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Reviews

Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances

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ABSTRACT

The inflammation theory of depression, proposed over 20 years ago, was influenced by early studies on T cell responses and since then has been a stimulus for numerous research projects aimed at understanding the relationship between immune function and depression. Observational studies have shown that indicators of immunity, especially C reactive protein and proinflammatory cytokines, such as interleukin 6, are associated with an increased risk of depressive disorders, although the evidence from randomized trials remains limited and only few studies have assessed the interplay between innate and adaptive immunity in depression. In this paper, we review current knowledge on the interactions between central and peripheral innate and adaptive immune molecules and the potential role of immune-related activation of microglia, inflammasomes and indoleamine-2,3-dioxygenase in the development of depressive symptoms. We highlight how combining basic immune methods with more advanced 'omics' technologies would help us to make progress in unravelling the complex associations between altered immune function and depressive disorders, in the identification of depression-specific biomarkers and in developing immunotherapeutic treatment strategies that take individual variability into account.

Contents

1. Introduction

The immune system consists of biological structures and processes that help the organism adapt to physiological or psychological stressors.

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The outcome, inflammation, is a part of this system. It is a biological host defence mechanism characterized by increased blood flow and recruitment of innate immune cells to the site of injury. The link between increased inflammation and depression was detected in the early 1990s (Maes et al., 1990; Maes et al., 1991), leading to the formulation of the macrophage hypothesis of depression (also known as the cytokine hypothesis of depression (Maes, 1995; Smith, 1991). This model proposes that external and internal stressors trigger depressive behaviour by elevating the production of proinflammatory cytokines interleukin-1 (IL-1) and IL-6, as well as activating cell-mediated immunity. More recently, an abundance of observational, experimental and clinical evidence has emerged to suggest that the activation of innate immune mechanisms, especially proinflammatory cytokines IL-1, IL-6 and tumor necrosis factor alpha (TNF-α), as well as C-reactive protein (CRP), may contribute to the initiation and progression of psychiatric diseases, such as depression (Capuron et al., 2003; Dowlati et al., 2010; Gimeno et al., 2009; Howren et al., 2009; Kivimaki et al., 2014; Liu et al., 2012; Raison et al., 2010; Valkanova et al., 2013). Several recent publications have focused on these associations (Capuron and Miller, 2011; Dantzer et al., 2008; Haroon et al., 2012; Jones and Thomsen, 2013; McCusker and Kelley, 2013; Mills et al., 2013; Mitchell and Goldstein, 2014; Quan and Banks, 2007; Raedler, 2011; Rivest, 2009) and while the majority of this evidence involves proinflammatory cytokines and CRP, changes in the function and numbers of innate immune cells, namely natural killer (NK) cells, have also been examined.

In addition to increased innate immune responses, activation of cell-mediated adaptive immunity has been described in depressed patients. This includes increased CD4+/CD8+ T cell ratios, i.e. higher percentage of CD4+ T cells and a lower percentage of CD8+ T suppressor cells (Darko et al., 1988; Maes et al., 1992b; Tondo et al., 1988). Furthermore, elevated numbers and a higher proportion of activated T cells bearing activation markers CD2+ CD25+, CD3+ CD25+, HLA-DR+ (Maes et al., 1992a), higher blood levels of IL-2R (Liu et al., 2012) and increased number of B cell subsets (Maes et al., 1992c; Robertson et al., 2005) have been detected in patients with major depressive disorder compared with controls. On the other hand, reduced proliferative response of T cells to mitogen in subjects with depression has been shown in a meta-analysis (Zorrilla et al., 2001), suggesting that depression may be associated with concurrent activation and suppression of immune responses.

In this review, we present a model on co-operative mechanisms between innate and adaptive immunity in the periphery and central nervous system (CNS), and the potential role of such molecules in the pathology of depressive mood. We discuss the interrelations between cytokines, T cells, NK cells, inflammasomes, microglia, indoleamine-2,3-dioxygenase (IDO) and neurotoxic vs. neurotrophic factors, all of which have been suggested to contribute to the initiation and progression of depressive symptoms. Finally, we discuss how novel methodologies, such as the 'omics' technologies, might represent the next step in uncovering the relations between altered immune function and depressive disorders.

