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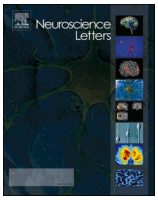

Decreased levels of cytokines implicate altered immune response in plasma of moderate-stage Alzheimer's disease patients

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain. However, increasing evidence suggests that the pathogenesis of the disease is associated with peripheral inflammation. Here, we aimed to determine plasma concentrations of multiple cytokines and chemokines from moderate-stage AD and age-matched controls. Changes in a total of 20 cytokines and chemokines in plasma of moderate-stage AD were evaluated by using quantitative microarray. Six of them, namely MCP-1, MIP-1a, MIP-1b, MMP-9, RANTES, and VEGF, were found to be significantly reduced in moderate-stage AD patients (n = 25) in comparison to age-matched and non-demented controls (n = 25). However, GM-CSF, GRO-α/β/γ, IFN- γ, IL-1α, IL-1β, IL-10, IL-12 p70, IL-13, IL-2, IL- 4, IL-5, IL-6, IL-8, and TNF-α showed no significant differences between the patient and control groups. On the contrary to previous early-stage AD studies that show increased plasma cytokine/chemokine levels, our results indicate that inflammatory plasma molecules are reduced in moderate-stage AD. This finding points out the reduced immune responsiveness, which is known to be directly correlated to the degree of AD.

1. Introduction

Alzheimer's disease (AD), a progressive and irreversible neurodegenerative disorder, is the most common form of dementia for older adults [1]. AD is characterized by a mental decline with a loss of cognitive skills and memory function [2]. Pathological protein deposits, amyloid-β peptides that form senile plaques, and hyperphosphorylated tau that aggregates into neurofibrillary tangles, have long been suggested to be the main reason for AD [3,4]. Chronic neuroinflammation, including microglial activation and extensive oxidative damage, complement this pathology [4,5]. Recent studies suggest that the pathogenesis of AD is mediated by innate immune system-mediated inflammation [6]. Increased Amyloid-β, which is normally cleared by microglia, can cause over-activation of microglia, resulting in chemokine release and local inflammation [7,8]. When inflammation spreads, it affects amyloid-β clearance and increases tau phosphorylation, and eventually leads to neurodegeneration [9]. Misfolded and aggregated proteins bind to receptors on microglia and astroglia and cause an innate immune response characterized by the release of inflammatory mediators that contribute to disease progression and severity [10].

Neuroinflammation and synapse failure have been linked to the pathogenesis of AD [11]. Neuroinflammation may trigger a cascade of microglial activation, proinflammatory factor production, and neuronal destruction in the preclinical stage of AD [6]. Disruption of the blood–brain barrier permeability, infiltration of peripheral immune cells, and abnormal microglia and astrocyte function might contribute to proinflammatory brain cytokine/chemokine signaling in AD [10]. Based on the results of disruption of the blood–brain barrier, it is reasonable to think that variations in specific inflammatory marker levels in body fluids are associated with shifting distribution between the periphery and CSF [12].

There is substantial evidence that peripheral and central inflammations play a key role in the pathogenesis of AD [13]. Although it is unclear how systemic inflammation affects the disease process in the

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brain, studies suggest that peripheral and central inflammation are closely linked [14]. The inflammatory biomarkers in the peripheral and cerebrospinal fluids (CSF) of the patients with mild cognitive impairment and AD were found to be significantly changed in clinical investigations [13,15]. Techniques for AD diagnosis, such as CSF amyloid-β and tau levels, and also structural and functional MRI and amyloid imaging, are more invasive than peripheral cytokine measurements [16]. Peripheral inflammatory markers can cross the blood–brain barrier and have neuromodulatory effects through regulated transport processes. Hence, the measurement of peripheral cytokines could be useful biomarkers for detecting AD progression [16].

Cytokines, including proinflammatory and anti-inflammatory cytokines, are crucial participants in the neuroinflammation process, and they are produced by astrocytes, *T*-lymphocytes, and microglial cells [17]. Many pro-anti inflammatory cytokines have been identified in neuroinflammation studies with AD. anti-inflammatory cytokines stimulate regulatory responses to prevent neuronal damage caused by proinflammatory cytokines, which promote inflammatory responses [17]. In accordance with this, in a study with aged transgenic mice, amyloid-β was associated with increased proinflammatory cytokines [18]. One of the studies with peripheral blood mononuclear cells has found higher cytokine levels in patients with mild cognitive decline (MCI) than in AD patients or the control group [19], while another study reported significantly lower levels of cytokines in severe AD patients [20]. Increased inflammatory markers in the peripheral blood are related to a higher risk of dementia later in life, suggesting that peripheral inflammation can occur before clinical symptoms appear [21].

Chemokines are chemotactic cytokines that were discovered to regulate immune cell migration to sites of inflammation [22]. Chemokines, in particular, may play a vital role in bi-directional immunological communication between the periphery and the central nervous system (CNS), where they mediate inflammatory responses and immune cell trafficking [23]. The levels of chemokines and their receptors are altered in patients with AD's plasma, CSF, and brain tissue. They contribute to neuroinflammation in AD by recruiting peripheral blood monocytes and triggering glial cell activation [2]. They also affect the blood–brain barrier permeability [24].

Dysregulation of the immune cascade is evident in aging and may cause pathological consequences. There are many studies on the effects of the peripheral immune system on cognitive aging [23,25,26,27,28]. Recent studies suggest that the peripheral environment actively communicates with the CNS, and thus immune markers in the blood may not only affect the peripheral aging process but also directly affect the CNS by exacerbating cognitive decline [29,30,23].

In the literature on this subject, the levels of cytokines and chemokines have generally been measured in plasma and CSF. Also, studies were mainly conducted with individuals with early-stage AD and mild cognitive impairment. While the results for many cytokines and chemokines generally show increased plasma and CSF levels in the early stage of the disease, there are also inconsistent results [31–34]. In our research, we studied plasmas of moderate-stage AD. One of the reasons for this was that plasma cytokine level studies were generally biomarker studies, and therefore they were studied with mild-stage AD and MCI groups. However, we aimed to elucidate the cytokine plasma level differences in the moderate-stage group, which is 30.3 % of the existing Alzheimer's patients [35], and the effect of these cytokine differences on the immune response with the progression of the disease as a contribution to the mild-stage studies in the literature.

2. Materials and methods

2.1. Ethical statement

The Clinical Research Ethics Committee (ATADEK) at Acibadem Mehmet Ali Aydınlar University approved this research (No: 2016/8–34, Date: 12 May 2016). All control subjects and patients and/or their caregivers' written informed consent.

2.2. AD diagnosis and collection of plasma samples

The study included all instances of AD that met the criteria of "The National Institute of Neurologic, Communicative Disorders, and Stroke–AD and Related Disorders Association (NINCDS-ADRDA)" [36]. The mini-mental scale examination (MMSE) was used to determine the severity of dementia in patients. In this study, subjects were chosen as moderate-stage AD patients. The Maltepe University Hospital, the Bezmialem University Hospital, and the Istanbul Capa University Hospital in Istanbul, Turkey, collected blood samples from moderate-stage AD patients and age-matched healthy controls. Exclusion criteria for the age-matched control group included neurological, psychiatric, and severe physical illness. When the blood samples from healthy control volunteers were collected, they had no cognitive or mental health issues. Furthermore, they were not using medications to treat AD or other forms of dementia. 25 healthy control and 25 moderate-stage AD subjects/or their caregivers who read and signed the consent form donated the peripheral blood samples.

2.3. Measurement of cytokines

Blood samples were collected from controls and AD patients in lithium-heparin tubes. Samples were centrifuged at 3000 rpm for 10 min, and obtained plasma was aliquoted and stored at −80 °C until the analysis. In this study, we used a commercial quantitative microarray (Quantibody Human Cytokine Array 1, RayBiotech, Inc., Norcross, GA) to profile the cytokine expression pattern in the plasma samples. We used four slides and each slide contained both plasmas of AD patients and age-matched controls and positive and negative control samples provided by the kit. A quantitative immuno-microarray measures the concentrations of 20 cytokines in plasma samples; GM-CSF, GRO-α/β/γ, IFN- γ, IL-1α (IL-1 F1), IL-1β (IL-1 F2), IL-10, IL-12 p70, IL-13, IL-2, IL- 4, IL-5, IL-6, IL-8 (CXCL8), MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL4), MMP-9, RANTES (CCL5), TNF-α and VEGF-A. We followed the manufacturer's protocol and used their service to analyze the results.

