately lead to a dysfunctional brain clearance.

Perivascular macrophages at CNS interfaces: new horizons in dementia

In the AD context, brain Aβ is released to the extracellular space at the Virchow-Robin space, and there, PVMs are essential for its phagocytic clearance (Figure 4) regulated by the scavenger receptor class B type I (SR-BI) (Hawkes & McLaurin, 2009). This was demonstrated by the fact that, when PVM was depleted in TgCRND8 mice using clodronate, the deposition of Aβ increased around cerebral blood vessels (Hawkes & McLaurin, 2009). Furthermore, the deletion of SR-BI

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increased vascular and parenchymal Aβ deposition in the hippocampus and exacerbated behavioural deficits in J20 mice (Thanopoulou et al., 2010). However, a detrimental role of PVMs in AD has been also described. In this regard, Park et al. found that intravascular Aβ crosses the vascular wall, enters the perivascular space, reaches PVMs, induces ROS production and alters neurovascular function, pointing to PVMs as responsible for vascular dysfunction in AD (Figure 4) (Park et al., 2017).

In stroke, Schwab et al. described the up-regulation of **COX-1** expression in PVMs restricted to the necrotic core and peri-infarct areas in human brains, not only in the acute phase but also at later times after the ischaemic event, where they would promote tissue remodelling and angiogenesis (Schwab et al., 2000). More recently, by using a cell depletion strategy, Pedragosa and co-workers. found that PVMs participate in granulocyte recruitment, promote the expression of vascular endothelial growth factor (VEGF), increase the permeability of pial and cortical blood vessels and contribute to neurological dysfunction in the acute phase of stroke (Pedragosa et al., 2018). Also, perivascular macrophages have been suggested to have a role in the development of hypertension-induced pathologies in the CNS vasculature (Faraco et al., 2017). This fact is remarkable because hypertension in one of the most important risk factors in cerebral ischaemia. Summing up, the evidence supporting a detrimental role of PVMs in the early stages of stroke suggests their potential involvement in PSCID, but further studies are required to elucidate this question.

2.2.2 | Microglia

Microglia are resident phagocytic cells that derive from an extraembryonic erythromyeloid precursor and persist in adulthood independently of haematopoiesis, making up around 10% of all cells in the CNS. Although *stricto* sensu they are not etymologically "myeloid" as they do not derive from the bone marrow, they belong to the macrophage lineage (Paolicelli et al., 2022), and they may be considered myeloid-like, so they will be studied here. Since these cells are not replaced by BM-derived cells, they are likely to be provided with a broad set of brain-related functions that peripheral myeloid cells do not have. They are the initial line of cellular defence against invading infections and other forms of brain damage (Town et al., 2005). Under homeostatic conditions, microglia remain in a resting state morphologically characterized by a small-shaped soma and highly ramified branches (Hristovska & Pascual, 2015). In response to invading pathogens or after sensing adjacent cell damage, microglia get activated and undergo morphological changes such as expansion of their soma and shortening of their cellular processes (Town et al., 2005). Activated microglia are critical in pathogen phagocytosis and in the elimination of cellular debris and degenerating cells at the lesion site (Beccari et al., 2023). The secretory properties of microglia have been well characterized. Initial studies showed that microglia are capable of releasing both anti- and pro-inflammatory cytokines depending on its status. Upon stimulation with **IL-4**/**IL-13** or **IL-10** signals, microglia can switch to a state characterized by the up-regulation of receptors such as CD206 and CD163, cytosolic enzymes (e.g., arginase-1) and secretory proteins (e.g., YM1) and by the release of anti-inflammatory cytokines (e.g., IL-4, IL-10, transforming growth factor [TGF]-β), which facilitate tissue repair and resolution of inflammation (Dionisio-Santos et al., 2019). Moreover, microglia can trigger inflammatory processes and accelerate neuronal death by expressing immunoglobulin Fc receptors (e.g., CD16/CD32), releasing pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), metabolic enzymes (e.g., **inducible nitric oxide synthase [iNOS]**), nitric oxide (NO) and metabolic byproducts (e.g., reactive oxygen species [ROS]) in response to pathological changes or various stimulants, including **LPS** and **interferon (IFN)-γ** (Dionisio-Santos et al., 2019). While the initial studies sought to categorize these cells into either proinflammatory or anti-inflammatory, the reality is that microglial phenotypes show greater diversity during development and pathology (Matcovitch-Natan et al., 2016).

