# ИММУНОЛОГИЧЕСКИЕ АСПЕКТЫ ПРИМЕНЕНИЯ МЕЛАТОНИНА ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ТЕРМИЧЕСКОЙ ТРАВМЕ

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**Резюме.** Распространенность термической травмы, высокий риск инфекционных и неинфекционных краткосрочных и долговременных осложнений, ограниченная эффективность применяемых терапевтических подходов являются предпосылкой для поиска и патогенетического обоснования новых средств терапии, среди которых внимание привлекает эндогенный регулятор гомеостаза с плейотропными свойствами мелатонин.

Цель работы – исследовать иммунологические аспекты эффективности внутрибрюшинного применения мелатонина (МТ) при экспериментальной термической травме (ТТ).

Работа выполнена на 158 крысах линии Wistar, ТТ IIIA степени и относительной площадью 3,5% моделировали погружением кожи в воду при 98-99 °С на 12 с. МТ применяли внутрибрюшинно ежедневно в дозе 10 мг/кг в течение 5 суток. Количественный состав клеток крови оценивали на гематологическом анализаторе. Концентрацию в плазме IL-4, TNFα, IFNγ, СРБ определяли на автоматическом иммуноферментном анализаторе с использованием специфических для крыс тест-систем, МТ – методом капиллярного электрофореза.

При экспериментальной ТТ на фоне прогрессивного от 5 к 20 суткам увеличения количества в крови лейкоцитов за счет нейтрофилов, моноцитов, базофилов, снижается количество лимфоцитов. При ТТ в сыворотке на 5 и 10 сутки возрастает концентрация СРБ, на 5-е, 10-е и 20-е сутки возрастает содержание TNF-α, IL-4 при отсутствии значимых изменений концентрации IFNγ. Концентрация сывороточного МТ значимо не изменяется. Внутрибрюшинное применение МТ при ТТ приводит к частичному восстановлению в крови количества лимфоцитов на 5-е сутки. Оценка цитокинового профиля в сыворотке выявила снижение концентрации TNFα на 10-е и 20-е сутки, значимых изменений концентрации IL-4 и IFNγ не зафиксировано, концентрация СРБ снижается на 5-е сутки. Концентрация сывороточного МТ увеличивается на 5-е сутки.

При ТТ на 5-е, 10-е, 20-е сутки эксперимента в крови увеличивается количество нейтрофилов, моноцитов, базофилов, снижается – лимфоцитов, в сыворотке возрастает содержание СРБ, TNFα, IL-4, содержание IFNγ и мелатонина не изменяется. Внутрибрюшинное применение МТ при ТТ частично восстанавливает в крови количество лимфоцитов, концентрацию СРБ, TNFα. Снижение концентрации в сыворотке TNFα и СРБ при ТТ в условиях применения МТ позволяют говорить об ограниче-

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нии острофазового ответа как следствие антиоксидантного, противовоспалительного действия МТ, что может способствовать ускорению заживления и уменьшению площади очага повреждения ТТ.

*Ключевые слова: термическая травма, мелатонин, СРБ, TNFα, IL-4, IFNγ*

# IMMUNOLOGICAL ASPECTS OF THE USE OF MELATONIN IN EXPERIMENTAL THERMAL TRAUMA

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**Abstract.** The prevalence of thermal trauma, the high risk of infectious and non-infectious short- and long-term complications, and the limited effectiveness of the therapeutic approaches used are prerequisites for the search and pathogenetic justification of new therapies, among which the endogenous homeostasis regulator with pleiotropic properties melatonin attracts attention.

The aim of the work is to investigate the immunological aspects of intraperitoneal use of melatonin (MT) in experimental thermal trauma (TT).

The work was performed on 158 rats of the Wistar line, grade III TT and a relative area of 3.5% were simulated by skin immersion in water at 98-99 °C for 12 s. MT was administered intraperitoneally daily at a dose of 10 mg/kg for 5 days. The quantitative composition of blood cells was evaluated on a hematological analyzer. Plasma concentrations of IL-4, TNFα, IFNγ, and CRP were determined on an automatic enzyme immunoassay using rat-specific test systems, and MT by capillary electrophoresis.

