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REVIEW OPEN ACCESS

The Role of Disease-Associated Microglia in Neurodegenerative Disease: A Review

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Abstract

Microglia are tissue-resident macrophages of the central nervous system and peripheral nervous system that mediate homeostasis, surveillance and clearance of foreign particles, and neuroinflammation. Advancements in single-cell RNA sequencing analyses have enabled the identification of a novel subset of microglia, termed disease-associated microglia (DAM), which localize to sites of neurodegeneration and exhibit a unique transcriptional and functional signature. This review examines characteristics of DAM, activation patterns, and specific implications for DAM in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Sources were identified from the NCBI PubMed database through a database search as well as manual identification. Keywords such as "disease-associated microglia" and "neurodegenerative" were incorporated into the search method and results were compiled into a literature review. Results show a consistent shift in gene expression in DAM, including downregulation of homeostatic genes, such as *P2ry12*, *Cx3cr1*, and *Tmem119*, and upregulation of phagocytic and metabolic genes, such as *Apoe*, *Lpl*, *Trem2*, and *Itgax*. Additionally, DAM recognize neurodegeneration-associated molecular patterns (NAMPs) across multiple pathologies and may become activated in a two-step sequential process, in which Triggering receptor expressed on myeloid cells 2 (TREM2) is required for full transcriptional activation. Future research is necessary to understand the mechanism of DAM contribution to the progression or amelioration of neurodegeneration, offering potential insights for druggable targets.

Keywords: microglia; disease-associated microglia; neurodegeneration; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; multiple sclerosis

Introduction

Microglia are tissue-resident macrophages of the central nervous system (CNS) and peripheral nervous system (PNS). Derived from myeloid precursors, they comprise 5-12% of the brain's glial cell population [1]. Microglia have three main functions: a homeostatic role in synaptic pruning and remodeling, a surveillance role that involves actively scanning for and phagocytosing environmental and cellular debris, and an innate immune role that initiates neuroinflammation in response to signs of damage or pathogenic breach [2]. Dysregulation of any of these three functions can initiate or propagate the process of neurodegeneration [2].

It is known that microglia influence the progression of a broad range of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). AD is associated with an accumulation of extracellular deposits of amyloid-beta (Aβ) and intracellular neurofibrillary tangles that can contribute to widespread neurodegeneration in the cerebral cortex, hippocampus, and forebrain structures [3]. PD is a motor neurodegenerative disease marked by progressive dopaminergic neuronal depletion in the substantia nigra and α-synuclein plaque aggregation, leading to motor symptoms such as resting tremor, bradykinesia, postural instability, and dystonia [3]. In AD and PD, microglial phagocytosis contributes to the efficient clearance of Aβ and α-synuclein plaques, respectively. However, excessive or prolonged stimulation of microglia may also lead to the induction of chronic neuroinflammation, potentially accelerating neurodegeneration [3]. Whether microglia preferentially polarize to the canonical M1 (pro-inflammatory) phenotype or the M2 (anti-inflammatory) phenotype also plays an important role in facilitating the neurodegenerative process. ALS and MS are both considered demyelinating diseases of the CNS that lead to significant motor deficits, including muscle weakness, loss of coordination, and paralysis [4, 5]. In ALS, the release of pro-inflammatory factors from M1 microglia contributes to motor neuron death while promoting the recruitment of peripheral immune cells to sites of neurodegeneration [4]. In MS, M2 microglia are involved in remyelination processes by expressing anti-inflammatory molecules, phagocytosing neuronal debris,

and promoting the recruitment and differentiation of myelin-generating oligodendrocytes. However, M1 microglia may promote demyelination through antigen presentation and the secretion of pro-inflammatory factors [5]. Therefore, characterizing how distinct microglial subtypes contribute to the process of neurodegeneration holds implications for improved understanding of neurodegenerative diseases.

Due to cellular heterogeneity in sites of neurodegeneration, defining the role of distinct microglial subsets in mediating neurodegenerative processes has proven to be a challenge [6]. However, recent advancements in single-cell RNA sequencing (sc-RNA-seq) analyses have enabled the identification of a novel subset of microglia, termed disease-associated microglia (DAM) [6]. DAM are found preferentially at sites of neurodegeneration and exhibit a unique transcriptional and functional signature relative to other microglial subsets [6]. This review will explore the role of this unique microglial subset in various neurodegenerative diseases, focusing on their capacity to modulate neurodegeneration as well as their potential neuroprotective role.

Methods

Literature Search Strategy

We conducted a review on studies investigating the role of DAM in neurodegenerative diseases. A literature search was performed using the National Center for Biotechnology Information (NCBI) PubMed database based on inclusion of the following keywords: “disease-associated microglia” OR “DAM” AND “neurodegenerative”. A total of 218 articles were retrieved from the database. Any duplicate articles or preprint articles were electronically removed before screening.

