

# Determination of CCL2 / MCP-1 levels in the serum of children with melanocytic nevus in the postoperative period after using different methods of surgical treatment

Oleh Pasichnyk<sup>1</sup>, Viktor Konoplytskyi<sup>1</sup>, Yurii Korobko<sup>1</sup>, Oleksandr Nazarchuk<sup>2</sup>, Dmytro Dmyrtriiev<sup>3</sup>, Yuliana Babina<sup>3</sup>

<sup>1</sup>Department of children surgery, National Pirogov Memorial Medical University (Vinnytsya, Ukraine); <sup>2</sup>Department of Microbiology, National Pirogov Memorial Medical University (Vinnytsya, Ukraine); <sup>3</sup>Department of Anesthesiology, Intensive care and Emergency Medicine, National Pirogov Memorial Medical University (Vinnytsya, Ukraine)

**Abstract.** To date, there are many methods and ways to remove pigmented skin tumors, which have their own indications and contraindications for use, early or late complications. *The aim of the study* was to determine the level of CCL2 / MCP-1 in the serum of patients with melanocyte skin nevi in the postoperative period with different methods of their removal. *Materials and methods of research.* The study involved 60 children with melanocyte skin nevi of different localization, who were hospitalized in the pediatric surgery clinic in the period from 2018 to 2020. All patients were divided into 3 groups: I group - the excision of the formation took place with a scalpel, group II - excision of the formation was performed using a high-intensity surgical laser, group III - excision of the formation using a high-frequency electro-surgical device «BOWA-ARC 350. *Results and discussion.* The results of our study showed an increase in the level of CCL2 / MCP-1 plasma level in the patients of group I in 2,6 times in 12 hours after surgery and in 3,15 times in 24 hours after surgery. A similar but more pronounced dynamics of CCL2 / MCP-1 plasma level was observed in patients of group II. The largest increase in CCL2 / MCP-1 levels was observed in the comparison group III. *Conclusions.* High CCL2 / MCP-1 plasma level in patients of groups II and III in 12 and 24 hours after surgery convincingly indicate the presence of a pronounced inflammatory reaction under the influence of thermal damaging factor on skin tissues. (www.actabiomedica.it)

**Key words:** children, pigmented nevi, CCL2 / MCP-1 level, operation.

## Introduction

Monocyte chemoattractant protein 1, monocyte chemoattractant and activating factor (MCP-1 / MCAF) or CCL2 (CC motif ligand 2) is a cytokine that belongs to the group of CC chemokines ( $\beta$ -chemokines). MCP-1 is the most potent factor in the chemotaxis and chemotaxis of, as well as memory of T-cells and dendritic cells to the foci of inflammation produced by tissue damage (1,2). MCP-1 is mainly secreted by monocytes, macrophages and dendritic cells (3). MCP-1

can be synthesized in a wide range of cells: fibroblasts, endothelial cells, osteoblasts, tumor cells, etc. MCP-1 increases the chemotactic activity of monocytes and basophils, with cell movement always directed along the chemokine growth gradient, but does not attract neutrophils and eosinophils to the site of inflammation, thus contributing to the inflammation associated with the underlying disease (4). MCP-1 increases the antitumor activity of monocytes and is required for the formation of granulomas. MCP-1 was first found in tumor leukemia cells in 1989.

Importantly, increased macrophage infiltration of tumor tissue and stimulation of angiogenesis indicate a prooncogenic effect of MCP-1 (5,6). Tumor infiltration by host cells is regulated by chemokines of tumor origin, a superfamily of anti-inflammatory cytokines, that are responsible for the selective recruitment and activation of mononuclear cells, targeted migration of leukocytes, stimulation of their adhesion and transendothelial migration. Due to the large number of chemokines produced by human tumors and the wide range of their biological functions their exact role in the development and progression of tumors yet remains uncertain (7).

