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REVIEW

Mitochondrial transplantation: new challenges for cancer

O. I. Kit, E. M. Frantsiyants, A. I. Shikhlyarova, I. V. Neskubina ✉

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ neskubina.irina@mail.ru

ABSTRACT

This review discusses the uniqueness of mitochondria providing normal cellular functions and at the same time involved in many pathological conditions, and also analyzes the scientific literature to clarify the effectiveness of mitochondrial transplantation in cancer treatment. Being important and semi-autonomous organelles in cells, they are able to adapt their functions to the needs of the corresponding organ. The ability of mitochondria to reprogram is important for all cell types that can switch between resting and proliferation. At the same time, tumor mitochondria undergo adaptive changes to accelerate the reproduction of tumor cells in an acidic and hypoxic microenvironment. According to emerging data, mitochondria can go beyond the boundaries of cells and move between the cells of the body. Intercellular transfer of mitochondria occurs naturally in humans as a normal mechanism for repairing damaged cells. The revealed physiological mitochondrial transfer has become the basis for a modern form of mitochondrial transplantation, including autologous (isogenic), allogeneic, and even xenogenic transplantation. Currently, exogenous healthy mitochondria are used in treatment of several carcinomas, including breast cancer, pancreatic cancer, and glioma. Investigation of the functional activity of healthy mitochondria demonstrated and confirmed the fact that female mitochondria are more efficient in suppressing tumor cell proliferation than male mitochondria. However, tissue-specific sex differences in mitochondrial morphology and oxidative capacity were described, and few studies showed functional sex differences in mitochondria during therapy. The reviewed studies report that mitochondrial transplantation can be specifically targeted to a tumor, providing evidence for changes in tumor function after mitochondrial administration. Thus, the appearance of the most interesting data on the unique functions of mitochondria indicates the obvious need for mitochondrial transplantation.

Keywords: mitochondria, mitochondrial therapy, mitochondrial transfer, malignant tumors

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For correspondence: Irina V. Neskubina – Cand. Sci. (Biol.), senior researcher at the laboratory for the study of the pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: neskubina.irina@mail.ru
ORCID: https://orcid.org/0000-0002-7395-3086
SPIN: 3581-8531, AuthorID: 794688
ResearcherID: AAG-8731-2019
Scopus Author ID: 6507509066

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3.1.6. Онкология, лучевая терапия
ОБЗОР

Митохондриальная трансплантация – новые вызовы раку

О. И. Кит, Е. М. Франциянц, А. И. Шихлярова, И. В. Нескубина✉

ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация
✉ neskubina.irina@mail.ru

РЕЗЮМЕ

В представленном обзоре обсуждаются вопросы, касающиеся уникальности митохондрий, обеспечивающих нормальные клеточные функции, в то же время их участие во многих патологических состояниях организма, а также анализируется существующая литература с целью разъяснения эффективности трансплантации митохондрий при лечении злокачественных заболеваний. Являясь важными и полуавтономными органеллами в клетках, они способны адаптировать свои функции к потребностям соответствующего органа. Возможность митохондрий перепрограммироваться важна для всех типов клеток, которые могут переключаться между состоянием покоя и пролиферацией. Вместе с тем митохондрии опухолей претерпевают адаптивные изменения для ускорения размножения опухолевых клеток в кислой и гипоксической микросреде. Согласно появляющимся данным стало известно, что митохондрии могут выходить за границы клеток, перемещаться между клетками организма. Межклеточный перенос митохондрий естественным образом происходит у людей как нормальный механизм восстановления поврежденных клеток. Выявленный физиологический митохондриальный перенос стал основой для создания современной формы трансплантации митохондрий, включая аутологичную (изогенную), аллогенную и даже ксеногенную трансплантацию. В настоящее время экзогенные здоровые митохондрии используются для лечения некоторых карцином, включая рак молочной железы, рак поджелудочной железы и глиому. Исследование функциональной активности здоровых митохондрий привело к обнаружению и доказательству того, что женские митохондрии обладают более высокой эффективностью подавления пролиферации опухолевых клеток, чем мужские митохондрии. Вместе с тем были описаны тканеспецифические половые различия в морфологии митохондрий и окислительной способности, и лишь немногие исследования показали функциональные половые различия митохондрий при терапии. Рассмотренные в обзоре исследования показывают, что трансплантация митохондрий может быть специфически нацелена на опухоль, с предоставлением доказательств изменений в функции опухоли после введения митохондрий. Таким образом, появление интереснейших данных об уникальных функциях митохондрий свидетельствуют об очевидной необходимости митохондриальной трансплантации.

