Shedding light on the role of CX3CR1 in the pathogenesis of schizophrenia

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Abstract
Schizophrenia has a complex and heterogeneous molecular and clinical picture. Over the years of research on this disease, many factors have been suggested to contribute to its pathogenesis. Recently, the inflammatory processes have gained particular interest in the context of schizophrenia due to the increasing evidence from epidemiological, clinical and experimental studies. Within the immunological component, special attention has been brought to chemokines and their receptors. Among them, CX3C chemokine receptor 1 (CX3CR1), which belongs to the family of seven-transmembrane G protein-coupled receptors, and its cognate ligand (CX3CL1) constitute a unique system in the central nervous system. In the view of regulation of the brain homeostasis through immune response, as well as control of microglia reactivity, the CX3CL1–CX3CR1 system may represent an attractive target for further research and schizophrenia treatment. In the review, we described the general characteristics of the CX3CL1–CX3CR1 axis and the involvement of this signaling pathway in the physiological processes whose disruptions are reported to participate in mechanisms underlying schizophrenia. Furthermore, based on the available clinical and experimental data, we presented a guide to understanding the implication of the CX3CL1–CX3CR1 dysfunctions in the course of schizophrenia.

Keywords Schizophrenia · CX3CL1 · CX3CR1

Introduction
Schizophrenia is a chronic and severe mental illness, ranked among the leading causes of disability worldwide in recent years [1–3]. Despite a relatively low prevalence, the condition is one of the major contributors to the global burden of disease [2, 3]. The onset of that disorder usually appears in late adolescence or early adulthood [4]. The diagnosis of schizophrenia is based on clinical criteria that consider varied symptomatology, generally categorized into three groups: positive symptoms including hallucinations, delusions or conceptual disorganization; negative symptoms consisting of blunted or loss of affect and conative functions, avolition or apathy; and cognitive deficits referring to impairment of various types of memory and difficulty processing and using information [5–7]. Although the causes of schizophrenia remain unclear, the heterogeneous nature of the condition implies the contribution of multiple aetiological factors. The reports have suggested that the development of this illness may result among others from genetics [8–10], altered brain connectivity [11–15], abnormalities in neurotransmission systems [16–21] and/or environmental factors, including childhood trauma [22, 23], maternal stress [24] and infections during pregnancy [25–27], obstetric complications [28] as well as prenatal malnutrition [29]. The interplay between some of these factors, for example, gene–environment interactions [30–33] with an increased focus on epigenetic regulation [34–36], has been also proposed as the basis of this disorder. Recently, even though diversity in research data emerges [37–39], multiple studies have strongly supported the role of an inflammatory component in the pathogenesis of schizophrenia [40–42]. It has been shown that patients with this disease suffer from disturbances in the expression of cytokines and chemokines with inter alia the affected levels of interleukin-1β (IL-1β), IL-2, IL-1 receptor antagonist (IL-1RA), and elevated production of IL-6, IL-8, tumour necrosis factor α (TNF-α),
monocyte chemoattractant protein-1 (MCP-1) and C–C motif chemokine ligand 5 (CCL5 or RANTES) in blood or cerebrospinal fluid [43–48]. Additionally, polymorphisms in cytokine genes such as \( \text{IL-2, IL-6, IL-10} \) and \( \text{TNF-\alpha} \) are likely to be a risk factor for this disease [49–51]. Some post-mortem studies have found the presence of activated microglia and changes in the levels of cytokines, chemokines and microglial markers [e.g., major histocompatibility complex class I (MHC1), MHCII, IL-1\( \beta \), IL-6, IL-8] in brain tissues [39]. In the central nervous system (CNS), microglia are the main immunocompetent cells and primary reservoirs of inflammatory factors [52]. Even though microglia constitute only about 10% of the total brain cells [53], they respond rapidly to even minor pathological changes in the CNS and may contribute directly to brain homeostasis. Therefore, interest in the role of critical molecules modulating functions of microglia has been prompted in the context of mechanisms underlying schizophrenia. Among them, chemokines, in particular, have gained special attention with recent evidence suggesting the importance of the CX3CL1–CX3CR1 axis to this condition.

