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Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases

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Abstract One of the most striking hallmarks shared by various neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease (AD), and amyotrophic lateral sclerosis, is microglia-mediated neuroinflammation. Increasing evidence indicates that microglial activation in the central nervous system is heterogeneous, which can be categorized into two opposite types: M1 phenotype and M2 phenotype. Depending on the phenotypes activated, microglia can produce either cytotoxic or neuroprotective effects. In this review, we focus on the potential role of M1 and M2 microglia and the dynamic changes of M1/M2 phenotypes that are critically associated with the neurodegenerative diseases. Generally, M1 microglia predominate at the injury site at the end stage of disease, when the immunoresolution and repair process of M2 microglia are dampened. This phenotype transformation is very complicated in AD due to the phagocytosis of regionally distributed β-amyloid (Aβ) plaque and tangles that are released into the extracellular space. The endogenous stimuli including aggregated α-synuclein, mutated superoxide dismutase, Aβ, and tau oligomers exist in the milieu that may persistently activate M1 pro-inflammatory responses and finally lead to irreversible neuron loss. The changes of microglial phenotypes depend on the disease stages and severity; mastering the stage-specific switching of M1/M2 phenotypes within appropriate time windows may provide better therapeutic benefit.

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Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APP	Amyloid precursor protein
Arg1	Arginase 1
Aβ	β-Amyloid
BDNF	Brain-derived neurotrophic factor
CD206	Mannose receptor
Chi3l3	Chitinase-3-Like-3
CNS	Central nervous system
DA	Dopaminergic
ECM	Extracellular matrix
FIZZ1	Found in inflammatory zone 1
IFN-γ	Interferon-γ
IGF-I	Insulin-like growth factor 1
IL	Interleukin
iNOS	Induced nitric oxide synthase
LBs	Lewy bodies
LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mSOD1	Mutated superoxide dismutase
NO	Nitric oxide
PD	Parkinson's disease
PET	Positron emission tomography
PS1	Presenilin-1
RELM	Resistin-like molecules
ROS	Reactive oxygen species
SN	Substantia nigra
SRA	Scavenger receptors
TAM	Tumor-associated macrophages
TDP-43	TAR DNA-binding protein 43

TGF-β	Transforming growth factor-β
TLRs	Toll-like receptors
TNF-α	Tumor necrosis factor-α
TTBK	Tau-tubulin kinase

Introduction

Neuroinflammation is a prominent feature shared by various neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) [1–3]. Microglial activation is the principal component of neuroinflammation in the central nervous system (CNS), which provides the first line of defense whenever injury or disease occurs [2, 4]. The molecular and clinical evidences from postmortem analysis and positron emission tomography (PET) imaging have shown an increase of microglial activation and an increasing accumulated inflammatory mediators during the pathogenesis of neurodegenerative diseases [5–7].

Neuroinflammation is now considered as a double-edged sword that executes both detrimental and beneficial effects on the neurons [8, 9]. Many evidences point to the neurotoxic nature of microglia [6], whereas others indicate that neuroinflammation is actually beneficial in certain circumstances to stimulate myelin repair, remove toxic aggregated proteins and cell debris from the CNS, as well as secretion of neurotrophic factors to prevent neural injury [10–12]. Immune cells within the CNS milieu such as microglia appear to be heterogeneous with diverse functional phenotypes that range from pro-inflammatory M1 phenotypes to immunosuppressive M2 phenotypes. In recent years, M1/M2 paradigm of microglial activation has been increasingly studied in several neurodegenerative diseases in attempt to uncover the mechanisms of immunopathogenesis. In this review, we focus on the roles of microglial phenotypes and their switch in multiple neurodegenerative diseases.

Microglial Phenotypes

M1/M2 Paradigm

Inside the human body, immune cells including peripheral macrophages and CNS microglia cells often communicate with the resident functional cells in the milieu. In the normal condition, the immune responses are fine-regulated in the process of either initiation or resolution, so as to keep tissue homeostasis. In the pathological condition, however, the immune responses are uncontrolled and skew to either extreme of the immune balance that highly integrates with cell loss or cell dysfunction occurred within the inflammatory processes.

The M1/M2 paradigm is a simplified model to decipher the two polars of the inflammatory responses, which resembles the "Ying and Yang" principles in the nature. M1 and M2 macrophages were extensively studied to differentially affect the functional cells in the inflammation-induced pathologies of several human diseases. For example, transition of tissue-resident macrophages (TAM) from the M2 to the M1 phenotype is tightly associated with obesity, insulin resistance, and type 2 diabetes that is also believed to be a chronic inflammatory disease [13–16]. Obesity induces the accumulation of newly recruited M1 macrophages overwhelming M2 macrophages in the adipose tissue which secrete pro-inflammatory mediators, thereby inducing an insulin-resistant state in the adipose tissue that is a strong risk factor for the development of type 2 diabetes mellitus [16, 13–15]. In spinal cord injury, an M1 macrophage response is rapidly induced and then maintained at sites of traumatic injury, and this action overwhelms a comparatively smaller and transient M2 macrophage response, which promotes a regenerative growth in adult sensory axons [17].

The already depicted "M1/M2 paradigm" in insulin resistance and spinal cord injury shed light on the research of microglial activation states in CNS. The category of M1 and M2 microglia is a common category shared by various neurodegenerative diseases. Depending on the milieu in which they become activated or the factors by which they are stimulated, microglia possess states of "classical activation," "alternative activation," and "acquired deactivation" [18, 19]. Classical activation is associated with the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), superoxide, nitric oxide (NO), reactive oxygen species (ROS), and proteases that have already been studied for a long time [6, 20, 21]. Microglia in this state are also termed "M1 microglia," whereas "M2 microglia" is used to include the states of both alternative activation and acquired deactivation (Fig. 1). Alternative activation is limited to the activation state treated by IL-4 or IL-13 and is closely associated with M2 genes that promote anti-inflammation, tissue repair, and extracellular matrix (ECM) reconstruction [19, 22]. Acquired deactivation is another state to alleviate acute inflammation and is induced primarily by uptake of apoptotic cells or exposure to the insult of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) [18, 19, 23].