2.4. Statistical analysis

We used SPSS 26.0 (SPSS Inc., USA) for statistical analysis and GraphPad Prism 9.0 to create the graphs (GraphPad Software Inc., USA). The normality of data obtained from each study group was tested with the Shapiro-Wilk normality test. In accordance with the results, normally distributed values were tested by independent T-test while non-normally distributed values were tested with Mann-Whitney U.

We also performed bioinformatic analysis to further investigate significantly altered cytokines. To this end, relationships between cytokines were investigated through protein–protein interactions via the STRING online tool (version 11.5) [37]. Also, Gene Ontology (GO), WikiPathways, and Reactome pathways were used to reveal in which functions or pathways these altered proteins were significantly enriched.

3. Results

3.1. Patient and control demographics

A total of 50 participants were included (AD = 25 controls = 25). The average age of AD is 74.5 years, and the control group is 65.4 years. In both groups, 44 % of participants are females. The participants' demographic and clinical features are summarized in Table 1.

3.2. Cytokine measurement

Twenty cytokines scans showed that six cytokines were significantly different in AD and control plasmas, while fourteen cytokines did not

Table 1
Demographic and clinical characteristics of AD and control.

Variable	Control (n = 25)	AD (n = 25)
Male/Female	14/11	14/11
Age	65.8 ± 7.02	73.2 ± 5.0
MMSE (score/30)	/	16.6 ± 3.3

change significantly. GM-CSF, GRO-α/β/γ, IFN- γ, IL-1α, IL-1β, IL-10, IL-12 p70, IL-13, IL-2, IL- 4, IL-5, IL-6, IL-8, and TNF-α were not significantly altered between AD and control groups. However, the levels of MCP-1, MIP-1α, MIP-1β, MMP-9, RANTES, and VEGF were significantly lower in AD than in the control. The scanned image and box-plot graphs for six significantly decreased cytokines are shown in Fig. 1.

3.3. Statistical analysis

In the statistical analysis, we first used the Shapiro-Wilk normality test, and as a result, only RANTES showed normal distribution. Then, we tested RANTES *(t(43) = 2.79, p = 0.008, d = 0.83)* with an independent *t*-test and found that it showed significant difference. Finally, we tested 19 non-normally distributed cytokines with Mann-Whitney U and found that MCP-1*(U = 179, p = 0.025, r = 0.32)*, MIP-1α *(U = 101, p = 0.001, r = 0.49)*, MIP-1β *(U = 90, p = 0.001, r = 0.52)*, MMP-9 *(U = 145, p = 0.009, r = 0.38)* and VEGF-A *(U = 184, p = 0.05, r = 0.28)* showed significant differences (Table 2).

To reveal the enrichment of significantly changed six cytokines, we also used the String online tool (version 11.5) (Fig. 2). Gene Ontology (GO), REACTOME (RP), and WikiPathways (WP) results obtained from the STRING analysis of six significantly changed cytokines are shown in

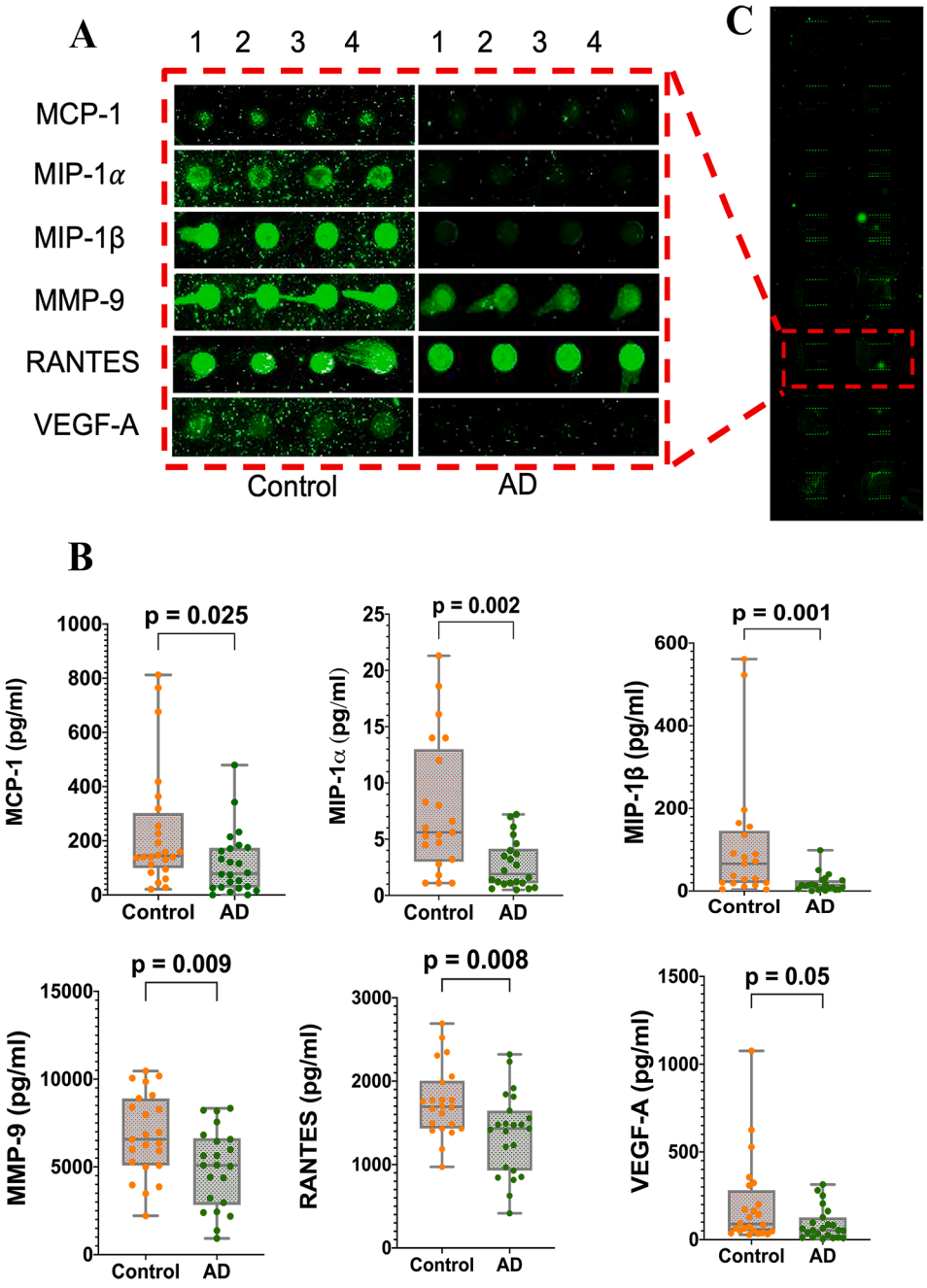

Fig. 1. (A) Fluorescence intensity from the laser scanner. (B) Levels of MCP-1, MIP-1α, MIP1β, MMP-9, RANTES, and VEGF in controls and AD.

Table 2
Plasma levels of 20 cytokines. The data is presented as average, minimum (Min) and maximum (Max) values. [1]Mann-Whitney U, [2]Independent *t*-test.

Cytokines (pg/ml)	Control	AD	p	AD/ Control
IL-1α	1026.8 (0.00–5109)	670.2 (55.5–2828.3)	0.648 [1]	↓
IL-1β	212.5 (6.7–1630.7)	61.7 (0.00–386.6)	0.121 [1]	↓
IL-2	1049.9 (0.00–4966.9)	1456.1 (30.7–6979.6)	0.93 [1]	↑
IL-4	137.3 (0.00–1696.6)	178.1 (0.00–992.4)	0.641 [1]	↑
IL-5	1150.9 (0.00–11463.6)	1238.7 (0.00–8445.1)	0.547 [1]	↑
IL-6	193.7 (0.00–1352.3)	273.9 (0.00–1587.2)	0.691 [1]	↑
IL-8	176.9 (7.6–1264.1)	236.3 (0.00–2562.7)	0.29 [1]	↑
IL-10	505.6 (0.00–1488.3)	753.7 (0.00–9163.5)	0.281 [1]	↑
IL-12p70	20 (0.00–99)	18.8 (0.00–164.3)	0.387 [1]	↓
IL-13	258 (21.3–1052.4)	394 (0.00–3101.9)	0.265 [1]	↑
GM-CSF	81.3 (0.00–280.7)	106.4 (0.00–659.3)	0.478 [1]	↑
GRO-α/β/γ	1806.5 (0.00–9270.1)	1546.2 (0.00–6910.6)	0.662 [1]	↓
IFN- γ	190.4 (9.6–1589)	155.5 (0.00–821.1)	0.432 [1]	↓
MCP-1	234.2 (21.2–812)	116.6 (0.00–479.4)	**0.025** [1]	↓
MIP-1α	8.7 (1.1–30)	2.8 (0.5–7.2)	**0.002** [2]	↓
MIP-1β	110.5 (3.7–561.3)	18.4 (0.00–98.7)	**0.001** [1]	↓
MMP-9	7270.8 (2217.3–17504.3)	4952.6 (928.7–8341.4)	**0.009** [1]	↓
RANTES	1747.8 (972–2690.4)	1364.7 (415.4–2321.5)	**0.008** [2]	↓
TNF-α	312.8 (31.2–1728.1)	129.9 (5.9–706.6)	0.132 [1]	↓
VEGF-A	197.1 (27.9–1075.5)	89 (3.7–314.3)	**0.05** [1]	↓