**The general characteristic of the CX3CL1–CX3CR1 system**

C-X3-C motif chemokine ligand 1 (CX3CL1) was firstly described in 1997 under the name “fractalkine” in humans [54] and simultaneously as “neurotactin” in mice [55]. This molecule differs notably from other classes of chemokines in terms of structure (Fig. 1). CX3CL1 is synthesized as an intracellular precursor (50–75 kDa) that undergoes rapid maturation processes to yield mature glycoprotein (95–100 kDa) transported to the cell surface [56, 57]. The full-length CX3CL1 is encoded by a 395–397-amino-acid chain and contains a chemokine domain, mucin-like stalk, transmembrane region and a cytoplasmic tail [54, 58, 59]. Due to the specific arrangement of two cysteine residues near

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**Fig. 1** Scheme illustrating the structure, localization and signaling pathways affected by the CX3CL1–CX3CR1 axis. CX3CL1, produced mostly by neurons, is a membrane-bound molecule with a chemokine domain, mucin-like stalk, transmembrane region and cytoplasmic tail. Cleavage of CX3CL1 is mediated under physiological or pathological conditions by ADAM10 or ADAM17, MMP-2, MMP-3 and cathepsin S, respectively. Binding CX3CL1 to CX3CR1, which is a seven-transmembrane domain \( G_i \) protein-coupled receptor expressed primarily on microglia, results in an intracellular transmission engaging multiple signaling pathways. \( TM \) transmembrane domain, \( EL \) extracellular loop, \( IL \) intracellular loop.
the amino terminus divided from each other by three amino acids, it was assigned to a separate type of chemokines (β subfamily) and it is the only known representative of the CX3C class so far [54, 55]. CX3CL1 appears in two forms: soluble (sCX3CL1) and membrane-bound (mCX3CL1) [60], which recently have been suggested to display differential activities within the CNS [61]. Under physiological conditions, the cleavage of sCX3CL1 is primarily carried out by a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) [62], while in the case of induction with a stress factor—by the TNF-α converting enzyme (TACE or ADAM17) [56, 63], matrix metalloprotease-2 (MMP-2) [64] and MMP-3 [65] or cathepsin S [66, 67]. It should be noted that there are some inconsistencies in the observed molecular weight of the secreted chemokine, possibly due to multiple forms of sCX3CL1 generated by the shedding from the cell surface at alternative sites [62, 68, 69]. Several reports have also shown that the CX3CL1 gene is polymorphic and its genetic variants may be related to HIV infection [70], postoperative chronic pain [71], coronary artery disease [72, 73] and carotid intima-media thickness [74] as well as a reduced risk of major depression [75]. CX3CL1 is vastly distributed throughout the body with the predominant expression in the brain [76] and to a lesser extent in the heart, kidney, lung and uterus [55]. In the CNS, the distribution of this chemokine varies between regions [77]. The highest protein levels of CX3CL1 were detected in the amygdala, cerebral cortex (particularly in layers II, III, V and VI), hippocampus (most intensely in CA1 field), basal ganglia and olfactory bulb. Other brain structures such as the hypothalamus and brainstem showed a scattered and scant presence of CX3CL1. Concerning the gene expression of this chemokine, it corresponds with protein localization, in an example with TNF-α and interferon γ (IFN-γ) [88].

CX3CL1 interacts with only one known receptor (Fig. 1). It was first described by the name RBS11 in rats [89] and later as V28 in humans [90]. However, since it has represented the first receptor for CX3CL1, it was accordingly designated as CX3C chemokine receptor 1 (CX3CR1) [91]. CX3CR1 is a seven-transmembrane domain G protein-coupled receptor (GPCR) and belongs to the A class, which includes rhodopsin-like receptors [91]. CX3CR1 (40 kDa) is composed of 355 amino acid residues forming an extracellular N-terminus, alternately arranged α-helical domains (TM1–TM7), intracellular (IL1–IL3) and extracellular (EL1–EL3) loops, and an intracellular C-terminus [92]. IL2 contains a DRY (also called DRYLAIV) motif, which is crucial for G protein interactions and signal transduction by the receptor [90, 91]. The research data have shown the presence of the receptor gene’s single-nucleotide polymorphisms (SNPs) resulting in two functional variants (V249I and T280M) [93], which to varying degrees have been associated with age-related macular degeneration [94], AIDS [95], amyotrophic lateral sclerosis [96, 97], coronary artery disease [98], Crohn’s disease [99], multiple sclerosis [100] and obesity [101]. Additionally, these SNPs may affect arterial blood volume in the precuneus, left posterior parietal cortex and left posterior cingulate cortex, structures with observed abnormalities in schizophrenia, bipolar disorder, autism and Alzheimer’s disease [102]. Recently, CX3CR1 V249I polymorphism has been also suggested as a factor that improved overall and progression-free survival in low-grade gliomas [103]. Regarding the expression, CX3CR1 is present on microglia [104, 105], dendritic cells [106], mast cells [107], monocytes [108, 109], macrophages [108], natural killer cells [91, 110], neutrophils [108], T lymphocytes [108] and thrombocytes [111].

