CCL11 OR EOTAXIN-1: AN IMMUNE MARKER FOR AGEING AND ACCELERATED AGEING IN NEURO-PSYCHIATRIC DISORDERS

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ABSTRACT

Background: CCL11 (eotaxin) is a chemokine with an important role in allergic conditions. Recent evidence indicates that CCL11 plays a role in brain disorders as well.

Aims: This paper reviews the associations between CCL11 and aging, neurodegenerative, neuroinflammatory and neuropsychiatric disorders.

Methods: Electronic databases were searched for original articles examining CCL11 in neuropsychiatric disorders.

Results: CCL11 is rapidly transported from the blood to the brain through the brain-blood barrier. Age-related increases in CCL11 are associated with cognitive impairments in executive functions, episodic and semantic memory and, therefore, this chemokine was described as an "endogenous cognition deteriorating chemokine" (ECDC) or "accelerated brain-aging chemokine" (ABAC). In schizophrenia, increased CCL11 is not only associated with impairments in cognitive functions, but also with key symptoms including formal thought disorders. Some patients with mood disorders and premenstrual syndrome show increased plasma CCL11 levels. In diseases of old age, CCL11 is associated with lowered neurogenesis and neurodegenerative processes and, as a consequence, increased CCL11 increases risk towards Alzheimer's Disease. Polymorphisms in the CCL11 gene are associated with stroke. Increased CCL11 also plays a role in neuroinflammatory disease including multiple sclerosis. In animal models, neutralization of CCL11 may protect against nigrostriatal neurodegeneration. Increased production of CCL11 may be attenuated by glucocorticoids, minocycline, resveratrol and anti-CCL11 antibodies.

Conclusions: Increased CCL11 production during inflammatory conditions may play a role in human disease including age-related cognitive decline, schizophrenia, mood disorders and neurodegenerative disorders. Increased CCL11 production is a new drug target in the treatment and prevention of those disorders.

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Keywords: eotaxin, immune marker, neuroinflammation, ageing, neuro-psychiatric disorder

INTRODUCTION

Chemokines consist of a family of small cytokines (7–12 kDa), which prompt directed chemotaxis in nearby responsive cells. Chemokines play a pivotal role in immune functions and inflammatory responses and facilitate leukocyte migration and trafficking (Foxman et al. 1997; Murphy et al. 2000; Springer, 1994). The discovery of chemokines goes back to 1977 (Wu et al. 1977; Callewaere et al. 2007), but their role in altering the neuroimmune and neurobiological processes gained notice until the mid-90s (Tani and Ransohoff, 1994). Recent studies show a direct role of chemokines in neuroendocrine function, neurotransmission, and neurodegeneration within the CNS (Central nervous system) (Reaux-Le Goazigo et al. 2013). Chemokines comprise four families characterized according to the relative position of their cysteine residues and their functions, with CCL (C-C motif chemokine) and CXCL (C-X-C motif ligand) being the largest. They act by binding to seven-transmembrane G protein-coupled receptors, which in turn activate signaling cascades and initiate shape rearrangement and cell movement.

One of those chemokines, namely CCL11 or eosinophil chemotactic protein (eotaxin), is involved in the selective recruitment of eosinophils into inflammatory sites during allergic reactions and this chemokine is extensively examined in asthma, allergic rhinitis, and other eosinophil-related conditions (Teixeira, 2018).

CCL11 production is induced by T-helper (Th)-2 cytokines, like IL-13 (Interleukin-13), IL-10 (Interleukin-10) and IL-4 (Interleukin-4). It is a product of eosinophils, B-cells, fibroblasts, endothelial cells, macrophages, chondrocytes and other cells (Sirivichayakul S et al. 2018; Kindstedt et al. 2017)(**Table 1**). CCL11 is transported from the blood to the brain through the brain-blood barrier (BBB) and also synthesized by microglia (Sirivichayakul S et

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al. 2018). Furthermore, there is some evidence that CCL11 is associated with aging and reduced neurogenesis (Villeda et al. 2011). Increased levels of CCL11 have been detected in numerous neuro-inflammatory disorders such as multiple sclerosis (Sorensen et al. 1999), as well as neurodegenerative and neuroprogressive disorders (Teixeira, 2018) and psychiatric illnesses including major depression, bipolar disorder and schizophrenia (Sorensen et al. 1999; Teixeira et al. 2018; Sirivichayakul et al. 2019; Eyre et al. 2016; Stuart and Baune. 2014). Moreover, increased CCL11 levels are also associated with neurocognitive deficits in aging, neurodegenerative disorders, and major psychiatric disorders such as schizophrenia (Sirivichayakul et al. 2019). This is important, because the association between CCL11 and hippocampal damage in aging may be important to understand the pathophysiology of Alzheimer's disease and old-age depression (Villeda et al. 2011; Baruch et al. 2013).