Article Screening

Using advanced filter settings, articles that were published prior to January 2017 or not written in the English language were excluded. A total of 207 articles were then evaluated for eligibility based on full-text review. Publications that did not directly discuss the involvement of DAM in neurodegenerative diseases or were not open access were excluded. No exclusions were made based on methodology or the type of neurodegenerative disease examined. Additionally, relevant articles identified manually by citation searching were included after screening for the above-described eligibility criteria. Full-text reviews were performed by two reviewers independently, with disagreements resolved by group discussions. A formal critical appraisal was not performed for this review. A total of 129 articles were included in the review (Figure 1).

Data Extraction and Results Synthesis

Articles eligible for data extraction were then compiled with the following information: first and last author names, year of publication, title of the article, abstract, study methodology, and specific neurodegenerative disease(s) examined, if any. The results were then described in a narrative summary.

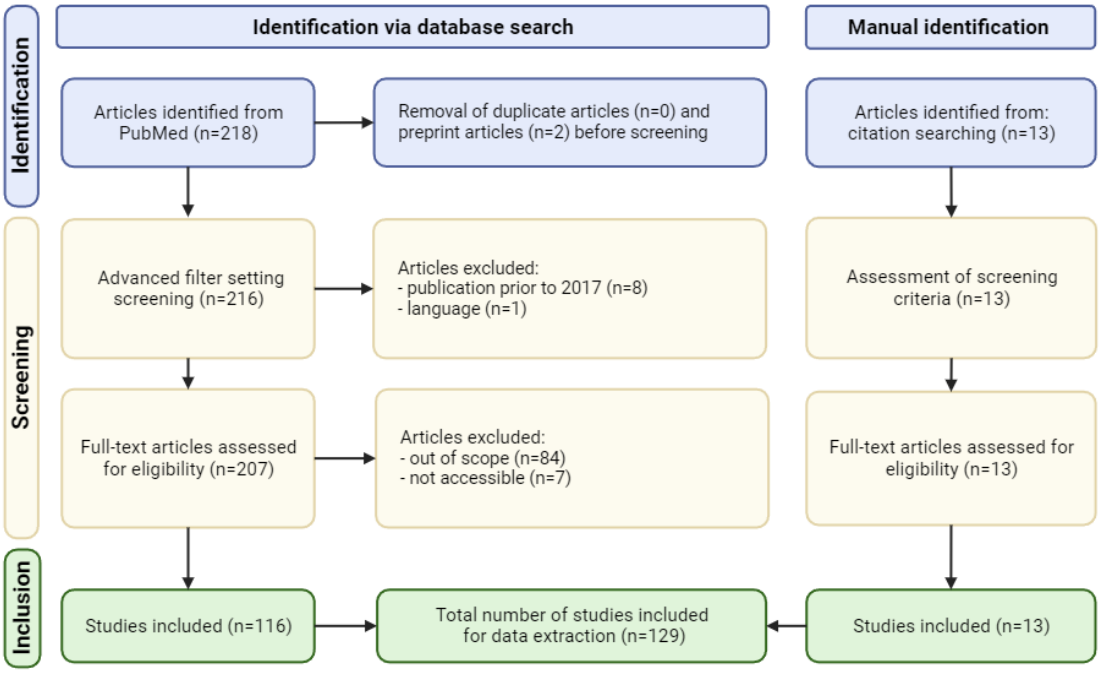

Figure 1. Flow chart of article selection procedure. Figure was made with BioRender.com.

Results

The Identification and Characterization of DAM

In 2017, Keren-Shaul et al. used sc-RNA-seq to identify a distinctive microglial state in the immune cell population of a mouse model of AD (5XFAD) not found in the wild-type (WT) background [6]. This identified microglial subset was termed DAM and was observed to display unique alterations in gene expression relative to other microglia subsets [6]. In particular, microglia homeostatic genes, such as *P2ry12*, *Cx3cr1*, and *Tmem119*, were downregulated, whereas AD risk genes, including *Apoe*, *Lpl*, *Trem2*, and *Itgax*, were upregulated by DAM [6]. Importantly, this microglial subset was primarily detected in the vicinity of Aβ plaques and was not observed in non-plaque areas [6]. Friedman et al. identified a similar microglia subset in the Tau P301L and Tau P301S mouse models of tauopathy, showing downregulation of *P2ry12* and upregulation of *Apoe*, *Lpl*, *Itgax*, *Cst7*, and *Axl*, among others [7]. Further, Cohn et al. also found a significant reduction of *P2ry12* and *Tmem119* and upregulation of *Trem2* in extracellular vesicles released by microglia derived from human AD brains [8]. Keren-Shaul et al. also performed scRNA-seq on a transgenic mouse model of ALS and found microglia that displayed an expression profile highly similar to the DAM profile they identified in the 5XFAD mice [6]. Downregulation of *P2ry12* and *Cx3cr1* and upregulation of *Trem2*, *Tyrobp*, *Lpl*, and *Cst7* were identified in these microglia [6]. Similarly, Krasemann et al. identified *P2ry12*, *Cx3cr1*, and *Tmem119* downregulation and *Apoe*, *Itgax*, and *Axl* upregulation on microglia isolated from an experimental autoimmune encephalomyelitis (EAE) model of MS [9].