A clear determination of the possible effects of chemokines is very important as the regulative mechanisms of melanocytes are preserved due to the expression of melanin in benign nevi, but not in metastatic melanoma. This is even of a greater importance in the inflammation of pigmented formations (8).

To date, there are a large number of methods and ways to remove pigmented skin tumors, which are based on various physical factors: mechanical (surgical excision with a scalpel), wave (laser ablation, radio surgical due to radiocoagulation), thermal (cryodestruction due to low temperatures, electrocoagulation due to high temperatures under the action of high frequency currents), etc (9,10).

Each of the existing methods of radical treatment of pigmented tumors has its indications and contraindications, benefits and visual early or late complications (bleeding, ulcers, recurrences, keloid scars, local hypopigmentation of the skin, etc.). Causes of such complications and adverse treatment effects depending on the type of action of the selected physical factor at the tissue / cellular and immunological levels are insufficiently studied at the present stage of medical science. This creates conditions for targeted study of the mechanism and severity of inflammation in the early postoperative period and implementation of the obtained results in clinical practice as an important factor in the staging of oncological skin pathology in childhood.

### **The aim of the study**

was to determine the level of CCL2 / MCP-1 in the serum of patients with melanocyte skin nevi in the

postoperative period after their removal with different methods.

### **Materials and methods of research**

The study involved 60 children with melanocyte skin nevi of different localization, 25 boys and 35 girls who were hospitalized in the pediatric surgery clinic of National Pirogov Medical University, Vinnitsia, Ukraine in the period from 2018 to 2020. The average age of patients was  $9.8 \pm 1.6$  years. In order to objectify the study in all patients, the area of melanocyte formations ranged from 1,0 to 2,5 cm<sup>2</sup>. We did not include patients with diabetes mellitus, congenital or acquired immunodeficiency, cancer, and any acute or chronic inflammatory processes, including inflammatory processes of the skin and subcutaneous fat tissue. In addition, in the process of intraoperative removal (excision) of formations, in all cases, only general anesthesia was used, without local anesthetics, and primarily to avoid a local increase in intra-tissue pressure and the formation of foci of inflammation.

All patients were divided into 3 groups depending on the chosen method of removing pigmented skin formations. Group I (n = 20) - excision of the formation was performed in a sharp way, using a scalpel. Group II (n = 20) - excision of the formation was performed using a high-intensity surgical laser "LIKA-surgeon", manufacturer PMPP "Photonic Plus", Ukraine, certificate of conformity assessment UA.TR.001.015917-18. The power of the device at the output of 10 W, wavelength 940 nm. Group III (n = 20) - excision of the formation using a high-frequency electrosurgical device "BOWA-ARC 350", manufacturer "BOWA-electronic Gmb & Co.", Germany, in monopolar cutting mode (initial parameters were determined individually).

All patients underwent venous blood sampling for the levels of CCL2 / MCP-1 inflammatory marker immediately before surgery and 12 and 24 hours after removal of the pigmented formation. The collected blood was placed in vacutainers with EDTA, in order to further obtain plasma by centrifugation. The resulting plasma was frozen and stored at -80 °C until further study. A set for enzyme-linked immunosorbent

assay was used to determine the level of CCL2 / MCP-1 (manufactured by Elabscience, Lot TM5T-MWVDI, USA), according to the manufacturer's instructions. The obtained results were determined by the level of absorption of the studied samples on the Microplate Reader "HUMAREADER", (Germany), at a wavelength of 450 nm. The minimum possible concentration of determination is 1 pg / ml.

All clinical and laboratory studies were conducted in accordance with the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study" (11). According to the current legislation, before the start of the study, each of its subjects (parents or adult guardians of the patient) signed a detailed form of informed consent for the study.

