Review Article

Complex role of chemokine mediators in animal models of Alzheimer's Disease

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ABSTRACT

Chemokines are a family of cytokines, first described to play a role in the immune system. However, neurons and glial cells also express chemokines and their receptors. In the central nervous system, chemokines are involved in several neural functions, in particular in the control of cell communications and neuronal activity. In pathological conditions, chemokines participate in neuroinflammatory and neurodegenerative processes. In Alzheimer's disease (AD), chemokines play a role in the development of the two main lesions, amyloid β plaques and neurofibrillary tangles. In addition, they contribute to the inflammatory response by recruiting T cells and controlling microglia/macrophages activation. Actually, targeting inflammatory pathways seems a promising therapeutic approach for the treatment of AD patients. This review summarizes our current knowledge on the roles of chemokines in AD animal models and the underlying mechanisms in which they take part. Better knowledge of the role of chemokines and their cellular receptors in AD could open new therapeutic perspectives.

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, with an increasing prevalence due to an aging population. AD is a fatal brain disease and currently, there is no cure or treatment which delays or stops the progression of AD. This neurodegenerative disease is characterized by two main lesions: senile plaques and neurofibrillary tangles. The exact processes that cause the disease are still poorly understood.

They might involve toxic oligomers of amyloid β (Aβ) peptides and/or the formation of amyloid (senile) plaques composed of extracellular aggregates of Aβ peptides, and/or rely on the formation of neurofibrillary tangles composed of intraneuronal aggregates of hyperphosphorylated Tau protein. The Aβ peptides are generated by the sequential cleavage of APP by two enzymes, the β-amyloid cleavage enzyme and the γ secretase complex composed of presenilin (PS), nicastrin, presenilin enhancer 2 and anterior pharynx-defective 1. Less than 1% of AD cases are caused by mutation in APP and PS

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genes. Mutations in the gene encoding Tau have not been identified in AD cases. However, Tau mutations found in other Tauopathies are co-expressed with APP and PS bearing AD familial mutations to model both neurofibrillary tangles and Aβ plaques in transgenic animals [1].

Alzheimer's disease and inflammation

Genetic studies have also identified polymorphisms, linked to AD, in genes involved in the innate immune system [2—5]. In AD patients, many activated microglial cells and astrocytes have been shown to be associated with lesions and inflammatory molecules. Microglial cells are the resident immune cells of the central nervous system (CNS) and derive from myeloid progenitors from the yolk sac before embryonic day 8 and maintain in the brain by self-renewal [6]. Microglia participate in the immune response in AD by activating the complement cascade and producing inflammatory cytokines such as IL-1β, IL-6 and TNF-α [7]. Early recruitment of microglia seems beneficial in AD by promoting phagocytosis and clearance of Aβ peptides. However, as disease progresses, microglia are overwhelmed by the excessive amount of Aβ and become more pro-inflammatory [8]. These chronic inflammatory processes lead to alteration of microglial functions creating a vicious circle. Consequently, microglia are unable to restrict the formation of Aβ plaques [9]. Thus, several studies on inflammatory mediators and immune pathways revealed that inflammatory and immunological processes are central to the progression of AD [10,11].

Chemokines

Among pro-inflammatory molecules, chemokines are a subfamily of chemotactic cytokines. Chemokines are a large family of over 50 small proteins. Chemokines exert their functions through chemokines receptors that belong to the superfamily of G-protein-coupled receptors. Chemokines were first named according to their biological functions. Since 2000, chemokines were classified in 4 subfamilies based on their structural shapes related to the number and spacing of conserved cysteine residues at the N-terminal domain (CXC, CC, CX3C and C) [12]. Chemokines bind to different receptors and several distinct chemokines share common receptor. Chemokines were first described to contribute to numerous aspects of immune function as recruitment of immune cells but they have also important roles in the CNS such as brain development, neuroinflammation and neuroendocrine functions [13]. CNS cells constitutively express chemokine receptors while chemokines are mainly produced during diverse pathological states [14]. In this review, we did not detail results on the expression of chemokines and chemokines receptor in AD patients and AD models. In general, most of them were overexpressed during the pathology with the exception of CX3CL1/CX3CR1 [15], for review see Refs. [14,16]. We preferred to focus on the molecular mechanisms triggered by chemokines receptors activation that contribute to the development of the disease.

