The Role of Neuroinflammation in Age-Related Dementias

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ABSTRACT

The most common dementias such as Alzheimer’s disease, vascular dementia, Lewy body dementia, and frontotemporal dementia are associated with a decline in cognitive and social abilities. Although the molecular mechanisms of tissue damage in these dementias are not completely understood, these neurodegenerative illnesses share certain alterations such as neuroinflammation and gliosis. Increasing evidence suggests that microgliosis and astrogliosis play a key role in neuroinflammation observed in these dementias. Here we provide an overview of the participation of microglia and astrocytes in the neuroinflammatory response in common dementias. (REV INVES CLIN. 2016;68:40-8)

Key words: Neuroinflammation. Dementia. Aging. Gliosis.

INTRODUCTION

Neuroinflammation is a complex inflammatory reaction in the central nervous system (CNS). It is a fundamental response triggered to isolate damaged tissue from uninjured areas, and clean and repair the extracellular matrix. Inflammation is orchestrated by the immune system, which is divided in two functional categories called innate and adaptive immunity. The innate immune response is the first line of defense against insult stimulus. In the CNS it is formed primarily by the blood-brain barrier (BBB), glial cells, and chemical mediators and constitutes the response mechanism to reset a baseline state following clearance of pathogens and tissue repair. The adaptive or acquired immune response is based on specific recognition of foreign antigenic substances by white blood cells, leukocytes, which can produce both humoral responses by synthesizing and secreting antibodies (B lymphocytes), and cellular responses (T lymphocytes) mediated by the secretion of immune-regulatory factors.

Following any damage, the CNS may set off and develop a complex, local and rapid immune response, resulting in the activation of glial cells (mainly microglia and astrocytes) and the release of inflammatory mediators (cytokines) to clear pathogens and cell debris. In general, acute inflammation is beneficial because it curbs the damage and promotes
regeneration. However, excessive and prolonged inflammation as well as stable low-grade damage are detrimental and can lead to the onset or exacerbation of cell injury. Moreover, if a tissue is unable to overcome inflammation, this response becomes a chronic condition that results in its continuous damage.

On injury in the CNS, cells of the innate immune system recognize molecules present in pathogens (called pathogen-associated recognition patterns) through receptors known as pattern recognition receptors (PRR). These can also recognize endogenous molecules released by damaged or dead cells that are generally known as damage-associated molecular patterns, such as heat-shock proteins (HSP), high-mobility group box 1 (HMGB-1) protein, and uric acid, a component of the extracellular matrix. Stimulation of these PRRs triggers intracellular signaling that induces phagocytosis of damaged or dead cells to promote tissue healing. There are different receptor families of PRRs such as toll-like receptors (TLR), nod-like receptors, scavenger receptors, complement receptors, and C-type lectins that upon stimulation can respond by differentiating phagocytes and/or secreting several factors that act against the pathogen. Other ways of responding to pathogens are by synthesizing and secreting proteins called cytokines, which are directly or indirectly involved in the elimination of pathogens. Cytokines are small proteins that act locally (paracrine or autocrine) to control numerous aspects of the cells, including proliferation, differentiation, and migration. They are divided into families such as interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), chemokines (CC), and growth factors.

CELLULAR COMPONENTS OF THE CENTRAL NERVOUS SYSTEM INNATE IMMUNE SYSTEM

The CNS innate immune system includes barriers that are formed mainly by the BBB, which consists of a tight barricade of endothelial cells, astrocytes and pericytes. Besides participating in blood flow regulation, structural and metabolic support, the BBB restricts the dispersal of both pathogens and large hydrophilic molecules to maintain homeostasis. Endothelial cells are immunologically quiescent under physiological conditions. However, when injured these cells can sense a pathogen and release pro-inflammatory interleukins (IL-1β), adhesion factors such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin-1 (ELAM-1) that can alter their tight junction to facilitate blood cell migration. Moreover, endothelial cells also express functional levels of several TLRs. Pericytes are the contractile cells that wrap the endothelial cell layer in vessels and regulate endothelial functions. Similar to endothelial cells, pericytes are immunologically quiescent under physiological conditions, but when there is tissue damage activation of TLR4, they can induce a macrophage-like activity and produce cytokines, chemokines, and nitric acid.

