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The complex role of the chemokine CX3CL1/Fractalkine in major depressive disorder: a review of preclinical and clinical studies

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Abstract

Evidence suggests that neuroinflammation exhibits a dual role in the pathogenesis of Major Depressive Disorder (MDD), both potentiating the onset of depressive symptoms and developing as a consequence of them. The chemokine fractalkine (FKN) (also known as CX3CL1) has gained increasing interest for its ability to induce changes to microglial phenotypes through interaction with its corresponding receptor (CX3CR1), which may impact neurophysiological processes relevant to MDD. Despite this, there is lack of a clear understanding of the role of FKN in MDD. Overall, our review of the literature shows the involvement of FKN in MDD, both in preclinical models of depression, and in clinical studies of depressed patients. Preclinical studies (N=8) seem to point towards two alternative hypotheses for FKN's role in MDD: a) FKN may drive pro-inflammatory changes to microglia that contribute towards MDD pathogenesis; or b) FKN may inhibit pro-inflammatory changes to microglia, thereby exerting a protective effect against MDD pathogenesis. Evidence for a) primarily derives from preclinical chronic stress models of depression in mice, whereas for b) from preclinical inflammation models of depression. Whereas, in humans, clinical studies (N=4) consistently showed a positive association between FNK and presence of MDD, however it is not clear whether FKN is driving or moderating MDD pathogenesis. Future studies should aim for larger and more controlled clinical cohorts, in order to advance our understanding of FKN role both in the context of stress and/or inflammation.

1. Introduction:

Neuroinflammation has garnered increasing interest for its bidirectional role in Major Depressive Disorder (MDD) (Slavich and Irwin, 2014). This bidirectionality involves not only neuroinflammation increasing the risk for the onset of depressive symptoms (Benros et al., 2013) but also neuroinflammation developing as a consequence of MDD. This reflects a complex interplay between inflammatory processes and the pathogenesis of MDD (see **Figure 1**). A pro-inflammatory bias observed in human evolution appears to have favoured the emergence of depressive symptoms during periods of heightened inflammation, potentially as an adaptive mechanism to reduce the risk of subsequent pathogen exposure (Miller and Raison, 2016). While meta-analyses have established C-reactive protein (CRP), interleukins (ILs)-3, 6, 12, 18, soluble IL-2R and tumour necrosis factor α (TNF-α) as common pro-inflammatory markers elevated in MDD (Osimo et al., 2020), it is crucial to examine the role of other unique mediators including chemokines. This will both allow us to gain a more comprehensive understanding of the pathogenesis of MDD and to discern potential therapeutic targets to improve outcomes for this complex condition (Maes et al., 2012). Fractalkine (FKN), also named CX3CL1, is one such chemokine that is gaining increasing interest.

FKN is the sole member of the CX3C family of chemokines and exists in both soluble and membrane bound isoforms (Bajetto et al., 2002). It is predominantly expressed within the CNS, with the ligand (CX3CL1) located on neurons and its corresponding receptor (CX3CR1) located exclusively on microglia and astrocytes. Ongoing research has implicated a role for FKN in the pathogenesis of a multitude of neuropsychiatric conditions including schizophrenia (SCZ), post-traumatic stress disorder (PTSD) and Alzheimer's disease (AD) (Arabska et al., 2022; Lee et al., 2010; Schubert et al., 2018). In these conditions, FKN has been proposed to drive microglial reactivity, which ultimately lead to SCZ behaviours (Zhou et al., 2020), impaired neuronal signalling within the limbic system involved in PTSD-related fear circuits (Schubert et al., 2018), as well as tau deposition in AD (Joaquín Merino et al., 2016). Within mood disorders, like MDD, FKN has been suggested to alter neuron-microglia crosstalk, which in turns leads to increased vulnerability to stress (Hinwood et al., 2019).

By reviewing the literature, we aim to address the absence of comprehensive investigations into both the updated preclinical and clinical evidence for the role of FKN in MDD. Additionally, we intend to identify areas for further research. We will begin by exploring the evidence for the differing roles of FKN in *in vivo* models of depression (*i.e.*, chronic stress (CS) and lipopolysaccharide (LPS)). We will then proceed to examine clinical evidence for FKN role in MDD patients, discussing studies measuring changes in serum FKN levels (sFKN) and FKN single nucleotide polymorphisms (SNP).