Continued interactions of microglia with Aβ can also lead to an inflammatory response resulting in neurotoxicity. It has been reported that Aβ binds TLR4 and its co-activator CD14, polarizing microglia towards an inflammatory phenotype which promotes the release of proinflammatory cytokines like IL-1β, IL-6 and TNFα, as well as the chemokine CCL2 (Wu et al., 2022). As described above, these cytokines aid in the activation of more microglial cells and in the recruitment of other peripheral myeloid cells. In addition, microglia are a key component of the neurovascular complex (NVC) (Schaeffer & Iadecola, 2021) where they play an important role in angiogenesis and BBB function (Haruwaka et al., 2019). However, activated microglia may affect the integrity of the brain endothelial barrier directly and/or indirectly by increasing pro-inflammatory elements such as cytokines, chemokines and ROS.

Through rapid change in gene expression, these cells can react in response to surrounding perturbations. Potential changes in cell heterogeneity during neurodegeneration confound the distinction between composition and activity changes in each cell type. For example, some microglial markers such as the P2RY12 receptor or CD45 are altered in the context of AD pathology (Reed-Geaghan et al., 2020). Therefore, the use of techniques such as cell flow cytometry or immunohistochemistry, limited to identifying cell populations according to a small set of canonical cell-surface markers, might obscure the presence of additional microglia subtypes and overlook the dynamic diversity of these cells in the brain (Wang, 2021). Single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) technologies have been a bastion to the field of myeloid cell biology by revealing anticipated heterogeneous cell states and underlying molecular pathways within the CNS, mainly microglia, in the case of neurodegenerative diseases (Keren-Shaul et al., 2017). Transcriptomic studies have allowed delineation of microglia from macrophages and other immune cells as well as different microglia phenotypes (Keren-Shaul et al., 2017; Krasemann et al., 2017). Two independent studies using single-cell RNA analysis of microglial cells identified a common activated microglia phenotype associated with different brain diseases, which was defined as either disease-associated microglia (DAM) (Keren-Shaul et al., 2017) or microglia neurodegenerative phenotype (MGnD) (Krasemann et al., 2017). A

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common feature of both phenotypes is the down-regulation of homeostatic microglial genes such as P2ry12, Cx3cr1, Hexb or Tmem119, along with up-regulation of genes, including Trem2, Apoe, Itgax, Spp1 and Clec7a (Keren-Shaul et al., 2017; Krasemann et al., 2017). Further studies by scRNA-seq technology identified white matter-associated microglia (WAM) as a novel microglia state associated with white matter ageing (Safaiyan et al., 2021). Functionally, WAM are engaged in clearing degenerated myelin (Safaiyan et al., 2021).

Microglia are also capable of sensing inflammatory signalling molecules originating outside the CNS. From all these observations derives the possibility that peripheral inflammation can affect the progression of neurological disorders later in life, where microglia would be players in their pathogenesis.

Microglia: a neuroimmunomodulatory driver of dementia

In AD, microglial cells act as a double-edged sword. Due to their high plasticity, their balance in homeostasis can be readily disrupted under pathological conditions. As we will see, whereas these cells are involved in Aβ clearance, on the other hand, their excessive activation causes neurotoxicity and synaptic loss (Figure 4) (Kulkarni et al., 2022).

These cells perform several strategies to contain and clear Aβ pathology. They can surround Aβ plaques in a bid to isolate them from the rest of the parenchyma (Condello et al., 2015), express receptors that promote Aβ clearance and phagocytosis (Koenigsknecht & Landreth, 2004) and release enzymes which contribute to plaque degradation (Yang et al., 2011). Microglia surrounding plaques acquire an amoeboid morphology. As it will be discussed below, a disease-associated microglia (DAM) (Figure 4) was identified in the brain of AD mice and patients, next to Aβ plaques and with intracellular phagocytic Aβ particles in both mouse and human brain slices (Keren-Shaul et al., 2017). Others subtypes have also been described in AD including the early-response microglia (ERM) (Mathys et al., 2017), the interferon-response microglia (IRM) (Sala Frigerio et al., 2019) and the transiting-response microglia (TRM) (Sala Frigerio et al., 2019), although their roles still remain elusive. AD microglia also show modifications that give evidence of adaptive processes mediated by trained immunity (Haley et al., 2019).

