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Elevated specific peripheral cytokines found in major depressive disorder patients with childhood trauma exposure: A cytokine antibody array analysis

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Abstract

Taking into consideration the previous evidence of revealing the relationship of early life adversity, major depressive disorder (MDD), and stress-linked immunological changes, we recruited 22 MDD patients with childhood trauma exposures (CTE), 21 MDD patients without CTE, and 22 healthy controls without CTE, and then utilized a novel cytokine antibody array methodology to detect potential biomarkers underlying MDD in 120 peripheral cytokines and to evaluate the effect of CTE on cytokine changes in MDD patients. Although 13 cytokines were identified with highly significant differences in expressions between MDD patients and normal controls, this relationship was significantly attenuated and no longer significant after consideration of the effect of CTE in MDD patients. Depressed individuals with CTE (TD patients) were more likely to have higher peripheral levels of those cytokines. Severity of depression was associated with plasma levels of certain increased cytokines; meanwhile, the increased cytokines led to a proper separation of TD patients from normal controls during clustering analyses. Our research outcomes add great strength to the relationship between depression and cytokine changes and suggest that childhood trauma may play a vital role in the co-appearance of cytokine changes and depression.

Abbreviations: AgRP, agouti-related protein; ANOVA, analysis of variance; b-FGF, basic fibroblast growth factor; BMI, body mass index; BTC, betacellulin; CI, Confidence interval; CRF, corticotropin-releasing factor; CRP, C reactive protein; CTE, childhood trauma exposure; CTQ, childhood trauma questionnaire; DM, diabetes mellitus; DSM, Diagnosis and Statistical Manual of Mental Disorders; GITR-L, glucocorticoid-induced tumor necrosis factor-ligand; GR, glucocorticoid receptor; HAMD, Hamilton Depressive Rating Scale; HPA, hypothalamic pituitary adrenocortical axis; I-TAC, interferon induced T cell α chemoattractant; IL, interleukin; IL-1 R1, interleukin-1 Receptor 1; MCP-1, monocyte chemotactic protein-1; MDD, major depressive disorder; MEC, mucosae-associated epithelial chemokine; MIP-1beta, macrophage inflammatory protein-1beta; NC, normal control; NT-4, neurotrophin-4; NTD, depression without childhood trauma; PTSD, post traumatic stress disorder; RA, rheumatoid arthritis; SCID, structured clinical interview for DSM-IV; SDS, Zung's Self-rating Depression Scale; SI, signal intensity; SPSS, statistical package for the social sciences; SSRI, selective serotonin reuptake inhibitor; TD, depression with childhood trauma; TECK, thymus-expressed chemokine; TGF-β3, transforming growth factor-β3; TNF, tumor necrosis factor; TRAIL-R4, tumor necrosis factor related apoptosis inducing ligand-receptor 4; VEGF, vascular endothelial growth factor.

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1. Introduction

Major depressive disorder (MDD) is an often debilitating mental illness that is characterized by persistent negative mood and altered cognitive functions [1]. A community-based survey report revealed that a 12-month prevalence rate for depression was 6.7%–8.3% [2]. Clinical and preclinical depression seriously affects social works, relationships, and physical health [3,4]. Depression requires the highest care cost, as compared to chronic physical diseases, such as diabetes mellitus (DM), asthma, and arthritis [5] and has been estimated to be the second leading cause of disability by year 2020 [6]. In recent years, several lines of research have been directed towards etiology, neurobiology and pathogenesis of depression, however, the mechanisms responsible underlying the development of depression remain unclear. Numerous hypotheses have been developed to elucidate its origins [7]. One of these is cytokine theory which focuses on the role of psycho-neuroimmunological dysfunctions where inflammation system is activated [8].

Cytokines are intercellular communication soluble protein or peptides secreted by various immune cells and can be often divided into pro-inflammatory or anti-inflammatory molecules [9,10]. Depression appears to be linked with complicated inflammatory processes and the subsequent release of cytokines in abundant studies [11–13]. Depressed patients often show depressive mood, fatigue, sleep disorder, cognitive disturbances and appetite suppression that are frequently seen in cytokine-induced chronic inflammatory disease, such as rheumatoid arthritis (RA), and in patients who take cytokines for treatment [14]. Consistent with these findings, animal studies have indicated that administration of different cytokines in rodents will display "sickness behavior" [15], including decreased social exploration, decreased intake of food and water, and decreased activities [16], that overlaps with symptoms of MDD. Depressed patients seem to have increased peripheral cytokines, even in the absence of physical illness, but these increases are much more modest than in infectious or autoimmune disease [11]. The most consistent findings refer to raised levels of interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNFα) and C reactive protein (CRP) in patients with MDD compared to normal controls, which have been highly corroborated by several systematic reviews and meta-analyses [17]. Higher levels of chemokine, adhesion molecules, inflammatory mediators, and other acute phase proteins are shown as well [8]. In depressed individuals, a positive correlation has been detected between specific depressive symptoms and presence of increased cytokines [18,19]. In addition, the disturbed cytokines can be restored by successful antidepressant therapy [20] which suggests that dysfunction of cytokine system could be state feature of MDD. Plenty of studies contribute to the relationship between cytokines and depression, however, not every depressed individual reflects elevated cytokines [21]. On the contrary, two studies [22,23] did find lower levels of serum IL-7 and 3 chemokines, monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1beta (MIP-1beta) and IL-8 in MDD than healthy controls. Interestingly, a recent community-based study evaluating a broad panel of cytokines failed to find any cytokine investigated that was associated with MDD [24]. All those remind us of inconsistent results in studies testing the association between depression and cytokines.

Depression-related alterations of cytokine markers may be much more complicated than previously described. The inconsistency could be due to heterogeneity in enormous aspects, for instance, biological markers correlated with MDD may vary with a history of childhood trauma.

Early life adversity, such as childhood trauma, is a great risk factor of developing depression, depressed individuals with childhood trauma could be treated as a special subtype of depression with unique pathogenesis which was complex and poorly understood until now [25]. A study that tested the life-course association between childhood maltreatment and adult inflammation in a cohort suggested that early adverse events seemed to be an independent risk factor for inflammation in adult, and that inflammation might be an important mediator provoking early adverse events to physical and mental disease [26,27]. Inflammation may be accompanied by depression through dysfunction of hypothalamic pituitary adrenocortical (HPA) axis [28,29], early adverse events have been reported to have potential influence on HPA axis, especially to be associated with insufficient glucocorticoid signaling [30], accordingly, a history of early life adversity may contribute to elucidate the co-appearance of inflammation and depression. Early life adversity might have a long-term effect on inflammation processes in depressed patients resulting from a study which showed an exaggerated cytokine response to acute stress in depressed subjects with early life adversity as compared to normal controls [31]. Measuring cytokine levels in depressed individuals with childhood trauma may be helpful to partly explain the inconsistency of current research outcomes because elevated cytokines could probably be observed in maltreated adults only, but not in depressed patients without childhood maltreatment exposure [32].

Most prior studies investigated limited cytokines only, and the diagnosis of depression was often heterogeneous. Due to those limitations and based on the previous evidence of revealing the relationship of early life adversity, depression and stress-linked immunological changes, we presumed that several specific cytokines might be associated with childhood trauma in MDD. We assessed the histories of childhood trauma exposure (CTE) in depressed subjects in order to reduce diagnostic heterogeneity as much as possible and utilized a novel cytokine antibody array methodology to detect potential biomarkers underlying MDD in 120 cytokines and to evaluate the effect of CTE on cytokine changes in MDD patients.