DAM Two-Step Activation Mechanism

Keren-Shaul et al. next identified potential regulators of DAM activation. Three distinct microglia groups were found with varying expression patterns of the DAM markers they had previously identified in the 5XFAD mouse model. These microglia groups were termed homeostatic microglia, stage 1 DAM, and stage 2 DAM [6]. Interestingly, Keren-Shaul et al. found that DAM activation is a two-step sequential process, wherein homeostatic microglia transition into stage 1 DAM and subsequently stage 2 DAM [6]. They did not identify any microglia expressing the stage 2 DAM program without the stage 1 DAM program, supporting that the stage 1 DAM transition is required for further activation of the stage 2 DAM program. The transition from homeostatic microglia to stage 1 DAM was characterized by reduced expression of microglia homeostatic genes *P2ry12*, *Cx3cr1* and *Tmem119* and upregulation of AD-associated genes *Apoe*, *Tyrobp*, and *Ctsd* [6]. Further activation of the microglia into stage 2 DAM involved upregulation of lipid metabolism and phagocytic genes, such as *Cst7* and *Lpl*, as well as *Trem2*, *Axl*, *Cd9*, and *Itgax* genes [6]. Importantly, the transition from stage 1 DAM to stage 2 DAM was observed to occur in a *Trem2*-dependent manner, whereas the transition from homeostatic microglia to stage 1 DAM was determined to occur in a *Trem2*-independent manner [6].

The Role of TREM2 in DAM Activation and Function

Since Keren-Shaul et al. first described the DAM two-step activation mechanism, analyses of which microglia genes are activated by *Trem2*-independent and *Trem2*-dependent pathways have yielded conflicting results. Like Keren-Shaul et al., Friedman et al. also observed a two-step process of DAM activation in *Trem2*-deficient 5XFAD mice. However, in contrast to Keren-Shaul et al., *Cd9* upregulation showed *Trem2* independence and *P2ry12* downregulation showed *Trem2* dependence [6, 7]. Moreover, Krasemann et al. profiled brain microglia from an AD mouse model (APP-PS1, overexpressing mutated genes for human amyloid precursor protein and presenilin 1) deficient in *Trem2* and found *P2ry12*, *Tmem119*, *Cx3Cr1*, *Tgfbr1*, *Tgfb1*, *Mef2a*, and *Mertk* downregulation showed *Trem2* independence, whereas *Trem2*, *Axl*, *Csf1*, *Itgax*, and *Apoe* upregulation showed *Trem2* dependence [9].

Interestingly, Krasemann et al. also found that the microglia phenotypic switch from a homeostatic to neurodegenerative phenotype is mediated by TREM2 and Apolipoprotein E (ApoE) in mouse models of ALS (SOD1) and AD (APP-PS1) [9]. Krasemann et al. demonstrated that homeostatic microglia migrate toward apoptotic neurons and subsequently upregulate *Apoe* after *Trem2*-mediated phagocytosis of apoptotic neurons. In turn, *Apoe* suppresses homeostatic genes, including *P2ry12* and *Tmem119*, as well as TGF-β signaling [9]. *Trem2* deletion in SOD1 and APP-PS1 mice resulted in *Apoe* downregulation and restoration of these homeostatic genes [9]. Leyns et al. found a similar neuroprotective role in which *Trem2* deficiency was found to attenuate neuroinflammation and tau-mediated neurodegeneration in a mouse model of tauopathy [10]. Indeed, cortical tissue derived from tau-transgenic mice deficient in *Trem2* were found to have significantly lower *Apoe* and *Cst7* transcripts relative to WT tau-transgenic mice [10].

DAM and Neurodegeneration-Associated Molecular Patterns

The signal that initiates the transition of homeostatic microglia into stage 1 DAM is still poorly understood. In 2018, Deczkowska et al. proposed a model by which the induction of the DAM phenotype is driven by neurodegeneration-associated molecular patterns (NAMPs) that accumulate in various neurodegenerative conditions [11]. NAMPs include components of neural tissue damage, such as neuronal apoptotic bodies, myelin debris, and lipid or protein aggregates [11]. Deczkowska et al. proposed that NAMPs generally follow the pathogen recognition paradigms of pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) [11]. That is, homeostatic microglia recognize NAMPs by a specific set of

constitutively expressed receptors, such as TREM2 and purinergic receptors, which triggers their transition into DAM. Induction of the DAM phenotype by NAMPs is concurrent with an increase in phagocytic activity [11].

