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ORIGINAL ARTICLE

The role of microglia in the development of neurodegeneration

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Abstract

Microglia-mediated central nervous system (CNS) inflammation is one of the key features of various neurodegenerative diseases, including Parkinson's and Alzheimer's diseases. In the last few years, a number of studies have investigated the link between neurodegenerative diseases and CNS glial cells, in particular microglia. Microglial cells are the main resident immune cells and comprise approximately 10–15% of all CNS cells. Microglia at rest regulates CNS homeostasis via phagocytic activity, by removing pathogens and cell detritus. "Resting" microglia cells transform into an activated form and produce inflammatory mediators, thus protecting neurons and providing defense against invading pathogens. Excessive inflammation leads to neuronal damage and neurodegenerative diseases. Various microglial reactions at different stages of the disease can open up new directions for treatment interventions and modification of the inflammatory activity. This review focuses on the potential role of microglia and the dynamic M1/M2 phenotype changes that are critically linked to certain neurodegenerative diseases.

Keywords Neurodegeneration · Neurodegenerative disease · Neuroinflammation · Microglia

Introduction

Microglial cells are the resident macrophages of the central nervous system. These cells of mesenchymal origin migrate to all areas of the central nervous system, traverse through the brain parenchyma, and assume a specific branched morphological phenotype, which is called "resting microglia." Microglial cells transform into activated microglia to protect CNS from neuronal damage or pathogenic invaders and ensuing neuroinflammatory reactions. Activated microglia is capable of proliferation, migration, and producing various substances that can have either neuroprotective or neurotoxic effects [1]. Apart from its well-known role in the immune system, microglia also has a fundamental role in the regulation of homeostasis via degradation and removal of cellular detritus [2]. Neuroinflammation is a characteristic feature of various neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD) [3]. Activation of microglia has a key role in the inflammation in the central nervous system and provides the first line of defense in trauma or disease [4]. Neuroinflammation plays a dual role; it has both deleterious and beneficial effects on neurons. Some data indicate the neurotoxic effects of microglia and others demonstrate that, under certain circumstances, neuroinflammation is actually beneficial for stimulation of myelin reparation, removal of toxic proteins and cellular detritus from CNS, and for the secretion of neurotrophic factors to prevent damage to the nervous system [5]. Immune cells in the CNS, such as microglia, seem heterogeneous with various functional phenotypes that vary from pro-inflammatory M1 phenotypes to immunosuppressive M2 phenotypes. Over the past years, the M1/M2 paradigm of microglial activation has been investigated more and more often in different neurodegenerative diseases in an attempt to uncover the mechanisms of immunopathogenesis.

In this review, we focused 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, especially PD and AD. From the therapeutic viewpoint, it would of interest various microglial reactions at different stages of the disease can open up new directions for treatment interventions and modification of the inflammatory activity.

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Materials and methods

Information sources

We conducted a literature search of the PubMed, SCOPUS, IEEE Xplore, ACM Digital Library, and Google Scholar (first 50 results) databases for all literature published through 2010–2019. We also hand searched the reference lists of the originally included publications for additional eligible studies.

Literature search

The searches were performed using keywords "neuroinflammation," "neurodegeneration," "Parkinson's disease," and "Alzheimer's disease," along with "microglia," and excluding the search word "review." The resulting articles and their references were examined to identify eligible studies. We included studies devoted to microglia, neurodegenerative diseases, particularly Parkinson's disease and Alzheimer's disease. We checked reference lists of the articles yielded by this search strategy and located relevant studies. We also searched studies that were included if they completed the following criteria: (1) the study analyzed the effects on microglia in the brain with PD and AD, (2) the studies were published in English, (3) the effects on microglia were determined with characteristic microglial markers, and (4) a group of control animals was explain. The quality of studies for each study was evaluated by a risk of deviation assessment, scoring external and internal validity. For exclusion of an article were as follows: (1) animal models in which the stimulus reached the brain and caused secondary complications; (2) any manipulation in the brain before; (3) the use of another disease in this group.

Full text articles of selected studies were obtained for further evaluation.

As it is clear that microglia are implicated as a part of all the neurodegenerative diseases described, but Parkinson's disease and Alzheimer's disease are the most prevalent form of neurodegeneration and the discoveries have established the role of microglia in disease progression, we decided to focus on these diseases.