Binding the ligand to CX3CR1 results in an intracellular transmission mediated by several second messengers and transcription factors, including for instance activator protein 1 (AP-1) [112], Ca2⁺ [113, 114], cAMP response element-binding protein (CREB) [115], inositol 1,4,5-trisphosphate (IP3) [114], nuclear factor erythroid-derived 2-like 2 (NRF-2) [116], nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [112, 115, 117, 118] as well as signal transducers and activators of transcription 1/3 (STAT1/3) [112, 119]. The signal transduction by the receptor affects pathways engaging protein kinase B (PKB or Akt) [120–122], extracellular signal-regulated kinase (ERK) [118, 120, 123], Janus kinase (JAK)/STAT [112, 119, 124], c-Jun N-terminal kinases (JNK) [118, 121], p38 mitogen-activated protein kinases (p38MAPKs) [112, 115], phosphoinositide-3-kinase (PI3K) [120, 125] and steroid receptor coactivator/focal adhesion kinase (Src/FAK) [126, 127] (Fig. 1). Regulation of these signaling pathways underlines the reported in literature roles of the CX3CL1–CX3CR1 axis both in physiological and pathological processes within the organism.

The involvement of the CX3CL1–CX3CR1 dyad in the brain physiology

The participation of CX3CR1 activation by its ligand in homeostatic conditions has been already addressed in impressive details in a few excellent articles, both experimental and review [128–133]. We invite the reader to...
get acquainted with these publications, and therefore in this chapter, we will briefly present only reports that are essential for understanding further data showing the CX3CL1–CX3CR1 system in the context of schizophrenia (Fig. 2).

The major role of the CX3CL1–CX3CR1 axis in the CNS covers control of the activation and functioning of microglia. For the first time, the phenomenon has been supported by the in vitro experiments, in which stimulation with the ligand triggered induction of Ca\(^{2+}\) mobilization, activation of MAPK and Akt, strong migratory activity and the reorganization of the actin cytoskeleton of these cells [104]. Additionally, Lyons et al. [134] described the decrease in CX3CL1 level in the hippocampus of aged rats that was accompanied by an increase of microglial activation. Treatment of those animals with the ligand diminished the activation, proving that CX3CL1 is required to maintain the cells in a quiescent state [134]. In line with this function, it has been shown that the interaction of CX3CL1 with CX3CR1 participates in the regulation of the inflammatory response of microglia, which includes a release of cytokines, nitric oxide and reactive oxygen species [122, 135–137]. The impairment of these processes, leading to prolonged microglial activation and neuroinflammation, has been indicated as part of schizophrenia pathology [138, 139].

It is widely recognized that the CX3CL1–CX3CR1 pair takes part in synapse-related processes, including synaptic formation, maturation, integration, pruning and transmission. The evidence has been provided by many data, including the research on Cx3cr1-deficient mice. In the article by Paolicelli et al. [140], these animals were characterized by transiently reduced microglia numbers in the developing brain and delayed synaptic pruning. The deficiency in this process resulted in an excess of dendritic spines and immature synapses and was associated with the persistence of electrophysiological and pharmacological indicators of immature brain circuitry [140]. Rogers et al. [141] demonstrated that mice lacking the Cx3cr1 gene displayed a significant decrease in hippocampal neurogenesis, impaired synaptic plasticity and up-regulated level of pro-inflammatory IL-1\(\beta\), followed by the behavioral changes (precisely, disrupted motor learning, associative and spatial memory). As presented by Bolós et al. [142], the depletion of the receptor caused the deficient synaptic integration of adult-born granule neurons in the hippocampal dentate gyrus, both at the afferent (a decreased number of dendritic spines) and efferent (a reduced area of axonal terminals) level. Other research revealed that Cx3cr1\(^{-/-}\) knockouts exhibited alterations in postnatal functional maturation of thalamocortical synapses [143]. The above-mentioned data are particularly important in the context of multiple synapse pathologies (e.g., reduction in spine density, enrichment of rare disruptive variations in synaptic genes and increased synaptic pruning) observed in the brains of patients with schizophrenia [144, 145].

