Review

Potential significance of CX3CR1 dynamics in stress resilience against neuronal disorders

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Introduction

“Resilience” refers to the ability to overcome and recover from stressful and/or adverse circumstances (Rutter, 1985; Grotberg, 2003). In addition to personal qualities, resilience can be affected by family, social, and other environmental factors, and it can lead to later onset of disorders caused by factors other than personal qualities, such as neuropsychiatric disorders caused by environmental changes. For example, it has been suggested that economic problems may contribute to 20% of depressions (Dudek et al., 2021), which should be other than personal qualities for many children. On the contrary, some of those disorders can be treated by acquiring stress resilience, which was not previously present (Federe et al., 2020). This suggests that a well-functioning society for the treatment of disease-related stress resilience could be the foundation for a healthy life that does not rely on medical costs and care, which is a global problem. Even if not at the level of diseases, this competence is required more than ever in a modern and complicated society where the spread of SARS-CoV-2 infection worldwide has brought economic depression and made it difficult to imagine a promising future with high expectations. In fact, COVID-19 can cause serious health, social, and economic crises for families, including children (Barzilay et al., 2020; Prime et al., 2020). Stress resilience is not only related to functional mental activity but also to substantial neurological impairment. For example, higher susceptibility to stress has been reported to result in a higher prevalence of stroke and to affect not only stroke onset but also post-stroke complications and recovery (Surtees et al., 2007; Bergh et al., 2014). Resilience also plays an important role in the pathogenesis of not only stroke but also dementia and other hereditary disorders (Bergman et al., 2010; Maul et al., 2020). In line with this, animal studies have clearly reported that stress during the perinatal period through to childhood influences the function of the hypothalamic-pituitary-adrenal axis, leading to a decrease in stress resilience in later life, and further understanding of stress resilience is an important issue for a better future (Liu et al., 1997; Sapolsky, 1997).

Thus, the term “resilience” or “stress resilience” has become very common in scientific papers over the past decade or so. For instance, a PubMed search for “stress resilience” retrieves 37 papers in 2000, 356 in 2010, and 2190 in 2020. This may also be due to the social and medical trend of considering “stress resilience” as a resource for mental health and survival. For example, psychologists sometimes speak of mental strength such as endurance and treatment and recovery from diseases not only from the physical but also the psychological level. Resilience also plays an important role in the pathogenesis of not only stroke complications and recovery (Surtees et al., 2007; Bergh et al., 2014). Stress resilience is not only related to functional mental activity but also to substantial neurological impairment. For example, higher susceptibility to stress has been reported to result in a higher prevalence of stroke and to affect not only stroke onset but also post-stroke complications and recovery (Surtees et al., 2007; Bergh et al., 2014). Resilience also plays an important role in the pathogenesis of not only stroke but also dementia and other hereditary disorders (Bergman et al., 2010; Maul et al., 2020). In line with this, animal studies have clearly reported that stress during the perinatal period through to childhood influences the function of the hypothalamic-pituitary-adrenal axis, leading to a decrease in stress resilience in later life, and further understanding of stress resilience is an important issue for a better future (Liu et al., 1997; Sapolsky, 1997).

Conclusion

In this review, I will give an overview of FKN and its signaling in microglia and review its possible significant involvement in the universal neuropsychiatric activity.

Search Strategy and Selection Criteria

Studies cited in this narrative review published from 1985 to 2021 were searched on the PubMed database. I used the following keywords: fractalkine, CX3CR1, stress, resilience, microglia, inflammation, stroke, Alzheimer’s disease, SARS-CoV-2, knockout mice.

Fractalkine and Its Receptor CX3CR1

Fractalkine (FKN) has been identified as a chemokine that exerts chemotactic activity on certain cells. Its receptor, CX3CR1, is expressed mainly in immune cells, such as macrophages and microglia, but it is also present in various other cells, such as neurons, astrocytes, and vascular endothelial cells (Meucci et al., 2000; Umehara et al., 2001; Limatola and Ransohoff, 2014; Lee et al., 2018). CX3CR1 is a G protein-coupled receptor, and its activation leads to Ca2+ influx and change in cAMP level, followed by transduction of downstream signals regarding cell differentiation and survival, such as MAPKs and Akt/PKB (Maciejewski-Lenior et al., 1999; Meucci et al., 2000; Kansra et al., 2001; Davis and Harrison, 2006; Dorcham et al., 2000). Its expression level is demonstrated to be increased by external stimuli in some cells (Maciejewski-Lenior et al., 1999; Fong et al., 2000; Sung et al., 2005; O’Sullivan et al., 2016; Ho et al., 2020; Kawamura et al., 2020), and the extent of its expression change contributes to changes in the intensity of the signal downstream of CX3CR1, as does the release of the ligand, FKN.