Analysis of the obtained results, statistical data processing was performed using the software package Statistica 6.0 for Windows and the licensed version of BioStat. The differences between the obtained indicators were considered statistically significant at  $p < 0,05$ . Data from continuous quantitative indicators, which obeyed the law of normal distribution, were compared with the use of Student's *t*-criterion for bound or unbound samples. In order to evaluate and compare different CCL2 / MCP-1 parameters, we used the ROC (receiver operating characteristic) curve (curve, which is a graphical representation of sensitivity (ordinate axis) and specificity (abscissa axis), and the area under the curve (AUC - area under the curve) demonstrates the accuracy of the indicator.

## Results and discussion

This study examined a inflammatory biomarker, namely the level of CCL2 / MCP-1, in pediatric patients who underwent surgical removal of pigmented skin tumors, and assessed the level of inflammatory response depending on the method of removal. The obtained levels of the studied inflammatory biomarker at certain stages of the early postoperative period are given in table №1.

According to the results of the study, the plasma level of CCL2 / MCP-1 in patients before surgery averaged  $15,27 \pm 3,31$  pg / ml.

The results of studies revealed an increase in the CCL2 / MCP-1 plasma level in patients of group I in 2,6 times 12 hours after surgery, respectively  $39,67 \pm 7,18$  pg / ml against  $15,27 \pm 3,31$  pg / ml before surgery ( $p < 0,05$ ), and 3,15 times in 24 hours after surgery, respectively  $48,18 \pm 7,62$  pg / ml against  $15,27 \pm 3,31$  pg / ml before surgery, ( $p < 0,05$ ).

A similar dynamics of CCL2 / MCP-1 plasma level was observed in patients of group II, but was more pronounced. Thus, 12 hours after surgery, the level of CCL2 / MCP-1 was 3,55 times higher than the preoperative level of cytokine, respectively  $54,26 \pm 9,12$  pg/ml against  $15,27 \pm 3,31$  pg/ml, ( $p < 0,05$ ), and 7,57 times higher 24 hours after surgery, respectively  $115,57 \pm 16,32$  pg / ml against  $15,27 \pm 3,31$  pg/ml, ( $p < 0,05$ ).

An even more pronounced increase in CCL2 / MCP-1 levels was observed in patients in comparison

**Table 1.** Dynamics of CCL2 / MCP-1 levels at different terms of the study among patients of all comparison groups

The MCP-1 plasma levels in patients	Time to the assessment of MCP-1 level after surgical operation	
	In 12 hours	In 24 hours
Before surgical operation (n=60)	$15,27 \pm 3,31$ pg/ml*	
I group (n=20)	$39,67 \pm 7,18$ pg/ml	$48,18 \pm 7,62$ pg/ml
P	<0,05	<0,05
II group (n=20)	$54,26 \pm 9,12$ pg/ml	$115,57 \pm 16,32$ pg/ml
P	<0,05	<0,05
III group (n=20)	$68,86 \pm 10,31$ pg/ml	$143,15 \pm 18,77$ pg/ml
P	<0,05	<0,05

\* - a significant difference in the level of MCP-1 before surgical operation.

group III. Thus, in patients of this group the level of cytokine was 4.5 times higher in 12 hours after surgery than before surgical removal of the pigmented formation, respectively,  $68.86 \pm 10.31$  pg / ml against  $15.27 \pm 3.31$  pg / ml, ( $p < 0.05$ ), and after 24 hours, the increase in cytokine levels significantly exceeded the value of CCL2 / MCP-1 before surgery in 9.37 times, respectively,  $143.15 \pm 18.77$  pg / ml against  $15.27 \pm 3.31$  pg / ml, ( $p < 0.05$ ).

A graphical view of the dynamics CCL2 / MCP-1 levels at different times of the study among patients of all comparison groups is shown in Figure. 1.

A number of studies that investigated potential biomarkers of acute inflammation, including melanin cell skin tumors, directly indicate a relationship between the degree of tissue damage and the level of proinflammatory mediators in the serum.

