

REVIEWS

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The Role of Mast Cells in Alzheimer's Disease

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Immunity and inflammation are deeply involved in Alzheimer's disease. The most important properties of pathological Alzheimer's disease are the extracellular deposits of amyloid β -protein plaque aggregates along with other unknown mutated proteins, which are implicated in immunity and inflammation. Mast cells are found in the brain of all mammalian species and in the periphery, and their biological mediators, including cytokines/chemokines, arachidonic acid products and stored enzymes, play an important role in Alzheimer's disease. Cytokines/chemokines, which are generated mostly by microglia and astrocytes in Alzheimer's disease, contribute to nearly every aspect of neuroinflammation and amyloid β -protein plaque aggregates may induce in mast cells the release of a plethora of mediators, including pro-inflammatory cytokines/chemokines such as interleukin-1, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor- α , vascular endothelial growth factor, transforming growth factor β , CXCL8 and CCL2-3-4. These proinflammatory cytokines/chemokines are prominent mediators of neuroinflammation in brain disorders such as Alzheimer's disease, and their inhibition may be associated with improved recovery. In this review, we summarize the current knowledge regarding the roles of mast cell mediators (stored and *de novo* synthesis) in the pathogenesis of Alzheimer's disease (*Adv Clin Exp Med* 2016, 25, 4, 781–787).

Key words: inflammation, immunity, mast cell, Alzheimer's disease.

Alzheimer's disease was first described in 1907. Currently, more than 35 million people worldwide (5.5 million in the United States) have it and 1 in 3 elderly people dies of some kind of dementia. More women are affected by Alzheimer's disease, which is the most common, irreversible, neurodegenerative disorder of the central nervous system in the elderly, resulting in cognitive impairment and dementia [1]. This disease is a very complex, predominantly idiopathic disorder, which is still poorly understood [2]. Several different mechanisms have been suggested to contribute to neuronal death in Alzheimer's disease, including environmental factors, nutritional habits, and genetic predisposition. Studies on DNA sequences in patients with Alzheimer's disease have revealed a mutation gene encoding the precursor protein amyloid β , on chromosome 21, and also two similar genes on chromosome 14, presenilin 1 and presenilin 2 on chromosome 1 [3]. Data is accumulating to support the hypothesis that aggre-

gates of amyloid- β along with other unknown mutated proteins are neurotoxic and may explain the pathogenesis in Alzheimer's disease [4]. To date, a great deal of laboratory and clinical data indicates that immunity and inflammation play an important role in the pathogenesis of Alzheimer's disease [5, 6]. This is supported by findings that the genes for immune receptors are associated with Alzheimer's disease [7]. The two most important characteristics of pathological Alzheimer's disease are extracellular deposits of amyloid β -protein plaques in the cerebral cortex and intracellular neurofibrillary tangles of hyperphosphorylated tau protein [8]. Also, the hippocampus and neocortex of patients affected by Alzheimer's disease include a high number of amyloid plaques, which can be detected with amyloid β protein antibody [9].

These pathological conditions lead to an inflammatory process and play an important role in the pathogenesis of this disease.

The brain of Alzheimer's disease patients contains plaques and neurofibrillary tangles, inflammatory markers such as C-reactive protein, proinflammatory cytokines/chemokines, and activated complement cascade proteins. The inflammatory process with the activation of inflammatory cytokines/chemokines, and neurotoxins is probably initiated or stimulated by amyloid β -protein peptides which are natural products of the metabolism consisting of 36 to 43 amino acids that exert local and general inflammatory effects [10]. High concentrations of cytosolic calcium stimulate amyloidogenesis and amyloid beta aggregation [11].

Many types of cells contribute to inflammation, including macrophages and mast cells [12, 13]. Mast cells are found in the brain of all mammalian species and in the periphery, and they are physiologically active [14]. Normal, healthy subjects present few mast cells in the perivascular area of the blood vessels of the brain, while patients with Alzheimer's disease have a higher number of infiltrated mast cells producing tryptase, and inflammatory cytokines/chemokines which contribute to patch generation, increase inflammatory processes and contribute to the degree of the disease [15]. For several years, a number of reports have indicated that brain proinflammatory cytokines play an important role in the pathogenesis of psychiatric disorders, and in particular in Alzheimer's disease [16], and the fact that this theory still provokes debate reflects the complexity of this disease. The increased gene expression of inflammatory cytokines and mitochondrial dysfunction are found in neuropsychiatric diseases, including bipolar disorders, depression and Alzheimer's disease [16]. These effects may be reduced by non-steroidal anti-inflammatory drugs, which reduce specific serotonin receptor antagonists and predisposes the patient to a lower risk of developing Alzheimer's disease. Corticosteroids are more potent anti-inflammatory drugs, exacerbate depression and probably do not impede the pathogenesis of Alzheimer's disease [17].

