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Стаття надійшла 12.02.2020 р.

DOI 10.26724/2079-8334-2021-2-76-37-42
UDC 616.517-056.5: 615.26

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IL-33 AS A BIOMARKER OF INFLAMMATORY ACTIVITY IN PSORIASIS PATIENTS WITH CONCOMITANT OBESITY

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Recently, there has been an increase in cases of comorbid psoriasis and obesity, which leads to severe, atypical, disabling, and therapy - resistant forms of dermatosis which form a vicious circle at the level of the immune system, which must be broken in order to treat these diseases successfully. In this study, we examined the serum IL-33 level and its association with rates of systemic inflammation, the severity of psoriasis and obesity. We applied the enzyme immunoassay to evaluate the severity of systemic inflammation. We determined the concentration of IL-33, interleukin-6, and high sensitivity C-reactive protein in the serum. PASI was used to assess the severity of psoriasis. We used BMI to determine the extent of alimentary obesity. There was a positive statistically significant correlation between the serum IL-33 concentration, the severity of psoriasis, the level of systemic inflammation, and the degree of alimentary obesity.

Key words: psoriasis, alimentary obesity, IL-33, clinic.

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ІЛ-33 ЯК БІОМАРКЕР АКТИВНОСТІ ЗАПАЛЕННЯ ХВОРИХ НА ПСОРІАЗ ІЗ СУПУТНІМ ОЖИРІННЯМ

Останнім часом спостерігається збільшення випадків коморбідності псоріазу та ожиріння, що призводить до тяжких, атипових, інвалідизуючих та резистентних до терапії форм дерматозу, які мають ідентичні патогенетичні механізми запальних процесів, що формують порочне коло на рівні імунної системи, яке необхідно розірвати для успішного лікування даних захворювань. У цьому досліджені ми вивчали рівень ІЛ-33 в сироватці крові та його зв'язки з показниками СЗ, тяжкістю перебігу псоріазу та ожиріння. Ми використовували імуноферментний метод для оцінки вираженості показників СЗ. В сироватці крові визначали концентрацію ІЛ-33, IL-6 та вч-СРБ. Для визначення тяжкості перебігу псоріазу використовували індекс PASI. Для визначення ступеня аліментарного ожиріння використовували ІМТ. Спостерігався позитивний статистично значимий кореляційний зв'язок між концентрацією ІЛ-33 в сироватці крові, тяжкістю перебігу псоріазу, рівнем показників системного запалення та ступенем аліментарного ожиріння.

Ключові слова: псоріаз, аліментарне ожиріння, ІЛ-33, клініка.

The study is a fragment of the research project "Study of the pathogenetic role of the circadian molecular clock in the development of metabolic diseases and systemic inflammation, and the development of a treatment methodology focused on these processes" state registration No. 0120U101166.

Psoriasis is a chronic, inflammatory, recurrent, immune-mediated disease of the skin involving several organs and systems in the pathological process. According to the results of clinical and epidemiological studies, about 3–4 % of the population of our planet, regardless of gender, age and ethnic group, suffers from psoriasis, and the share of this pathology in the general structure of skin diseases, according to various authors, ranges from 1 % to 40 %. However, despite the considerable spread of psoriasis and a large amount of research on this problem, there is still no single view of the pathogenesis

of this dermatosis. In order to objectively understand the pathogenesis of psoriasis, it is necessary to take into account the understudied comorbidity of this disease [4].

Numerous clinical studies show that the number of cases of comorbid psoriasis and obesity has recently increased, leading to severe, atypical, disabling, and therapy-resistant forms of dermatosis. All this significantly impairs the quality of life and reduces the capacity and social activity of patients with psoriasis, which determines not only the medical but also the social significance of the problem [2]. Obesity can be both an independent multifactorial disease – primary obesity (alimentary-constitutional), and a syndrome that accompanies the course of other diseases – secondary obesity (symptomatic). In the structure of morbidity, primary obesity occurs in 95 % of patients, secondary – only in 5 % [9]. The main etiological reason for the development of primary obesity is the alimentary factor. Alimentary obesity develops because of metabolic and eating behavior disorders. It is characterized by the accumulation of adipose tissue in the body. The inhabitants of developed countries are currently the hostages of readily available food. In this context, the food moves from the category of necessity to the category of pleasure. Thus, eating disorders are gradually formed, which anticipates the development of obesity. Most often, obesity occurs because of consuming foods of high-energy value (caloric content) in combination with insufficient physical activity and a factor of genetic susceptibility. However, in isolated cases, the occurrence of the disease against the background of genetic endocrine disruptions or malignancies was observed. A person is considered obese if the body mass index (BMI) exceeds 30 kg/m² [1].

