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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[1]. Inflammation is orchestrated by the immune system, which is divided in two functional categories called innate and adaptive immunity[2]. 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[3,4]. 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[2].

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[5]. In general, acute inflammation is beneficial because it curbs the damage and promotes

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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[3,5].

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[6,7]. Stimulation of these PRRs triggers intracellular signaling that induces phagocytosis of damaged or dead cells to promote tissue healing[6,7]. 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[6,7]. 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[6,7].

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[8,9]. Endothelial cells are immunologically quiescent under physiological conditions[10]. However, when injured these cells can sense a pathogen and release pro-inflammatory interleukins (IL-1b), 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[11-13]. Moreover, endothelial cells also express functional levels of several TLRs[14]. Pericytes are the contractile cells that wrap the endothelial cell layer in vessels and regulate endothelial functions[15]. 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[16,17]. Microglia constitute approximately 10% of glial cells; they are resident macrophages of the CNS and the primary responders to any kind of damage[18,19]. 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[20,21]. 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)[20]. Microglia also participate in refining synapses by phagocyte dysfunctional synapses and release neurotrophic factors to modulate neuron networks[22].

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[21]. 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-1b, IL-6, IL-12, IL-23, and TNF-α), cytotoxic substances such as quinolinic acid and reactive oxygen species[6,19,23]. In addition to the proinflammatory cytokines, M1 phenotype microglia also secrete several chemokines such as CXCL9, CXCL10, CXCL11, CCL2, CCL3, CCL4, CCL5, and CXCL8[6,19,23]. 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[24]. 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)[6,19,23]. 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[6,19,23]. 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[25]. 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[26]. 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[27]. 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[28-30].

Astrocytes are specialized glial cells that perform several important functions to maintain homeostasis of the CNS such as release neurotransmitters (glutamate, ATP); express neurotransmitter receptors (glutamate, GABA, glycine); up-take and clear neurotransmitters (glutamate and GABA); participate in homeostasis preservation of extracellular ions, pH and water; supply energy metabolites to neurons (lactate); and modulate blood flow and synapses[31,32].

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[33]. 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[34]. 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[35].

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[36-39].

Oligodendrocytes are glial cells that produce myelin to insulate axons and permit saltatory conduction in the CNS[40]. Oligodendrocytes express several ionic channels and cytokines (IL-1β, IL-6, IL-8, 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[40,41].

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[42-44].

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[45]. 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[46], which leads to tissue damage and degeneration[47]. Evidence from both human and experimental models suggests that immunosenescence also takes place in the CNS and promotes dysfunction in different cellular populations[48]. Immunosenescence probably results from lifelong exposure to pathogens and antigens, intrinsic changes in immune cells, and possibly genetic predisposition[47]. Both microglia and astrocytes are cellular components of the CNS innate immune system that present altered physiology in aging and neurodegeneration[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[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)[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[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[53]. Pre-clinical, genetic, and epidemiological evidence have shown that neuroinflammation is an important contributor to AD pathogenesis[54]. In addition, nonsteroidal anti-inflammatory drugs have been reported to reduce the risk of developing AD[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[56-59]. Ongoing neuroinflammation can be seen in patients by using positron emission tomography (PET) ligand [^{11}C](*R*)-PK11195, and this helps to identify patients who are likely to progress from experiencing mild cognitive impairment to developing clinical AD[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[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)[63-66]. Such binding results in the production of inflammatory cytokines and chemokines[67-69], which are known to alter the expression and processing of β-amyloid precursor proteins[70,71]. Postmortem studies of AD brains reveal the presence of intense inflammatory markers in senile plaques and neurofibrillary tangles[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[54].

