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REVIEW ARTICLE

The Role of Chemokines in Alzheimer's Disease

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Abstract: ***Objective:*** The most common multifactorial neurodegenerative disorder occurring in old age is Alzheimer's disease. The neuropathological hallmarks of that disorder are amyloid plaques with the presence of β-amyloid aggregates, intraneuronal tau protein tangles, and chronic inflammation. Brain cells such as microglia and astrocytes are inflammatory cells associated with Alzheimer's disease and involved in the production of inflammatory mediators, such as cytokines and chemokines. Chemokines consist of a large family of protein mediators with low molecular weight, which able to control the migration and residence of all immune cells. In pathological conditions, such as Alzheimer's disease, chemokines contribute to the inflammatory response by recruiting T cells and controlling microglia/macrophages activation.

Methods: The present study focuses on the role that chemokines and their receptors play in Alzheimer's disease and in processes such as inflammation and oxidative stress.

Results: Chemokines are important mediators in AD and inflammation. They promote Aβ deposition and TAU hyperphosphorylation aggravating and increasing the progression of AD. Moreover, they affect the processing of senile plaques and produce abnormal TAU phosphorylation.

Conclusion: There is no cure for AD but the therapeutic potential of chemokines to control the development of the disease may be a field of study to consider in the future.

Keywords: Alzheimer's disease, amyloid precursor protein, β-amyloid, chemokines, chemokine receptors, inflammation.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common multifactorial neurodegenerative disorder, within old age. The disorder consists mainly of progressive and irreversible deterioration in mental functions, such as cognition and memory, progressing to remote memory impairment as the disorder progresses. The neuropathological hallmarks of AD are amyloid plaques with β-amyloid depositions and intraneuronal hyperphosphorylated amyloid precursor protein (APP) tangles [1, 2]. The distribution of β -amyloid depositions is located throughout the brain, most specifically, in the cerebral cortex and in the hippocampus of AD patients [3].

A neuropathological process to consider in AD is inflammation. The cells involved in this process are neurons, astrocytes, and microglia which, when stimulated, produce inflammatory mediators [4, 5]. Microglia and astrocytes normally react to disease stress to resolve pathological states. However, in chronic neurodegenerative diseases, microglia and astrocytes can change the phenotype, with subsequent alteration in their helpful functions. These cells can sometimes release reactive oxygen species (ROS), reactive nitrogen species (RNS), chemokines, and cytokines [6, 7] and are known as reactive glial cells which can promote neuronal death. These cells use gene expression and glial scar formation mechanisms to promote functional changes, which can be either beneficial [8] or detrimental [9] to cells. A co-localization of neurofibrillary tangles and amyloid-β with reactive glial cells have been detected in animal models and in brains of AD patients [10, 11].

This review focuses on the role that chemokines play in Alzheimer's disease.

2. MATERIAL AND METHODS

This review focuses on the most recent studies on the implication of chemokines and their cellular receptors in Alzheimer's disease and underlying processes, such as inflammation and oxidative stress. In this sense, the physiopathological role of chemokines in relation to amyloid plaques development and TAU hyperphosphorylation was analyzed. The research for the most relevant studies in the field was carried out by consulting MEDLINE (1991-2019) and EMBASE (1991-2019).

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3. CHEMOKINES. RESULTS AND DISCUSSION

Chemokines are small heparin-binding proteins that generally have a low molecular weight from 7 to 15 kDa. This family of proteins is divided into four subcategories, depending on the number of amino acids separating two cysteine residues, therefore: α (CXC), β (CC), γ (CX3C), and δ (C) [12, 13]. Chemokines carry out their function through chemokine receptors from a superfamily of G-protein-coupled receptors and are classified in the same manner. Many Chemokines bind to more than one receptor and many receptors conjugate to various Chemokines. Immune cells and cells from the nervous system such as microglia, astrocytes, oligodendrocytes, Schwann cells, endothelial cells, and neurons can release chemokines after being stimulated by pathogens or unregular cells [14] (Ramesh *et al*., 2013). Regarding receptors, specifically, neurons express CXCR2, CXCR3, and CXCR4, microglia express CCR2, CCR5, and CX3CR1, and astrocytes express CXCR2, CXCR4, CCR1, CCR2, CCR3, CCR5, CCR10, CCR11, and CX3CR1 [13]. Chemokines and their receptors are able to control the migration and the residence of all immune cells. Some of them are considered pro-inflammatory and can induce immune response at the site of infection, and others are considered homeostatic, controlling cell migration during development and the maintenance of the tissue (Table **1**) [15, 16].