FKN is released from various types of cells, including neuronal, vascular endothelial, intestinal, and epithelial cells. While the stationary release is recognized, the amount of release is altered by stimuli. In both cases, FKN acts as a paracrine factor on the peripheral cells and as a hormone remotely (Dreyfus et al., 2012; Lee et al., 2018). Thus, FKN is a released protein that is initially translated as a membrane surface protein with a transmembrane region (Bazan et al., 1997; Fong et al., 2000; Popiatowska et al., 2017; Lee et al., 2018). It is excited at the region slightly closer to the...
N-terminal side from the transmembrane domain by serine proteases, such as ADAM17 and ADAM10, and released into the bloodstream. This soluble FKN accounts for FKN blood level. Apart from the soluble form, FKN often remains uncut and unreleased and acts on the cellular membrane. For example, CX3CR1-expressing microglia or monocytes are trapped on membrane-bound (uncut) FKN-producing vascular endothelial cells, using them as a scaffold to assist penetration and migration of CX3CR1-positive cells (Bazan et al., 1997; Fong et al., 2000). As a timely topic, it has been reported that angiogenesis-induced neuroinflammatory processes can be mediated by soluble FKN in vivo (Lebovics et al., 2009; Rius et al., 2013). In addition, it has been suggested that FKN may play a role in severe SARS-CoV-2 infections caused by cytokine storms because of the relationship between angiotensin II and an angiotensin II-degrading enzyme ACE2, which is a target of the SARS-CoV-2 protein (Banu et al., 2020; Gracia-Hernandez et al., 2020; Rivas-Fuentes et al., 2021).

### Current Status of FKN Signaling in Human Diseases

Genetic mutations of human CX3CR1 are associated with the risk of cardiovascular and psychiatric diseases, such as schizophrenia. For example, mutation of T280M in FKN makes less activation of Ca\(^{2+}\) influx-mediated cell signaling compared to wild-type FKN, resulting in weakened adhesion and invasion of CX3CR1-positive leukocytes into the vascular wall. This reduces cardiovascular diseases, such as atherosclerosis (McDermott et al., 2003). In addition, mutation of A57T in FKN attenuates at least Akt signaling, and the changes in the signaling strength may modulate cellular function, leading to altered brain functions or development of neurological diseases (Ishizuka et al., 2012).

Considering that attenuated activity of FKN signaling decreases disease incidence, increased intensity may enhance disease development. Other than mutation, recent findings have revealed that FKN signals are abnormally evoked in human diseases such as rheumatoid arthritis, Crohn’s diseases, and systemic scleroderma, and the FKN neutralizing antibody therapy may be functional (Muelhoefer et al., 2000; Ruth et al., 2001; D’Haeze et al., 2012; Luong et al., 2019; Matsuoka et al., 2021; Tanaka et al., 2021a). In fact, a phase II clinical trial has been conducted using FKN neutralizing antibody in rheumatoid arthritis patients who did not respond well to methotrexate, a commonly used anti-rheumatic drug. Although the patients were treated for short as long as 6 months, there seemed to be a significant effect on moderate (Tanaka et al., 2021a). These reports explore the possibility that modulation of FKN signaling could become curable therapeutic strategies for human diseases.

