



REVIEW ARTICLE

The role of glial cells in Alzheimer disease: potential therapeutic implications[☆]

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Received 30 August 2012; accepted 4 October 2012

Available online 21 May 2014

KEYWORDS

Alzheimer's disease;
Microglia;
Astrocytes;
Degeneration;
Inflammation;
Dementia

PALABRAS CLAVE

Alzheimer;
Microglía;
Astrocitos;
Degeneración;
Inflamación;
Demencia

Abstract

Introduction: Alzheimer disease (AD) is a complex neurodegenerative disease characterised by inflammation, neurotoxicity, oxidative stress, and reactive gliosis. Microglia and astrocytes not only act as antigen-presenting cells, but also function as effector cells releasing pro-inflammatory molecules that promote excitotoxicity and neurodegeneration.

Objective: In the present review we discuss the role of glia, specifically microglia and astrocytes, in the pathophysiology of AD and possible therapeutic implications.

Development: The growing body of evidence suggesting that microglia and astrocytes play a pathogenic role and activate inflammation pathways, the neurotoxic factors released by these cells when activated, and the way these factors may disrupt the homeostasis of the central nervous system all support the hypothesis that glia-induced inflammation exacerbates AD.

Conclusions: Inhibiting inflammation by deactivating glial cells may reduce the production of factors which contribute to neurotoxicity, and therefore result in clinical improvement. Microglia and astrocytes are therapeutic targets for the development of new drugs to combat this disease. Therapeutic strategies designed to counter the detrimental effects of overactivation of these cell populations should be investigated.

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Papel de la glía en la enfermedad de Alzheimer. Futuras implicaciones terapéuticas

Resumen

Introducción: La enfermedad de Alzheimer (EA) es una compleja enfermedad neurodegenerativa caracterizada por inflamación, neurotoxicidad, estrés oxidativo y gliosis reactiva. La microglía y los astrocitos no solo actúan como células presentadoras de antígenos, sino que constituyen células efectoras, liberando moléculas proinflamatorias que promueven la excitotoxicidad y la neurodegeneración.

[☆] Please cite this article as: Lopategui Cabezas I, Herrera Batista A, Pentón Rol G. Papel de la glía en la enfermedad de Alzheimer. Futuras implicaciones terapéuticas. Neurología. 2014;29:305–309.

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Objetivo: En la presente revisión bibliográfica se discute el papel de la glía, específicamente de la microglía y el astrocito en la fisiopatología de la EA y las posibles implicaciones terapéuticas. **Desarrollo:** La emergente evidencia del papel patogénico y la activación de vías de inflamación a partir de la microglía y el astrocito, los factores neurotóxicos liberados por estas células cuando están activadas, y cómo estos pueden desestabilizar la homeostasis del sistema nervioso central, sostienen la idea de que la inflamación inducida por la glía amplifica la EA.

Conclusiones: La inhibición de la inflamación por inactivación de la glía, pudiera reducir la producción de factores que contribuyen con la toxicidad, resultando ser un beneficio clínico. La microglía y el astrocito constituyen blancos terapéuticos en el desarrollo de nuevos fármacos para combatir esta enfermedad. Estrategias terapéuticas diseñadas para contrarrestar el efecto perjudicial de la sobreactivación de estas poblaciones celulares deben ser investigadas.

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Introduction

Alzheimer's disease (AD), the most prevalent form of dementia in the world, accounts for approximately 50% to 60% of all dementia cases.¹ Considering that ageing is one of the main risk factors in AD,² and given the rise in life expectancy in some countries, the prevalence of AD is likely to increase. At present, no drugs or drug combinations have shown high levels of both safety and efficacy for treating AD.

Many factors are involved in the pathogenesis of this complex disease. Although there have been many advances in AD research, unanswered questions remain. This study will discuss the role of glial cells, especially microglia and astrocytes, in AD pathophysiology. It also focuses on potential therapeutic interventions that would target these cells.

Procedure

AD is a neurodegenerative disorder characterised at the tissue and molecular levels by excessive accumulation of extracellular aggregates formed by amyloid peptides, mainly A β ₄₀ and A β ₄₂. These peptides are deposited in plaques on the cerebral parenchyma, particularly near the hippocampus and cerebral cortex. We do not yet know the main cause of processing the amyloid precursor protein (APP), a protein measuring approximately 110 kDa, by the amyloidogenic pathway.³ By means of that pathway, APP is initially cleaved by β -secretase, yielding a membrane-bound peptide of 99 amino acids; this is the C-terminal fragment β (CTF β). The other fragment, β -APP, is soluble and located outside the cell. Next, the CTF β fragment is acted on by the γ -secretase complex to yield the A β peptide towards the cell exterior and AICD (APP intracellular domain) in the cell interior. In the non-amyloidogenic pathway, which is dominant in healthy individuals, APP is initially cleaved by α -secretase to produce the CTF α fragment with 83 amino acids (CTF α). The action of α -secretase will later yield AICD and p3 peptides; both are soluble and tend not to form plaques.^{4,5}