3.1. CCL1 and its Receptor CCR8

CCL1 is the ligand of CCR8 that encodes a member of the β-chemokine receptor family [17]. A decrease in CCL1 expression and an increased expression of CCR8 in APP/PS1 mice compared to Wild type mice has been demonstrated [7], indicating a rise in receptor expression to supply downregulation of its chemokine. CCR8 is expressed in neurons, microglia, and astrocytes [18] and is furtherly controlled by skin-specific factors. Furthermore, CCR8 accumulates microglial cells in the CNS of APP/PS1 mice [18], promoting chemotaxis of mononuclear cells and phagocytosis. Inflammation occurred during Alzheimer's disease produced high liberation of cytokines and chemokines, which accelerated the inflammatory cascade [19]. Stimulation of primary microglial cultures by lipopolysaccharides diminished the expression of CCL1 in a mouse model of diabetic neuropathy [20] and CCL1/CCR8 cross-talk promoted the development of inflammation in AD with decreases in CCL1 expression [7]. Regarding microglial phagocytosis: CCL1 eliminated neurotoxic molecules, debris, or microbes [21]. A decrease in CCL1 production may explain the decline in phagocytic elimination of Aβ detected in AD [22]. Furthermore, in Taiep rats, an accumulation of microglial cells in the CNS, with a subsequent increase in chemotaxis and phagocytosis, was detected, with an upregulation in CCR8 expression (mRNA and protein) [23].

3.2. CCL3, CCL4, CCL5 and its Receptor CCR5

Macrophages, monocytes, astrocytes, microglia, epithelium, endothelium, vascular smooth muscle, fibroblasts, and memory-associated neurons express CCL3, CCL4, CCL5, and its receptor CCR5 [24]. In addition to the modulation of the immune response, CCR5 could influence neuronal survival whilst being involved in neuroprotective mechanisms [25]. A downregulation of CCR5 was detected in APP/PS1 mice with the upregulation of CCL3 and CCL4 [7]. The increase in chemokines could lead to a decrease in the expression of the receptor, and, at the same time, the decrease in the CCR5 receptor could lead to an increase in the expression of their chemokines, but this point should be studied in the future research. Neuronal survival can be influenced by CCR5 and could be involved in neuroprotective mechanisms [26]. In CCR5-/- mice, a greater number of reactive astrocytes was detected in comparison with CCR5+/+ mice, indicating that the absence of CCR5 leads to astrocyte activation [27]. Furthermore, cell death in CCR5-/- mice brains are significantly higher than in CCR5+/+ mice [27]. Furthermore, CCR5 elimination could be involved in inadequate development and maturation of dopaminergic neurons and in the prevention of macrophage infiltration and demyelination [28, 29].

LPS injection significantly induced astrogliosis, Aβ deposition, and β -secretase expression in CCR5 knockout mice, compared with CCR5 wild type mice [30]. In addition, an increase in impaired memory and in Aβ deposits could explain the cell death that takes place in AD patients.

Regarding CCR5 chemokines, high levels of CCL3 in peripheral T lymphocytes have been found in AD patients, as compared to healthy patients [31]. In addition, an increase in CCL3 expression in 7-month-old APP/PS1 mice cortex was detected [7]. CCL3 is likely to contribute to the pathogenesis of AD since an increase of that chemokine has been observed, alongside an accumulation of lymphocytes, monocytes, and glial cells in a hypoxic mouse model [32]. CCL3 is found in higher concentrations in microglia, astrocytes, and perivascular macrophages in Alzheimer's disease [33, 34], and involved in cellular infiltration via leucocyte recruitment. Cognitive impairment caused by TAU protein accumulation could likely be promoted by CCL3 cell infiltration in the brain [35]. CCL4 expression is higher in APP/PS1 mice as compared to wild type mice along with an increase in Aβ deposition [36, 7] which also occurs with a common location of CCL4, Aβ, and astrocytes in this mice. Astrocytes from AD produce a β-secretase enzyme that binds to amyloid precursor protein (APP) increasing Aβ production [37]. This data indicates that an acceleration in Aβ deposition leads to a likely deterioration in memory functions [38]. Furthermore, an increase in $A\beta_{1-42}$ deposition in the brains of those mice bearers of a mutation in Toll-like receptor 4 was associated with a decrease in CCL3 and CCL4 expression, by thus ameliorating cognitive functions in these mice. Therefore, in the neurotoxicity mediated by Aβ, the reduction of Aβ deposits and preservation of cognitive functions were carried out in microglia by TLR4 signaling [39].