Ключевые слова: митохондрии, митохондриальная терапия, митохондриальный перенос, злокачественные новообразования

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Для корреспонденции: Нескубина Ирина Валерьевна – к.б.н., старший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей, ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации,
г. Ростов-на-Дону, Российская Федерация
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14 линия, д. 63
E-mail: neskubina.irina@mail.ru
ORCID: https://orcid.org/0000-0002-7395-3086
SPIN: 3581-8531, AuthorID: 794688
ResearcherID: AAG-8731-2019
Scopus Author ID: 6507509066

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INTRODUCTION

Mitochondria have played a fundamental role in the evolution of complex organisms. Being important and semi-autonomous organelles in cells, they are able to adapt their functions to the needs of the corresponding organ. Mitochondria can reprogram their intended purpose for the desired result: for an exceptional supply of energy to maintain the functioning of heart muscle cells throughout life or to control metabolic processes in secreting organs, for example, to support the work of hepatocytes and the liver. The ability of mitochondria to reprogram is important for all cell types that can switch between resting and proliferation, such as stem cells and immune cells. Most chronic diseases are characterized by a violation of mitochondrial regulation, which has been revealed in cardiovascular diseases, metabolic syndrome, neurodegenerative diseases, immune system disorders and malignant neoplasms [1–7].

The purpose of this review article was to evaluate new possibilities in the treatment of malignant neoplasms during mitochondrial transplantation.

Functional and dysfunctional multiplicity of mitochondria

Malignant tumors invariably rearrange their metabolism, promoting cellular plasticity with adaptation to the constantly changing availability of nutrients and the acquisition of aggressive disease traits, including the ability to metastasize. Cancer metabolism has long been equated with the predominant use of glycolysis by tumor cells even in the presence of oxygen, the so-called Warburg effect [8]. However, it is now known that the functions of mitochondria in tumor metabolism are broader, e. g. the use of oxidative bioenergetics, a change in the redox balance, the inclusion of multiple mechanisms of cell survival and retrograde expression of nuclear genes, as well as the effect on the primary and metastatic spread of a malignant tumor [9–11]. Interestingly, just like differentiated cells, mitochondria perform specialized functions unique to specific organs and tissues. For example, mitochondria in the liver are mainly involved in biosynthetic processes, and mitochondria in the heart or muscles mainly produce ATP. Mitochondria in adipocytes play a crucial role in regulating adipocyte differentiation, insulin sensitivity, and adaptive thermogenesis [12]. Analysis of the mitochondrial proteome isolated from various tissues such as the brain, liver, heart and kidneys of rats showed mitochondrial heterogeneity specializing in different functions between tissues. Abnormalities in mitochondria disrupt basic physiological functions such as ATP production, oxidative phosphorylation, reactive oxygen species (ROS) production and Ca^{2+} regulation, all of which are considered mitochondrial dysfunction. In addition, these unique organelles, which are important for normal cellular function, can be involved in many pathological conditions. Mitochondria are present in every cell of the human body, with the exception of red blood cells – erythrocytes. The production of ATP by mitochondria leads to the formation of small amounts of potentially destructive free radicals known as reactive oxygen species (ROS). These radicals are secondary messengers in vital cellular signaling cascades for normal biological processes. However, the accumulation of byproducts of ATP production can harm the cell and provoke damage to cellular organelles, as well as disruption of metabolic processes [13].

It is obvious that mitochondria are the most important organelles responsible for cell survival and apoptosis. Healthy mitochondria are essential for maintaining the normal functioning of cells. At the same time, accumulated research data indicates that tumor mitochondria undergo adaptive changes to accelerate the proliferation of tumor cells in an acidic and hypoxic microenvironment [14]. There is increasing evidence that mitochondrial metabolism and function are indispensable in oncogenesis and cancer progression, which makes mitochondria and their functions likely targets for antitumor therapy [15].

Although the mechanisms of mitochondrial reprogramming in cancer have recently received more attention, the role of organelle in this process has not been widely considered [16, 17]. In fact, the microenvironment in which the tumor grows is extremely unfavorable for mitochondria, since unstable oxygen concentrations and oxidative radicals can disrupt the integrity of organelles, disintegrate the regulation of many mitochondrial functions and activate cellular death [18]. Therefore, the way how mitochondria cope with the loss of their "functional form" remains unclear, and the effect of substandard or damaged mitochondria on tumor signs has not been studied [19]

Mitochondrial movement as a basis for mitochondrial therapy

Endosymbiotic theory suggests that mitochondria were once primary free-living unicellular organisms that may have been absorbed by larger, probably anaerobic cellular organisms in order to use them for more efficient aerobic energy production [20]. This "adoption" and billions of years of evolution have led to the complexity of eukaryotes. The proof of this theory is that mitochondria contain their own DNA (mtDNA) in the form of ring DNA, similar to that found in bacteria, and also contains two lipid bilayers. Mitochondria, like bacteria, are equipped with an intracellular mechanism necessary to produce 13 of their own mitochondrial proteins, but at the same time use nuclear DNA to produce other key proteins. It is due to this endosymbiotic origin that the internalization of mitochondria by recipient cells is possible [21].