Chemokines and animal models of Alzheimer's disease

CX3CR1

In the CNS, microglia constitutively express the receptor CX3CR1 and neurons its unique ligand CX3CL1 as a transmembrane protein. The interaction between CX3CL1 (also named fractalkine) and CX3CR1 is important in neuronal-microglial communication, throughout the life span, allowing neurons to regulate microglia activation [17]. Microglia control synaptic pruning during development, survey neuronal damages as well as sensing the presence of danger signals. CX3CL1 can be cleaved by a disintegrin and metalloprotease (ADAM10, 17) or a cysteine protease cathepsin S and subsequently induces the recruitment of leucocytes expressing CX3CR1 from the periphery, such as monocytes. In the CNS, CX3CL1/CX3CR1 signalling controls the production of growth factor and cytokines, in particular IL-1β [18], microglial phagocytic activity but also proliferation and survival of neural progenitor cells [17]. Globally, neuron controls microglial functions through this interaction. On the other hand, disruption of CX3CL1/CX3CR1 pathway in physiological conditions leads to impairment of hippocampal neuronal functions (reduction of adult hippocampal neurogenesis, impairment in long-term potentiation (LTP), and deficits in contextual fear conditioning and Morris water maze tests) suggesting a role in cognitive deficits present in AD [19—21]. In AD model, CX3CR1 & CX3CL1 have opposite roles on the Aβ and Tau pathologies. Deletion of CX3CR1 enhances Tau phosphorylation and aggregation of hyperphosphorylated Tau that increase behavioral impairments in the humanized Tau transgenic mice. The authors propose a model where CX3CR1-defiency induces an increase of IL-1β release that binds to IL1 receptor on neurons and activates the p38 MAPkinase leading to hyperphosphorylation of Tau [22]. This result was confirmed in another Tau model of AD i.e. the Tg4510 mice which express the human Tau containing the P301L mutation [23]. Overexpression of soluble CX3CL1 using adeno-associated viral vector (AAV) reduces Tau phosphorylation, microglia activation and neuronal loss observed in this model.

In Aβ models of AD, the results are more divergent and can be explained by the different animal models used. Overall, the data suggest a protective effect of CX3CR1 deficit on Aβ lesions. These studies were performed in three different Aβ models of AD: (1) TgCRND8 which expresses the human APP containing KM670/671NL and V717F mutations; (2) the double transgenic model APP/PS1 expressing the human APP containing K670M/N671L mutations and PS1 harboring the L166P mutation; (3) the R1.40 transgenic line which contains a yeast artificial chromosome (YAC) expressing the human APP containing K670M/N671L mutations. In these models, the introduction of CX3CR1 deficiency was shown to increase phagocytosis and reduce Aβ lesions [24,25]. In these studies, the memory deficits were not assessed, thus the overall beneficial vs. pathological role of CX3CL1/CX3CR1 on cognitive functions were not determined. In contrast, using the J20 transgenic mouse model in which the human APP containing KM670/671NL and V717F mutations are expressed under the control of the PDGF-β promoter, Cho et al.
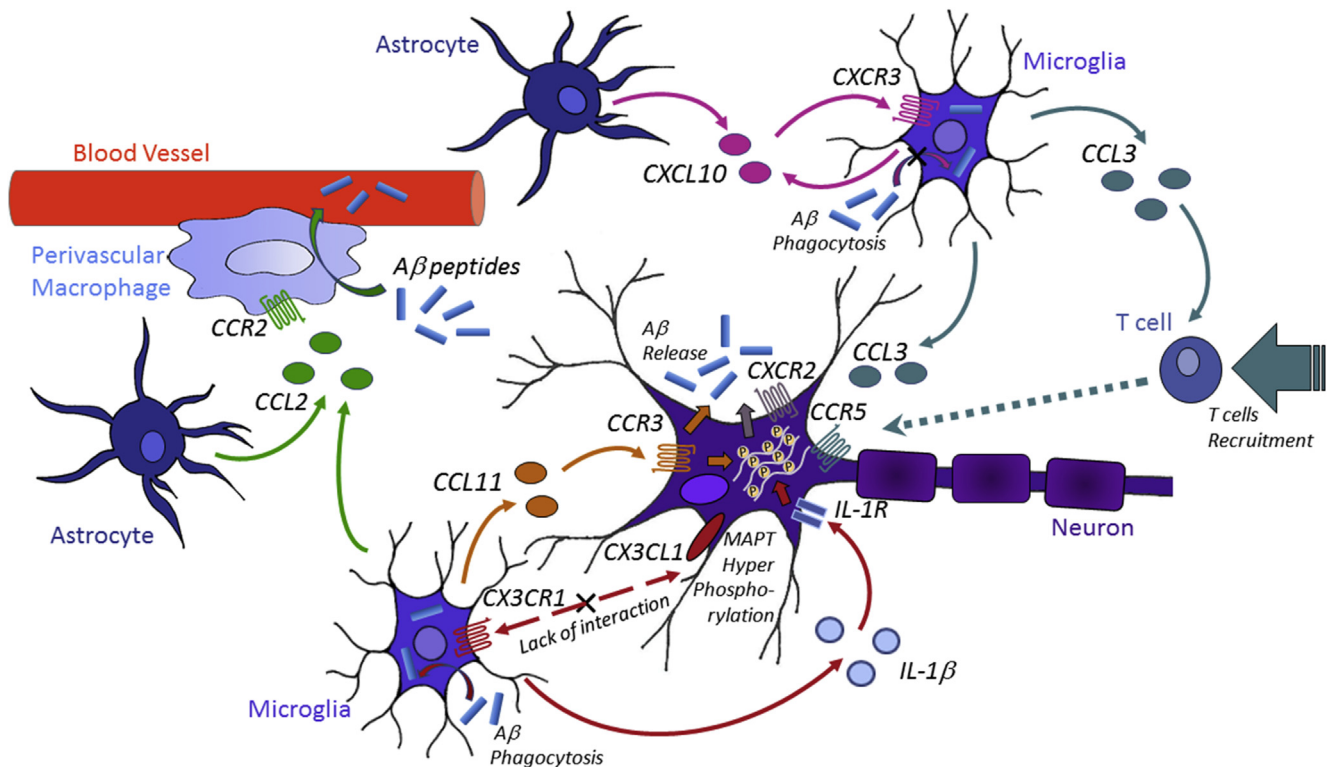
Fig. 1 **Roles of chemokines in AD disease.** Lack of CX3CR1/CX3CL1 interaction induces the release of IL-1β that binds to IL-1 receptor and leads to hyperphosphorylation of Tau but also to phagocytosis of Aβ peptides. Aβ peptides induce CXCL10 release from glial cells; its binding to CXCR3 may in turn inhibit microglial phagocytosis. CCR2-expressing perivascular macrophages contribute to clearance/transport of Aβ peptides outside the brain. CCR3 activation by CCL11 contributes to the formation of AD lesions via Tau phosphorylation and production of Aβ peptides. CXCR2 activation also mediates the release of Aβ peptides. CCR5/CCL3 overexpression induces the recruitment of peripheral T cells and participates to neuronal damages.