CCL5 appears on endothelial cells, glia, and neurons. Treatment with CCL5 increases neuronal survival and diminishes cell death produced by the toxic peptide Aβ [40, 41]. *In vivo* studies demonstrated no changes in CCL5 expression in APP/PS1 compared with wild type mice [7]. On the contrary, other authors demonstrated an increase in CCL5 expression in transgenic mice brain and in AD human brain [41, 42, 43]. After all these data, CCL5 function and its mechanisms remain unclear and yet to be established.

Table 1. Effects of the chemokines and the chemokine receptors.

Chemokine Receptor	Chemokines		References
CCR8		Accumulation of microglial cells	[18]
		Increase in inflammation and chemokines	[18, 19, 23]
	Decrease in CCL1	Decrease elimination of Aβ	[22]
		Decrease elimination of debris	[21]
		Decrease elimination of neurotoxic molecules	[21]
CCR5		Involve in neuronal survival and neuroprotective mechanisms	[25]
Elimination of CCR5		Activation of astrocytes and neuronal cell death	[27]
		Decrease development and maturation of neurons	[28, 29]
	Increase of CCL3	Increase lymphocytes, monocytes and glial cells	[32]
		CCL3 increase in AD	[33, 34]
	Increase of CCL4	Appear in APP/PS1	[36, 7]
		Increase Aβ deposition	[36, 7]
	Treatment with CCL5	Increase neuronal survival	[40, 41]
		Decrease cell death	[40, 41]
Decrease of CCR2		Increase in disease progression in AD	[54, 55]
		Increase amyloid pathology	[54, 55]
	Increase of CCL2	Increased in AD	[46, 47]
		Decrease cognitive state	[50, 51, 52]
		Increase disease progression	[50, 51, 52]
		Increase inflammation	[44]
Deletion of CXCR3		Produce Aβ decrease	[61]
		Produce inflammation decrease	[61, 59]
		Rescue the behavioural deficits	[61]
	CXCL10	Increase detected in AD astrocytes	[56]
		Located with Aβ in mild AD patients	[57, 58]
		Increase inflammation	[59]
CX3CR1 deficiency		Increase TAU pathology	[69]
		Increase inflammatory mediators	[63, 67]
		Increase neural death	[67]
	CX3CL1	Increased in brain and plasma of AD patients	[65]
		Increase microglial activation	[62, 63]
		Increase cytokines production	[63]
		Increased cognitive decline	[66]
CXCR2		High levels in AD	[70, 71]
		Role in cognitive functions	[72]

Table (1) contd….

Chemokine Receptor	Chemokines		References
		Depletion produces decrease in Aβ formation	[74]
		Injection of Aβ1-42 produced CXCR2 up-regulation in T cells associated with high entry of those cells in the brain	[75]
	CXCL1	Increase inflammation	[71]
	CXCL8	Increased in AD brain, CSF and plasma	[70, 71]
		Decrease in long term potentiation (LTP)	[72]
CXCR4		Administration of CXCR4 antagonist produces reduction in memory and learning	[80]
		Downregulated in Tg2576 mouse with cognitive impairment	[78, 79]
	CXCL12	Present in plasma and CSF of AD	[76]
		Positively correlated with decrement in cognitive functions	[77]
		Prevent dendritic regression and neuronal apoptosis induced by Aβ	[81]

3.3. CCL2 and its Receptor CCR2

Data the literature suggest a crucial role for CCL2-CCR2 signalling in Alzheimer's disease. Microglia and astrocytes mostly produce CCL2 [44]. Clinical data of AD patients report no association between CCL2 plasma levels and AD [45]. On the other hand, most authors provided evidence of a detrimental role in AD pathogenesis with overexpression of CCL2 in the brain [46, 47], in microglia, microvessels, and in mature senile plaques [48]. Furthermore, CCL2 expression in the cerebrospinal fluid (CSF) and the brain is a good predictor of AD strictness [46, 49] and moreover, the CCL2 increase correlates directly with cognitive decline and the disease progression [50, 51, 52]. Overexpression of APP and CCL2 did not produce alterations in APP processing. Nevertheless, increases in Aβ levels ended up in their aggregation and deposition in APP/CCL2 mice [53]. CCL2 receptor (CCR2) was the first chemokine receptor associated with AD. Decreases in CR2 contribute to disease progression and amyloid pathology, such as in Tg2576 and APP/PS1 mice [54, 55]. These authors indicate that the progression of the disease could be due to a decrease in the accumulation of microglia, elimination of Aβ all led by a reduction in macrophage recruitment. Moreover, CCL2/CCR2 is involved in inflammation due to its capability to trigger inflammatory mediators that carry out the inflammation cascade, thus initiating the entire inflammatory process.

