

Chemoattractants and receptors in Alzheimer's disease

Lingfei Ruan¹, Yan Kong¹, Ji Ming Wang², Yingying Le¹

¹Key Laboratory of Nutrition and Metabolism, Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences; Graduate School of the Chinese Academy of Sciences, Shanghai, China. ²Laboratory of Molecular Immunoregulation, Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, Maryland, USA

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1. ABSTRACT

Chemoattractants, including classical chemoattractants and chemokines, are mediators of leukocyte trafficking in physiological immunosurveillance as well as recruitment of leukocyte to the sites of inflammation and injury. Besides their well-established role in the immune system, recent researches have demonstrated that chemoattractants and their receptors are also involved in brain development and in the maintenance of normal brain homeostasis. Evidence is emerging that chemoattractants and their receptors play important roles in neuroinflammation, neuronal death and hence neurodegenerative diseases. In this review, we summarize recent progress regarding the involvement of chemoattractants and their receptors in Alzheimer's disease and their potential as therapeutic targets.

2. INTRODUCTION

Chemoattractants, including classical chemoattractants and a superfamily of chemokines, function as inducers of leukocyte trafficking and activation. Classical chemoattractants include N-formyl-methionyl-leucyl-phenyl-alanine (fMLF), activated complement component 5 (C5a), leukotriene B4 and platelet activating factor. Chemokines are subdivided into four groups based on the number and spacing of the conserved cysteine residues in the N-terminus and are named CXC, CC, CX3C, and C chemokines. Both classical chemoattractants and chemokines activate seven-transmembrane, G protein-coupled receptors (GPCRs) expressed not only on cells of hematopoietic origin, but also on other cell types. Chemokine receptors are divided into CXCR, CCR, CX3CR and XCR subgroups based on their chemokine

Table 1. Chemoattractants and receptors in AD

Receptors	Expression in AD	Ref	Chemoattractants	Expression in AD	Ref
FPRL1	Elevated in microglia	(11)	Abeta	amyloid deposits	
CCR1	Present in neurons and dystrophic neuritis associated with amyloid plaques	(63)	CCL3/MIP-1alpha	Elevated in brain microvessels and peripheral T lymphocytes	(48, 49)
			CCL5/RANTES	Elevated in brain microvessels	(52)
CCR2	Elevated in PBMC ¹	(64)	CCL2/MCP-1	Elevated in senile plaques, neurons, astrocytes, microglia, microvessels, serum and csf ²	(29-31, 34, 35)
CCR3	Elevated in microglia associated with Abeta deposits	(47)	CCL3/MIP-1alpha	Elevated in brain microvessels and peripheral T lymphocytes	(48, 49)
			CCL4/MIP-1beta	Present in a subpopulations of reactive astrocytes spread in ad brain	(47)
			CCL5/RANTES	Elevated in brain microvessels	(52)
CCR5	Elevated in some microglia associated with amyloid plaques; elevated in PBMC ¹	(47, 64)	CCL3/MIP-1alpha	Elevated in brain microvessels and peripheral T lymphocytes	(48, 49)
			CCL4/MIP-1beta	Present in a subpopulations of reactive astrocytes spread in ad brain	(47)
			CCL5/RANTES	Elevated in brain microvessels	(52)
CCR10			CCL27/ILC	Elevated in ad brain	(62)
CXCR2	Elevated in a subpopulation of neuritic plaques and peripheral t lymphocytes	(78, 80)	CXCL1/GROalpha	Elevated in ad brain	(70)
			CXCL8/IL-8	Elevated in neurons, brain microvessels and csf ²	(30, 34, 59)
CXCR3	Expressed by neurons	(81, 82)	CXCL10/IP-10	Elevated in astrocyte associated with amyloid plaques; increased in csf ² of mild ad but decreased with the progression of ad	(34, 81, 84)
CXCR4	Elevated in AD brain	(62)	CXCL12/SDF-1	Decreased in plasma	(94)
CX3CR1	Expressed by neurons and microglia	(96, 97)	CX3CL1/fractalkine	Decreased in brain of young app transgenic mice;elevated in the plasma which negatively correlated with the severity of cognitive impairment	(100)

Abbreviations: ¹peripheral blood mononuclear cell, ²cerebrospinal fluid

ligand specificity. To date, more than 50 chemokines and about 20 chemokine GPCRs have been identified (1, 2). Some chemokines bind only to one receptor and vice versa, such as CXCL16 to CXCR6 and CCL20 (MIP-3alpha, LARC) to CCR6. However, most chemokines bind to more than one receptor, and most chemokine receptors are capable of binding and responding to more than one ligand. For example, chemokine CCL5 (RANTES) binds to at least CCR1, CCR3 and CCR5, while CCR3 binds to CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL11 (eotaxin), CCL13 (MCP-4), CCL24 (eotaxin-2), and CCL26 (eotaxin-3). Therefore, chemokines within a subgroup frequently exhibit overlapping biological activities which implies functional redundancy. However, studies of receptor gene knockout mice have revealed that each chemokine GPCR is involved in one or multiple pathophysiological processes (3).

Chemoattractants and their receptors are implicated in leukocyte trafficking, coagulation, hematopoiesis, development, wound healing, allergy, atherogenesis, angiogenesis/angiostasis, malignancy, and HIV infection (4, 5). Accumulating evidence suggests that chemoattractants and their receptors are important not only in central nervous system (CNS) homeostasis and neuronal patterning during ontogeny, but also in the inflammation and neurological disorders, such as multiple sclerosis, trauma, stroke, and Alzheimer's disease (AD) (6, 7). Amyloid beta (Abeta) deposition, neurofibrillary tangle formation, glial cell activation and neuritic degeneration are characteristic features of AD. Although genetic defects account for a minority of AD cases, the precise cause has yet to be determined for majority cases. A bulk of evidence suggests that inflammatory responses play an important role in the pathogenic process of AD, either in the initiation or as amplifiers of the disease. Recent studies also suggest the importance of limited inflammation in the clearance of

Abeta peptide deposits and the amelioration of AD syndrome in animal models (8). This review will discuss the involvement of chemoattractants and their receptors in the inflammatory responses and pathogenesis of AD (Table 1).