Emerging data show that mitochondria can transcend cell boundaries, move between mammalian cells, radically challenging the concepts of intracellular segregation of mitochondria and inheritance of mitochondrial DNA, i. e. the mtDNA. Their signaling role may extend to intercellular communication, showing that the mitochondrial genome and even entire mitochondria are indeed mobile and can mediate information transfer between cells. This newly discovered process of mobile transfer of mitochondria and mtDNA has been called the "momiome" to denote all "mobile functions of mitochondria and the mitochondrial genome" [22]. Mitochondrial intercellular transfer promotes the integration of mitochondria into the endogenous mitochondrial network of recipient cells, contributing to changes in their bioenergetic status and other functional properties of recipient cells not only *in vitro*, but also *in vivo*. Moreover, transcellular transfer of mitochondrial genes can have serious consequences in the pathophysiology of mitochondrial dysfunction [23].

It has been reported that intercellular mitochondrial transfer naturally occurs in humans as a normal mechanism for repairing damaged cells [24, 25]. This physiological phenomenon inspired researchers to create a modern form of mitochondrial transplantation, including autologous (isogenic), allogeneic and even xenogenic transplantation [4, 26, 27]. Given that mitochondrial dysfunction may be at the center of devastating pathological conditions, mitochondrial transfer, called mitochondrial transplantation, has high therapeutic potential in modern medicine.

Mitochondrial transplantation is an innovative strategy for the treatment of mitochondrial dysfunction, which allows overcoming the limitations of agent–based therapy. Mitochondrial replacement, transplantation, or transfer is a new intervention and treatment for patients diagnosed with mitochondrial disease [28]. Mitochondrial transfer is based on the concept of targeted tRNA therapy. Treatment strategies for mitochondrial dysfunction are usually divided into the following categories: enhancing mitochondrial biogenesis; reducing dysfunctional mitochondria and replacing them with active ones; delivery or replacement of dysfunctional components; intervention in the consequences of mitochondrial dysfunction and reprogramming of the mitochondrial genome [29, 30]. It is believed that mitochondria persist in cells throughout their lives. The prerequisite for mitochondrial transfer is that the cell can perceive many different environmental signals and subsequently absorb, transfer, process and integrate foreign material. Which signals trigger mitochondrial transfer is of great importance for further theory and treatment. Current data have proven that mitochondrial transfer between cells is often triggered by multiple intracellular and extracellular events of the recipient cell. These events can act as "find me" or "save me" signals, recruiting the appropriate donor mitochondria to provide them to recipient cells [13].

Several *in vitro* studies have shown that intercellular mitochondrial transfer occurs naturally. When DsRed-labeled mitochondria isolated from mesenchymal cells (EMC) originating from the endometrial glands of the human uterus were co-incubated with isogenic EMC for 24 hours, the accumulation of exogenous mitochondria in the cytoplasm of recipients was observed using imaging of living fluorescent cells [31]. In another study, it was also observed that xenogenic transfer of mitochondria isolated from mouse liver tissue to human cells devoid of functional mitochondria (cells p 0) restores respiratory function [32]. These results prove the possibility of treating mitochondrial diseases with mitochondrial transplantation.

In addition to the observed transfer of mitochondria in *in vitro* experiments, the possibility of introducing mitochondria directly into living organisms seems relevant. The mitochondria used for injection can be autologous, allogeneic, or even xenogenic. Doulamis I. P. et al. injected allogeneic or autologous mitochondria of muscle cells into damaged areas of the heart of rats with diabetes, both variants of mitochondria led to the restoration of left ventricular function and a decrease in the size of infarction [33]. Mitochondria can be injected directly into the damaged area or elsewhere. For example, Lin H. S. et al. mitochondria were injected into the spleen for the treatment of ischemically damaged liver [34]. In addition, in the past, researchers more often injected mitochondria directly into the regional ischemic zone to repair myocardial damage, and recently decided to inject mitochondria into the left coronary mouth or coronary artery [33, 35]. Local intracerebral or systemic intraarterial injection of mitochondria can significantly restore the area of cerebral infarction and the death of neuronal cells [36]. In addition, intraarterial injection or intravascular delivery of mitochondria into blood vessels has been performed to treat acute kidney injury or lung injury [37]. A recent study has shown the existence of intact and functional mitochondria in human peripheral blood [26]. Moreover, there is much evidence that there are many mitochondrial components in the blood, such as cell-free circulating mtDNA, vesicles of mitochondrial origin and peptides of mitochondrial origin, and these components increase in disease [38–40]. Although the significance of their presence in the blood and their association with disease are unclear, the presence of these components demonstrates that mitochondria can play a signal-regulating role through circulation in distant cells, even if they are fragmented. Accordingly, intravascular administration of mitochondria can be promising if we understand in advance the existence of mitochondria in the blood, the biological role of mitochondrial components.