did not observe any effects on Aβ load but an increase in memory deficits associated with higher levels of phospho-Tau [15]. CX3CR1-deficiency in APP/PS1 mice also induces hyper-phosphorylation of Tau, thus the beneficial effect of CX3CR1 on Tau pathology could be predominant compared to the detrimental effect on Aβ deposits [26]. These effects on the levels of Aβ peptides and phospho-Tau were also observed in APP/PS1 mice by knocking-out the ligand CX3CL1, confirming the role of CX3CL1/CX3CR1 in AD model [26]. In the APP/PS1 model, the authors also determined the role of membrane-anchored and soluble forms of CX3CL1. They introduced a bacterial artificial chromosome (BAC) transgene encoding truncated/soluble CX3CL1 into CX3CL1 knock-out mice. Expression of soluble CX3CL1 does not compensate for lack of CX3CL1 expression suggesting that the effects of CX3CL1 deficiency are mediated by the membrane anchored form in Aβ model. In a different AD model, obtained by crossing Tg2576 mouse line and the mutant PS1M146L transgenic line, Nash et al. also found no effect of overexpression of soluble CX3CL1 using a CX3CL1 expressing AAV on Aβ lesions but a reduced Tau pathology in the Tau model Tg4510 [23]. The validation of the precise role of each form requires further experiments, using transgenic mice expressing CX3CL1 mutated at the (ADAM10/17) cleavage site as proposed by Lee et al. [26].

In contrast with these studies, Fuhrmann et al., using two-photon microscopy, reported that CX3CR1 deficiency prevents neuronal loss without affecting Aβ levels and Tau phosphor-ylation [27]. Their observations contrary to previous studies may be explained by their use of a very aggressive model of AD characterized by high amounts of intracellular Aβ peptides. Their experimental model consists in triple transgenic mice expressing PS1 bearing the M146V mutation, APP containing K670M/N671L mutations and Tau with P301L mutation [27].

In summary, the lack of CX3CL1/CX3CR1 interaction could lead mainly to microglia activation, interleukin 1 release and subsequent hyperphosphorylation of Tau via p38 MAPkinase [22] while triggering phagocytosis of Aβ peptides (Fig. 1 & Table 1).

CXCR2

CXCL1 and IL-8 are the main ligands for CXCR2 and are expressed by immune and non immune cells.