3. THE ROLE OF CLASSICAL CHEMOATTRACTANT GPCRS IN AD

Abeta is a major contributor to the pathogenesis of AD. Abeta is not only directly neurotoxic, but also causes indirect neuronal damage by activating microglia and astrocytes that accumulate in and around amyloid plaques in AD brain. Several cell-surface molecules have been reported to act as putative receptors for Abeta, including the receptor for advanced glycation-end products (RAGE) and scavenger receptor (9, 10). Our previous studies have revealed that a formylpeptide receptor-like-1 (FPRL1) in human and its mouse homologue mFPR2 are functional receptors for Abeta (11, 12). FPRL1 is a classical chemoattractant GPCR and binds the bacterial chemotactic peptide fMLF with low affinity. FPRL1 is expressed at high levels in microglia infiltrating senile plaques in the brain tissue of AD patients (11). *In vitro*, FPRL1 and its mouse homolog mFPR2 mediate the chemotactic activity of Abeta₄₂ for phagocytic leukocytes and trigger the release of neurotoxic superoxide and proinflammatory cytokines by these cells (11, 12). The proinflammatory cytokine TNF-alpha up-regulates mFPR2 in microglia and enhance their chemotactic responses to Abeta₄₂, suggesting the role of TNF-alpha in amplifying inflammatory response in AD (13). FPRL1 and mFPR2 also mediate Abeta₄₂ internalization in mononuclear phagocytes and its cytotoxicity for neuronal cells (14, 15). Consistent with these observations, Brandenburg *et al.* (16) reported rapid internalization of Abeta₄₂ via

FPRL1 in primary rat astrocytes and microglia, with signaling pathway dependent on phospholipase D. Activation of Toll-like receptor 4 (TLR4), TLR9 or TLR2 also enhances mFPR2 expression and Abeta uptake by mouse microglial cells (15, 17, 18). In addition, a recent study reveals that TLRs are crucial for the capacity of microglia to endocytose and degrade Abeta peptides, which likely involve upregulation of mFPR2 (8). Therefore, molecules associated with inflammation and microbial infection are important regulators of FPRL1/mFPR2 in microglial cells, which may profoundly affect the pathologic processes of AD, in particular in Abeta uptake and clearance.

Locus ceruleus (LC) degeneration and loss of cortical noradrenergic innervation occur early in AD. In AD patient, a decrease in LC neuron numbers is correlated with the increase in amyloid plaques, neurofibrillary tangles, and the severity of dementia (19-22). In rodent AD models, LC neuron degeneration exacerbates several features of AD, including Abeta deposition, inflammation, neurodegeneration and cognitive impairment (23-25). Norepinephrine (NE) supplement can ameliorate the inflammation induced by LC degeneration in AD mouse models (23). Our studies found that NE and isoproterenol induce mFPR2 expression in microglia through beta adrenergic receptor (beta AR)-mediated activation of MAP kinases ERK1/2 and p38, as well as transcription factor NF-kappaB. betaAR agonist markedly enhances Abeta₄₂ uptake and degradation in microglia, likely due to the upregulation of mFPR2 expression and increase in Abeta degrading enzyme neprilysin, respectively. Thus, noradrenergic innervation from LC is needed to maintain adequate Abeta uptake and clearance by microglia through mFPR2. NE pathway is a potential therapeutic target for AD.

Humanin is a 24-amino acid peptide expressed in the occipital region of AD which is rarely affected by the disease. Accumulating evidence demonstrates that Humanin and its derivative peptides had a broad spectrum of neuroprotective capabilities against diverse AD-related insults (26). Humanin could induce chemotaxis of mononuclear phagocytes (monocytes and microglia) by using FPRL1/mFPR2 (27), which coincidentally are also functional receptors used by Abeta₄₂ to chemoattract and activate phagocytic leukocytes. Humanin inhibits Abeta₄₂ uptake and fibril formation in monocytic cells. In neuroblastoma cells, Humanin and Abeta₄₂ both activate FPRL1, however, only Abeta₄₂ caused apoptotic death of the cells. These results suggest that by sharing human FPRL1 and mouse mFPR2 with Abeta₄₂, Humanin may exert neuroprotective effects by competitively inhibiting the access of FPRL1 to Abeta₄₂. Nevertheless, the potential involvement of other cell surface receptors should not be excluded in the neuroprotective effects of Humanin (28). Further understanding the regulation of Humanin expression in the brain and its mechanisms of function may provide very useful means for preventing or retarding the progression of AD.

4. CHEMOKINES AND THEIR RECEPTORS IN AD

4.1. CC chemokines and receptors in AD

4.1.1. CC chemokines in AD

4.1.1.1. CCL2

CCL2 is originally named monocyte chemotactic protein-1 (MCP-1). It is a key molecule for monocyte chemotaxis and tissue extravasation and for the modulation of leukocyte function during inflammation. In AD, CCL2 expression is upregulated in senile plaques, neurons, astrocytes, reactive microglia and microvessels (29-31). CCL2 overexpression was also observed in the brain tissue of AD mouse models (32, 33). Increased levels of CCL2 are also found in the sera and cerebrospinal fluid of AD patients, as well as in patients with mild cognitive impairment (MCI) who later develop AD (34, 35). It has been shown that a single nucleotide polymorphism occurring at position -2518 (A/G) in the promoter region of CCL2 gene may affect CCL2 expression (36). The -2518 A/G polymorphism of the CCL2 gene is reported as an independent risk factor for AD in Italians but not in a Spanish cohort (37, 38). Therefore, differences in geographical and ethnic background may affect the susceptibility of a population to AD despite a same polymorphism in CCL2 gene.

In vitro studies have shown that Abeta can induce CCL2 expression in monocytes/macrophages, microglia, astrocytes and brain endothelial cells (39-41). Acute intracerebroventricular injection of Abeta₄₂ induces production of CCL2, IL-1 and IL-6 in the hippocampus and cortex of mice (42). *In vivo*, transgenic overexpression of CCL2 in the brain results in increased microglial accumulation and diffuse amyloid plaque deposition in a mouse model of AD expressing Swedish APP mutant (43). APP/CCL2 mice show an early onset of spatial learning impairment and Abeta oligomer formation, whereas CCL2 transgenic mice show normal learning, suggesting that although CCL2 does not induce memory dysfunction by itself, it acts as a cofactor in Abeta-induced memory impairment in APP mice (43). Therefore, targeted reduction of CCL2 in CNS may be beneficial. Indeed, delivery of a dominant-negative CCL2 mutant to APP/presenilin-1 (APP/PS1) bigenic mice reduced astro/microgliosis, beta-amyloidosis including both fibrillar and oligomer Abeta accumulation, in association with improved spatial learning (44). These results suggest CCL2 as a therapeutic target for neuroinflammation and progression of AD.

4.1.1.2. CCL3 and CCL4

Macrophage inflammatory protein-1 (MIP-1) includes two major forms MIP-1alpha and MIP-1beta that are now officially named CCL3 and CCL4, respectively. Recently, an association between CCL3 gene polymorphism and AD was reported in a Chinese population (45). The CSF levels of CCL3 do not differ in AD and control groups (46). Immunohistochemical studies showed that CCL3 was present predominantly in neurons and weakly in some microglia in both AD and controls, while CCL4 was expressed predominantly in a subpopulation of reactive astrocytes, which were more

widespread in AD brain. Many CCL4-positive reactive astrocytes were found to be associated with amyloid deposits (47). Elevated CCL3 was found in brain microvessels and peripheral T lymphocytes of AD patients (48, 49). CCL3 can induce the expression of its receptor CCR5 on human brain microvascular endothelial cells (HBMECs). The interaction between CCL3 overexpressed by T cells and CCR5 on HBMECs is involved in T cell migration from blood to the brain of AD patients (49). *In vitro* studies demonstrated that Abeta enhanced the expression of CCL3 in monocytes and microglia, and CCL4 in monocytes/macrophages (39, 40, 50, 51). Thus, CCL3 and CCL4 are involved in glial cell activation and T cell infiltration in AD brain.