Microglia constitute approximately 10% of glial cells; they are resident macrophages of the CNS and the primary responders to any kind of damage. In the healthy CNS, microglial cells are known as resting microglia, to differentiate them from activated or reactive microglia seen after brain insult. Resting microglia has a characteristic morphology: a small cell body with several fine processes extending in all directions. Resting microglia are very active cells that move constantly to detect and remove any cellular debris and toxic metabolites in their microenvironment that might produce alterations in the CNS homeostasis.

Microglial cells express receptors for different neurotransmitters (e.g., dopamine, glutamate, GABA), neurohormones (e.g., somatostatin, angiotensin), neuromodulators (e.g., histamine, opioids), cytokines (e.g., IL-1, IL-4, IL-10), and chemokines (e.g., CCR1, CCR5). Microglia also participate in refining synapses by phagocyte dysfunctional synapses and release neurotrophic factors to modulate neuron networks.

During an injury event, microglial cells change both their physiology and morphology to become active. Activated microglia display different phenotypes; however, in general, they present an enlarged cell body with short thick processes, and in the final stage of activation show an amoeboid shape. Additionally, there are two phenotypes similar to those identified in macrophages, known as M1 and M2. The M1 state (classical activation or microglial “priming”), shows a phagocytic phenotype associated with the activation of mitogen-activated protein kinase and transcription factor nuclear factor kappa B (NFκB),
and the production and release of proinflammatory cytokines (IL-1β, IL-6, IL-12, IL-23, and TNF-α), cytotoxic substances such as quinolinic acid and reactive oxygen species. In addition to the proinflammatory cytokines, M1 phenotype microglia also secrete several chemokines such as CXCL9, CXCL10, CXCL11, CCL2, CCL3, CCL4, CCL5, and CXCL8. Because the M1 phenotype releases proinflammatory compounds that might be toxic for the cells, it has been suggested that this phenotype can increase neurotoxicity in neurodegenerative diseases. In contrast to the M1 state, the M2 state (alternative activation) is neuroprotective, showing a phagocytic phenotype and release of anti-inflammatory interleukins IL-10, and transforming growth factor beta (TGF-β). The M2 state is induced by anti-inflammatory cytokines (e.g., IL-4 and IL-13). Microglial activation may start with an M1 phenotype and later adopt an M2 phenotype to mediate repair by releasing growth factors and phagocyte cell debris. Based on evidence from aging animals, it has been proposed that microglia in the aging brain mainly presents an M1 phenotype that may result in an exaggerated immune response that can trigger age-related cognitive damage. The M1 phenotype can be toxic due to the production of cytokines (IL-6, IL-2, TNF-α), reactive oxygen species, and release of glutamate. Moreover, there is yet another microglial phenotype related with cognitive decline and impairment in aging: dystrophic microglia. This was observed in postmortem human brains and shows cytoplasmic degeneration. It has been suggested that this phenotype experiences replicative senescence, which can result in the generation of senescent and/or dysfunctional cells. Dystrophic microglia has also been found in mice models of aging, where this phenotype precedes neurodegeneration, as well as in Huntington’s disease in mice models and Alzheimer’s disease.

Astrocytes react to all kinds of CNS damage through a complex process known as reactive astrogliosis, which is a histopathological hallmark of CNS lesion. Reactive astrogliosis is a context-regulated process produced by specific signaling molecules that can induce reversible changes from gene expression and cell hypertrophy, to long-lasting ones such as glial scars. Under physiological and pathological conditions astrocytes express receptors to several cytokines and inflammatory mediators such as IL-1β, IL-6, interferon-γ (IFN-γ), TNF-α, TGF-β, CXCL12 (SDF-1), thrombin, and endothelin-1, TLR-2, TLR-3 and TLR-4. In the context of neuroinflammation, reactive astrocytes can release different mediators that may exert either protective or toxic effects. Reactive astrocytes can release growth factors (NGF, GDNF, BDNF, IGF), interleukins (IL-1β, IL-6, IL-11), chemokines (CXCL1, CXCL10, CCL2, CCL7), tumor necrosis factors (TNF-α) and thrombospondins. Various lines of evidence suggest that in the aging process, several brain regions show astrogliosis and increased expression of proinflammatory cytokines such as IL-1β and TNF-α. Oligodendrocytes are glial cells that produce myelin to insulate axons and permit saltatory conduction in the CNS. Oligodendrocytes express several ionic channels and cytokines (IL-1β, IL-6, IL-17A, IL-18), chemokines (CCL2, CCL3, CCL5, CXCL5, CXCL10), and antigen presentation molecules (MHC class I, MHC class II, CD274, PDCD1LG2) that prove that these cells may be immunologically active. Neurons also produce cytokines (IL-6), chemokines (GRO-α) and express several receptors to these mediators, such as TLR3, TLR7, TLR8, TLR9, CCR1, CCR3, CCR4, CCR5, CXCR3 and CXCR4.