Mast Cells

Mast cells, first described in 1876 by Paul Ehrlich, are hematopoietically-derived immune cells, which are commonly found adjacent to blood vessels in the lamina propria of airway mucosa and produce pathophysiological changes in various organs, leading to the development of different inflammatory disorders [18, 19] (Fig. 1).

Mast cells are important for the development of allergic reactions through cross-linking of their surface high affinity receptors for IgE (Fc ϵ RI),

Mast cells \rightarrow activation (Fc ϵ RI) \rightarrow c-Jun N-terminal kinase \rightarrow generation:

- tryptase, histamine, chymase, NO, 5-HT, TNF, PAF
- cytokines: IL-1, IL-6, IL-4, IL-5, IL-6, IL-8 and IL-33, GMCSF, TGF β
- chemokines: CXC and CC
- arachidonic acid products: PGD₂, LTB₄, LTC₄

Fig. 1. Mast cell activation and mediators release

TNF - tumor necrosis factor; IL - interleukin; PAF - platelet activating factor; CC - chemokine; PG - prostaglandin; LT - leukotriene

leading to immediate degranulation and slow release of newly synthesized vasoactive, pro-inflammatory and nociceptive mediators, including histamines, cytokines, arachidonic acid metabolites, proteolytic enzymes and PAF, which all participate in the inflammatory reaction (Table 1) [20, 21]. We have recently found that some compounds, such as cytokines/chemokines, and growth factors can be released selectively without degranulation, then participate in inflammatory disorders and autoimmunity [22]. Cytokines/chemokines, which are generated mostly by microglia and astrocytes in Alzheimer's disease, contribute to nearly every aspect of neuroinflammation [19]. The intracellular protease caspase 1, which cleaves the precursor of interleukin (IL)-1 and IL-18 into bioactive cytokines, is detected in the brains of patients with Alzheimer's disease. Ageing TgAPPsw and PSAPP transgenic mice show an increase of amyloid beta concentration along with an augmentation of proinflammatory cytokines, such as IL-1, tumor necrosis factor (TNF), IL-6, and GM-CSF, which are further increased in the microglia treated with pre-aggregated A β ₁₋₄₂ [23]. In addition, IL-1 can be generated by the microglia after stimulation with amyloid beta *in vitro* [24]. Mast cells promote angiogenesis by generating vascular endothelial growth factor (VEGF), proteases and cytokines/chemokines [25, 26]. VEGF is an angiogenic factor expressed in the central nervous system (CNS) which increases neuroinflammatory disorders, including Alzheimer's disease, and plays an important role in acute and chronic inflammation, secreted mast cells and mediators. In particular, vasoactive compounds such as serotonin, histamine, TNF, heparin and proteases, modulate inflammation and regulate the permeability in several disorders of the CNS [23]. Research efforts in the past decade have highlighted that the activation of mast cells plays a role in neuroinflammation [27].

Table 1. Biological effects of mast cell mediators

Mediators	Biological effect
<u>Cytokine</u> : TNF, IL-1, 2, 3, 5, 6, 7, 9, 13, 16, and 33	inflammation IL-4, IL-10, IL-13, IL-37
<u>Chemokines</u> : IL-8, RANTES, MCP-1, 3, and 4	chemo-attraction
<u>Growth factors</u> : CSF, GM-CSF, SCF, VEGF, and NGF	neuronal cell growth
<u>Stored enzymes</u> : Trypsase	tissue damage inflammation
Chymase	angotensin II synthesis
Phospholipases	arachidonic acid activation
Kinogenases	pain; kinins synthesis vasodilation
Carboxypeptidase A	peptide processing
Cholinesterase	neurotransmitter catabolism
<u>De novo synthesized compounds</u> : LTB4	leukocyte chemotaxis
LTC4	pain and vasoconstriction
Prostaglandin D2	pain and vasodilation
NO	vasodilation
PAF	platelet activation and 5HT release
Biogenic amines (histamine & 5HT)	inflammation and vasodilation

TNF – tumor necrosis factor; IL – interleukin; RANTES – regulated on activation normal T expressive and secreted; MCP – monocyte chemotactic protein; CSF – colony stimulating factor; SCF – stem cell factor; VEGF – vascular endothelial growth factor; NGF – nerve growth factor.