Table 1. CCL11 (eotaxin), cells producing CCL11 and cytokines inducing CCL11

Cells producing CCL11	**Cytokines inducing CCL11**
Eosinophils	Th-2 cytokines
Macrophages	Interleukin IL-4
T and B-cells	Interleukin IL-10
Fibroblasts	Interleukin IL-13
Endothelial cells	Complement factors
Epithelial cells	Immune complexes
Chondrocytes	
Microglia	
Keratinocytes	
Smooth muscle cells	

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AIMS of the REVIEW

This paper aims to review the associations between CCL11 and psychiatric disorders and its possible role as an immune biomarker in those disorders.

METHODS

We searched online libraries, including PubMed/MEDLINE, Google Scholar, and Scopus. The main search terms were “Chemokine CCL11” [MeSH] or “biomarkers” [MeSH] and “stress” [MeSH]” and “Chemokine CCL11” [MeSH], “schizophrenia”, and “CCL11” [MeSH] and “brain” [MeSH] with filters activated, namely publication date from 01/01/1990 to 31/12/2019 and papers written in English.

CCL11 AND CCR3 IN ALLERGIC INFLAMMATION

Chemokine receptors (CCRs) can bind to different ligands (CCLs) and chemokines can interact with more than one receptor. The MCP (monocyte chemoattractant protein) family of chemokines bind most often to CCR2, but MCP-2, MCP-3, and MCP-4 can also interact with CCR1 and CCR3 (Yamagami et al. 1997). CCL11 shows very high homology with the MCP family (Jose et al. 1994) and CCL11 signals via the chemokine receptor CCR3 (Ponath et al. 1996). This receptor is expressed on eosinophils, basophils, and Th-2 type lymphocytes, making it an attractive target for allergic disease therapies (Ponath et al. 1996; Salusto et al.1997). CCL11, CCL24 (eotaxin-2) and CCL26 (eotaxin-3) bind all to CCR3 (Pease, 2006). There is some evidence that high concentrations of CCL11 are sufficient to activate CCR2 in chemotaxis assays and that substimulatory concentrations of CCL11 can antagonize MCP-1 activity at CCR2, indicating that CCL11 behaves as a partial agonist at CCR2 (Martinelli et al. 2001). This is in contrast with Ogilvie et al. (2001) who described CCL11 as a natural antagonist of CCR2 and an agonist of CCR5 (Oglivie et al. 2001). CCL11 shows a low affinity

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for binding with CXCR3 (C-X-C chemoreceptor 2) expressed on Th-1 cells, but it is postulated that this binding can play a role in impaired Th-1 response in pathological conditions (Weng et al. 1998). CCL11 production is stimulated by IL-4, IL-13,IL-10, IL-1β and TNF-α in epithelial cells of the lung and the gastrointestinal tract or fibroblasts (Paplińska M et al. 2007; Sato et al. 2001; Lavy, 2017). In 1994, CCL11 was identified as a highly specific eosinophil chemokine that can be produced by lymphocytes, macrophages, bronchial smooth muscle cells, endothelial cells, and eosinophils and that this chemokine is responsible for the regulation of chemotaxis through binding to the CCR3 (Amerio et al. 2003).

Allergic diseases can be caused by complex interactions between Th-2 cells, mast cells, basophils, and eosinophils, which all express CCR3 (Erin et al. 2002, Lacy P, 2017). Romagnani (2002) showed that Th-2 cytokines contribute to the pathogenesis of allergic inflammation as well as to the manifestation of allergy and asthma and that this proceeds al teast in part through the expression of CCR3, which interacts with CCL11, allowing the recruitment of basophils, eosinophils and mast cells (Romagnani, 2002). CCL11 plays a role in the pathogenesis of allergic airway diseases, inflammatory bowel disorder disease and gastro-intestinal allergic hypersensitivity. Garcia et al. (2005) confirmed the role of CCR3 and CCL11 (as well as CCR4, CCR8) in allergic inflammation using in vitro/in vivo experimental studies and clinical studies in patients with asthma (Garcia et al. 2005). The binding of CCL11 (but also CCL24 and CCL26) to CCR3 is involved in the development of asthma symptoms (Pease, 2006).

Due to the significant role of CCR3 in allergic diseases, research has focused on treatments with chemokine receptor antagonists (Elsner et al. 2004). For example, inhibition of CCR3 to selectively inhibit eosinophil recruitment into tissue sites can have beneficial effects and be used as an effective therapy for allergic diseases (Erin et al. 2002).

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CCL11, THE BLOOD BRAIN BARRIER (BBB) and THE CNS

CCL11 is transferred from the blood to brain tissues with a slow phase of influx prior to the rapid phase (Erickson et al. 2014). The striatum shows an early rapid-uptake phase, in contrast to other regions, which present with a delayed-uptake phase (Erickson et al. 2014). CCL11 may have biphasic effects with neuroprotective and neurotoxic effects, which are detected at physiological and pathological levels of this chemokine, respectively (Erickson et al. 2014). The same authors also concluded that CCL11 does not cause a disturbance in the BBB (Erickson et al. 2014). Nevertheless, CCL11 may downregulate, in a concentration-dependent manner, the tight junctions proteins occludin, zona occludens-1 and claudin-1 in human coronary artery endothelial cells (Jamaluddin et al. 2009), suggesting that CCL11 may also affect the BBB. In a study that examined patients with schizophrenia, significant associations between increased CCL11 plasma concentrations and IgA levels directed to claudin-5 (an indicant of BBB breakdown) were found suggesting that CCL11 or associated mechanisms may affect the BBB (Maes et al. 2019).

