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The Role of Microglia in the Injured Neurosystem

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Abstract

Microglia is the brain's innate neuroprotective actor responsible for maintaining neuroplasticity and directing a remedial response when confronted with a pathogenic insult or physical trauma. Microglia are enabled to defend the central nervous system to ensure that homeostasis is maintained. Unfortunately, the pro-inflammatory responses microglia use to shield the neurons from threats also have the capability to cause damage detrimental to cognitive stability. This review covers some of these pathways involved in both neuroprotective and neurodegenerative outcomes, then moves on to possibilities on how these results can lead to diseases, specifically Alzheimer's disease. Finally, we comment on the opportunities and challenges of various experimental models currently being used for microglia studies.

Keywords: Microglia; Oxidative stress; Reactive oxygen species; Neuroinflammation; Animal models; Alzheimer's disease; Parkinson's disease; Aging

Introduction

Microglia, the resident immune and phagocytic cells of the neural system, were observed and studied intensively for decades before they were named and identified. As far back as 1841, anatomists were identifying these cells in damaged brains as being of mesodermal origin, their role being similar to macrophages, and concluded their loss of function led to disease. Researchers showed that these cells enter the brain in the second month of life, colonize both white and grey matter, and function as brain macrophages. In 1932 these cells were defined with embryonic origins as we are familiar with today with the demonstration that microglia were a distinct group of glial cells that made up the mesoglia [1]. Further research has refined our understanding of these cells as the descendants of myelomonocytic lineages derived from progenitors in the primitive yolk sac that seed the brain rudiments and enter the embryonic neuroepithelium when neurulation is completed [2]. These cells convert to amoeboid microglia later in life and are positioned in the neuroectoderm even before vascularization is complete, eventually switching into a different ramified state to function in their neuroprotective duties for the brain [3].

Microglia have two primary functions: immune defence and maintenance of the central nervous system (CNS). As immune cells, they detect tissue damage and pathogenic infections using numerous cell receptor pathways specific to different invasions [4]. Feedback systems must be in place to support tissue repair, remodeling and manage the potential damage to the CNS caused by reactive oxygen species (ROS). Recent studies reveal new details about the role microglia plays in controlling neuronal proliferation and differentiation [5]. Research shows a tight neuronal management, implying that microglia have a direct effect on neuronal disease progression.

Microglia compose 2.5-10% of all brain cells, equivalent one-to-one with the number of neurons. The close association between these two cell types correlates to a vital role in maintaining neural homeostasis, as well as facilitating the removal of apoptotic neurons and weakly connected synapses during brain development. After a hotly contested race to define the origins and characteristics of microglia, neuroresearch has shifted focus mainly toward neurons and often glial cells. Currently, microglial research is undergoing a significant revival (a PubMed search for the keyword "microglia" reveals 87 papers published in 1990, 568 papers in 2000, 1198 papers in 2010 and 2313 papers in 2016), likely due to recognition of their important role in neuronal health and degeneration. This review focuses on the role microglia fulfils when the neurosystem is injured with regards to immune protection, when that protection goes awry, and how this pathway can lead to neurodegenerative conditions and diseases.

Microglia Function to Provide Brain Immune Protection

When the brain suffers a disturbance such as infection, disease, trauma or other injury, microglia respond with a change in morphology and behavior [6,7]. As a part of the innate immune system, microglia detects pathogens through toll-like receptors (TLRs) and phosphatidylserine receptors [8-10]. Microglia react to stimuli within a matter of minutes and retain their active states for days after traumatic brain insult [11,12]. Microglia can also increase their population density to provide a better defence against antagonistic bacteria, releasing chemo attractive factors that attract immune cells to the CNS and aid T-cells across the blood-brain barrier [4]. When necessary, activated microglia will physically migrate to specific sites of infection or injury, retracting and extending protrusions to navigate towards the target [13,14].

Microglia use a variety of methods to clear harmful debris, misfolded proteins and damaged cells. Bacterial invasions activate microglia to their defensive role. Lipopolysaccharides (LPS), the main component of the gram-negative bacterial cell wall, stimulate microglia to produce prostaglandins, cytokines and chemokines. More responsive than astrocytes, microglia can also develop an adaptive response to repetitive exposure to LPS with decreased cytokine responses (lower levels of TNF-α and NO secreted) [15]. Streptococcus pneumoniae brings serious cases of meningitis, and microglia may have a role in producing cytokines and chemokines at the blood-brain barrier [16]. These bacteria can cross the BBB, so microglia may be responding directly to the pathogen itself, and NO production contributes to the neuronal damage seen in this case. Multiple bacterial species cause

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microglia to react in a cytoprotective manner through a series of chemokine and phagocytic responses [17,18]. Immunocompromised patients (such as those diagnosed with AIDS) are at risk to additional viral infections such as human cytomegalovirus (HCMV) which attack the CNS and lead to congenital encephalitis and cognitive defects [19]. Infected astrocytes secrete CCL2/MCP-1 signals to attract microglia to attack the virus. Microglia in turn produce the TNF-α antiviral cytokine to suppress viral replication in astrocytes, though HCMV gene products can also act as analogues to human interleukin molecules and negatively impact microglial defence. When microglia are infected with herpes simplex virus (HSV) they reduce release TNF-α, IL-1β, CXCL10/IP-10 and other signals that inhibit cellular replication and result in neurodegeneration [20,21].

