EDITORIAL

Inflammatory and Immune Responses in Depression

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With high global chronic disease burden [1] and prevalence [2], mental illness is presently facing an enormous drug development challenge. In stark contrast to revolutionary, mostly serendipitous, discovery of psychiatric drugs between the end of 1940's and late 1950's, followed by a period of stagnancy during the next half a century, the last decade has witnessed drug development pipeline for nervous system disorders drying up, and major pharmaceutical companies deemphasizing or exiting neuroscience in turn [3-6]. According to one estimate, over 50% of patients with depression do not completely respond to treatment of approved antidepressant drugs [7]. Fortunately, the initial clinical observation of rapid antidepressant effects of the anesthetic ketamine [8] leading to further supporting evidence [9-11] and identification of glutamate pathway as a new drug target in depression [4, 12, 13] has recently revitalized neuropsychiatric therapeutics [14-16]. Not surprisingly, given the success of serendipity in brain treatments, the idea of undertaking a systematic search for reported psychiatric benefits of existing drugs has been proposed [17]. Similarly, other drug repurposing approaches may also seem promising [18-22]. However, irrespective of discovery route, the future of brain drug development is considered to benefit greatly from understanding biological mechanisms involved in pathophysiology and effective therapies [23-25]. It is in this context that the present thematic issue on inflammatory and immune responses in depression was conceived. From the initial observation in late 1980s that a subset of hepatitis C patients treated with interferon alpha develops psychiatric side effects including depression [26], to the findings in 1990s that subsets of patients with major depressive disorder show elevated levels of circulating leukocytes and the proinflammatory cytokine interleukin-6 [27, 28], evidence has accumulated in recent years to suggest a role of peripheral and central inflammation, and innate and adaptive immune systems in the development of depressive symptoms [29-31]. The present issue is in keeping with immense significance of this newly emerging concept in developing new therapeutics for mood disorders.

This special issue contains eight articles. Won and Kim (Korea) discuss how stress induced activation of autonomic nervous system may result in inflammatory conditions which can cause an imbalance between neuroprotective and neurotoxic kynurenine metabolites and, in turn, lead to neurodegenerative changes that render the brain susceptible to depression. Zhang *et al.* (Japan) review clinical and preclinical findings that support a role of pro-inflammatory cytokines in inducing depressive behavior, and discuss the consequences of inflammation in terms of altered brain-derived neurotrophic factor signaling, considered integral to the pathophysiology of depression. Slusarczyk *et al.* (Poland) outline the role of chemokines in the central nervous system under physiological and pathological conditions, and examine experimental and clinical evidence implicating chemokine network disturbances in depressive disorders. Pinto and Andrade (India) focus on depression occurring as an adverse effect of interferon therapy. The authors introduce the interferon superfamily of pro-inflammatory cytokines, describe clinical indications for use of different interferons, and discuss possible mechanisms, treatment and prevention of interferon-related depression. Ronovsky *et al.* (Austria) review molecular, cellular and behavioral studies in animal models of prenatal immune activation, and examines potential mechanisms involved in the development of depression following early life adversity. Schmidt *et al.* (Germany and Australia) discusss cytokines as markers of depression and response to pharmacological and non-pharmacological antidepressive treatment, describe antidepressant potential of agents with immunmodulatory properties, and provide a perspective on possible immune targets for developing novel antidepressants. Köhler *et al.* (Denmark) offer a review of clinical trials of anti-inflammatory agents in depression, discuss the associated efficacy and side effects profiles, and address questions and challenges that are relevant to future investigations on anti-inflammatory therapy of depressive symptoms. Finally, Sharma (India) presents an analysis of genomic, transcriptomic and proteomic studies in depression and antidepressant action, and examines if these unbiased, hypothesis free high throughput approaches support immune and inflammation hypothesis of depression. Notably, available data related to human depression and animal models of depression and antidepressant action does seem consistent with the hypothesis.

The collection of papers presented here is aimed at providing a holistic perspective of inflammatory and immune responses in depression. We sincerely hope that this thematic issue will be of special interest to clinical and preclinical researchers in the field of neuropharmacology and psychiatry. The insights gained from various analyses presented herein may stimulate further research towards development of neuropsychiatric drugs.

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