Microglia possess the machinery to degrade soluble Aβ species via extracellular proteases such as neprilysin and insulin-degrading enzyme, and it has been shown that Aβ is cleared by microglia *in vitro* through receptor-mediated phagocytosis and degradation[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[75]. Most importantly, efficient phagocytosis has recently been shown to involve a component of the

autophagy pathway, namely beclin 1, the levels of which were found to be markedly reduced in microglia derived from people with AD[76]. Microglia from AD patients show an increased expression of CD33, a receptor expressed at the surface of myeloid cells; its activation was shown to suppress the production of proinflammatory cytokines and prevent microglial cell-mediated removal of Aβ *in vitro* and *in vivo*[77]. These findings support the idea that impaired clearance mechanisms of Aβ may be responsible for most sporadic, non-hereditary cases[78]. Microglia impairment is also accompanied by a loss of trophic functions (brain-derived neurotrophic factor production)[79], eliminating certain protective properties, which may impact neuronal integrity in the course of AD. Paradoxically, microglial impairment might be sustained by inflammatory cytokines such as TNF, IL-1, IL-12, and IL-23[62], suggesting that AD pathology could be accelerated through this negative feedback loop, which may begin in the early stages of AD. Although the role of astrocytes is less well known than that of microglia, there is solid evidence of their participation in the pathology of AD. Postmortem samples from AD patients and animal models show that generalized astrogliosis and reactive astrocytes are associated with some amyloid plaques[80-82] and that astrocytes release pro-inflammatory cytokines[83]. Moreover, experimental evidence shows that APP production and apolipoprotein E (APOE) are related with astroglioisis[84,85]. These data suggest that reactive astrocytes participate in the neuroinflammatory response and may contribute to aggravate the damage.

VASCULAR DEMENTIA

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[86]. Vascular dementia is the second most common dementia after AD and represents nearly 17% of all dementias[87]. 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[88]. 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[88]. Together with aging, other risk factors such as vascular (hypertension, hyperlipidemia, diabetes), behavioral (obesity, physical inactivity), and genetic (APOE ε4) are involved in VaD[89]. Despite the lack of validated neuropathological criteria for pure VaD due to a high variability in the cerebrovascular pathology, a histopathological exam would show evidence of cerebrovascular disease without Alzheimer-type lesions exceeding those expected for age and other conditions causing dementia[86]. A wide range of vascular brain lesions can lead to VaD, and these include multiple large and small infarcts due to atherosclerosis, thromboembolism or hypoperfusion, lacunes or microinfarcts and microbleeds, mainly involving central white matter and subcortical structures such as the thalamus, basal ganglia, and brainstem as well as hemorrhagic stroke[89]. Ischemic and hemorrhagic events occurring in VaD can activate several cell mechanisms that damage brain tissue such as excitotoxicity and ionic imbalance, oxidative/nitrosative stress, apoptosis, and neuroinflammation[90]. Experimental evidence suggests that after a stroke, the microglia shows an M2 phenotype, which gradually transforms into a proinflammatory M1 phenotype in the peri-infarct area[91]. The pathologic mechanisms such as oxidative/nitrosative stress and apoptosis can stimulate the release of a proinflammatory mediator by reactive glial cells (microglia and astrocytes), and this effect can be exacerbated by an increase in BBB permeability, thus enabling the infiltration of proinflammatory factors such as interleukins (IL-1, IL-6) and TNF-α and lead to neurodegeneration and cell death in different cerebral regions, including those involved in cognitive functions such as the hippocampus[92,93].

MIXED DEMENTIA

Mixed dementia is recognized as a subtype of VaD[88] 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[94]. This dementia is observed in approximately 50% of all dementia cases[89]. Cognitive impairment in this mixed neuropathology

depends on the location of vascular lesions and AD pathology[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[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.