Neuroinflammation

Brain injury promotes an inflammatory response by microglia that both engage the immune system and tissue repair pathways. Under normal physiological conditions, relevant genes that play a major role in this pathway are repressed, only to be activated when injury or infection is detected by TLRs or similar recognition receptors [22]. Once the receptors bind to the signals of infection, the transduction system is activated to begin transcription of relevant pathways (such as NF-κB and AP-1) as part of the inflammatory response. These signals (including cytokines such as TNF-α and IL-1β) are then amplified to recruit additional cells to the infection site and induce a protective response. ROS are generated to act as an antimicrobial defence mechanism, but an error in regulation can cause neuronal damage if left to run unimpeded. Microglia are equipped for initiating and maintaining the inflammatory response, can also accept responsibility when the pathway ceases to be regulated and leads to neurodegenerative conditions. Additionally, a recent study has shown that a change in ANK1 gene expression has been observed in brain's microglia cells associated with neuroinflammation [23]. A persistent stimulus or a breakdown in negative feedback systems may promote an overwhelming imbalance of inflammatory signals, leading to neurotoxic factors that simply exacerbate the harmful physiological state.

Neurodegenerative diseases, including Alzheimer's and Parkinson's, have distinct inflammatory induction pathways and mechanisms. Interestingly, these pathways seem to converge rather quickly at the amplification step, with similar or identical mechanisms for neurotoxicity and neuronal apoptosis [22]. Microglial pattern recognition receptors are likely shared between these pathologies, as well as signal transduction pathways (like NF-κB and AP-1) and NADPH oxidase for ROS release. It is possible that induced positive feedback loops between astrocytes and microglia to explain are responsible for the sustained inflammatory responses that drive neurotoxic environments, creating an independently running pathologic system.

Some work has been done in looking at targeting the inflammatory pathway as a preventative measure or therapeutic intervention. Using the anti-inflammatory agent Luteolin to treat CNS inflammation in mice led to the animals performing better in mental tests, but this hasn't been reproduced into human treatments [24]. Alzheimer's cytokine treatments and amyloid-beta (Aβ) vaccines have shown no improvement in patients' cognitive abilities, regardless of how early the preventative treatment is given [25,26]. Anti-inflammatory drugs do not reverse neuronal tau pathology in AD either [27].

Aging Microglia May Lead to Neurodegeneration

Like all other cells in an organism, microglia has a defined lifespan. Murine models have shown an increase from 2% positive readings of MCH II (specific marker to aged microglia) in adult mice to 25% in aged mice microglia [28]. Human microglia loses genes involved in remodeling the cytoskeleton, preventing them from moving towards damage sites [29]. Ageing leads to the cells becoming dysfunctional and increasingly sensitive to minor stimuli. This outcome is most likely due to "microglia priming", a morphological change to the microglia which puts the cell in a state of alertness and ensures the response to a second pathogenic insult would cause the cells to go through phenotypic switching [30]. Exposure to additional concentrations of human leukocyte antigen (HLA) can cause aging microglia to prime the CNS [31]. Microglia activation in white matter increases with age and resting microglia also express basal levels of HLA [32]. Tests done in aged mice show learning and memory impairments associated with deficiencies that come with a decline in neuronal plasticity and CNS inflammation, generating surplus ROS, inflammatory markers, scavenger receptors and TLRs [28,33,34]. A simplified model of aging microglia produces ROS, leading to the activation of redox-sensitive transcription factors, proinflammatory genes and eventual neuroinflammation and neurotoxicity [35].