Synaptic remodeling and plasticity contribute to the development of neural networks [146–148]. Therefore, it seems natural that the CX3CL1–CX3CR1 dyad is engaged in the formation of these circuits within the brain. This subject was reviewed extensively in the article by Paolicelli et al. [129], where the authors collected convincing data implicating the interaction of CX3CL1 with its receptor in the formation and reconstruction of neural connectivity. The research findings have shown that anomalous circuitry is one of the hallmarks of schizophrenia as the changes in neural

Fig. 2 The role of the CX3CL1–CX3CR1 signaling pathway in the pathology of schizophrenia. In physiological conditions, the interaction of CX3CL1 with CX3CR1 is essential for the regulation of multiple processes in the brain. The disturbances within this axis and subsequent disruptions within these mechanisms implicate the CX3CL1–CX3CR1 dyad in schizophrenia.

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networks of, inter alia, the prefrontal cortex and hippocampal formation of the individuals with the illness have been found [149–153].

The implication of the CX3CL1–CX3CR1 signaling pathway in schizophrenia

Clinical data

To date, only a few studies have evaluated the expression of CX3CL1 and CX3CR1 in patients with schizophrenia (Table 1). As reported by Bergon et al. [154], meta-analyses of microarray data from postmortem brain and blood

Table 1  Summary of alterations in the CX3CL1–CX3CR1 axis protein levels and mRNA expression reported in the studies in patients with schizophrenia

| Study                  | CX3CL1 | CX3CR1 | Comment                                                                 |
|------------------------|--------|--------|------------------------------------------------------------------------|
| Bergon et al. [154]    | NA     | mRNA expression, decreased | Meta-analyses of postmortem brain and blood samples from patients with schizophrenia Brain regions included in the study: the prefrontal, frontal and temporal cortices, cerebellum, hippocampus, striatum and thalamus RT-qPCR examination of peripheral blood mononuclear cells from patients with schizophrenia |
| Fries et al. [155]     | NA     | mRNA expression, decreased | Genome-wide analysis of peripheral blood mononuclear cells from veterans with schizophrenia |
| Li et al. [156]        | NA     | mRNA expression, decreased | Datasets integrated analysis of samples from patients with schizophrenia Hippocampus |
| Gandal et al. [157]    | Differential gene expression, decreased | Differential gene expression, decreased | Analyses of microarray gene expression data of postmortem samples from patients with schizophrenia Frontal and parietal cortex |
| [158] Differential gene expression, decreased; variously expressed isoforms | Differential gene expression, decreased; variously expressed isoforms | Analyses of RNA-sequencing data of postmortem samples from patients with schizophrenia Frontal and temporal cortex |
| Ishizuka et al. [159]  | NA     | Ala55Thr variant in CX3CR1 gene | Destabilization of the receptor gene's conformation leading to the increased risk of schizophrenia |
| Ormel et al. [160]     | NA     | mRNA expression, increased in one of the phenotypes within the cells | Monocyte-derived microglia-like cells obtained from peripheral blood mononuclear cells of patients with schizophrenia |
| Zhang et al. [161]     | NA     | mRNA expression | Postmortem samples from patients with schizophrenia Dorsolateral prefrontal cortex, anterior cingulate cortex |
| Hill et al. [162]      | mRNA expression, unchanged | mRNA expression, unchanged | Postmortem samples from patients with schizophrenia Orbitofrontal cortex |