4.1.1.3. CCL5

CCL5 is also known as RANTES (an acronym for Regulated on Activation, Normal T Expressed and Secreted). The expression of CCL5 in AD-derived microvessels was significantly higher than in microvessels from normal brain (52). *In vitro*, Abeta has been shown to induce the expression of CCL5 in astrocytes, oligodendrocytes, PBMC, and lymphocytes (53-55). Oxidative stress has also been shown to induce CCL5 expression in cultured brain endothelial cells and astrocytes (52, 56).

Several studies have shown a neuroprotective effect for CCL5. Treatment of primary cortical neuronal cultures with CCL5 enhances neuronal survival. CCL5 protects neurons against the toxicity of Abeta, thrombin and sodium nitroprusside (SNP) (52, 57, 58). The ability of CCL5 to decrease neuronal cell death in response to these molecules could be protective in AD, since Abeta, thrombin and nitric oxide (an active species released from SNP) are neurotoxic and elevated in the AD brain and microcirculation (59, 60). The neuroprotective effect of CCL5 is mediated by a G protein-coupled receptor 75 (GPCR75) (58), suggesting the potential for CCL5/GPCR75 as targets for prevention of Abeta-induced neuronal loss.

4.1.1.4. Other CC chemokines

In vitro study showed that Abeta₄₂ induced CCL7 (MCP-3) expression in murine primary microglia and a microglia cell line, through phosphatidylinositol 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) related pathways (61). Microarray and real-time PCR revealed the upregulation of CCL27 in AD brain tissue (62). Although the precious role of these CC chemokines in AD brain tissues has yet to be elucidated, their elevation in AD brain tissue implies involvement in neuroinflammatory responses.

4.1.2. CC chemokine receptors in AD

CCR1 can bind CCL3 (MIP-1 alpha), CCL5 (RANTES), CCL7 (MCP-3) and CCL23 (MPIF-1). In AD patients, CCR1 expressed in neurons and dystrophic neurites associated with senile plaques containing Abeta₄₂, but not associated with diffuse deposits of Abeta₄₂. CCR1 was rarely detected in brains from age-matched, nondemented individuals (63). The number of CCR1-

positive plaque-like structures in the hippocampus and entorhinal cortex of AD brains is highly correlated to the degree of dementia (63), suggesting that CCR1 expression in brains is part of the neuroimmune responses caused by Abeta₄₂-positive neuritic plaques.

CCR2 binds chemokines CCL2 (MCP-1), and CCL7 (MCP-3). Peripheral blood mononuclear cells isolated from AD patients express higher levels of CCR2 than those from healthy controls (64). In a transgenic mouse model of AD (Tg2576), CCR2 deficiency accelerates early disease progression and markedly reduces microglial accumulation. AD mice deficient in CCR2 showed earlier Abeta accumulation in the brain and died prematurely, in a manner that correlates with the levels of CCR2 expression, indicating that the absence of early microglial accumulation leads to decreased Abeta clearance and increased mortality (65). Thus, CCR2-dependent microglial accumulation plays a protective role in the early stages of AD by promoting Abeta clearance.

Both CCR3 and CCR5 can bind ligands CCL3, CCL4 and CCL5. Microarray assay revealed an increased expression of CCR3 in AD brain tissue. In the majority of AD brain, the elevation of CCR3 level was correlated with the activation of PKC, a downstream mediator of CCR3 signaling (62). Immunohistochemistry analysis demonstrated that CCR3 was present on microglia of both control and AD brains, with increased expression on some reactive microglia in AD. Many of the CCR³⁺ reactive microglia were found to be associated with amyloid deposits (47). Another chemokine GPCR CCR5 is present on microglia of both control and AD brains, with an increase on some reactive microglia associated with AD amyloid plaques (47). Elevated CCR5 expression is also present on peripheral blood mononuclear cells (PBMC) of AD patients (64). Abeta induces CCR5 expression in human PBMC (66). Thus, CCR3 and CCR5 may be involved in Abeta-induced inflammation in AD. It is interesting to note that the natural CCR5 mutant Delta32 renders human subjects resistant to HIV infection but not AD (67, 68).

4.2. CXC chemokines and receptors in AD

4.2.1. CXCL1, CXCL2, CXCL8 and CXCR2 in AD

CXCL1, previously called GROalpha in human and KC in mice, signals through the receptor CXCR2. CXCL1 gene SNPs are not associated with AD as examined in a Japanese population (69). CXCL1 is upregulated in AD brains (70). *In vitro* studies showed that CXCL1 induced hyperphosphorylation of the tau protein in mouse primary cortical neurons (70), suggesting that CXCL1 may play pathophysiological role in AD. However, *in vitro* study also showed that CXCL1 protected hippocampal neurons against Aβ induced death (71). After short-term exercise, Tg2576 mice exhibited cognitive improvement with increased levels of CXCL1 in the brain, suggesting this chemokine mediated inflammatory response in exercise may induce cognitive amelioration (72).

CXCL2, also named macrophage inflammatory protein 2, is another ligand for CXCR2. Abeta₄₂ induces

CXCL2 expression by microglia (61), and this chemokine may protect hippocampal neurons against Abeta₄₂ induced death, through MEK1-ERK1/2 and PI3K-Akt signaling pathways (71).

CXCL8 (IL-8) is produced by many cell types including macrophages and epithelial cells. CXCL8 binds to two GPCRs CXCR1 and CXCR2. CXCL8 is consistently upregulated in the brain tissue of AD patients. It is colocalized with neurons and amyloid plaques in AD brain (30). Microvessels isolated from AD patients also showed higher expression of CXCL8 compared to control vessels (59). Cerebrospinal fluid CXCL8 levels were increased in mild cognitive impairment (MCI) and AD patients (34). *In vitro*, Abeta alone or with IL-1beta induced microglia, astrocytes and peripheral monocytes to produce CXCL8 (73, 74). Abeta also induces chemokine (including CXCL8) secretion and monocyte migration across a human blood-brain barrier model (75). CXCL8 enhances Abeta-induced expression and production of pro-inflammatory cytokines and COX-2 in cultured human microglia, and induces the expression of matrix metalloproteinases, cell cycle and pro-apoptotic proteins, and cell death in cultured neurons (76, 77). These results suggest that among the proinflammatory cytokines induced by Abeta in AD brain, CXCL8 may further exacerbate detrimental inflammatory responses in the brain by inducing neurotoxins, recruiting peripheral monocytes to brain tissue, and promoting neuron apoptosis.