3.4. CXCL10 and its Receptor CXCR3

CXCL10 is primarily and mainly expressed in astrocytes transgenic mice bearers of AD [56], where it is located alongside Aβ [57, 58] and in CSF of mild AD patients [59]. Furthermore, CXCL10 is involved in inflammatory processes because LPS injection increases CXCL10 in the rat brains and in cultured astrocytes and microglia [60]. In APP/PS1 mice models, CXCR3-deficiency, produced by the deletion of CXCR3, reduced significantly the Aβ toxic peptide and the plaque formation in the brain. Furthermore, microglial activation took place, indicating the existence of its recruitment in the plaque borders [61]. In addition, CXCR3-deficiency enhanced behavioral alterations and decreased neural inflammation. On the contrary, in tau pathology, the role of CX3CR1 remained uncertain.

3.5. CX3CL1 and its Receptor CX3CR1

CX3CL1 is a transmembranous protein produced by neurons and astrocytes and its receptor CX3CR1 is expressed constitutively in microglia and, partially, in astrocytes and neurons [62, 63]. In this way, neurons can regulate microglial activation via CXC3CL1/CX3CR1 pathways [64]. These mechanisms control growth factor genesis, cytokines production (IL-1β) [63], microglial phagocytosis, and progenitor cells' activity [64]. In patients with mild AD, CX3CL1 serological concentrations are increased and their posterior decline is directly correlated with cognitive deterioration [65]. On the other hand, in the hippocampus of AD patients, a CX3CL1 overexpression was detected [66]. In AD mouse models, changes in CX3CL1/CX3CR1 can be both neuroprotective and neurotoxic. In APP/PS1, R1.40, and CRND8 mouse models, a deficit in CX3CR1 meant a reduction in amyloid deposits and, thereby, an increase in microglial Aβ phagocytic capacity [63, 67], both associated with a decrease in TNF levels and an increase in IL-1β levels. Furthermore, in rats injected with $A\beta_{1\text{-}40}$ an upregulation of CX3CR1 occurred with microglial activation and an ulterior increase in cognitive impairment [68]. On the other hand, in mice expressing human APP, CX3CL1 deficiency meant an increase in tau pathology, expression of pro-inflammatory mediators, and neural death all affecting negatively both cognition and memory as a final effect [69].

3.6. CXCL1, CXCL8 and its Receptor CXCR2

CXCL1 and CXCL8 are ligands of CXCR2. They are expressed in neurons, astrocytes, and microglia as one of the final products following pro-inflammatory signals. CXCL1 is furtherly expressed in immune and CNS cells. In AD CXCL8 is increased in CSF, serum, and brain [70, 71]. Experiments with hippocampal slices, CXCL8 inhibits LTP which is reversed after incubation with CXCR2 demonstrat-