DAM in Alzheimer's Disease

Like conventional microglia in AD, DAM also respond specifically to Aβ plaques. For instance, Keren-Shaul et al. localized DAM activity to cortical regions affected by Aβ plaques in 5XFAD and APP/PS1 mouse models, with no DAM activity in other regions such as the cerebellum [6, 11]. These findings have been validated in human AD postmortem brains, in which microglia with DAM-like profiles were shown to co-localize with Aβ plaques [6, 7, 11]. The novel transcriptional profile displayed by DAM, namely reduced expression of homeostatic microglial genes (*P2ry12*, *P2ry13*, *Cx3cr1*, *CD33*, and *Tmem119*) and upregulation of AD-risk genes (*Apoe*, *Ctsd*, *Lpl*, *Tyrobp*, and *Trem2*), was originally identified in these AD mouse models [11]. As a result of these transcriptional differences, DAM in AD typically display greater activation of lysosomal, phagocytic, and lipid metabolism pathways. Additionally, Galectin-3, a β-galactoside-binding secreted protein, has been explored as a marker of DAM transition in AD, among other neurodegenerative diseases. In DAM, Galectin-3 is upregulated, and is capable of interaction with TREM2 and Toll-like receptor 4 (TLR4) receptors, which may indicate its potential function as a NAMP [12, 13]. Zhao et al. also demonstrated that Aβ may serve as a NAMP for TREM2 to induce clearance of Aβ plaques and TREM2-dependent microglial activation [14]. Indeed, *Trem2*-deficient microglia showed significantly reduced Aβ degradation and attenuated migration and cytokine release [14].

DAM in Parkinson's Disease

Normal microglia respond to degenerating neurons by polarization towards the classically activated M1 phenotype, while exposure to α-synuclein can facilitate the release of pro-inflammatory cytokines and reactive oxygen species. Microglia have also been shown to mediate both cell-to-cell transfer and clearance of α-synuclein [15, 16]. The current literature suggests that DAM exist in PD pathology, responding to NAMPs in the form of α-synuclein aggregates, and share many of the same DAM markers first identified in AD mouse models. There are also shared transcriptomic signatures between DAM in AD and PD brains, including enriched expression of *Apoe*, *B2M*, and *Tyrobp* [17]. Bido et al. found a DAM-like phenotype in mouse models of PD that co-localized with α-synuclein aggregates and neuronal death in the substantia nigra [18]. The transcription profile they identified included suppression of homeostatic microglial genes (*Mef2a*, *Csf1r*, *Mertk*, *Tgfbr1*, and *Jun*) and upregulation of genes associated with the complement system, major histocompatibility complex (MHC) class II, pro-inflammatory pathways, glycolytic pathways, and *Apoe* [18]. Thus, DAM in PD exhibit similarities with those in AD, but lack firmly established PD-specific markers.

DAM in Amyotrophic Lateral Sclerosis

In the seminal paper of Keren-Shaul et al., sc-RNA-seq analysis of the cells from the spinal cords of SOD1 mice revealed a distinct population of microglia characterized by upregulation of *Trem2*, *Tyrobp*, *Lpl*, and *Cst7* and downregulation of *P2ry12* and *Cx3cr1*. These transcriptional changes are similar to the DAM profile observed in the AD mouse model from the same study. Keren-Shaul et al. also found that the percentage of DAM relative to CD45+ cells of the spinal cord increased from 6% at early disease to nearly 30% at late disease stage [6]. Moreover, there are conflicting findings regarding the relationship between TDP-43 protein aggregates, which are associated with ALS pathology, and induction of DAM transition. Xie et al. found that TDP-43 interaction with microglia caused downregulation of homeostatic genes *P2ry12* and *Tmem119* in microglia. In contrast, there was no change in the expression levels of these genes after *Trem2*-knockout microglia contact with TDP-43 [19]. Further, *Trem2*-deficient mice had significantly more TDP-43 accumulation relative to WT mice [19]. Therefore, *Trem2* deficiency may be a mechanism by which the microglia to DAM transition is inhibited, locking microglia in a homeostatic state despite the presence of TDP-43, thus leading to an accumulation of TDP-43. However, these results conflict with those of Spiller et al., who observed minimal changes in homeostatic microglial gene expression after TDP-43 contact with WT microglia of a TDP-43 model of ALS [20]. Only upon TDP-43 removal did microglia show DAM-like transcriptional profiles, including elevated expression of *Apoe*, *Lpl*, *Ctsb*, and *Itgax*.