Apart from the amyloid deposits between cells in AD, we also find neurofibrillary tangles, aggregates of hyperphosphorylated tau protein that form within neurons.⁵ Oxidative stress and mitochondrial dysfunction have also been identified as determinants of neurodegeneration.⁶ Disease progression is partially attributed to abnormal local immune

responses⁷ in an environment characterised by inflammation, abundant astrocytes, and activated microglia.⁸

Microglia and astrocytes, cell populations that are present near neurons, play an important role in AD pathogenesis.⁵

Microglia are hematopoietic in origin, have phagocytic capability, and are found in the central nervous system (CNS). They perform functions related to the immune response in a wide variety of neuroinflammatory processes. Their high functional plasticity is demonstrated by the fact that they are activated by a number of different diseases that affect the CNS.⁹ Activated microglia express different types of cell surface molecules, including Fc receptors, scavenger receptors, cytokine and chemokine receptors, CD11b, CD11c, CD14, and major histocompatibility complex (MHC) molecules.¹⁰

Activated microglia have a wide variety of pattern recognition receptors from the Toll-like receptor group (TLR) that detect microbial intruders.¹¹ Thirteen types of TLR receptors have been identified in mammals and microglia express TLRs 1 through 9 at the very least.¹⁰

Conflicting opinions exist regarding the role of neuroinflammation; some authors attribute a protective effect to this process.^{12,13} Researchers have hypothesised that microglial activation in some CNS disorders may counteract pathogenic changes by facilitating the release of immune-suppressing and neurotrophic factors.^{14,15}

In other diseases including AD, Creutzfeldt–Jakob disease, HIV-associated dementia, cerebral infarct, and multiple sclerosis, findings seem to show that microglial activation is harmful, since activated microglia act as antigen-presenting cells (APC) and produce neurotoxic molecules.¹⁶

In AD, activated microglia have been found in strategic locations around senile plaques; the A β peptide itself activates microglia and astrocytes through TLRs 2, 4, and 9.¹⁰

After stimulation, TLRs initiate a signal cascade that involves MYD88 and the activation of transcription factors including NF- κ B and AP-1.¹⁷

Recent publications have established an inverse relationship between microglial activation and neurogenesis.^{18–20}

Following activation, microglia are able to trigger a proinflammatory cascade that results in the release of cytotoxic molecules such as cytokines, complement

proteins, proteases, and other acute-phase proteins. Microglia release cytokines (IL-1 α , IL-1 β , IL-6, IL-10, IL-12, IL-16, IL-23, TNF- α , TGF- β); chemokines (CC [CCL2/MCP-1, CCL3/MIP-1 α , CCL4/MIP-1 β , CCL5/RANTES]; CXC [CXCL8/IL-8, CXCL9/MIG, CXCL10/IP-10, CXCL12/SDF-1 α]; CX3C [CX3CL1/fractalkine]); matrix metalloproteinases (MMP-2, MMP-3, MMP-9); and eicosanoids (PGD₂, leukotriene C₄, cathepsins B and L, and complement factors C1, C3, and C4),²¹ which also induce astrocyte chemotaxis around plaques.²²

High levels of chemokines, and chemokine receptors IL-1a, CXCR2, CCR3, CCR5, and TGF- β , have been reported in postmortem studies of individuals with AD.²²

Activated microglia also release excessive quantities of glutamate, thereby inducing excitotoxicity and neurodegeneration.¹⁰

The inflammatory response in AD includes morphological changes in microglia, producing forms that range from ramified quiescent cells to active amoeboid cells.^{5,22}

Several articles have indicated that cells from the bone marrow may cross the blood–brain barrier and differentiate into microglial cells within the CNS, and that these cells surround amyloid plaques.^{23,24} Researchers have focused on this finding in particular²⁵ because if resident activated microglia are not competent to eliminate amyloid deposits, peripheral microphages may be able to remove them through phagocytosis.

In light of the above, being able to distinguish resident microglia from microphages is critical for determining the functional role played by these cells. However, our ability to distinguish these cells' origin and lineage remains limited.