Numerous attempts to research the neurotoxic effects of aged microglia have been devised. Microglial activity is regulated by anti-inflammatory cytokines, including IL-10, IL-4 and TFGβ. Unnecessary microglial activation becomes difficult to prevent as numerous key regulatory systems are impaired with age. In studies done with rodents, IL-10 decreases in microglia in aged animals after immune challenge, but is increased significantly in aged microglia [28]. IL-4 sees an overall decreased in aged rat brains, resulting in increased neuroinflammation and reduced LTP [36,37]. Evidence shows a logarithmic age-dependent increase of oxidized proteins and oxidized DNA lesions with age, beyond any loss of protection from antioxidant enzymes. Non-steroidal anti-inflammatory drugs (NSAIDs) are a possible treatment mechanism. Clinical trials with NSAIDs show an AD incidence reduction among asymptomatic patients compared to increased risk among those with AD symptoms [38]. Antioxidants such as Coenzyme Q and Vitamin E do not provide any measurable improvements in cognition [22]. It is possible therapeutics based on blocking neuroinflammatory pathways could provide an avenue for treating human cognitive decline [39].

Alzheimer's Disease and Neurodegenerative Conditions

Microglia assist in neuronal modeling via synaptic pruning: the process of removing cells from the neocortex during postnatal development [40]. While this process is vital for the brain to grow during infancy and adolescence, uncontrolled synaptic loss is the defining element of Alzheimer's disease where amyloid-beta (Aβ) can promote microglia to engage in undesired synaptic removal [41]. Dysregulation of Amyloid Precursor Protein (APP) leads to an accumulation of Aβ peptides, impairing APP trafficking and causing neurons to degenerate. Aβ is produced from these stressed cells [42]. Microglia is known to be highly effective for clearing Aβ, phagocytic and chemotactic responses to remove the peptide from the brain parenchyma [43]. While the majority of Aβ goes undigested and is released from the cell, it has been shown that microglia degrades fibrillar Aβ within 3 days through phagocytosis [44]. Fibrillar Aβ can be degraded and phagocytized by peripheral macrophages [45]. Soluble Aβ is internalized and quickly released without degradation. When neuritic plaques are formed, microglia will rise to clear dead or dying neurons, but these microglial responses to environmental challenges can have detrimental effects on the neurons [46]. One proposed mechanism involves Aβ causing synaptic damage and promoting microglia to release mediators such

as NO and TNF-α. These mediators are cytotoxic, leading to further synaptic and axonal injury [9]. Another proposed mechanism involves the loss of TDP-43 (DNA-RNA binding protein and transcriptional repressor) functionality, leading to synaptic decreases, reducing or eliminating phagocytic regulation and Aβ clearance [47]. Furthermore, more than half of the genes expressed that are associated with AD are found to be expressed highly in microglia as compared with other brain cells [48].

Microglial activation has been noted in Parkinson's disease (PD), where pro-inflammatory signals are possible contributors to neuronal loss [49,50]. A LPS-triggered UDP secretion causes the P2Y6 receptor to initiate activation of microglia to express cytokines through the ERK1/2 pathway [51]. Translocator protein (TSPO), which is normally found in mitochondrial membranes, is increased in PD. These proinflammatory signals in microglia could contribute to the neuroprotective reactions seen from phagocytosis and glial propagation [52]. Microglia expresses a pro-inflammatory phenotype in multiple sclerosis as well, initiating demyelination and neurodegeneration. Inactive lesions saw a reduction of microglia density [32,53].

An alternative hypothesis is that microglial loss rather than over activation is responsible for neurodegeneration, as some studies show that activated microglia are not consistently present among the range of AD severities. There is histological evidence showing microglial deterioration before neurofibrillary pathology begins, providing a possible explanation to why drugs targeting anti-inflammation factors have failed to provide an adequate avenue for treatment [27,54,55]. Additionally, fragmented microglia co-localize with neurofibrillary tables.

Neurodegeneration may also come from viral insults. HIV primarily targets microglia, forcing the cell to activate and secrete neurotoxic factors, leading to neurodegeneration [15]. HIV-associated dementia (HAD) is a complex process, one in which microglia plays a central role. Recent work in mice have shown improper activation of cyclin-dependent kinase 5 (Cdk5) under stress conditions, contributes to tau phosphorylation, Aβ deposits, microgliosis and astrocytosis [56]. Targeting Cdk5 appears to have reduced these AD-related products.

Complement

Cerebral amyloid angiopathy (CAA) is a microvasculopathy found in 75-90% of AD cases [57]. The high rate of this comorbidity renders the pathology highly relevant when studying AD. CAA involves the deposition of Aβ in penetrating cortical arteries coupled with degeneration of vascular smooth muscle cells, leading to vascular fragility and intracerebral hemorrhaging [58,59]. These microbleeds will lead to the cognitive decline associated with AD. The pore-forming complex of proteins that constitute the membrane attack complex (MAC) is associated with CAA-affected blood vessels. A conceivable mechanism for clearing Aβ by activating the protein CD11b in microglia will also deliver Aβ and C3b to microvascular walls vessels in AD, leading to Aβ deposition is accompanied by complement to form cytolytic MAC to result in vascular fragility [46]. Microglia recognizes complement components and eliminate the synapses that are tagged with them. These can be activated in the aged human brain and drive the system towards neurodegeneration. C1q and C3 are the initiators of the complement cascade. C1q activates C3b which subsequently tags deposits on neurites for elimination. A lack of C1q results in increased C3 levels [60]. It is possible that C1q deposits induce microglial migration and phagocytosis [61].