Results

Microglia phenotypes

Various disease models underlie the level of complexity of cytokine environment and its role in modification of microglia activation states (Table 1).

Immune cells, including peripheral macrophages and CNS microglia cells, often cooperate with resident functional cells in the environment. Under normal circumstances, in order to maintain tissue homeostasis, immune reactions are finely regulated during the process of initiation or resolution. However, in a pathological state, immune reactions are uncontrollable, and the shift to any of the extremes of the immune balance, which is highly integrated with cell loss or cellular dysfunction, occurs in inflammatory processes. The M1/M2 paradigm constitutes a simplified model for interpreting two opposite inflammatory reactions. M1 and M2 macrophages have been widely researched to differentially influence functional cells in diseases caused by inflammation. For instance, transition of resident tissue macrophages from M2 to M1 phenotype is closely associated with obesity, insulin resistance, and type 2 diabetes, which are also considered to be chronic inflammatory diseases [6]. Obesity induces amassment of newly accumulated M1 macrophages, thus suppressing M2 macrophages in adipose tissue, which secrete pro-inflammatory mediators. This, in turn, induces an insulin-resistant state in adipose tissue, which is a significant risk factor for developing type 2 diabetes mellitus [6].

Table 1 M1 and M2 markers. The markers determined may have a specific role in the pathogenesis and/or the progression of PD and AD

Markers (reference)	Parkinson's disease		Alzheimer's disease	
	M1	M2	M1	M2
TNF-α [6]	+	−	+	−
IL-6 [7]	+	−	+	−
IL-4 [8]	+	+	++	+
IL-13 [9]	+	+	+	−
IL-10[10]	+	−	+	−
Toll-like receptors [11]	+	+	++	+

The "–" means microglia non-activation; "+" means microglial activation; "++" means microglial activation more

The outlined "M1/M2 paradigm" in insulin-resistance and spinal cord injuries sheds light on research of microglial activation states in CNS. M1 and M2 microglia category is a common one for various neurodegenerative diseases. Depending on the environment in which they are activated, or on factors that stimulate them, microglial cells have states of "classical activation," "alternative activation," and "acquired deactivation" [7]. Classical activation is associated with pro-inflammatory cytokine production, such as tumor necrosis factor- α (TNF-α), interleukin-1β (IL-1β), superoxide, nitric oxide (NO), reactive oxygen species (ROS), and proteases, which are well studied [8]. Microglia in this state is also called "M1 microglia," whereas the "M2 microglia" term is used both for alternative activation and for acquired deactivation states. Alternative activation is limited to the activation state exposed to IL-4 or IL-3, and is closely associated with M2 microglia genes that promote reparation of anti-inflammatory tissue and reconstruction of extracellular matrix (ECM) [9]. Acquired deactivation is another state for

resolution of acute inflammation and is induced primarily by absorption of apoptotic cells or by exposure to inflammatory cytokines like IL-10 and transforming growth factor β (TGF-β) [10]. It is still not clear whether there are morphological differences between the two phenotypes or whether they can coexist. Nonetheless, the two phenotypes can transform into each other in different contexts, which can promote the pathogenic form of inflammation in neurodegenerative diseases. Notably, M1/M2 microglia state in AD is a lot more complex than in other diseases, possibly because of different triggers. The main triggers in AD are extracellular oligomers of β-amyloid. Also, infiltrated peripheral macrophages or monocytes in AD penetrate the CNS more frequently, thus aiding the elimination of extracellular oligomeric Aβ antigens and tau protein [11]. Additional difficulties arise because in some models of diseases M2 microglia can also be marginally activated, not being suppressed by M1 microglia.

Microglial phenotypes in certain neurodegenerative diseases: microglia in Parkinson's disease