In the CNS, CXCR2 was shown to play a major role in migration of oligodendrocyte precursors during the devel-opment of the spinal cord [28]. CXCR2 is expressed in the CA1 region of the hippocampus, which is involved in learning and memory functions. Treatment of rat hippocampal slice with IL-8 was shown to inhibit LTP and this inhibition was reversed by preincubation with CXCR2 antibody suggesting a role for this receptor in cognitive functions [29]. *In vitro* treatment of cell lines with CXCR2 agonist, SB225002, leads to

Table 1 Roles of chemokine receptors in biological functions involved in AD.

Effects on	Receptor	Biological and molecular consequences	Refs
Aβ levels	CX3CR1	Inhibition of microglial phagocytosis of Aβ peptides	[24,25]
	CXCR2	Production of Aβ peptides	[30,31]
	CXCR3	Inhibition of microglial phagocytosis of Aβ peptides	[33]
	CCR2	Clearance of Aβ peptides	[37,40,43,44]
	CCR3	Production of Aβ peptides	[47]
Tau phosphorylation	CX3CR1	Inhibition of hyperphosphorylation of Tau	[15,22,23,26]
	CCR3	Hyperphosphorylation of Tau	[47]
Synaptic function	CX3CR1	Regulation of cognitive function, loss of neurons	[19−21,27]
	CXCR2	Impairment of long-term potentiation	[29]
	CXCR3	Impairment of long-term potentiation	[34]
	CCR3	Loss of dendritic spines	[47]
	CCR5	Impairment of memory and synaptic plasticity	[48,52,53]
Neuroinflammatory response	CX3CR1	Control of microglial activation and IL-1β release	[22]
	CCR3	Microglial activation	[47]
Cellular chemotaxis	CXCR2	Recruitment of T-lymphocytes in the brain	[32]
	CCR2	Recruitment of perivascular macrophages	[40]
	CCR5	Recruitment of T-lymphocytes in the brain	[49,50]

Aβ release and increased expression of γ-secretase components [30]. These results were confirmed in PS/APP mice, in this model, CXCR2-deficiency reduces Aβ levels associated with a lower expression of the γ-secretase components including presenilin [31]. Furthermore, intracerebral injection of Aβ peptides in rat or mouse was used to study the pathogenesis of AD. In this model, Aβ peptides injection induces the recruitment of peripheral pathogenic T cells and the treatment of Aβ-injected rat with the specific CXCR2 antagonist SB332235-Z significantly decreases the number of T cells in the brain [32].

Thus, CXCR2 seems to be involved in cognitive dysfunction associated with AD, Aβ peptides release through increased expression of γ-secretase complex and also in the Aβ-induced recruitment of T cells in the brain (Fig. 1 & Table 1).

CXCR3

Different ligands, CXCL9, CXCL11 and CXCL10, bind to the receptor CXCR3. CXCR3 is involved in different immune functions such as leukocyte trafficking but is also expressed in neuronal and glial cells suggesting a role in the CNS. The role of CXCR3 was investigated in the AD animal model APPswe/PSEN1dE9 which expresses PS1 gene deleted of exon 9 and the chimeric human/mouse APP containing K670M/N671L mutations [33]. CXCR3-deficiency rescues the cognitive deficits and decreases Aβ plaques and neuroinflammation. The authors demonstrated that the reduced level of Aβ peptides associated with CXCR3-deficiency can be attributed to increased microglial Aβ uptake rather than alteration in APP processing as shown in vitro in primary glial cells culture and in vivo in AD mouse model. Furthermore, Aβ stimulation of primary culture of astrocytes and microglia induces the release of CXCL10. Thus, this production of CXCR3 ligands by glial cells may in turn inhibits microglial phagocytosis leading to Aβ accumulation (Fig. 1 & Table 1). Furthermore, exposure of brain slice of wild-type mice to the ligand CXCL10 inhibited LTP while no change is observed in slice from CXCR3-deficient mice exposed to CXCL10 [34].These results suggest a direct involvement of CXCR3 ligands in cognitive impairments observed in AD model (Table 1).

CCR2

CCR2 is activated by several chemokines (CCL2, 7, 8, 12, 13, 16), CCL2 being the most potent one. In the CNS, CCL2 is mostly produced by microglia and astrocytes during pathological conditions [13]. In the brain, CCR2 is expressed by neurons, astrocytes and infiltrating leukocytes but not by resident microglia [35,36]. The main described function of CCL2 in neurological disease is the recruitment of peripheral inflammatory monocytes expressing CCR2 at lesion sites. In 2007, El Khoury et al. demonstrated that lack of CCR2 in the AD mouse model Tg2576 (expressing human APP containing K670M/N671L "Swedish" double mutation) accelerates disease progression with increased Aβ load and mortality [37]. In this model, CCR2-deficiency impaired mononuclear phagocytes accumulation that may lead to a decrease of Aβ phagocytosis. In vitro experiments on peritoneal macrophages demonstrate that the lack of CCR2 affects their ability to migrate suggesting that in this AD model peripheral recruitment of macrophages contributes to Aβ clearance as was shown in a study using bone marrow chimeric mice [38]. However, additional later works using alternative strategies to follow peripheral macrophages, have demonstrated that peripheral macrophages engraftment in the brain does not occur in absence of total-body irradiation in healthy and intact animals [39], these observations were also confirmed in AD model [40].

