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The Role of Interleukin-17A (IL-17A) in Depression

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Abstract

Context: The aim of this review was to address the recent data regarding the role of IL-17A in the pathogenesis of depression and its complications, such as cancer.
Evidence Acquisition: This review article summarizes the recent data on the role of IL-17A in depression, using the PubMed and Google Scholar databases.
Results: It has been documented that depression may alter the immune response via unknown mechanism/s. It is possible that immune responses and depression are linked via several molecules, including cytokines. IL-17A, a pro-inflammatory cytokine, participates in the pathogenesis of several inflammatory-based diseases, such as autoimmunity.
Conclusions: Due to the comorbidity of depression and chronic inflammatory processes, and depression's effect on the immune system, it may be hypothesized that the IL-17A cytokine plays a key role in the pathogenesis of depression.

Keywords: Depression, IL-17A, Th17

1. Context

Previous investigations have demonstrated that depressed patients have an altered immune response, ranging from the stimulation of inflammation to suppression of the immune response (1). Additionally, it has been documented that these patients suffer from several immune-related diseases, including cancers, chronic infections, and autoimmune diseases such as multiple sclerosis (2). According to these data, it has been suggested that depression may influence or alter the immune response. Although knowledge regarding depression is growing, the main responsible mechanism(s) regarding the altered immune response during depression has yet to be clarified. Recent investigations revealed that cytokines play a critical role in regulation of the immune response against microbial infections and the incidence of immune-related complications (3). IL-17A is an interesting cytokine whose function against infections and in immune-related complications, such as autoimmunity and inflammatory disease, has been identified (4-7). Moreover, it has been reported that IL-17A participates in the induction of tissue injury, especially in the central nervous system (8). Based on the fact that depressed patients suffer from altered immune responses, ranging from chronic inflammation to an impaired immune response (9), and also according to the important roles played by IL-17A in the outcome of the immune response (10), it may be hypothesized that this cytokine is significantly involved in complications of the immune response during depression. Therefore, the main aim of this review was to compile recent studies and findings regarding the relationship between IL-17A and depression.

2. Evidence Acquisition

This review aimed to address the recent data regarding the role of IL-17A in the pathogenesis of depression and its complications, such as cancer. This article summarizes the data based on a search of the PubMed and Google Scholar databases. The keywords used were "depression" and "IL-17A". Among the papers found in this search, 40 were selected for inclusion in the review.

3. Results

3.1. IL-17A: Structure, Receptors, and Main Source

Previous studies revealed that IL-17A, as a homodimeric protein, consists of 123 amino acids with a molecular

weight of 35 kDa (11). The T helper lymphocyte subsets are derived from precursor, naive T lymphocytes. Exposure to microenvironmental parameters, such as cytokines, as well as developmental history, determine which types of T helper will develop (12). It has been documented that cytokines play key roles in determining the outcome of naive T lymphocytes; accordingly, IFN-γ and IL-12 induce the Th1 subtype, while IL-4 develops the Th2 differentiation (13). Th17 differentiation is also induced by IL-6 in parallel with TGF-β and IL-1β (13). IL-23 and IL-21, respectively, participate in cell maintenance and Th17 lineage development in an autocrine manner (14). The cytokines implicated in Th17 development lead to upregulation of retinoic-acid-receptor (RAR)-related orphan receptor gamma t (RORγt) and RAR-related orphan receptor alpha (RORα), which are transcription factors that stimulate Th17 differentiation by upregulation of Th17-related genes, such as IL-21, IL-22, IL-26, IL-17A, and IL-17F (15). IL-17A participates either in the immune response against infection (a beneficial effect) (16) or in the pathogenesis of autoimmunity and immune-related disorders (17). Although IL-17A participates in autoimmunity, there is limited data regarding its role in the pathogenesis of immune-related disease, including inflammatory conditions and depression (18). On the other hand, IL-17A activates innate immune cells, playing an important role in the pathogenesis of immune-related disease (19).

3.2. Depression

Depression is a prevalent mental disorder that can be categorized as major depression, clinical depression, unipolar depression, or unipolar disorder (20). Depressed patients can suffer from a loss of interest or pleasure in enjoyable activities, very low mood, poor concentration and memory, reduced sex drive, insomnia, headaches, stroke, cardiovascular disease, and chronic obstructive pulmonary disease (21, 22). Depression is also strongly associated with suicide. The time of depression onset is between 20 and 30 years, when the immune system works on top activities (23). Interestingly, previous investigations have revealed that depressed patients have a shorter life expectancy because of greater susceptibility to infectious disease and inflammation-based diseases, such as autoimmunity and cancer (24). An altered immune response is a predisposing factor that exposes depressed patients to the risk of several types of chronic infections and cancers (2). Based on the aforementioned data, it has been suggested that depression may have detrimental effects on immune responses (25).