It is still not clear whether there are any morphology differences between the two phenotypes or whether they can coexist. Nevertheless, the two phenotypes could be transited into each other in different context that may contribute to pathogenic forms of inflammation in neurodegenerative diseases.

Resolution Mechanisms of M2 Microglia

M1 microglia originally respond to the injury and infection, and generally act in the first line to defense tissue and promote

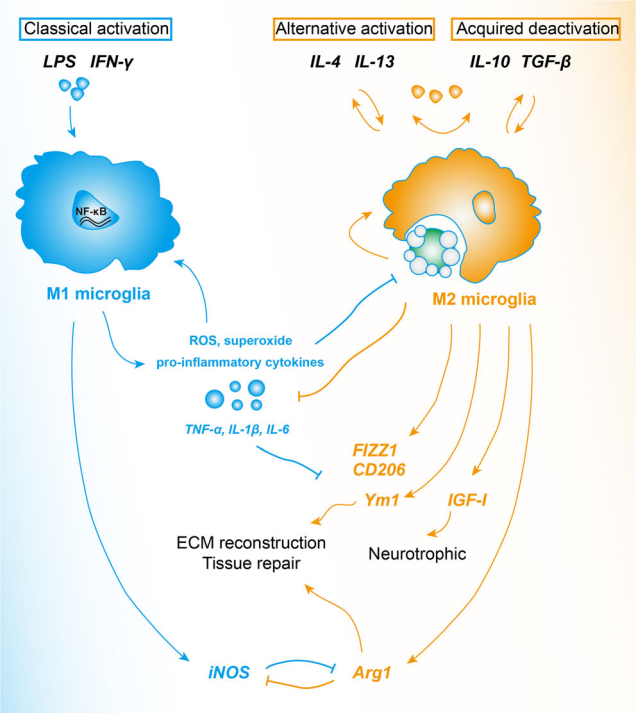

Fig. 1 M1 and M2 microglia. Microglia possess states of "classical activation," "alternative activation," and "acquired deactivation," depending on the milieu in which they become activated and the factors they are stimulated. Microglia in classical activation state are also termed M1 microglia, which induce iNOS and NF-κB pathways and produce various pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as superoxide, ROS and NO. M2 microglia include the states of both alternative activation and acquired deactivation, which are induced by IL-4/IL-13 and IL-10/TGF-β, respectively. M2 microglia facilitate phagocytosis of cell debris and misfolded proteins, promote ECM reconstruction and tissue repair, and support neuron survival by neurotrophic factors. M2 microglia are driven by the coordinated regulation of various anti-inflammatory factors and antagonize the M1 pro-inflammatory responses that finally results in immunosuppression and neuron protection

the destruction of invading pathogens. However, they also induce neurotoxicity due to the release of pro-inflammatory factors and various neurotoxic mediators and often setup a vicious cycle between dying neurons and acute inflammation [6, 24]. After the onset of classical activation, an anti-inflammatory and repair phase is rapidly initiated that leads to wound healing and brings back tissue homeostasis. M2 microglia are the major effector cells with the potential to dampen pro-inflammatory immune responses and promote the repair genes expression (Fig. 1).

Four major anti-inflammatory cytokines including IL-4, IL-13, IL-10, and TGF-β are employed by M2 microglia to antagonize the pro-inflammatory responses [25, 26]. IL-4 and IL-13 are well-described anti-inflammatory cytokines, which could suppress the production of pro-inflammatory cytokines such as IL-8, IL-6, and TNF-α, and reduce NO release, which collectively protect against lipopolysaccharide (LPS)-induced neuron injury both in vitro and in vivo [25, 27–29]. TGF-β is a pleiotropic cytokine with diverse functions on angiogenesis, ECM deposition, and participates in suppressing microglial responses [30, 31]. Upregulation of scavenger receptors (SRA) such as CD163 are observed in acquired deactivation to promote debris clearance [32–34]. Besides that, M2 microglia can also enhance neurotrophic factors, such as insulin-like growth factor 1 (IGF-I) release to assist inflammation resolution and promote neuron survival [35]. Anti-inflammatory factors are also released when apoptotic cells or myelin debris are removed [36], accompanied by the induction of typical M2 markers, such as Arginase 1 (Arg1), Mannose receptor (CD206), Found in inflammatory zone 1 (FIZZ1), and Chitinase-3-Like-3 (Chi3l3) to help tissue reconstruction [37, 22].

Notably, these neuroprotective signals are orchestrating each other in a coordinated way against the pro-inflammation responses (Fig. 1). For example, TGF-β can enhance IL-4-induced M2 microglia by increasing the expression of Arg1 and Ym1; whereas in turn, treatment with IL-4 can increase the level of TGF-β2, suggesting that TGF-β and IL-4 signals are working together in promoting protective effects [26].

Functions of Typical M2 Markers

The resolution states are critically important in chronic neuroinflammation; thus, the genes specifically associated with these states are of great importance. Although the exact functions of many of those genes are not clear in the CNS, some alternative activation genes such as Arg1 have been well studied in peripheral macrophages, which provide a link between M2 microglia and immunosuppression or repair processes.