On the other hand, in bone marrow chimeric mice, graft of CCR2−/− vs. CCR2+/+ cells into APPswe/PSEN1(A246E) double transgenic mice which express chimeric mouse/human APP containing KM670/671NL mutations and PS1 harboring A246E mutation have shown that parenchymal macrophages recruitment was dependent on CCR2 expression [40]. Moreover, the beneficial effects of the graft on memory capacities rely on CCR2 expression while the effect on Aβ level was not clearly established [40,41]. Thus, the effects observed in CCR2-deficient mice could not be attributed to peripheral macrophages infiltration in AD mouse model. Two studies reported that in Tg2576 mice deficient in CCR2, Aβ peptides are principally located in and around blood vessels [37,40] suggesting a role for perivascular macrophages. In addition, Mildner et al. observed

an increased number of perivascular macrophages containing Aβ peptides in Tg2576xCCR2−/− mice. In favor of this hypothesis, depletion of perivascular macrophages was shown to increase Aβ deposits in cortical blood vessels in the mouse model TgCRND8 while stimulation of these macrophages reduced Aβ load [42]. Furthermore, using head protected chimeric mice (to protect CNS from irradiation), the authors could assess the role of CCR2 expression in peripheral macrophages without monocyte derived macrophages infiltrating the brain [40]. Thus, Mildner et al. demonstrated that perivascular macrophages through CCR2 expression modulate Aβ clearance/transport [40]. It is worth noticing that the survival of Tg2576xCCR2−/− mice was decreased compared to Tg2576 mice in both studies [37,40]. This increased mortality rate can be explained by intracerebral hemorrhages due to accumulation of Aβ deposits in blood vessels that ultimately lead to death of AD mice. The role of CCR2/CCL2 was also confirmed in different AD models. Using the APPswe/PSEN1(A246E) double transgenics, Naert et al. found that CCR2-deficiency accelerates the memory deficits and aggravates cognitive impairment [43]. Furthermore, they analyzed by western-blot various Aβ species and observed an increase in soluble Aβ peptides [43]. These results are in agreement with the work of Kiyota et al. showing that CCL2-deficiency also increases Aβ load and in particular Aβ soluble peptides and accelerates memory impairment in Tg2576 AD mice model [44]. Soluble Aβ peptides were shown to present toxic properties [45] and their higher level in APP mice deficient in CCR2 or CCL2 could explain the increase in cognitive deficits observed in these AD models.

Overall, these studies suggest that CCR2-expressing perivascular macrophages contribute to the clearance of Aβ peptides out of the brain, thus reducing the levels of soluble toxic Aβ peptides (Fig. 1 & Table 1).

CCR3

CCR3 is expressed by astrocytes, neurons and microglia in the CNS. This receptor binds to several chemokines CCL5, 7, 11, 13, 26 and was notably described as a co-receptor for HIV entry in microglia [46]. The interaction CCR3/CCL11 was explored in the AD animal model APPswe/PSEN1dE9 [47]. Knocking-down of CCR3 in this model rescues neuronal impairments i.e. loss of dendritic spines and spatial memory deficits and reduces also Tau phosphorylation and Aβ load. *In vitro* studies showed that CCL11 stimulation of hippocampal neurons induced hyperphosphorylation of Tau, production of Aβ peptides and dendritic spine losses and these effects were reversed by treatment with the CCR3-specific antagonist GW766994. These results indicate that CCR3 expression on neurons may contribute to the development of AD brain lesions that leads to cognitive deficits. However, CCR3 was shown to play also a role in microglia activation and CCR3-deficiency in AD model leads to reduced microgliosis. Thus, CCR3 may also be involved in the innate immune response in this disease (Fig. 1 & Table 1).