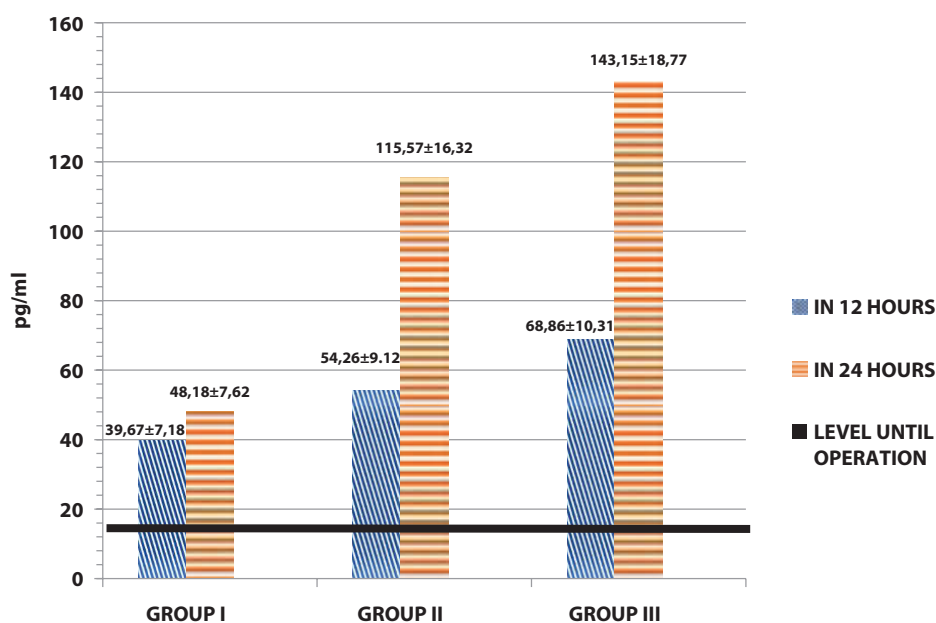
As an inflammatory mediator, MCP-1 stimulates vascular smooth cell proliferation and secretion of anti-inflammatory cytokines that promote disease progression due to vascular damage (MCP-1 is not detected in the normal vascular wall). Thus, an increased serum level of such a mediator of inflammation and angiogenesis as MCP-1 contributes to

the development of the initial stages of vascular lesions or metabolic imbalance, which cause intermittent damage to the vascular wall and accompanies catabolic processes, differentiation of endothelial and smooth cells.

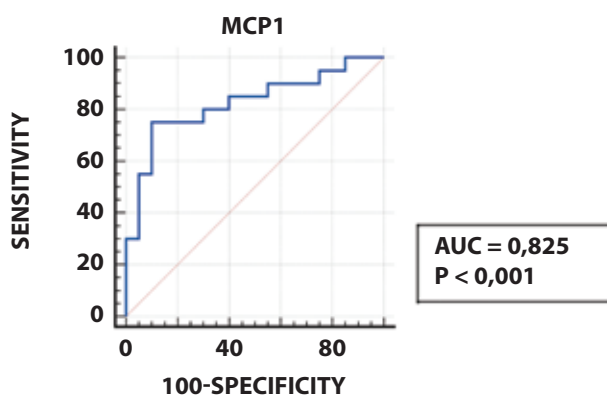
In order to assess and compare the levels of CCL2 / MCP-1 in all study groups, the ROC curve was constructed to determine the sensitivity and specificity of the data obtained regarding the chosen method of removing pigmented skin tumors in children.

Analysis of the assessment of the specificity and sensitivity of the content of MCP-1 in the serum of children of group I showed that the area of AUC under the ROC curve was 0.825 [confidence interval – 0,672-0,925 95%]. The cut-off point is at the level of 45.4 pg / ml (sensitivity 75.0%, specificity 90.0%) (Figure. 2).