Previous research (Parajuli et al. 2015) showed that CCL11 is released by activated astrocytes while the CCR3 receptor is expressed by microglia, causing microglial production of reactive oxygen species (ROS) by up-regulating NADPH Oxidase 1 (NOX1) leading to excitotoxic neuronal death while inhibition of NOX1 can reverse these effects. The same authors showed that the release of CCL11 by activated astrocytes causes oxidative stress due to microglial NOX1 activation thereby inducing increased neurotoxicity (an event linked to the pathogenesis of various neurological disorders) (Parajuli, 2015). Zhu et al. (2017) concluded that CCR3 is expressed by hippocampal neurons and that treatment of primary hippocampal neuronal cultures with CCL11 (*in vitro*) causes activation of cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase-3β (GSK3) (Zhu et al. 2017) and that these effects could be

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blocked using CCR3 specific antagonists. CCR3 and CCR5 are present on microglia of both control and Alzheimer's disease (AD) brains (Xia et al. 1998).

CCL11: AN ENDOGENOUS COGNITIVE DETERIORATING CHEMOKINE (ECDC)

Villeda et al. (2011) established that, in animal models, age-associated rises in CCL11 are associated with deficits in cognitive functions due to decreased neurogenesis and diminished hippocampal-related learning and memory. Young mice administered CCL11, developed decreased adult neurogenesis in addition to diminished memory and learning, hence identifying CCL11 as a chemokine that decreases hippocampal functions with increasing age (Villeda et al. 2011). However, another study could not find a direct effect of CCL11 on neuronal cells but established that CCL11 promotes microglial migration and activation with subsequent production of ROS which leads to glutamate-induced neuronal cell death (Parajuli, 2015). Baruch et al. (2013) showed that a local (choroid plexus epithelium) shift toward Th-2 (T-helper 2) activation initiates IL-4 and subsequently CCL11 production in association with cognitive deficits (Baruch et al. 2013). Thus, based on these findings and those of Villeda and Baruch, it may be concluded that age-related increases in CCL11 may have detrimental effects on central neuronal functions (Hoefer et al. 2017). The latter authors also confirm that with age CCL11 levels rise in both plasma and Cerebral Spinal Fluid (CSF) and also in different neurodegenerative diseases (Huber et al. 2018).

Peripheral CCL11 levels increase with age and people with cognitive impairments tend to present with higher plasma CCL11 levels than those without (Hoefer et al. 2017). This suggests that CCL11 could be a means of predicting cognitive impairments in older individuals (Butcher et al. 2017). In normal healthy volunteers, CCL11 is significantly associated with age and the results of different neurocognitive probes as assessed with the neuropsychological tests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Sirivichayakul

et al. 2019). More specifically, higher serum levels of CCL11 are significantly correlated with lower scores on assessments of semantic and episodic memory, including the Verbal Fluency Test, Word List Memory, and Word List True Recall. Moreover, CCL11 was also associated with lowered scores on the Mini-Mental State Examination (MMSE) and diverse executive tests as measured with the Cambridge Neuropsychological Test Automated Battery (CANTAB), including Spatial Working Memory, which probes task strategy employed by the central executive and executive working memory ability, and One-Touch Stockings of Cambridge (OTS), which probes spatial planning (Sirivichayakul et al. 2019). Moreover, age and CCL11 have similar effects on all those neuro-cognitive tests, while CCL11 is a partial mediator of the effects of age on these tests. Furthermore, a "super-variable" comprising both age and CCL11 exerted much stronger effects on these different tests. For example, this super-variable explained 75% of the variance in executive functions and 44.3% of the variance in an index of semantic memory. Therefore, these authors concluded that CCL11 is an endogenous cognition deteriorating chemokine (ECDC) or "accelerated brain-aging chemokine" (ABAC) (Sirivichayakul et al. 2019).

CCL11 IN SCHIZOPHRENIA

Schizophrenia (SCZ) is a chronic psychiatric disorder characterized by neuroprogression (Davis et al. 2003) and its etiology is multifactorial, with genetic and environmental components. There is evidence that acute psychotic episodes, chronic schizophrenia, and first-episode psychosis are associated with activated macrophage M1, Th-1, Th-2, Th-17 and T regulatory (Treg) responses (Maes et al. 1995; Noto et al. 2014, 2016; Roomruangwong et al. 2019).

CCL11, as well as other cytokines/chemokines (including CCL2, CCL17, CCL22), are significantly higher in schizophrenic patients as compared with controls (Hong, 2017).