CCR5

CCR5 is another co-receptor used by HIV to infect host cells. CCR5 ligands are the chemokines CCL3, CCL4 and CCL5. Intracerebral injection of Aβ peptides in rodent induces memory deficits and glial cell activation. In this AD model, CCL3 or CCR5-deficiency rescues the Aβ-induced cognitive impairments and decreases the inflammatory response [48]. These results suggest that CCR5/CCL3 pathway contributes to pathological processes in AD model. Moreover, anti-CCL3 treatment blocks the recruitment of T cells in the brain of intra-hippocampal Aβ-injected rat [49]. In this AD model, the authors demonstrated that Aβ peptides induce the expression of CCR5 by brain microvascular endothelial cells via the activation of the receptor for advanced glycation end products that allows the migration of T cells through the blood brain barrier [50]. In addition using the AD model THY-Tau22 transgenic line in which the human Tau harboring the G272V and P301L mutations are expressed, the authors found that T cell infiltration in the hippocampus of transgenic mice developing neurofibrillary tangles, was associated with increased level of CCL3 and neuronal damages [50]. These studies suggest that CCL3/CCR5 may play a role in AD through pathogenic T cells recruitment [51]. However, glial cells and neurons also express CCR5 suggesting that this receptor could also play a central role in the brain. Intracerebroventricular injection of CCL3 in mice induces synaptic plasticity and spatial memory impairments and these effects were reversed by the CCR5 antagonist, maraviroc [52]. Furthermore, CCR5-deficiency results in enhanced learning and memory performances in different cognitive tasks without affecting other behavioral tasks, while transgenic mice overexpressing CCR5 in excitatory neurons show deficits in cognitive tasks [53]. Overall, these data indicate that CCR5 may play a role in synaptic plasticity and memory. Thus, CCR5/CCL3 interaction may participate to neurodegenerative processes in AD. However, the signaling pathways involved in these pathological processes still need to be explored (Fig. 1 & Table 1).

Conclusion

In this review, we have analyzed the scientific literature showing that chemokines and their receptors play a major role in AD with various functions in inflammatory and neurodegenerative processes. Several studies have highlighted the involvement of chemokines in the regulation of cognitive functions. A better understanding of underlying pathways could help identify new pathogenic mechanisms involved in AD. In addition, chemokines contribute to the development of Aβ lesions by inducing the production of Aβ peptides (CXCR2, CCR3) but also regulate Aβ peptides clearance (CX3CR1, CXCR3, CCR2) (Fig. 1 & Table 1). On the other hand, chemokines receptor activation is involved in phosphorylation of Tau (CX3CR1, CCR3) (Fig. 1 & Table 1). The spatiotemporal progression of Tau pathology relies more on cognitive symptoms observed in AD than Aβ lesions [54−56]. Given that chemokines can have opposite effects on both lesions (CX3CR1), there is a crucial need to determine the roles of chemokines on Tau phosphorylation to identify chemokine receptors as important therapeutic targets in AD. Validation of beneficial effects of chemokine inhibitors in preclinical studies would be particularly useful because several chemokine-targeted drugs, which have been developed already to treat HIV infection [57], as well as inflammatory or autoimmune diseases, could be applied to AD.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

[1] Gotz J, Ittner LM. Animal models of Alzheimer's disease and frontotemporal dementia. Nat Rev Neurosci 2008;9:532–44.

[2] Lambert JC, Grenier-Boley B, Chouraki V, Heath S, Zelenika D, Fievet N, et al. Implication of the immune system in Alzheimer's disease: evidence from genome-wide pathway analysis. J Alzheimer's Dis JAD 2010;20:1107–18.

[3] Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, et al. TREM2 variants in Alzheimer's disease. N Engl J Med 2013;368:117–27.

[4] Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 2011;43:436–41.

[5] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 2009;41:1094–9.

[6] Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 2010;330:841–5.

[7] Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 2006;12:1005–15.

[8] 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.

[9] Martin E, Boucher C, Fontaine B, Delarasse C. Distinct inflammatory phenotypes of microglia and monocyte-derived macrophages in Alzheimer's disease models: effects of aging and amyloid pathology. Aging Cell 2017;16:27–38.

[10] Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nat Immunol 2015;16:229–36.

[11] Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci 2015;16:358–72.

[12] Murphy PM, Baggiolini M, Charo IF, Hebert CA, Horuk R, Matsushima K, et al. International union of pharmacology. XXII. Nomenclature for chemokine receptors. Pharmacol Rev 2000;52:145–76.

[13] Reaux-Le Goazigo A, Van Steenwinckel J, Rostene W, Melik Parsadaniantz S. Current status of chemokines in the adult CNS. Prog Neurobiol 2013;104:67–92.

[14] Cartier L, Hartley O, Dubois-Dauphin M, Krause KH. Chemokine receptors in the central nervous system: role in brain inflammation and neurodegenerative diseases. Brain Res Brain Res Rev 2005;48:16–42.

