Editorial paper

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Interleukin 17 and Treg – a common pathomechanism and a new target of therapy in rheumatic diseases and depression

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Depression is one of the most common mental disorders. It affects 10–15% of the population [1]. Depression is closely linked with deterioration of the quality of life of patients and has a negative impact on the course of coexisting diseases. in Europe, 4.5% of the population suffer from rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, psoriatic arthritis, and ankylosing spondylitis. The percentage of people in this group suffering from depression is elevated threefold – to approximately 50% [2]. Therefore, it is extremely important to learn about the interdependence of these diseases.

Research conducted in the last decade shows that the inflammatory process, which is the basis for the development of both diseases, is a significant aspect of this co-morbidity. In the course of depression, it reduces the availability of tryptophan for serotonin production. This leads to intensification of neurodegenerative processes [3]. A proper cognitive and emotional response requires balanced cooperation of the limbic system structures with the amygdala and the hippocampus as well as the prefrontal cortex. This area has a regulatory role. An imbalance in the presence of the inflammatory process causes hyperactivity of limbic structures accompanied by decreased inhibitory capacity of the prefrontal cortex. It is manifested among others in the form of depression. Patients show persistent overreaction to negative stimuli [4].

The immune and affective responses are inseparable aspects of the response to changes in the body (biological or psychological stressors). The immune system has been a coordinating and integrating system since the very beginning. Its nature and significance in the occurrence of depressive disorders are confirmed by its systemic omnipresence. Additionally, both systems have the same critical developmental moments [5]. They can have a protective role or amplify harmful reactions, such as an increase in interleukin 6 (IL-6) or anxiety, which are a source of proinflammatory activity of the immune system. This is possible by deregulating the hypothalamic –pituitary–adrenal axis (HPA) [6].

The process of differentiation of CD4+ lymphocytes is important in the development of the immune system. It enables conversion of one type of cells into another type but is also flexible because the transformations can be reversible. The phenotypic and functional boundaries between their subpopulations are fluid. An important aspect is the interaction between the environment and genes. Fetal life and the time after childbirth, until about the first year of life, is a period of particular susceptibility to epigenetic factors. There are important developmental periods in prenatal life during which gene expression is reprogrammed, referred to as different genome methylation patterns. The cytotoxic effect modulates physiological epigenetic processes, which affects gene expression and the determination of the phenotype characteristic for various forms of pathology. These may cause life-long ailments, including depression and rheumatic diseases [7].

When both IL-6 and TNF are found in the environment of a CD4+ T cell, the AHR receptor (aryl hydrocarbon receptor) is activated. Its presence specifically influences the expression of cytokines characteristic for Th17 [8]. A significant increase in the concentration of proinflammatory cytokine IL-1, IL-6, TNF-α and others in the mother's organism during the fetal period, as well as in the subsequent development of the child's organism, affects the differentiation of CD4+ T cells into Th17 lymphocytes in inflammation [9].

The T helper 17 cell (Th17) profile and regulatory T cells (Tregs) are important in the development of depressive disorders. Patients have decreased Treg levels and elevated IL-17 levels [10]. Co-morbidity and coordi-

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nated treatment of rheumatic diseases and depression are of high importance. The impact of both diseases is directly proportional. Due to the common inflammatory background, the presence of one symptom intensifies the other; hence it is crucial to treat the first symptoms of depression, which will prevent the exacerbation of rheumatic disease, and vice versa.

To sum up, the common therapeutic approach makes it possible to achieve remission of symptoms with a single treatment regimen. The use of biological drugs inhibiting the action of proinflammatory cytokines or their signal pathways, especially adalimumab, etanercept and ustekinumab, significantly improves the mood of patients and is associated with a statistically significant reduction in the assessment of depressive symptoms by patients [11]. At the same time, anti-inflammatory drugs increase the effectiveness of antidepressants [12]. A new direction of treatment is Treg transplantation – as in the treatment of diabetes in early stages [13]. Simultaneous administration of IL-6 blocker could be a novelty. This protocol inhibits the inflammatory reaction and strengthens the influence of T lymphocytes, causing a strong inhibitory effect when the immune system starts to destroy its own tissues and organs. Therefore, the immunosuppressive action of Treg lymphocytes is sometimes referred to by analogy as "smart steroids".

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References

1. Bromet E, Andrade LH, Hwang I, et al. Cross national epidemiology of DSM-IV major depressive episode. BMC Med 2011; 9: 90.
2. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29: 201-217.
3. Gałecki P, Talarowska M. Neurodevelopmental theory of depression. Prog Neuropsychopharmacol Biol Psychiatry 2018; 80: 267-272.
4. Talarowska M, Galecki P. Cognition and emotions in recurrent depressive disorders – the role of inflammation and the kynurenine pathway. Curr Pharm Des 2016; 22: 955-962.
5. Talarowska M, Szemraj J, Berk M, et al. Oxidant/antioxidant imbalance is an inherent feature of depression. BMC Psychiatry 2015; 15: 71.
6. Hodes GE, Ménard C, Russo SJ. Integrating Interleukin-6 into depression diagnosis and treatment. Neurobiol Stress 2016; 4: 15-22.
7. Petronis A. Epigenetics and unifying principle in the aetiology of complex traits and disease. Nature 2010; 465: 721-727.
8. Ziegler SF, Buckner JH. FOXP3 and the regulation of Treg/Th17 differentiation. Microbes Infect 2009; 11: 594-598.
9. Wilson CB, Rowell E, Sekimata M. Epigenetic control of T-helper-cell differentiation. Nat Rev Immunol 2009; 9: 91-105.
10. Waisman A, Hauptmann J, Regen T. The role of IL-17 in CNS diseases. Acta Neuropathol 2015; 129: 625-637.
11. Fleming P, Roubille C, Richer V, et al. Effect of biologics on depressive symptoms in patients with psoriasis: a systematic review. J Eur Acad Dermatol Venereol 2015; 29: 1063-1070.
12. Gałecki P, Szemraj J, Bieńkiewicz M, et al. Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients. Hum Psychopharmacol 2009; 24: 277-286.
13. Marek-Trzonkowska N, Myśliwiec M, Dobyszuk A, et al. Therapy of type 1 diabetes with CD4+CD25 high CD127-regulatory T cells prolongs survival of pancreatic islets – Results of one year follow-up. Clin Immunol 2014; 153: 23-30.