



Changes in cytokine and chemokine expression distinguish dysthymic disorder from major depression and healthy controls



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ABSTRACT

An important area of uncertainty is the inflammatory degree to which depression occurring as part of dysthymic disorder may differ from major depression. Using a 27-plex cytokine assay, we analyzed the serum of 12 patients with dysthymic disorder, 12 with major depression, and an age-, sex-, and body mass index-matched control group of 20 healthy volunteers. We observed that patients with dysthymic disorder exhibited aberrant cytokine and chemokine expression compared with healthy controls and patients with major depression. The levels of interferon- γ -induced protein 10 highly predicted dysthymic disorder. Network analyses revealed that in patients with dysthymic disorder, the vertices were more sparsely connected and adopted a more hub-like architecture, and the connections from neighboring vertices of interleukin 2 and eotaxin-1 increased. After treatment with the same antidepressant, there was no difference between dysthymic disorder and major depression regarding any of the cytokines or chemokines analyzed. For dysthymic disorder, changes in the levels of interferon- γ -induced protein 10 and macrophage inflammatory protein-1 α correlated with depression improvement. The findings suggest that the cytokine milieu in dysthymic disorder differs either at the level of individual expression or in network patterns. Moreover, chemokines play an important role in driving the pathophysiology of dysthymic disorder.

1. Introduction

Depression, by its very nature, is a condition with multifactorial etiology and complex neurobiology. Two decades ago, researchers discovered increased inflammation in patients with depression (Maes et al., 1990). However, it is only in recent years that the pathophysiology of depressive disorders transcended beyond monoamine-based hypotheses. Among the theories of the neurobiological underpinnings of depression, the inflammatory hypothesis has garnered significant attention (Furtado and Katzman, 2015; Ovaskainen et al., 2009; Rudolf et al., 2014). Emerging data based on preclinical and clinical studies suggest that the depression-inflammation relationship is bidirectional in that depression increases inflammatory biomarkers, and inflammatory cytokines exert depressogenic effects (Dantzer et al., 2008; Dowlati et al., 2010; Rosenblat et al., 2014).

Dysthymia is a chronic, fluctuating, low-grade form of depression, with an emphasis on symptoms of low-esteem and hopelessness. It is the key component of persistent depressive disorders (Rhebergen and Graham, 2014), a newly introduced diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Although the inflammatory hypothesis of depression is a popular research topic, the inflammatory degree to which depression occurring as a part of dysthymic disorder differs from major depression remains unclear. Previous studies have demonstrated increased levels of interleukin (IL)-1 β (Anisman et al., 1999a, 1999b; Brambilla et al., 2004; Schlatter et al., 2001) and IL-6 (Schlatter et al., 2001), and decreased levels of IL-2 (Anisman et al., 1999a) and tumor necrosis factor (TNF)- α (Brambilla et al., 2004) in patients with dysthymic disorder. However, the alterations in cytokine expression were not consistent across studies.

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; IL, interleukin; TNF- α , tumor necrosis factor alpha; HADM, Hamilton Depression Rating Scale; BMI, body mass index; MD, major depression; DD, dysthymic disorder; HC, healthy controls; IL-1RA, interleukin-1 receptor antagonist; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon gamma; IP-10, interferon gamma-induced protein 10; MCP-1, monocyte chemoattractant protein 1; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; RANTES, regulated on activation, normal T cell expressed and secreted; VEGF, vascular endothelial growth factor; CNS, central nervous system

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Discerning which cytokines drive the pathophysiology of depressive disorders can be complex because immune cells can produce various cytokines. In addition, numerous cytokines can cause either a specific disease or several diseases. The cytokines are characterized by pleiotropy, redundancy, synergy, antagonism, and cascade induction, thus creating an intricate cytokine network (Tayal and Kalra, 2008). A limited number of cytokines measured cannot reflect the immunological context of depressive disorders, and can easily lead to diverse conclusions, as previously discussed (Ho et al., 2015). In order to fully understand the dysthymia-associated cytokine milieu, it is important to reliably and validly quantify a wide range of cytokines across studies. To date, however, most dysthymia research investigated only 2–3 cytokines. Moreover, no study has investigated the aberrations in chemokines, which are chemotactic cytokines crucially involved in immunomodulation (Zlotnik and Yoshie, 2000) as well as the pathophysiology of chronic inflammation, tumorigenesis, and autoimmune diseases (Raman et al., 2011).

The purpose of this study was to thoroughly investigate the cytokine and chemokine profiles of drug-naïve patients with dysthymic disorder using multiplexed immunoassays (a total of 27 cytokines analyzed). We examined whether at baseline and after treatment with the same antidepressant agent, the cytokine and chemokine profiles were different for dysthymic disorder and major depression. Network analysis was also performed with emphasis on the patterns of coordinated cytokine and chemokine expression. Since comparative biological analyses of dysthymic disorder and major depression is limited in the literature, this study helps to identify the key elements driving dysthymia-related neuroinflammatory pathogenesis.

