CCL-11 or Eotaxin-1

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CCL-11 (eotaxin) is a chemokine with an important role in allergic conditions. Recent evidence indicates that CCL-11 plays a role in brain disorders as well. CCL-11 is rapidly transported from the blood to the brain through the blood-brain barrier. Age-related increases in CCL-11 are associated with cognitive impairments in executive functions and episodic and semantic memory, and therefore, this chemokine has been described as an "Endogenous Cognition Deteriorating Chemokine" (ECDC) or "Accelerated Brain-Aging Chemokine" (ABAC).

brain, behavior, cytokines, CCL-11, eotaxin

1. Introduction

One of those chemokines, namely CCL-11 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 [1].

CCL-11 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 [2][3] (Tables 1 and 2).

Table 1. Cells producing CCL-11.

Cells Producing CCL-11 [1][2][3]
Eosinophils
Macrophages
T and B-cells
Fibroblasts
Endothelial cells
Epithelial cells

Cells Producing CCL-11 [1][2][3]
Chondrocytes
Microglia
Keratinocytes
Smooth muscle cells

Table 2. Cytokines and other molecules inducing CCL-11.

Cytokines and Other Molecules Inducing CCL-11	References
Th-2 cytokines	[1] (Teixeira AL et al., 2018) [2] (Sirivichayakul S et al., 2018) [3] (Kindstedt E et al., 2017)
Interleukin IL-4	
Interleukin IL-10	
Interleukin IL-13	
Complement factors	
Immune complexes	

CCL-11 is transported from the blood to the brain through the Blood-Brain Barrier (BBB) and also synthesized by microglia [4]. Furthermore, there is some evidence that CCL-11 is associated with aging and reduced neurogenesis [5]. Increased levels of CCL-11 have been detected in numerous neuro-inflammatory disorders such as multiple sclerosis [6], as well as neurodegenerative and neuroprogressive disorders including Alzheimer's disease [1] and psychiatric illnesses including major depression, bipolar disorder and schizophrenia [1][4][6][7][8]. Moreover, increased CCL-11 levels are also associated with neurocognitive deficits in aging, neurodegenerative disorders and major psychiatric disorders such as schizophrenia [4]. This is important, because the association between CCL-11 and hippocampal damage in aging may be important to understand the pathophysiology of Alzheimer's disease and old-age depression [5][9]. This paper aims to review the associations between CCL-11 and psychiatric disorders and its possible role as an immune biomarker in those disorders.

2. CCL-11 and CCR3 in Allergic Inflammation

Chemokine Receptors (CCRs) can bind to different ligands (CCLs), and chemokines can interact with more than one receptor [10]. The MCP (Monocyte Chemoattractant Protein) family of chemokines binds most often to CCR2, but MCP-2, MCP-3 and MCP-4 can also interact with CCR1 and CCR3 [10]. CCL-11 shows very high homology

with the MCP family [11] and CCL-11 signals via the chemokine receptor CCR3 [12]. This receptor is expressed on eosinophils, basophils and Th-2-type lymphocytes, making it an attractive target for allergic disease therapies [12] [13]. CCL-11, CCL-24 (eotaxin-2) and CCL-26 (eotaxin-3) all bind to CCR3 [14]. There is some evidence that high concentrations of CCL-11 are sufficient to activate CCR2 in chemotaxis assays and that substimulatory concentrations of CCL-11 can antagonize MCP-1 activity at CCR2, indicating that CCL-11 behaves as a partial agonist at CCR2 [15]. This is in contrast with Ogilvie et al. (2001) who described CCL-11 as a natural antagonist of CCR2 and an agonist of CCR5 [16]. CCL-11 shows a low affinity for binding with CXCR3 (C-X-C chemokine Receptor 3) expressed on Th-1 cells, but it is postulated that this binding can play a role in impaired Th-1 response in pathological conditions [17]. CCL-11 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 [18][19]. In 1994, CCL-11 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 [20].

Allergic diseases can be caused by complex interactions between Th-2 cells, mast cells, basophils and eosinophils, which all express CCR3 [21][22]. 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 at least in part through the expression of CCR3, which interacts with CCL-11, allowing the recruitment of basophils, eosinophils and mast cells [23]. CCL-11 plays a role in the pathogenesis of allergic airway diseases, inflammatory bowel disorder disease and gastro-intestinal allergic hypersensitivity [23]. Garcia et al. (2005) confirmed the role of CCR3 and CCL-11 (as well as CCR4, CCR8) in allergic inflammation using in vitro/in vivo experimental studies and clinical studies in patients with asthma [24]. The binding of CCL-11 (but also CCL24 and CCL26) to CCR3 is involved in the development of asthma symptoms [14].

Due to the significant role of CCR3 in allergic diseases, research has focused on treatments with chemokine receptor antagonists [25]. 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 [21].