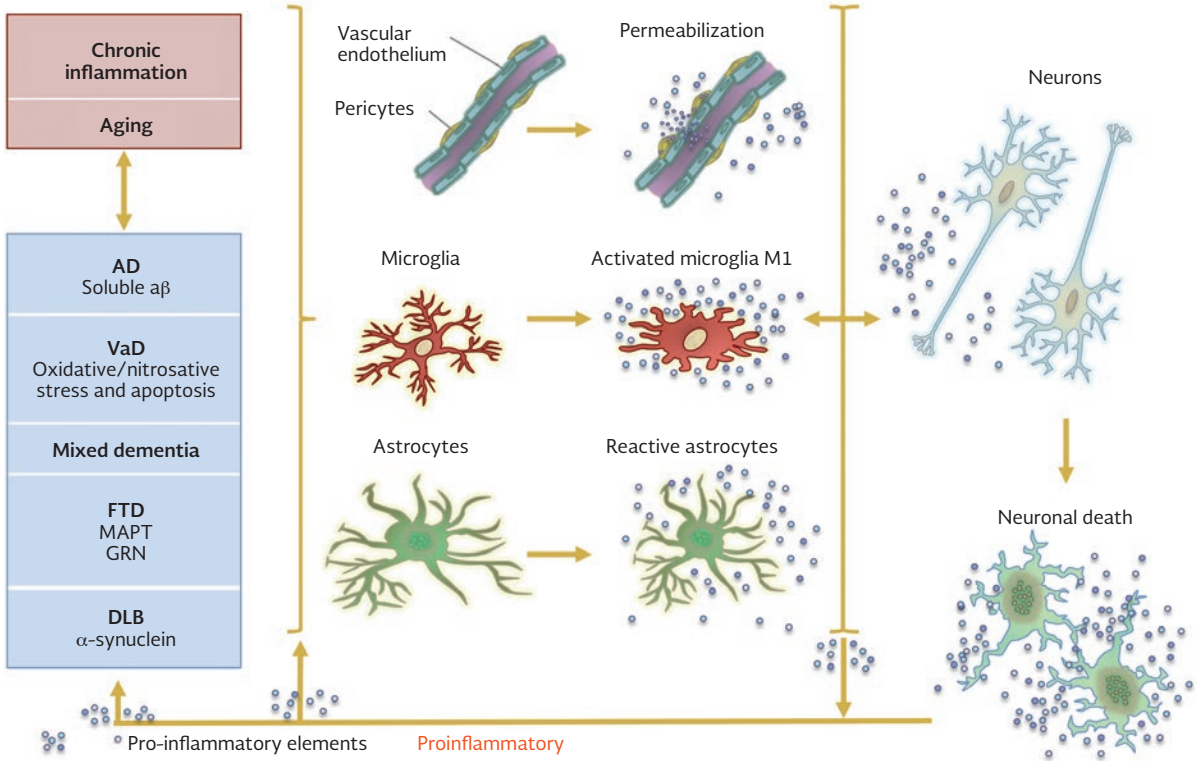
LEWY BODY DEMENTIA

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[99,100]. The level of neuroinflammation observed in patients with DLB seems to be lower than that of patients with other dementias[101]. Nevertheless, a higher number of activated microglia have been found in patients with DLB[102]. Alpha-synuclein is itself a potent activator of microglia and an increased expression of IL-1α and TNFa has been observed in microglia in close proximity to neurons bearing inclusions[103]. In DLB, there is a progressive association of microglia with degenerating Lewy body-containing neurons[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[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[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[106,107]. Moreover, some patients present associated parkinsonism, as in progressive supranuclear palsy and corticobasal syndrome, or motor neuron disease (FTD-MND)[108]. Genetic studies have identified several genes associated with monogenic FTD. The first mutations identified in families with FTD and parkinsonism were in the microtubule-associated protein tau (MAPT) gene in chromosome 17[109]. Forty-four pathogenic mutations in the *MAPT* gene have been identified[110], causing the accumulation of hyperphosphorylated tau protein in neurons and glial cells[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[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[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[112]. Some granulin peptides are able to attract and activate microglia in the brain and increase their phagocytic function[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[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.

Figure 1. The interrelationship between chronic inflammation and dementias in aging.
AD: Alzheimer's disease; VaD: vascular dementia; FTD: frontotemporal dementia; MAPT: microtubule-associated protein tau; GRN: granulin; DLB: dementia with Lewy bodies.



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[116,117]. 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

1. Minghetti L. Role of inflammation in neurodegenerative diseases. Curr Opin Neurol. 2005;18:315-21.
2. Actor JK. A Functional Overview of the Immune System and Immune Components. In: Actor JK (ed.) Introductory Immunology: Basic Concepts for Interdisciplinary Applications. London, UK: Academic Press; 2014. p. 1-15.
3. Licastro F, Candore G, Lio D, et al. Innate immunity and inflammation in ageing: a key for understanding age-related diseases. Immun Ageing. 2005;18:2:8.
4. Shastri A, Bonifati DM, Kishore U. Innate immunity and neuroinflammation. Mediators Inflamm. 2013;2013:342931.
5. Bernardino L, Malva JO. Inflammation and neuronal susceptibility to excitotoxic cell death. In: Malva JO, (ed.) Interaction between Neurons and Glia in Aging and Disease. Boston, MA, USA: Springer; 2007. p. 3-36.
6. Moore CS, Durafourt BA, Antel JP. Innate immunity in the CNS – a focus on the myeloid cell. In: Woodroofe N, Amor S (eds.) Neuroinflammation and CNS Disorders. West Sussex, UK: John Wiley & Sons, LTD; 2014. p. 9-35.
7. Wood P. The immediate response to infection: innate immunity and the inflammatory response. In: Wood P (ed.) Understanding Immunology. 3rd ed. Harlow, England: Pearson; 2011. p. 22-48.
8. Broux B, Gowing E, Prat A. Glial regulation of the blood-brain barrier in health and disease. Semin Immunopathol. 2015;37:577-90.