The literature has broadly covered the issue of identical pathogenetic mechanisms of inflammatory processes in psoriasis and obesity, which form a vicious circle at the level of the immune system, which must be broken in order to treat these diseases successfully [3]. Recently proved that the general pathogenesis of the inflammatory process may underlie comorbidity, such as activation of the kappa – B nuclear factor (NF-κB) caused by interleukin-33 (IL-33). IL-33 expression is observed in adipocytes and macrophages in adipose tissue, and its production by adipose tissue increases with weight gain, which reflects a close link between obesity and inflammation [9, 11].

IL-33, in turn, activates mast cells, basophils, eosinophils, and natural killer cells, promoting inflammatory and autoimmune diseases. In patients with obesity, chronic low - intensity inflammation can be detected by elevating the levels of hs - CRP and inflammatory cytokines such as IL – 33 and interleukin-6 (IL-6) in the blood plasma. The results of the studies show a threefold increase in the expression of IL-33 subcutaneous adipose tissue in patients with obesity. In psoriasis, IL-33 is secreted during cell damage to alert the immune system and initiate inflammation by activating the NF-κB immune response pathway [10, 13].

The purpose of the study was to establish the level of IL-33 in serum, and its relationship with indicators of systemic inflammation, the severity of psoriasis, the degree of obesity in patients with psoriasis and concomitant obesity.

Materials and methods. The study embraced 80 patients, diagnosed with psoriasis vulgaris, advanced stage, moderate severity, with concomitant grade I-II alimentary obesity, 51 (64 %) men, and 29 (36 %) women, aged from 35 to 65 years. The research was approved by the Bioethics and Ethical Issues Committee of the Poltava State Medical University. All patients signed an informed consent form to participate in the study. All patients had extensive psoriatic lesions. In determining the number of psoriasis recurrences per year, we found that relapse was observed once a year in 2 (2.5 %) patients, 2 times a year in 11 (14 %) patients, 3 times a year in 46 (57.5 %) patients, and 4 times a year in 21 (26 %) patients. The Psoriatic Area and Severity Index (PASI) [14] was used to assess the severity of psoriasis.

We determined the body mass index (BMI) to assess the severity of alimentary obesity [7]. The study included individuals with a BMI of 30–40 kg/m².

To assess the severity of systemic inflammation (SI), we determined the concentration of interleukin-33 (IL-33), interleukin-6 (IL-6), and high sensitivity C-reactive protein (hs-CRP) in the serum of patients by the enzyme immunoassay using a multichannel photometer “STATFAX – 303” (USA). For the quantitative measurement of indicators, we used commercial test systems “interleukin-6 – ELISA – BEST” (Russia), “CRP – ELISA – BEST” (Russia), “Human IL-33 ELISA Kit” “eBioscience™/Affymetrix” (USA) according to recommended techniques. The obtained results were compared with the reference values as recommended by manufacturers of diagnostic test systems. Statistical analysis of the results was performed using Statistica 7.0. The research found a normal

distribution of indicators in the studied groups. The difference with indicators in apparently healthy subjects was considered reliable with a probability of error p<0.001. A paired factor correlation analysis was conducted to determine the linear regression and to calculate the Pearson correlation coefficient (R).

Results of the study and their discussion. In all patients of the study group, we measured anthropometric parameters, determined the degree of obesity by BMI, analyzed the anamnesis of life, disease, and conducted research of SI according to the level of IL-33, IL-6, and hs-CRP in the serum of patients.

In the process of examination of patients who made up the group of study and calculation of BMI under the classification of obesity by BMI, we found that 29 (36.25 %) patients had grade 1 obesity, whereas 51 (63.75 %) patients had grade II obesity.

Based on the clinical presentation of psoriatic lesions, we calculated the PASI index to determine the severity of psoriasis. The average index of the PASI index in the studied patients was (21.8±1.4), which corresponds to the average severity of psoriasis (table 1).