NA not assessed
samples highlighted down-regulation of \( CX3CR1 \) mRNA levels in the subjects affected by this condition. The finding was further confirmed by RT-qPCR examination in the peripheral blood mononuclear cells (PBMCs) obtained from the suffering from schizophrenia. The dysregulation of the gene expression in PBMCs was independent of confounding variables (including tobacco smoking, age, gender or antipsychotic medication) and correlated with a depression–anxiety phenotype [154]. Comparable results were presented by Fries et al. [155] whose genome-wide research revealed the diminished \( CX3CR1 \) level in PBMCs from veterans with a diagnosis of schizophrenia. Similarly, the datasets-integrated analysis showed that the \( CX3CR1 \) expression was decreased in the hippocampi of individuals with this illness [156]. Another evidence for this phenomenon was delivered by Gandal et al. [157] whose multifaceted and complex microarray study revealed a robust reduction in both \( CX3CL1 \) and \( CX3CR1 \) levels in postmortem cortical samples from patients with schizophrenia. The authors confirmed and expanded these findings in further examinations applying large-scale RNA-sequencing-based quantifications that integrated genetic and genomic data from numerous well-curated, high-quality postmortem brain specimens from individuals with the disease and controls [158]. The analyses of a transcriptomic organization at the levels of a gene, isoform, local splicing and gene networks indicated down-regulation in differential expression of \( CX3CL1 \) and \( CX3CR1 \) as well as the presence of variously expressed isoforms [158]. Possibly such changes regarding genetic variants may exhibit distinct biological effects and consequently result in heterogeneity in pathology progression or symptom manifestation in schizophrenia. In parallel to these observations, it was shown that the rare variant (Ala55Thr) in the \( CX3CR1 \) gene contributes to the increased risk of this condition [159]. The researchers proved that the mutation could destabilize the conformation of the receptor by weakening the hydrophobic interaction between TM1 and helix 8 in the structure of \( CX3CR1 \). Consequently, the Ala55Thr variant affected the gene interplay with a G protein and resulted in inhibition of the \( CX3CL1–CX3CR1 \) signaling. Complementary experiments on HEK293 cells transfected with Ala55Thr-expressing vector demonstrated a reduction in Akt phosphorylation-mediated signaling upon \( CX3CL1 \) treatment [159]. A characterization of microglia-like cells derived from patients with schizophrenia demonstrated the presence of two unique inflammatory phenotypes within these cells [160]. It is noteworthy that one out of the significantly abundant clusters was distinguished by higher expression of \( CX3CR1 \). In another study, Zhang et al. [161] showed that \( CX3CR1 \) transcript level was increased in the anterior cingulate cortex of suicide completers with schizophrenia when compared to the subjects affected by this condition who died of other causes. However, when the investigated cohort was analysed holistically and compared to controls, the mRNA expression of the receptor was unchanged in this brain structure (as well as in the dorsal lateral prefrontal cortex). These postmortem data emphasized the importance of accurate characteristic of examined groups in terms of symptoms of the disease and anamneses. Nonetheless, the latest articles implicate that the disruption in the \( CX3CL1–CX3CR1 \) signaling in schizophrenia may be limited to a shift in the ligand production. Hill et al. [162] described diminished protein release of \( CX3CL1 \) with no change in the level of \( CX3CR1 \) in the postmortem dorsolateral prefrontal cortex from individuals with this disorder. The decline in the expression of the ligand was not accompanied by the difference in ADAM10 production, suggesting that the lower level of \( CX3CL1 \) was not caused by the altered cleavage conducted by this sheddase. Additional analysis of the samples from patients with schizophrenia revealed a subtle but significant negative correlation between \( CX3CL1 \) protein level and lifelong antipsychotic dose. This association implies the possibility that chronic medication with antipsychotics may contribute to the reduced production of this chemokine [162]. In the same study, no discrepancies between control subjects and those affected by schizophrenia were found in terms of the transcript expression of neither \( CX3CL1 \) nor \( CX3CR1 \) in the orbitofrontal cortex. The observations regarding the protein and mRNA levels of the \( CX3CL1–CX3CR1 \) dyad were unrelated to such contributory factors as body mass index, serum C-reactive protein release, alcohol consumption, prescribed antidepressants or mood stabilizers, death by suicide and a subtype of schizophrenia (undifferentiated or paranoid). As noted by the authors, sex had an effect only on the \( CX3CL1 \) production in the control group as males were characterized by higher levels of the ligand than females [162].