9. Lampron A, Elali A, Rivest S. Innate immunity in the CNS: redefining the relationship between the CNS and its environment. Neuron. 2013;78:214-32.
10. Alvarez JI, Dodelet-Devillers A, Kebir H, et al. The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. Science. 2011;334:1727-31.
11. Creagh EM, O'Neill LA. TLRs, NLRs and RLRs: a trinity of pathogen sensors that co-operate in innate immunity. Trends Immunol. 2006;27:352-7.
12. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol. 2009;27:519-50.
13. Etienne-Manneville S, Manneville JB, Adamson P, et al. ICAM-1-coupled cytoskeletal rearrangements and transendothelial lymphocyte migration involve intracellular calcium signaling in brain endothelial cell lines. J Immunol. 2000;165:3375-83.
14. Nagyoszi P, Wilhelm I, Farkas AE, et al. Expression and regulation of toll-like receptors in cerebral endothelial cells. Neurochem Int. 2010;57:556-64.
15. Hellström M, Gerhardt H, Kalén M, et al. Lack of pericytes leads to endothelial hyperplasia and abnormal vascular morphogenesis. J Cell Biol. 2001;153:543-53.
16. Graeber MB, Streit WJ, Kiefer R, et al. New expression of myelomonocytic antigens by microglia and perivascular cells following lethal motor neuron injury. J Neuroimmunol. 1990;27: 121-32.
17. Kovac A, Erickson MA, Banks WA. Brain microvascular pericytes are immunoactive in culture: cytokine, chemokine, nitric oxide, and LRP-1 expression in response to lipopolysaccharide. J Neuroinflammation. 2011;8:139.
18. Cartier N, Lewis C-A, Zhang R, et al. The role of microglia in human disease: therapeutic tool or target? Acta Neuropathol (Berl). 2014;128:363-80.
19. Chen Z, Trapp BD. Microglia and neuroprotection. J Neurochem. 2015. [Epub ahead of print].
20. Noda M, Verkhratsky A. physiology of microglia. In: Kettenmann H, Ransom BR, (eds.) Neuroglia. 3rd ed. New York, NY, USA: Oxford University Press; 2013. p. 223-37.
21. Verkhratsky A, Butt AM. Microglia. In: Verkhratsky A, Butt AM, (eds.) Glial Physiology and Pathophysiology. West Sussex, UK: John Wiley & Sons, Ltd; 2013. p. 343-80.
22. Vukovic J, Colditz MJ, Blackmore DG, et al. Microglia modulate hippocampal neural precursor activity in response to exercise and aging. J Neurosci. 2012;32:6435-43.
23. Sundal C. Microglia: multiple roles in surveillance, circuit shaping, and response to injury. Neurology. 2014;82:1846.
24. Block ML, Zecca L, Hong J-S. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci. 2007; 8:57-69.
25. Godbout JP, Johnson RW. Age and neuroinflammation: a lifetime of psychoneuroimmune consequences. Immunol Allergy Clin North Am. 2009;29:321-37.
26. Loane DJ, Byrnes KR. Role of microglia in neurotrauma. Neurother. 2010;7:366-77.
27. Streit WJ. Microglial senescence: does the brain's immune system have an expiration date? Trends Neurosci. 2006;29: 506-10.
28. Hasegawa-Ishii S, Takei S, Chiba Y, et al. Morphological impairments in microglia precede age-related neuronal degeneration in senescence-accelerated mice. Neuropathol. 2011;31:20-8.
29. Ma L, Morton AJ, Nicholson LF. Microglia density decreases with age in a mouse model of Huntington's disease. Glia. 2003; 43: 274-80.
30. Streit WJ, Braak H, Xue Q-S, et al. Dystrophic (senescent) rather than activated microglial cells are associated with tau pathology and likely precede neurodegeneration in Alzheimer's disease. Acta Neuropathol (Berl). 2009;118:475-85.
31. Anderson MA, Ao Y, Sofroniew MV. Heterogeneity of reactive astrocytes. Neurosci Lett. 2014;565:23-9.
32. Kimelberg HK, Nedergaard M. Functions of astrocytes and their potential as therapeutic targets. Neurother. 2010;7:338-53.
33. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol (Berl). 2010;119:7-35.
34. Sofroniew MV. Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neuroscientist. 2014;20: 160-72.