CXCR2 is a GPCR recognizing multiple chemokine ligands, such as CXCL1, CXCL2 and CXCL8. In normal individuals, CXCR2 is expressed at high levels by subsets of projection neurons in diverse regions of the brain and spinal cord. In AD, CXCR2 is strongly upregulated in a subpopulation of neuritic plaques (78). Recently CXCR2 is reported to promote Abeta production by regulating gamma-secretase activity in neurons (79). *In vitro* study showed that treatment of APP expressing cells with CXCR2 agonists CXCL1 and CXCL8 leads to enhanced Abeta production. Treatment of the cells with antagonists or depletion of endogenous CXCR2 agonists leads to inhibition of Abeta production. The inhibitory effect of the antagonist of CXCR2 on production of Abeta₄₀ and Abeta₄₂ is mediated *via* reduction of presenilin (PS), one of the gamma-secretase components. Also, treatment of APP/PS transgenic mice with a CXCR2 antagonist inhibited Abeta₄₀ and Abeta₄₂ production. These findings strongly suggest that up-regulation of CXCR2 is a driving force in increased production of Abeta. CXCR2 is overexpressed in T cells from AD patients (80). Abeta injection in rat hippocampus upregulated CXCR2 expression accompanied with increased T cell accumulation in the brain. This enhanced T cell entry was effectively blocked by a CXCR2 antagonist. T cell migration through *in vitro* blood-brain barrier model was effectively blocked by antibodies against CXCR2 or CXCL8 (IL-8) (80). These results suggest that overexpression of CXCR2 in peripheral T cells contribute to T cell transendothelial migration in AD brain, which may amplify proinflammatory and immune responses.

4.2.2. CXCL10 and CXCR3 in AD

CXCL10 is also named interferon-gamma-induced protein (gamma-IP10 or IP-10) in human and cytokine responsive gene-2 (CRG- 2) in murine. It elicits multiple effects by binding to the cell surface receptor CXCR3. In normal brain, CXCL10 is expressed in a subpopulation of astrocytes, CXCR3 is detected constitutively on neurons and neuronal processes in various cortical and subcortical regions, suggesting the involvement of CXCL10/CXCR3 in neuronal-glial interaction (81, 82). In the brain tissues of AD patients, CXCL10 was upregulated in reactive astrocytes and CXCL10 positive astrocytes were associated with senile plaques (81). Similarly, increased CXCL10 expression was found in cerebral cortex and hippocampus of aged APP transgenic mice. The intense CXCL10 expression was co-located with Abeta positive plaques (83). Intrathecal level of CXCL10 was increased in mild cognitive impairment (MCI) patients and mild AD patients and decreased with the progression of AD (34, 84). Serum CXCL10 level has a tendency of increase with aging in healthy individuals, but not in MCI and AD patients (85-87). *In vitro*, Abeta₄₂ stimulated human monocytic cell line THP-1 to express CXCL10 (88). CXCL10 induces neuron apoptosis (89). Thus, CXCL10/CXCR3 may play an important role in inflammatory responses and the loss of neurons in AD.

4.2.3. CXCL12 and CXCR4 in AD

The chemokine CXCL12 is also known as stromal cell-derived factor 1 (SDF-1). CXCR4 is initially believed to be the sole receptor for CXCL12, but recently CXCR7 has also been shown to bind CXCL12 (90). CXCL12 and CXCR4 are widely expressed by glial and neuronal cells in the developing and adult cerebral cortex and they exert various functions in the brain. CXCL12 directs neuronal migration and axonal pathfinding in the developing nervous system. In the adult brain, CXCL12 is thought to influence neurogenesis as well as recruitment of brain resident and non-resident circulating cells toward sites of lesions (91). CXCL12 has been reported to affect the function of neurons by multiple regulatory pathways (92). In human, CXCR4 is elevated in AD brain tissues (62). However, the expression of both CXCL12 and CXCR4 decreases in an APP transgenic AD mouse model (Tg2576) coinciding with cognitive deficits (93). Short-term exercise in Tg2576 mice increases brain CXCL12 level and improves cognition (72). Chronic treatment of young, normal mice with an antagonist to the CXCL12 receptor CXCR4 resulted in selectively impaired learning and memory (93). These results suggest that CXCL12/CXCR4 may improve neuron-glia/neuron-neuron communication thereby improving and enhancing learning and memory. In human, CXCL12 plasma levels in healthy elderly increase with age but significantly decrease in AD patients. Higher CXCL12 plasma levels in AD patients are weakly associated with lower tau protein levels in CSF and better preservation of cognitive functions of AD patients (94). As CXCL12 plays an important role in mobilization, migration and homing of bone marrow-derived stem cells to the sites of lesions, it is reasonable to assume that decreased CXCL12 plasma levels may contribute to a

deficient mobilization of hematopoietic stem cells from the bone marrow crucial for sustaining brain homeostasis.

4.3. CX3CL1 and CX3CR1 in AD

CX3CL1 is the only known member of the CX3C chemokine subfamily so far. It is also named fractalkine in human and neurotactin in mice. CX3CL1 exists in both membrane-bound and soluble forms. While membrane-bound form serves as an adhesion molecule for leukocytes expressing the receptor CX3CR1, soluble CX3CL1 functions as a pro-inflammatory chemoattractant that activates a number of cells involved in inflammatory responses (95-97).

In human CNS, CX3CL1 is mainly expressed on neurons, while astrocytes and cerebral vascular endothelia also express CX3CL1. CX3CR1 is expressed on human neurons and microglia but not astrocytes, indicating that CX3CL1 secreted by neurons, astrocytes and endothelia is a communicator among many cell types in CNS (96, 97).

In an APP transgenic mouse model, CX3CL1 expression in cerebral cortex and hippocampus was decreased at 9-month, but not 11- and 17-month of age (83). As CX3CL1 has been proposed to function as an intrinsic inhibitor of neurotoxicity mediated by activated microglia (98, 99), decreased CX3CL1 in neurons may favor the activation and neurotoxicity of microglia in mouse AD model. Thus, it is proposed that decreased CX3CL1 expression contribute to the inflammatory responses at early stages of AD. The levels of plasma soluble CX3CL1 in patients with MCI and AD significantly increased with higher levels in MCI. There was a negative correlation between the severity of cognitive impairment and the plasma soluble CX3CL1 level in the patients with AD (100). These data indicate the protective role of soluble CX3CL1 in AD and its serum level could be used as a biomarker of early stages of AD.