**Experimental data**

One of the approaches to investigate schizophrenia-like disturbances in animals involves the maternal immune activation (MIA) paradigm [163, 164] (Table 2). Most often, MIA is generated by the administration of immunostimulants, for example, lipopolysaccharide (LPS) [165–169] or polyinosinic:polycytidylic acid (Poly I:C) [170, 171] to pregnant females of rodents. Current evidence showed alterations in the \( CX3CL1–CX3CR1 \) system in male offspring of MIA-treated Wistar rat dams [172]. The changes were present already in the early life of animals when an increase in the hippocampal \( Cx3cl1 \) expression and \( CX3CR1 \) level, as well as cortical \( CX3CL1 \) production, was observed in descendants prenatally exposed to LPS. At the same time, MIA with Poly I:C elevated \( CX3CL1 \) level in the frontal cortex and decreased \( CX3CR1 \) release in the hippocampus of young rats. The disturbances of the \( CX3CL1–CX3CR1 \) axis were accompanied by alterations in the expression of microglial
| MIA induction agent | Sex, strain and species | CX3CL1–CX3CR1 axis | Additional information | References |
|---------------------|------------------------|--------------------|------------------------|------------|
| LPS | Male Wistar rats | ↑ Cx3ell (hippocampus), ≡ Cx3ell (frontal cortex) and Cx3cr1 (hippocampus, frontal cortex), ↑ CX3CL1 (frontal cortex) and CX3CR1 (hippocampus), ≡ CX3CL1 (hippocampus) and CX3CR1 (frontal cortex) in young offspring | Alterations in the mRNA expression of microglial markers and the profile of cytokines released in the brains of young offspring | [172] |
| | | ↓ CX3CL1 (hippocampus), ≡ CX3CL1 (frontal cortex) and CX3CR1 (hippocampus, frontal cortex) in adult offspring | Behavioral schizophrenia-like disturbances (e.g., PPI deficits and an aggressive phenotype) in adulthood | |
| Poly I:C | | ≡ Cx3ell and Cx3cr1 (hippocampus, frontal cortex), ↑ CX3CL1 (frontal cortex), ≡ CX3CL1 (hippocampus), ↓ CX3CR1 (hippocampus), ≡ CX3CR1 (frontal cortex) in young offspring | | |
| | | ↑ CX3CL1 (frontal cortex), ≡ CX3CL1 (hippocampus) and CX3CR1 (hippocampus, frontal cortex) in adult offspring | Behavioral schizophrenia-like changes (increased exploratory activity and anxiety-like behaviors) in adulthood | [173] |
| | | ↓ CX3CL1 (frontal cortex) and CX3CR1 (hippocampus), ≡ CX3CL1 (hippocampus) and CX3CR1 (frontal cortex) in adult offspring with a deficit in PPI | Occurrence of two phenotypes in PPI (with and without deficit) | |
| | | ↓ CX3CL1 (hippocampus) in offspring with PPI deficit after additional challenge with LPS in adulthood | Adult offspring were additionally exposed to the acute challenge with LPS in adulthood, according to the “two-hit” hypothesis of schizophrenia | |
| | | ↓ CX3CR1 (frontal cortex) in adult offspring without PPI deficit after additional challenge with LPS in adulthood | | |
| Poly I:C | Male Sprague-Dawley rats | ↓ Cx3cr1 (microglial cells isolated from the hippocampus) in adult offspring | Behavioral schizophrenia-like disturbances (diminished number of aggressive interactions, depressive-like episodes, increased exploratory activity) | [174] |
| | | ≡ Cx3cell and Cx3cr1 (frontal cortex) in adult offspring with a deficit in PPI | Occurrence of two phenotypes in PPI (with and without deficit) | |
| | | ≡ Cx3cell and Cx3cr1 (hippocampus, frontal cortex) in adult offspring without a deficit in PPI | Adult offspring were additionally exposed to the acute challenge with Poly I:C in adulthood, according to the “two-hit” hypothesis of schizophrenia | |
| | | ↓ Cx3cell (hippocampus) in adult offspring without PPI deficit after additional challenge with Poly I:C in adulthood | | |
| | | ≡ CX3CL1 and CX3CR1 (hippocampus, frontal cortex) in adult offspring with a deficit in PPI | | |
| | | ↑ CX3CL1 and CX3CR1 (frontal cortex), ≡ CX3CL1 and CX3CR1 (hippocampus) in adult offspring without a deficit in PPI | | |
| | | ↓ Cx3cr1 (frontal cortex) in offspring without PPI deficit after additional challenge with Poly I:C in adulthood | | |
| | | ↑ CX3CL1 (hippocampus) in offspring without PPI deficit after additional challenge with Poly I:C in adulthood | Deficits in social behavior and PPI (in part of animals) as well as working memory impairment | [175] |
| Poly I:C | Male C57BL/6 mice | | | |