AGE-RELATED DEMENTIAS

Aging is a complex process that involves several alterations, of which the most well known is dysregulation of the immune system, possibly resulting from deficiencies in both initiation and resolution of the immune response. This age-related dysregulation of the immune system, or immunosenescence, can be explained by alterations in the inflammatory and anti-inflammatory networks, resulting in a low-grade
chronic status known as inflammaging\textsuperscript{46}, which leads to tissue damage and degeneration\textsuperscript{47}. Evidence from both human and experimental models suggests that immunosenescence also takes place in the CNS and promotes dysfunction in different cellular populations\textsuperscript{48}. Immunosenescence probably results from lifelong exposure to pathogens and antigens, intrinsic changes in immune cells, and possibly genetic predisposition\textsuperscript{49}. Both microglia and astrocytes are cellular components of the CNS innate immune system that present altered physiology in aging and neurodegeneration\textsuperscript{28,49,50}. Certain age-related illnesses show brain degeneration and dementia. Dementia is a syndrome characterized by memory, cognitive, and behavior impairments as well as the inability to perform everyday activities\textsuperscript{51}, in which both genetic and environmental factors participate. The latest estimation of people suffering from dementia amounted to 44.5 million worldwide and the most common dementing illnesses associated with aging is Alzheimer’s disease (AD) accounting for 60-70\%, followed by vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD)\textsuperscript{51}.

**ALZHEIMER’S DISEASE**

Alzheimer’s disease is a progressive brain disorder that damages and eventually destroys brain cells, leading to memory decline and cognitive dysfunction. It is characterized by the accumulation of amyloid-β (Aβ), neuritic plaques and intraneuronal neurofibrillary tangles, in addition to widespread synaptic loss, inflammation and oxidative damage, and neuronal death\textsuperscript{52}. Most cases of AD are late-onset and the prevalence of the disease increases with life expectancy, affecting more than one-third of people over the age of 90\textsuperscript{53}. Pre-clinical, genetic, and epidemiological evidence have shown that neuroinflammation is an important contributor to AD pathogenesis\textsuperscript{54}. In addition, nonsteroidal anti-inflammatory drugs have been reported to reduce the risk of developing AD\textsuperscript{55}. Moreover, several lifestyle factors and events known to increase the risk of developing AD have an association with inflammation and oxidative damage, and neuronal death\textsuperscript{52}. Most cases of AD are late-onset and the prevalence of the disease increases with life expectancy, affecting more than one-third of people over the age of 90\textsuperscript{53}. Pre-clinical, genetic, and epidemiological evidence have shown that neuroinflammation is an important contributor to AD pathogenesis\textsuperscript{54}. In addition, nonsteroidal anti-inflammatory drugs have been reported to reduce the risk of developing AD\textsuperscript{55}. Moreover, several lifestyle factors and events known to increase the risk of developing AD have an associated inflammatory component; such is the case of obesity, severe infections, and chronic periodontitis, among others.