5. PERSPECTIVES

Chemoattractants were originally described to be involved mainly in leukocyte trafficking. Research over the last decade has shown that chemoattractants are involved in a broader spectrum of pathophysiological processes. In the brain, chemoattractant receptors are not only found in microglia, but also in astrocytes, oligodendrocytes and neurons. There is growing evidence to suggest that chemoattractants and their receptors contribute to the development and progression of AD. Chemokines may induce neuronal death either directly through activation of receptors on neurons or indirectly through activation of glial cells to produce pro-inflammatory cytokines and neurotoxins. Due to the promiscuity of chemokine/receptor interactions, it is unlikely that any therapy targeting on one chemokine or receptor will be successful in AD management. Emerging literature also suggests that neuroinflammation in the AD brain is a double-edged sword and that chemoattractant and receptor interaction in the CNS can mediate neuroprotection. For example, CCL5 protects neurons against toxicity of AD-associated neurotoxins (52, 57, 58). Likewise, CXCR2 ligands

CXCL1, CXCL2 and CXCL8 protect neurons against Abeta-induced death (71); CX3CL1 functions as an intrinsic inhibitor against neurotoxicity mediated by activated microglia (98, 99); FPRL1/mFPR2 and CCR2 can mediate Abeta uptake and clearance by microglia (14-16, 65). Whether inflammation is neurotoxic or neuroprotective in AD brain may depend on the context, location and timing of inflammatory responses. Plasma/CSF levels of chemokines, such as CCL2, CX3CL1, and other inflammatory molecules might be useful bio-markers of the progression of AD (35, 100).

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7. REFERENCES

1. PM Murphy: International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. *Pharmacol Rev* 54, 227-229 (2002)
2. A Zlotnik, O Yoshie, H Nomiyama: The chemokine and chemokine receptor superfamilies and their molecular evolution. *Genome Biol* 7, 243 (2006)
3. Y Le, Y Cui, P Iribarren, G Ying, JM Wang: Manipulating chemoattractant and receptor genes. *In vivo* 16, 1-23 (2002)
4. Y Le, W Gong, W Shen, B Li, NM Dunlop, JM Wang: A burgeoning family of biological mediators: chemokines and chemokine receptors. *Arch Immunol Ther Exp (Warsz)* 48, 143-150 (2000)
5. R Bonecchi, E Galliera, EM Borroni, MM Corsi, M Locati, A Mantovani: Chemokines and chemokine receptors: an overview. *Front Biosci* 14, 540-551 (2009)
6. G Banisadr, W Rostène, P Kitabgi, SM Parsadaniantz: Chemokines and brain functions. *Curr Drug Targets Inflamm Allergy* 4, 387-399 (2005)
7. L Cartier, O Hartley, M Dubois-Dauphin, KH Krause: Chemokine receptors in the central nervous system: role in brain inflammation and neurodegenerative diseases. *Brain Res Brain Res Rev* 48, 16-42 (2005)
8. K Tahara, HD Kim, JJ Jin, JA Maxwell, L Li, K Fukuchi: Role of toll-like receptor signalling in Abeta uptake and clearance. *Brain* 129, 3006-3019 (2006)
9. Y Verdier, M Zarandi, B Penke: Amyloid beta-peptide interactions with neuronal and glial cell plasma membrane:

- binding sites and implications for Alzheimer's disease. *J Pept Sci* 10, 229-248 (2004)
10. Y Verdier, B Penke: Binding sites of amyloid beta-peptide in cell plasma membrane and implications for Alzheimer's disease. *Curr Protein Pept Sci* 5, 19-31 (2004)
11. Y Le, W Gong, HL Tiffany, A Tumanov, S Nedospasov, W Shen, NM Dunlop, JL Gao, PM Murphy, JJ Oppenheim, JM Wang: Amyloid (beta)42 activates a G-protein-coupled chemoattractant receptor, FPR-like-1. *J Neurosci* 21, RC123 (2001)
12. HL Tiffany, MC Lavigne, YH Cui, JM Wang, TL Leto, JL Gao, PM Murphy: Amyloid-beta induces chemotaxis and oxidant stress by acting at formylpeptide receptor 2, a G protein-coupled receptor expressed in phagocytes and brain. *J Biol Chem* 276, 23645-23652 (2001)
13. YH Cui, Y Le, X Zhang, W Gong, K Abe, R Sun, J Van Damme, P Proost, JM Wang: Up-regulation of FPR2, a chemotactic receptor for amyloid beta 1-42 (A beta 42), in murine microglial cells by TNF alpha. *Neurobiol Dis* 10, 366-377 (2002)
14. H Yazawa, ZX Yu, Takeda, Y Le, W Gong, VJ Ferrans, JJ Oppenheim, CC Li, JM Wang: Beta amyloid peptide (Abeta42) is internalized via the G-protein-coupled receptor FPRL1 and forms fibrillar aggregates in macrophages. *FASEB J* 15, 2454-2462 (2001)
15. P Iribarren, K Chen, J Hu, W Gong, EH Cho, S Lockett, B Uranchimeg, JM Wang: CpG-containing oligodeoxynucleotide promotes microglial cell uptake of amyloid beta 1-42 peptide by up-regulating the expression of the G-protein- coupled receptor mFPR2. *FASEB J* 19, 2032-2034 (2005)
16. LO Brandenburg, M Konrad, C Wruck, T Koch, T Pufe, R Lucius: Involvement of formyl-peptide-receptor-like-1 and phospholipase D in the internalization and signal transduction of amyloid beta 1-42 in glial cells. *Neuroscience* 156, 266-276 (2008)
17. YH Cui, Y Le, W Gong, P Proost, DJ Van, WJ Murphy, JM Wang: Bacterial lipopolysaccharide selectively up-regulates the function of the chemotactic peptide receptor formyl peptide receptor 2 in murine microglial cells. *J Immunol* 168, 434-442 (2002)
18. K Chen, P Iribarren, J Hu, J Chen, W Gong, EH Cho, S Lockett, NM Dunlop, JM Wang: Activation of Toll-like receptor 2 on microglia promotes cell uptake of Alzheimer disease-associated amyloid beta peptide. *J Biol Chem* 281, 3651-3659 (2006)
19. B Marcyniuk, DM Mann, PO Yates: Loss of nerve cells from locus coeruleus in Alzheimer's disease is topographically arranged. *Neurosci Lett* 64, 247-252 (1986)
20. W Bondareff, CQ Mountjoy, M Roth, MN Rossor, LL Iversen, GP Reynolds, DL Hauser: Neuronal degeneration in locus ceruleus and cortical correlates of Alzheimer disease. *Alzheimer Dis Assoc Disord* 1, 256-262 (1987)
21. A Grudzien, P Shaw, S Weintraub, E Bigio, DC Mash, MM Mesulam: Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. *Neurobiol Aging* 28, 327-35 (2007)
22. D Weinshenker: Functional consequences of locus coeruleus degeneration in Alzheimer's disease. *Curr Alzheimer Res* 5, 342-345 (2008)
23. MT Heneka, E Galea, V Gavriluyk, L Dumitrescu-Ozimek, J Daeschner, MK O'Banion, G Weinberg, T Klockgether, DL Feinstein: Noradrenergic depletion potentiates beta -amyloid-induced cortical inflammation: implications for Alzheimer's disease. *J Neurosci* 22, 2434-2442 (2002)
24. S Kalinin, V Gavriluyk, PE Polak, R Vasser, J Zhao, MT Heneka, DL Feinstein: Noradrenaline deficiency in brain increases beta-amyloid plaque burden in an animal model of Alzheimer's disease. *Neurobiol Aging* 28, 1206-1214 (2006)
25. MT Heneka, M Ramanathan, AH Jacobs, L Dumitrescu-Ozimek, A Bilkei-Gorzo, T Debeir, M Sastre, N Galldiks, A Zimmer, M Hoehn, WD Heiss, T Klockgether, M Staufenbiel: Locus coeruleus degeneration promotes Alzheimer pathogenesis in amyloid precursor protein 23 transgenic mice. *J Neurosci* 26, 1343-1354 (2006)
26. T Arakawa, Y Kita, T Niikura: A rescue factor for Alzheimer's diseases: discovery, activity, structure, and mechanism. *Curr Med Chem* 15, 2086-2098 (2008)
27. G Ying, P Iribarren, Y Zhou, W Gong, N Zhang, ZX Yu, Y Le, Y Cui, JM Wang: Humanin, a newly identified neuroprotective factor, uses the G protein-coupled formylpeptide receptor-like-1 as a functional receptor. *J Immunol* 172, 7078-7085 (2004)
28. M Ikonen, B Liu, Y Hashimoto, L Ma, K W Lee, T Niikura, I Nishimoto, P Cohen: Interaction between the Alzheimer's survival peptide humanin and insulin-like growth factor-binding protein 3 regulates cell survival and apoptosis. *Proc Natl Acad Sci U S A* 100, 13042-13047 (2003)
29. K Ishizuka, T Kimura, R Igata-yi, S Katsuragi, J Takamatsu, T Miyakawa: Identification of monocyte chemoattractant protein-1 in senile plaques and reactive microglia of Alzheimer's disease. *Psychiatry Clin Neurosci* 51, 135-138 (1997)
30. A Sokolova, MD Hill, F Rahimi, LA Warden, GM Halliday, CE Shepherd: Monocyte Chemoattractant Protein-1 Plays a Dominant Role in the Chronic Inflammation Observed in Alzheimer's Disease. *Brain Pathol* 19, 392-398 (2008)
31. P Grammas, R Ovase: Inflammatory factors are

