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EDITORIAL

Chronic stress and complement system in depression

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Stress is a part of everyday life. It represents an individual's emotional or physical response to the pressures resulting from many factors in life, including work, relationships, and illness. Although the adaptive response system acts effectively during acute stressful conditions, prolonged and excessively stressful situations lead to changes in mood and behavior. In particular, chronic stress increases depression and/or anxiety in many individuals. Understanding how chronic stress can accelerate behavioral abnormalities is important for improving treatments for such disorders. Although the underlying mechanisms are not well understood, recent studies have shown that the inflammatory pathway plays an important role in this process. Once considered immune privileged, the brain is now known to communicate with the immune system via multidimensional crosstalk. These brain-peripheral immune interactions play important roles in both normal physiology and pathological conditions. Increasing evidence indicates that chronic stress promotes elevated inflammation and inflammatory responses in both humans and animal models.[1] In addition, increased levels of pro-inflammatory markers have been found in brain and peripheral tissue of depressed subjects, which suggests that low-grade inflammation plays a key role in the development of one or more of depressive symptoms in all depressed subjects.[2] Evidence also indicates that anti-inflammatory agents have significant beneficial effects on depressive symptoms.[2]

Recent studies have indicated that the complement system could be an important mediator of inflammation-related changes in cellular and behavioral processes in neuropsychiatric conditions.[1] The complement system is a part of innate immunity and involves more than 30 proteins regulated in three pathways: lectin, alternative, and classical. These pathways participate in the host defense mechanism by regulating inflammation. The C1 protein complex, consisting of C1q, C1r and C1s, initiates the classical pathway, in which activated C1s cleaves C4 and C2. The lectin pathway is activated when mannose-binding lectin (MBL) encounters pathogenic carbohydrate motifs. MBL forms complexes with MBL-associated serine proteases 1 and 2 (MASP-1 and MASP-2), resulting in cleavage of C4 and C2. The cleavage products induce the formation of C3 convertase C4bC2a, which cleaves C3 into C3b and C3a. The alternative pathway is activated by the spontaneous hydrolysis of C3 into C3 (H_2O). All three pathways result in the formation of the convertases, which in turn induce the formation of major effectors of the complement system: anaphylatoxins (C4a, C3a, and C5a), the membrane attack complex, and opsonins (C3b). Anaphylatoxins activate proinflammatory signaling, whereas membrane attack complex formation is involved in the lysis of target surfaces.

The complement system plays important roles in developing and adult brains. During development, the complement system acts as a mediator of phagocytosis.[3] C3 tags synapses for removal by microglia in the synaptic pruning process. In the adult brain, activation of the complement system leads to synapse loss and cognitive impairment. Chronic stress has been shown to increase C3 levels in the prefrontal cortex (PFC) of rodents.[4] Furthermore, increases in C3 mRNA levels have been found in the PFC of depressed suicide subjects.[4] On the other hand, inhibition of C3a signaling attenuates chronic stress-induced depressive-like behavior in mice.[4,5] Increased levels of components C3a and C5a were found in patients suffering from bipolar disorder.[6] In addition, it has been reported that patients with major depression have higher C5 levels in cerebrospinal fluid than healthy controls.[7] Although C3 deficiency has been shown to attenuate chronic stress-induced behavioral deficits, C1q deficiency exacerbated stress-induced learned helplessness behavior in mice.[8] Furthermore, increased levels of proinflammatory markers have been found in the PFC of C1q knockout mice.[8] These findings suggest that component- and/or pathway-specific effects of the complement system mediate stress-induced behavioral changes. Moreover, the complement system can be activated in the periphery and/or central nervous system (CNS) following chronic stress. It is known that peripherally derived immune regulators, such as cytokines, can interact with the CNS and induce change in

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neuroplasticity at functional and behavioral levels.[1] Type I interferon, a classic example of the cytokine family, has been shown to induce severe depression and cognitive dysfunction when administered as a therapy for chronic hepatitis C infections. C3 inhibition has been shown to attenuate interferon beta-induced social behavior deficits and neuroinflammation in mice.[5] These findings suggest that complement proteins, together with cytokines and chemokines, can regulate neuroplasticity in neuropsychiatric conditions such as depression.

While the complement system's role in the pathophysiology of depression is an emerging field of interest, more mechanistic studies will help us understand the role of the complement system in neuro-immune crosstalk. Some of these questions include: Do complement proteins have brain region-specific effects on synaptic plasticity in depression? Do complement proteins have cell-specific molecules/pathways in the periphery/CNS that mediate change in neuronal function and behavior? Are specific complement pathways activated in major depressive disorder vs. bipolar disorder? If so, what triggers such differential response? Are complement components potential targets for novel antidepressants? Further insights into these questions will enhance our understanding of complement proteins in depression and related neuropsychiatric disorders.

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