Parkinson's disease is a chronic progressive neurodegenerative disorder, and the prevalence of Parkinson's disease is increasing each year [12]. The most common manifestation in patients with Parkinson's disease is the degeneration and loss of dopaminergic neurons in the substantia nigra in the midbrain. Microglia-mediated neuroinflammation is an important component of the pathogenesis of Parkinson's disease and is negatively correlated with dopaminergic neuron survival in patients [13]. Altogether, activated microglia surrounds dopaminergic neurons and exhibits classical activated M1 microglia phenotypes. The role and function of M2 microglia in neurodegenerative diseases, especially in Parkinson's disease, has not been studied sufficiently. The activation of microglia in Parkinson's disease can be initiated directly or indirectly via damaged proteins, pathogens, or ecological toxins. α-Synuclein is one of the prevalent pathological proteins altered in hereditary Parkinson's disease and acts primarily as an intracellular component located on the presynaptic terminals [14]. Multiple studies show that aggregated α-synuclein that is released into extracellular space by dying or dead dopaminergic neurons can directly induce microglia into M1 phenotype, with NADPH-oxidase activation, an increase in production of ROS, and pro-inflammatory cytokines [15]. Excessive expression of mutant α-synuclein transforms microglia into a more reactive M1 phenotype, which is characterized by an increased level of pro-inflammatory cytokines, including TNF- α and NO [16]. However, a deficit of α-synuclein in microglia impairs phagocytic capacity and enhances secretion of TNF- α and IL-6 after stimulation by lipopolysaccharides [17]. These studies indicate a more complex role of α-synuclein in the microglia, and at the same time, point to an autonomic microglial reaction in the transgenic model of α-synuclein. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a specific toxin for nigrostrial dopaminergic neurons that is used for creating animal models for Parkinson's disease [18]. MPTP induces destruction of dopaminergic neurons by blocking electron transport chain of mitochondria, thus indirectly activating microglia [19]. Similarly, characteristic M1 phenotype features were observed in models of MPTP intoxication, including activation of NADPH oxidase and NF-kB pathways, and release of various pro-inflammatory mediators [20]. Little is known about M2 phenotype activation in the pathogenesis of Parkinson's disease. To assess a possible link between alternative activation and α-synuclein, a group of researchers developed a mouse model with an active human α-synuclein gene using a recombinant adeno-associated viral vector (AAV2-SYN). However, the results showed that expression of IL-4 and IL-13 cytokines, as well as of M2 microglia marker Arg1 in the substantia nigra of mice treated with AAV2-SYN, did not significantly change neither in 2 nor in 4 weeks. Considering that M2 microglia is usually involved in immunoresolution at a later stage, the collected data might not be sufficient. Given that the two microglia phenotypes can transition into each other, the activation of a protective function of microglia might be possible via phenotype switching. Research at the later stages of the disease, with a more pronounced neurodegeneration, deserves further attention.

Dual role of microglia in Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia, affecting more than 24 million people worldwide, and the prevalence is expected to double or even triple by 2030, as the world population ages [21]. The two main features of the disease are the accumulation of amyloid plaques (Aß) and the accumulation of intracellular neurofibrillary tangles, which are accompanied by mass neuronal death in several brain structures. Neurofibrillary tangles are associated with the late stage of the pathology, when the symptoms are primarily irreversible, whereas plaque accumulation occurs at earlier stages, before the manifestation of cognitive deficits [22]. In the last decade, it has been established that the innate immunity has a critical role in the development of AD. Regarding the innate immunity, microglia cells have pivotal importance for the homeostatic clearance of β-amyloid, and for the modulation of synaptic formation, which are presumed to be involved in the pathogenesis of Alzheimer's disease [23]. Microglia cells are capable of binding to soluble β-amyloid oligomers and to fibrils of amyloid peptide via receptors, including class A receptors A1, CD36, CD14, integrin α6β1, CD47, and toll-like receptors (TLR2, TLR4, TLR6, and TLR9), which are involved in the inflammatory reaction in Alzheimer's disease [24]. In AD, the inflammatory reaction caused by microglial cells is associated with their activation

by various types of β-amyloid [25]. It is possible that early activation of microglia is one of the first pathological processes involved in the initiation of the disease, as the low-molecular forms of β-amyloid cause activation of microglial cells in vitro [26]. These β-amyloid molecules can be detected in the extracellular environment even before the characteristic plaque accumulation and can activate microglia or alter its function. This process can potentially initiate and stimulate the disease progression, not only via induction of pro-inflammatory microglia activation but also by affecting the homeostatic function of microglia, which impacts other cells in the brain, such as neurons and astrocytes [27].