With experimental TT, against the background of a progressive increase in the number of leukocytes in the blood from 5 to 20 days due to neutrophils, monocytes, basophils, the number of lymphocytes decreases. With TT, the concentration of CRP increases in serum on days 5 and 10. The content of TNFα, IL-4 increases on days 5, 10 and 20 in the absence of significant changes in the concentration of IFNγ. The concentration of serum MT does not change significantly. Intraperitoneal use of MT in TT leads to a partial restoration of the number of lymphocytes in the blood on day 5. Evaluation of the cytokine profile in serum revealed a decrease in the concentration of TNFα on days 10 and 20, no significant changes in the concentration of IL-4 and IFNγ were recorded, the concentration of CRP decreased on day 5. The concentration of serum MT increases by 5 days.

With TT on the 5$^{th}$, 10$^{th}$, 20$^{th}$ day of the experiment, the number of neutrophils, monocytes, basophils in the blood increases, decreases – lymphocytes, the serum content of CRP, TNFα, IL-4 increases, the content of IFNγ and melatonin does not change. Intraperitoneal use of MT in TT partially restores the number of lymphocytes in the blood, the concentration of CRP, TNFα. A decrease in serum concentrations of TNFα and CRP in TT under the conditions of MT use suggests a limitation of the acute phase response as a consequence of the antioxidant, anti-inflammatory effect of MT, which can accelerate healing and reduce the area of the lesion of TT.

*Keywords: thermal injury, melatonin, CRP, TNFα, IL-4, IFNγ*

## Introduction

Burns are one of the important medical and social issues. Notwithstanding significant progress in kombustiology, slow healing and attachment of infection are major problems in patients with burns, which cause emotional distresses, prolonged hospitalization, decreased quality of life [1]. Thermal trauma (TT) obstacles are mostly associated with infections, primarily urinary tract infections and pneumonia. The infectious complication (sepsis) after TT is connected with immunosuppressive reactions as compensation of lasting stable proinflammatory response, especially in connection with excessive synthesis of overproduction of TGF-β, IL-10, IL-4 [2]. Immune reactions play a pivotal role in the TT pathogenesis and its complications at each stage. Understanding of the burn's pathophysiology is a precondition for the pathogenetically reasonable therapies development, as also methods of wound suturing and safe necrectomy [3]. In this attitude, endogenous homeostasis controllers are of specific interest. They can influence the increasing immune reaction to TT and be involved as immunocorrect agents.

In previous studies, we have demonstrated the healing-accelerating effects of the use of erythropoietin (locally and systemically), just as the local administration of EGF at TT expedite the burns healing and the immune status reconstruction in experimental and clinical stipulations [4, 5]. It is

known that melatonin (MT) is a homeostasis adjuster. At the same time, it has pleiotropic effects: regulation of the sleep-wake cycle, changing the redox factor due to the realization of the antioxidant effect, modulation of immunity and inflammation with its suppression and stimulation, influence on cellular differentiation, proliferation and apoptosis [7]. One of the sources of MT is epidermocytes. Also, in the study of keratinocytes, melanocytes, skin fibroblasts, MT metabolites were found in them [8]. According to research data, receptors for MT (MT1, MT2, RORa) are found in skin fibroblasts, keratinocytes, hair follicle cells and dermal blood vessels, as well as in melanocytes [9].

It is known that pharmaceutical forms of MT for topical use in case of skin damage are not accessible in the Russian Federation. There are no indications in the official recommendations for the use of oral forms of MT in TT.

**The aim of the study** is to explore the impact of the effect of intraperitoneal use of melatonin in experimental thermal trauma on some indicators of immune status.

## Materials and methods

Experimental studies were performed on 158 Wistar rats weighing 240-250 g in the vivarium of the Federal State Budgetary Educational Institution of the Southern State Medical University of the Ministry of Health of Russia. The experiment was conducted in strict accordance with the experimental animals' care and maintenance requirements, as also their elimination from the experiment with subsequent utilization in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes (ETS No. 123 of 03/18/1986, Strasbourg), Recommendations of the European Commission 2007/526/EC of June 18, 2007, Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22 September 2010 on the protection of animals used for scientific purposes. The study organization was confirmed by the ethics commission of the Federal State Budgetary Educational Institution of the Ministry of Health of the Russian Federation (Protocol No. 10 of 15.11.2019, Protocol No. 13 of 12/28/2020).