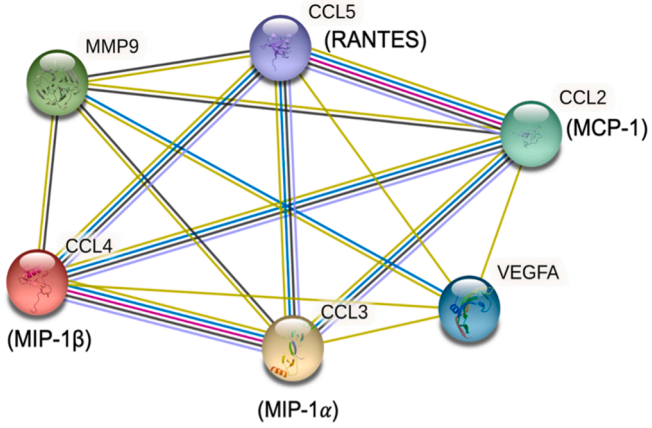

Fig. 2. Protein-protein interaction map of six significantly changed cytokines, constructed with STRING [14].

Fig. 3. As a result of our analysis, we saw that these cytokines are highly interacting proteins. The top five significant biological processes in which six cytokines were involved are as follows: monocyte chemotaxis, lymphocyte chemotaxis, granulocyte chemotaxis, regulation of leukocyte chemotaxis, and positive regulation of Erk1 and Erk2 cascade, as shown in Fig. 3. Also, the top five significant molecular functions are CCR1 chemokine receptor binding, CCR5 chemokine receptor binding, chemokine activity, cytokine activity, and cytokine receptor binding, as shown in Fig. 3. In addition, the pathways including all of the six significantly changed cytokines are the IL-18 signaling pathway (WP), signaling by interleukins (RP), and signal transduction (RP).

4. Discussion

Dysregulation of the immune cascade is suggested as a key component of aging and has been linked to negative pathological outcomes [23]. AD is the leading neurodegenerative disease that is not considered a single unified condition but a complex syndrome. Recently, there has been a lot of discussion about how neuroinflammation plays a role in the progression of AD [38]. AD inflammation from early to late-stage significantly contributes to AD pathogenesis [39,40]. Also, studies suggest that inflammation as cytokine dysregulation precedes the clinical development of AD [41]. Inflammatory pathogenesis is primarily based on the presence of activated immune cells and proinflammatory cytokines [39]. The peripheral innate immune responses, cytokines in the central nervous system (CNS), are important regulators of neuroinflammation [38]. At this time, it appears that a chronic inflammatory state is responsible for the activation of glial cells, resulting in a more persistent inflammatory state and neurodegeneration [42]. Given the significance of neuroinflammation in AD, it is crucial to evaluate the impact of peripheral inflammation on the progression of AD [38].

Proinflammatory cytokines are involved in nervous and peripheral systems in AD [43,44]. The immune system cells secrete chemokines that are small signaling proteins and chemotactic cytokines. They regulate other cells' movement in response to the chemical stimulus [45]. Chemokines are secreted from immune cells such as monocytes, T cells, and B cells but also are found in AD brain because they migrate from the periphery through the blood–brain barrier [46]. Chemokines, in particular, may play a vital role in bi-directional immunological communication between the periphery and the CNS [23]. There are studies with chemokine levels in the brain and different body fluids such as plasma, CSF, peripheral mononuclear cells (PBMC), and blood–brain barrier models, which differ in AD compared to controls [47,48,12,49,11].

Monocyte chemoattractant protein-1 (MCP-1) chemokine, which we found significantly less in AD group, directs the migration and infiltration of monocytes, microglia, and memory *T*-cells to the site of injury and infection in various disorders [50]. In studies with early-stage AD and mild cognitive impairment patients, high MCP-1 levels in plasma have been associated with cognitive impairment [51]. However, it has also been shown that plasma MCP-1 levels decrease with the progression of the disease in mild cognitive impairment and mild AD [52]. There are studies demonstrating that MCP-1 deficiency causes accelerated AD pathology because it leads to an increased level of amyloid-β in the brain and impaired microglial accumulation [30,53]. Considering the possible neuroprotective role of MCP-1, the increase of MCP-1 in the early stage may be related to the prevention of the amyloid-β plaque formation by glial cells to neuronal death. However, with the disease's progression, an insufficient immunological response can cause the death of neurons, and cytokines and chemokines production decrease [52]. There are also studies about the differences of MCP-1 in other neurodegenerative diseases. For example, a study suggested that MCP-1 levels in CSF positively correlate with PD progression [54]. In other neurodegenerative disorders, the levels of MCP-1 have been found to be reduced in Multiple Sclerosis(MS) patients, and were found to increase in Amyotrophic lateral sclerosis (ALS) patients [55,56]. Besides, age-related immune system remodeling is thought to be affected by cytokine dysregulation [57]. In a study of asymptomatic aging adults, increase in plasma MCP-1 levels were related to a decline in memory [23]. In this research, we found a reduced plasma level of MCP-1 in moderate-stage AD.

Macrophage inflammatory proteins (MIP) are one of the chemokines. MIP-1α and MIP-1β, known as CCL3 and CCL4, respectively, are the two major types in humans. They perform various biological functions such

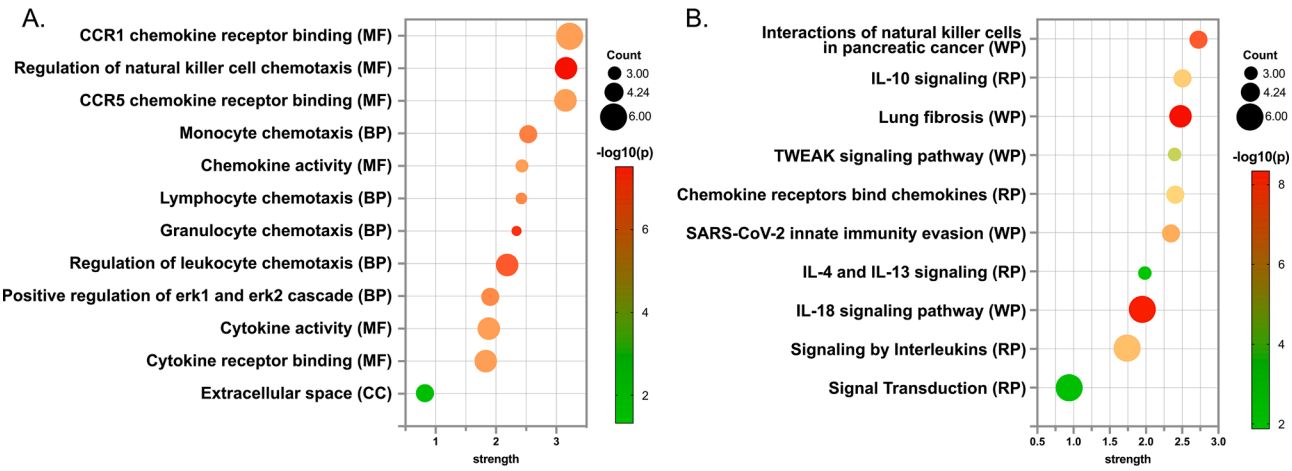

Fig. 3. Enrichment analysis of six significantly changed cytokines in plasma of the moderate stage AD patients. A. GO and B. WP and RP results were given as bubble plot graphs. The y axis represents either GO (MF: Molecular function, BP: Biological process, CC: cellular component) or WP/RP terms, while the × axis indicates strength. Circle size represents the count, and the color reflects the adjusted p-value. The analysis was carried out in STRING [14], visualization performed in Graphpad Prism (version 9.2) and inkscape software (version 1.0.1).