DAM in Multiple Sclerosis

Myelin and axonal debris from demyelination may act as TREM2-dependent NAMPs for DAM activation. For instance, following cuprizone-induced demyelination, Poliana et al. found that *Trem2*-knockout microglia failed to increase expression of genes involved in phagocytic uptake of myelin debris (*Axl*), and lipid metabolism (*Apoe*, *Apoc1*, *Lpl*, and *Ch25h*), unlike WT microglia. Accordingly, TREM2 deficiency was associated with impaired clearance of damaged myelin and reduced oligodendrocytes, which in turn mediate remyelination [21, 22]. Moreover, Spleen tyrosine kinase (SYK), a mediator of multiple intracellular signaling pathways, including those downstream to TREM2, may also play a role in DAM transition. Ennerfelt et al. found that deficiency of the *Syk* gene prevents the induction of DAM transcriptional changes in an EAE mouse model, implicating it as a potential factor in abnormal DAM responses. Similar to TREM2 deficiency, *Syk* deficiency was associated with myelin debris accumulation and impaired oligodendrocyte proliferation in response to

cuprizone-induced demyelination [23]. In an EAE mouse model of MS, the distinction between a cluster of microglia characterized by loss of homeostatic genes and a cluster characterized by upregulation of inflammatory genes has been identified, consistent with the DAM-like transcriptomic changes observed in AD and ALS models [9]. Importantly, in addition to the DAM-like transcriptional changes common to AD, PD, and ALS models, EAE models exhibit a DAM profile that is differentiated by a greater skew towards an inflammatory DAM phenotype [21]. For example, EAE-specific changes include increased inflammatory signaling, through Nuclear factor kappa B (NF-κB), Mitogen-activated protein kinase (MAPK), and cAMP response element binding protein (CREB) pathways, as well as downregulation of CD14 and upregulation of MHC class II and Sca1 [21]. Consistent with this proinflammatory shift, Jordão et al. identified four transcriptionally distinct subsets of DAM in EAE mice [24]. The most inflammatory DAM subsets strongly downregulated several core microglial genes, such as *P2ry12*, *Tmem119*, and *Selplg*, and up-regulated *Ly86* [24, 25]. ApoE signaling has also been implicated in MS. At peak EAE, Krasemann et al. found that DAM exhibited the highest expression of *Apoe* and an inability to suppress T-cell proliferation, unlike non-DAM microglia. Interestingly, EAE mice with *Apoe*-knockout microglia re-gained the ability to suppress T-cell proliferation at peak EAE [9].

Discussion

Since the initial discovery of DAM in the 5XFAD mouse model of AD by Keren-Shaul et al., further validations across diverse models including tauopathy, ALS, PD, and MS have reinforced the existence of DAM-like profiles in various neurodegenerative conditions. DAM express a transcriptional signature characterized by the downregulation of homeostatic microglial genes (*P2ry12*, *Tmem119*, *Cx3cr1*, *Csf1r*, *Mertk*) and upregulation of inflammatory, phagocytic, and lipid metabolism genes (*Apoe*, *Itgax*, *Ctsd*, *Lpl*, *Axl*, *Tyrobp*, *Trem2*) [6]. The upregulation of genes involved in lipid metabolism and phagocytosis likely corresponds to the increased demand for clearance of protein aggregates and cellular debris associated with neurodegenerative diseases, including Aβ, α-synuclein, TDP-43, and myelin debris.

The loss of homeostatic microglial function is thought to be a key factor in triggering and sustaining inflammatory responses within the CNS. For instance, the homeostatic gene *P2ry12* codes for a purinergic receptor that recognizes extracellular ADP or ATP [26]. ADP and ATP microgradients are released by apoptotic cells and serve as 'find me' signals to promote microglial chemotaxis towards sites of necrotic and apoptotic cells. Thus, it is possible for homeostatic microglia to migrate toward these stressed regions by P2RY12-mediated chemotaxis and subsequently initiate transition into DAM. DAM transition would lead to downregulation of *P2ry12*, which is thought to maintain microglia at sites of neuroinflammation [26]. The exact role of purines and other nucleic acid residues in DAM activation, and their potential to be NAMPs for purinergic receptors like *P2ry12*, remains to be further explored.

