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Commentary

IL-17-mediated depression in psoriatic disease: why the brain is not the only one that matters

Running title: IL-17 and depression in psoriatic disease

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Abstract

This commentary discusses the role of IL-17 in the depression associated with chronic immune-mediated diseases. It uses as psoriatic disease as a model, since there is a consensus regarding the pivotal role of IL-17 mediated immunity in the induction of psoriasis and psoriatic arthritis in a considerable proportion of the affected patients. We argue that if IL-17 plays a role in the induction of depression and/or its progression overtime, patients treated with blockers of IL-17 must show a significant improvement, and that their improvement must be analogous to- or closely related to- the extent of IL-17 inhibition. Though we understand that such a scenario is very simplistic, taking into account the complex interaction between the brain and the affected tissues, we postulate that it can be still possible to dissect the underlying pathophysiological mechanisms, if the focus of the translational research is to be directed towards assessing the IL-17 axis and its relation to brain development and depressive disorders.

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I. INTRODUCTION

The role of the cytokine milieu in the induction of depression is a topic, which warranties immediate attention. Patients with chronic inflammatory diseases, such as patients with psoriatic disease, irrespectively of whether they suffer from psoriasis or psoriatic arthritis, experience depressive disorders. Those disorders are not always analogous to the degree of the underlying inflammation, raising concerns as to whether the progress of the disease per se or the underlying cause of the inflammatory disease has an impact in the induction of depression. Amongst the inflammatory cytokines, which are placed on the center of the ongoing research, IL-17 has received special attention (1). Others and we have considered that IL-17 and/or IL-17/IL/23 axis may indeed participate in the development and perpetuation of depression in patients with IL-17-mediated immune/autoimmune disorders (2). We used psoriatic disease as a model to study that hypothesis, as we have been able to witness in clinical and experimental grounds the instrumental role of IL-17 in these disorders (2-12). In fact, we have gone one step further to formulate the hypothesis that depression, obesity and IL-17 are interlinked, at least in psoriatic disease. Our hypothesis was based on solid grounds provided by emerging basic and clinical research [reviewed in].

Herein, we discuss some recent findings that we feel can participate in the ongoing debate.

II. IL-17, TH17 AND DEPRESSION

In a recent study, Kim et al have provided interesting data. These investigators have postulated that stressful events during brain development are associated with increased expression of IL-17. Such an increase may lead to undesirable persistent effects, namely long-lasting depression in young adulthood. To assess their hypothesis, they performed experiments in a murine model asking

whether IL-17 is involved at any stage of chronic depression-like behaviour induced by cumulative mild stress during a critical developmental period.

Over the years, it has become apparent that that IL-17 and IL-17-producing cells are involved directly or indirectly in the induction of major depressive disorders, irrespectively of whether those disorders are associated with immune-mediated and autoimmune diseases or not (13-16). Clinical data provided evidence of higher levels of IL-17 in adult patients with depression compared to healthy controls (14, 17). The percentage of Th17 cells in those patients appears to be higher compared to their control counterparts (18). In experimental animals, Th17 cells are increased (compared to what is expected in normal brains) in the brains of the learned helplessness rodent model (19, 20). Also in experimental depression, data suggest that behavioral changes may intently correlate with the imbalance between Th17 and Treg cell subsets (21). In the clinical setting such a fine balance and in particular its disturbance may play a vivacious role in autism spectrum disorders (22). Also, the imbalance of Th17/Tregs may also participate in the induction and/or progression of depression and anxiety during pregnancy (23). Th17-induced neuronal dysfunction can be irreversible, and this may be important for medications able to inhibit IL-17 or Th17-mediated inflammatory processes (24-26).