There is evidence that immune system activation mediated mainly by glial cells such as microglia and astrocytes follow Aβ deposition. However, recent studies have identified various novel alterations in immune system molecules, pathways, and genes in AD and have shifted our understanding of the timing of immune system changes in the course of this disease\textsuperscript{56-59}. Ongoing neuroinflammation can be seen in patients by using positron emission tomography (PET) ligand \([11C](R)-PK11195\), and this helps to identify patients who are likely to progress from experiencing mild cognitive impairment to developing clinical AD\textsuperscript{60,61}. These observations imply that immune processes may drive AD pathology independently of Aβ deposition and sustain increased soluble Aβ levels, thus exacerbating pathology and culminating in a vicious, pathophysiological cycle\textsuperscript{62}. The inflammatory response in AD is primarily driven by microglia and is the most intimately associated with tissue changes observed in AD. Soluble Aβ oligomers and Aβ fibrils can bind to various receptors expressed by microglia, including CD14, CD36, CD47, α6β1 integrin, class A scavenger receptors, receptors for advanced glycosylation end products, and toll-like receptors (TLR)\textsuperscript{63-66}. Such binding results in the production of inflammatory cytokines and chemokines\textsuperscript{67-69}, which are known to alter the expression and processing of β-amyloid precursor proteins\textsuperscript{70,71}. Postmortem studies of AD brains reveal the presence of intense inflammatory markers in senile plaques and neurofibrillary tangles\textsuperscript{72,73}. Analysis of gene regulatory networks involved in late-onset AD has identified genes associated with innate immune pathways and microglial cells. Remarkably, these findings reveal a set of genes that point to a pathogenic role for neuroinflammation in AD, including several pathways involved in phagocytosis and therefore, presumably, Aβ clearance\textsuperscript{54}.

Microglia possess the machinery to degrade soluble Aβ species via extracellular proteases such as nephrilysin and insulin-degrading enzyme, and it has been shown that Aβ is cleared by microglia in vitro through receptor-mediated phagocytosis and degradation\textsuperscript{74}. However, there is now strong evidence for a progressive, Aβ-dependent impairment of microglial function, as shown by morphological and detrimental phagocytic functional changes, as well as reductions in the levels of Aβ-binding scavenger receptors and Aβ-degrading enzymes in mice models of AD\textsuperscript{75}. Most importantly, efficient phagocytosis has recently been shown to involve a component of the
Vascular dementia (VaD) is a disease which involves ischemia and/or vascular brain lesions with variable etiology, pathogenesis, location and extent, resulting in progressive impairment of memory and other cognitive functions. Vascular dementia is the second most common dementia after AD and represents nearly 17% of all dementias. It has been recently referred to as part of a wider concept called vascular cognitive impairment that includes a heterogeneous group of cognitive disorders with an alleged vascular cause, including cognitive impairment with or without dementia. The most common subtypes of VaD are multi-infarct dementia (multiple small strokes), single infarct dementia (single major stroke with hippocampal damage), small vessel disease, and mixed dementia. Together with aging, other risk factors such as vascular (hypertension, hyperlipidemia, diabetes), behavioral (obesity, physical inactivity), and genetic (APOE ε4) are involved in VaD.

Mixed dementia is recognized as a subtype of VaD and the pathologic diagnosis is based on the presence of a combination of AD and VaD including multiple ischemic lesions comprising multiple strokes, white matter lesions, amyloid plaques, and neurofibrillary tangles. This dementia is observed in approximately 50% of all dementia cases. Cognitive impairment in this mixed neuropathology...
depends on the location of vascular lesions and AD pathology\textsuperscript{95}. In general, for every given level of cognitive deficit, patients with cerebrovascular lesions show no difference or lower densities of plaques and tau pathology compared to those with only AD. However, this is not true for certain areas of the brain, such as the temporal lobe and hippocampus, which show higher densities of plaques and tau pathology\textsuperscript{96-98}. Though neuroinflammation and gliosis (microglia and astrocytes) play an important role in both AD and VaD pathology, there is no evidence of a synergistic neuroinflammation in mixed dementia.