Concurrent with the loss of homeostatic genes, the transition from homeostatic microglia to stage 1 DAM was also found to involve upregulation of several known AD genetic risk factors such as *Apoe*, *Ctsd*, *Lpl*, *Tyrobp*, and *Trem2*. TREM2 and TYRO protein tyrosine kinase-binding protein (TYROBP) are thought to form a signaling complex that recognizes ApoE, Aβ, and neuronal debris. In turn, initiation of the TREM2 signal transduction pathway leads to the recruitment of SYK, transcription of *Tyrobp* and *Apoe*, and ultimately results in homeostatic microglia transition to DAM [27]. TYROBP can also act as a downstream adaptor for microglial receptors other than TREM2, including SIRP1β, CD33, CR3 [27]. Therefore, it is possible that TYROBP complexes can sense ApoE or Aβ and drive the phenotypic switch to DAM, independently of TREM2. This model aligns with the findings of Keren-Shaul et al., who found that stage 1 DAM express *Tyrobp* and *Apoe* in a *Trem2*-independent manner, and Audrain et al. who found that microglial Aβ sensing followed by upregulation of *Tyrobp* and *Apoe* is preserved in *Trem2*-deficient mice [6, 28]. Conflicting results were presented by Krasemann et al., showing that genetic targeting of *Trem2* suppressed the ApoE pathway and restored homeostatic microglial genes, and that the TREM2-ApoE signaling pathway is necessary for the switch from a homeostatic to neurodegenerative phenotype [9]. Parhizkar et al. similarly reported that the absence of functional TREM2 significantly reduces ApoE accumulation in Aβ plaques [29]. In light of these studies, it has been proposed that activation of TYROBP-ApoE signaling could be the initiating step in the transformation of homeostatic microglia to an early *Trem2*-independent DAM phenotype, which Keren-Shaul et al. initially described as stage 1 DAM. TREM2 would then become critical for the transition of stage 1 DAM to the fully activated stage 2 DAM [17, 28].

The extent of transcriptional and phenotypic differentiation in DAM across pathologies remains debated. For instance, some regard the DAM phenotype as a common microglial program in response to neurodegenerative disease, regardless of the disease etiology and types of NAMPs present [11, 30]. However, others argue that considerable heterogeneity in DAM profiles and responses may arise due to variations in disease stage, activation time-frames, NAMP burden and type, and individual patient differences [31]. A recent example was provided by Jay et al., where TREM2 deficiency was found to reduce amyloid pathology early but increase it later in disease stage [32]. Furthermore, while DAM-like profiles were found across all neurodegenerative diseases investigated in this study, distinct disease-specific DAM profiles have also been recognized. For instance, using

single-nucleus transcriptome comparison of AD and PD striata, Xu et al. identified common microglia activation-associated genes shared by both conditions, irrespective of the brain region studied. However, they also identified regional differences in microglia activation-associated gene expression, which linked the microglia to disease-specific pathologies [17]. Likewise, Voet et al. found that EAE models of MS exhibit a more inflammatory DAM profile relative to models of AD, PD, and ALS [21]. Future experiments utilizing sc-RNA-seq analyses will assist in understanding how DAM responses vary within and between different neurodegenerative diseases.

Lastly, our findings provide support for the model of DAM induction initially proposed by Deczkowska et al., in which microglia recognize NAMPs by a specific set of receptors across various neurodegenerative diseases. Potential NAMPs may include Aβ plaques in AD, α-synuclein in PD, TDP-43 in ALS, and myelin and axonal debris in MS. Further evidence of the interactions between NAMPs and their potential receptors, such as TYROBP and TREM2, throughout DAM activation is needed.

This review is not without limitations. The term "disease-associated microglia" was introduced after 2017 by Keren-Shaul et al. [6] Given that this was one of the keywords of our search strategy, we could have potentially excluded studies that discussed DAM-like profiles without explicitly using the term “DAM” prior to this publication. Also, the fact that our study compared results across multiple different animal and human models may have limited the robustness of our conclusions, as the generalizability of the observed results of each respective study are variable across pathologies. Finally, the exclusion of articles that were not open access may limit the comprehensiveness of our findings.

Conclusions

This review reinforces the growing body of literature that supports the importance of microglia in neurodegenerative disease. It also highlights the dual nature of DAM, showcasing their potential in mitigating neurodegenerative damage while also posing the risk of immune dysregulation and tissue harm. However, the current research does not agree whether microglia to DAM transition ameliorates or worsens the progression of neurodegeneration. Therefore, despite the identification of a transcriptionally distinct subset of microglia that could offer novel therapeutic targets, further research is essential to identify more specific correlates of DAM transition to disease outcomes before establishing DAM-directed therapeutics.

List of Abbreviations Used

Aβ: amyloid-beta
AD: Alzheimer’s disease
ALS: amyotrophic lateral sclerosis
ApoE: apolipoprotein E
CNS: central nervous system
CREB: cAMP response element binding protein
DAM: disease-associated microglia
DAMP: damage-associated molecular pattern
EAE: experimental autoimmune encephalomyelitis
MAPK: mitogen-activated protein kinase
MHC: major histocompatibility complex
MS: multiple sclerosis
NAMP: neurodegeneration-associated molecular pattern
NCBI: National Center for Biotechnology Information
NF-κB: nuclear factor kappa B
PAMP: pathogen-associated molecular pattern
PD: Parkinson’s disease
PNS: peripheral nervous system
sc-RNA-seq: single-cell RNA sequencing
SYK: spleen tyrosine kinase
TLR4: toll-like receptor 4
TREM2: triggering receptor expressed on myeloid cells 2
TYROBP: TYRO protein tyrosine kinase-binding protein
WT: wild-type

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval or participant consent because the study took the form of a literature review.