In the case of PSCID, microglia have been implicated in BBB leakage and vascular remodelling following vascular injuries that occur in this pathology. The mechanisms by which microglia contribute to pathogenesis are multifactorial (Yang et al., 2022). Chemokines generated by endothelial cells after vascular injury (chemokine CCL5) attract microglia to the vessels, where they initially play a beneficial function in the maintenance of BBB integrity (Figure 4) (Haruwaka et al., 2019); however, due to sustained inflammation, microglia can switch from a protective to a detrimental phenotype. Increased BBB permeability also leads to the focal activation of microglia (Haruwaka et al., 2019). The activation of harmful microglia would lead to pro-inflammatory cytokine release and astrocytic end-feet and axon phagocytosis, aggravating BBB damage (Figure 4) (Yang et al., 2022). Apart from microglial effects in the acute post-stroke environment that can have an impact later in the chronic phase of the pathology, an increase of microglial activation has been observed in the ipsilateral distal regions, as well as in the contralateral hemisphere, at 3–4 weeks after injury in ischaemic stroke patients (Price et al., 2006). Similar results have been described in a mouse model of ischaemia (Kluge et al., 2019) as well as by neuroimaging in stroke patients (Thiel et al., 2010). Of note, a study using permanent MCAO in rats demonstrated that, although inflammation had ceased in the primary infarct site, an increased inflammatory response was observed in the ipsilateral thalamus 7 months following stroke (Walberer et al., 2014). This phenomenon, termed secondary neurodegeneration (SND), involves the progressive death of neurons in distal regions of the brain that are anatomically connected to the site of infarction, not only the thalamus but also the hippocampus and the basal ganglia (Abe et al., 2003). This process can be detected by neuroimaging techniques (Abe et al., 2003). It is likely that secondary neurodegeneration is associated with the concept of "inflammageing" and may be a key factor in the development of ongoing degeneration of neuronal tissue (Stuckey et al., 2021). Taken all these data together, it is clear that the role of microglia in the post-stroke neural environment is complex, with both beneficial and detrimental effects, and mediated by the high plasticity of these cells. Future research will be necessary to elucidate microglia dynamic functions in the progression of post-stroke secondary neurodegeneration and their relevance as modulators or therapeutic targets for stroke recovery. More specifically, given that neuroinflammation has been found to be a significant driver in the post-stroke secondary neurodegenerative process, a persistent neuroinflammatory response, which does not resolve after the initial insult, may play a key role in worsened long-term outcomes, specifically, the latter onset of PSCID (Stuckey et al., 2021).

3 | PHARMACOLOGICAL TARGETING OF PERIPHERAL MYELOID CELLS

In dementia, central immunity cells, especially microglia, have been well studied and extensively reviewed (reviewed by Romero-Molina et al., 2022; Silvin et al., 2022). Immunotherapy has gradually gained attention, in particular, antibody-mediated stimulation of the triggering receptor of myeloid cells 2 (TREM2), which is on the forefront of candidate therapeutic approaches (Lewcock et al., 2020). However, in this section, we will focus on two powerful pathways related to peripheral myeloid cells and dementia, NETosis, and TLR4 activation. In addition, other important pathways such as the **mCSF/CSF1R** axis and the **nucleotide-binding oligomerization domain–containing 2 receptors (NOD2)** in the context of AD have been extensively reviewed elsewhere (Pons & Rivest, 2022).

3.1 | NETs inhibition

The inhibition of NET formation could offer a novel therapeutic approach to limit the extensive damage caused by this mechanism in AD and PSCID.

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NET-targeted therapy has shown beneficial effects in disease animal models, such as those for systemic lupus erythematosus (SLE), atherosclerosis or rheumatoid arthritis (Khandpur et al., 2013; Knight et al., 2014). In the case of ischaemic stroke, the presence of NETs is critical in acute phase recanalization processes where the use of type I DNases (enzymes that promote the degradation of NETs) facilitates the recanalization of platelet-rich thrombi, a type of thrombus characteristic of patients resistant to the action of **tissue plasminogen activator (tPA)** (Peña-Martínez et al., 2019). Similarly, the presence of neutrophils and NETs seems to contribute to the microvascular, acute phase "non-reflow phenomenon" that, as mentioned above, consists of the non-reperfusion of distal tissues and small capillaries, even after successful recanalization of the occluded vessel by thrombolytics (El Amki et al., 2020). Finally, the involvement of neutrophils and NETs in revascularization processes at later stages of ischaemic stroke is noteworthy, as the increased presence of these elements correlates with a decrease in neovascularization and vascular repair (Kang et al., 2020). All these studies point to the idea that NET formation might contribute to PSCID and their inhibition would be a potential therapeutic target.