In Alzheimer's disease, microglia can have a neuroprotective function, as it destroys and clears amyloid plaques [28]. Most likely, this is achieved chiefly by blood cells entering the brain, and later transforming into microglia, which has been shown in an animal model of AD, in APPswe/PS1-transgenic mice [29]. After training, that in itself has consequences, and bone marrow cell transplantation, the majority of microglial cells associated with the plaques are sampled again from the blood. However, an age-related increase in size and quantity of β-amyloid plaques in AD can reflect a decrease of the phagocytic capacity of microglia [30]. Microglial depletion can also lead to an increased plaque burden, which indicates that the characteristics of the newly repopulated microglia are different to those of the resident microglia. 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. Pro-inflammatory factors IL-1β and IFN-γas, as well as lipopolysaccharides, suppress microglial phagocytosis of fibrillary β-amyloid, that is antagonized by pro-inflammatory cytokines, including IL-4, IL-13, TGF-β, and IL-10, both in vitro and in vivo. Activation of M1 microglia leads to an increased iNOS (nitric oxide synthase) expression. Ablation of iNOS in the APP/PS1 transgenic mouse models protects mice from plaque formation and premature death [31]. Similar effects were observed in TgCRND8 mice with various pro-inflammatory mediators, such as IFN-γ, TNF-α, and IL-6 [17]. Overall, in a closed in vivo system, the role of pro-inflammatory cytokines that impair the clearance of β-amyloid remains contradictory, as not all data correspond with the results of in vitro studies. Anti-inflammatory factors were considered promising for the AD treatment. Intracerebral injection of IL-4 and IL-3 decreases β-amyloid plaque burden in APP23 mice, and is accompanied by an improvement in cognitive function and upregulation of Arg1 and YM1 in M2 microglia cells [32]. Five months after an intrahippocampal injection of AAV2, including IL-4, a reduction of amyloid plaques and an improvement in spatial memory were observed in APP/PS1 mice [33]. Another study used rAAV2/1 for overexpression of mouse IL-4 in the hippocampus of TgCRND8 mice with pre-existing amyloid plaques, which led to establishing an "M2-like" phenotype in the brain, but exacerbated amyloid deposition after 6 weeks [6]. Treatment with IL-4 was shown to decrease uptake of soluble β-amyloid-40 by microglia but did not affect aggregated internalization of β-amyloid-42 by microglia or internalization of soluble β-amyloid-40 by astrocytes. This short-term focal expression of IL-4 led to decreased glial phagocytois and acute suppression of glial clearance mechanisms. It would appear that β-amyloid clearance in AD can be driven by a moderate level of M1 microglia activation and be maintained by M2 microglia polarization, as amyloid deposition is associated with high expression of alternative activation and deactivates genes. The acute inclusion of any pro- or anti-inflammatory factors can lead to unwelcome results.

Discrepancies in the gene expression patterns in different models and at different stages of the disease suggest an extremely complex organization of cytokine environment in the brain and indicate the importance of its role in the modification of microglial responses to β-amyloid plaques. Microglia can have distinct dominant phenotypes in chronic inflammatory processes. Hence, understanding the sequence and timeline of changes in M1/M2 phenotypes in AD is highly important.

Discussion

Throughout life, a reliable and regular communication between various cell types in the brain is crucial. The connections change or fade with aging and diseases. In the brain of older adults, microglia cells undergo various molecular and cellular changes, as well as changes in morphological features that reflect aging, such as fragmented cytoplasmic processes, which result in the loss of the ability to protect the brain [34]. More importantly, aging microglia also exhibits an altered inflammatory profile. Normal aging of the brain is accompanied by an increase in pro-inflammatory mediators, such as IL-1β and IL-6, with a concurrent decrease of IL-10 [35]. Since classical activation in the CNS amplifies with aging, alternative activation is, apparently, attenuated, which manifests as downregulation of IL-4/IL-13 signaling pathway [36].

Activation of microglia is one of the key events in the development of the Alzheimer's disease. A recent study demonstrated microglial changes at a very early stage of AD pathogenesis, before the plaque deposition, in a 5xFAD mouse model [37]. This approach can be used to improve understanding of cellular pathways involved in the early progression of the disease, before any clinical manifestations. Using mass spectrometry and bioinformatics analysis to identify early microglial changes, the dynamics of the inflammatory response in a 5XFAD mouse model have been described at 2 to 10 weeks of age. Increase in the levels of IL1β and IL10 cytokines was discovered in the brain of 5xFAD mice only

as old as 10 weeks, after the amyloid plaque formation. Jak/STAT, P38 MAPK, and interleukin pathways were affected in the microglial cells before the plaque deposition at 6 weeks. These results point out the early inflammatory alterations in microglial cells that occur before β-amyloid deposition.