Arg1

Arginine metabolism varies in tissues throughout the body including the brain due to the differential activation of multiple enzymatic pathways [38]. Arg1 is a typical marker for M2 macrophage/microglia activation that participates in arginine metabolism. Specifically, both Arg1 and induced nitric oxide synthase (iNOS) expressed in the CNS utilize arginine as the sole substrate for biosynthetic pathways [37, 39]. On one hand, arginine is catalyzed by iNOS to produce citrulline and NO. On the other hand, Arg1 metabolizes arginine into urea and ornithine, which are further metabolized into hydroxyproline and proline, and polyamine. The enzymatic products in the Arg1 pathway contribute greatly to the tissue repair [40]. For instance, hydroxyproline and proline are important sources of collagen synthesis, or by large, ECM synthesis that helps to physically strengthen the tissue and are also used for repair at the sites of injury [41, 42]. Polyamines such as spermines are multivalent cations required for cell proliferation and differentiation [43], and could help protect neurons

from injury by pro-inflammatory cytokines [44]. Arg1 is induced by IL-4 or IL-13 insult and produced anti-inflammatory effects by competing utilization of the common substrate arginine to suppress NO production [45]. The maintenance of high Arg1 expression directs arginine metabolism toward the production of proline or polyamines and keep NO production at a low level, which therefore contributes to the neuroprotection [45].

FIZZI

FIZZ1 (also known as RELM-α) encodes a 9.4-kDa cysteine-rich protein that is induced by IL-4 and IL-13 and increases collagen expression and myofibroblast differentiation [46, 47]. FIZZ1 belongs to the resistin-like molecule (RELM) family of secreted mammalian proteins, the members of which are upregulated in several infectious and inflammatory settings, including helminth infection, allergic airway inflammation, and colitis [48–50]. FIZZ1 limited Th2 cytokine-dependent inflammatory responses in lung through immunoregulatory effects on $CD4^+$ T cell responses [47]. After challenge with *Schistosoma mansoni* eggs, FIZZ1-deficient mice develop exacerbated lung inflammation [47]. FIZZ1 promotes the activation of innate immune cells in the intestine, including macrophages and eosinophils, in the chemically induced colitis [49, 50]. FIZZ1 may also contribute to insulin resistance linking with the effects of promotion of angiogenesis, stimulation of collagen synthesis, and inhibition of apoptosis [49].

Chi3l3

Chi3l3 (also known as YM1) is a secretory protein of 45 kDa synthesized by activated peripheral macrophages that binds saccharides and heparin sulfate on cell surfaces [51], and helps protect the ECM scaffold at the injury sites [52, 53]. Heparin sulfate serves as a docking site for growth factors in the ECM and is degraded by heparinases during inflammation. Ym1 thus acts by binding to heparin so as to slow the loss of growth factors which may be required for the tissue reconstruction [52, 54]. Ym1 is induced by IL-4 or IL-13 stimulation by a STAT6-dependent mechanism [55] and is essential for alternative activation of the microglia/macrophages that are antagonized by LPS and interferon-γ (IFN-γ) [22, 56, 54, 57].

CD206

CD206 is a transmembrane glycoprotein in the macrophage/microglia or dendrite cells and is a member of the C-type lectin family [58]. The N-terminal cysteine-rich domain of CD206 plays an important role in recognizing terminal mannose, sulfated glycoproteins as well as fucose residues on glycans attached to proteins on the surface of several microorganisms and then helps their clearance from the circulation [59]. To ensure inflammatory agents are removed, CD206 is expressed at low levels during inflammation and at high levels during the resolution of inflammation [60]. In general, CD206 initiates phagocytosis of its ligand and activates immunosuppressive pathways that results in decreased TNF-α and IL-12, whereas increased the expression levels of anti-inflammatory factors such as IL-10 and IL-1Rα [61, 62]. In line with the immunosuppressive effects, CD206 is a characteristic of the alternative activated state that could promote CNS repair in the spinal cord injury while limiting secondary inflammatory-mediated injury [63, 64].

Microglial Phenotypes in Neurodegenerative Diseases

Microglial Phenotypes in PD

PD is clinically manifested by progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN) of the midbrain and pathologically characterized by the accumulation of protein aggregates called Lewy bodies (LBs) in the remaining DA neurons [65, 66]. Microglia-mediated neuroinflammation is an important component in PD pathogenesis that shows inversely correlated with the DA neuron survival in patients [5]. In general, activated microglia are prominent and surround DA neurons exhibiting classically activated M1 phenotypes. Among those neurodegenerative diseases, the role and function of M2 microglia specifically in PD are not well studied.

In PD, microglial activation might be initiated either directly or indirectly by the misfolded proteins, pathogens or environmental toxins. *α-Synuclein* is one of the most prevalent pathological genes altered in familial PD, and it is originally acts as an intracellular component localized at presynaptic terminals [67–69]. Generally, the mutated forms of α-synuclein are released and aggregated, nitrated, or oxidized, which constitute the major components of LBs [67, 70]. Numerous studies have shown that aggregated α-synuclein released into the extracellular space from dying or dead DA neurons can directly induce microglia towards M1 phenotype with the activation of NADPH oxidase, increasing production of ROS and pro-inflammatory cytokines [71–75]. Overexpression of mutant α-synuclein solely in microglia switches microglia into a more reactive M1 phenotype characterized by

elevated levels of pro-inflammatory cytokines including TNF-α and NO [76]. However, a contradictory conclusion comes from a study to characterize the microglial phenotype differences caused by lack of α-synuclein expression [77]. Deficient of α-synuclein in microglia impairs the phagocytic ability and enhances the secretion of TNF-α and IL-6 after LPS stimulation [77]. Those studies complicate the role of α-synuclein in microglia but indeed hint an autonomous microglial reaction in the α-synuclein transgenic model (Fig. 2).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is an environmental toxin that causes parkinsonism and is used to establish the animal model of PD [65, 78]. MPTP induces DA neuron injury by blocking the electron transport chain of the mitochondria, and thereby indirectly activates microglia [65]. Similarly, typical characteristics of M1 phenotype including the activation of NADPH oxidase and NF-κB pathways, as well as the release of various pro-inflammatory mediators were observed in the MPTP-intoxicated models [79–81]. LPS as a classical ligand of toll-like receptors (TLRs) is definitely evoking M1 microglial activation. And therefore, administration of LPS causes extensive DA neuron death both in vitro and in vivo [20, 21, 82].