2. Preclinical and clinical evidence for the role of FKN in MDD

2.1 Preclinical studies: chronic stress models

A substantial body of evidence for FKN involvement in MDD comes from five studies exposing CX3CR1 knockout (KO) mice to acute or CS conditions (Hellwig et al., 2016; Liu et al., 2020; Milior et al., 2016; Rimmerman et al., 2017; Winkler et al., 2017). Although protocols for stress induction varied extensively throughout these experiments (see **Table 1**), all observed mice deficient for CX3CR1 were found to be resistant to developing depressive-like behaviours. Lower levels of liking-type anhedonia were observed through greater saccharin or sucrose preference in the Saccharin Preference (Milior et al., 2016) or Sucrose Preference Tests respectively (Rimmerman et al., 2017). Lower levels of despair and anxiety, characterised by increased locomotor activity, were observed in the Open Field Test (Hellwig et al., 2016; Liu et al., 2020; Winkler et al., 2017), Forced Swim Test (Liu et al., 2020; Winkler et al., 2017), Tail Suspension Test (Hellwig et al., 2016; Winkler et al., 2017), Wire Hang Test (Hellwig et al., 2016), and Elevated Plus Maze Test (Hellwig et al., 2016; Winkler et al., 2017). One study also observed increased cognitive performance, which was measured using the Morris Walter Maze (Liu et al., 2020). Overall, this indicates that FKN's action on its selective receptor plays a critical role in the development of depressive behaviours.

With respect to the cellular and molecular underlying mechanisms mediating the aforementioned behavioural effects, the FKN-CX3CR1 axis plays a crucial role in the mediation of environmental cues via microglia-neuronal crosstalk (Biber et al., 2008; Harrison et al., 1998). In particular, in three studies, when compared to CX3CR1 deficient mice, wild-type (WT) mice showed a greater extent of microglia hyper-ramification/arborisation (Hellwig

et al., 2016; Liu et al., 2020; Milior et al., 2016) and higher expression of pro-inflammatory cytokines like IL-1β/IL-6/TNF-α (Liu et al., 2020). Furthermore, WT mice showed greater microglial density, denoted by a shorter nearest neighbour distance (Winkler et al., 2017). In addition, WR mice's microglia demonstrated increased M1/"classically activated" but decreased M2/"alternatively activated" phenotypes (Liu et al., 2020). M1 and M2 phenotypes have been proposed as mediating pro-inflammatory (Frank-Cannon et al., 2009) and anti-inflammatory (Colonna and Butovsky, 2017) effects, respectively. However, it should be noted that this dichotomous classification has been recognised as oversimplifying the multidimensional nature of microglial behaviour (Paolicelli et al., 2022; Ransohoff, 2016). Overall, these changes illustrate some of the ways in which FKN drives changes in the morphological and inflammatory states of microglia, which ultimately may regulate depressive-like behaviours.

Analysing functional implications from FKN-driven changes to microglial morphology is challenging due to the inherent complexity of such associations (Paolicelli et al., 2022). However, there is some suggestion that microglia utilise ramifications for phagocytosis, particularly their terminal "en passant" branches (Sierra et al., 2010; VanRyzin et al., 2019). This may offer an explanation as to the presence of increased phagocytic inclusions of Cornu Ammonis 1 (CA1) hippocampal pre-synaptic axon terminals and post-synaptic dendritic spines observed in one study, especially in WT, but not in CX3CR1 deficient, mice following CS (Milior et al., 2016). Similarly, synaptic phagocytosis may offer aetiological explanations for the observed neuroplasticity impairment in Long Term Potentiation (LTP) in the same study, and in another study, particularly in the Dentate Gyrus (DG) (Liu et al., 2020) and CA1 regions (Milior et al., 2016) of the hippocampus.