Authors' Contributions

VL: conceptualized and charted out the study, collected and analyzed data, drafted and revised the manuscript, and gave final approval of the version to be published.
MAS: conceptualized and charted out the study, collected and analyzed data, drafted and revised the manuscript, and gave final approval of the version to be published.

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References

[1] Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science. 2010 Nov 5;330 (6005):841-5. http://doi.org/10.1126/science.1194637
[2] Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. Nat Neurosci. 2018 Oct;21(10):1359-1369. http://doi.org/10.1038/s41593-018-0242-x

[3] Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. Annu Rev Immunol. 2017 Apr 26;35:441-468. http://doi.org/10.1146/annurev-immunol-051116-052358
[4] Frakes AE, Ferraiuolo L, Haidet-Phillips AM, Schmelzer L, Braun L, Miranda CJ, et al. Microglia induce motor neuron death via the classical NF-κB pathway in amyotrophic lateral sclerosis. Neuron. 2014 Mar 5;81(5):1009-1023. http://doi.org/10.1016/j.neuron.2014.01.013
[5] Luo C, Jian C, Liao Y, Huang Q, Wu Y, Liu X, et al. The role of microglia in multiple sclerosis. Neuropsychiatr Dis Treat. 2017 Jun 26;13:1661-1667. http://doi.org/10.2147/NDT.S140634
[6] Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, et al. A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. Cell. 2017 Jun 15;169(7):1276-1290.e17. http://doi.org/10.1016/j.cell.2017.05.018
[7] Friedman BA, Srinivasan K, Ayalon G, Meilandt WJ, Lin H, Huntley MA, et al. Diverse Brain Myeloid Expression Profiles Reveal Distinct Microglial Activation States and Aspects of Alzheimer's Disease Not Evident in Mouse Models. Cell Rep. 2018 Jan 16;22(3):832-847. http://doi.org/10.1016/j.celrep.2017.12.066
[8] Cohn W, Melnik M, Huang C, Teter B, Chandra S, Zhu C, et al. Multi-Omics Analysis of Microglial Extracellular Vesicles From Human Alzheimer's Disease Brain Tissue Reveals Disease-Associated Signatures. Front Pharmacol. 2021 Dec 2;12:766082. http://doi.org/10.3389/fphar.2021.766082
[9] Krasemann S, Madore C, Cialic R, Baufeld C, Calcagno N, El Fatimy R, et al. The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. Immunity. 2017 Sep 19;47(3):566-581.e9. http://doi.org/10.1016/j.immuni.2017.08.008
[10] Leyns CEG, Ulrich JD, Finn MB, Stewart FR, Koscal LJ, Remolina Serrano, et al. TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. Proc Natl Acad Sci U S A. 2017 Oct 24;114(43):11524-11529. http://doi.org/10.1073/pnas.1710311114
[11] Deczkowska A, Keren-Shaul H, Weiner A, Colonna M, Schwartz M, Amit I. Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration. Cell. 2018 May 17;173(5):1073-1081. http://doi.org/10.1016/j.cell.2018.05.003
[12] García-Revilla J, Boza-Serrano A, Espinosa-Oliva AM, Soto MS, Deierborg T, Ruiz R, de Pablos RM, Burguillos MA, Venero JL. Galectin-3, a rising star in modulating microglia activation under conditions of neurodegeneration. Cell Death Dis. 2022 Jul 20;13(7):628. http://doi.org/10.1038/s41419-022-05058-3
[13] Ge MM, Chen N, Zhou YQ, Yang H, Tian YK, Ye DW. Galectin-3 in Microglia-Mediated Neuroinflammation: Implications for Central Nervous System Diseases. Curr Neuropharmacol.2022;20(11):2066-2080. http://doi.org/10.2174/1570159X20666220201094547
[14] Zhao Y, Wu X, Li X, Jiang LL, Gui X, Liu Y, et al. TREM2 Is a Receptor for β-Amyloid that Mediates Microglial Function. Neuron. 2018 Mar 7;97(5):1023-1031.e7. http://doi.org/10.1016/j.neuron.2018.01.031
[15] Duffy SS, Hayes JP, Fiore NT, Moalem-Taylor G. The cannabinoid system and microglia in health and disease. Neuropharmacology. 2021 Jun 1;190:108555. http://doi.org/10.1016/j.neuropharm.2021.108555
[16] George S, Rey NL, Tyson T, Esquibel C, Meyerdirk L, Schulz E, et al. Microglia affect α-synuclein cell-to-cell transfer in a mouse model of Parkinson's disease. Mol Neurodegener. 2019 Aug 16;14(1):34. http://doi.org/10.1186/s13024-019-0335-3
[17] Xu J, Farsad HL, Hou Y, Barclay K, Lopez BA, Yamada S, et al. Human striatal glia differentially contribute to AD- and PD-specific neurodegeneration. Nat Aging. 2023 Mar;3(3):346-365. http://doi.org/10.1038/s43587-023-00363-8
[18] Bido S, Muggeo S, Massimino L, Marzi MJ, Giannelli SG, Melacini E, et al. Microglia-specific overexpression of α-synuclein leads to severe dopaminergic neurodegeneration by phagocytic exhaustion and oxidative toxicity. Nat Commun. 2021 Oct 29;12(1):6237. http://doi.org/10.1038/s41467-021-26519-x
[19] Xie M, Liu YU, Zhao S, Zhang L, Bosco DB, Pang YP, et al. TREM2 interacts with TDP-43 and mediates microglial neuroprotection against TDP-43-related neurodegeneration. Nat Neurosci. 2022 Jan;25(1):26-38. http://doi.org/10.1038/s41593-021-00975-6
[20] Spiller KJ, Restrepo CR, Khan T, Dominique MA, Fang TC, et al. Microglia-mediated recovery from ALS-relevant motor neuron degeneration in a mouse model of TDP-43 proteinopathy. Nat Neurosci. 2018 Mar;21(3):329-340. http://doi.org/10.1038/s41593-018-0083-7
[21] Voet S, Prinz M, van Loo G. Microglia in Central Nervous System Inflammation and Multiple Sclerosis Pathology. Trends Mol Med. 2019 Feb;25(2):112-123. http://doi.org/10.1016/j.molmed.2018.11.005