Table 1

Clinical and anthropometric parameters in patients with extensive psoriasis and concomitant alimentary obesity (n = 80)

Parameter	BMI (kg/m²)	PASI (points)
Value	36.7±2.04	21.8±1.4

In the study of SI indicators, we calculated the average IL-33, IL-6, and hs-CRP values. The analysis of the obtained results revealed that all patients demonstrated an increase of hs-CRP (13.99±2.98 IU/l), 79 patients – increased IL-33 index (73.69±7.5 pg/ml) and 78 patients – increased IL-6 (13.01±1.54 pg/ml), indicating the presence of a systemic inflammatory process in all examined patients (Table 2).

Table 2

Indicators of systemic inflammation in patients with extensive psoriasis with concomitant alimentary obesity (n=80)

Parameter	IL-33 (pg/ml)	IL-6 (pg/ml)	hs-CRP (IU/l)
Value	73.69±7.5	13.01±1.54	13.99±2.98
Reference value	0-54.8	0-10	0.068-8.2

We performed a paired correlation analysis of the studied indices to identify the relationship between IL-33 indices by SI clinical manifestations of psoriasis and the degree of alimentary obesity.

Investigating the comorbidity of psoriatic disease and obesity, we conducted a correlation analysis between the PASI index and BMI. The results of the study showed a strong positive correlation between these parameters (R=+0.79; p<0.001) (fig. 1D).

Investigating the role of SI in the pathogenesis of psoriasis, we performed a paired correlation analysis between the PASI index and the level of SI in the serum (IL-33, IL-6, hs-CRP). The results of the study showed a very strong positive correlation between the PASI index and IL-33 (R=+0.91; p<0.001) (fig. 1A), a strong positive correlation between the PASI index and hs-CRP (R=+0.78; p<0.001) (fig. 1F), and a moderate correlation between the PASI index and IL-6 (R=+0.69; p<0.001) (fig. 1G).

Investigating the role of SI in the pathogenesis of obesity, we conducted a paired correlation analysis of BMI and serum levels of SI (IL-33, IL-6, hs-CRP). The results of the study showed a strong positive correlation between BMI and IL-33 (R=+0.86; p<0.001) (fig. 1E), between BMI and hs-CRP (R=+0.71; p<0.001) (fig. 1F), and a moderate positive correlation between BMI and IL-6 (R=+0.59; p<0.001) (fig. 1G).

Investigating the dependence of SI in the serum of psoriasis patients with concomitant obesity, we conducted a correlation analysis between IL-33, hs-CRP, and IL-6. The results of the study showed a strong positive correlation analysis between IL-33 and hs-CRP (R=+0.77; p<0.001) (fig. 1H), between IL-6 and hs-CRP (R=+0.76; p<0.001) (fig. 1I), and a moderate positive correlation between IL-33 and IL-6 (R=+0.69; p<0.001) (fig. 1J).

Correlation analysis: (A) BMI with the PASI index; (B) IL-33 with the PASI index; (C) hs-CRP with the PASI index; (D) IL-6 with the PASI index; (E) BMI with IL-33; (F) BMI with hs-CRP; (J) BMI with IL-6; (H) IL-33 with hs-CRP; (I) hs-CRP with IL-6; (J) IL-33 with IL-6.