as recruitment of inflammatory cells, wound healing, inhibition of stem cells, and maintenance of effector immune response [58]. It has been shown that the CCL3 gene, expressed by neurons and microglia, is upregulated in the postmortem brains of AD and in experimental models of both amyloid-beta and tau deposition [59]. In addition, studies show that MIP-1α expression is increased in T cells of AD. This increased expression results in increased transendothelial migration of T cells across the blood–brain barrier [60]. Although these high levels of MIP in relation to AD pathogenesis, a study found that MIP-1α and MIP-1β levels (in CSF) are not associated with the amyloid status [61]. However, study showed there is a negative association between the CSF amyloidogenic nanoplaque levels and MIP-1α and MIP-1β. Given their protective role, levels of cytokines were found to be negatively correlated with AD progression [61]. In other neurodegenerative disorders, the CSF levels of MIP-1α increased in patients with ALS and MIP-1β reduced in patients with MS [56,62]. Furthermore, MIP-1α levels were found to be significantly reduced in the aging group compared to young adult controls [63]. We found levels of both MIP-1α and MIP-1β were decreased in moderate-stage AD plasmas. We are speculating that decreased levels of MIP-1a and MIP-1β that we found in moderate-stage AD, might be related with reduced protection against AD pathogenesis which is consistent with previous reports.

RANTES (Regulated upon activation normal *T*-cell expressed and secreted) is a chemokine that regulates cell migration and circulation of classical lymphoid cells such as T cells, monocytes, basophils, eosinophils, natural killer cells, dendritic and mast cells [64]. It also induces the migration of mononuclear phagocytes across the blood–brain barrier to sites of inflammation [65]. RANTES has been associated with preventing amyloid-related death. RANTES levels increased in microglia and cerebrovascular tissue during the initial phase after amyloid exposure but decreased after prolonged exposure [66,67]. Studies show that RANTES level increases in AD patients' brains and decreases in serum [68,69]. Controversially, another study reported high RANTES plasma levels in the early AD group that was negatively correlated with disease duration and age [70]. They indicate that the increased plasma RANTES levels in early AD show an early protective peak of inflammation against beta-amyloid oligomeric peptides [70]. Some studies show increased RANTES levels in PBMC from patients with AD relative to controls [71]. However, in the study with the human blood–brain barrier model with PBMC, the RANTES level is decreased in moderate-stage AD patients compared to mild AD patients [48]. They found that RANTES level is decreased during the progression of AD, which may be related to its neuroprotective role [48]. These interesting results highlight the importance of including the different stages of AD in the study groups. Additionally, the studies found that serum RANTES levels in patients with PD were higher than in controls and reduced in patients with MS [72,73,62]. We found the decreased level of the RANTES in moderate-stage AD plasma, is consistent with that of the studies which reported a decrease. Thus, we can infer that as the disease progresses the immune response of RANTES to increased amyloid levels and prolonged amyloid exposure is decreased in AD.

Matrix metalloproteinases (MMPs) play roles in regulating various biological processes under pathological and normal conditions, including embryonic development, inflammatory diseases, cancer, and neurodegenerative diseases such as AD [74]. MMPs can degrade and remodel the extracellular matrix to regulate many signaling and homeostatic systems [75]. Inflammatory cells in the brain are activated by amyloid-β oligomers, and then microglia change their form, move near plaques and release proinflammatory cytokines and MMPs. Afterward, MMPs degrade amyloid-β and aggravate inflammation and neuron death [76]. Studies are showing that MMPs take a part in the inflammatory process of AD. MMP-9 is elevated in the brain, especially in astrocytes surrounding amyloid-β plaque which implicates its role in amyloid-β degradation and its clearance in the brain [77]. In addition to brain studies, MMP-9 plasma level was elevated in AD [78,32,79]. Another study found that MMP-9 levels in CSF samples from controls with risk markers for AD (such as low amyloid-β, high tau, and the ApoE4 genotype) were significantly higher than in controls without these markers [80]. However, there are also studies showing the beneficial effects of MMP-9 [81]. One study found a positive correlation between the mRNA level of MMP-9 and cognitive tasks [82]. Some previous studies suggested that MMP-9 could slow the progression of amyloid-β pathology [83,84]. Also, a study found that the MMP-9 levels in CSF decreased in patients with ALS, and increased in MS [76]. Given that, we speculate the protective effect of MMP-9 against amyloid-β might be impaired due to the reduced plasma level of MMP-9 that we detected in moderate-stage AD.

Vascular endothelial growth factor (VEGF, also known as VEGF-A), a signaling protein, is a physiological regulator of blood vessel growth, oxygen and glucose delivery, and blood–brain barrier integrity. It supports vascular and neuronal functions [85]. The VEGF-A signaling pathway is linked to angiogenic, neurotropic, and cytoprotective processes [86]. The high levels of VEGF-A in preclinical AD models are associated with a neuroprotective effect [87,88]. There are inconsistent results in studies with VEGF-A levels in AD [85]. However, among the studies focusing on the neuroprotective effect of VEGF-A, it has been

shown that the level of VEGF-A in AD serum is decreased [89,25]. In addition, a study shows that memory impairment and amyloid-β accumulation are reduced as a result of treating APP transgenic mice with VEGF-A [90]. It is thought that the elevation of VEGF-A may be protective against the pathological damages of AD with vascular improvements. Less cognitive decline and hippocampal atrophy have been associated with higher VEGF-A levels. It has been suggested that the neuroprotective effect of VEGF-A is strongest in the presence of AD biomarkers and that angiogenic factors may be critical in individuals showing early hall-marks of AD [91]. Also, studies suggest that VEGF-A levels in CSF is increased in patients with PD and ALS [92,56]. In our study, we found decreased VEGF-A levels in moderate-stage AD patients' plasma. Therefore, this decrease might have contributed to a loss of the protective effect of VEGF-A against AD pathogenesis.

Lastly, we examined the relationship between the aforementioned six significantly changed cytokines; we found that all of them are related to the IL-18 signaling pathway via WikiPathways [93]. IL-18, a member of the IL-1 cytokine family, activation leads to producing and releasing cytokines, chemokines, and cellular adhesion molecules [94,95]. IL-18-mediated signaling is essential for cytokines involved in host defense, inflammation, and tissue regeneration. The induction of various inflammatory factors involved in both innate and adaptive immune responses is mediated by the IL-18 signaling [96]. Several studies have demonstrated the presence of IL-18 and its receptor subunit in neurons confirming its ability to cross the blood–brain barrier and its role in neurophysiological and neuropathological diseases [97]. There are studies in which IL-18 level was measured in plasma and brain in individuals with AD [98,99]. A study reported that, while the plasma IL-18 level was highest in mild-AD patients, this level was low in moderate-AD patients, but there was no significant difference between severe-AD and healthy-aged control [39]. In another study conducted with plasma IL-18 levels, IL-18 level was higher in the MCI group than AD [98]. The high levels of IL-18 found in both central and peripheral levels in AD may reflect an unbalanced response that results in an exacerbated activation of innate immune cells, which in turn may promote a dysregulated, persistent inflammatory cascade, becoming a driving force in the chronic progression to irreversible neurodegeneration [100].

5. Conclusion

In conclusion, we found six cytokine levels, namely MCP-1, MIP-1a, MIP-1b, MMP-9, RANTES, and VEGF, are lower in plasmas of moderate-stage AD patients than their age-matched healthy controls. As the severity of AD increases, the decrease in cytokine levels is associated with a decreased immune response to many stimuli. To summarize, the decreased immune responses for six significantly changed cytokines; decreased *T*-cell activation, protective effect, and amyloid-β clearance. In addition, the decrease in cytokine level may be associated with impaired phagocytic activity, and this impairment can lead to the accumulation of amyloid proteins.

Declaration of Competing Interest

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

Data availability

The authors are unable or have chosen not to specify which data has been used.

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References

[1] R.A. Sperling, P.S. Aisen, L.A. Beckett, D.A. Bennett, S. Craft, A.M. Fagan, T. Iwatsubo, C.R. Jack, J. Kaye, T.J. Montine, D.C. Park, E.M. Reiman, C.C. Rowe, E. Siemers, Y. Stern, K. Yaffe, M.C. Carrillo, B. Thies, M. Morrison-Bogorad, M. V. Wagster, C.H. Phelps, Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimer's Dement. 7 (2011) 280–292, https://doi.org/10.1016/j.jalz.2011.03.003.