FKN-driven effects on microglia may result in decreased neuroplasticity via a multitude of mechanisms (see **Figure 2**) (Innes et al., 2019): 1) CS-induced microglial state changes have been shown to result in unpotentiated (Petersen et al., 1998) and silent synapses (Kerchner and Nicoll, 2008; Liao et al., 1995), which are unable to undergo multiple episodes of LTP; 2) Hyper-ramified microglia may identify and phagocytose silent synapses by recognising their membranes as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor deficient (Kerchner and Nicoll, 2008; Liao et al., 1995); and 3) FKN-driven changes to

microglia may induce Long-Term Depression (LTD) (Bertollini et al., 2006), via the activation of adenosine receptors (AdR) (Lauro et al., 2008). The latter mechanism would allow post-synaptic Calcium ion influx that inhibits Adenylate Cyclase (AC) and subsequently drives LTD by increasing levels of protein phosphatases (PP) and decreasing protein kinases (PKA) (Ragozzino et al., 2006). FKN's effects on LTP in mouse models are salient as they could explain how FKN potentiates MDD symptoms in humans. Hippocampal LTP is essential to learning and memory (Luscher and Malenka, 2012; LYNCH, 2004), and these two aspects of impaired cognition are important features of MDD (Lam et al., 2014). Abnormalities in this brain region have additionally been observed in MDD patients (Cantone et al., 2017; Geerlings and Gerritsen, 2017), and so FKN's effects on hippocampal LTP due to microglial state change in CS models offers a potential explanation for the development of this symptom.

In addition to LTP, other mechanisms were identified in studies of FKN in CS murine models of MDD (see **Figure 3)**. Previous evidence has shown a decrease in hippocampal volume in MDD patients (Videbech, 2004), potentially due to stress-induced suppression of hippocampal neurogenesis (Duman and Monteggia, 2006). In line with this, CX3CR1 deficient mice demonstrated resistance to stress-induced reductions in hippocampal neurogenesis in one study (Rimmerman et al., 2017). It should be noted that the baseline level of neurogenesis within the DG of CX3CR1 deficient mice before stress induction was lower than that of the WT group. This may be due to CX3CL1-CX3CR1 axis involvement in neuron-microglia crosstalk that leads to the removal of apoptotic cells, allowing space for the genesis of new neurons (Bachstetter et al., 2011). Whether a lower baseline level of hippocampal neurogenesis decreases susceptibility to depressive-like behaviour following CS however needs further investigation.

Another significant finding was that CX3CR1 deficiency attenuated stress-induced Blood Brain Barrier (BBB) permeability (Liu et al., 2020) in one study, implying that FKN drives this process. The attenuation was suggested by the authors to be a consequence of M1 towards M2 polarisation in microglial phenotypes, with the former expressing pro-inflammatory cytokines (IL-6 and IL-1β) implicated in potentiating BBB hyperpermeability (Obermeier et al., 2013). BBB permeability may be a mechanism through which peripheral

inflammation could drive neuroinflammation, leading to MDD symptoms and the observed changes in depression-related brain networks (Kitzbichler et al., 2021).

FKN may additionally play a role in suppressing hypothalamic-pituitary-adrenal axis (HPAa) reactivity in MDD (Winkler et al., 2017) as WT mice showed lower HPAa activity than their CX3CR1 deficient counterparts in one study. The HPAa has been hypothesised as a determinant in stress-coping styles (Koolhaas et al., 2010). While heightened HPAa activity and subsequent cortisol elevation are often observed in melancholic depression (Keller et al., 2017), atypical depression is instead characterised by decreased cortisol level and HPAa hypoactivation (Juruena et al., 2018). These findings suggest that FKN may play a role in the pathogenesis of atypical depressive symptoms.

