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RECEIVED 24 September 2025
ACCEPTED 09 October 2025
PUBLISHED 22 October 2025

CITATION
Iyer AK, Moutinho M, Ayata P and Karahan H
(2025) Editorial: Myeloid cells as active players
in human neurodegenerative diseases.
Front. Neurosci. 19:1712394.
doi: 10.3389/fnins.2025.1712394

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Editorial: Myeloid cells as active players in human neurodegenerative diseases

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KEYWORDS

microglia, myeloid cells, Alzheimer's disease, Parkinson's disease, neurodegeneration, aging, biomarkers

Editorial on the Research Topic

Myeloid cells as active players in human neurodegenerative diseases

An emerging theme across various neurodegenerative diseases is the crucial role of myeloid cells, including brain-resident microglia as well as perivascular and border-associated macrophages, in driving neuroinflammation and contributing to disease progression (Zhang et al., 2023; Heneka et al., 2025). This Research Topic brings together up-to-date reviews and original research on how these immune cells shape disease risk, progression, and modulate aging-related changes within the brain. Additionally, the collected work highlights the emerging potential of myeloid biomarkers as diagnostic or monitoring tools for neurodegenerative diseases.

Aging is a significant risk factor for all neurodegenerative diseases (Hou et al., 2019). In addition to neuronal changes, brain aging involves microglia-specific cellular processes, including impaired homeostatic functions, chronic inflammation, cellular dystrophy and senescence, as well as lipid droplet accumulation (Antignano et al., 2023). The original research article by Assale et al. investigates how *SIGLEC11*, a recently identified Alzheimer's disease (AD) risk gene (Bellenguez et al., 2022) and exclusively expressed in microglia, affects the functions of microglia and macrophages in the context of aging. The authors demonstrate that overexpression of *SIGLEC11* in aged mice reduces the number of activated microglia, as well as inflammatory and oxidative stress markers and lipid droplet accumulation. Importantly, *SIGLEC11* overexpression prevented the dopaminergic neuron loss in the substantia nigra that typically accompanies aging. This study identifies *SIGLEC11* as a crucial microglia-specific brake on age-associated neuroinflammatory processes, highlighting that microglial immune checkpoints can be leveraged to promote neuronal survival and health. This research also opens the possibility of testing *SIGLEC11* ligands as potential therapies to slow neurodegeneration in aging brains. While this research avenue is promising, further investigation is warranted for a deeper understanding of how *SIGLEC11* interacts with other microglia-specific AD risk factors and key regulators, such as *TREM2*, *MS4A4A*, and *CD33* (McQuade and Blurton-Jones, 2019), across different stages of aging and disease progression.

In addition to AD, there is a growing appreciation for the role of microglia in Parkinson's disease (PD) (Kam et al., 2020). The mini-review article by Trainor et al. presents evidence supporting microglia as both responders and contributors to PD pathogenesis and progression, in contrast to the historical perspective of microglia as secondary responders to the neurodegeneration process. The authors discuss the impact of PD risk genes (*SNCA*, *PRKN*, *PINK1*, *PARK7*, *GBA1*, *LRRK2*, and *VPS35*) on key microglial functions, including vesicular trafficking, lysosomal machinery, and mitochondrial function. While these processes have traditionally been studied from a neuron-centric perspective (Kam et al., 2020), the authors emphasize ongoing research efforts to delineate the diversity of cell types involved and the cellular functions that go awry. Cell-type-specific manipulation of disease risk genes, along with the broader use of disease-specific human stem cell-based models, is highlighted to gain a more comprehensive understanding of the mechanisms underlying neurodegeneration.

The immune system's involvement in neurodegeneration is not limited to microglia. Several emerging studies implicate a role of conventional (CD4+ and CD8+) and invariant (NKT and MAIT) T cells in neurological diseases (Wyatt-Johnson et al., 2024). However, very few studies exist on the *a priori* steps of antigen presentation, a requisite for T cell activation in the context of neurodegeneration. Afify et al. discuss the limited scientific literature investigating the role of classical (MHC class I and II) and non-classical (CD1d and MR1) antigen-presenting molecules in neurological diseases, such as AD and related dementias, Amyotrophic Lateral Sclerosis, Multiple Sclerosis (MS), and PD. The authors emphasize the importance of advancing this research area to better understand T cell involvement in neurodegeneration and to develop readily accessible, peripheral immune-centric therapeutic approaches aimed at modulating neuroinflammation.

Myeloid cells have garnered significant attention not only for their influence on disease pathogenesis but also for their potential as biomarkers for diagnosing or monitoring neurodegenerative diseases (Noh et al., 2025). Building on this perspective, Kodosaki et al. review the role of the myeloid branch of hematopoietic stem cells, including monocyte, macrophage, and dendritic cell lineages, granulocytes, such as neutrophils, erythrocytes/platelets, and the brain-resident innate immune sentinels—microglia, across three major neurodegenerative diseases: AD, PD, and MS. The authors highlight the potential of leveraging myeloid biomarkers as prognostic, diagnostic, or monitoring tools for these diseases. The review also highlights the gaps, challenges, and recent advances in methodologies to improve biofluid and imaging myeloid biomarker research for neurological diseases, emphasizing the variability within and across different neurodegenerative diseases.

From novel myeloid biomarkers and antigen presentation pathways to the impact of PD risk genes on microglia biology, and the striking discovery of SIGLEC11 as a crucial microglia receptor that limits neuroinflammation and neuronal loss during aging, these articles collectively highlight novel and promising research directions for diagnosis, therapy, and mechanistic understanding of neurodegenerative diseases. Together, they underscore the growing

importance of studies focusing on myeloid cells to gain insights and ultimately modulate neurodegeneration.

Author contributions

AI: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. PA: Writing – original draft, Writing – review & editing. HK: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by 1R01AG085404 (PA), The Professional Staff Congress (PSC) of CUNY (PA), Alzheimer's Association AARG-22-974642 (PA), Alfred P. Sloan Foundation JFRASE (PA), CurePSP Pathway and Pipeline Research Grant 703-2025-02 (AI), and Washington University in St. Louis Knight Alzheimer Disease Research Center Research Education Component (REC) Scholar Program through NIH Grant Number P30 AG066444 (AI).

Acknowledgments

We thank the authors for contributing to this Research Topic and our fellow co-editors for their support.

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