Experimental rats were randomly separated into groups: group 1 (n = 33) – intact control, group 2 (n = 67) – animals with TT and daily aseptic dressing, group 3 (n = 58) – animals with TT with aseptic dressing and intraperitoneal administration of melatonin ("Flamma Sp", Italy) in a daily single dose of 10 mg/kg for 5 days. To simulate grade III TT and a relative area of 3.5%, an isolated interscapular area of rat skin was immersed in purified water at 98-99 °From to 12 s. The depth of the burn was verified by morphological methods. For anesthesia, the drug "Zoletil-100" ("Virbac SanteAnimale", France) was used at a dose of 20 mg/kg. On the 5th, 10th and 20th days from the moment of TT induction in groups 2 and 3, blood was taken under anesthesia after thoracotomy by heart puncture in the left ventricle into vacuum tubes "Vacuette" ("Greiner BioOne", Austria). The absolute number of leukocytes was evaluated on an automatic hematological analyzer for veterinary medicine, calibrated for rats, "VS-2800Vet" ("Mindray", China). The leukocyte formula was calculated in blood smears stained with azur II-eosin (Gemstandart-R, Russia). Plasma concentrations of IL-4, TNFα, IFNγ, CRP were determined on an automatic enzyme immunoassay analyzer "Personal LAB" (Italy) using rat-specific test systems "Cloud-Clone Corp." (China) the results were expressed in pg/ml. The concentration of MT in plasma was determined by capillary electrophoresis on the device "Kapel-105M" (Lumex, St. Petersburg), the results were expressed in pg/ml (Kim Y.O. et al., 1999). Statistical processing of the results was carried out using the IBM SPSS Statistics 19 program. The characteristics of the samples are presented in the format "Me ($Q_{0.25}$-$Q_{0.75}$)", where Me is the median, Q1 and Q3 are the values of the lower and upper quartile, respectively. The significance of the differences between the groups was assessed using the criteria of Kruskal–Wallis, Mann–Whitney.

## Results and discussion

Primary and secondary alteration of the skin in the lesion of TT leads to systemic changes in homeostasis, among which the key position is occupied by the reactions of the immunobiological surveillance system aimed at ensuring the inflammatory process in the lesion, maintaining its sterility, repair, but can lead to excessive tissue damage in situ and at removal with hyperergia. On the 5th day of TT, the total number of leukocytes in the blood increases due to rod-shaped and segmented neutrophils, monocytes, the absolute number of lymphocytes decreases (Table 1). On the 10th day of TT, the total number of leukocytes in the blood does not change, the absolute number of rod-shaped and segmented neutrophils increases, the absolute number of lymphocytes decreases. On the 20th day of TT, no significant changes in the number of leukocytes were detected. In the dynamics of observation on day 10, the number of rod-shaped and segmented neutrophils, the total number of neutrophils, the number of monocytes was less than on day 5 TT (Table 1). On the 20th day, the total number of leukocytes, neutrophils, and rod–shaped neutrophils in the blood was less than on the 5th day of TT, the number of monocytes was less than on the 5th and 10th days of TT (Table 1).

On the 5th day of TT, the concentration of CRP in serum increases by about 10 times in the median relative to the values in the group of intact animals, and by about 2 times on the 10th day (Table 2). On day 20, there were no significant changes in the

concentration of CRP in serum, since it belongs to the reactants of the acute phase of the first echelon, the concentration of which reaches a maximum on the first day after tissue damage. In the dynamics of TT, the concentration of CRP in serum on the 10th day is significantly lower than on the 5th day, on the 20th day – lower than on the 5th and 10th days. Note that when studying the concentration of serum MT, we found no significant changes on the 5th, 10th and 20th days of the experimental TT. On the 5th, 10th and 20th days of TT, an increase in the concentration of TNFα, IL-4 was found in the absence of significant changes in IFNγ (Table 2). In the dynamics of TT, the concentration of TNFα and IL-4 on the 10th day of TT was higher than on the 5th day and did not differ from the values on the 20th day, which allows us to talk about the maximum level of TNFα and IL-4 on the 10th day.

With intraperitoneal administration of melatonin in TT, it was found that the quantitative composition of leukocytes in the blood on the 10th and 20th days of observation did not significantly change relative to the comparison group (Table 1). In dynamics, the total number of leukocytes, the total number of neutrophils, rod-shaped neutrophils, monocytes on the 10th and 20th days are less than on the 5th day, the total number of neutrophils on the 20th day is less than on the 10th day, the number of lymphocytes on the 10th day is more than on the 5th day, and on the 20th day is more than 10 a day. Relative to the group of intact animals, significant differences remain on day 5 with the total number of leukocytes, the total number of neutrophils, rod-shaped neutrophils, segmented neutrophils, lymphocytes, monocytes; on day 10 – with the total number of neutrophils, segmented neutrophils, lymphocytes, monocytes; on day 20, there were no significant differences with the group of intact animals.