2.2 Preclinical studies: acute inflammation models

Only two studies investigated the role of FKN in depressive-like behaviour following LPS challenge (Corona et al., 2013, 2010), see **Table 2**. In contrast with the aforementioned studies using models of stress, the two studies show that CX3CR1 deficient mice exhibited a protracted period of depressive behaviour following LPS injection (Corona et al., 2013, 2010), when compared with the WT group (Corona et al., 2010). Both studies used the tail suspension test, an assay aimed to measure anhedonic behaviour. In addition, this behavioural outcome was accompanied by an increased cortical concentration of IL-1β and a protracted period of pro-inflammatory microglial state. In addition, within the CX3CR1 deficient group, there was an exaggerated induction of indoleamine 2,3-dioxygenase (IDO) which catabolises tryptophan (TRP), a serotonin precursor, into kynurenine (KYN) (Guillemin et al., 2005). KYN metabolites have been found to exert a depressive-like behaviour inducing effect via interruption of glutamatergic and dopaminergic neurotransmission (Dantzer et al., 2011; Haroon et al., 2012) (see **Figure 4**). Of relevance, inhibition of IDO by 1-methyl-tryptophan was shown to attenuate depressive-like behaviour following LPS in the same study (Corona et al., 2013).

Overall, these results suggest that while FKN is involved in the development of depressive-like behaviour and in the activation of pro-inflammatory pathways in the context of

stress, it can instead play a protective role when in presence of LPS, leading to a reduction of depressive symptoms and of microglial reactivity. Whilst these findings offer valuable insight into the role of FKN in an acute inflammatory model of MDD, it is critical to note the small number of studies (N=2) currently available investigating FKN in this context. Further research is therefore needed to validate these findings.

2.3 Clinical studies: serum FKN concentration and FKN polymorphisms in human MDD patients

Three studies compared the concentration of serum FKN in MDD patients versus healthy controls (Merendino et al., 2004; Miranda et al., 2017; Zhou et al., 2021) (see **Table 3** and **Figure 5**). The first cross-sectional study compared concentration of s[FKN] in 9 female patients diagnosed with MDD and 15 healthy volunteers (Merendino et al., 2004). In all 9 MDD patients, s[FKN] levels were found to be significantly elevated, at a mean of 1078.29±302.3 pg/ml. In contrast, only 4/15 healthy controls exhibited detectable levels of s[FKN], at a mean of 212.59±63.5 pg/ml. Despite the small sample size, this study provides evidence for the association between FKN and depressive symptoms, also in humans. Furthermore, it points to FKN as a potential biomarker in MDD.

Similarly, a larger study examined s[FKN] in 33 treatment-resistant MDD patients (trMDD), 33 treatment-resistant MDD patients with chronic pain, and 60 healthy controls (Zhou et al., 2021). Mean s[FKN] at baseline was significantly elevated ($p<0.05$) in patients with trMDD (~250pg/ml) and trMDD with chronic pain (~400pg/ml), when compared with healthy controls (~200pg/ml). Interestingly, s[FKN] concentration decreased following treatment with intravenous ketamine (0.5mg/kg), a psychotropic agent with established antidepressant and analgesic effects (Nikolin et al., 2023), and this was associated with a reduction in MDD symptoms, again suggesting that s[FKN] may serve as a putative biomarker in MDD.

The third study examined the relationship between s[FKN] and MDD in colorectal cancer (CRC) patients versus healthy controls (Miranda et al., 2017). The CRC cohort consisted of four groups undergoing treatment (n=20/group): those who had not undergone

tumour surgical resection (Group 1); patients who underwent resection but were not started on adjuvant therapy (Group 2); those undergoing chemotherapy for ~3 months (Group 3); and patients who completed adjuvant chemotherapy regimen for ~6 months (Group 4). Within all groups, except healthy controls and CRC patients who had completed adjuvant chemotherapy, results show a significant correlation between s[FKN] concentration and high scores on the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Within the healthy control group, a mean s[FKN] ~60pg/ml was measured and 0% of the group had HADS≥19; in Group 1, the mean s[FKN] was ~200pg/ml, and 65% had HADS≥19; in Group 2, the mean s[FKN] was ~175pg/ml and 60% had HADS≥19; in Group 3, the mean s[FKN] was ~85pg/ml and 60% had HADS≥19; in Group 4, the mean s[FKN] was ~75pg/ml and 40% had HADS≥19. These findings not only imply the involvement of FKN in MDD, but also point to an association between s[FKN] and symptom severity. Overall, clinical findings support studies in pre-clinical models in establishing an association between FKN and MDD as well as pointing to FKN as a potential biomarker.