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Increased CCL11 levels have negative correlation with telomere length and grey matter volume (Czepielewski LS et al. 2018). Combining CCL11 with 4 other biomarkers (namely sTNF-R1, sTNF-R2, IL-10 and IL-4) allows predicting the diagnosis of schizophrenia with a sensitivity of 70% and a specificity of 89.4% (Noto et al. 2015). Frydecka et al. (2018) observed that schizophrenia is accompanied by simultaneous increases in CCL11 and CCL2 while increases in both chemokines are known to cause more severe age-related deficiencies in cognitive functions (Frydechka et al. 2018; Bettcher et al. 2016). Recently, it was shown that a combination of CCL11 with IL-1, IL-1RA, TNF-α, sTNFR1, sTNFR2 and CCL2 predicts deficit schizophrenia with a bootstrapped (2000 bootstraps) area under the Receiver Operating Curve of 0.985 (Al-Hakeim et al. 2019 in press). Increased levels of CCL11 coupled with increased IL-6 and dickkoph-1 related-protein (DKK1) also predict a non-response to treatment with antipsychotics (Al-Dujaili et al. 2019).

Most importantly, in schizophrenia, increased levels of CCL11 strongly impact many neurocognitive tests. Sirivichayakul et al. (2018) established that CCL11 was highly significantly associated with impairments in many CERAD and CANTAB tests including probes of semantic and episodic memory as well as executive functions. For example, CCL11 alone explained 16.0% of the variance in the Verbal Flueucy Test (VFT) results and 11.0% of the variance in an index of semantic memory (Sirivichayakul et al. 2018). Interestingly, also formal thought disorders, a key symptom of schizophrenia, was significantly associated with increased levels of CCL11 (Sirivichayakul et al. 2018). Another study observed highly significant associations between increased CCL11 levels and cognitive impairments in attention, working memory, episodic and semantic memory and executive functions (Al-Hakeim et al. 2019 in press).

Moreover, increased CCL11 plasma levels are also associated with increased severity scores on different symptom domains of schizophrenia. First, in schizophrenia, positive

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correlations were established between increased CCL11 levels and negative symptoms (Teixeira et al. 2008; Teixiera et al. 2018; Sirivichayakul et al. 2018; Al-Hakeim et al. 2019), but also with psychosis, hostility, excitation, mannerism and psychomotor retardation (Sirivichayakul et al. 2018; Al-Hakeim et al. 2019; Aldujaili et al. 2019). The impact of CCL11 on these symptoms may be increased by combining CCL11 levels with other neurotoxic compounds including tryptophan catabolites such as picolinic and xanthurenic acid (Sirivichayakul et al. 2019).

Therefore, it was concluded that CCL11 alone or together with other immune products including TRYCATs, IL-1β, IL-6, and TNF-α, exerts neurotoxic effects on neuronal cells thereby causing neurocognitive impairments and the symptom domains of schizophrenia. Moreover, such effects may be aggravated by impairments in the compensatory immune-regulatory system (CIRS), including lowered levels of natural IgM directed against oxidative specific epitopes (Roomruangwong et al. 2019).

CCL11 IN MOOD DISORDERS (Table2)

A first study reporting increased levels of CCL11 in patients with major depression, especially associated with suicidal ideation was published in 2012 (Grassi-Oliveira R, 2012). Major depressed subjects with suicidal ideation presented lower levels of CCL2 and CCL5 and higher levels of CCL11 as compared with healthy controls (Grassi-Oliveira, 2012). Magalhaes et al. (2014) and Barbosa et al. (2013) also reported increased levels of CCL11 in patients with bipolar disorder (Magalhaes et al. 2014; Barbosa et al. 2013). Not only in bipolar disorder also in persistent depressive disorder or dysthymia CCL11 are found to be increased (Ho Ps et al. 2017). Simon et al. (2008) assessed serum levels of 22 cytokines/chemokines, including CCL11, in 49 patients with major depression and 49 matched controls, and reported increased

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levels of CCL11 in a context of "generalized chronic inflammatory state" (Simon et al. 2008). Texeira and al. (2018) reported similar results in an independent cohort of patients with major depression, indicating that increased serum levels of CCL11 were associated with suicidal ideation (Texeira et al. 2018). Nevertheless, a recent meta-analysis of studies evaluating CCL11 in depression including 454 participants failed to identify significant differences in CCL11 between depressed and control subjects (Leighton et al. 2018). It is possible, however, that this meta-analysis also included patients with milder depression symptoms or different comorbidities explaining the differences between studies. It should be added that a recent paper was unable to detect significant alterations in serum CCL11 in children with major depression as compared with controls while immune-inflammatory markers were clearly elevated (Al-Hakeim et al. 2019). In cocaine use disorder, CCL11 combined with TNF-α, IL-1β, CXCL12, CCL2, and CX3CL1 (C-X3-C Motif Chemokine Ligand 1) can be used to distinguish primary major depression from substance-induced major depression, indicating that plasma concentrations of CCL11 may be used as a potential biological marker to differentiate between primary and substance-induced depression (Marchena et al. 2019).