However, little is known about the activation of the M2 phenotype in the PD pathogenesis. To evaluate the possible link of alternative activation and α-synuclein, Theodore et al. established a mouse model overexpressing human α-synuclein by a recombinant adeno-associated virus vector (AAV2-SYN) [83]. However, the results come out that the expression of cytokines IL-4 and IL-13 as well as M2 marker Arg1 in the SN of mice treated with AAV2-SYN was not significantly changed after 2 or 4 weeks [83]. Considering that M2 microglia generally execute immunoresolution at a later phase, the detected endpoints in the early time may not be convincing. It will be interesting to examine at later time points when neurodegeneration becomes apparent.

As the two microglia phenotypes can transit each other, it might be available to make microglia protective by switching their phenotypes. For instance, treatment with LPS primed microglia into the M1 phenotype in both BV2 cells and primary microglia, while the addition of fasudil, one type of Rho

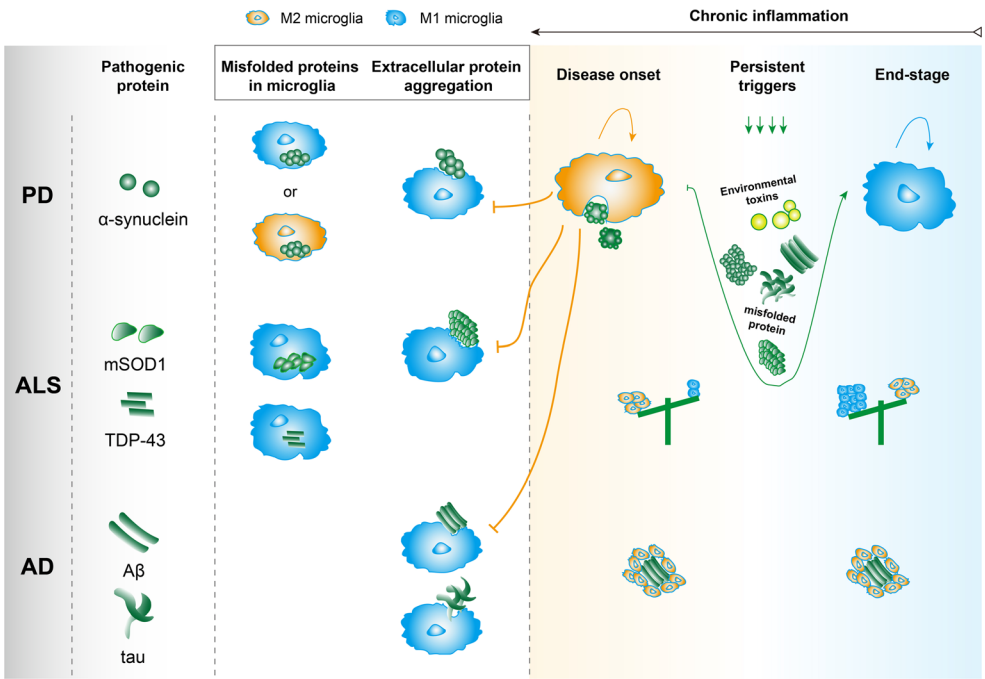

Fig. 2 Microglial phenotypes in neurodegenerative diseases. Microglial activation states are closely associated with the aggregated misfolded proteins seen in various neurodegenerative diseases including PD, AD, and ALS. Mutant α-synuclein in microglia is potential to switch microglia to either M1 or M2 phenotype. Microglia harboring excessive mSOD1 or TDP-43 are easily induced to be more M1-like phenotypes. Aggregated α-synuclein, mSOD1, or Aβ/tau oligomers released into the extracellular space from neurons can directly induce microglia towards M1 phenotypes. At the stage of disease onset, M2 microglia might be predominated to phagocytize cell debris, enhance tissue reconstruction, and produce anti-inflammatory factors, in attempt to quench pro-inflammation and keep tissue homeostasis. However, the endogenous stimuli including aggregated α-synuclein, mSOD1, Aβ plaques, and tau oligomers, as well as environmental toxins persistently exist in the milieu that skew microglia into M1 phenotypes and compromise the immunoresolution process at the later stage of disease progression, which eventually leads to irreversible neuron loss. Notably, the regional distributed Aβ plaque are surrounded by M2 microglia that is observed till the end stage of pathology, which may complicate the changing M1 microglial phenotypes during the disease development

kinase inhibitor, skews M1 toward M2 microglia characterized by lower NF-κB activity and pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) as well as increases anti-inflammatory cytokines (IL-10) [84]. Administration of fasudil in the LPS model increases $Arg1^{+}/CD11b^{+}$ M2 microglia while decreases $iNOS^{+}/CD11b^{+}$ M1 microglia [84]. Inhibition of NADPH oxidase or genetic deletion of its functional $p47^{phox}$ subunit switches microglial activation from M1 to M2 in response to LPS challenge [57]. Apart from drug treatment, an epigenetic machinery is employed to modulate M2 microglial phenotype. The histone H3K27me3 demethylase Jmjd3 was demonstrated to be essential for alternative microglial activation [45]. Suppression of Jmjd3 inhibits the expression of Arg1 and CD206 in IL-4-treated microglia, whereas enhances the production of pro-inflammatory cytokines and NO, which eventually causes more DA neuron death [45]. Since targeting M1/M2 microglia is promising to halt the PD development, the dynamic changes of microglial activation states should be explored in depth, whatever in MPTP or α-synuclein induced animal models, or most importantly in PD patients.