Microglial degeneration in the human brain is a progressive process that occurs slowly over time and causes breakdown of connections with other types of cells. Among the affected pathways necessary for maintaining the correct interactions between neurons and microglia, TREM2-DAP12 and CX3CL1-CX3CR1 axes are the key factors [38, 39]. The role of the TREM2-DAP12 axis, a signaling complex that is expressed exclusively in the microglia, can be fundamental, considering that by regulating the phagocytic function of microglia and its general fitness during its life, TREM2 signaling is of crucial importance for maintaining the CNS tissue homeostasis. TREM2-DAP12-mediated phagocytosis of apoptotic cells is a useful function of microglia that is performed without inflammation. However, excessive neuronal cell death during aging can cause massive inflammatory processes, leading to detrimental consequences for the brain. Microglia can assume various TREM2-positive phenotypes depending on the spatial and temporal circumstances, with or without inflammation, having protective or harmful effects [39]. Similarly, the CX3CL1-CX3CR1 pathway can have either a destructive or a beneficial role. CX3CL1/CX3CR1 acts in many physiological phenomena that occur in the central nervous system, regulating interactions between neurons, microglia, and immune cells [40]. The CX3CL1-CX3CR1 axis generally counteracts neuroinflammation, which is important in the hippocampal neurons in older age, where physiological decrease of CX3CL1 correlates with cognitive impairments discovered in older animals [41].

The number of activated microglia cells in the postmortem brain, levels of cytokines in the CNS and in the blood, and presence of IgG and T cell infiltration in the CNS lead us to assume that this process involves not only the local immune system but also the peripheral immune system. Reports on neuroprotection based on various strategies, aimed at different inflammatory mechanisms or pathways either on a central or on a peripheral level, hypothesize that these therapeutical approaches can be useful for patients with PD, to delay or attenuate the start of movement symptoms. However, we must keep in mind that these strategies should be aimed not just at counteracting neuroinflammation or microglia activation, but at modulating the response of these cells via shifting the M2 to M1 phenotype ratio, or the Th2/Treg to Th1 phenotype ratio [41]. In this context, the role of α-syn is vital not only as the initiator of pathogenesis but as a factor promoting persistent microglial activation. Thus, neuroprotective strategies should be aimed not only at limiting harmful effects of microglial activation but also at the neuronal processing of α-syn and clearance of extracellular α-syn, which is most efficiently accomplished by microglia. It is quite likely that a successful outcome will warrant a combination of immunomodulation strategies, and not just one aimed at distinct inflammatory factors elevated in PD and involved in the pathophysiology of the disease.

Therefore, age-specific inflammation profiles can switch microglia phenotypes to more M1-like ones, which makes the aging brain more susceptible to neurodegenerative diseases.

Conclusion

The balance of microglial M1 and M2 activation is disrupted in progression of chronic inflammation in neurodegenerative diseases; this disruption is particularly severe in Alzheimer's disease. Determining the standard for measuring M1/M2 ratio can have decisive significance, as in some cases, M2 microglia is increased as well. Switching microglial M1/M2 phenotypes at appropriate time slots can provide diagnostic and therapeutic advantages. Also, M1 and M2 microglia phenotypes can have detrimental or beneficial outcomes depending on the context of the disease, and a more thorough analysis is needed. In addition, in vivo human research based on animal models can help better define the role of microglia activation in dynamic stages of disease. It is interesting to note that microglia is, apparently, closely tied to tau pathology propagation; however, it is still unclear whether microglia promotes the development of tau pathology via failure to phagocytize the pathological tau, or via releasing factors that exacerbate this pathology. From the therapeutic viewpoint, it would of interest to determine the role of microglial phenotypes specific to the disease during the progression of the neurodegenerative disease, in order to develop immunotherapy that could amplify or attenuate inflammation depending on the specific stage of the disease. Ample evidence supports the dual nature of neuroinflammation in the early and late stages of PD and AD. Moreover, M1 and M2 microglia phenotypes can have detrimental or beneficial outcomes depending on the context of the disease, and a more thorough analysis is needed.

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Data availability Data will be available on request.

Compliance with ethical standards

Conflict of interest Authors have no potential conflicts of interest do disclose.

Ethical approval The study was approved by the Ethical Committee of Bashkir State Medical University and I.M. Sechenov First Moscow State Medical University.

Informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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