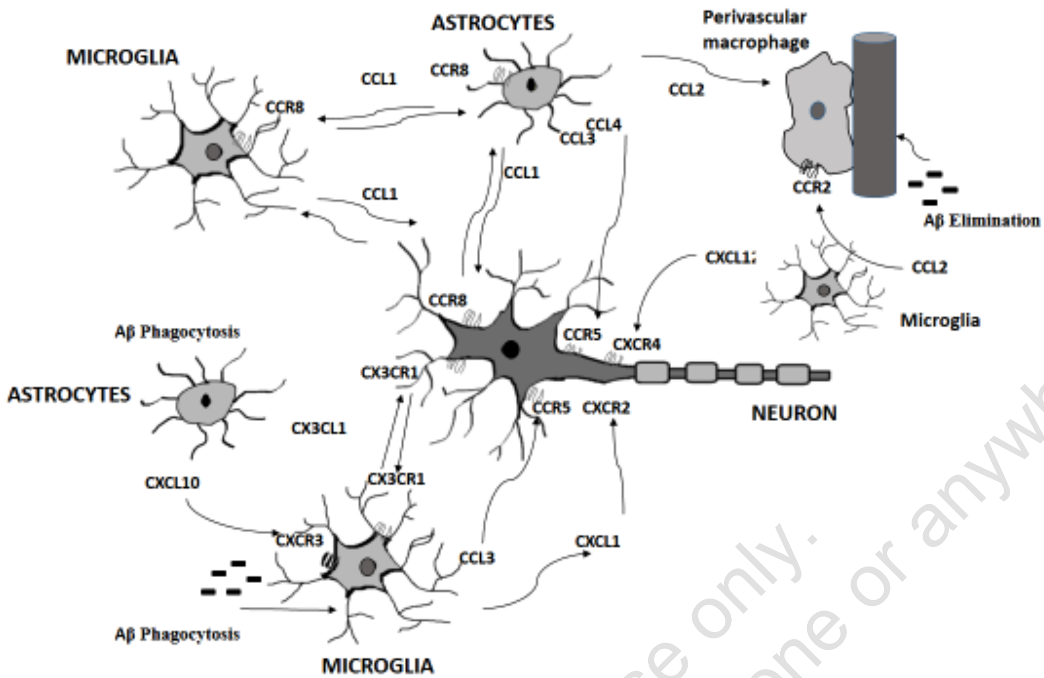

Fig. (1). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ing a role in cognitive functions [72]. Furthermore, high levels of CXCR2 in microglia and astrocytes in AD bearers were detected [73]. Knockdown or depletion of CXCR2 antagonists (SB2250002) decreased Aβ1-42 and Aβ1-40 expression and the accumulation of γ-secretase elements. On the other hand, an increase of $A\beta_{1\text{-}40}$ production was detected after treatment with agonists [74]. Moreover, injection of Aβ1-42 produced CXCR2 up-regulation in T cells associated with the high entry of those cells in the brain [75]. CXCR2 is involved in cognitive dysfunction in AD, by increasing T-cell recruitment via Aβ induction and liberation following an increased expression of γ-secretase complex.

3.7. CXCL12 and its Receptor CXCR4

CNS express both of them [76]. They regulate neuronal excitability and synaptic transmission. In patients with early AD, CXCL12 is present in plasma and CSF and inversely correlated with the levels of tau protein in CSF. Furthermore, these chemokines and their receptors showed a direct relation with cognitive function detriment [77]. In animal models of AD, the CXCR4 receptor and CXCL12 are downregulated in Tg2576 mouse with cognitive impairment [78, 79]. Moreover, the administration of CXCR4 antagonist brought upon memory and cognitive reduction in young, non-transgenic mice, showing that low levels of CXCL12/CXCR4 produced cognitive deficits [80]. In addition, CXCL12 inhibited the effects of Aβ toxic peptide possibly by the prevention of dendritic destruction and apoptosis occasioned by Aβ [81]. CXCL2 produced neuroprotection and anti-amyloidogenic actions in 5xFAD mice treated painlessly with hNGFp [82].

CONCLUSIONS

This review summarizes the role of chemokines and their receptors as important mediators in AD and inflammation. They promote Aβ deposition and TAU hyperphosphorylation aggravating and increasing the progression of AD. There remains, though, a long road to clarify and fully understand the specific actions of chemokines in the inflammatory processes in AD. Pharmacotherapy may have a promising future in detaining or decelerating the development of this neurodegenerative disease (Fig. **1**).

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
ROS	=	Reactive Oxygen Species
APP/PS1	=	Amyloid Precursor Protein/Presenilin 1
LPS	=	Lipopolysaccharides
TLR	=	Toll-like Receptor
IL	=	Interleukin
CSF	=	Cerebrospinal Fluid
Aβ	=	Amyloid β
CCR	=	C-C Chemokine Receptor type
CXCR	=	C-X-C Chemokine Receptor type
CCL	=	Chemokine (C-C motif) Ligand
CXCL	=	C-X-C Motif Chemokine Ligand
CNS	=	Central Nervous system

AUTHOR CONTRIBUTIONS

All authors made substantive intellectual contributions to the present study and approved the final manuscript. A.J. drafted and revised the manuscript and collected the bibliography. J.C.C. drafted and revised the manuscript. A.I. pro-

vided technical assistance conducting to the preparation of the paper. M.A. revised the manuscript. C.A. checked English. J.M.V. revised the manuscript. S.L.V. designed the manuscript; draft revised the manuscript; and chose the bibliography.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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