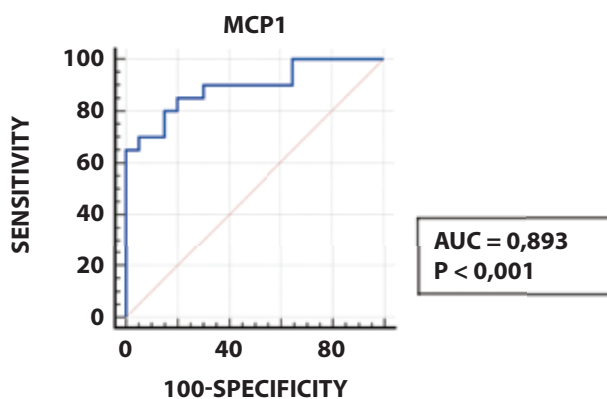
Analysis of the assessment of the specificity and sensitivity of the content of MCP-1 in the serum of children of group II determined that the area of AUC under the ROC curve was 0.893 [confidence interval – 0,754-0,968 95%]. The cut-off point is at the level of 75.3 pg / ml (sensitivity 85.0%, specificity 80.0%) (Figure. 3).



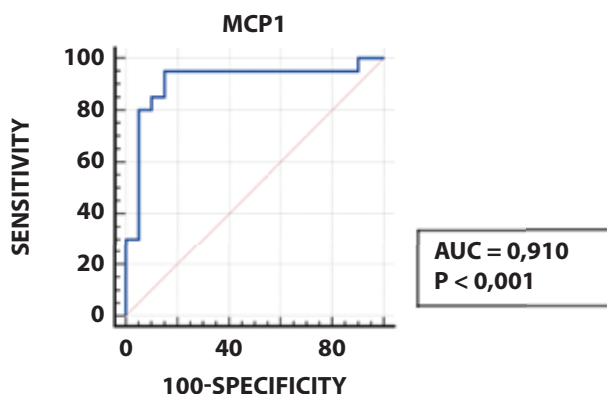
**Figure 1.** Graph of the dynamics of CCL2 / MCP-1 level in all comparison groups in the relation to the level of cytokine before surgery.



**Figure 2.** ROC curve of CCL2 / MCP-1 in group I patients 12 and 24 hours after surgery.



**Figure 3.** ROC curve of CCL2 / MCP-1 in group II patients 12 and 24 hours after surgery.



**Figure 4.** ROC curve of CCL2 / MCP-1 in group III patients 12 and 24 hours after surgery.

Analysis of the assessment of the specificity and sensitivity of MCP-1 in the serum of children of group III, showed that the area of AUC under the ROC

curve was 0.910 [confidence interval – 0.776-0.977 95%]. The cut-off point is at the level of 92.4 pg / ml (sensitivity 95.0%, specificity 85.0%) (Figure. 4).

Recent studies have shown that MCP-1 promotes the induction of proliferation of normal human melanocytes without significant changes in melanin content in epidermal cells, which can be regarded as a factor in the relationship between melanocyte nevi and melanoma, given its aggressive ability to metastasize and resistance to therapy (12,3,13,14) . The malignant course of melanoma is due to the fact that tumor cells produce excessive levels of cytokines, which play different biological roles in the dynamics of both the tumor and its metastases due to macrophage infiltration due to prostaglandin PGE2, which is an endogenous stimulator of MCP-1 (15,16). According to some researchers, high levels of MCP-1 stimulate the development of an abundant vascular network, which in turn contributes to the development of pigment tumors (14).

In an experimental model of colon cancer in laboratory mice, it was shown that MCP-1 as an important regulator of macrophages, T-cells and inflammatory reactions in the tumor microenvironment, can lead to increased cancer in tumor tumorigenesis (10). It has been experimentally proven that the increase in micro-metastases in mice is associated with an increase in the level of MCP-1 (17).