### Dynamics of Microglial CX3CR1 and Its Effects on Neuronal Function

As mentioned above, FKN signals play critical roles in the modulation of neuronal function. The deficiency of FKN has often resulted in neurological defects, but their phenotypes are not so severe (Cook et al., 2001; Sokolowski et al., 2014; Winter et al., 2020). CX3CR1-deficient mice have also been reported to have a variety of neurological problems. For example, information-induced neurotoxicity in various models is reduced in CX3CR1-deficient mice, whereas neurotoxicity appears to be increased by CX3CR1-deficiency in Parkinson’s disease and amyotrophic lateral sclerosis (ALS) models (Cardona et al., 2006; Tang et al., 2014; Wang et al., 2018). A report comparing the behavior of CX3CR1-deficient mice with CX3CR1-expressing mice, in which the deficiency reduces stress-induced memory and cognitive impairment and alleviates depressive symptoms (Rimmerman et al., 2017; Liu et al., 2020).

Indeed, phenotypes exhibited in CX3CR1-deficient mice could be referable. However, it is almost impossible for real animals to lose the expression of CX3CR1 to the same extent as knockout mice do, and therefore it is reasonable to presume that the effect of signaling intensity is attributable to changes in CX3CR1 expression level. Tables 1 and 2 list examples of reports concerning changes in microglial CX3CR1 expression levels (both protein and gene expressions) due to various stresses since it would not be meaningful to describe details of knockout mice. In the tables, brain regions (Table 1) and cell types (Table 2), in which CX3CR1 changes, are described along with stimuli and models that cause these changes and with the subsequent results. Detection methods are also mentioned. From these tables, it should be understood that CX3CR1 is altered by a variety of stimuli, which in turn changes the phenotypes, including neurological symptoms. As shown in Table 1, while the stimuli affecting the expression are not identified in some in vivo data, responsive stimuli are mostly identified, and the available literature implies that a variety of stimuli can modify the expression of CX3CR1. Of note, promoter analysis of human CX3CR1 has been performed, and the importance of the family of transcription factors, nuclear factor of activated T cells, has been highlighted (Samuelsson et al., 2004). Nonetheless, the expression of activated CX3CR1 is mainly present in immune, cardiovascular, neuronal, and muscular cells. They are dephosphorylated by calcineurin, a phosphatase that is activated through intracellular Ca\(^{2+}\) elevation, resulting in nuclear translocation and activation of the transcription factor NFATc3 (Fris et al., 2012; Fong et al., 2000). Hence, it is activated by stimuli, such as lipopolysaccharide (LPS) and enhances gene expression (Nagamoto-Combis and Combis, 2010; Fris et al., 2012), it would not play a leading role in the response to LPS stimulation, which decreases the expression level of CX3CR1, as reported by several groups, including ours (Zujovic et al., 2000; Wynne et al., 2010; Wang et al., 2020; Inoue et al., 2021). In addition, downstream effects, such as the survival of circumferential photoreceptors or neuronal cells, are reported (Roche et al., 2008). Notably, CX3CR1 has been expressed widely in many types of cells (Keren-Shaul et al., 2017), suggesting that activation of FKN signaling may exacerbate symptoms in Alzheimer’s disease. Their report indicates that attenuation of FKN signaling intensity in local brain regions may have the potential to decrease their detrimental effects on brain. This is consistent with previous studies showing that inhibition of microglial activation inhibits microglial-mediated immune responses, leading to an increase in immunological activities including phagocytosis of β-amyloid. However, on the other hand, Gonzalez-Prieto et al. (2021) have reported that Alzheimer’s patients have a higher expression of CX3CR1, which suggests that further investigation would be expected. They have also noted microglia with lower expression of CX3CR1 accumulated in the lesion of ALS model mice. On the contrary, ALS model derived from CX3CR1-deficient mice show a more intense immune response, resulting in higher lethality. There is one thing of concern, and at first glance of the tables, it appears that CX3CR1 is often decreased by stimulation in cultured cells, while it is still increased in various in vivo reports. Although the reason for this is unclear, it has been reported that the expression level of CX3CR1 itself is much higher in human microglia than in cultured cells (Gosselin et al., 2017), and the analysis of CX3CR1 expression in microglia may not be meaningful without using in vivo reports. Therefore, it is still controversial whether changes in the CX3CR1 level are beneficial. To resolve this, recently, a CX3CR1 antagonist has been synthesized (Karlström et al., 2013; Cederblad et al., 2016; Ho et al., 2020), and changes in phenotypes can be referable by the antagonist. The next step is to apply this to human diseases. Most of the data shown in Table 1 are derived from animal models, and there is a possibility that the dynamics of CX3CR1 are consistent between humans and those models. Nevertheless, if they are similar, human psychiatric diseases such as schizophrenia, bipolar disease, and mood disorders are signified with abnormally increased FKN expression in microglia as a result of the expression of FKN receptor, CX3CR1, and exchange signals with ligand-expressing neurons and other cells. The amount and form of the ligand FKN (membrane-bound or soluble) can influence the functional effects of the ligand, ultimately modifying brain and nerve functions. In addition, other studies have shown that FKN expression in microglia can be increased in various psychiatric diseases such as Alzheimer’s diseases (Gonzalez-Prieto et al., 2021; Rivas-Fuentes et al., 2021). In conclusion, these findings suggest that FKN signaling in microglia may be increased in peripheral blood in patients with various psychiatric diseases, which may be used to understand and treat various psychiatric diseases.