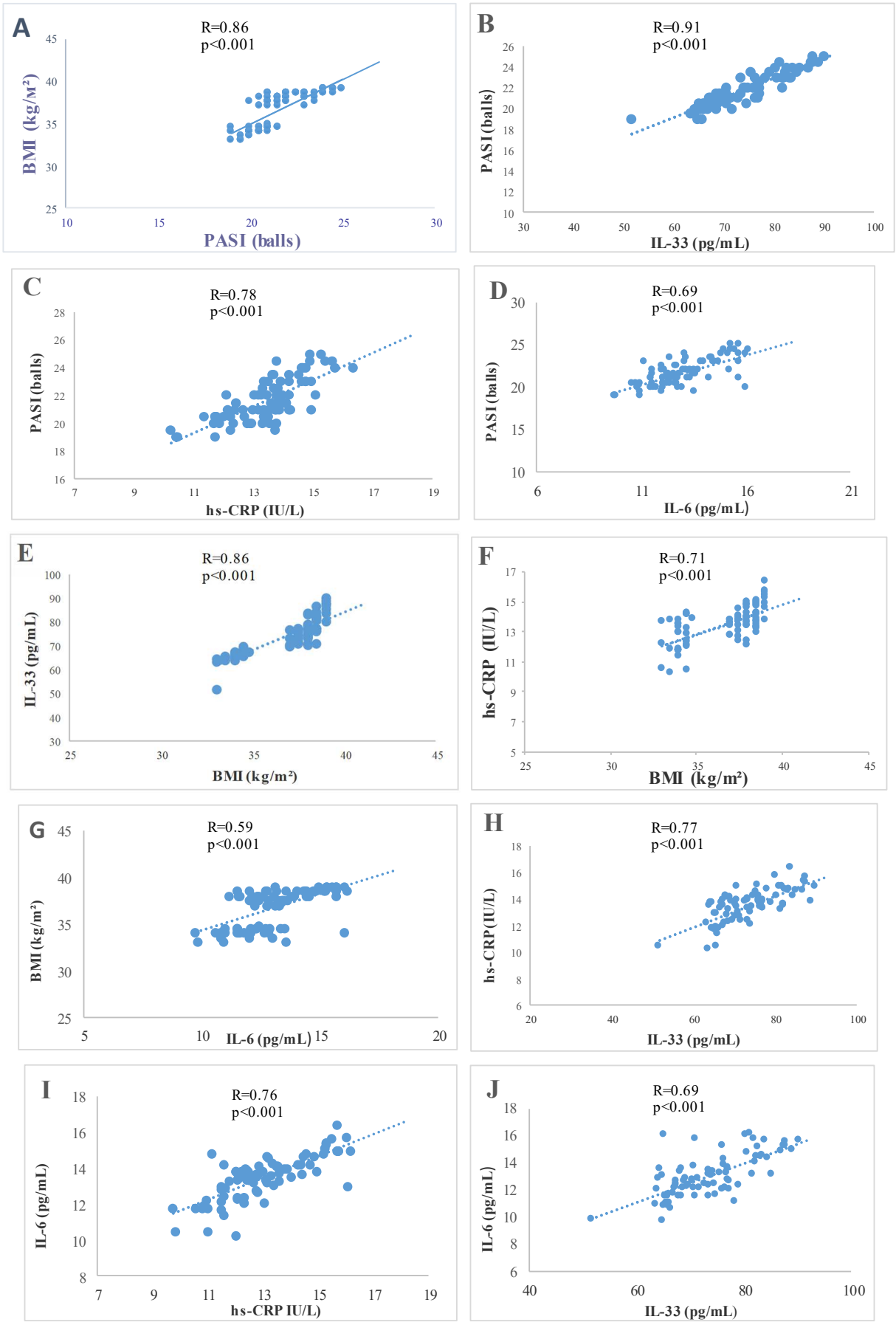

Fig. 1. Correlation relationship between interleukin-33 and clinical and laboratory parameters in psoriasis patients with concomitant grade I-II alimentary obesity. Abbreviations: BMI – body mass index; hs-CRP – high sensitivity C-reactive protein; IL-33 – interleukin-33; IL-6 – interleukin-6.

The severity of psoriasis in patients with grade I-II alimentary obesity is associated with increased expression of IL-33. The results of correlation analysis showed a very strong correlation between the level of IL-33 in serum and the severity of psoriasis by the PASI index. Thus, IL-33 is a significant biomarker of psoriasis intensity. IL-33, as the major cytokine in the pathogenesis of psoriasis, acts as a signaling molecule for type I macrophages that produce inflammatory cytokines, enhancing the inflammatory response. This is evidenced by the fact that local skin damage, which is caused by dryness and itching, manifested as a positive Koebner's symptom, contributes to the increase of IL-33 in skin biopsy specimens and the bloodstream in patients with psoriasis. IL-33 is known to belong to the IL-1 family and has similar properties to IL-1 and fibroblast growth factor. Expression of IL-33 occurs mainly in skin fibroblasts, epithelial cells of the bronchi and lower respiratory tract, smooth muscle cells of the lungs and skin. IL-33 expression is activated after pro-inflammatory stimulation, and its level correlates with the level of inflammation in the tissue. IL-33 is a dual - function cytokine that acts as a traditional cytokine through the activation of the ST2L receptor complex and as an intracellular nuclear factor with regulatory transcriptional properties. Scientists from all around the world have studied the role of IL-33 in the pathogenesis of psoriasis. The researchers found a correlation of IL-33 level with itching, dryness, erythema, edema, skin lichenification, and the PASI index in psoriasis patients. Investigation of IL-33 in skin biopsies of psoriasis-positive skin with a positive Koebner's symptom showed an increase in its levels at days 3 and 7. Studies have shown a strong activation of IL-33 expression in the nucleus of keratinocytes and the serum of patients with psoriasis [3, 11].