elevated in brain microvessels in Alzheimer's disease. *Neurobiol Aging* 22, 837-842 (2001)

32. MC Janelins, MA Mastrangelo, S Oddo, FM LaFerla, HJ Federoff, WJ Bowers: Early correlation of microglial activation with enhanced tumor necrosis factor- α and monocyte chemoattractant protein-1 expression specifically within the entorhinal cortex of triple transgenic Alzheimer's disease mice. *J Neuroinflammation* 2, 23 (2005)

33. L Ruan, Z Kang, P Pei, Y Le: Amyloid Deposition and Inflammation in APPswe/PS1dE9 Mouse Model of Alzheimer's Disease. *Curr Alzheimer Res* in press

34. D Galimberti, N Schoonenboom, P Scheltens, C Fenoglio, F Bouwman, E Venturelli, I Guidi, MA Blankenstein, N Bresolin, E Scarpini: Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer disease. *Arch Neurol* 63, 538-543 (2006)

35. D Galimberti, C Fenoglio, C Lovati, E Venturelli, I Guidi, B Corra, D Scalabrini, F Clerici, C Mariani, N Bresolin, E Scarpini: Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease. *Neurobiol Aging* 27, 1763-1768 (2006)

36. BH Rovin, L Lu, R Saxena: A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. *Biochem Biophys Res Commun* 259, 344-348 (1999)

37. R Pola, A Flex, E Gaetani, AS Proia, P Papaleo, GA Di, G Straface, G Pecorini, M Serricchio, P Pola: Monocyte chemoattractant protein-1 (MCP-1) gene polymorphism and risk of Alzheimer's disease in Italians. *Exp Gerontol* 39, 1249-1252 (2004)

38. O Combarros, J Infante, J Llorca, J Berciano: No evidence for association of the monocyte chemoattractant protein-1 (-2518) gene polymorphism and Alzheimer's disease. *Neurosci Lett* 360, 25-28 (2004)

39. LF Lue, R Rydel, EF Brigham, LB Yang, H Hampel, GM Murphy, Jr L Brachova, SD Yan, DG Walker, Y Shen, J Rogers: Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro. *Glia* 35, 72-79 (2001)

40. HA Smits, A Rijmsmus, JH van Loon, JW Y Wat, J Verhoef, LA Boven, HS LM Nottet: Amyloid-[β]-induced chemokine production in primary human macrophages and astrocytes. *J Neuroimmunol* 127, 160-168 (2002)

41. V Vukic, D Callaghan, D Walker, LF Lue, QY Liu, PO Couraud, IA Romero, B Weksler, DB Stanimirovic, W Zhang: Expression of inflammatory genes induced by β -amyloid peptides in human brain endothelial cells and in Alzheimer's brain is mediated by the JNK-AP1 signaling pathway. *Neurobiol Dis* 34, 95-106 (2009)

42. AM Szczepanik, GE Ringheim: IL-10 and glucocorticoids inhibit Abeta(1-42)- and lipopolysaccharide-induced pro-inflammatory cytokine and chemokine induction in the central nervous system. *J Alzheimers Dis* 5, 105-117 (2003)

43. M Yamamoto, M Horiba, JL Buescher, D Huang, HE Gendelman, RM Ransohoff, T Ikezu: Overexpression of monocyte chemotactic protein-1/CCL2 in β -amyloid precursor protein transgenic mice show accelerated diffuse β -amyloid deposition. *Am J Pathol* 166, 1475-1485 (2005)

44. T Kiyota, M Yamamoto, B Schroder, MT Jacobsen, RJ Swan, MP Lambert, WL Klein, HE Gendelman, RM Ransohoff, T Ikezu: AAV1/2-mediated CNS gene delivery of dominant-negative CCL2 mutant suppresses gliosis, β -amyloidosis, and learning impairment of APP/PS1 mice. *Mol Ther* 17, 803-809 (2009)

45. K Li, D Dai, L Yao, X Gu, K Luan, W Tian, Y Zhao, B Wang: Association between the macrophage inflammatory protein-1 α gene polymorphism and Alzheimer's disease in the Chinese population. *Neurosci Lett* 433, 125-128 (2008)

46. I Blasko, W Lederer, H Oberbauer, T Walch, G Kemmler, H Hinterhuber, J Marksteiner, C Humpel: Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. *Dement Geriatr Cogn Disord* 21, 9-15 (2006)

47. MQ Xia, SX Qin, LJ Wu, CR Mackay, BT Hyman: Immunohistochemical study of the β -chemokine receptors CCR3 and CCR5 and their ligands in normal and Alzheimer's disease brains. *Am J Pathol* 153, 31-37 (1998)

48. D Tripathy, L Thirumangalakudi, P Grammas: Expression of macrophage inflammatory protein 1- α is elevated in Alzheimer's vessels and is regulated by oxidative stress. *J Alzheimers Dis* 11, 447-455 (2007)

49. SM Man, YR Ma, DS Shang, WD Zhao, B Li, DW Guo, WG Fang, L Zhu, YH Chen: Peripheral T cells overexpress MIP-1 α to enhance its transendothelial migration in Alzheimer's disease. *Neurobiol Aging* 28, 485-496 (2007)