2. Evidence on immune–brain relations

In animal experiments, peripherally administered proinflammatory cytokines IL-1β and TNF-α as well as lipopolysaccharide (LPS) and synthetic compound mimicking viral infection (Poly (I:C)) have induced 'sickness behaviour' characterized by lethargy, depression, anxiety, loss of appetite, and sleepiness (Dantzer, 2001; Gibney et al., 2013). This response is thought to be caused by pro-inflammatory cytokines temporarily expressed in the brain during infection (Dantzer et al., 2008). In humans, injections with LPS (Reichenberg et al., 2001) or administration of typhoid vaccine (Harrison et al., 2009) have been shown to be related to an increased production of proinflammatory cytokines and subsequent decline in mood, while pre-treatment with an antidepressant drug, citalopram, a selective serotonin reuptake inhibitor, has reduced LPS-induced depressive symptoms in healthy subjects (Hannestad et al., 2011).

Information on brain-immune relations in the CNS has also been acquired using positron emission tomography (PET) to measure the density of translocator protein (TSPO), a microglia-derived protein showing increased expression during neuroinflammation. In one PET study, $TSPOV_T$ (volume distribution) was elevated in patients with more severe forms of depression (Setiawan et al., 2015). Another study failed to find differences in the levels of [^{11}C]PBR28VT, a ligand binding to TSPO, between individuals with mild-to-moderate depression and control subjects (Hannestad et al., 2013). These results suggest that neuroinflammatory activation via TSPO may only be observed in more severe forms of depression, but more research is needed to confirm these relations. Furthermore, cross-sectional design of these studies cannot inform about whether inflammation is a cause of a consequence of depression.

Additional evidence for immune–brain associations has emerged from clinical studies. For example, approximately 20–50% of cancer and hepatitis C patients treated with injections of interferon-α (IFN-α) have been estimated to develop clinically significant depression (Raison et al., 2005). IFN-α-induced depression has been associated with elevated serum levels of sIL-2r, TNF-α, and IL-6 (Wichers et al., 2007). Interestingly, there is also evidence to suggest that this IFN-α induced depression is responsive to conventional antidepressant treatments, an observation consistent with the hypothesized shared pathways between inflammation and idiopathic major depression (Capuron et al., 2002; Musselman et al., 2001).

Epidemiological studies provide further support for the association between altered inflammatory profile and depression. A recent cumulative meta-analysis on 31 cross-sectional studies on IL-6 and 20 studies on CRP showed a robust association between increased levels of these two inflammatory markers and major depression, although the relations between TNF-α and major depression were not confirmed in a total of in 31 studies due to extensive heterogeneity in study-specific effect estimates and inconsistencies between subgroups (Haapakoski et al., 2015). No consistent evidence support a link between IL-1β and depression (14 studies), which may in part be related to the very low concentrations of this cytokine in peripheral blood and a lack reliable detection methods. At least two meta-analyses support the existence of reduced proliferative activity of lymphocytes and lowered NK cell activity in depression (Herbert and Cohen, 1993; Zorrilla et al., 2001). Furthermore, increased number of leukocytes has been associated with depression (Zorrilla et al., 2001) whereas evidence regarding the number of different subsets of T cells, B cells, NK cells and NKT cells in depression is inconclusive. These findings suggest specificity in the associations of various inflammatory markers and depression but several methodological issues may also contribute to the observed inconsistencies, including the heterogeneity of depressive disorder and imprecise measurement of some subsets of immune cells.

Longitudinal analyses of observational data provide inconsistent information on the temporal order between CRP, proinflammatory cytokines and depression. In the Whitehall II study, for example, high levels of CRP and IL-6 at baseline have been associated with an increased risk of future cognitive symptoms of depression whereas baseline symptoms of depression did not predict the level of CRP or IL-6 at follow-up (Gimeno et al., 2009). This finding is in agreement with a study showing that elevated levels of IL-6 in childhood are associated with an increased risk of depression in young adulthood (Khandaker et al., 2014). Chronically elevated inflammation in the development of psychiatric symptoms is supported by data from Whitehall II study showing repeated measurements of IL-6 dose-dependently increasing the risk of future common mental disorder (Kivimaki et al., 2014). On the other hand, at least one study has found that somatic-vegetative symptoms of depression predicted 6-year change in IL-6 levels whereas baseline levels of neither IL-6 nor CRP were predictors of change in