However, the role of MCP-1 in the development and progression of tumors has not been definitively elucidated, although the fact of expression of MCP-1 in malignant cells has been established due to the constitutional production of growth activating factors, cytokines and platelet growth factor. In turn, the expression of MCP-1 leads to infiltration by macrophages, which in turn produce growth-promoting factors for both tumor cells and the vascular network (18). Such infiltration of the skin by macrophages / monocytes in malignant melanomas is crucial in their progression to an aggressive phenotype, which is confirmed by the fact that most primary melanomas or their metastatic formations produce MCP-1, and macrophage infiltration correlates with tumor stage and angiogenesis (18). Based on the results, some researchers believe that the level of MCP-1 determines the development of the tumor, based on the fact that

intermediate levels of MCP-1 stimulate the angiogenic effect that leads to tumor growth, while significant levels of MCP-1 contribute to massive monocyte infiltration. / macrophages and tumor tissue destruction and induction of angiogenesis (20).

It is proved that MCP-1 as a powerful monocytic chemoattractant, tends to increase its level during inflammatory reactions of skin tissue (21,22).

In the course of the study, important data were obtained, which showed different severity of the inflammatory reaction in all comparison groups in the early postoperative period, which had different correlations depending on the method of removal of pigmented nevi. This difference in CCL2 / MCP-1 levels, in our opinion, is to some extent modified by different types of effects of different physical factors on skin tissues.

The predominance at all stages of the study of the level of CCL2 / MCP-1 in the serum of patients of II and III comparison groups over group I confirms the functional activity and significance of the marker as a proinflammatory cytokine, which may be due to the predominance of inflammatory tissue infiltration in the operating field. (mechanical, thermal, radiation, etc.).

In all comparison groups, we observed higher levels of the inflammatory biomarker in the early postoperative period than before surgery. This may be explained by the fact that any surgical trauma promotes the production of cytokines and the development of an inflammatory response in general, while the severity of the surgical trauma determines the severity of the inflammatory response.

According to the results of our studies, significantly higher levels of MCP-1 were characteristic in those groups of patients who underwent excision of pigmented nevi with the influence of wave (group II) and thermal (group III) energies on biological tissues.

Laser irradiation, due to the phenomenon of collimation, transfers wave energy almost without loss to biological tissues according to the law of Bouguer-Lambert-Ber. That is, photothermolysis and photomechanical reactions are realized during the absorption of radiation by tissues due to the conversion of laser radiation energy to a greater extent into thermal energy and to a lesser extent into mechanical energy on the skin containing melanin chromophore, which leads to thermal destruction of

targets (27). At the same time, a number of changes in tissues consistently occur, namely: coagulation → burns → charring → combustion → evaporation. During the interaction of laser irradiation with liquid media, water boils with the phenomena of micro-explosions and the corresponding pressure on the tissues. Thus, the total shock effect of laser irradiation consists of the sum of the light pressure and the vapor pressure (24).

Immediately after the action of high-energy laser radiation on the skin there is a significant local increase in its temperature and increase in blood flow, which also persists for an hour in the postoperative period during thermal damage to the skin in the form of destructive changes and focal destruction (25,26).

It is noteworthy that the highest levels of CCL2 / MCP-1 at different times of the early postoperative period were observed in the removal of pigmented skin tumors by high-frequency soft tissue cutting in monopolar mode due to the fact that high-frequency current with a frequency of more than 200 kHz, the thermal mechanism of action prevails, causes the greatest damaging effect on all layers of a dermis.

Elevated serum CCL2 / MCP-1 levels in the postoperative period in patients after removal of skin pigments should to some extent be considered as a criterion for the activity of the body's cellular immunity in response to an inflammatory response due to surgical trauma.

## Conclusions.

Because CCL2 / MCP-1 plays an important role as a chemoattractant for macrophages and monocytes in the lesion, the effect of this chemokine on the development of the inflammatory response in the postoperative period due to inflammatory cells is obvious, proven and requires further detailed study.