Evidence from animal models and human patients suggests that targeting NET components could be used to develop effective therapies for AD. However, the effects of blocking NET formation in animal models of AD have not yet been demonstrated and further studies are required to determine whether this approach has relevance. It would also be interesting to identify whether NETs induce the generation of autoantibodies in AD and whether they could constitute an AD biomarker (Manda-Handzlik & Demkow, 2019).

Finally, a recent study directly associates the presence of NETs in the perivascular space after *S. pneumoniae* infection with cerebral oedema formation by CSF accumulation. Degrading NETs by DNase treatment restored glymphatic transport and eliminated the increase in brain weight in rats (Pavan et al., 2021). Therefore, given the role of the glymphatic system in brain clearance of Aβ, NETs could be a promising target to prevent dysfunction leading to AD and, possible, to PSCID. So far we have focused on degradation of NETs by using deoxyribonuclease I (DNase I), which, since its first description in 2004 (Brinkmann et al., 2004), has been widely demonstrated as a promising therapy to pharmacologically target NETs. However, other drugs are also able to do so. In this context, disulfiram, an FDA-approved drug for treating alcohol addiction, has been recently demonstrated to efficiently block NET formation (Silva et al., 2021), and therefore is potentially useful for different pathologies involving NETs including thrombosis (Fuchs et al., 2010) and AD (Zenaro et al., 2015). In addition, a peptidylarginine deminase (PAD)-4 (PAD4) inhibitor, such as **Cl-amidine**, has been also demonstrated to inhibit NET formation, with a beneficial impact in the context of stroke (Peña-Martínez et al., 2019, 2022). As mentioned above, a key component found in abundance in NETs is neutrophil **elastase (NE)**, one of the primary enzymes stored in neutrophils granules. A highly selective and potent NE inhibitor, GW311616A, has been developed that could be orally administered to block chromatin decondensation (Macdonald et al., 2001), and has been demonstrated to significantly reduce atherosclerosis in a mouse model (Wen et al., 2018). MPO is another key component found in NETs; however, despite several efforts to develop MPO inhibitors, only molecules that attenuate and/or delay NET formation have been achieved (Metzler et al., 2011). Therefore, despite several compounds have been developed to target NETs by different approaches, DNase-I is still the most potential and most widely use.

Based on recent findings of the role of NET formation in the pathogenesis of various diseases, the potential use of NET inhibitors requires further studies to fully understand the regulation and balance of NET induction, inhibition and degradation without compromising the patient's immune defences (Chamardani & Amiritavassoli, 2022). For instance, the administration of NET inhibitors in immunocompromised patients should be carefully considered.

3.2 | Myeloid TLR4 receptor

Targeting TLRs has raised great interest for many diseases. As previously described, TLR4 is a transmembrane PRR of the catalytic receptors family that recognize pathogen-associated molecular patterns such as lipopolysaccharides (LPS), and damage associated molecular patterns, such as high mobility family protein box 1 (HMGB1) and Aβ (Alexander et al., 2021; Wu et al., 2022). In mice, as in humans, cells of myeloid origin exhibit the highest levels of TLR4 expression (Vaure & Liu, 2014).

Microglia, the main CNS cell type expressing TLR4, perform a double-edged role in AD pathogenesis. On the one hand, microglia may improve clearance of neurotoxic proteins, such as Aβ and its aggregates, through enhanced phagocytic and autophagic activity upon TLR4 activation (Tahara et al., 2006). On the other hand, following the disruption of microglial phagocytosis and degradation, the persistence of Aβ plaques and the release of inflammatory factors switch microglia to a proinflammatory phenotype related to inflammation, neuronal injury, and death (reviewed by Wu et al., 2022). This is supported by many reports that consider microglia the key cells in TLR4-mediated neuroinflammatory responses, and which may be involved in AD via the production of neurotoxic and pro-inflammatory mediators, such as IL-1β or inducible nitric oxide synthase (iNOS) (Vaure & Liu, 2014).