35. Sofroniew MV. Astrocyte responses to central nervous system injury and disease. In: Kettenmann H, Ransom BR (eds.) Neuroglia. 3rd Ed. New York, NY, USA: Oxford University Press; 2013. p. 653-64.
36. Han S, Rudd JA, Hu ZY, et al. Analysis of neuronal nitric oxide synthase expression and increasing astrogliosis in the brain of senescence-accelerated-prone 8 mice. Int J Neurosci. 2010; 120:602-8.
37. Jiang T, Cadenas E. Astrocytic metabolic and inflammatory changes as a function of age. Aging Cell. 2014;13:1059-67.
38. Jyothi HJ, Vidyadhara DJ, Mahadevan A, et al. Aging causes morphological alterations in astrocytes and microglia in human substantia nigra pars compacta. Neurobiol Aging. 2015;36: 3321-33.
39. Rodríguez JJ, Yeh C-Y, Terzieva S, et al. Complex and region-specific changes in astroglial markers in the aging brain. Neurobiol Aging. 2014;35:15-23.
40. Gallo V, Mangin J-M. Physiology of oligodendrocytes. In: Kettenmann H, Ransom BR (eds.) Neuroglia. 3rd ed. New York, USA: Oxford University Press; 2013. p. 238-53.
41. Zeis T, Enz L, Schaeren-Wiemers N. The immunomodulatory oligodendrocyte. Brain Res. 2015. [Epub ahead of print].
42. Bajetto A, Bonavia R, Barbero S, et al. Chemokines and their receptors in the central nervous system. Front Neuroendocrinol. 2001;22:147-84.
43. Gruol DL, Nelson TE. Physiological and pathological roles of interleukin-6 in the central nervous system. Mol Neurobiol. 1997; 15:307-39.
44. Hanke ML, Kielian T. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. Clin Sci (Lond). 2011;121:367-87.
45. Deleidi M, Jäggle M, Rubino G. Immune aging, dysmetabolism, and inflammation in neurological diseases. Front Neurosci. 2015;9:172.
46. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev. 2007; 128:92-105.
47. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69(Suppl 1):S4-9.
48. Streit WJ, Xue Q-S. Human CNS immune senescence and neurodegeneration. Curr Opin Immunol. 2014;29:93-6.
49. Rodríguez-Arellano JJ, Parpura V, Zorec R, et al. Astrocytes in physiological aging and Alzheimer's disease. Neuroscience. 2015. [Epub ahead of print].
50. Streit WJ, Xue Q-S, Tischer J, et al. Microglial pathology. Acta Neuropathol Commun. 2014;2.142.
51. WHO. Dementia. World Health Organization. Available at: http://www.who.int /mediacentre /factsheets/fs362/en/. Accessed September 29, 2015.
52. Rombouts SA, Barkhof F, Witter MP, et al. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. Neurosci Lett. 2000;285:231-3.
53. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med. 2010;362:329-44.
54. Zhang B, Gaiteri C, Bodea L-G, et al. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell. 2013;153:707-20.
55. in t' Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. N Engl J Med. 2001;345:1515-21.
56. Cunningham C, Campion S, Lunnon K, et al. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. Biol Psychiatry. 2009;65: 304-12.
57. Gandy S, Heppner FL. Microglia as dynamic and essential components of the amyloid hypothesis. Neuron. 2013;78:575-7.
58. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol. 2014;14:463-77.
59. Hickman SE, El Khoury J. TREM2 and the neuroimmunology of Alzheimer's disease. Biochem Pharmacol. 2014;88:495-8.
60. Cagnin A, Brooks DJ, Kennedy AM, et al. In-vivo measurement of activated microglia in dementia. Lancet. 2001;358:461-7.
61. Yasuno F, Kosaka J, Ota M, et al. Increased binding of peripheral benzodiazepine receptor in mild cognitive impairment-dementia converters measured by positron emission tomography with [11C]DAA1106. Psychiatry Res. 2012;203:67-74.
62. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015; 16:358-72.
63. Bamberger ME, Harris ME, McDonald DR, et al. A cell surface receptor complex for fibrillar beta-amyloid mediates microglial activation. J Neurosci. 2003;23:2665-74.
64. Khoury J El, Hickman SE, Thomas CA, et al. Scavenger receptor-mediated adhesion of microglia to beta-amyloid fibrils. Nature. 1996;382:716-9.