Various differences are present: quiescent microglia are characterised by their small soma and numerous branches, while resting monocytes/macrophages have a round, oval, or amoeboid appearance. Nevertheless, this observation is not very useful; after being activated, microglial cell processes become shorter and the soma are enlarged, meaning that the cell's shape resembles that of a peripheral macrophage.²⁴

Resting macrophages are characterised by constitutive expression of specific cell surface antigens, including class II MHC molecules, CD45, CD64, and CD68, CD86, and F4/80 antigens. Although microglia may be induced to express the same markers after they are activated, it is generally accepted that expression of CD45 is more abundant in peripheral macrophages than in activated microglia.²⁶

With this in mind, it is useful to study levels of specific markers such as CD45, Ly-6C, Ly-6G, and the chemokine receptor CCR2 in mononuclear phagocytes, since these markers are thought to be expressed when macrophages migrate to the CNS.²⁷

Microglial activation elicits the proliferation of astrocytes,²⁸ which are the most abundant glial cells. Under physiological conditions, they perform important functions within the CNS: they provide physical and metabolic support to neurons, participate in the formation and maintenance of the blood–brain barrier, produce neurotrophic and neuroprotective factors, and participate in CNS repair processes.²⁹

The role of microglia as APCs has been thoroughly documented. How astrocytes contribute to this process is

still being debated, however. Astrocytes require activation, which involves IFN- γ inducing expression of class I or II MHC molecules; the former present antigens to CD8+ cells while the latter present them to CD4+ cells. Microglia are more effective as APCs when they are previously stimulated with IFN- γ . However, astrocytes are considered non-professional APCs.²⁹

In AD, astrogliosis manifests as increases in the number, size, and motility of the astrocytes surrounding senile plaques.²⁹

Grathwohl et al. used ganciclovir to provoke complete ablation of microglia in transgenic mouse models of AD and found that the deposition and maintenance of amyloid plaque did not depend on the presence of these glial cells.³⁰ In contrast, other authors reported that the NF- κ B signal pathway in microglia was critically involved in neuron death induced by amyloid- β peptide.³¹

The products derived from cell death activate not only microglia, but also astrocytes through engagement of the receptor for advanced glycation end products (RAGE).¹⁰

In the environment of chronic inflammation that characterises AD, activated astrocytes produce numerous proinflammatory molecules just as microglia do. One of these molecules is S100 β , which is overexpressed by reactive astrocytes located near amyloid- β plaques. The authors of one interesting study show that prolonged astrocyte activation has a detrimental effect on neuron survival and find S100 β directly responsible for this effect. They suggest that inhibiting both S100 β biosynthesis and astrogliosis constitutes a promising therapeutic strategy for delaying AD progression.³²

Several epidemiological studies have found that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may protect individuals bearing one or more ϵ 4 alleles of apolipoprotein E (*APOE***E*4) from developing AD. NSAID use is associated with a greater level of protection against this disease.^{33–35}

Some authors have indicated that when the A β deposition process has reached advanced stages, NSAID treatment is no longer effective.³³ We stress that these results are inconclusive and that further investigation of this subject is needed.

A recent article states that inhibition of caspase 3 and 7, important apoptosis executioners, hinder microglial overactivation and consequently impede neurotoxicity.³⁶ These results reawaken interest in caspase inhibitors as potential therapeutic agents in CNS diseases that progress with neuroinflammation and glial overactivation.

García Alloza et al. analysed the direct effects of microglial activation and inhibition on A β peptide clearance. After deactivating microglia with minocycline, they detected peptide clearance³⁷; this points to the role of microglia in pathogenesis and identifies these cells as potential therapeutic targets.

Using minocycline to limit microglial overactivation in animal models of AD (double-transgenic mice, APP/PS1) increases survival of new dentate granule cells, which is accompanied by improvements in hippocampus-dependent learning.³⁸ These results show that microglia play a crucial role in the survival of new neurons, and also demonstrate that modulating microglial function with minocycline may protect hippocampal neurogenesis in individuals with AD.

Conclusions

Emerging evidence of the role that microglia and astrocytes play, and how they activate common inflammation pathways, supports the hypothesis that these inflammation-inducing cells act as AD amplifiers.

Although inhibiting inflammation by means of the molecules and cells that mediate the process may not alter the underlying causes of the disease, it may reduce the proliferation of factors contributing to neurotoxicity and therefore yield clinical benefits. A firm understanding of all types of inducers, sensors, transducers, and effectors of neuroinflammation may make it possible to achieve this goal.

As our knowledge of this disease's pathogenic mechanisms increases, findings suggest that molecular events related to microglia and astrocytes play a fundamental part and require further investigation.

Limiting overactivation of microglia and astrocytes may be a treatment target for AD. Future treatment strategies designed to counteract the harmful effects of overactivation in these cell types should be researched.

Conflicts of interest

The authors have no conflicts of interest to declare.

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