Microglial Phenotypes in AD

AD is the most common form of dementia, the hallmarks of which are abundant numbers of "plaques" and "tangles" by postmortem examination [85]. Senile plaques are extracellular deposits of fibrils and aggregates of β-amyloid (Aβ), which are derived from altered proteolytic processing of the amyloid precursor protein (APP) with the help of presenilin-1 (PS1) [85, 86]. Amyloid plaques can attract and stimulate microglia cells in vivo [87], and Aβ peptides are found to induce activation of primary microglia and stimulate the NO production in vitro [88, 89]. However, the activated microglia could adopt different phenotypes, which is much complicated by the presence of extracellular Aβ peptides and amyloid fibrils.

Microglia can be neuroprotective by degrading Aβ plaques as a reaction against Aβ accumulation [90]. However, an age-dependent increase in both the number and size of Aβ plaques in AD might reflect a diminution in the microglial phagocytic capability [91, 92]. Microglia surrounding the plaques for Aβ phagocytosis generally manifest M2 activation phenotype as labeled by Ym1 [92]. The phagocytic activity of microglia is attenuated by pro-inflammatory cytokines such as IFN-γ, IL-1β, and TNF-α, which most likely shifts microglia into the pro-inflammatory M1 state [93].

Aβ peptides have the capacity to self-assemble, transforming from monomeric to oligomeric, and then to insoluble heavy aggregates. Oligomeric Aβ, with a molecular weight of around 56 kDa, has the most markable toxic effects on the neuronal functions. Interestingly, different forms of Aβ peptides may induce different inflammatory profiles of microglia. The oligomeric Aβ appears to be a stronger M1-inductor than the fibrillar form [94]. Moreover, a cytokine-induced anti-inflammatory environment reduces the microglial reactivity towards oligomeric Aβ [94].

In the hippocampus of $PS1^{M146L}/APP^{751SL}$ double transgenic AD mice, an age-dependent phenotypic change of microglial activation is an active processing [92]. M2 microglia with Aβ phagocytic capabilities in AD mice at 6 months of age can switch into M1 phenotypes at 18 months of age, which is coincident with accumulated levels of soluble Aβ oligomers [92]. The YM1 positive and TNF-α negative microglia cells are exclusively located surrounding and infiltrating the Aβ plaques (Fig. 2). Furthermore, this M2 phenotype seems to maintain even at relative old ages, suggesting that activated microglia surrounding Aβ plaques adopted an alternative phenotype, regardless of the age [92]. In the mice of 18 months old, microglial activation is expanded into hippocampal areas free of plaques, showing that classic M1 phenotypes producing cytotoxic effects to neurons [92].

Pro-inflammatory factors IL-1β and IFN-γ as well as LPS suppress the microglial phagocytosis of fibrillar Aβ peptides, which are antagonized by anti-inflammatory cytokines including IL-4, IL-13, TGF-β, and IL-10 both in vitro and in vivo [25, 95–98]. Activation of M1 microglia results in an increase of iNOS expression. Ablation of iNOS in the APP/PS1 mice can protect the mice from plaque formation and premature mortality [99]. However, in other reports, microglial activation by acute LPS treatment reduces Aβ load in APP transgenic mice, which is prevented by co-treatment with dexamethasone [100–102]. APPSwDI mice deficient in iNOS displayed extensive tau pathology associated with regions of dense microvascular amyloid deposition [103]. Similar effects with different pro-inflammatory mediators such as IFN-γ, TNF-α, and IL-6 were observed in the TgCRND8 mice [104–106]. Thus in the closed in vivo system, the role of inflammatory cytokines impairing Aβ clearance is still controversial, as seen not all consistent with the in vitro results.

Anti-inflammatory factors were believed to be promising molecules in AD therapy. Intra-cerebral injection of IL-4 and IL-13 reduced Aβ plaque load in APP23 mice, accompanied with improved cognition and upregulation of Arg1 and YM1 positive M2 cells [107]. There was a reduction in Aβ plaques and an improvement in spatial memory of APP/PS1 mice 5 months after the intrahippocampally injected AAV2 carrying IL-4 while not IL-10 [108, 109]. In another study, however, Chakrabarty et al. utilized rAAV2/1 to overexpress murine IL-4 expression in the hippocampus of TgCRND8 mice with preexisting amyloid plaques, which resulted in establishment of an "M2-like" phenotype in the brain but exacerbated amyloid deposition after 6 weeks [110]. They showed that IL-4 treatment attenuated soluble Aβ40 uptake by microglia but does not affect aggregated Aβ42 internalization by microglia or soluble Aβ40 internalization by astrocytes [110]. This short-term focal IL-4 expression led to reduced glia phagocytosis and acute suppression of glial clearance mechanisms. It

appears that Aβ clearance in AD might be primed by moderate level of M1 microglial activation and maintained by M2 microglia polarization, since amyloid deposition is associated with high expression of alternative activation and acquires deactivation genes. The acute incorporation of either pro-inflammatory or anti-inflammatory factors might cause unwarranted effects.