[2] A.R. Zuena, P. Casolini, R. Lattanzi, D. Maftei, Chemokines in Alzheimer's disease: new insights into prokineticins, chemokine-like proteins, Front. Pharmacol. (2019) 622, https://doi.org/10.3389/FPHAR.2019.00622.

[3] J.M. Rubio-Perez, J.M. Morillas-Ruiz, A review: Inflammatory process in Alzheimer's disease, role of cytokines, Sci. World J. 2012 (2012), https://doi.org/10.1100/2012/756357.

[4] M.J. Sharman, G. Verdile, S. Kirubakaran, C. Parenti, A. Singh, G. Watt, T. Karl, D. Chang, C.G. Li, G. Münch, Targeting inflammatory pathways in Alzheimer's disease: a focus on natural products and phytomedicines, CNS Drugs. 33 (2019) 457–480, https://doi.org/10.1007/s40263-019-00619-1.

[5] M. Rösler, W. Retz, J. Thome, P. Riederer, Free radicals in Alzheimer's dementia: currently available therapeutic strategies, J. Neural Transm. Suppl. (1998) 211–219, https://doi.org/10.1007/978-3-7091-7508-8_21.

[6] C.S. Liang, C.L. Tsai, G.Y. Lin, J.T. Lee, Y.K. Lin, C.S. Chu, Y.F. Sung, C.K. Tsai, T. C. Yeh, H. Te Chu, M.W. Su, F.C. Yang, Better identification of cognitive decline with interleukin-2 than with amyloid and tau protein biomarkers in amnestic mild cognitive impairment, Front. Aging Neurosci. 13 (2021), https://doi.org/10.3389/fnagi.2021.670115.

[7] M.T. Heneka, M.P. Kummer, E. Latz, Innate immune activation in neurodegenerative disease, Nat. Rev. Immunol. 14 (2014) 463–477, https://doi.org/10.1038/NRI3705.

[8] J.M. Long, D.M. Holtzman, Alzheimer disease: an update on pathobiology and treatment strategies, Cell. 179 (2019) 312–339, https://doi.org/10.1016/J.CELL.2019.09.001.

[9] T.O. Klyucherev, P. Olszewski, A.A. Shalimova, V.N. Chubarev, V.V. Tarasov, M. M. Attwood, S. Syvänen, H.B. Schiöth, Advances in the development of new biomarkers for Alzheimer's disease, Transl. Neurodegener. 11 (2022) 25, https://doi.org/10.1186/S40035-022-00296-Z.

[10] M.T. Heneka, M.J. Carson, J. El Khoury, G.E. Landreth, F. Brosseron, D. L. Feinstein, A.H. Jacobs, T. Wyss-Coray, J. Vitorica, R.M. Ransohoff, K. Herrup, S.A. Frautschy, B. Finsen, G.C. Brown, A. Verkhratsky, K. Yamanaka, J. Koistinaho, E. Latz, A. Halle, G.C. Petzold, T. Town, D. Morgan, M. L. Shinohara, V.H. Perry, C. Holmes, N.G. Bazan, D.J. Brooks, S. Hunot, B. Joseph, N. Deigendesch, O. Garaschuk, E. Boddeke, C.A. Dinarello, J.C. Breitner, G. M. Cole, D.T. Golenbock, M.P. Kummer, Neuroinflammation in Alzheimer's Disease, Lancet. Neurol. 14 (2015) 388, https://doi.org/10.1016/S1474-4422(15)70016-5.

[11] M.V. Lourenco, F.C. Ribeiro, L.E. Santos, D. Beckman, H.M. Melo, F.K. Sudo, C. Drummond, N. Assunção, B. Vanderborght, F. Tovar-Moll, F.G. De Felice, P. Mattos, S.T. Ferreira, R. Maccioni, Cerebrospinal fluid neurotransmitters, cytokines, and chemokines in Alzheimer's and Lewy body diseases, J. Alzheimer's Dis. 82 (3) (2021) 1067–1074.

[12] B.R. Ott, R.N. Jones, L.A. Daiello, S.M. de la Monte, E.G. Stopa, C.E. Johanson, C. Denby, P. Grammas, Blood-cerebrospinal fluid barrier gradients in mild cognitive impairment and Alzheimer's disease: relationship to inflammatory cytokines and chemokines, Front. Aging Neurosci. 10 (2018) 245, https://doi.org/10.3389/FNAGI.2018.00245.

[13] E. King, J.T. O'Brien, P. Donaghy, C. Morris, N. Barnett, K. Olsen, C. Martin-Ruiz, J.P. Taylor, A.J. Thomas, Peripheral inflammation in prodromal Alzheimer's and Lewy body dementias, J. Neurol. Neurosurg. Psychiatry. 89 (2018) 339–345, https://doi.org/10.1136/jnnp-2017-317134.

[14] C. Holmes, C. Cunningham, E. Zotova, J. Woolford, C. Dean, S. Kerr, D. Culliford, V.H. Perry, Systemic inflammation and disease progression in Alzheimer disease, Neurology. 73 (2009) 768–774, https://doi.org/10.1212/WNL.0B013E3181B6BB95.

[15] X.-N. Shen, L.-D. Niu, Y.-J. Wang, X.-P. Cao, Q. Liu, L. Tan, C. Zhang, J.-T. Yu, Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies, J. Neurol. Neurosurg. Psychiatry. 90 (2019) 590–598, https://doi.org/10.1136/jnnp-2018-319148.

[16] K.S.P. Lai, C.S. Liu, A. Rau, K.L. Lanctôt, C.A. Köhler, M. Pakosh, A.F. Carvalho, N. Herrmann, Peripheral inflammatory markers in Alzheimer's disease: a systematic review and meta-analysis of 175 studies, J. Neurol. Neurosurg. Psychiatry. 88 (2017) 876–882, https://doi.org/10.1136/jnnp-2017-316201.

[17] M.A. Rather, A. Khan, S. Alshahrani, H. Rashid, M. Qadri, S. Rashid, R. M. Alsaffar, M.A. Kamal, M.U. Rehman, Inflammation and Alzheimer's disease: mechanisms and therapeutic implications by natural products, Mediators Inflamm. 2021 (2021), https://doi.org/10.1155/2021/9982954.

[18] N.S. Patel, D. Paris, V. Mathura, A.N. Quadros, F.C. Crawford, M.J. Mullan, Inflammatory cytokine levels correlate with amyloid load in transgenic mouse models of Alzheimer's disease, J. Neuroinflammation. 2 (2005) 1–10, https://doi.org/10.1186/1742-2094-2-9.

[19] S. Magaki, C. Mueller, C. Dickson, W. Kirsch, Increased production of inflammatory cytokines in mild cognitive impairment, Exp. Gerontol. 42 (2007) 233–240, https://doi.org/10.1016/J.EXGER.2006.09.015.

[20] G. Sala, G. Galimberti, C. Canevari, M.E. Raggi, V. Isella, M. Facheris, I. Appollonio, C. Ferrarese, Peripheral cytokine release in Alzheimer patients:

correlation with disease severity, Neurobiol. Aging. 24 (2003) 909–914, https://doi.org/10.1016/S0197-4580(03)00010-1.
[21] A. Koyama, J. O'Brien, J. Weuve, D. Blacker, A.L. Metti, K. Yaffe, The role of peripheral inflammatory markers in dementia and Alzheimer's disease: a meta-analysis, J. Gerontol. Ser. A. 68 (2013) 433–440, https://doi.org/10.1093/GERONA/GLS187.
[22] F.H. Epstein, A.D. Luster, Chemokines — chemotactic cytokines that mediate inflammation, N. Engl. J. Med. 338 (7) (1998) 436–445.
[23] B.M. Bettcher, J. Neuhaus, M.J. Wynn, F.M. Elahi, K.B. Casaletto, R. Saloner, R. Fitch, A. Karydas, J.H. Kramer, Increases in a pro-inflammatory chemokine, MCP-1, are related to decreases in memory over time, Front. Aging Neurosci. 10 (2019), https://doi.org/10.3389/fnagi.2019.00025.
[24] W.L. Thompson, W.J. Karpus, L.J. Van Eldik, MCP-1-deficient mice show reduced neuroinflammatory responses and increased peripheral inflammatory responses to peripheral endotoxin insult, J. Neuroinflammation 51 (5) (2008) 1–13, https://doi.org/10.1186/1742-2094-5-35.
[25] L. Huang, J. Jia, R. Liu, Decreased serum levels of the angiogenic factors VEGF and TGF-β1 in Alzheimer's disease and amnestic mild cognitive impairment, Neurosci. Lett. 550 (2013) 60–63, https://doi.org/10.1016/j.neulet.2013.06.031.
[26] J.A. Pillai, J. Bena, G. Bebek, L.M. Bekris, A. Bonner-Jackson, L. Kou, A. Pai, L. Sørensen, M. Neilsen, S.M. Rao, M. Chance, B.T. Lamb, J.B. Leverenz, Inflammatory pathway analytes predicting rapid cognitive decline in MCI stage of Alzheimer's disease, Ann. Clin. Transl. Neurol. 7 (7) (2020) 1225–1239, https://doi.org/10.1002/acn3.51109.
[27] K. Abe, Y. Chiba, S. Hattori, A. Yoshimi, T. Asami, O. Katsuse, A. Suda, A. Hishimoto, Influence of plasma matrix metalloproteinase levels on longitudinal changes in Alzheimer's disease (AD) biomarkers and cognitive function in patients with mild cognitive impairment due to AD registered in the Alzheimer's Disease Neuroimaging Initiative da, J. Neurol. Sci. 416 (2020), 116989, https://doi.org/10.1016/j.jns.2020.116989.
[28] A.P. Keegan, D. Paris, C.A. Luis, L. Abdullah, G. Ait-Ghezala, D. Beaulieu-Abdelahad, M. Pryor, J. Chaykin, G. Crynen, F. Crawford, M. Mullan, Plasma cytokine IL-6 levels and subjective cognitive decline: preliminary findings, Int. J. Geriatr. Psychiatry. 33 (2018) 358–363, https://doi.org/10.1002/gps.4752.
[29] C. Cunningham, S. Campion, K. Lunnon, C.L. Murray, J.F.C. Woods, R.M. J. Deacon, J.N.P. Rawlins, V.H. Perry, Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease, Biol. Psychiatry. 65 (2009) 304–312, https://doi.org/10.1016/j.biopsych.2008.07.024.
[30] K. Westin, P. Buchhave, H. Nielsen, L. Minthon, S. Janciauskiene, O. Hansson, CCL2 is associated with a faster rate of cognitive decline during early stages of Alzheimer's disease, PLoS One. 7 (2012), https://doi.org/10.1371/journal.pone.0030525.
[31] K. Abe, Y. Chiba, S. Hattori, A. Tamazawa, A. Yoshimi, O. Katsuse, A. Suda, Influence of plasma cytokine levels on the conversion risk from MCI to dementia in the Alzheimer's disease neuroimaging initiative database, J. Neurol. Sci. 414 (2020), 116829, https://doi.org/10.1016/j.jns.2020.116829.
[32] D. Gu, F. Liu, M. Meng, L. Zhang, M.L. Gordon, Y. Wang, L. Cai, N. Zhang, Elevated matrix metalloproteinase-9 levels in neuronal extracellular vesicles in Alzheimer's disease, Ann. Clin. Transl. Neurol. 7 (2020) 1681, https://doi.org/10.1002/ACN3.51155.
[33] G. Tuna, G.G. Yener, G. Oktay, G.H. Işlekel, F.G. Kirkali, Evaluation of matrix metalloproteinase-2 (MMP-2) and-9 (MMP-9) and their tissue inhibitors (TIMP-1 and TIMP-2) in plasma from patients with neurodegenerative dementia, J. Alzheimer's Dis. 66 (2018) 1265–1273, https://doi.org/10.3233/JAD-180752.
[34] J.C. Park, S.H. Han, I. Mook-Jung, Peripheral inflammatory biomarkers in Alzheimer's disease: a brief review, BMB Rep. 53 (2020) 10–19, https://doi.org/10.5483/BMBRep.2020.53.1.309.
[35] Half of Alzheimer's disease cases may be mild | National Institute on Aging, (n.d.). https://www.nia.nih.gov/news/half-alzheimers-disease-cases-may-be-mild (accessed December 2, 2021).
[36] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease, Neurology. 34 (1984) 939–944, https://doi.org/10.1212/WNL.34.7.939.
[37] D. Szklarczyk, A.L. Gable, D. Lyon, A. Junge, S. Wyder, J. Huerta-Cepas, M. Simonovic, N.T. Doncheva, J.H. Morris, P. Bork, L.J. Jensen, C. Von Mering, STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, Nucl. Acids Res. 47 (2019) D607–D613, https://doi.org/10.1093/NAR/GKY1131.
[38] A. Webers, M.T. Heneka, P.A. Gleeson, The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease, Immunol. Cell Biol. 98 (2020) 28–41, https://doi.org/10.1111/imcb.12301.
[39] M. Motta, R. Imbesi, M. Di Rosa, F. Stivala, L. Malaguarnera, Altered plasma cytokine levels in Alzheimer's disease: correlation with the disease progression, Immunol. Lett. 114 (2007) 46–51, https://doi.org/10.1016/j.imlet.2007.09.002.
[40] N.W. Group, H. Akiyama, S. Barger, S. Barnum, B. Bradt, J. Bauer, G.M. Cole, N.R. Cooper, P. Eikelenboom, M. Emmerling, B.L. Fiebich, C.E. Finch, S. Frautschy, W. S.T. Griffin, H. Hampel, M. Hull, G. Landreth, L.-F. Lue, R. Mrak, I.R. Mackenzie, P.L. Mcgeer, M. Kerry O'banion, J. Pachter, G. Pasinetti, C. Plata-Salaman, J. Rogers, R. Rydel, Y. Shen, W. Streit, R. Strohmeyer, I. Tooyoma, F.L. Van Muiswinkel, R. Veerhuis, D. Walker, S. Webster, B. Wegrzyniak, G. Wenk, T. Wyss-Coray, Inflammation and Alzheimer's disease, (2000).
[41] R.C. Petersen, G.E. Smith, S.C. Waring, R.J. Ivnik, E.G. Tangalos, E. Kokmen, Mild cognitive impairment: clinical characterization and outcome, Arch. Neurol. 56 (1999) 303–308, https://doi.org/10.1001/archneur.56.3.303.
[42] V. Calsolaro, P. Edison, Neuroinflammation in Alzheimer's disease: current evidence and future directions, Alzheimer's Dement. 12 (2016) 719–732, https://doi.org/10.1016/j.jalz.2016.02.010.
[43] C. Schwab, P.L. McGeer, J. Miklossy, R.N. Martins, Inflammatory aspects of Alzheimer disease and other neurodegenerative disorders, J. Alzheimer's Dis. 13 (4) (2008) 359–369, https://doi.org/10.3233/JAD-2008-13402.
[44] W. Swardfager, K. Lanctt, L. Rothenburg, A. Wong, J. Cappell, N. Herrmann, A meta-analysis of cytokines in Alzheimer's disease, Biol. Psychiatry. 68 (2010) 930–941, https://doi.org/10.1016/j.biopsych.2010.06.012.
[45] A. Zlotnik, O. Yoshie, Chemokines: a new classification system and their role in immunity, Immunity. 12 (2000) 121–127, https://doi.org/10.1016/S1074-7613(00)80165-X.
[46] G. Azizi, N. Khannazer, A. Mirshafiey, The potential role of chemokines in Alzheimer's disease pathogenesis, Am. J. Alzheimers. Dis. Other Demen. 29 (2014) 415–425, https://doi.org/10.1177/1533317513518651.
[47] J. Vérité, T. Janet, D. Chassaing, B. Fauconneau, H. Rabeony, G. Page, Longitudinal chemokine profile expression in a blood-brain barrier model from Alzheimer transgenic versus wild-type mice, J. Neuroinflammation. 15 (2018), https://doi.org/10.1186/S12974-018-1220-7.
[48] J. Vérité, G. Page, M. Paccalin, A. Julian, T. Janet, M.A. Deli, Differential chemokine expression under the control of peripheral blood mononuclear cells issued from Alzheimer's patients in a human blood brain barrier model, PLoS One. 13 (8) (2018) e0201232.
[49] V. Boccardi, L. Paolacci, D. Remondini, E. Giampieri, G. Poli, N. Curti, R. Cecchetti, A. Villa, C. Ruggiero, S. Brancorsini, P. Mecocci, Cognitive decline and Alzheimer's disease in old age: a sex-specific cytokinome signature, J. Alzheimer's Dis. 72 (2019) 911–918, https://doi.org/10.3233/JAD-190480.
[50] S. Singh, D. Anshita, V. Ravichandiran, MCP-1: Function, regulation, and involvement in disease, Int. Immunopharmacol. (2021), https://doi.org/10.1016/j.intimp.2021.107598.
[51] W.J. Lee, Y.C. Liao, Y.F. Wang, I.F. Lin, S.J. Wang, J.L. Fuh, Plasma MCP-1 and cognitive decline in patients with Alzheimer's disease and mild cognitive impairment: A two-year follow-up study, Sci. Rep. 8 (2018), https://doi.org/10.1038/s41598-018-19807-y.
[52] D. Galimberti, C. Fenoglio, C. Lovati, E. Venturelli, I. Guidi, B. Corrà, D. Scalabrini, F. Clerici, C. Mariani, N. Bresolin, E. Scarpini, Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease, Neurobiol. Aging. 27 (2006) 1763–1768, https://doi.org/10.1016/j.neurobiolaging.2005.10.007.
[53] J. El Khoury, M. Toft, S.E. Hickman, T.K. Means, K. Terada, C. Geula, A.D. Luster, Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease, Nat. Med. 13 (2007) 432–438, https://doi.org/10.1038/nm1555.
[54] A. Santaella, H.B. Kuiperij, A. van Rumund, R.A.J. Esselink, A.J. van Gool, B. R. Bloem, M.M. Verbeek, Cerebrospinal fluid monocyte chemoattractant protein 1 correlates with progression of Parkinson's disease, Npj Park. Dis. 61 (6) (2020) 1–5, https://doi.org/10.1038/s41531-020-00124-z.
[55] E. Scarpini, D. Galimberti, P. Baron, R. Clerici, M. Ronzoni, G. Conti, G. Scarlato, IP-10 and MCP-1 levels in CSF and serum from multiple sclerosis patients with different clinical subtypes of the disease, J. Neurol. Sci. 195 (2002) 41–46, https://doi.org/10.1016/S0022-510X(01)00680-3.
[56] X. Chen, Y. Hu, Z. Cao, Q. Liu, Y. Cheng, Cerebrospinal fluid inflammatory cytokine aberrations in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis: a systematic review and meta-analysis, Front. Immunol. 9 (2018) 2122, https://doi.org/10.3389/FIMMU.2018.02122/FULL.
[57] I.M. Rea, D.S. Gibson, V. McGilligan, S.E. McNerlan, H. Denis Alexander, O. A. Ross, Age and age-related diseases: role of inflammation triggers and cytokines, Front. Immunol. 9 (2018) 586, https://doi.org/10.3389/FIMMU.2018.00586/BIBTEX.
[58] I. Bhavsar, C.S. Miller, M. Al-Sabbagh, Macrophage inflammatory protein-1 alpha (MIP-1 alpha)/CCL3: as a biomarker, Gen. Methods Biomark. Res. Their Appl. 1–2 (2015) 223, https://doi.org/10.1007/978-94-007-7696-8_27.
[59] K. Li, D. Dai, L. Yao, X. Gu, K. Luan, W. Tian, Y. Zhao, B. Wang, Association between the macrophage inflammatory protein-l alpha gene polymorphism and Alzheimer's disease in the Chinese population, Neurosci. Lett. 433 (2008) 125–128, https://doi.org/10.1016/j.neulet.2008.01.002.
[60] D. Tripathy, L. Thirumangalakudi, P. Grammas, Expression of macrophage inflammatory protein 1-α is elevated in Alzheimer's vessels and is regulated by oxidative stress, J. Alzheimer's Dis. 11 (2007) 447–455, https://doi.org/10.3233/JAD-2007-11405.
[61] M. Aksnes, H.C.D. Aass, A. Tiiman, T.H. Edwin, L. Terenius, N. Bogdanović, V. Vukojević, A.B. Knapskog, Associations of cerebrospinal fluid amyloidogenic nanoplaques with cytokines in Alzheimer's disease, Transl. Neurodegener. 10 (2021), https://doi.org/10.1186/S40035-021-00244-3.
[62] M. Tejera-Alhambra, A. Casrouge, C. de Andrés, A. Seyfferth, R. Ramos-Medina, B. Alonso, J. Vega, L. Fernández-Paredes, M.L. Albert, S. Sánchez-Ramón, Plasma biomarkers discriminate clinical forms of multiple sclerosis, PLoS One. 10 (2015) e0128952.
[63] A. Tennakoon, V. Katharesan, I.F. Musgrave, S.A. Koblar, R.L.M. Faull, M. A. Curtis, I.P. Johnson, Normal aging, motor neurone disease, and Alzheimer's disease are characterized by cortical changes in inflammatory cytokines, J. Neurosci. Res. 100 (2022) 653–669, https://doi.org/10.1002/JNR.24996.