III. IL-17, TH17, STRESS AND DEPRESSION

In their murine model exposed to cumulative mild stress (CPMS; cumulative mild prenatal stress, mild maternal separation, and mild social defeat), Kim et al (27) found that their CPMS mice had raised IL-17 levels in the brain and activated microglia. In view of those findings, the Authors speculated that elevated IL-17 levels initiated by cumulative mild stress in early life might represent a likely facilitator in provoking and supporting anxiety- and depression-like behavior in young adulthood. To provide further support for that, they compared the depressive symptoms and the level of IL-17 in the CPMS group with a single or double combinations group of mild stress including mild social defeat stress. Indeed, IL-17 levels in the brain of CPMS mice were higher than single (S) or double stressor groups (PS, MS) (27). Of importance, the extent of depressive symptoms appeared to be correlated with the elevated levels of IL-17 in the brain. Moreover, they have found an increase of Th17 cells in the brains of CPMS mice. Finally, they provided data supporting that nti-IL-17 treatment ameliorates anxiety- and depression-like behaviors in those mice (27). Indeed, when they inhibited IL-17 via anti-IL-17/IL-17A antibody treatment those mice had significantly less anxiety compared the untreated mice. According to the investigators the effect of anti-IL17/IL17A treatment is further indicating that accumulative mild stress in early life is indeed induced by disproportionate IL-17, which is most likely produced by Th17 cells (27). These cells and their produced pro-inflammatory cytokine may provoke a persistent inflammatory response, which can lead to brain damage and induction of depressive symptoms in young adulthood (27).

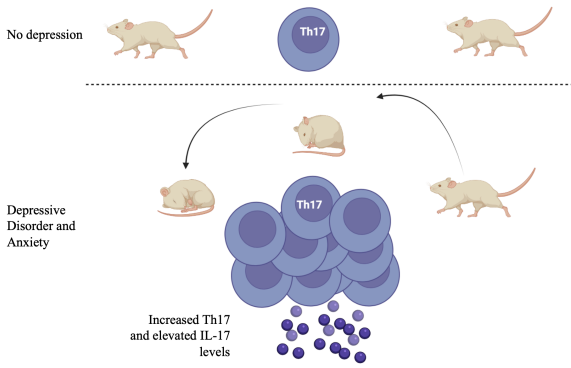

Fig. 1 A hypothesis of Th17/IL-17 mediated depression.

IV. ANTI-IL-17 AND DEPRESSION IN PSORIATIC DISEASE

A recent study has reported data suggesting that coptisine significantly reduces imiquimod-induced psoriasis-like skin lesions, as well as anxiety-like behavior in a murine model (28). This is important because Coptidis Rhizoma, a coptisine-containing herb also known as Huanglian in China, as well as coptisine itself appear to exert anti-neuroinflammatory effects in stress-exposed mice. Coptisine is one of the major alkaloids of Coptidis Rhizoma, a traditional medicinal herb, which is widely used in China to treat a broad range of inflammatory diseases, including immune-mediated skin diseases, such as psoriasis and atopic dermatitis (29, 30).

At the clinical level, it is well known that patients with psoriatic disease who have elevated IL-17A have also increased risk for depressive and anxiety disorders. A recent clinical report publishing data extrapolated from the

SUPREME study raised further expectation on the likely link between IL-17 inhibition and depression-free symptoms (31). The study reports on the post hoc analysis of 433 patients with psoriasis receiving 300mg secukinumab, a fully human IgG1κ mAb inhibiting IL-17A, in achieving minimal disease activity (MDA). The Authors reported that amongst the clinical factors that positively influenced MDA at Week 16 were absence of depression and anxiety (31). Rivera-Oyola et al reported three patients with moderate-to-severe psoriasis and comorbid depression, who were successfully treated with brodalumab, a fully human IgG2 mAb that binds and inactivates the IL-17A receptor (32). Of interest, in two of those, depression was partially or fully resolved following treatment, suggesting that the blocking of the IL-17 receptor had a direct or indirect effect on their depressive disorder (32).

V. CONCLUSIONS

In conclusion, the effect of IL-17 neutralization in depressive disorders and anxiety related to psoriatic diseases remains elusive. While some data suggest that IL-17A blocking may exert a beneficial effect in ameliorating anxiety and depressive mood, meticulous assessement in clinical and basic research is needed to provide conclusive results. The wide clinical application of IL-17 inhibitors in the routine treatment of psoriatic disease may assist efforts to conclude on this matter in the near future.

AUTHORS CONTRIBUTIONS

EZ and DPB had the original idea and scripted the original draft and subsequent drafts; AID and ST scripted parts of the manuscript and reviewed the literature. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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