Increased CCL11 levels may also play a role in premenstrual syndrome (PMS), re-labelled as a menstrual cycle-associated syndrome (MCAS) (Roomruangwong et al. 2019). Thus, a recent paper shows that CCL11 is (along with CCL2 and CCL5) significantly increased in MCAS as compared with women without MCAS. The increased levels of CCL11 (and CCL2, CCL5, CXCL10, and CXCL8) are highly significantly associated with the severity of MCAS symptoms as measured with the Daily Record of Severity of Problems (DRSP) score. Moreover, the sum of three neurotoxic chemokines (namely CCL2 + CCL11 + CCL5) is significantly associated with the depressive and anxiety subdomains of the MCAS (Roomruangwong et al. 2019). This is important as MCAS/PMS is one of the predictors of

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mood disorders including major depression and, therefore, these findings further suggest that CCL11 may be associated with the pathophysiology of depression.

CCL11 in OTHER PSYCHIATRIC DISORDERS (Table2)

CCL11 in obsessive-compulsive disorder (OCD)

In the study of Fontenelle (2012), forty patients with OCD and 40 healthy controls had their plasmas assessed for chemokines including CCL11 (and CCL2, CCL3, CCL24, CXCL8, CXCL9, CXCL10), and other immune mediators like TNF-α, sTNFR1, sTNFR2 and interleukin-1 receptor antagonist (Fontenelle et al. 2012). However, there were no significant differences in the blood levels of CCL11 between patients with OCD and controls, whereas CCL3, CXCL8, sTNFR1, and sTNFR2 were significantly increased (Fontenelle et al. 2012).

CCL11 in autism spectrum disorder (ASD)

There are few studies that show high levels of CCL11 in ASD (Ashwood P et al. 2006; Cunha et al. 2015; Masi et al. 2015). A meta-analysis reviewed the results of 17 ASD studies with a total sample size of 743 patients with ASD versus 592 healthy controls (Masi et al. 2015). This study examined 19 cytokines and reports significantly higher plasma/serum levels of 12 of the cytokines/chemokines in ASD *versus* controls including CCL11 ($p=0.01$), IL-1β ($p<0.001$), IL-6 ($p=0.03$), IL-8 ($p=0.04$), IFN-γ ($p=0.02$), and CCL2 ($p<0.05$), whereas TGF-β1 levels were significantly lower in ASD ($P<0.001$) (Masi et al. 2015). Importantly, increased CCL11 (and IL-6, IL-10, and MCP-3) were found in the anterior cingulate gyrus and increased CCL2 and TGF-β1 in the CSF, anterior cingulate gyrus and cerebellum of ASD brain tissues (Zimmerman et al. 2005).

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CCL11 in substance abuse disorders

Kuo et al. (2018) included 344 heroin-dependent, Taiwanese patients under methadone maintenance treatment as compared with 87 normal control subjects in order to investigate plasma CCL11 and a SNP (single-nucleotide polymorphism) of the CCL11 gene and fibroblast growth factor - 2 (FGF-2). In patients, but not normal controls, CCL11 showed an adequate sensitivity and specificity in association with age using a cut-off at 45 years whilst increased plasma FGF-2 levels were correlated with high CCL11 level (Kuo et al. 2018). Decreased plasma levels of CCL11 were observed in 87 abstinent patients with alcohol use disorder as compared with 55 controls (Garcia-Marchena et al. 2016). Moreover, subjects with mood disorders and/or anxiety had lower CCL11 concentrations than non-comorbid patients and this effect was pronounced in women (Garcia-Marchena et al. 2016). Preclinical models of alcohol use in male Wistar rats showed alcohol-induced circulating chemokine alterations in CCL11, CXCL12, and CX3CL1 (Garcia-Marchena et al. 2016), indicating an important contribution of CCL11 to alcohol use disorder.

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Table 2. - Studies on CCL11 regarding different psychiatric disorders

Psychiatric disorder	**Findings for CCL11**	**References**
Schizophrenia	Increased blood levels; Negative correlation with telomere length and grey matter volume; Negative correlation with cognitive measures; Positive correlation with negative symptoms.	[56](Teixeira et al., 2008) [64](Czepielewski LS et al., 2018) [A63](Hong S et al., 2017) [67](Al-Hakeim et al., 2019) [68](Al-Dujaili et al., 2019)
Deficit schizophrenia	Increased plasma CCL11 levels	[13, 69](Sirivichayakul et al., 2018; 2019)
Bipolar disorder	Increased blood levels; Association with illness stage.	[72](Barbosa IG et al., 2013)
Major depression	Inc.reased blood levels; Association with suicidal ideation.	[74](Simon NM et al., 2008)
Dysthymia	Increased blood levels.	[73](Ho PS et al., 2017) [71](Magalhaes PV et al., 2014)
Premenstrual syndrome	Increased plasma CCL11.	[57] (Roomruangwong et al., 2019)
OCD (Obsessive compulsive disorder)	Blood levels similar to controls.	[58](Fontenelle LF et al., 2012)
Autism spectrum disorder	Increased blood levels. Increased CCL11, IL-6, IL-10, and MCP-3 in the anterior cingulate gyrus in ASD brain specimens.	[59](P. Ashwood et al. 2006) [60](Cunha GR et al., 2015) [61](Masi et al., 2015) [62](Zimmerman A et al., 2005)