The dynamics of CCL2 / MCP-1 levels in the early postoperative period showed the lowest rates in patients of group I, which proves minimal manifestations of inflammatory response both 12 and 24 hours after surgery compared with proinflammatory mediator before surgery, respectively  $39.67 \pm 7.18$  pg / ml and  $48.18 \pm 7.62$  pg / ml versus  $15.27 \pm 3.31$  pg / ml ( $p < 0.05$ ).

High levels of CCL2 / MCP-1 in the plasma of patients of groups II and III 12 and 24 hours after surgery convincingly indicate the presence of a pronounced inflammatory reaction under the influence of thermal damaging factor on skin tissues. Therefore, the choice of method for removing pigmented skin tumors in pediatric patients should take into account the possible dangers in the postoperative period, which are associated with perioperative immunosuppression, which depends on the local and systemic inflammatory response of the body.

The lack of targeted studies on the clinical significance of elevated postoperative CCL2 / MCP-1 levels in patients with pigmented nevi leaves a wide range of possibilities for studying the probable recurrence of the pathology and preventing unsatisfactory treatment outcomes.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

## References

- Kolotov KA. Monotsitarnyy khemotaksicheskiy protein-1 v fiziologii i meditsine. Permskiy meditsinskiy zhurnal. 2018; T.35, №3: 99 – 105. [ in Russian ]
- Takahashi M. Induction of monocyte chemoattractant protein-1 synthesis in human monocytes during transendothelial migration in vitro. Circulation Research. 1995; 76 (5): 750 – 57. doi: 10.116/01.RES.76.5.750
- Liu S. Increased serum MCP-1 levels in systemic vasculitis patients with renal involvement. J. of Interferon & Cytokine Research. 2018; 38 (9): 406 – 12. doi.org/10.1089/jir.2017.0140
- Traves SL. Increased levels of the chemokines GRO $\alpha$  and MCP-1 in sputum samples from patients with COPD . Thorax. 2002; 57:590 – 95.
- Matveyeva LV. Izmeneniya monotsitarnogo khemoattraktantnogo proteina-1 pri Helicobacter pylori-assotsirovannykh gastroduodenal'nykh zabolovaniyakh. Infektsiya i immunitet. 2018; 8 (2): 150 – 56. [ in Russian ]
- Jin HJ. Senescence associated MCP-1 secretion is dependent on a decline in BMI1 in human mesenchymal stromal cells. Antioxid. Redox. Signal. 2015; 17. doi: 10.1089/ars.2015.6359
- Balatskaya NV., Kulikova IG., Kovaleva LA., Makarov PV. Proinflammatory chemokines in the development of systemic organ-specific sensitization in infectious corneal ulcers. Russian Ophthalmological Journal. 2020;13(2):65-70 <https://doi.org/10.21516/2072-0076-2020-13-2-65-70>
- McNeill MS. Cell death of melanophores in zebrafishtrpm7 mutant embryos depends on melanin synthesis. J. of Investigative Dermatology. 2007; 127: 2020 – 30.
- Ponomarev IV., Andrusenko YUN., Topchiy SB., Shakina LD. Udalenieye pal'pebral'nykh melanotsitarnykh nevosov dvukhvolnovym izlucheniyyem lazera na parakh medi. Vestnik dermatologii i venerologii. 2020;96(5):47–52. doi: <https://doi.org/10.25208/vdv1138-2020-96-5-47-52> [ in Russian ]
- Ikonnikova EV., Stenko AG., Korchazkina NB. The modern methods for the correction of non-neoplastic melanin hyperpigmentation of the skin and the integrated approach to their treatment. Fizioterapiya, Bal'neologiya i Reabilitatsiya (Russian Journal of the Physical Therapy, Balneotherapy and Rehabilitation). 2017; 16 (2): 84-88. (In Russ.). DOI: <http://dx.doi.org/10.18821/1681-3456-2017-16-2-84-88>
- Helsinki Declaration of the World Medical Association “Ethical principles of medical research with human participation as an object of study”: adopted by the 18th General Assembly of the Military Medical Academy, Helsinki, Finland, June 1964; edition from 01.10.2008 [Electronic resource] // Legislation of Ukraine. - Available: [http://zakon5.rada.gov.ua/laws/show/990\\_005](http://zakon5.rada.gov.ua/laws/show/990_005)
- Lee WJ. The effect of MCP-1/CCR2 on the proliferation and senescence of epidermal constituent cells in solar lentigo. Int. J. Mol. Sci. 2016; 17: 948; doi:10.3390/ijms17060948
- Damsky WE. Melanocytic nevi and melanoma: unraveling a complex relationship. Oncogene. 2017; 36(42): 5771 – 92/ doi:10.1038/ncr.2017.189
- Noemi GS. Targeting tumor-associated macrophages and inhibition of MCP-1 reduce angiogenesis and tumor growth in a human melanoma xenograft. J. of Investigative Dermatology. 2007; 127(8) : 2031 – 41.
- Wang X. Serum cytokine profiles of melanoma patients and their association with tumor progression and metastasis. Hindawi J. of Oncology. 2021; 1: 9. doi: org.10.1155/2021/6610769
- Tang M. Endogenous PGE<sub>2</sub> induces MCP-1 expression via EP4/p38 MAPK signaling in melanoma. Oncology letters. 2013; 5: 645 – 50. doi: 10.3892/ol.2012.1047
- Was H. Effect of heme oxygenase-1 on melanoma development in mice – role of tumor-infiltrating immune cells. Antioxidants. 2020; 9: 1 – 21. doi: 10.3390/antiox9121223
- McNeill M.S. Cell death of melanophores in zebrafishtrpm7 mutant embryos depends on melanin synthesis. J. of Investigative Dermatology. 2007; 127: 2020 – 30.
- Behfara S. A brief look at the role of monocyte chemoattractant protein-1 (CCL2) in the pathophysiology of psoriasis. Cytokine. 2018;110:226-31. doi.org/10.1016/j.cyto.2017.12.010
- Nesbit M. Low-level monocyte chemoattractant protein-1 stimulation of monocytes leads to tumor formation in