Evaluation of the cytokine profile in serum revealed a decrease in the concentration of TNFα on days 10 and 20; no significant changes in the concentration of IL-4 and IFNγ were recorded (Table 2). At all follow-up periods, the concentration of TNFα and IL-4 in serum was higher than in the group of intact animals. The use of MT in TT leads to an increase in the concentration of MT in serum on day 5, without significant changes in this indicator on days 10 and 20; the concentration of MT in serum on day 5 is significantly higher than in the group of intact animals (Table 2). The concentration of CRP

**TABLE 1. EFFECT OF SYSTEMIC USE OF MT ON THE QUANTITATIVE COMPOSITION OF LEUKOCYTES IN THE BLOOD DURING TT, Me ($Q_{0.25}$-$Q_{0.75}$)**

| Indicator | Group 1 Intact (n = 33) | Group 2 TI + AsD | | | Group 3 TI + MT | | |
|---|---|---|---|---|---|---|---|
| | | 5 days (n = 22) | 10 days (n = 26) | 20 days (n = 19) | 5 days (n = 25) | 10 days (n = 15) | 20 days (n = 18) |
| **White blood cells, × 10⁹/L** | 5.70 (4.00-6.70) | 6.30 (5.10-8.50) * | 5.50 (4.30-7.20) | 4.60 (4.30-6.20) ^ | 6.70 (6.40-7.30) * | 5.40 (4.90-6.00) & | 5.70 (4.30-5.90) & |
| **Basophils, × 10⁹/L** | 0 | 0 (0.00-0.31) * | 0 (0.00-0.10) * | 0 | 0 (0.00-0.06) | 0 (0.00-0.05) | 0 |
| **Eosinophils, × 10⁹/L** | 0.22 (0.04-0.39) | 0.15 (0.05-0.25) | 0.22 (0.09-0.30) | 0.16 (0.06-0.17) | 0.12 (0.06-0.24) | 0.12 (0.09-0.23) | 0.12 (0.06-0.12) & |
| **Rod – shaped neutrophils, × 10⁹/L** | 0 (0.00-0.04) | 0.27 (0.00-0.58) * | 0.04 (0.00-0.29) ^ | 0 | 0.27 (0.10-0.32) * | 0 (0.04-0.05) & | 0.04 (0.00-0.06) & |
| **Segmented neutrophils, × 10⁹/L** | 1.65 (1.09-1.88) | 2.78 (2.05-4.55) * | 2.48 (1.31-3.65) * ^ | 2.05 (1.27-2.94) ^ | 2.92 (2.52-3.32) * | 2.59 (2.34-2.90) * | 1.99 (1.89-2.56) & |
| **Neutrophils, × 10⁹/L** | 1.70 (1.09-1.88) | 2.98 (2.43-5.39) * | 2.58 (1.31-3.88) * ^ | 2.05 (1.27-2.94) ^ | 3.15 (2.77-3.57) * | 2.59 (2.35-2.93) * & | 2.02 (1.94-2.71) & && |
| **Lymphocytes, × 10⁹/L** | 3.40 (2.32-3.77) | 2.49 (2.00-2.86) * | 2.27 (2.00-3.69) * | 2.79 (2.05-3.92) | 2.71 (2.51-2.96) * # | 2.11 (1.91-2.34) * & | 2.69 (2.26-2.94) && |
| **Monocytes, × 10⁹/L** | 0.28 (0.21-0.41) | 0.71 (0.29-0.83) * | 0.33 (0.22-0.60) ^ | 0.22 (0.17-0.29) ^ ^^ | 0.67 (0.53-0.76) * | 0.54 (0.34-0.54) * & | 0.35 (0.24-0.57) & |

Note. *, significant ($p < 0.01$) differences with group 1; ^, with group 2 on day 5; ^^, with group 2 on day 10; #, with group 2 on the corresponding day; &, with group 3 on day 5, &&, with group 3 on day 10.

