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...
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 sub-family 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. 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 to 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].

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-deficiency 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 deficiency 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.
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 hyperphosphorylation 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 phosphorylation [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 development 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
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 pathogenetic 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).

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]|
|                          | CXCR3    | 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]       |

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 engulfment 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 Tg2576xCCL2−/− 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 derive 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 Tg2576xCCL2−/− 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 APPsw/PSEN1(A246E) double transgenics, Naer 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 APPsw/PSEN1(A246E) double transgenics. Kiyota et al. found that CCR2-deficiency accelerates the memory deficits and aggravates cognitive impairment [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.

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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