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CCL11 IN NEURO-INFLAMMATORY DISORDERS

CCL11 and Parkinson's Disease

Parkinson's disease is a neuro-inflammatory disorder in which immune-inflammatory processes are involved in the degeneration of dopaminergic neurons via, amongst other mediators, chemokines. Scalzo et al. (2011) found no significant differences in chemokine levels between patients with Parkinson's Disease and controls (Scalzo et al. 2011). Lindqvist et al. (2013) measured immune-inflammatory biomarkers in CSF samples from Parkinson's disease patients to determine the relationships with non-motor Parkinson's Disease symptoms and they reported increased levels of CSF CCL11, C-reactive protein, IL-6 and TNF-α in association with depression, fatigue, and cognitive impairments (Lindqvist et al. 2013). On the other hand, Moghadam-Ahmadi et al. (2018) concluded that CCL11 is not involved in the diagnosis or treatment of Parkinson's Disease (Moghadam-Ahmadi et al. 2018). In animal models, Chandra et al. (2017) reported that neutralization of CCL11 and CCL5 may protect against nigrostriatal neurodegeneration and therefore the progression of Parkinson's Disease (Chandra G et al. 2017).

CCL11 and Alzheimer's Disease

As mentioned above, CCL11 is known to cause cognitive decline with age, but less is known regarding its involvement in the pathogenesis of Alzheimer's diseases. CCL11 is considered to contribute a probable risk factor for the development of Alzheimer's disease (Zhu et al. 2017). CCR3 and CCR5, which are present on microglia, are more expressed by reactive microglia of patients with Alzheimer's Disease than controls (Xia et al. 1998). Lalli et al. (2015) identified a haplotype of single-nucleotide polymorphisms (SNPs) on chromosome 17

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within a chemokine gene cluster that modifies age of onset of Alzheimer's Disease and additionally confers a strong protective effect. Importantly, this haplotype disrupts the associations between increasing age and increasing CCL11 levels, suggesting CCL11 may be a novel modifier of Alzheimer's Disease (Lalli et al. 2015). Guerreiro et al. (2015) reported that the association between the age of onset of Alzheimer's Disease and CCL11 could lead to the development of immunomodulating therapies, which could be used to delay the onset of the disease (Guerreiro and Bras, 2015). Nevertheless, another study showed that CCL2 is a better biomarker than CCL11 for the progression of Alzheimer's Disease although both chemokines employ the same CCR2 signaling pathway for the accumulation of microglia at sites of neuroinflammation (Westin et al. 2017). Deleting CCR3 in mice induces a decrease in synaptic loss as well as a decrease in spatial learning and memory deficits, further suggesting that age-related increments in CCL11 confer risk to Alzheimer's Disease (Zhu C et al. 2017). Similar findings were reported by Baruch et al. (2013) who showed that increased production of CCL11 due to destructive Th-2 inflammation is associated with cognitive dysfunctions (Baruch et al. 2013). Overall, it appears that age-related increases in CCL11 confer risk for Alzheimer's Disease while antagonizing CCR3 may lead to therapeutic benefits (Zhu et al. 2017).

CCL11 and multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune and neuro-inflammatory disease of the central nervous system characterized by damage to myelinated axons with varying degrees of destruction of myelin and axons (Hauser et al. 2008; Weinshenker, 1996). In a meta-analysis, which reviewed 226 research papers and 13.526 patients, Bai et al. (2019) found that 13 CSF cytokines (from a list of 26) and 21 blood cytokines (from a list of 37) were elevated in MS as compared with controls and that CSF CCL11 was significantly increased with a large effect

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size in patients with MS (Bai Z et al. 2019). Huber et al. (2018) reported that during the relapse phase, CCL11 may be down-regulated while during the secondary progressive phase, CCL11 is upregulated to achieve plateau levels (Huber et al. 2018). In other studies, it was detected that CCL11 (and CCL5) may discriminate clinical subtypes of multiple sclerosis. Thus, both CCL11 and CCL5 were lowered during the inflammatory phase as compared with progressive multiple sclerosis (Tejera-Alhambra et al. 2015). Michael et al. (2013) identified important chemokine profile markers including CCL11 in patients with neuromyelitis optica (NMO), which were additionally different from those with MS (Michael et al. 2013). These authors examined 29 aquaporin antibody-positive NMO patients and found CCL11 (and CCL4, G-CSF, and myeloperoxidase) to be an important marker in NMO (Michael et al. 2013). In NMO spectrum disorders (NMOSD), increasing production of TNF-α and interleukin-1β can stimulate CCL11 binding to CCR3, which may lead to eosinophil hypersensitivity during remission but not in MS (Tong et al. 2018). Moreover, increased CCL11 levels may be a critical step in NMOSD eosinophil restoration during remission (Tong et al. 2018) while both elevated levels of CCL11 and CCL13 may be important in eosinophil recruitment during NMOSD remission (Fernandez et al. 2018).