[22] Poliani PL, Wang Y, Fontana E, Robinette ML, Yamanishi Y, Gilfillan S, et al. TREM2 sustains microglial expansion during aging and response to demyelination. J Clin Invest. 2015 May;125(5):2161-70. http://doi.org/10.1172/JCI77983
[23] Ennerfelt H, Frost EL, Shapiro DA, Holliday C, Zengeler KE, Voithofer G, et al. SYK coordinates neuroprotective microglial responses in neurodegenerative disease. Cell. 2022 Oct 27;185(22):4135-4152.e22. http://doi.org/10.1016/j.cell.2022.09.030
[24] Jordão MJC, Sankowski R, Brendecke SM, Sagar, Locatelli G, Tai YH, et al. Single-cell profiling identifies myeloid cell subsets with distinct fates during neuroinflammation. Science. 2019 Jan 25;363 (6425):eaat7554. http://doi.org/10.1126/science.aat7554
[25] Zia S, Rawji KS, Michaels NJ, Burr M, Kerr BJ, Healy LM, et al. Microglia Diversity in Health and Multiple Sclerosis. Front Immunol. 2020 Nov 6;11: 588021. http://doi.org/10.3389/fimmu.2020.588021
[26] Walker DG, Tang TM, Mendsaikhan A, Tooyama I, Serrano GE, Sue LI, et al. Patterns of Expression of Purinergic Receptor P2RY12, a Putative Marker for Non-Activated Microglia, in Aged and Alzheimer's Disease Brains. Int J Mol Sci. 2020 Jan 20;21(2):678. http://doi.org/10.3390/ijms21020678
[27] Haure-Mirande JV, Audrain M, Ehrlich ME, Gandy S. Microglial TYROBP/DAP12 in Alzheimer's disease: Transduction of physiological and pathological signals across TREM2. Mol Neurodegener. 2022 Aug 24; 17(1):55. http://doi.org/10.1186/s13024-022-00552-w
[28] Audrain M, Haure-Mirande JV, Mleczko J, Wang M, Griffin JK, et al. Reactive or transgenic increase in microglial TYROBP reveals a TREM2-independent TYROBP-APOE link in wild-type and Alzheimer's-related mice. Alzheimers Dement. 2021 Feb;17(2):149-163. http://doi.org/10.1002/alz.12256
[29] Parhizkar S, Arzberger T, Brendel M, Kleinberger G, Deussing M, Focke C, et al. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nat Neurosci. 2019 Feb;22(2):191-204. http://doi.org/10.1038/s41593-018-0296-9
[30] Yerbury JJ, Ooi L, Dillin A, Saunders DN, Hatters DM, Beart PM, et al. Walking the tightrope: proteostasis and neurodegenerative disease. J Neurochem. 2016 May;137(4):489-505. http://doi.org/10.1111/jnc.13575
[31] Prater KE, Green KJ, Mamde S, Sun W, Cochoit A, Smith CL, et al. Human microglia show unique transcriptional changes in Alzheimer's disease. Nat Aging. 2023 Jul;3(7):894-907. http://doi.org/10.1038/s43587-023-00424-y
[32] Jay TR, Hirsch AM, Broihier ML, Miller CM, Neilson LE, Ransohoff RM, et al. Disease Progression-Dependent Effects of TREM2 Deficiency in a Mouse Model of Alzheimer's Disease. J Neurosci. 2017 Jan 18;37(3):637-647. http://doi.org/10.1523/JNEUROSCI.2110-16.2016

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