[15] Cho SH, Sun B, Zhou Y, Kauppinen TM, Halabisky B, Wes P, et al. CX3CR1 protein signaling modulates microglial activation and protects against plaque-independent cognitive deficits in a mouse model of Alzheimer disease. J Biol Chem 2011;286:32713–22.

[16] Domingues C, da Cruz ESOAB, Henriques AG. Impact of cytokines and chemokines on Alzheimer's disease neuropathological hallmarks. Curr Alzheimer Res 2017;14:870–82.

[17] Limatola C, Ransohoff RM. Modulating neurotoxicity through CX3CL1/CX3CR1 signaling. Front Cell Neurosci 2014;8:229.

[18] Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, et al. Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci 2006;9:917–24.

[19] Paolicelli RC, Bisht K, Tremblay ME. Fractalkine regulation of microglial physiology and consequences on the brain and behavior. Front Cell Neurosci 2014;8:129.

[20] Sheridan GK, Wdowicz A, Pickering M, Watters O, Halley P, O'Sullivan NC, et al. CX3CL1 is up-regulated in the rat hippocampus during memory-associated synaptic plasticity. Front Cell Neurosci 2014;8:233.

[21] Rogers JT, Morganti JM, Bachstetter AD, Hudson CE, Peters MM, Grimmig BA, et al. CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. J Neurosci 2011;31:16241–50.

[22] Bhaskar K, Konerth M, Kokiko-Cochran ON, Cardona A, Ransohoff RM, Lamb BT. Regulation of tau pathology by the microglial fractalkine receptor. Neuron 2010;68:19–31.

[23] Nash KR, Lee DC, Hunt Jr JB, Morganti JM, Selenica ML, Moran P, et al. Fractalkine overexpression suppresses tau pathology in a mouse model of tauopathy. Neurobiol Aging 2013;34:1540–8.

[24] Lee S, Varvel NH, Konerth ME, Xu G, Cardona AE, Ransohoff RM, et al. CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. Am J Pathol 2010;177:2549–62.

[25] Liu Z, Condello C, Schain A, Harb R, Grutzendler J. CX3CR1 in microglia regulates brain amyloid deposition through selective protofibrillar amyloid-beta phagocytosis. J Neurosci 2010;30:17091–101.

[26] Lee S, Xu G, Jay TR, Bhatta S, Kim KW, Jung S, et al. Opposing effects of membrane-anchored CX3CL1 on amyloid and tau pathologies via the p38 MAPK pathway. J Neurosci 2014;34:12538–46.

[27] Fuhrmann M, Bittner T, Jung CK, Burgold S, Page RM, Mitteregger G, et al. Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. Nat Neurosci 2010;13:411–3.

[28] Tsai HH, Frost E, To V, Robinson S, Ffrench-Constant C, Geertman R, et al. The chemokine receptor CXCR2 controls positioning of oligodendrocyte precursors in developing spinal cord by arresting their migration. Cell 2002;110:373–83.

[29] Xiong H, Boyle J, Winkelbauer M, Gorantla S, Zheng J, Ghorpade A, et al. Inhibition of long-term potentiation by interleukin-8: implications for human immunodeficiency virus-1-associated dementia. J Neurosci Res 2003;71:600–7.

[30] Bakshi P, Margenthaler E, Laporte V, Crawford F, Mullan M. Novel role of CXCR2 in regulation of gamma-secretase activity. ACS Chem Biol 2008;3:777–89.

[31] Bakshi P, Margenthaler E, Reed J, Crawford F, Mullan M. Depletion of CXCR2 inhibits gamma-secretase activity and amyloid-beta production in a murine model of Alzheimer's disease. Cytokine 2011;53:163–9.

[32] Liu YJ, Guo DW, Tian L, Shang DS, Zhao WD, Li B, et al. Peripheral T cells derived from Alzheimer's disease patients

overexpress CXCR2 contributing to its transendothelial migration, which is microglial TNF-alpha-dependent. Neurobiol Aging 2010;31:175—88.

[33] Krauthausen M, Kummer MP, Zimmermann J, Reyes-Irisarri E, Terwel D, Bulic B, et al. CXCR3 promotes plaque formation and behavioral deficits in an Alzheimer's disease model. J Clin Invest 2015;125:365—78.

[34] Vlkolinsky R, Siggins GR, Campbell IL, Krucker T. Acute exposure to CXC chemokine ligand 10, but not its chronic astroglial production, alters synaptic plasticity in mouse hippocampal slices. J Neuroimmunol 2004;150:37—47.

[35] Mizutani M, Pino PA, Saederup N, Charo IF, Ransohoff RM, Cardona AE. The fractalkine receptor but not CCR2 is present on microglia from embryonic development throughout adulthood. J Immunol 2012;188:29—36.