Autoimmune encephalomyelitis (EAE), an experimental model of multiple sclerosis, is accompanied by elevated levels of CCL11 in the CSF, a tighter blood-brain barrier, reduced antigen-specific responses and a predominant anti-inflammatory Th-2 phenotype suggesting that CCL11 may protect against neuroinflammation in this model (Adzemovic et al. 2012).

CCL11 and stroke

CCL11 is not only an immune marker, which has great importance in aging, neuroinflammation and neurodegeneration, but this chemokine is also associated with stroke. Khavinson et al. (2016) reviewed that cardiovascular disorders are accompanied by increased

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CCL11 concentrations and, accordingly, these authors proposed to use the term "protein of senility" to describe the detrimental effects of CCL11, this in contrast to lowered levels of plasma growth differentiation factor (GDF)11, which increase risk towards myocardial infarction and stroke and, therefore, should be considered as a "protein of juvenility" (Khavinson et al. 2016). Bone GDF11 or morphogenetic protein 11 (BMP 11) is a transforming growth factor β (TGF β) family member protein that is produced by humans, rats, and mice (Jamaiyar et al. 2017). Interestingly, GDF11 has paradoxical effects starting from embryonic development, the role of GDF11 in aging and medical disease varies throughout the lifespan (Jamaiyar et al. 2017). A survey performed by Sharma et al. (2014) indicates that CCL11 may be employed as one of the most important biomarkers for acute stroke even in patients with stroke-like symptoms (Sharma et al. 2014). Selected from a list of 262 potential biomarkers, the latter authors selected 5 biomarkers, which were combined in a model built with stepwise selection and validated by bootstrapping and included CCL11, epidermal growth factor receptor, S100A12, metalloproteinase inhibitor-4, and prolactin. This model could not only be used as an external validating criterion for the diagnosis stroke, but also as a biomarker for the management of stroke and stroke-like symptoms in patients (Sharma et al. 2014). Roy-O'Reilly et al. (2017) showed lower CCL11 levels in stroke patients as compared with controls and, additionally, that lower post-stroke CCL11 levels predict increased stroke severity and poorer functional outcomes 12 months after ischemic stroke (Roy-O'Reilly et al. 2017). Moreover, a CCL11 gene polymorphism is associated with different types of ischaemic stroke (Liang et al. 2017). A study on various CCL11 gene variants in Chinese people suggest a strong association with ischaemic stroke although there were no associations with ischaemic stroke subtypes (Zhao et al. 2012). Six tag SNPs in the CCL11 gene (rs1129844, rs17809012, rs1860183, rs1860184, rs4795898, and rs4795895) were studied in 620 patients with stroke and in a control group of 425 Han population patients in China (Liang et al. 2017). These authors reported that

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all polymorphisms of the CCL11 gene had different effects on the pathogenesis of lacunar stroke (Liang et al. 2017). Another large-n study stratified 1500 ischaemic stroke patients into TOAST (Trial of ORG 10172 in acute stroke treatment) subtypes and reported significant associations among the -1382A>G variant of the CCL11 gene with intracranial large artery atherosclerosis and small-vessel occlusion (Munshi et al. 2014).

POSSIBLE NOVEL TREATMENTS TARGETING CCL11

Resveratrol and its metabolites modulate the expression of CCL11. In 2011, Yang et al. investigated the effects of resveratrol in modulating inflammation by determining the expression and release of CCL11 in cultured human pulmonary artery endothelial cells (HPAEC) treated with the proinflammatory cytokines IL-13 and TNF-α (Yang et al. 2011). Exposure to resveratrol suppressed IL-13 and TNF-α induced CCL11 gene expression as well as attenuated CCL11 promoter activity, in association with inhibition of Janus Kinase-1 (JAK-1) expression, reduction in phosphorylated-STAT6 and decrements in the p65 subunit of NF-κB (Yang et al. 2011). Not only resveratrol has the ability to modulate CCL11, but also piceatannol, one of resvera2trol's metabolites, had a similar potency as resveratrol (Yang et al. 2011). This in vitro model can be used for further screening and discovering polyphenols with anti-inflammatory activities.