Finally, a case-control genomic study of 502 MDD patients and 504 healthy controls revealed an association between SNP of rs170364 in the FKN gene and diagnoses of MDD (Peng et al., 2020). However, the T allele and GT + TT genotype, identified in this study, were found to be protective against MDD. This is supported by evidence suggesting that FKN inhibits nitric oxide and TNF-α synthesis (Mattison et al., 2013), and may act in human MDD in a similar way as in animal studies upon LPS exposure.

3. General conclusions and limitations

Overall, our review strongly suggests the involvement of FKN in MDD both in preclinical and clinical studies. Preclinical studies seem to point towards two alternative hypotheses for FKN role in MDD, namely that FKN either drives pro-inflammatory changes to microglia that contribute to MDD pathogenesis; or it inhibits pro-inflammatory changes to microglia thereby exerting a protective effect against MDD pathogenesis. Evidence for the former primarily derives from preclinical CS models in mice, whereas for the latter from preclinical LPS models. Whereas, in humans, clinical studies consistently showed a positive association between FNK and the presence of MDD, it is not clear whether FKN is driving or moderating the pathogenesis of MDD.

Firstly, it is fundamental to mention that evidence is relatively limited at present, and therefore a comprehensive understanding of the complexity of the FNK involvement in MDD remains incomplete. Furthermore, whilst behavioural findings in CS murine models were generally homogenous, there were a wide array of histological changes in mice exposed to stress. Some studies observed increased microglial soma size (Rimmerman et al., 2017), others observed hyper-ramification (Hellwig et al., 2016; Liu et al., 2020; Milior et al., 2016), and others reported increased pro-inflammatory cytokine expression (Liu et al., 2020). This may be a consequence of the different stress paradigms employed across the studies (*i.e.*, food deprivation, forced swimming, predator scent exposure), and different timing schedules of experimental manipulation (*i.e.*, time of treatment, time of behavioural/histological assessments). To add, only one of the five CS studies was conducted both in male and female mice (Hellwig et al., 2016), therefore making it difficult to generalise the validity of the finding in relation to gender.

Another important limitation is the fact that a single dose of LPS is mimetic of an acute inflammatory response within the murine central nervous system (Yin et al., 2023) that may not be an effective representation of the chronic low-grade inflammation observed in MDD patients (Berk et al., 2013). Acute inflammation may result in compensatory anti-inflammatory microglial mechanisms (Qin et al., 2023) in which FKN may act as a mediator. Hence, the roles of FKN in acute inflammatory responses in mice may vary from those observed in MDD patients – potentially explaining the discrepancies between LPS and CS murine models.

Similarly, clinical research has thus far been very limited, with only 1 out of 3 studies assessing s[FKN] in healthy controls versus MDD patients without comorbidities (Merendino et al., 2004). The other 2 studies assessing s[FKN] did so in the context of CRC (Miranda et al., 2017) and chronic pain (Zhou et al., 2021). This may limit their applicability to isolated MDD, given that variation in stressors may lead to FKN exhibiting either a pro-depressive or anti-depressive role, evinced by the discrepancies between LPS and CS preclinical models. The Merendino et al. study suffered from a small sample size of only 9 patients, all of whom were female and were not screened for possible confounding comorbidities that are additionally associated with s[FKN] elevation. For example, common pathologies like atherosclerosis,

diabetes (Shah et al., 2015) and poly-cystic ovarian syndrome (Demir et al., 2019) have been associated with elevations in s[FKN]. Therefore, more research into s[FKN] in larger cohorts, without comorbidities (or controlling for comorbidities), and inclusive of both sexes, should be conducted to validate these findings.

To conclude, the present review of preclinical and clinical evidence for FKN role in MDD reveals a complex and multifaceted relationship. Preclinical evidence from murine models, particularly in their response to CS and LPS challenges, suggest a critical role for FKN in MDD, albeit with contrasting findings. Similarly, clinical evidence of elevated s[FKN] in MDD patients suggests its involvement in MDD, although the study on FKN gene polymorphisms proposes a potential protective role of FKN in MDD pathogenesis. Future research should aim for a better understanding of FKN's role in stress versus inflammation paradigms.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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