[36] Saederup N, Cardona AE, Croft K, Mizutani M, Cotleur AC, Tsou CL, et al. Selective chemokine receptor usage by central nervous system myeloid cells in CCR2-red fluorescent protein knock-in mice. PLoS One 2010;5:e13693.

[37] El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, et al. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. Nat Med 2007;13:432—8.

[38] Simard AR, Soulet D, Gowing G, Julien JP, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron 2006;49:489—502.

[39] Larochelle A, Bellavance MA, Michaud JP, Rivest S. Bone marrow-derived macrophages and the CNS: an update on the use of experimental chimeric mouse models and bone marrow transplantation in neurological disorders. Biochim Biophys Acta 2016;1862:310—22.

[40] Mildner A, Schlevogt B, Kierdorf K, Bottcher C, Erny D, Kummer MP, et al. Distinct and non-redundant roles of microglia and myeloid subsets in mouse models of Alzheimer's disease. J Neurosci 2011;31:11159—71.

[41] Naert G, Rivest S. A deficiency in CCR2+ monocytes: the hidden side of Alzheimer's disease. J Mol Cell Biol 2013;5:284—93.

[42] Hawkes CA, McLaurin J. Selective targeting of perivascular macrophages for clearance of beta-amyloid in cerebral amyloid angiopathy. Proc Natl Acad Sci USA 2009;106:1261—6.

[43] Naert G, Rivest S. CC chemokine receptor 2 deficiency aggravates cognitive impairments and amyloid pathology in a transgenic mouse model of Alzheimer's disease. J Neurosci 2011;31:6208—20.

[44] Kiyota T, Gendelman HE, Weir RA, Higgins EE, Zhang G, Jain M. CCL2 affects beta-amyloidosis and progressive neurocognitive dysfunction in a mouse model of Alzheimer's disease. Neurobiol Aging 2013;34:1060—8.

[45] Benilova I, Karran E, De Strooper B. The toxic Abeta oligomer and Alzheimer's disease: an emperor in need of clothes. Nat Neurosci 2012;15:349—57.

[46] He J, Chen Y, Farzan M, Choe H, Ohagen A, Gartner S, et al. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. Nature 1997;385:645—9.

[47] Zhu C, Xu B, Sun X, Zhu Q, Sui Y. Targeting CCR3 to reduce amyloid-beta production, tau hyperphosphorylation, and synaptic loss in a mouse model of Alzheimer's disease. Mol Neurobiol 2017;54:7964—78.

[48] Passos GF, Figueiredo CP, Prediger RD, Pandolfo P, Duarte FS, Medeiros R, et al. Role of the macrophage inflammatory protein-1alpha/CC chemokine receptor 5 signaling pathway in the neuroinflammatory response and cognitive deficits induced by beta-amyloid peptide. Am J Pathol 2009;175:1586—97.

[49] Man SM, Ma YR, Shang DS, Zhao WD, Li B, Guo DW, et al. Peripheral T cells overexpress MIP-1alpha to enhance its transendothelial migration in Alzheimer's disease. Neurobiol Aging 2007;28:485—96.

[50] Li M, Shang DS, Zhao WD, Tian L, Li B, Fang WG, et al. Amyloid beta interaction with receptor for advanced glycation end products up-regulates brain endothelial CCR5 expression and promotes T cells crossing the blood-brain barrier. J Immunol 2009;182:5778—88.

[51] Laurent C, Dorothee G, Hunot S, Martin E, Monnet Y, Duchamp M, et al. Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. Brain 2017;140:184—200.

[52] Marciniak E, Faivre E, Dutar P, Alves Pires C, Demeyer D, Caillierez R, et al. The Chemokine MIP-1alpha/CCL3 impairs mouse hippocampal synaptic transmission, plasticity and memory. Sci Rep 2015;5:15862.

[53] Zhou M, Greenhill S, Huang S, Silva TK, Sano Y, Wu S, et al. CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory. ELife 2016;5:e20985.

[54] Duyckaerts C, Bennecib M, Grignon Y, Uchihara T, He Y, Piette F, et al. Modeling the relation between neurofibrillary tangles and intellectual status. Neurobiol Aging 1997;18:267—73.

[55] Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158—65.

[56] Grober E, Dickson D, Sliwinski MJ, Buschke H, Katz M, Crystal H, et al. Memory and mental status correlates of modified Braak staging. Neurobiol Aging 1999;20:573—9.

[57] Proudfoot AE, Power CA, Schwarz MK. Anti-chemokine small molecule drugs: a promising future? Expert Opin Investig Drugs 2010;19:345—55.