markers and the profile of cytokines released in the brains of juveniles in both MIA models [172]. Along with these results, the MIA-subjected offspring displayed multiple behavioral schizophrenia-like disturbances (e.g., PPI deficits and an aggressive phenotype) in adulthood. These malfunctions depended on the immunostimulant used and were accompanied by a reduction in hippocampal and a raise in cortical CX3CL1 levels in LPS- and Poly I:C-exposed animals, respectively [172]. In another article from this research group [173], the expression of the Cx3cl1–Cx3cr1 dyad was not affected, while the protein levels of CX3CL1 in the hippocampus and CX3CR1 in the frontal cortex were downregulated after MIA with LPS in adult offspring without a deficit in PPI. The additional acute challenge with LPS later in life, according to the “two-hit” hypothesis of schizophrenia, decreased levels of hippocampal CX3CL1 in rats with altered PPI and cortical CX3CR1 in animals without such behavioral deficiency [173]. In similar experimental conditions, yet applying MIA with Poly I:C, the mRNA expression of both Cx3cl1 and Cx3cr1 was reduced in the hippocampus of adult descendants without PPI deficit [174]. The additional injection of Poly I:C in adulthood decreased cortical Cx3cr1 expression and increased hippocampal CX3CL1 level in offspring without impairment in PPI [174]. The results came from the experiments on Sprague-Dawley rats, which suggests that the different strains exert notable effects on the outcome of examinations in MIA models. Abnormalities in CX3CR1 levels have been also measured in microglia isolated from brains of mice subjected to prenatal Poly I:C injection [175, 176]. Mattei et al. [175] presented the diminished mRNA expression of the receptor in these cells obtained from the hippocampus of male offspring. The alteration was accompanied by deficits in social behavior and PPI (in part of animals) as well as working memory impairment [175]. In contrast, flow cytometry revealed that the cells of female descendants prenatally challenged with MIA were characterized by a significantly bigger population of microglia expressing CX3CR1 [176]. The change did not persist until adulthood and preceded deficits in PPI as those were noted only in the later stage of a female’s life. As postulated by the authors, these observations may indicate intensified synaptic processes occurring in response to Poly I:C administration. Furthermore, MIA did not influence PPI and led to a lasting decrease in CX3CR1 level in male offspring as the reduction was detected both in adolescence and adulthood [176]. Hui et al. [177] showed data, where prenatal immune challenge with Poly I:C in mice resulted in partly sex-dependent behavioral schizophrenia-like disturbances (for instance increased repetitive behavior, anxiety, reduced sociability and deficits in PPI) but no disturbances in Cx3cl1 and Cx3cr1 gene expression in brains of offspring.
were identified. A significant, although preliminary observation in the context of schizophrenia-associated abnormalities implementing the MIA model with Poly I:C was also provided by Estes et al. [178] in their preprint article. In the frontal cortex of male offspring mice, the Cx3cr1 expression was oscillating throughout development with a decrease in mRNA levels at birth and postnatal day 14 (P14) and an increase at P7 and P60. It showed that the expression of the receptor gene was particularly up-regulated at the beginning of synaptogenesis (P7) and declined during the peak of this process and spine formation (P14). These age-specific changes in the Cx3cr1 transcript level implicate MIA-induced microglial dysfunctions that trigger alterations in cortical networks [178]. The evidence seems to support the reports on impaired anatomical and functional connectivity in the cerebral cortex of patients with schizophrenia [179–181]. Consistent results were described by Garré et al. [182]. MIA with Poly I:C in mice caused dendritic spine loss, impairments in learning-dependent dendritic spine formation and deficits in learning tasks which were mediated by CX3CR1-highly expressing monocytes via TNF-α-dependent mechanisms. Recently, Bordeleau et al. [183] reported a different approach in inducing MIA and showed that exposure to a high-fat diet resulted in maternal systemic inflammation and simultaneously decreased the mRNA expression of Cx3cr1 in the hippocampus of male offspring mice.

