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Hypothesis

Interleukin-10: A Key Cytokine in Depre

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Abstract

An increasing body of evidence implicates proinflammatory cytokin
Of notice, recent studies showed that anti-inflammatory cytokin
behavior. In this article, we propose that the anti-inflammatory c
most widely reported phenomenon observed in depressed patie
adrenal axis and the imbalanced production of cytokines. If
antidepressant therapy.

1. Introduction

The establishment of a bidirectional interaction between the immu
remarkable findings of the last decades. These two systems accor
body of evidence shows that both share common mediators, inclu
altered expression of these molecules, triggered by one of the sys
[1]. As a consequence, a disruption in this cross-talk has been
associated with several psychiatric disorders, in particular depressi

Major depression is a global public-health problem and a leading c

contributor to the global burden of disease in 2000 (in terms of DALYs). Depression is a heterogeneous disorder with a variable set of symptoms, diverse etiologies, and varied treatment. The etiology of depression is still controversial, and several models have been proposed to account for the communication between the immune and central nervous systems. One of the most proposed a role for cytokines in depression [4]. The “cytokine theory of depression” in the last two decades, proposes that enhanced production of pro-inflammatory cytokines is a pathogenesis of depression. Indeed, several studies show a significant association between pro-inflammatory cytokines (namely, IL-6, IL-1, IFN- γ , and TNF) among depressed patients. The administration of IFN- γ and IL-2, which is frequently used in the treatment of viral hepatitis and certain cancers, has been associated with depressed mood and symptoms of depression [8 - 10]. The fact that the symptoms associated with depression are relieved by the administration of antidepressant drugs [11].

The “cytokine theory of depression” has also been supported by animal models. Studies using these models demonstrated that alteration in the pro-inflammatory cytokine profile, changes overlapping with those found in depressed patients, including inflammation, immune dysfunction, and altered sleep patterns [12]. In further support of this theory, the chronic mild stress (CMS) protocol, which induces symptoms of depressive-like behavior in mice, is associated with increased expression of pro-inflammatory cytokines in the hippocampus [13]. Furthermore, the depressive-like behavior observed in mice is reversed by the administration of IL-1 [13] and, when mice lacking the expression of IL-1 are used in the CMS paradigm, the behavioral changes do not occur [13]. Interestingly, several cytokines more consistently upregulated in depression, such as IL-1, IL-6, and TNF, are also upregulated in the FST, that is, decreased signs of depressive-like behavior in mice. The FST is considered one of the gold standard tests to evaluate depression in mice. In addition, TNF activation also mediates depressive-like behavior in mice.

Although most studies on the “cytokine theory of depression” focus on pro-inflammatory cytokines, the role of anti-inflammatory cytokines has been receiving increasing attention. IL-10, an important anti-inflammatory cytokine, has been shown to be relevant in depression. Mice lacking expression of IL-10 (IL-10KO) show a decreased latency to immobility in the FST compared to wild-type (WT) mice in the FST [15]. These results demonstrate that IL-10 is a protective factor against a sign of depressive-like behavior in rodents. Remarkably, the depressive-like phenotype observed in the IL-10KO animals [15]. In further support of this theory, mice overexpressing this cytokine show a decreased depressive-like behavior in the FST [15]. In addition to the increased helplessness in mice that lack IL-10, the depressive-like behavior that modulation of IL-10 impacts on psychophysiological alterations in mice is the impairment in sleep behavior [16]. Interestingly, IL-10KO mice show increased sleep behavior. Exogenous administration of IL-10 modulates sleep behavior [17 -

Another feature commonly associated with depression is altered pain perception. Using the IL-10KO mouse model, that the absence of this anti-inflammatory cytokine leads to increased pain perception (i.e., the ability to sense painful stimuli). This study shows that the time to paw licking (the time that mice spend to avoid a heat stimulus) is significantly longer in IL-10KO mice compared with WT mice, and this result was confirmed by the blockage of IL-10 receptors. This evidence that IL-10 can also be involved in the common biological processes associated with depression.

The studies described above show that modulation of IL-10 impacts on several symptoms of depression, namely, helplessness, sleep disturbances, and pain perception. The fact that these symptoms which suggests a putative antidepressant effect of IL-10. The relevance for this hypothesis is the observation, in depressed patients, that the administration of increased IL-10 levels after treatment with several classes of antidepressant drugs.

Although it is becoming clear that modulation of IL-10 can lead to behavioral changes in animals, the mechanisms behind these alterations remain to be determined. One of the most obvious mechanisms through which IL-10 influences behavior is its effect on the levels of proinflammatory cytokines. In IL-10^{-/-} mice, the lack of IL-10 leads to an increased production of proinflammatory cytokines, which, according to the “cytokine theory of depression”, trigger depression. This mechanism suggests that depressive-like behavior in IL-10^{-/-} mice upon IL-10 administration is due to the increased levels of proinflammatory cytokines [26]. However, this possibility is not yet confirmed because we did not detect two of the most relevant proinflammatory cytokines (IFN- γ and TNF- α). Further studies are certainly necessary to clearly define how the lack of IL-10 influences behavior. It is possible that subtle (below currently detectable) levels of proinflammatory cytokines are present in the serum of IL-10^{-/-} mice, and/or that proinflammatory cytokines are present in specific brain regions, which may not be detectable in the serum.