2. Methods

2.1. Subjects

Eligible study participants were subjects who voluntarily sought treatment for clinical depression and were hospitalized. A total of 44 subjects were recruited, including 12 patients with dysthymia, 12 with major depression, and 20 healthy controls. The diagnosis of first-episode major depression and dysthymia – meeting the DSM-IV criteria—was made by two certified psychiatrists. The severity of depression was measured according to the 17-item Hamilton Depression Rating Scale (HADM) (Hamilton, 1960).

In order to avoid potential confounders, patients were required to be **male**, drug-naïve, between the ages of 20 and 40, and in good health, and were treated with the same antidepressant drug (escitalopram; 10 mg per day) for 4 weeks. Body mass index (BMI), sex, and age are clear confounders in inflammation research. A recent study reported a clear effect of BMI on cytokine and chemokine levels in cerebrospinal fluid (Larsson et al., 2015). The levels of inflammatory biomarkers may fluctuate during the menstrual cycle, menopause, as well as with the use of hormonal contraceptives or estrogen (O'Brien et al., 2007; Willis et al., 2003). Moreover, late-onset depression has been associated with elevated inflammation (Thomas et al., 2005).

The exclusion criteria were as follows: (1) a history of major medical or neurological disorder; (2) a diagnosis of substance-related disorders; (3) onset of depression after 40 years of age; (4) previous head trauma with loss of consciousness; and (5) previous exposure to psychotropic agents (e.g., antidepressants, mood stabilizers, or antipsychotics). The control group consisted of 20 physically and psychiatrically healthy male volunteers recruited from the community. Healthy controls did not take placebo and escitalopram, and their cytokine profiles were only examined at baseline. Tobacco use and alcohol consumption were not allowed during the study period.

The protocol was approved by the Institutional Review Board for the Protection of Human Subjects at the Tri-Service General Hospital, a medical teaching hospital within the National Defense Medical Center in Taiwan. Participants were recruited from the inpatient division of

Beitou Branch, Tri-Service General Hospital, National Defense Medical Center. Written informed consent was obtained in accordance with the National Health and Medical Research Council guidelines. All subjects were fully informed regarding the aims and details of the study and were free to withdraw their consent at any time.

2.2. Cytokine measurement

Detailed procedures for detection of soluble cytokines by multiplex bead array assays have been previously reported and are only briefly summarized here (Dehqanzada et al., 2007). Methodological techniques such as sampling, processing, and storage conditions can substantially increase the variability of cytokine measurements (Zhou et al., 2010). Therefore, the procedures for collection, preparation, freezing, and thawing of all the serum samples used in this study were performed in a highly consistent manner, including the collection and handling of commercial samples. After fasting, peripheral venous blood samples were collected in the morning between 8:00 and 9:00 by venipuncture from patients prior to and after a 4-week treatment with escitalopram. For the preparation of serum samples, 10 mL of peripheral blood was drawn into a Vacutainer Gel and Clot Activator tube and centrifuged in order to separate the serum, which was then aliquoted into NUNC-cryovial tubes and stored at -84°C . None of the serum samples had been previously thawed prior to thawing for the Luminex assay.

Simultaneous analysis of 27 cytokines was performed by Luminex technology. Luminex is a suspension assay that combines the principles of a standard sandwich immunoassay with flow cytometry, thus allowing the multiplex analysis of up to 100 individual cytokines in a single microtiter plate well (Richens et al., 2010). The human 27-Plex cytokine panel (M50-00031YV Pro Human Cytokine 27-plex) was used to analyze serum samples (pg/mL) according to the manufacturer's instructions on Luminex analyzers (Bio-Plex 200, Genmab Biotechnology Co., LTD., Taipei, Taiwan). The surveyed cytokines included IL-1 β , IL-1 receptor antagonist (RA), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17, fibroblast growth factor (FGF) basic, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage (GM)-CSF, interferon (IFN)- γ , IFN- γ -induced protein 10 (IP-10), monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1 α , MIP-1 β , platelet-derived growth factor (PDGF), regulated on activation, normal T cell expressed and secreted (RANTES), eotaxin-1, TNF- α , and vascular endothelial growth factor (VEGF). Some of the above cytokines are classified as chemokines, including CC chemokines [CCL2 (MCP-1), CCL3 (MIP-1 α), CCL4 (MIP-1 β), CCL5 (RANTES), CCL11 (eotaxin-1)] and CXC chemokines [CXCL8 (IL-8), CXCL10 (IP-10)]. Standard curves were created from duplicate values and all samples were analyzed as single determinations. All analyses were performed in one batch using kits from the same production lot.

2.3. Statistical analysis

Group differences in continuous variables were analyzed using the Kruskal-Wallis and Mann-Whitney *U* tests because of the non-normally distributed variables. Within-group differences in continuous variables were examined using the Wilcoxon signed-rank test. Data for the significant group differences in cytokines and chemokines were used to perform binary logistic regression analyses and receiver operating characteristic curves, which helped to distinguish between dysthymic disorder and major depression.

To determine whether the changes in cytokine and chemokine expression levels were similar for dysthymic disorder and major depression after treatment with the same antidepressant agent, a general estimating equation was applied according to the first-order autoregressive working correlation structure since the cytokines and chemokines were repeatedly measured on the same individual across

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