**LEWY BODY DEMENTIA**

Lewy body dementia (DLB) is a type of dementia characterized by changes in thinking and reasoning, confusion and alertness that vary significantly from one time of day to another or from one day to the next. There is an extreme reaction to narcoleptic drugs, visual hallucinations, REM sleep disorders, and sometimes Parkinson’s symptoms due to abnormal microscopic deposits of a-synuclein that gradually destroy certain brain cells. The a-synuclein protein is a major component of Lewy bodies and is found extensively in the brain; however, its normal function is as yet unknown\textsuperscript{99,100}. The level of neuroinflammation observed in patients with DLB seems to be lower than that of patients with other dementias\textsuperscript{101}. Nevertheless, a higher number of activated microglia have been found in patients with DLB\textsuperscript{102}. Alpha-synuclein is itself a potent activator of microglia and an increased expression of IL-1\textalpha and TNF\alpha has been observed in microglia in close proximity to neurons bearing inclusions\textsuperscript{103}. In DLB, there is a progressive association of microglia with degenerating Lewy body-containing neurons\textsuperscript{104}. What DLB has in common with other dementias like AD is increased neuroinflammatory states driving progression of the disease.

**FRONTOTEMPORAL DEMENTIA**

Frontotemporal dementia (FTD) is a genetically and pathologically heterogeneous disorder characterized by personality changes, language impairment, and deficits in executive functions, associated with frontal and temporal lobe degeneration\textsuperscript{105}. It is a form of progressive neuronal atrophy characterized by the loss of cells from the frontal and temporal cortices. Histopathologically, most patients show intraneuronal inclusions of the cytosolic phosphorylated TAR DNA binding protein-43 (TDP43) also known as TARDBP\textsuperscript{105}. Different phenotypes have been recognized based on clinical symptoms, namely the behavioral variant of FTD, the agrammatic variant of primary progressive aphasia, and the semantic variant of PPA\textsuperscript{106,107}. Moreover, some patients present associated parkinsonism, as in progressive supranuclear palsy and corticobasal syndrome, or motor neuron disease (FTD-MND)\textsuperscript{108}. Genetic studies have identified several genes associated with monogenic FTD. The first mutations identified in families with FT and parkinsonism were in the microtubule-associated protein tau (MAPT) gene in chromosome 17\textsuperscript{109}. Forty-four pathogenic mutations in the MAPT gene have been identified\textsuperscript{110}, causing the accumulation of hyperphosphorylated tau protein in neurons and glial cells\textsuperscript{109}. About 69 distinct pathogenic mutations have been identified in the GRN gene, accounting for up to 20\% of familial and 5\% of sporadic FTD cases\textsuperscript{110}. Progranulin is expressed in many cell types; expression of GRN in the brain is restricted to microglia and neurons under physiological conditions, but it is selectively upregulated in microglia after excitotoxic activation\textsuperscript{111}, and is a secreted growth factor known for its role in biological processes, including cellular and tissue development, inflammation, wound healing, and cancer, and for its neurotrophic properties. Several findings suggest that progranulin acts as a mediator of the inflammatory response. It is proteolytically processed into peptides called granulins, of which their function in the nervous system is still largely speculative\textsuperscript{112}. Some granulin peptides are able to attract and activate microglia in the brain and increase their phagocytic function\textsuperscript{113}. Deficient production of progranulin leads to high levels of proinflammatory cytokines and low levels of anti-inflammatory cytokines, thus promoting neuronal cell death, according to studies using progranulin knockout mice and conditioned media from progranulin-deficient microglia\textsuperscript{114,115}. These results suggest that the loss of progranulin may result in a dysregulated inflammatory response in microglia that could have detrimental effects on neuronal cell survival and promote the development of FTD.
CONCLUSIONS

It is well established that in aging there is a loss of immune homeostatic regulations. Primary lesions in dementias may exacerbate and prolong dysregulation of the innate immune system in the CNS and cause a chronic condition that is recognized as a common characteristic in the dementias related with aging (Fig. 1). The most prominent sign in neuroinflammation is the gliosis in which persistent microglia of the M1 phenotype and astrogliosis release proinflammatory mediators, which can result in neurotoxicity to all kinds of CNS cells, contributing to an exaggerated and prolonged inflammatory response that could be conducive to the development of neurodegeneration observed in dementias. However, the relevance of neuroinflammation in aging-related dementias may be underestimated, as suggested by the negative results of anti-inflammatory therapy in clinical trials to evaluate the cognitive decline in the development of AD. Nevertheless, the relevance in the various aging-related dementias may be different. Moreover, knowledge on the modulatory effects of anti-inflammatory drugs on gliosis is partial, and more studies are needed to identify new molecular targets that can be used to regulate the gliosis.

REFERENCES

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