The observations that systemic IL-10 administration to WT animals leads to increased motor activity and abnormal exploratory patterns [27] are similar to the hyperactive-like behavior observed in IL-10^{-/-} mice [15] indicate that peripheral actions of IL-10 may be involved. However, it is not clear how this cytokine acts within the central nervous system. IL-10 does not seem to cross the intact blood-brain barrier, at least in mice [28]. IL-10, like other cytokines, acts directly in the brain through regional actions in circumventricular organs and the choroid plexus, or by activating signals to specific brain nuclei [5]. Moreover, IL-10 has been detected in the brain [29]. Possible sites of expression are the endothelial cells of the brain capillaries (from where it would be secreted into the cerebrospinal fluid), and a recent study showed that several immune mediators are produced in the brain in response to inflammatory stimuli [32]. In addition, the IL-10 receptor has been found in oligodendrocytes [29, 30, 33]; probably because of a general distribution of the receptor in all five brain regions they analyzed (cortex, cerebellum, hippocampus, thalamus, and hypothalamus) [34].

A direct action of IL-10 within the central nervous system might be to prevent neuronal apoptosis. IL-10 has been shown to prevent cell death of glial cells [33, 35, 36]. Since an increase in neuronal apoptosis in the hippocampus has been observed in IL-10^{-/-} mice [38], this putative role of IL-10 in increasing neuronal survival should be considered as a possible mechanism of action in preventing depressive-like behavior.

The observation that IL-10^{-/-} mice show an increase in the activity of the hypothalamic-pituitary-adrenal (HPA) axis [15] offers another alternative mechanism for the action of IL-10. Indeed, it was shown that, even in the presence of corticosterone and that in the presence of a stressor the increase in corticosterone levels was significantly higher in IL-10^{-/-} mice [39]. These findings strongly suggest that IL-10 may have a role in the regulation of the HPA axis. The most consistent neurobiological alterations in depressed subjects are the hyperactive HPA axis and the associated glucocorticoid feedback sensitivity. It is plausible that IL-10 modulation of depressive-like behavior is mediated through its effect on the HPA axis. In accordance, IL-10 is able to suppress, in a dose dependent manner, corticosterone production in adrenal cells [41]. This effect appears to be mediated through the biosynthetic pathway of corticosterone [21, 40]. IL-10 is expressed in the zona fasciculata (the region responsible for the production of corticosterone) in the adrenal gland [41]. Accordingly, *in vivo* studies demonstrated that, under conditions of HPA axis activation, such as increased adrenal glands, decreased corticosterone levels were observed in IL-10^{-/-} mice [15, 39]. These findings strongly suggest that IL-10 acts through the regulation of corticosterone production by the adrenal gland [41]. A microarray analysis of the adrenal gland treated with IL-10 clearly showed that this anti-inflammatory cytokine downregulates several genes of the HPA axis [42]. Of notice, murine pituitary cells were found to express IL-10 [43].

IL-10 [43], and the presence of IL-10 was also found in human pituitary, IL-10 seems to have the same effect already described for the positive regulation of corticotrophin releasing factor (CRF) and ACTH. We noticed that while the studies in the hypothalamus and pituitary were in vivo, IL-10 in corticosterone production by the adrenal gland is a more in vivo studies. Taking into account that depression is often associated with a hypoactive HPA axis, we hypothesize that IL-10 has a pivotal role in the modulation of the impact on the etiology of depression.

Increases in glucocorticoid levels can occur daily in response to stress, leading to an enhanced production of IL-10 [47] which, in normal situations, maintains the HPA axis (Figure 1(a)). However, if these raises in glucocorticoids lead to a “resistance to glucocorticoid action” [40, 48]. In fact, impaired response to glucocorticoids is a hallmark of major depression and is reflected by decreased IL-10 production. This resistance to glucocorticoids was also described in IL-10 producing cells. A decrease in the production of IL-10 which might impact on the negative feedback loop of the adrenal glands. In addition, decreased IL-10 can promote an impaired HPA axis (Figure 1(b)). This hypothesis fits well with the idea that glucocorticoids trigger a proinflammatory action [49].

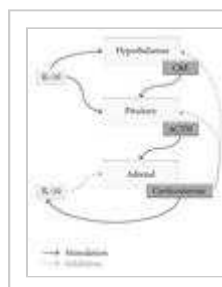


Figure 1: Schematic representation of the HPA axis regulation (a) in the normal situation and (b) during depression.

In the hypothesis outlined here we proposed IL-10 as an important cytokine in the milieu that are of recognized relevance for depression. This represents a link between the modulation of neural, endocrine, and immune systems. To further understand the etiology of depression, the cross-talk between these systems should become a target for novel antidepressant therapies.

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