**TABLE 2. EFFECT OF SYSTEMIC USE OF MT ON SERUM CONCENTRATIONS OF MELATONIN AND CRP IN EXPERIMENTAL TT, Me ($Q_{0.25}$-$Q_{0.75}$)**

| Indicator | Group 1 Intact (n = 33) | Group 2 TI + AsD | | | Group 3 TI + MT | | |
|---|---|---|---|---|---|---|---|
| | | 5 days (n = 10) | 10 days (n = 12) | 20 days (n = 10) | 5 days (n = 10) | 10 days (n = 8) | 20 days (n = 8) |
| **MT, pg/mL** | 24.08 (11.56-28.00) | 26.32 (13.36-33.88) | 22.35 (13.70-28.81) | 21.57 (15.27-28.15) | 32.14 (23.47-39.08) * # | 24.61 (18.31-27.98) | 23.78 (15.26-27.79) |
| **CRP, pg/mL** | 1.29 (0.89-1.66) | 12.14 (11.67-15.32) * | 2.37 (1.42-5.32) * ^ | 1.46 (1.38-1.73) ^ ^^ | 9.23 (7.02-10.05) * # | 1.98 (1.98-2.31) * & | 1.29 (1.18-1.35) & && |
| **TNFα, pg/mL** | 1.18 (0.84-1.96) | 2.25 (2.02-2.92) * | 3.42 (2.72-6.14) * ^ | 3.48 (1.77-5.05) * | 2.33 (1.85-3.03) * | 2.69 (2.19-3.03) * # | 1.91 (1.35-3.03) * # |
| **IFNγ, pg/mL** | 0.83 (0.29-1.24) | 0.73 (0.12-1.15) | 0.98 (0.59-1.35) | 1.06 (0.65-1.74) ^ | 0.84 (0.51-1.49) | 0.76 (0.52-1.08) | 1.08 (0.66-1.22) |
| **IL-4, pg/mL** | 0.79 (0.50-1.75) | 1.93 (1.36-2.51) * | 3.26 (2.58-5.65) * ^ | 2.97 (1.57-4.97) * ^ | 2.11 (1.79-2.86) * | 2.79 (2.43-3.36) * & | 2.18 (1.79-3.01) * |

Note. As for Table 1.

in serum decreases on day 5 and does not change on days 10 and 20 relative to the group of rats without the use of MT; on days 5 and 10, the concentration of CRP in serum is higher than in intact animals. In the dynamics of TT under the conditions of MT application, the concentration of CRP in serum on days 10 and 20 is less than on day 5, and on day 20 is less than on day 10 of observation.

We believe that the changes in hematological parameters detected by us during experimental TT are a reflection of tissue alteration and the development of the inflammatory process in the skin. In response to thermal damage, inflammatory mediators (including proinflammatory cytokines, arachidic acid cascade products, catecholamines, etc.) are released in the TT focus, which stimulate the myeloid bone marrow sprout, including CFU-HME, cause demargination of the parietal neutrophil pool and are associated with an increase in the number of neutrophils, monocytes, platelets in the blood, infiltration foci of neutrophils and monocytes. Lymphocytopenia in TT is registered after 48 hours and persists for up to 4 weeks, mainly due to the effects of TNFα mediated by the TIPE-2 protein (part of the TNFα-induced protein family) and an increase in the activity of caspase-3, caspase-8, caspase-9, cytochrome C, a decrease in the membrane potential of mitochondria, which initiates cell death by apoptosis [6]. A decrease in the number of lymphocytes in the blood and the focus of TT limits their participation in wound repair: secretion of growth factors, restriction of vascular exudative reactions, activation of angiogenesis, etc. In TT, a decrease in the number of lymphocytes in the blood, among other things, is associated with the activation of their death in conditions of increased TNFα production, changes in the acid-base state, and other factors [6].

Changes in gene expression, synthesis and secretion of cytokines in the focus of TT have been recorded by many researchers in relation to pro-inflammatory and anti-inflammatory cytokines depending on the depth, area and localization of burns, age, concomitant pathology, and other factors [7, 10]. The source of cytokines are activated neutrophils, macrophages, dendritic cells, lymphocytes, endotheliocytes, etc. The entry of cytokines from the TT focus into the systemic circulation leads to the activation of circulating leukocytes, platelets, endotheliocytes – additional sources of cytokines. Dysfunction of these cells, violation of the change of their phenotype leads to contradictory results in different researchers on the concentration of cytokines in serum and in the lesion of TT.

A decrease in serum concentrations of TNFα and CRP suggests a decrease in the severity of the acute phase response due to a decrease in destructive events in the focus of TT with intraperitoneal administration of MT. With accelerated healing and a decrease in the area of the TT focus, less lymphocytes enter it from the bloodstream. The suppressive effect of TNFα on lymphopoiesis decreases. An increased number of lymphocytes in the blood can result in an increase in the Ig concentration in the blood serum.