3. CCL-11, the Blood-Brain Barrier and the CNS

CCL-11 is transferred from the blood to brain tissues with a slow phase of influx prior to the rapid phase [26]. The striatum shows an early rapid uptake phase, in contrast to other regions, which present with a delayed uptake phase [26]. CCL-11 may have biphasic effects with neuroprotective and neurotoxic effects, which are detected at physiological and pathological levels of this chemokine, respectively [26]. The same authors also concluded that CCL-11 does not cause a disturbance in the BBB [26]. Nevertheless, CCL-11 may downregulate, in a concentration-dependent manner, the tight junction proteins occludin, zona occludens-1 and claudin-1 in human coronary artery endothelial cells [27], suggesting that CCL-11 may also affect the BBB. In a study that examined patients with schizophrenia, significant associations between increased CCL-11 plasma concentrations and IgA levels directed to claudin-5 (an indicant of BBB breakdown) were found, suggesting that CCL-11 or associated mechanisms may affect the BBB [28].

4. CCL-11: An Endogenous Cognitive Deteriorating Chemokine

Villeda et al. (2011) established that, in animal models, age-associated rises in CCL-11 are associated with deficits in cognitive functions due to decreased neurogenesis and diminished hippocampal-related learning and memory. Young mice administered CCL-11 developed decreased adult neurogenesis in addition to diminished memory and learning, hence identifying CCL-11 as a chemokine that decreases hippocampal functions with increasing age [5]. However, another study could not find a direct effect of CCL-11 on neuronal cells, but established that CCL-11 promotes microglial migration and activation with subsequent production of ROS, which leads to glutamate-induced neuronal cell death [29]. Baruch et al. (2013) showed that a local (choroid plexus epithelium) shift toward Th-2 (T-helper 2) activation initiates IL-4 and subsequently CCL-11 production in association with cognitive deficits [9]. Thus, based on these findings and those of Villeda and Baruch, it may be concluded that age-related increases in CCL-11 may have detrimental effects on central neuronal functions [30]. The latter authors also confirmed that with age, CCL-11 levels rise in both plasma and Cerebral Spinal Fluid (CSF) and also in different neurodegenerative diseases [31].

Peripheral CCL-11 levels increase with age, and people with cognitive impairments tend to present with higher plasma CCL-11 levels than those without [30]. This suggests that CCL-11 could be a means of predicting cognitive impairments in older individuals [32]. In normal healthy volunteers, CCL-11 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) [4]. More specifically, higher serum levels of CCL-11 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 [4]. Moreover, CCL-11 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 the task strategy employed by the central executive and executive working memory ability, and One-Touch Stockings of Cambridge (OTS), which probes spatial planning [4]. Moreover, age and CCL-11 have similar effects on all those neuro-cognitive tests, while CCL-11 is a partial mediator of the effects of age on these tests [4]. Furthermore, a "super-variable" comprising both age and CCL-11 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 CCL-11 is an Endogenous Cognition Deteriorating Chemokine (ECDC) or "Accelerated Brain-Aging Chemokine" (ABAC) [4].

5. CCL-11 in Schizophrenia

Schizophrenia (SCZ) is a chronic psychiatric disorder characterized by neuroprogression, and its aetiology is multifactorial, with genetic and environmental components [33][34]. 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 [33][34][35][36].

CCL-11, as well as other cytokines/chemokines (including CCL-2, CCL-17, CCL-22) are significantly higher in schizophrenic patients as compared with controls [37]. Increased CCL-11 levels show a negative correlation with telomere length and grey matter volume [38]. Combining CCL-11 with four other biomarkers (namely sTNF-R1, sTNF-R2, IL-10 and IL-4) allows predicting the diagnosis of schizophrenia with a sensitivity of 70.0% and a specificity of 89.4% [39]. Frydecka et al. (2018) observed that schizophrenia is accompanied by simultaneous increases in CCL-11 and CCL-2, while increases in both chemokines are known to cause more severe age-related deficiencies in cognitive functions [40]. Recently, it was shown that a combination of CCL-11 with IL-1, IL-1RA, TNF-α, sTNF-R1, sTNFR2 and CCL-2 predicts deficit schizophrenia with a bootstrapped (2000 bootstraps) area under the receiver operating curve of 0.985 [41]. Increased levels of CCL-11 coupled with increased IL-6 and Dickkoph-1-related protein (DKK1) also predict a non-response to treatment with antipsychotics [42].

Most importantly, in schizophrenia, increased levels of CCL-11 strongly impact many neurocognitive tests [2]. Sirivichayakul et al. (2018) established that CCL-11 was highly significantly associated with impairments in many CERAD and CANTAB tests including probes of semantic and episodic memory, as well as executive functions [2]. For example, CCL-11 alone explained 16.0% of the variance in the Verbal Fluency Test (VFT) results and 11.0% of the variance in an index of semantic memory [2]. Interestingly, also formal thought disorders, a key symptom of schizophrenia, were significantly associated with increased levels of CCL-11 [2]. Another study observed highly significant associations between increased CCL-11 levels and cognitive impairments in attention, working memory, episodic and semantic memory and executive functions [41].

Moreover, increased CCL-11 plasma levels are also associated with increased severity scores on different symptom domains of schizophrenia [1][2][41][42][43]. First, in schizophrenia, positive correlations were established between increased CCL-11 levels and negative symptoms [1][3][41][43], but also with psychosis, hostility, excitation, mannerism and psychomotor retardation [2][41][42]. The impact of CCL-11 on these symptoms may be increased by combining CCL-11 levels with other neurotoxic compounds including tryptophan catabolites such as picolinic and xanthurenic acid [4].

Therefore, it was concluded that CCL-11 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 [36]. 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 [36].

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