[64] V. Appay, S.L. Rowland-Jones, RANTES: A versatile and controversial chemokine, Trends Immunol. 22 (2001) 83–87, https://doi.org/10.1016/S1471-4906(00)01812-3.

[65] E.E. Ubogu, M.K. Callahan, B.H. Tucky, R.M. Ransohoff, Determinants of CCL5-driven mononuclear cell migration across the blood-brain barrier. Implications for therapeutically modulating neuroinflammation, J. Neuroimmunol. 179 (2006) 132–144, https://doi.org/10.1016/j.jneuroim.2006.06.004.

[66] A.L. Teixeira, H.J. Reis, F.M. Coelho, D.S. Carneiro, M.M. Teixeira, L.B. Vieira, M. A. Mukhamedyarov, A.L. Zefirov, Z. Janka, A. Palotás, All-or-nothing type biphasic cytokine production of human lymphocytes after exposure to Alzheimer's β-amyloid peptide, Biol. Psychiatry. 64 (2008) 891–895, https://doi.org/10.1016/j.biopsych.2008.07.019.

[67] M. Johnstone, A.J.H. Gearing, K.M. Miller, A central role for astrocytes in the inflammatory response to β- amyloid; chemokines, cytokines and reactive oxygen species are produced, J. Neuroimmunol. 93 (1999) 182–193, https://doi.org/10.1016/S0165-5728(98)00226-4.

[68] M.I. Kester, W.M. Van Der Flier, A. Visser, M.A. Blankenstein, P. Scheltens, C. B. Oudejans, Decreased mRNA expression of CCL5 wRANTESx in Alzheimer's disease blood samples, Clin. Chem. Lab. Med. 50 (2012) 61–65, https://doi.org/10.1515/CCLM.2011.731.

[69] D. Tripathy, L. Thirumangalakudi, P. Grammas, RANTES upregulation in the Alzheimer's disease brain: a possible neuroprotective role, Neurobiol. Aging. 31 (2010) 8–16, https://doi.org/10.1016/j.neurobiolaging.2008.03.009.

[70] G. Vacínová, D. Vejražkova, R. Rusina, I. Holmerová, H. Vaňková, E. Jarolímová, J. Včelák, B. Bendlová, M. Vaňková, Regulated upon activation, normal T cell expressed and secreted (RANTES) levels in the peripheral blood of patients with Alzheimer's disease, Neural Regen. Res. 16 (2021) 796, https://doi.org/10.4103/1673-5374.295340.

[71] M.J. Stuart, B.T. Baune, Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies, Neurosci. Biobehav. Rev. 42 (2014) 93–115, https://doi.org/10.1016/j.neubiorev.2014.02.001.

[72] P. Tang, L. Chong, X. Li, Y. Liu, P. Liu, C. Hou, R. Li, Correlation between serum RANTES levels and the severity of Parkinson's disease, Oxid. Med. Cell. Longev. 2014 (2014), https://doi.org/10.1155/2014/208408.

[73] T.W. Liu, C.M. Chen, K.H. Chang, Biomarker of Neuroinflammation in Parkinson's Disease, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/IJMS23084148.

[74] G.A. Rosenberg, Matrix metalloproteinases and their multiple roles in neurodegenerative diseases, Lancet Neurol. 8 (2009) 205–216, https://doi.org/10.1016/S1474-4422(09)70016-X.

[75] V.W. Yong, C. Power, P. Forsyth, D.R. Edwards, Metalloproteinases in biology and pathology of the nervous system, Nat. Rev. Neurosci. 2 (7) (2001) 502–511, https://doi.org/10.1038/35081571.