65. Paresce DM, Ghosh RN, Maxfield FR. Microglial cells internalize aggregates of the Alzheimer's disease amyloid beta-protein via a scavenger receptor. Neuron. 1996;17:553-65.
66. Yan S Du, Zhu H, Fu J, et al. Amyloid-beta peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: a proinflammatory pathway in Alzheimer's disease. Proc Natl Acad Sci U S A. 1997;94:5296-301.
67. Berg J Vom, Prokop S, Miller KR, et al. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. Nat Med. 2012;18:1812-9.
68. Fillit H, Ding WH, Buee L, et al. Elevated circulating tumor necrosis factor levels in Alzheimer's disease. Neurosci Lett. 1991; 129:318-20.
69. Patel NS, Paris D, Mathura V, et al. Inflammatory cytokine levels correlate with amyloid load in transgenic mouse models of Alzheimer's disease. J Neuroinflammation. 2005;2:9.
70. Forloni G, Demicheli F, Giorgi S, et al. Expression of amyloid precursor protein mRNAs in endothelial, neuronal and glial cells: modulation by interleukin-1. Brain Res Mol Brain Res. 1992; 16:128-34.
71. Vasilakos JP, Carroll RT, Emmerling MR, et al. Interleukin-1 beta dissociates beta-amyloid precursor protein and beta-amyloid peptide secretion. FEBS Lett. 1994;354:289-92.
72. Duong T, Nikolaeva M, Acton PJ. C-reactive protein-like immunoreactivity in the neurofibrillary tangles of Alzheimer's disease. Brain Res. 1997;749:152-6.
73. Iwamoto N, Nishiyama E, Ohwada J, et al. Demonstration of CRP immunoreactivity in brains of Alzheimer's disease: immunohistochemical study using formic acid pretreatment of tissue sections. Neurosci Lett. 1994;177:23-6.
74. Cunningham C. Microglia and neurodegeneration: the role of systemic inflammation. Glia. 2013;61:71-90.
75. Hickman SE, Allison EK, El Khoury J. Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. J Neurosci. 2008;28:8354-60.
76. Lucin KM, O'Brien CE, Bieri G, et al. Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease. Neuron. 2013;79:873-86.
77. Griciuc A, Serrano-Pozo A, Parrado AR, et al. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron. 2013;78:631-43.
78. Mawuenyega KG, Sigurdson W, Ovod V, et al. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science. 2010;330:1774.
79. Parkhurst CN, Yang G, Ninan I, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell. 2013;155:1596-609.
80. Armstrong RA. The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease. Folia Neuropathol. 2009;47:289-99.
81. Lukiw WJ, Bazan NG. Neuroinflammatory signaling upregulation in Alzheimer's disease. Neurochem Res. 2000;25:1173-84.
82. Rodríguez JJ, Olabarria M, Chvatal A, et al. Astroglia in dementia and Alzheimer's disease. Cell Death Differ. 2009; 16:378-85.
83. Heneka MT, O'Banion MK, Terwel D, et al. Neuroinflammatory processes in Alzheimer's disease. J Neural Transm. 2010;117: 919-47.
84. Heneka MT, Sastre M, Dumitrescu-Ozimek L, et al. Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APP[V717I] transgenic mice. J Neuroinflammation. 2005;2:22.
85. Rossner S, Lange-Dohna C, Zeitschel U, et al. Alzheimer's disease beta-secretase BACE1 is not a neuron-specific enzyme. J Neurochem. 2005;92:226-34.
86. Jellinger KA. The enigma of vascular cognitive disorder and vascular dementia. Acta Neuropathol (Berl). 2007;113:349-88.
87. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29:125-32.
88. Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments. Lancet Neurol. 2008; 7:246-55.
89. Jellinger KA. Pathology and pathogenesis of vascular cognitive impairment-a critical update. Front Aging Neurosci. 2013;5:17.
90. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci. 2003;4:399-415.
91. Hu X, Li P, Guo Y, et al. Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. Stroke. 2012;43:3063-70.
92. Iadecola C. The pathobiology of vascular dementia. Neuron. 2013;80:844-66.
93. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. Exp Neurol. 2015;272:97-108.
94. Jellinger KA. The enigma of mixed dementia. Alzheimers Dement. 2007;3:40-53.
95. Gold G, Giannakopoulos P, Herrmann FR, et al. Identification of Alzheimer and vascular lesion thresholds for mixed dementia. Brain. 2007;130:2830-6.
96. Sachdev PS, Chen X, Joscelyne A, et al. Hippocampal size and dementia in stroke patients: the Sydney stroke study. J Neurol Sci. 2007;260:71-7.
97. Del Ser T, Hachinski V, Merskey H, et al. An autopsy-verified study of the effect of education on degenerative dementia. Brain. 1999;122:2309-19.
98. Zekry D, Duyckaerts C, Moulias R, et al. Degenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly. Acta Neuropathol (Berl). 2002;103:481-7.
99. Burkhardt CR, Filley CM, Kleinschmidt-DeMasters BK, et al. Diffuse Lewy body disease and progressive dementia. Neurology. 1988;38:1520-8.
100. Graeber MB, Müller U. Dementia with Lewy bodies: disease concept and genetics. Neurogenetics. 2003;4:157-62.
101. Shepherd CE, Thiel E, McCann H, et al. Cortical inflammation in Alzheimer's disease but not dementia with Lewy bodies. Arch Neurol. 2000;57:817-22.
102. Mackenzie IR. Activated microglia in dementia with Lewy bodies. Neurology. 2000;55:132-4.
103. Katsuse O, Iseki E, Kosaka K. Immunohistochemical study of the expression of cytokines and nitric oxide synthases in brains of patients with dementia with Lewy bodies. Neuropathol. 2003;23:9-15.
104. Iseki E, Marui W, Akiyama H, et al. Degeneration process of Lewy bodies in the brains of patients with dementia with Lewy bodies using alpha-synuclein-immunohistochemistry. Neurosci Lett. 2000;286:69-73.
105. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol. 2001;58:1803-9.
106. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011; 76:1006-14.
107. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456-77.
108. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013;80:496-503.
109. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998;393:702-5.
110. Cruts M, Theuns J, Van Broeckhoven C. Locus-specific mutation databases for neurodegenerative brain diseases. Hum Mutat. 2012;33:1340-4.
111. Petkau TL, Neal SJ, Orban PC, et al. Progranulin expression in the developing and adult murine brain. J Comp Neurol. 2010; 518:3931-47.
112. Bateman A, Bennett HP. The granulin gene family: from cancer to dementia. BioEssays. 2009;31:1245-54.
113. Pickford F, Marcus J, Camargo LM, et al. Progranulin is a chemoattractant for microglia and stimulates their endocytic activity. Am J Pathol. 2011;178:284-95.
114. Martens LH, Zhang J, Barmada SJ, et al. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. J Clin Invest. 2012;122:3955-9.
115. Yin F, Banerjee R, Thomas B, et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. J Exp Med. 2010;207:117-28.
116. Jaturapatporn D, Isaac MGEKN, McCleery J, et al. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. Cochrane Database Syst Rev. 2012;2:CD006378.
117. Miguel-Álvarez M, Santos-Lozano A, Sanchis-Gomar F, et al. Non-steroidal anti-inflammatory drugs as a treatment for Alzheimer's disease: a systematic review and meta-analysis of treatment effect. Drugs Aging. 2015;32:139-47.