50. L Meda, P Baron, E Prat, E Scarpini, G Scarlato, MA Cassatella, F Rossi: Proinflammatory profile of cytokine production by human monocytes and murine microglia stimulated with β -amyloid[25-35]. *J Neuroimmunol* 93, 45-52 (1999)

51. RK Giri, V Rajagopal, VK Kalra: Curcumin, the active constituent of turmeric, inhibits amyloid peptide-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor. *J Neurochem* 91, 1199-1210 (2004)

52. D Tripathy, L Thirumangalakudi, P Grammas: RANTES upregulation in the Alzheimer's disease brain: A possible neuroprotective role. *Neurobiol Aging* [Epub ahead of print] (2008)
53. M Johnstone, AJ Gearing, KM Miller: A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. *J Neuroimmunol* 93, 182-193 (1999)
54. C Iarlori, D Gambi, F Gambi, I Lucci, C Feliciani, M Salvatore, M Reale: Expression and production of two selected beta-chemokines in peripheral blood mononuclear cells from patients with Alzheimer's disease. *Exp Gerontol* 40, 605-611 (2005)
55. AL Teixeira, HJ Reis, FM Coelho, DS Carneiro, MM Teixeira, LB Vieira, MA Mukhamedyarov, AL Zefirov, Z Janka, A Palotas: All-or-nothing type biphasic cytokine production of human lymphocytes after exposure to Alzheimer's beta-amyloid peptide. *Biol Psychiatry* 64, 891-895 (2008)
56. V Sharma, M Mishra, S Ghosh, R Tewari, A Basu, P Seth, E Sen: Modulation of interleukin-1[beta] mediated inflammatory response in human astrocytes by flavonoids: Implications in neuroprotection. *Brain Res Bull* 73, 55-63(2007)
57. V Bruno, A Copani, G Besong, G Scoto, F Nicoletti: Neuroprotective activity of chemokines against N-methyl-D-aspartate or beta-amyloid-induced toxicity in culture. *Eur J Pharmacol* 399, 117-121 (2000)
58. A Ignatov, J Robert, C Gregory-Evans, HC Schaller: RANTES stimulates Ca²⁺ mobilization and inositol trisphosphate (IP₃) formation in cells transfected with G protein-coupled receptor 75. *Br J Pharmacol* 149, 490-497 (2006)
59. P Grammas, PG Samany, L Thirumangalakudi: Thrombin and inflammatory proteins are elevated in Alzheimer's disease microvessels: implications for disease pathogenesis. *J Alzheimers Dis* 9, 51-58 (2006)
60. MA Dorheim, WR Tracey, JS Pollock, P Grammas: Nitric oxide synthase activity is elevated in brain microvessels in Alzheimer's disease. *Biochem Biophys Res Commun* 205, 659-665 (1994)
61. S Ito, M Sawada, M Haneda, Y Ishida, KI Isobe: Amyloid-[beta] peptides induce several chemokine mRNA expressions in the primary microglia and Ra2 cell line via the PI3K/Akt and/or ERK pathway. *Neurosci Res* 56, 294-299 (2006)
62. AT Weeraratna, A Kalehua, I Deleon, D Bertak, G Maher, MS Wade, A Lustig, KG Becker, WIII Wood, DG Walker, TG Beach, DD Taub: Alterations in immunological and neurological gene expression patterns in Alzheimer's disease tissues. *Exp Cell Res* 313, 450-461 (2007)
63. M Halks-Miller, ML Schroeder, V Haroutunian, U Moenning, M Rossi, C Achim, D Purohit, M Mahmoudi, R Horuk: CCR1 is an early and specific marker of Alzheimer's disease. *Ann Neurol* 54, 638-646 (2003)
64. M Reale, C Iarlori, C Feliciani, D Gambi: Peripheral chemokine receptors, their ligands, cytokines and Alzheimer's disease. *J Alzheimers Dis* 14, 147-159 (2008)
65. J El Khoury, M Toft, SE Hickman, TK Means, K Terada, C Geula, AD Luster: Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nat Med* 13, 432-438 (2007)
66. RK Giri, V Rajagopal, S Shahi, BV Zlokovic, VK Kalra: Mechanism of amyloid peptide induced CCR5 expression in monocytes and its inhibition by siRNA for Egr-1. *Am J Physiol Cell Physiol* 289, C264-C276 (2005)
67. CR Balistreri, MP Grimaldi, S Vasto, F Listi, M Chiappelli, F Licastro, D Lio, C Caruso, G Candore: Association between the polymorphism of CCR5 and Alzheimer's disease: results of a study performed on male and female patients from Northern Italy. *Ann N Y Acad Sci* 1089,454-461(2006)
68. O Combarros, J Infante, J Llorca, N Pena, C Fernandez-Viadero, J Berciano: The chemokine receptor CCR5-Delta32 gene mutation is not protective against Alzheimer's disease. *Neurosci Lett* 366, 312-314 (2004)
69. Y Tamura, Y Sakasegawa, K Omi, H Kishida, T Asada, H Kimura, K Tokunaga, NS Hachiya, K Kaneko, H Hohjoh: Association study of the chemokine, CXC motif, ligand 1 (CXCL1) gene with sporadic Alzheimer's disease in a Japanese population. *Neurosci Lett* 379, 149-151 (2005)
70. M Xia, BT Hyman: GROalpha/KC, a chemokine receptor CXCR2 ligand, can be a potent trigger for neuronal ERK1/2 and PI-3 kinase pathways and for tau hyperphosphorylation-a role in Alzheimer's disease? *J Neuroimmunol* 122, 55-64 (2002)
71. K Watson, GH Fan: Macrophage inflammatory protein 2 inhibits beta-amyloid peptide (1-42)-mediated hippocampal neuronal apoptosis through activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling pathways. *Mol Pharmacol* 67, 757-765 (2005)
72. A Parachikova, KE Nichol, CW Cotman: Short-term exercise in aged Tg2576 mice alters neuroinflammation and improves cognition. *Neurobiol Dis* 30, 121-129 (2008)
73. DG Walker, LF Lue, TG Beach: Gene expression profiling of amyloid beta peptide-stimulated human post-mortem brain microglia. *Neurobiol Aging* 22, 957-966 (2001)
74. SJ Kim, HJ Jeong, BK Kim, NH Kim, JS Kim, KS Choi, HJ Lee, ST Kang, SS Shin, WI Kim, HS Eom, KM