A human single-chain fragment variable antibody that neutralizes human CCL11 (CAT-212) was produced using antibody phage display and converted to whole antibody IgG4 format (CAT-213) (Main et al. 2006). Further optimization entailed a reduction of the length of the variable heavy chain complementarity-determining region 3 by one amino acid resulting in a 1000-fold increase in potency compared with the parent anti-CCL11 antibody (Main et al. 2006). CAT-213 neutralizes the ability of CCL11 to increase intracellular calcium signaling (with an IC(50) value of 2.86 nM), migration of CCR3-expressing L1.2 cells (with an IC(50)

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value of 0.48 nM), and inhibition of the CCL11-evoked shape change of human eosinophils in vitro (Main et al. 2006). CAT-213 and CAT-212 do not bind or neutralize MCP-1 a chemokine with a similar structure (Main et al. 2006). *In vivo* and *in vitro* probes conducted by those authors with recombinant human CCL11 (Cambridge Bioscience and R&D Systems), mouse CCL11 (R&D Systems) and synthetic human, rat, and monkey CCL11 (Albachem Limited) showed that CAT-212 and CAT- 213 are potent and may be used as therapy targeting high CCL11 levels (Main et al. 2006). New clinical trials with anti-CCL11 neutralizing antibodies are expected to have encouraging results in inflammatory diseases.

Inhibition of CCR3 receptor with small-molecule antagonists is thought to provide a valuable approach for the treatment of diseases which are associated with increased CCL11 production (Willems and Ijzerman, 2010). Chemical classes of small molecule CCR3 antagonists comprise (bi)piperidine and piperazine derivatives, N-arylalkylpiperidine urea derivatives and (N-ureidoalkyl)benzylpiperidines, phenylalanine derivatives, morpholinyl derivatives, pyrrolidinohydroquinazolines, aryl sulfonamides, amino-alkyl amides, imidazole- and pyrimidine-based antagonists, and bicyclic diamines (Willems and Ijzerman, 2010). The best-studied class with high affinity and promising antagonizing potential from all molecules mentioned above are (N-ureidoalkyl) benzylpiperidines (Willems and Ijzerman, 2010).

Another nanoparticle peptide-based CCR3 antagonist, namely R321, was studied in an acute allergic airway disease mouse model at a dose of 2mg/kg i.v. and showed adequate efficacy when used both prophylactically and therapeutically (Grozdanovic et al. 2018). The efficacy of R321 should be tested in chronic models of allergic disease and also in other diseases with high CCL11 levels in order to evaluet its clinical efficacy (Pease and Williams, 2019).

Minocycline treatment can significantly reduce the amounts of several inflammatory factors, including CCL11 (and CCL2, MCP-5, IL-6, and IL-10) and, therefore, this drug has

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potent anti-inflammatory and neuroprotective properties in rodent models of Huntington's, Parkinson's, Alzheimer's and motor neuron disease (Garwood et al. 2010).

The glycosaminoglycan heparin has anti-inflammatory activity and is exclusively found in mast cells, which are localized within airway smooth muscle (ASM) bundles of asthmatic airways. Interleukin -13 induces the production of multiple inflammatory mediators from ASM including CCL11 (Kanabar et al. 2008). Inhibition of IL-13-dependent CCL11 release by heparin involves but does not depend on sulphation, though the loss of N-sulphation reduced the attenuating activity, which could be restored by N-acetylation (Kanabar et al. 2008).

In vitro studies have shown an inhibitory effect of glucocorticosteroids on CCL11 production although there are few in vivo studies. The use of glucocorticosteroids to inhibit CCL11 mRNA expression was studied by Jahnsen et al. (1999) who examined transcript levels and chemotactic activity of CCR3-binding chemokines in nasal polyps. Treatments with glucocorticosteroids reduce mRNA levels in polyps to levels that are found in turbinate mucosa for all chemokines (Jahnsen et al. 1999). Whether this result was caused indirectly via extracellular mediators that regulate chemokine production or by a direct effect of glucocorticoids could not be determined. Nevertheless, glucocorticoids may inhibit directly cytokine-induced production of CCL11 (and MCP-4 and CCL5) in epithelial cells in vitro (Stellato et al. 1997; Lilly et al. 1997).

Interestingly, the detrimental effects of CCL11 suppressing hippocampal neurogenesis can be attenuated by supra-lactate threshold exercise, hence supporting the benefits of exercise on the aging brain (E L et al. 2014).

CONCLUSION

Increased CCL11 production in the course of immune-mediated inflammatory conditions may play a role in age-related cognitive decline, schizophrenia, mood disorders,

Alzheimer's disease, OCD and ASD. Plasma levels of CCL11 are increased not only in schizophrenia and aging-related cognitive impairments, but also in some patients with mood disorders and premenstrual syndrome. Increased CCL11 levels including in old age are associated with neurodegeneration, reduced neurogenesis and with an increased risk of Alzheimer's disease. Increased CCL11 also plays a role in neuroinflammatory disease including multiple sclerosis. Therefore, increased CCL11 is a new drug target for the treatment and prevention of those disorders. The production of CCL11 may be attenuated by glucocorticoids, minocycline, resveratrol, CCR3 antagonists (R321) and anti–CCL11 antibodies including CAT-212 and CAT-213. In sum, these findings have real encouraging results for future treatment of all conditions with CCl11 involvement.

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Conflict of interest

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Author's contributions

All the contributing authors have participated in the manuscript. MI and MiMa designed the study. All authors (MI, MiMa, MaMu, AM and ZA) contributed to the interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.

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