3.3. IL-17A and Depression

Based on the aforementioned data with regard to the natural properties of IL-17A and its role in the pathogenesis of inflammatory conditions, and due to the fact that depressed patients suffer from chronic and morbid inflammatory processes, it can be hypothesized that IL-17A may play a key role in the pathogenesis of depression. Choy et al. showed that IL-17A can promote depression via effects on the hypothalamic-pituitary-adrenal axis (26). Interestingly, elevated serum levels of IL-17A and decreased indexes of immunity in depressed animal models have been previously reported (27). These results were confirmed by Chen et al. who revealed that the number of Th17 cells, and the ratio of Th17/T regulatory cells and serum levels of IL-17A, were significantly increased in depressed patients compared to healthy controls (18). Upregulation of IL-17A in an animal model of depression has also been reported by Kim et al. (25). Overall, according to the literature, it appears that Th17 cells and/or the expression of IL-17A are significantly associated with the pathogenesis of depression, and the parameters that decrease the expression of IL-17A can be considered potential candidates for adjuvant therapy of depression. Several studies have investigated the effects of antidepressant drugs on the expression of this cytokine. For example, Munzer et al. reported that escitalopram, an antidepressant drug, decreased IL-17A levels in depressed patients (28). Another study demonstrated that desipramine, another antidepressant drug, leads to attenuation of Th17 cells (29). Tallerova et al. showed that treatment of depressed C57BL/6 male mice with an antiasthenic drug, ladasten [N-(2-adamantyl)-N-(para-bromophenyl)amine], led to downregulation of IL-17A (27). Another study demonstrated that quetiapine, an atypical antipsychotic drug that is used for treating depression, could decrease expression of IL-17A in a depressed animal model (30). Recently, Brunoni et al. reported that antidepressant treatment with sertraline and transcranial direct current stimulation (tDCS) resulted in decreased serum levels of IL-17A in depressed patients compared to non-treated patients (31). Therefore, based on the presented data, it may be concluded that one of the main mechanisms of these drugs is to downregulate IL-17A expression and to diminish the number of Th17 lymphocytes. In contrast, there are studies revealing that some antidepressant drugs lack these effects; for instance, Kim et al. reported that serum levels of IL-17A and its related cytokine, IL-23, were not altered after antidepressant treatment (32). Furthermore, it has been established that ladasten is unable to change the expression of IL-17A in mice with experimental depression-like syndrome (33). Since these studies are different in terms of sample sizes, ethnic groups, and the states of depression, more studies are warranted to shed more light on this subject.

Cancer incidence is higher in depressed patients than in healthy controls, and it has been shown that an atten-

uated immune response is one of the main responsible mechanisms for this (34). It appears that the upregulation of IL-17A is responsible for attenuating the immune response in these patients. Zhao et al. reported that IL-17A promotes the development of B7-H1(+) macrophages (Mphis), which in turn suppresses T cytotoxic lymphocyte functions (35). It seems that IL-17A is also directly involved in the promotion of cancer in depressed patients. Gu et al. demonstrated that IL-17A induces hepatocellular carcinoma (HCC) development via the protein kinase B (PKB) molecule, also known as Akt, which results in activation of the IL-6/JAK2/signal transducer and activator of the transcription 3 (STAT3) pathway (36). Additionally, it has been demonstrated that IL-17A induces STAT3, an important transcription factor involved in the pathogenesis of cancer, phosphorylation, and tumor vascularity (36). Previous studies reported that nuclear factor-κB (NF-κB) signaling is an important pathway that is involved in the pathogenesis of cancer via increased expression of matrix metalloproteinase (MMP)2 and MMP9 (37). MMP2 and MMP9 play critical roles in the induction of metastasis (37). Interestingly, it has been documented that IL-17A is able to increase the activity of the NF-kB signaling pathway (37). Induction of neoplastic transformation via activation of tumor progression locus 2 (TPL2) is another function of IL-17A (38). Based on these studies, it may be concluded that upregulation of IL-17A in depressed patients can be considered one of the main responsible mechanisms that results in the increased risk of cancer in these patients.

Interestingly, in addition to depression, other psychiatric disorders are also associated with upregulation of IL-17A. For instance, a positive association between IL-17A and mental disorders such as anxiety was previously reported (39). Thus, it appears that IL-17A may participate in the pathogenesis of many psychiatric disorders, including depression.

4. Conclusions

According to the studies presented here, it seems that IL-17A plays an important role in the pathogenesis of depression, especially via its detrimental effects on the immune response. Meanwhile, the studies suggest that IL-17A may be significantly involved in the development of depression-related cancers. Furthermore, it has been shown that depressed patients suffer from chronic inflammatory conditions, and according to the findings presented in this study, it seems that IL-17A is a critical factor that accelerates these processes. Therefore, it can be concluded that the control of Th17 function can be considered as a future therapy to improve the quality life of these patients.

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