In most cases, microglia in AD patients may exhibit mixed activation phenotypes. Colton et al. probed cortical tissue from two transgenic mouse models and from AD patients for evidence of alternative activation [46]. Interestingly, the results are always correlated in those animal models and AD patients. Cortical tissue from the Tg2576 mouse and individuals with AD demonstrate a mixed profile of alternative activation and classical activation genes, while the Tg-SwDI mouse primarily demonstrates classical activation [46]. Alternative activation genes such as Arg1, CD206, and YM1 were greatly increased in the Tg2576 mice while TNF-α and iNOS, respectively, increase or have no change. In AD patients, TNF-α, Arg1, CD206, Chi3l1, and Chi3l12 are found significantly increased while iNOS and IL-1β mRNA levels are unchanged [46]. Microarray analysis on brain samples from AD subjects shows up-regulation of apoptotic and pro-inflammatory signaling represented by major histocompatibility complex (MHC) class II, IFN-γ, and IL-1β elevation [111, 112]. The discrepancies of gene expression patterns in different models and in different stages of disease suggest a very complicated cytokine environment in the brain and its role in modifying microglial responses to Aβ plaques. Microglia might exhibit specific dominant phenotypes during a chronic neuroinflammatory process. Hence, understanding the sequence and timing of the alterations in M1/M2 phenotypes in AD is important.

As another hallmark of AD, misfolded tau protein plays a crucial role in the formation of intracellular tangles, which is a driving force of neurofibrillary degeneration in AD or other diseases. Oligomeric tau can also be released into the extracellular space and spread throughout the brain. Activated microglia have been frequently present in the proximity of neurofibrillary tangles and tangle-bearing neurons in the hippocampus of AD patients, as well as various tau transgenic models at early and late stages of tangle formation, indicating a close relationship between inflammatory response and tau neurofibrillary lesions [113–117]. Tau oligomers and fibrils which were induced by arachidonic acid in vitro can augment the production of nitrites and pro-inflammatory cytokine IL-6 in microglia cells [118].

In early stages of tau structural metamorphosis, some pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, as well as fractalkine (CX3CL1) can modify tau phosphorylation patterns and alter the structure and function of tau proteins [119]. Enhanced pro-inflammatory activation of microglia by disruption of CX3CR1, an anti-inflammatory CX3CL1 receptor, accelerates tangle formation [120]. Inflammatory changes were shown to be tau-dependent in the Tg4510 mice, which overexpress a mutant form of human tau, as they were reversed by the suppression of tau expression [121]. While treatment with immunosuppressant drug FK506 can attenuate microglial activation and delay the tau-related neuropathology in P301S tau mice [122].

In the cortical area of transgenic mice expressing P301L mutant tau (JNPL3) [123], immunoreactivity of phosphorylated tau (AT8) was closely associated with the number of Iba1-positive microglia [117]. Tau-associated microglia showed lower expression of MHC class II antigen and SRA. Interestingly, in the affected spinal cord region, JNPL3 mutant mice showed accumulation of alternatively activated microglia [124]. Tau-tubulin kinase 1 (TTBK1) expression is significantly elevated in AD brains, and directly phosphorylates tau protein, especially at Ser422 [125]. By crossing the JNPL3 mice with TTBK1 transgenic mice, there was a striking switch in activation phenotypes in the anterior horn of the spinal cord from alternative activated microglia (M2 state) in P301L tau mutant mice to pro-inflammatory infiltrating monocytes (M1 state), showing that tau phosphorylation is responsible for mediating M1-activated microglia-induced neurotoxicity [124].

Microglial Phenotypes in ALS

ALS, commonly known as Lou Gehrig's disease, is an adult-onset progressive disorder that selectively affects upper and lower motoneurons [126, 127]. The common hallmark shared by familial and sporadic ALS patients is neuroinflammation, characterized by microglial/astroglial activation and infiltration of peripheral T cells. Accumulation of misfolded human mutated forms of Cu, Zn-superoxide dismutase (mSOD1), or TAR DNA-binding protein 43 (TDP-43) seen in inherited ALS is critically contributing to the neurotoxic M1 inflammatory responses [126, 128] (Fig. 2). Mutant TDP-43^{M337V} evoked robust microglial activation around diseased motoneurons in the ventral horns [129]. Microglia expressing higher amounts of TDP-43 produced more pro-inflammatory cytokines and neurotoxic mediators after stimulation with LPS or ROS, due to the activation of p65 subunit of NF-κB that interacts with TDP-43 as a coactivator [128]. Compared to TDP-43, SOD1 is extensively studied in the immunopathogenesis of ALS. Intracellular and extracellular mSOD1 employs different pathways to enhance the production of ROS and exaggerates the pro-inflammatory signaling in microglia [130, 131]. Whereas treatment with IL-4 suppresses M1 microglial activation by reducing the release of ROS and promotes an M2 phenotype by enhancing IGF-I secretion that improves motoneuron survival [28].

Microglia harboring excessive mSOD1 are easily induced to be more M1-like phenotypes. Following activation with

LPS, primary microglia isolated from mSOD1^{G93A} transgenic mice are more neurotoxic than activated wild-type microglia, due to the increased production of superoxide, NO, and pro-inflammatory cytokines IL-1β and TNF-α, as well as the less release of IGF-I [132]. A lack or reduction of mSOD1 expression in microglia could slow disease progression and prolong the survival of mSOD1^{G93A} or mSOD1^{G37R} mice [133, 134].

Microglia in mSOD1^{G93A} mouse model appear to switch from an M2 microglial phenotype observed at the beginning of pathology to an M1 phenotype as disease progresses with increasing expressions of CD86, iNOS, and the NADPH oxidase isoform NOX2 and pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [135, 136]. Microglia isolated from mSOD1^{G93A} mice at disease onset express higher levels of Ym1, CD163, brain-derived neurotrophic factor (BDNF), and IGF-I, and lower levels of NOX2 compared with those isolated from mSOD1^{G93A} mice at end-stage [137, 138]. This may indicate the diminished function of neuroprotective microglia in the late disease stage. What's more, end-stage M1 microglia are toxic to cocultured motoneurons, whereas those M2-like microglia at disease onset are neuroprotective to promote motoneuron survival [137].