In the last few years, evidence have come up suggesting the presence of distinct neutrophil subsets in different pathologies such as infections, inflammation, cancer (Cuartero et al., 2013; Fridlender et al., 2009; García-Culebras et al., 2019) and in cardiovascular diseases (Adrover et al., 2019). TLR4 drives neutrophil reprogramming towards ageing, driven by the microbiota through the TLR pathway (Zhang et al., 2015). As we have previously stated, the lack of TLR4 on neutrophils can modulate its function and reprogram them to an alternative phenotype in brain ischaemia that confers a neuroprotective effect (García-Culebras et al., 2019) as the dynamics of these are modified and alter their ability to phagocyte, their capacity to form NETs and to produces ROS (Durán-Laforet et al., 2021). Thus, the study of different subsets of neutrophils could be also vital to implement therapies based on selective intervention on a certain phenotype in AD and PSD. Apart from neutrophils, as previously reviewed, platelets do

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also play a key role in the context of neurodegenerative disease and targeting these cells and, specifically platelet TLR4, could have an impact on cognitive impairment in both AD and PSCD.

In 2018, the protective effect of an ApToll, a TLR4-binding aptamer, against acute stroke in animal models was reported (Fernández et al., 2018). This molecule is especially interesting in the context of peripheral immune cells since the aptamer mainly binds to granulocytes (Fernández et al., 2018). The absence of toxicological effects and its safety profile (Completed Phase 1 clinical trial; NCT04742062) made it an ideal candidate for clinical positioning in neurological diseases therapy (Hernández-Jiménez et al., 2022). Notably, a phase Ib/IIa clinical trial has now demonstrated its efficacy in stroke patients (Hernández-Jiménez et al., 2023).

It is also important to extend the studies targeting TLR4 further in time, not limiting the study to the acute phase, since several pieces of evidence suggest a possible role of both TLR4 and circulating cells in the chronic stage. All those aspects should be considered in future investigations to achieve a more extensive vision of the implication and possible role of TLR4 as a therapeutic asset for AD and VD treatment. On the other hand, after stroke, a second phase takes place to repair the tissue. The so-called "remodelling phase" starts hours to days after the insult and shares some of the elicitors involved in the acute-harmful phase. TLR4 also plays an important role in this phase: inducing neurogenesis by promoting neuroblast migration and increasing the number of new cortical interneurons in the chronic phase of stroke (Moraga et al., 2014) or orchestrating the phagocytosis by microglia, which is of extreme relevance in stroke pathology (Leitner et al., 2019). On the other hand, brain inflammation may lead to opposing local and systemic effects. Suppression of systemic immunity by the CNS could protect the brain from additional inflammatory damage; however, it could increase the susceptibility to infection. Pneumonia and urinary tract infections are the most common complications in patients after stroke (Santos Samary et al., 2016). Of note, there is evidence of an association between these common infections and PSCID (Morton et al., 2020). Therefore, short half-life and/or cell-specific approaches should be used in order to reduce adverse effects that could occur after TLR4 antagonist administration, providing the opportunity of blocking the first acute phase, but neither interfering in the remodelling phase of inflammation nor increasing the possibility of infection after stroke.

4 | CONCLUSIONS AND PERSPECTIVES

It is clearly established that myeloid cells have an important role in the pathophysiology of AD and PSCID both peripherally and locally in the damaged brain. However, it is crucial to acknowledge that myeloid cell response could have opposite functions in the different stages of the pathologies and even in different subsets of cells. Hence the importance of the identification and characterization of myeloid cell subsets and their activation states, and how these states may determine AD and VD progression and outcome. The comprehension of these processes may pave the way to novel therapeutic avenues for the treatment of dementia.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos et al., 2021; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Beuve et al., 2021, Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Pawson, Southan, Davies, Boison et al., 2021; Alexander, Kelly et al., 2021).

AUTHOR CONTRIBUTIONS

Alicia García-Culebras, María Isabel Cuartero and María Ángeles Moro conceptualized the study. Ignacio Lizasoain and María Ángeles Moro were responsible for the funding acquisition. Alicia García-Culebras, María Isabel Cuartero and María Ángeles Moro contributed to the writing (original draft). Alicia García-Culebras, María Isabel Cuartero, Carolina Peña-Martínez, Ana Moraga, Sandra Vázquez-Reyes, Francisco Javier de Castro-Millán, Marta Cortes-Canteli, Ignacio Lizasoain and María Ángeles Moro contributed to the writing (review and editing). All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have not any potential conflict of interest in relation with this submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study (it is a review article).

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