[76] M. Brkic, S. Balusu, C. Libert, R.E. Vandenbroucke, Friends or foes: matrix metalloproteinases and their multifaceted roles in neurodegenerative diseases, Mediators Inflamm. 2015 (2015), https://doi.org/10.1155/2015/620581.

[77] W. Li, E. Poteet, L. Xie, R. Liu, Y. Wen, S.-H. Yang, Regulation of matrix metalloproteinase 2 by oligomeric amyloid β protein, Brain Res. 1387 (2011) 141–148, https://doi.org/10.1016/j.brainres.2011.02.078.

[78] S. Lorenzl, D.S. Albers, N. Relkin, T. Ngyuen, S.L. Hilgenberg, J. Chirichigno, E. Cudkowicz, M. Flint Beal, Increased plasma levels of matrix metalloproteinase-9 in patients with Alzheimer's disease, Neurochem. Int. 43 (2003) 191–196, https://doi.org/10.1016/S0197-0186(03)00004-4.

[79] C.D. Whelan, N. Mattsson, M.W. Nagle, S. Vijayaraghavan, C. Hyde, S. Janelidze, E. Stomrud, J. Lee, L. Fitz, T.A. Samad, G. Ramaswamy, R.A. Margolin, A. Malarstig, O. Hansson, Multiplex proteomics identifies novel CSF and plasma biomarkers of early Alzheimer's disease, Acta Neuropathol. Commun. 7 (2019) 1–14, https://doi.org/10.1186/s40478-019-0795-2.

[80] E. Stomrud, M. Björkqvist, S. Janciauskiene, L. Minthon, O. Hansson, Alterations of matrix metalloproteinases in the healthy elderly with increased risk of prodromal Alzheimer's disease, 2010. doi:10.1186/alzrt44.

[81] A. Beroun, S. Mitra, P. Michaluk, B. Pijet, M. Stefaniuk, L. Kaczmarek, MMPs in learning and memory and neuropsychiatric disorders, Cell. Mol. Life Sci. 7616 (76) (2019) 3207–3228, https://doi.org/10.1007/S00018-019-03180-8.

[82] K. Bobińska, J. Szemraj, P. Gałecki, M. Talarowska, The role of MMP genes in recurrent depressive disorders and cognitive functions, Acta Neuropsychiatr. 28 (2016) 221–231, https://doi.org/10.1017/NEU.2015.72.

[83] P. Yan, X. Hu, H. Song, K. Yin, R.J. Bateman, J.R. Cirrito, Q. Xiao, F.F. Hsu, J. W. Turk, J. Xu, C.Y. Hsu, D.M. Holtzman, J.M. Lee, Matrix metalloproteinase-9 degrades amyloid-β fibrils in vitro and compact plaques in situ, J. Biol. Chem. 281 (2006) 24566–24574, https://doi.org/10.1074/JBC.M602440200.

[84] S. Guo, S. Wang, W.J. Kim, S.R. Lee, M.P. Frosch, B.J. Bacskai, S.M. Greenberg, E. H. Lo, Effects of apoE isoforms on beta-amyloid-induced matrix metalloproteinase-9 in rat astrocytes, Brain Res. 1111 (2006) 222–226, https://doi.org/10.1016/J.BRAINRES.2006.06.041.

[85] M.A. Tubi, D. Kothapalli, M. Hapenney, F.W. Feingold, W.J. Mack, K.S. King, P. M. Thompson, M.N. Braskie, Regional relationships between CSF VEGF levels and Alzheimer's disease brain biomarkers and cognition, Neurobiol. Aging. 105 (2021) 241–251, https://doi.org/10.1016/j.neurobiolaging.2021.04.025.

[86] S.J. Cho, M.H. Park, C. Han, K. Yoon, Y.H. Koh, VEGFR2 alteration in Alzheimer's disease, Sci. Rep. 7 (2017), https://doi.org/10.1038/s41598-017-18042-1.

[87] P. Religa, R. Cao, D. Religa, Y. Xue, N. Bogdanovic, D. Westaway, H.H. Marti, B. Winblad, Y. Cao, VEGF significantly restores impaired memory behavior in Alzheimer's mice by improvement of vascular survival, Sci. Rep. 3 (2013), https://doi.org/10.1038/srep02053.

[88] C. Spuch, D. Antequera, A. Portero, G. Orive, R.M. Hernández, J.A. Molina, F. Bermejo-Pareja, J.L. Pedraz, E. Carro, The effect of encapsulated VEGF-secreting cells on brain amyloid load and behavioral impairment in a mouse model of Alzheimer's disease, Biomaterials. 31 (2010) 5608–5618, https://doi.org/10.1016/j.biomaterials.2010.03.042.

[89] I. Mateo, J. Llorca, J. Infante, E. Rodríguez-Rodríguez, C. Fernández-Viadero, N. Peña, J. Berciano, O. Combarros, Low serum VEGF levels are associated with Alzheimer's disease, Acta Neurol. Scand. 116 (2007) 56–58, https://doi.org/10.1111/j.1600-0404.2006.00775.x.

[90] P. Wang, Z.H. Xie, Y.J. Guo, C.P. Zhao, H. Jiang, Y. Song, Z.Y. Zhu, C. Lai, S.L. Xu, J.Z. Bi, VEGF-induced angiogenesis ameliorates the memory impairment in APP transgenic mouse model of Alzheimer's disease, Biochem. Biophys. Res. Commun. 411 (2011) 620–626, https://doi.org/10.1016/j.bbrc.2011.07.003.

[91] T.J. Hohman, S.P. Bell, A.L. Jefferson, for the A.D.N. Initiative, The role of vascular endothelial growth factor in neurodegeneration and cognitive decline: exploring interactions with biomarkers of Alzheimer disease, JAMA Neurol. 72 (2015) 520–529, https://doi.org/10.1001/JAMANEUROL.2014.4761.

[92] J.W. Shim, J.R. Madsen, VEGF signaling in neurological disorders, Int. J. Mol. Sci. 19 (2018) 1–22, https://doi.org/10.3390/ijms19010275.

[93] IL-18 signaling pathway (Homo sapiens) - WikiPathways, (n.d.). https://www.wikipathways.org/index.php/Pathway:WP4754 (accessed November 3, 2021).

[94] V.S. Reddy, R.E. Harskamp, M.W. Van Ginkel, J. Calhoon, C.E. Baisden, I.S. Kim, A.J. Valente, B. Chandrasekar, Interleukin-18 stimulates fibronectin expression in primary human cardiac fibroblasts via PI3K-Akt-dependent NF-κB activation, J. Cell. Physiol. 215 (2008) 697–707, https://doi.org/10.1002/jcp.21348.

[95] S. Hyun Kim, L.L. Reznikov, R.J.L. Stuyt, C.H. Selzman, G. Fantuzzi, T. Hoshino, H.A. Young, C.A. Dinarello, Functional reconstitution and regulation of IL-18 activity by the IL-18Rβ chain, J. Immunol. 166 (2001) 148–154, https://doi.org/10.4049/jimmunol.166.1.148.

[96] D.A.B. Rex, N. Agarwal, T.S.K. Prasad, R.K. Kandasamy, Y. Subbannayya, S. M. Pinto, A comprehensive pathway map of IL-18-mediated signalling, J. Cell Commun. Signal. 14 (2020) 257–266, https://doi.org/10.1007/s12079-019-00544-4.

[97] S. Alboni, D. Cervia, S. Sugama, B. Conti, Interleukin 18 in the CNS, (2010). doi: 10.1186/1742-2094-7-9.

[98] D. Scarabino, M. Peconi, E. Broggio, G. Gambina, E. Maggi, F. Armeli, E. Mantuano, M. Morello, R.M. Corbo, R. Businaro, Relationship between proinflammatory cytokines (Il-1beta, Il-18) and leukocyte telomere length in mild cognitive impairment and Alzheimer's disease, Exp. Gerontol. 136 (2020), 110945, https://doi.org/10.1016/j.exger.2020.110945.

[99] J. Ojala, I. Alafuzoff, S.K. Herukka, T. van Groen, H. Tanila, T. Pirttilä, Expression of interleukin-18 is increased in the brains of Alzheimer's disease patients, Neurobiol. Aging. 30 (2009) 198–209, https://doi.org/10.1016/j.neurobiolaging.2007.06.006.

[100] P. Bossù, A. Ciaramella, F. Salani, D. Vanni, I. Palladino, C. Caltagirone, G. Scapigliati, Interleukin-18, from neuroinflammation to Alzheimer's disease, Curr. Pharm. Des. 16 (2010) 4213–4224.