Deletion of the pro-inflammatory factors such as NOX2 rescues almost three times motoneuron death in the spinal cords of mSOD1^{G93A} mice [139]. NF-κB is upregulated in spinal cords of ALS patients and mSOD1^{G93A} mice. Ablation of NF-κB signaling in microglia rescues motoneurons in vitro and extends survival in mSOD1^{G93A} mice [140]. The number of iNOS^{+}/Iba1^{+} cells and CD86^{+}/Iba1^{+} cells is significantly decreased in mice with microglial NF-κB inhibition [140], while the levels of M2 markers as CD206, Arg1, or CD204 assessed by immunostaining are not altered, suggesting that NF-κB inhibition does not promote an M2 phenotype [140]. Similarly, administration of minocycline delays the pathogenesis of mSOD1^{G93A} mice by selectively attenuating the induction of M1 microglia markers during the progressive phase, without affecting the transient enhancement of expression of M2 microglia markers at the early onset stage [141].

The Arg1/iNOS balance, however, seems to be in a more complicated condition. By immunostaining, Arg1-positive and iNOS-positive microglia were found to increase 18-fold and 7-fold, respectively, between 10 and 25 weeks of age in the lumbar spinal cord of mSOD1^{G93A} mice compared to the control mice [142]. This appears to contradict the notion that M2 microglia activation is dampened in ALS progression, which hints the complexity of Arg1/iNOS unbalance in ALS development.

Collectively, microglia have both neuroprotective and cytotoxic functions in ALS. In the first response, M2 microglia may augment a neuroprotective effect, and then following sustained neuronal stress and signaling, a transformation of microglial phenotypes happens. During the disease progression, M1 microglia predominate in the milieu, which may be promoted and amplified by misfolded and aggregated SOD1 proteins, and eventually exacerbate motoneuron injury (Fig. 2).

Complexity of Microglial Phenotypes

Different models and different stages of disease underlie the complexity of the cytokine environment and its role in modifying microglial activation states. Thus, there exist various controversial results that link M1/M2 microglia switch and disease development. Notably, the status of M1/M2 microglia in AD is much more complicated than other two diseases, probably because of different triggers. The major trigger in AD is the extracellular Aβ oligomers, whereas the synuclein or SOD1 aggregation is mostly intracellular, which may play a greatest role after their release from injured or dead cells. Secondly, the regionally distributed Aβ plaques also make the unevenly distribution of M1/M2 microglia in the lesion area, which is different in PD and ALS. Thirdly, infiltrated peripheral macrophages or monocytes in AD are more often to penetrate into the CNS to help eliminate the extracellular oligomeric Aβ or tau antigens [143]. Those peripheral macrophages are also undergoing phenotypic switch that may compromise the role of microglia. Therefore, it is not easy to make a quick conclusion regarding the role of M1/M2 microglia in AD, considering the molecular mechanisms of M2 microglia are still less studied in this disease. The extra complexity arises from that M2 microglia might be also activated slightly in some models while not suppressed by M1 microglia along the disease pathogenesis. So far, the majority of studies on microglial phenotypes are focused on the various animal models, the in-depth functions of microglial phenotype switch in neurodegenerative diseases especially in AD are still very open. Establishment of an animal model showing pathology that truly represents those neurodegenerative diseases especially progressive neuronal loss in human body may partially mitigate those discrepancies.

Aging and Microglial Phenotypes

Neurodegenerative diseases are usually seen in the middle-age to elderly people. In the aged brain, many microglia cells undergo various molecular and cellular changes and even morphological features indicative of senescence, such as fragmented cytoplasmic processes, rendering them lose the ability to protect the brain [144, 145]. It is also hypothesized as "microglia dysfunction or dystrophic" that provides initial evidence for the age-associated changes in microglia. More importantly, aged microglia are also manifested by altered inflammatory profiles [146]. Normal aging in the brain is accompanied by increasing number of pro-inflammatory mediators such as IL-1β and IL-6 while compromising IL-10 level [147–150, 45]. The DNA-binding activity of NF-κB is increased in aged brain compared to adult and juvenile brain that

contributes to more IL-6 expression [150]. Additionally, treatment with MPTP in aged mice can cause severer DA neuron loss and greater microglial activation in the SN [151]. As the classical activation in the CNS is enhanced along aging, alternative activation appears to be mitigated, which is manifested by the reduction in the IL-4/IL-13 signaling pathway [152]. Therefore, the age-associated inflammation profiles might switch microglia phenotypes to be more M1-like, which renders aging brains are more easily affected by genetic or environmental insults during the onset of neurodegenerative diseases.

Therapeutic Perspectives

Switching of M1/M2 Phenotypes

Neurodegenerative diseases commonly implicate the failure in the resolution of neuroinflammation and presence of a defective repair process. Clinical therapy of neurodegenerative diseases faces numerous challenges with respect to timing, efficacy, and safety. Targeting any one of the vast pro-inflammatory mediators or pathways may not be efficacious, and the anti-inflammatory strategy varies in different diseases. Early stage intervention with drugs targeting dysregulated pro-inflammatory cytokine production might be therapeutically beneficial. A small molecule named MW-151 has been tested during two distinct but overlapping therapeutic time windows at the early pathological stage in APP/PS1 transgenic mice. MW-151 treatment attenuates the microglial activation and the production of pro-inflammatory cytokines in the cortex, which protects from synaptic dysfunction implicated in learning and memory [153].