Alzheimer's disease and autoimmune diseases have increased dramatically over the years. Perhaps, a possible common link between mast cells, which participate in innate, acquired immunity, autoimmunity and inflammation, and Alzheimer's disease exists. Resident phagocytes and mast cells of the CNS, are ubiquitously distributed in the brain. In particular, 97% of mast cells are found in the perivascular zone of the microvasculature, while others are found in the brain parenchyma, leptomeninges, and choroid plexus. It has also been reported that mast cells form part of the neurovascular unit and are key players in the inflammatory response [28]. Neuroinflammation may contribute significantly to the pathogenesis of several neurodegenerative disorders including Alzheimer's disease. Mast cells play a relevant role in the pathogenesis of Alzheimer's disease. In fact, a large number of mast cells have been detected in the brains of Alzheimer patients [28]. In patients with Alzheimer's disease, mast cells migrate into the brain and play a significant role in the pathophysiology of the disease through the release of multiple mediators. Mast cells also mediate the effect of stress and, after activation, they rapidly secrete histamine, prostaglandin D₂ (PGD₂), leukotriene C₄ (LTC₄) and trypsin, which induce vasoconstriction and edema along with preformed protein, such as TNF, that contributes to the inflammatory reaction [29].

Proinflammatory cytokines are prominent mediators of neuroinflammation in brain disor-

ders and the inhibition of inflammatory cytokines is associated with improved recovery. Astrocytes and microglia are the most important source of cytokines in Alzheimer's disease and chemokines regulate microglial migration to areas of neuroinflammation [23]. In addition, activated microglia generates CCL2, CCR3, and CCR5 in Alzheimer's disease; while astrocytes which are located near amyloid beta plaques produce CCL4 [30]. In an experimental animal model, amyloid beta also generated CXC chemokine (CXCL8) and CC (CCL2, CCL3, and CCL4) mediating inflammation [31].

Activated mast cells also release newly synthesized chemokines (CXC and CC) such as macrophage inflammatory protein (MIP)-1 β , MIP-1 α and cytokines IL-1, IL-4, IL-5, IL-6, IL-8 and IL-33, which increase smooth muscle hyper-responsiveness [32]. The activated MC product recruits other immune cells, including T cells [22]. Activated mast cells also release granulocyte macrophage colony stimulating factor (GM-CSF) and transforming growth factor β (TGF β), which are important factors for the maturation and production of Th17 cells, while TNF drives IL-6-independent Th17 cell maturation [33]. Mast cells oppose Treg cell suppression and promote the development of T17 cells involved in autoimmune disorders [34]. They can also induce TGF β 1 expression in SMC via release of trypsin and can be activated by various immune and environmental triggers including

toll-like receptor (TLR) ligands, leading to a release of different cytokines/chemokines [35].

Therefore, mast cells play a major role in inflammation and they are recruited by human recombinant RANTES (hrRANTES) and hrMCP-1 in mice, generating a marked inflammatory state [36]. RANTES and MCP-1 are C-C chemokines, members of the β intercrine subfamily, reported to be selective chemoattractants for the recruitment of inflammatory cells including monocytes and mast cells, with chemoattraction potential, that mediates the complement component C5a in allergic diseases. RANTES and MCP-1 do not contribute to the accumulation of PMN. Mice of a mutant genotype are useful in investigations of the origin of tissue mast cells and for analyses of mast cell biology. When hrRANTES and hrMCP-1 are injected into genetically mast cell-deficient W/W^v mice, with mutant alleles at the W locus (the number of mast cells in the tissue of WBB6F1) (WB-W/1C57BL/6-W^v/0W/W^v is less than 1%), the inflammatory effect is not present. In addition, human RANTES and MCP-1 provoke increased transcription of histidine decarboxylase mRNA in the muscle tissue of mice. We showed a lack of effects in genetically mast cell-deficient W/W(V) mice, a result specifically inhibited by an anti-RANTES antibody [36].

These studies clearly demonstrate that hrRANTES acts mainly on bone marrow-derived tissue mast cell recruitment in producing inflammation. Injection of hrRANTES and MCP-1 into normal mice also induced histamine generation, due to the accumulation of mast cells recruited by these two chemokines, and the production of histidine decarboxylase mRNA level which is an important basophilic cell, and a biochemical and functional marker responsible for the formation of histamine from histidine.

hrRANTES and hrMCP-1 induce histidine decarboxylase expression, which is evidenced at the mRNA level compared to the controls. This effect can be abolished in the presence of actinomycin D, which inhibits mRNA transcription [36].

These studies contribute to the understanding of the mechanisms by which mast cells profoundly affect acute inflammatory responses *in vivo* and suggest that the antagonist(s) of RANTES and MCP-1 may have inhibitory biological effects on inflammatory conditions and, therefore, in Alzheimer's disease. This may lead to the inhibition of neuroinflammation and reduction of amyloid plaque pathology.