These changes make it possible to state to a certain extent a decrease in the severity of the acute phase response in TT in the conditions of systemic use of MT. This fact is a reflection of the events in the TT focus aimed at limiting the oxidative destruction of lipids and proteins, reducing the zone of secondary alteration, infiltration of the focus by neutrophils and lymphocytes, accelerating the burn healing. MT receptors are found in skin fibroblasts, keratinocytes, cells of hair follicle, eccrine glands, skin vessels,

melanocytes [7]. *In vitro*, MT has a protective effect on skin cells damaged by ultraviolet radiation due to the regulation of redox status and bioenergetic homeostasis, activation of DNA repair, NRF2-dependent pathways [10]. The MT anti-inflammatory effect is associated with limiting restriction of NF-kB-dependent pathways and the expression of pro-inflammatory factors (TNFα, COX-2, iNOS, etc.) [10].

## Conclusions

Primary and secondary skin alteration in the lesion of TT leads to changes in the immunobiological surveillance system aimed at ensuring the inflammatory process in the lesion. During experimental TT, we recorded on the 5th, 10th, 20th day of the experiment, the number of monocytes, basophils, neutrophils in the circulating blood increases, the number of lymphocytes decreases, the content of CRP, TNFα, IL-4 increases in the serum, the content of IFNγ and melatonin does not change.

Intraperitoneal use of MT in TT partially restores the number of lymphocytes in the blood, the concentration of CRP, TNFα. A decrease in serum concentrations of TNFα and CRP in TT under the conditions of MT use suggests a limitation of the acute phase response as a consequence of the MT anti-inflammatory, antioxidant effect, which can accelerate healing and reduce the area of the lesion of TT.

## References

1. Boutin J.A., Ferry G. Is there sufficient evidence that the melatonin binding Site MT3 is Quinone Reductase 2? J. Pharmacol. Exp. *Ther., 2019, Vol. 368, no. 1, pp. 59-65.*
2. Dong K., Goyarts E., Rella A., Pelle E., Wong Y.H., Pernodet N. Age associated decrease of MT-1 melatonin receptor in human dermal skin fibroblasts impairs protection against UV-induced DNA damage. *Int. J. Mol. Sci. 2020, Vol. 21, no. 1, 326*. doi: 10.3390/ijms21010326.
3. Favero G., Franceschetti L., Bonomini F., Rodella L.F., Rezzani R. Melatonin as an anti-inflammatory agent modulating inflammasome activation. *Int. J. Endocrinol. 2017, Vol. 2017, 1835195.* doi: 10.1155/2017/1835195.
4. Galano A., Tan D.X., Reiter R.J. Melatonin: a versatile protector against oxidative DNA damage. *Molecules, 2018, Vol. 23, no. 3, 530.* doi:10.3390/molecules23030530.
5. Hardeland R. Aging, melatonin, and the pro- and anti-inflammatory networks. *Int. J. Mol. Sci., 2019, Vol. 20, no. 5, 1223.* doi: 10.3390/ijms20051223.
6. Huang H., Cui Y., Tian Z. Tumor necrosis factor-α-induced protein 8-like 2 downregulation reduces $CD4^+$ T lymphocyte apoptosis in mice with thermal injury. *Med. Sci. Monit., 2019, Vol. 25, pp. 7547-7556.*
7. Lateef Z., Stuart G., Jones N., Mercer A., Fleming S., Wise L. The cutaneous inflammatory response to thermal burn injury in a murine model. *Int. J. Mol. Sci. 2019, Vol. 20, no. 3, 538.* doi: 10.3390/ijms20030538.
8. Loynes C.A., Lee J.A., Robertson A.L., Steel M.J., Ellett F., Feng Y., Levy B.D., Whyte M.K., Renshaw S.A. PGE2 production at sites of tissue injury promotes an anti-inflammatory neutrophil phenotype and determines the outcome of inflammation resolution *in vivo*. *Sci. Adv., 2018, Vol. 4, no. 9, eaar8320.* doi: 10.1126/sciadv.aar8320.
9. Mayo J.C., Aguado A., Cernuda-Cernuda R., Alvarez-Artime A., Cepas V., Quiros-Gonzalez I., Hevia D., Sáinz R.M. Melatonin uptake by cells: an answer to its relationship with glucose? *Molecules, 2018, Vol. 23, no. 8, 1999.* doi: 10.3390/molecules23081999.
10. Wu D., Zhou M., Li L. Severe burn injury progression and phasic changes of gene expression in mouse model. *Inflammation. 2019, Vol. 42, no. 4, pp. 1239-1251.*

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