In our study, a high correlation of BMI with the PASI, IL-33, hs-CRP index was obtained and may indicate the mutual aggravation of psoriasis and alimentary obesity. According to statistics conducted in the US for two years, patients with psoriasis have an average body weight of more than 90 kg. Analyzing BMI and severity of psoriasis using the PASI index, patients with psoriasis had significantly higher BMI. A positive correlation was observed between BMI and the PASI index, indicating high comorbidity of obesity and psoriasis [12]. A statistically significant increase in systemic cytokine pro-inflammatory potential is a specific feature of pathogenesis in patients with obesity psoriasis, in contrast to patients without obesity. One should keep in mind that excessive fat deposition embraces not only the accumulation of excess fat cells overloaded with triglycerides but also an essential element of the endocrine system, which has endo-, auto- and paracrine functions that determine the development of the subclinical inflammatory process. Thus, obesity causes a chronic non-intensive systemic inflammatory response. Non-adipose tissues do not exhibit a clear inflammatory response. However, they are exposed to elevated adipokine levels, which are secreted by activated and hypertrophied adipocytes. The action of cytokines consists in their ability to increase the inflammatory response, which can lead to intensified tissue damage and subsequently to organ dysfunction. Changes in understanding the role of adipose tissue as not a passive energy storage body but an active participant in hormonal regulation have occurred relatively recently. In addition to the accumulation of fatty acids, cholesterol, retinol, and steroid hormones, white adipose tissue is one of the major organs of the endocrine system. It secretes a wide range of protein factors and hormone-like peptides, defined as adipokines. They act via autocrine, paracrine, and endocrine ways, thereby controlling various metabolic functions. Currently, various functions of more than 50 adipokines have been identified. However, leptin, adiponectin, and cytokines: IL-33 and IL-6 are the most extensively studied at present [8].

Our study demonstrated a high correlation between IL-33 and hs-CRP, a moderate correlation between IL-33 and IL-6, and a high correlation between hs-CRP and IL-6, which implies the role of IL-33 in the development of systemic inflammation and is confirmed by the results of other studies. In turn, IL-33 increases the synthesis of IL-6, IL-13, IL-1β, and hs-CRP. Hence, one multicenter clinical study found that IL-33 is an inducer of IL-6 in mast cells, an essential cytokine in the development of obesity and, unlike other interleukins, a true endocrine cytokine. This means that most cellular targets of this cytokine are distant from the site of synthesis, so the effects of IL-6 correlate with its serum concentration [5]. Adipocytes and macrophages secrete IL-6 in adipose tissue. Measurements of the arteriovenous difference of cytokine showed an increase in its concentration in serum, indicating the secretion of IL-6 by adipose tissue, which produces approximately 30 % of circulating IL-6 in humans. Both leptin and the production of IL-6 by adipose tissue augment with increasing body weight.

Circulating IL-6 is one of the most important determinants of acute-phase protein production by the liver. This provides a rapid coordinated physiological response to tissue damage or infection aimed at activating the body's defense mechanisms: the destruction of pathogens, the elimination of damaged

cells, and the repair of damaged tissues. In turn, one of the most significant proteins of the acute phase is hs-CRP, which attaches to the membrane of damaged cells and causes their death by activating the responses of the complement cascade. In turn, hs-CRP is a marker of IL-6 action. It should also be noted that the production of hs-CRP in the liver is regulated by circulating IL-6. Hence, one can assert that this cytokine, whose concentration increases in obesity, significantly contributes to the occurrence of chronic systemic inflammatory response. Other studies conducted in patients with psoriasis demonstrated a positive correlation between IL-33 and TNF-α levels, as well as a decrease in IL-33 after anti-TNF-α treatment. Therefore, IL-33 can activate cells of both the innate and adaptive immune systems. Depending on the type of disease, it can either contribute to the resolution of inflammation or cause a chronic pathological process [6, 12]. Thus, the comorbidity of psoriatic disease and obesity involves the formation of a vicious circle at the level of the immune system, which must be broken to treat these diseases successfully.

Conclusions

1. In patients with concomitant obesity, the intensity of systemic inflammation is associated with the severity of psoriasis, and the degree of alimentary obesity.

2. The concentration of IL-33 in the serum of psoriasis patients with concomitant alimentary obesity can be used as a biomarker of the severity of the inflammatory process.

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Стаття надійшла 12.05.2020 р.