- nontumorigenic melanoma cells. *The Journal of Immunology*. 2001; 166: 6483 – 6490.
21. Behfara S. A brief look at the role of monocyte chemoattractant protein-1 (CCL2) in the pathophysiology of psoriasis. *Cytokine*. 2018; 110: 226-31. doi.org/10.1016/j.cyto.2017.12.010
22. Yoshimura T. Non-myeloid cells are major contributors to innate immune responses via production of monocyte chemoattractant protein-1/CCL2. *Frontiers in immunology*. – 2014; 4 (482): 1 – 6.
23. Dmytriiev D., Dmytriiev K., Stoliarchuk O., & Semenenko, A. (2019). Multiple organ dysfunction syndrome: what do we know about pain management? A narrative review. *Anaesthesia, Pain & Intensive Care*. 2019; 23(1): 84-91
24. Kruglov SS., Gelfond ML., Tyndyk ML., Maydin MA., Grishacheva TG., Basina RM., Gubareva EA., Plakhov EA., Kireeva GS., Panchenko A.V. Methodological aspects of photodynamic therapy of ehrlich solid carcinoma in BALB/C mouse strain with various tumor localization. *Siberian Journal of Oncology*. 2020; 19(6): 82-92. – doi: 10.21294/1814- 4861-2020-19-6-82-92.

---

**Correspondence:**

Received: 2 September 2021

Accepted: 14 September 2021

Yuliana Babina, PhD student of Department of anesthesiology and intensive care, National Pirogov Memorial Medical University, Pirogov, 56

Vinnytsia, 21018, Ukraine

Phone: +380687000694 E-mail: ulianababina1989@gmail.com

ORCID: <https://orcid.org/0000-0003-4399-5178>