### Conclusion

The term “stress resilience” has become more common in medical biology papers in the last decade or so. It appears to be related not only to the development of neuropsychiatric disorders but also to exacerbations of Alzheimer’s disease and post-stroke neurodegeneration, and its detailed molecular pathology is expected to be elucidated for the treatment of neuropsychiatric diseases. FKN expression is a significant indicator of the response of microglia that affects stress resilience. Microglia express an FKN receptor, CX3CR1, and exchange signals with ligand-expressing neurons and other cells. The amount and form of the ligand FKN (membrane-bound or soluble) can influence the functional effects of the ligand, ultimately modifying brain and nerve functions. Changes in CX3CR1 expression in microglia have been reported often, and it is generally accepted that increased expression is always injurious, and decreased expression is associated with disease. However, at the level where mental function is involved, there have been no studies utilizing neutralizing antibodies or the inhibitor, but as in the case of rheumatoid arthritis mentioned above, its increased activity may lead to exacerbation of the condition. We found that the expression level of CX3CR1 in microglia is reduced by stimulation with alcohol or LPS, albeit in cultured cells (Inoue et al., 2021). Since it is often reported that stimulation of CX3CR1 suppresses microglial inflammatory responses in common LPS-based microglial immune research, we consider that if such a situation occurs in vivo and in humans, various stresses may cause suppression of CX3CR1 expression and the consequent FKN signaling function in microglia, thereby reducing the ability of microglia to suppress runaway. Unfortunately, however, there is currently no clinical direction as to whether this variation is uniformly good or bad for certain conditions. Nonetheless, this is also the case in humans, if we can prove beneficial changes in CX3CR1 for the treatment of neuropsychiatric disorders, we may be able to acquire beneficial stress resilience through FKN signaling.

### Author contributions: KI designed, wrote this review, and approved the final version of the manuscript.

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The dynamics of microglial CX3CR1 by stimuli