As stated above, it might be interesting to manipulate microglia phenotypes from cytotoxic to neuroprotective by drug treatment or genetic modification. To be clinically effective, targeting M1/M2 balance also depends on the time window, since the timing, stages, and severity of diseases are critically associated with the changing microglial activation states (Fig. 3). Anti-inflammatory therapies will have to gain access to the CNS; it is not realistic that cytokines are used to modulate microglia polarization because most of the cytokines cannot enter brain tissue. The chemicals as fasudil [84] and minocycline [141], which have the superior ability to cross the blood–brain barrier, have demonstrated to enhance M2 microglial anti-inflammatory responses, and importantly manipulating the demethylase Jmjd3 is capable to skew microglia towards beneficial M2 phenotype [45]. Therefore, it is necessary to further delve into the effects of this manipulation within appropriate time windows. In addition, as the cell replacement therapy emerges in recent years to replace damaged neurons with fresh ones derived from embryonic stem cells or induced pluripotent stem cells, the immunosuppressive milieu modified through M1/M2 switching might help achieve a beneficial clinical outcome.

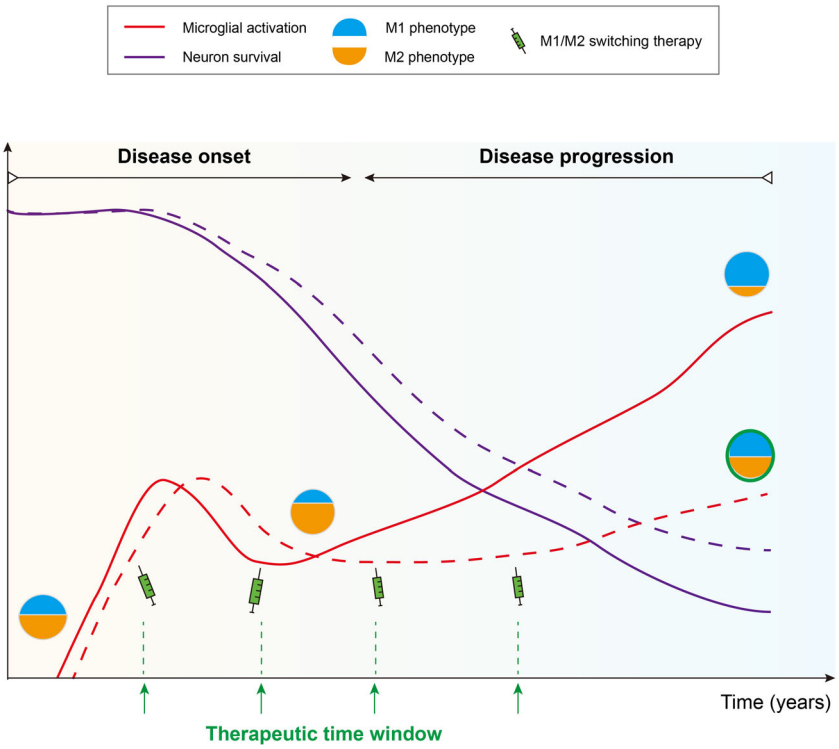

Fig. 3 Therapeutic perspectives on switching of M1/M2 phenotypes. In the progression of neurodegenerative diseases, it might be possible to switch microglial phenotypes from cytotoxic to neuroprotective by drug treatment or genetic modification, so as to alleviate pro-inflammation and attenuate neuron loss. To be clinically effective, targeting M1/M2 balance greatly depends on the optimal therapeutic time windows, since the timing, stages, and severity of diseases are critically associated with the changing microglial phenotypes. The treatment before or after the stage of disease onset may produce different therapeutic outcomes and may also vary in different neurodegenerative diseases. *Dash lines* indicate the neuron survival and microglial activation after M1/M2 switch therapy

Too Much or too Little?

After learning the optimal time window to manipulate M2 microglia in different diseases, there is still a long way to go to understand to which extent this balance of M1/M2 may skew, neither too much nor too little. M2 microglia might resemble M2 macrophages to participate in the immunosuppressive and repair process. A long-term repair phase after a rapid pro-inflammatory response that is driven principally by M2 macrophages results in fibrosis and other aberrant repair. For example, alternatively activated alveolar macrophages contribute to the fibrotic lesion in idiopathetic pulmonary fibrosis and in the liver fibrosis associated with *S. mansoni* [48, 46, 154]. Elevated arginase activity shifts the metabolism of L-arginine dramatically to produce increased ornithine and proline that stimulate cell division leading to hyperplasia and fibrosis, and meanwhile an uncoupling decrease in NO production results in endothelial dysfunction [154, 155]. Moreover, loss of iNOS and NO also dampens the effectiveness of the innate immune response against bacteria and virus, since NO-mediated modification of bacterial proteins is an efficient way to kill bacteria [156]. Considering the M1/M2 microglia switching requires fine regulation, more in-depth investigations are urgently needed.

Conclusion

The demonstrated role of microglial phenotypes may boost the research of M1/M2 paradigm in the human body. The balance of M1 and M2 microglial activation is broken down during the chronic inflammation progress in neurodegenerative diseases, with the highest complexity in AD. Setting a standard for measuring M1/M2 ratio might be critical, since M2 microglia also increases to a certain extent on some occasions. The endogenous stimuli including aggregated α-synuclein, mSOD1, and Aβ plaques persistently exist in the milieu that compromise the immunoresolution process and finally lead to irreversible neuron loss. Thus, stage-specific switching of the M1/M2 microglial phenotypes within appropriate time windows may produce therapeutic benefits.

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Conflict of Interest The authors declare no conflicts of interest.

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