Metals and Oxidative Stress

Copper is a vital element to redox reactions and specific enzymatic pathways, thus studies of the transport and homeostasis of this metal are the subject of intense research [62]. Copper's role in catalytic reactions is due to its high reactivity. Levels need to be tightly regulated to prevent ROS being produced in inappropriate areas of the cell [63]. Copper binds tightly to Aβ and produces a very flexible compound that, depending on the conformation, can produce ROS [64]. When combined with Aβ1-40, Cu(II) has been shown to enhance microglial activation greater than either on their own. The Cu(II)-Aβ complex requires NF-κB for microglial activation and induces mitochondrial super oxide production, promoting neurotoxicity [43]. Glutathione (GSH) can suppress copper toxicity by binding to it and preventing its redox participation [65,66] and GSH depletion may be a contributing factor to neurotoxicity involving the element.

Microglia take, store and release more iron (stored in ferritin) than any other cell in the CNS except oligodendrocytes [67,68]. Iron has been shown to activate microglia through melanotransferrin (MTf), which releases cytokines and nitric oxide. MTf has been detected by active microglia in AD patients, where expression levels are unchanged in Parkinson's disease [69]. Microglia accumulates iron during aging [67]. Advanced age also correlates with an increase in ferritin levels in microglia, along with oligodendrocytes and astrocytes [67]. Activated microglia induces the release of iron from ferritin as well as oxidative stress and proinflammatory cytokines, contributing to PD pathogenesis [70-72].

Animal Models

A variety of animal models have been used for in studying microglia with leeches being the first animal model because of a tightly defined neural system [1]. The invertebrate has a simple system to explore, making it easy to image and manipulate signalling pathways. Rats have been used to harvest brain tissue for microglia activation, while mice have been used to test anti-inflammatory treatments, and derive possible pathways for the mechanisms used [12,73]. Mouse brains are generally difficult to access, particularly in utero when conducting developmental studies [74]. APP23 mouse models have been used in imaging studies in which anti-AB antibody injection was compared with initial levels of AB, showing a microglial overreaction in immunotherapy in subjects with abundant levels of AB [75].

While mice are easier to work with and sidestep ethical issues with regards to human studies, it remains contested whether they are an appropriate substitute for mimicking human pathology. While generally similar between human and mice, human microglia express several unique immune genes and cell cycle regulators. The differences in age-associated gene expression result in a difficult comparison [29]. For example, the study used six-month-old mice with few immune challenges tested against human cells that are exposed to insults every day. Human microglia expresses pro-inflammatory markers where mice do not [32]. Ideally animal models would translate perfectly to human pathology, but when inconsistencies arise, it becomes difficult to read in relation to human subjects. The differences in animal microglial models warrant further study.

Recently, animal models have been used as blueprints for generating human cells for research use. Murine microglia has been created using induced pluripotent stem cells with exposure to differentiation factors, confirming a potential use in medical applications [76]. Human DNA regulatory elements from human microglia have been compared to

similar mouse factors using tissue culture [48]. Transmembrane protein 119 (Tmem119) is a recently identified microglial marker expressed in both humans and mice, and can be used in studies involving both types of tissue environments [77]. Finally, zebra fish have been a recent animal model to gain traction for in vivo work due to its optical transparency and ease of manipulation.

Concluding Remarks

Beyond their role as immune effectors and deliberate shaping of the developing CNS, there is a solid body of evidence to establish the role microglia play in neurodegenerative diseases. Based on the mechanisms involved in initiating neuroprotective responses to foreign pathogens and physical brain injury, microglial regulation of these pathways can become cytotoxic for the neurons that are meant to be protected. While pathways can go awry at any point for numerous reasons, aging greatly affects microglia functionality leading to less regulation of neuroprotective systems. This ineffectiveness is vital to the development of neurodegenerative diseases that are commonly found in elderly patients such as AD and PD. It is imperative to invest in the research that has accumulated to understand these pathologies and their relation to microglia, to uncover potential targets for potential therapeutic value.

There is a need for further studies to be done in further defining the stages microglia have, as evidence questions the two clear states and reveals more of a fluid matter in which these cells switch between their active and non-active states. Additional effort needs to go into verifying the animal models that are used and how they differ from humans. Understanding the strengths and limitations of the tools we use to understand a process involved in such widespread neurological diseases can potentially open the door to a possible therapeutic intervention.

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