•Forum•

Is depression the result of immune system abnormalities?

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Summary: The etiology of Major Depressive Disorder (MDD) is still unclear. We reviewed the literature for the relationship between inflammatory signaling and cytokines in the pathogenesis of MDD. In addition, we provid evidence for adjunctive treatment using anti-inflammatory drugs to improve the therapeutic effect and prognosis. Finally, we explore the possible relationship between the pathogenesis of MDD and immune disturbances.

Key words: major depressive disorder; cytokines; neuroimmunology; China

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Major Depressive Disorder (MDD) is characterized by serious mental impairment, which endangers a person's overall health. MDD has high morbidity, high recurrence rate, high disability rate, high suicide rate and a heavy economic burden. It is reported that the lifetime prevalence of MDD ranges from 10% to 20%, annual prevalence rate from 2% to 5%, and suicide rate from 15% to 20%.[1,2] The economic burden of MDD is not only on those individuals, but also their family and community. According to the Global Burden of Disease Study conducted by the World Health Organization (WHO) in 2003, MDD had already become the world's number two most disabling disease.[3] In 2014 it became the number one disabling disease when *Nature* reported that 350 million people in the world were diagnosed with MDD. Currently, the disease burden is up to 10.3% (the highest of all ten major diseases).[4] Although the etiology of MDD is currently unclear, numerous studies have indicated that the imbalance of neurotransmitters and receptors, especially those in monoamines signaling pathways, are involved in both the etiology of MDD and the pharmacological mechanism of antidepressants.[5] Despite this, the current findings for MDD are still insufficient to establish a reliable theory that could explain the etiology of MDD. Indeed, further exploration of both the etiological mechanism and potential treatment for MDD is still a key priority for modern psychiatry.

Immune response (Immune Response, IR) is the physiological process induced by the body's immune system. This process is the body's reaction to the stimulation of exogenous antigens, which can eventually be eliminated. IR is divided into two parts: innate immunity and adaptive immunity. Adaptive immunity is also called specific immunity, which is further divided into cellular immunity and humoral immunity. Cellular immunity is mainly accomplished by CD4+ T cells and B cells to produce antibodies and cytokines, to recruit mononuclear macrophages, and to activate other lymphocytes. CD8+ T cells can kill virus infected cells directly. Humoral immunity is mainly accomplished by B cells, including the process of antigen recognition and antibody production. In recent years, the focus of immunological research on MDD is on cellular immunity, especially on cytokines. These studies suggest that inflammatory cytokines can lead to the pathological behavior in depressive disorder.[5] In addition, immunization and inflammation were found to be closely related to the pathogenesis of MDD and patients' treatment response to antidepressants. Depressive disorder showed an increased systemic inflammation reaction, and serum inflammatory biomarkers were associated with a poor prognosis for MDD.[6] By reducing serum concentration of various inflammatory cytokines, and by affecting immune functioning in both cerebral tissues and peripheral serum, antidepressants

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could improve the physical, affective, cognitive and behavioral symptoms effectively. Antidepressants are able to reduce inflammatory activity by influencing the neuroendocrine and neurotransmitter systems as well.

Recent studies found a close correlation between the specific area in the brain and various inflammatory cytokines in the serum. Felger and colleagues'[7] recruited 48 non-medicated MDD or Bipolar Disorder (BP) patients with a current depressive episode. They found increased C-reactive protein (CRP) was associated with decreased connectivity between ventral striatum and ventromedial prefrontal cortex (vmPFC), which in turn correlated with increased anhedonia. Increased CRP similarly predicted decreased dorsal striatal to vmPFC and presupplementary motor area connectivity, which correlated with decreased motor speed and increased psychomotor slowing. In addition, increased serum concentration of interleukin-6 (IL-6), interleukin-1β (IL-1β) and IL-1 antagonist were negatively correlated with cortico-striatal connections. All of the findings listed above indicate that the cortico-striatal circuit could be a target for anti-inflammatory treatment, which potentially could be an effective treatment for MDD patients with reduced motivation and movement in particular.

In addition, various methods that target the inflammatory pathway could be considered as possible effective treatment approaches for MDD. These methods include cytokine antagonists, omega-3 polyunsaturated fatty acid,[8] celecoxib[9] (one of NSAIDs) and physical exercise.[10] Especially in situations when inflammation is prominent in MDD patients, the combined administration of antidepressant and anti-inflammatory drugs could be effective in improving the therapeutic effect and reducing the risk of recurrence.[11] An 8-weeks randomized double-blind controlled study recruited 30 female MDD outpatients to test the treatment effect of sertraline plus celecoxib 100 mg twice daily or sertraline plus placebo. They used Hamilton Depressive and Anxiety Scales (HAMD and HAMA) at baseline, fourth week and eighth week to evaluate the symptoms. Results showed that the efficacy of sertraline plus celecoxib was observed earlier than controls, and both the efficacy rate and remission rate were greater than in the control group. [9]

In ancient times, inflammation was a major cause of death. The symptoms of depression such as fatigue, lack of activity, social avoidance and loss of appetite could be considered as adaptive behaviors related with inflammation.[12] The insomnia in depression could also be regarded as the initial need of being awakened in order to defend oneself against natural enemies. There are many interesting new branches in the research of the etiology and treatment of MDD, including study of the efficacy of anti-inflammatory drugs in MDD treatment. The inflammation theory of depression appeared as early as in the 1950s, however, the debate surrounding it is still ongoing. The latest research on the brain imaging, pharmacology and pharmacodynamics of MDD has given us many new clues, such as how important the role of inflammation is in the etiology of MDD. All of the above has enriched our ideas about the pathology of MDD. There is one theory that focused on the regulatory effect of the hypothalamic-pituitary-adrenal axis (HPA) and sympathetic nervous system (SNS) on the human immune system. In trauma, infection and stress, the HPA and SNS activate and release inflammatory compounds, which probably affect the central nervous system via three pathways: (a) the neurological pathway via the Vigus nerve, (b) the humoral pathway, (c) the pathway of activating astrocytes in the central nervous system (CNS) and promoting the release of Monocyte Chemotactic and Activating Factor (MCP), which causes mononuclear cells to migrate into the CNS directly. Effects of inflammatory cytokines on CNS include the reduction of monoamine synthesis, which in turn increases monoamine synaptic membrane reuptake and its neurotoxic effect. These effects cause depressive symptoms such as loss of interest, melancholia, anxiety and other mental conditions. Accumulating evidence suggests trauma can lead to activation of the immune system, which could cause depression. In summary, the inflammatory process and neuroendocrine, neurotrophic, nerve regeneration, monoamine neurotransmitter synthesis transport and release process may have a wide range of interactions. Further understanding of the inflammatory process of MDD may provide a breakthrough for the etiology and pathogenesis research of MDD.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

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抑郁障碍——免疫异常的结果?

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概述：抑郁障碍病因仍不清楚。本文综述了相关文献，提供了炎症信号和细胞因子在抑郁障碍的发病机制中的作用、及抗炎机制药物的辅助性治疗对提高抑郁症治疗疗效、改善预后的证据，并进一步探讨了抑郁障碍发病机制与免疫异常的可能联系。

关键词：抑郁障碍，细胞因子，神经免疫

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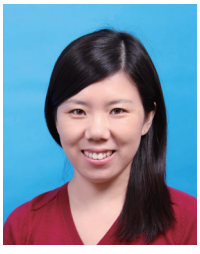

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