**Table 1 | Dynamics of microglial CX3CR1 by stimuli in vivo**

| Strain/species | Type of microglia | Increase/ decrease | Stimuli/models | Verification procedures | (Possible) downstream events by changes in CX3CR1 level | Others | References |
|----------------|------------------|-------------------|----------------|------------------------|------------------------------------------------------|--------|-----------|
| BALB/c mouse   | Whole brain, cortex and hippocampus | Decrease | LPS injection | FCM, qPCR | Sickness behavior | | Wynne et al., 2009 |
| B6 mouse       | Male hypothalamic microglia | Decrease | High fat diet | qPCR | Microglial dysregulation by cholesterol accumulation and following p38 MAPK activation, leading to the facilitation of neuronal injury and microgliosis | KO mice show the consistent results | Dorfman et al., 2017 |
| B6 mouse       | Microglia of whole brain excluding cerebellum | Decrease | LPS injection | qPCR | KO mice have fewer β-amyloid deposit (Lee et al., 2010; Liu et al., 2010). | Keren-Shaul et al., 2017 |
| B6 mouse       | Disease-associated microglia | Decrease | 5xFAD Alzheimer’s model | RNA-seq | Enhanced phagocytosis | KO mice have fewer β-amyloid deposit (Lee et al., 2010; Liu et al., 2010). | Keren-Shaul et al., 2017 |
| B6 mouse       | Disease-associated microglia | Decrease | ALS model | RNA-seq | Neurodegradation and mortality are exacerbated in KO mice (Liu et al., 2019). | | |
| B6 mouse       | Retinal microglia | Increase | Norgesterol (progestosterone analog) | qPCR | Protection of retinal photoreceptors along with circumferential FKN increase | | Roche et al., 2016 |
| B6 mouse       | Cerebral cortex | Increase | 5xFAD Alzheimer’s model | qPCR, FCM, IHC | | | Gonzalez-Prieto et al., 2021 |
| B6 mouse       | Cerebral cortex | Increase | Reboxetine (noradrenaline reuptake inhibitor) | qPCR | | | |
| B6 mouse       | CA1 | Increase | Prion | IHC | | | Hughes et al., 2002 |
| B6 mouse       | Substantial nigral microglia | Increase | α-Synuclein | qPCR | Enhancement of inflammatory responses by FKN signal | Delayed increase may be due to macrophage entry into lesion. KO mice show better recovery | Donnelly et al., 2011 |
| B6 mouse       | Spinal cord | Decrease, then increase | Spinal cord (T9–T10) contusion | IB | | | Mao et al., 2020 |
| SD rat         | Hippocampus | Increase | 2-Vessel occlusion | IHC, IB | Microglial polarization | MCAO in KO mice show reduced injury (Tang et al., 2014). | Gao et al., 2017 |
| SD rat         | Spinal cord | Decrease | Electroacupuncture | IB | Attenuation of algesia | | Zhang et al., 2012 |
| SHR/WHY rat    | Microglia in RVLM | Decrease | Blood pressure (?) | qPCR | Microglial morphological change | Microglial cell numbers are lowered, so net reduction of CX3CR1 mRNA might be overestimated. | Cohen et al., 2019 |
| Human          | Brain (region not identified) | Decrease | Acute ischemia | RNA-seq | | | Castro-Sanchez et al., 2018 |
| Human          | Frontal cortex | Increase | Alzheimer’s disease | qPCR, ELISA, IHC | | | |

FCM: Flow cytometry; IB: immunoblotting; IHC: immunohistochemistry; qPCR: quantitative PCR; RNA-seq: RNA sequencing; RVLM: rostral ventrolateral medulla. Isolated microglia are shown underlined.

**Table 2 | Dynamics of microglial CX3CR1 by stimuli in vitro**

| Strain/species | Type of microglia | Increase/ decrease | Stimuli/models | Verification procedures | (Possible) downstream events by changes in CX3CR1 level | References |
|----------------|------------------|-------------------|----------------|------------------------|------------------------------------------------------|-----------|
| ICR mouse      | PMG              | Decrease | LPS injection | qPCR | Survival of co-cultured neurons | Wang et al., 2020 |
| PMG            | Decrease | ATP              | qPCR | | | |
| PMG            | Decrease | Ethanol          | qPCR | | | |
| SD rat         | PMG              | Decrease | α-Synuclein | qPCR | | | Zupovic et al., 2000 |
| Rat            | PMG              | Decrease | LPS injection | PCR | | | Gonzalez-Prieto et al., 2021 |
| Wistar rat     | PMG              | Decrease | Noradrenaline | IHC | | | |
| Human          | HMC3 (cell line) | Decrease | Noradrenaline | IHC, promoter assay, FCM | | | |
| Mouse          | BV-2 (cell line) | Increase | TGF-β | qPCR, IHC | | | Wynne et al., 2009 |

FCM: Flow cytometry; IHC: immunohistochemistry; PMG: primary microglial cells; qPCR: quantitative PCR.
Review

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Carbana AE, Piro EP, Sasse ME, Kosteren V, Cardona JM, Dijkstra RM, Huang D, Gidds K, Dombrowski S, Dutta R, Jie JC, Cook DN, Jung S, Lira SA, Utrun DR, Rossnow RM (2006) Control of microglial neurotoxicity by histamine and putative nuclear hormone receptors. Nat Neurosci 9:1762-1767.

Cederlind L, Roder S, Ryberg E, Hermansson NO (2016) AD2777 is an altlastic noncompetitive modulator of the human CX3CR1 receptor. Biochem J 473:641-649.