- Lee, JY Um, SH Hong, HM Kim: Anti-inflammatory effect of jeongshintang through suppression of p38 activation in human astrocytoma, U373MG cells. *Exp Mol Pathol* 81, 85-91 (2006)
75. M Fiala, L Zhang, X Gan, B Sherry, D Taub, MC Graves, S Hama, D Way, M Weinand, M Witte, D Lorton, Y M Kuo, AE Roher: Amyloid-beta induces chemokine secretion and monocyte migration across a human blood--brain barrier model. *Mol Med* 4, 480-489 (1998)
76. S Franciosi, HB Choi, SU Kim, JG McLarnon: IL-8 enhancement of amyloid-beta (Abeta 1-42)-induced expression and production of pro-inflammatory cytokines and COX-2 in cultured human microglia. *J Neuroimmunol* 159, 66-74(2005)
77. L Thirumangalakudi, L Yin, HV Rao, P Grammas: IL-8 induces expression of matrix metalloproteinases, cell cycle and pro-apoptotic proteins, and cell death in cultured neurons. *J Alzheimers Dis* 11, 305-311 (2007)
78. M Xia, S Qin, M McNamara, C Mackay, BT Hyman: Interleukin-8 receptor B immunoreactivity in brain and neuritic plaques of Alzheimer's disease. *Am J Pathol* 150, 1267-1274 (1997)
79. P Bakshi, E Margenthaler, V Laporte, F Crawford, M Mullan: Novel role of CXCR2 in regulation of gamma-secretase activity. *ACS Chem Biol* 3, 777-789 (2008)
80. YJ Liu, DW Guo, L Tian, DS Shang, WD Zhao, B Li, WG Fang, L Zhu, YH Chen: Peripheral T cells derived from Alzheimer's disease patients overexpress CXCR2 contributing to its transendothelial migration, which is microglial TNF-alpha-dependent. *Neurobiol Aging* [Epub ahead of print](2008)
81. MQ Xia, BJ Bacsikai, RB Knowles, SX Qin, BT Hyman: Expression of the chemokine receptor CXCR3 on neurons and the elevated expression of its ligand IP-10 in reactive astrocytes: *in vitro* ERK1/2 activation and role in Alzheimer's disease. *J Neuroimmunol* 108, 227-235 (2000)
82. SH Goldberg, MP van der, J Hesselgesser, S Jaffer, DL Kolson, AV Albright, F Gonzalez-Scarano, E Lavi: CXCR3 expression in human central nervous system diseases. *Neuropathol Appl Neurobiol* 27, 127-138 (2001)
83. RS Duan, X Yang, ZG Chen, MO Lu, C Morris, B Winblad, J Zhu: Decreased fractalkine and increased IP-10 expression in aged brain of APP(swe) transgenic mice. *Neurochem Res* 33, 1085-1089 (2008)
84. D Galimberti, N Schoonenboom, P Scheltens, C Fenoglio, E Venturelli, YA Pijnenburg, N Bresolin, E Scarpini: Intrathecal chemokine levels in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 66, 146-147 (2006)
85. A Antonelli, M Rotondi, P Fallahi, P Romagnani, SM Ferrari, E Ferrannini, M Serio: Age-dependent changes in CXC chemokine ligand 10 serum levels in euthyroid subjects. *J Interferon Cytokine Res* 25, 547-552 (2005)
86. H Bruunsgaard, M Pedersen, BK Pedersen: Aging and proinflammatory cytokines. *Curr Opin Hematol* 8, 131-136 (2001)
87. D Galimberti, E Venturelli, C Fenoglio, C Lovati, I Guidi, D Scalabrini, C Mariani, N Bresolin, E Scarpini: IP-10 serum levels are not increased in mild cognitive impairment and Alzheimer's disease. *Eur J Neurol* 14, e3-e4 (2007)
88. R Grzanna, P Phan, A Polotsky, L Lindmark, CG Frondoza: Ginger extract inhibits beta-amyloid peptide-induced cytokine and chemokine expression in cultured THP-1 monocytes. *J Altern Complement Med* 10, 1009-1013(2004)
89. Y Sui, L Stehno-Bittel, S Li, R Loganathan, NK Dhillon, D Pinson, A Nath, D Kolson, O Narayan, S Buch: CXCL10-induced cell death in neurons: role of calcium dysregulation. *Eur J Neurosci* 23, 957-964 (2006)
90. JM Burns, BC Summers, Y Wang, A Melikian, R Berahovich, Z Miao, ME Penfold, MJ Sunshine, DR Littman, CJ Kuo, K Wei, BE McMaster, K Wright, MC Howard, TJ Schall: A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. *J Exp Med* 203, 2201-2213 (2006)
91. R Stumm, V Höllt: CXC chemokine receptor 4 regulates neuronal migration and axonal pathfinding in the developing nervous system: implications for neuronal regeneration in the adult brain. *J Mol Endocrinol* 38, 377-382 (2007)
92. A Guyon, JL Nahon: Multiple actions of the chemokine stromal cell-derived factor-1alpha on neuronal activity. *J Mol Endocrinol* 38, 365-376 (2007)
93. A Parachikova, CW Cotman: Reduced CXCL12/CXCR4 results in impaired learning and is downregulated in a mouse model of Alzheimer disease. *Neurobiol Dis* 28, 143-153 (2007)
94. C Laske, K Stellos, GW Eschweiler, T Leyhe, M Gawaz: Decreased CXCL12 (SDF-1) plasma levels in early Alzheimer's disease: a contribution to a deficient hematopoietic brain support? *J Alzheimers Dis* 15, 83-95 (2008)
95. JF Bazan, KB Bacon, G Hardiman, W Wang, K Soo, D Rossi, DR Greaves, A Zlotnik, TJ Schall: A new class of membrane-bound chemokine with a CX3C motif. *Nature* 385, 640-644 (1997)
96. Y Pan, C Lloyd, H Zhou, S Dolich, J Deeds, JA Gonzalo, J Vath, M Gosselin, J Ma, B Dussault, E Woolf, G Alperin, J Culpepper, JC Gutierrez-Ramos, D Gearing: Neurotactin, a membrane-anchored chemokine upregulated in brain inflammation. *Nature* 387, 611-617 (1997)

97. K Hatori, A Nagai, R Heisel, JK Ryu, SU Kim: Fractalkine and fractalkine receptors in human neurons and glial cells. *J Neurosci Res* 69, 418-426 (2002)

98. T Mizuno, J Kawanokuchi, K Numata, A Suzumura: Production and neuroprotective functions of fractalkine in the central nervous system. *Brain Res* 979, 65-70 (2003)

99. AE Cardona, EP Pioro, ME Sasse, V Kostenko, SM Cardona, IM Dijkstra, D Huang, G Kidd, S Dombrowski, R Dutta, JC Lee, DN Cook, S Jung, SA Lira, DR Littman, RM Ransohoff: Control of microglial neurotoxicity by the fractalkine receptor. *Nat Neurosci* 9,917-924 (2006)

100. TS Kim, HK Lim, JY Lee, DJ Kim, S Park, C Lee, CU Lee: Changes in the levels of plasma soluble fractalkine in patients with mild cognitive impairment and Alzheimer's disease. *Neurosci Lett* 436,196-200 (2008)

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Send correspondence to: Yingying Le, Institute for Nutritional Sciences, SIBS, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai, 200031, China, Tel: 86-21-54920901; Fax: 86-21-54920291, E-mail: yyle@sibs.ac.cn

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