Experimental animals with caspase 1 deficiency have less incidence of contracting Alzheimer's disease and neuroinflammatory disorders [37]. TNF, IL-6, IL-1 from caspase 1 activation [38] and

other mast cell-generated cytokines, and innate immune receptors such as TLR4, along with the chemokines MCP-1 and RANTES, can be detected at increased levels in microglial and mast cells surrounding amyloid beta plaques in the brains of patients with Alzheimer's disease. This situation might impair neuronal function even before leading to structural changes [39]. Moreover, the innate immune receptor TLR4 is responsible for increased concentrations of TNF α and MIP-1 α in mouse models of Alzheimer's disease [40].

The inhibition of these cytokines/chemokines may reduce Alzheimer's disease-like pathology. On the other hand, some beneficial forms of pro-inflammatory microglia activation potentially help to reduce Alzheimer's disease-like pathology in mouse models [41].

Therefore, more *in vivo* and *in vitro* studies on the effect of RANTES and MCP-1 are required to clarify the specificity of the pro-inflammatory effect of these and other chemokines on Alzheimer's disease. However, to better understand the new evidence revealed in this report, studies involving the antagonisms of RANTES, MCP-1 and other chemokines through competitive receptor binding are underway.

Data is accumulating to support the notion that the pathogenesis of Alzheimer's disease is not restricted to the neuronal compartment, but includes other interactive mechanisms, such as inflammatory and immunological reactions, contributing to the pathogenesis of the plaques and tangles. Tryptase is a protease generated by human activated and degranulated mast cells with pro-inflammatory activity, present in the human brain and localized in the perivascular of human blood vessels in low concentrations [42].

Immunopositive patches of Alzheimer's disease patients generate tryptase from the brain blood vessel wall where a great number of mast cells are infiltrated, compared to normal subjects [30]. These findings suggest that stimulated mast cells are present in the brain of Alzheimer's disease patients, thus implicating an active immune mechanism with cytokine released in the pathogenesis of Alzheimer's disease. Research efforts in the past decade have highlighted a relevant role for cytokines and chemokines released systemically in the brain as well as locally by activated mast cells, and macrophages [43]. The inflammatory cytokines favor the formation and intracellular accumulation of amyloid beta, and also contribute to the activation of protein complexes, such as inflammasomes [44]. Mast cell immune activation causes functional and structural changes and leads to chronic neuroinflammation and neuronal degeneration, which contribute significantly to the pathogenesis of sev-

eral neurodegenerative disorders, including Alzheimer's disease [45].

Type 1 transmembrane amyloid precursor protein is cleaved by two proteases, beta-site amyloid precursor protein that cleaves enzyme 1 to generate a C-terminal fragment and secreted soluble peptide amyloid precursor protein beta [23]. In turn, the C-terminal fragment is processed by presenil 1 and 2 to release amyloid β peptide. Amyloid beta clusters bind to cell receptors, including TLRs, causing the generation and release of pro-inflammatory cytokines such as IL-1, IL-18, IL-32, TNF and arachidonic acid products, such as the PGD2 released by mast cells [10]. Therefore, these findings support the theory that inflammatory cytokines/chemokines contribute to the development and progression of Alzheimer's disease. Resident mast cells in the plaque also generate and release histamine, which activates other immune cells, such as microglia, through the histamine receptors H₁ and H₄, to generate pro-inflammatory cytokines, including IL-6 and IL-33, and inducible nitric oxide synthase (iNOS) [30]. Inflammatory mediators released by mast cells, such as PGD2, histamine, and cytokine/chemokine, exacerbate the inflammatory process in Alzheimer's disease and other neurodegenerative disorders.

It has been reported that several antidepressants attenuate the neuroinflammatory response through stabilizing mast cells and blocking their activation [46].

The inhibition of mast cell receptors and therefore, inflammatory mediators, may represent a new therapeutic strategy for Alzheimer's disease and other neurological pathologies.

Since Alzheimer's disease begins years before memory confusion symptoms become evident, some substances in saliva may signal the first mild cognitive impairment, which often precedes Alzheimer's disease. In this respect, two drugs that soak up the amyloid plaques and reduce the damaging protein deposits are being studied with many effective therapeutic expectations.

In this report we support the hypothesis that inflammatory mast cells may play an important role in the pathogenesis of Alzheimer's disease, even though a lot of the data on the potential role of inflammation on Alzheimer's disease is contradictory.

Our studies contribute to an understanding of the mechanisms by which mast cells profoundly participate and affect neuroinflammation in Alzheimer's disease and suggest that the antagonist(s) of its mediators, including inflammatory cytokines/chemokines may have beneficial effects.

Nonetheless, this hypothesis requires further research, since it may help to identify new treatment targets for Alzheimer's disorder and other debilitating disorders.

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