Cohen MA, Gudjonsdottir MG, Nebbe PP, Schlief CM, Mlozyk PM (2019) Microglia in the PVLM of SHRs have reduced PY212 and CY213 expression, shorter processes, and lower cell density. Auton Neurosci 196:16-19.

Cook DNS, Chen SC, Sullivan JR, Ritter DJ, Weihoek MT, Perras DM, Gass L, Lira SA (2001) Generation and analysis of mice lacking the chemokine fractalkine. Mol Cell Biol 21:3135-3146.

D’Haese J, Hoey C, Gyawali GD (2013) Potential therapeutic of the chemokine-receptor duo fractalkine-CX3CR1. Opin Ther 13:663-668.

Davis CN, Harrison JK (2006) Proline 326 in the C-terminus of murine CX3CR1 prevents G-protein and phospholipidhydrolysis-kinase 3-kinase dependent-stimulation of Akt and extracellular signal-regulated kinase signalling pathways. J Biol Chem 281:3565-3568.

Donnelly DJ, Longtire BB, Shaw TM, Kierf F, Lai W, Tovar CA, Rossnow RM, Popovich PG (2017) Deficient CX3CR1 in microglia and the recovery of function by limiting the recruitment and activation of uFNSK/macrophages. J Neurosci 31:9910-9922.

Dornfeld MD, Knoll DJ, Eaglefield J, Larrain P, Meek T, Shi T, Duan X, Giamn D, Nguyen V, Matren ME, Morton GI, Thaler JP (2017) Sex differences in microglial CX3CL1 signaling defining obesity susceptibility in mice. Nat Commun 8:14556.

Dorhag K, Ghiad A, Hermand P, Rodere M, Poplev P, Lira M, Hartley O, Gorovitch C, Comberade C, Derdor P (2019) An engineered CX3CR1 antagonist endowed with anti-inflammatory activity. J Leuko Bl 86:903-911.

Dreymuel D, Martin C, Kogel T, Prussmann J, Hoe MS, Horuchi K, Ueh H, Ludwig A (2012) Long endostatin administration regulates the acute inflammatory response to lipopolysaccharide. EMBO Mol Med 4:422-433.

Dudek DA, Dorn LS, Kaufmann FN, Tuck E, Lebel M, Dombrowski D (2021) P326 deletion in the chemokine receptor CX3CR1 attenuates stress in a mouse model of Parkinson’s disease. J Biol Chem 296:17622-17632.

Eliasson M, Yang M, Shibuya K, Goto T, Wang Y, Kawanoto T, Ima T, Kana T (2017) Phase 1 study on the safety and efficacy of E6011, an antiflagrant antibody, in patients with Crohn’s disease. J Gastroenterol Hepatol 38:2230-2238.

Erickson EF, Hedges JF, Cardona AE, Ransohoff RM, 2000) Fractalkine is an endothelial cell-derived chemoattractant for intraepithelial lymphocytes in the small intestinal mucosa. J Immunol 164:3368-3374.

Enomoto-Kato S, Kuniyoshi Y, Ahsan I, Ashikawa M, Arakawa M, Cho H, Koyama H, Goto T, Kawanoto T, Ima T, Kana T (2021) Phase 1 clinical trial of a novel three-step radiopharmaceutical: PET imaging of microglial activation and migration in experimental mouse models of systemic sclerosis. Arthritis Rheumatol 71:1932-1934.

Maciejewski-Lenior D, Chen S, Feng F, Maki R, Kazin BB (2019) Characterization of fractalkine in rat hippocampal cells: migration and activator signal for CX3CR1-expressing microglia. J Immunol 163:1632-1635.

Maio M, Yu Z, Zhang X, Yang L, Liu KB, Yu Q, Chen Y, Wang Y, Li TT, Liu J (2020) MicroRNA-195 promotes microglial polarization via C-X-C chemokine receptor type 1 (CX3CR1) and brain hypothermia regulating CX3CL1/CX3CR1 signaling. J Neuroinflammation 17:244.

Matsuda Y, Nakajima M, Hori T, Yone Y, Ohyama H, Hayashi M, Toma Y, Noma O, Hasegawa M (2019) Inhibition of the progression of glioblastoma by blockade of the CX3CR1/CX3CL1 pathway in experimental mouse models of systemic sclerosis. Arthritis Rheumatol 71:1932-1934.

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