Further evidence regarding the involvement of the CX3CL1–CX3CR1 pair in the pathogenesis of schizophrenia has been contributed by multiple studies on genetic models with a knockout of the receptor gene. Zhou et al. [184] applied a social isolation model of the disease in Cx3cr1-deficient mice and examined the schizophrenia-related behaviors. Unlike control animals exposed to the procedure, the knockouts did not display deficits in PPI. Moreover, the CX3CR1 level was up-regulated in the medial prefrontal cortex, hippocampus and nucleus accumbens of the isolated wild-type mice, suggesting that the receptor might participate in the examined schizophrenia-like behaviors [184]. Another feature observed for Cx3cr1−/− animals was a transient reduction of microglia during the early postnatal period that resulted in impaired synaptic pruning [185]. The authors stated that the lack of the receptor gene caused a decrease in synaptic transmission, attenuation of functional brain connectivity, intensified repetitive behavior and deficits in social interaction. Squarzoni et al. [186] suggested that a mild shift in neocortical positioning of microglia depicted in mice lacking the Cx3cr1 gene could contribute to defects in postnatal synaptogenesis and cortical networks. Besides, Cx3cr1 knockouts exhibited reduced baseline connectivity from the prefrontal cortex to the dorsal hippocampus during the habituation phase in the social interaction test [187].

This report seems to be particularly relevant in the context of data in the suffering from schizophrenia for whom sorely impaired connectivity between the hippocampus and the prefrontal cortex was shown [188, 189].

The current study by Lebovitz et al. [190] revealed that antibiotics-driven maternal microbiome dysbiosis (MMD), which is considered a model of neurodevelopmental disorders including schizophrenia, led to social impairments in male offspring. The deficiency coincided with an increased protein level of CX3CR1 in the prefrontal cortex of those mice. The application of Cx3cr1ΔGPRGPP knockout animals allowed to demonstrate that MMD-reared descendants developed the changes in behavior due to dysfunction of the CX3CL1–CX3CR1 signaling and disrupted synaptic modeling. Notably, the presence of a gut commensal bacterium strain, *Lactobacillus murinus* HU-1, was sufficient to prevent social alterations and microglial activation in MMD-affected offspring [190]. Experiments in a pharmacological model of schizophrenia-like cognitive deficits induced by repeated ketamine administration showed the effect of cannabidiol (CBD) on the Cx3cr1 transcript level [191]. As presented by the researchers, the CBD treatment caused the up-regulation of the receptor expression in the prefrontal cortex of male offspring of Sprague-Dawley rats. Therefore, the evidence implies that the CX3CL1–CX3CR1 axis might be crucial in the disease course and could provide a new target for future therapy.

**Conclusions**

The literature data from reports in patients concerning the role of the CX3CL1–CX3CR1 axis in the pathogenesis of schizophrenia remain inconsistent and, thus, difficult to unambiguously interpret. More information has been provided by the studies in animal models of the disease (e.g., implementing MIA); however, those are often confounded with the discrepancies in experimental conditions, including species or strains of animals, a protocol of immunostimulant administration or even paradigm of behavioral examinations. Nevertheless, all of the observations shed a light and increasingly implicate the involvement of CX3CR1 and its ligand in mechanisms underlying schizophrenia. To date, the particular interest in the CX3CL1–CX3CR1 system seems to indirectly result from its extensive role in maintaining the homeostasis of processes in the CNS that are often indicated as disturbed in the course of that disorder (Fig. 2). Yet, further research is needed to a profound understanding of the exact contribution of this signaling pathway in schizophrenia.

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Declarations

Conflicts of interest The authors declare no conflict of interest, financial or otherwise.

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