Dysfunctional dominance of malignant mitochondria and the possibility of counteraction

The mitochondria of malignant cells play a key role in the interaction of tumor cells with the tumor microenvironment [41]. As recent scientific studies have shown, tumors are not only composed of malignant cells, they are a complex system of tumor and non-tumor cells that create symbiotic relationships in the tumor microenvironment, contributing to survival and resistance to chemotherapy. Malignant cells are able to displace entire mitochondria or some of their components, including mtDNA, cytochrome C, and formylated peptides into the tumor microenvironment [42]. They, in turn, function as damage-associated molecular patterns (DAMPs) that are released from damaged or "dying" cells and activate the innate immune system.

Elliott R. L. et al. (2012) found that mitochondria purified from immortalized, untransformed MCF-12A breast epithelial cells can successfully penetrate human breast cancer cell lines and suppress them depending on the dose. Mitochondria from MCF-12A cells can also be transferred to human breast cancer MCF-7 cell lines, which is accompanied by increased sensitivity to chemotherapy with doxorubicin, abraxane or carboplatin [43]. This is the first publication concerning the transfer of mitochondria that promote apoptosis of malignant cells and increase sensitivity to drugs.

Accumulating research data show that tumor mitochondria undergo adaptive changes to accelerate the rapid proliferation of tumor cells in an acidic and hypoxic microenvironment [14]. Thus, it is assumed that the introduction of healthy mitochondria into tumor cells is highly effective in preventing tumor growth [44]. Currently, exogenous healthy mitochondria are used to treat several carcinomas, including breast cancer, pancreatic cancer and glioma, and excellent antitumor efficacy of healthy mitochondria has been shown [45–47]. At the same time, the authors, based on the obtained biochemical data, noted the fact that healthy mitochondria after mitochondrial transplantation can significantly reduce the ability to oxidative phosphorylation (OXPHOS) and induce apoptosis in tumor cells. However, the molecular signaling mechanism of this process remains unclear.

The mechanism of mitochondrial penetration, immune reactions

Intercellular mitochondrial transfer occurs through tunneling nanotubes (TNT), extracellular vesicles (EV) and cell fusion. Recently, functionally active mitochondria free of cells and cytoplas-

mic membrane have been observed in blood and conditioned medium for cell culture [48]. Although the role of extracellular mitochondria in intercellular communication has yet to be fully understood, practical approaches aimed at transferring intact mitochondria to target cells have been developed previously.

The mechanism of mitochondrial penetration into cells may be related to macropinocytosis-mediated endocytosis, since a macropinocytosis inhibitor can prevent the internalization of mitochondria by cells. Moreover, mitochondria are considered as systemic intermediaries in intercellular communication [49]. It is also known that mitochondria can be absorbed by various cell types, as has been shown in *in vitro* and *in vivo* studies [50]. In addition, mitochondria in the blood can activate the immune system by increasing the activity of phagocytes and T cells, which can to a certain extent enhance the antitumor effect of mitochondria [51].

To date, some studies have discussed the immune reactions that occur during mitochondrial transplantation – MT. Understanding their involvement in the effectiveness of MT would be valuable to reduce possible risks. With existing mitochondrial disease, transplantation of mitochondria obtained from autologous cells is possible without inflammation and autoimmune reactions [52]. Some researchers believe that autologous mitochondrial transplantation may have more effective results. However, in some cases, including diseases associated with mitochondria, or in some of the most severe patients, isolation of their own mitochondria is impossible. On the other hand, some patients require multiple series of injections. Therefore, in this regard, transplantation of heterologous mitochondria is inevitable [53]. The main possible problems of heterogeneous mitochondrial transplantation are immune system reactions and damage-related molecular pattern (DAMP). It should be noted that in all previous studies, only one injection of mitochondria was reported. And what happens after a series of injections of mitochondria into damaged tissues? McCully J. D. et al. (2017) conducted a study to find out the behavior of the immune system after direct or indirect autogenic and allogeneic injections, single and serial injections, as well as various numbers of isolated mitochondria (1×105, 1×106 or 1×107 mitochondria). The data obtained showed that the level of immune system profiles, including IL-1, IL-4, IL-6, IL-12, IL-18, IP-10, macrophage inflammatory protein MIP-1 α and MIP-1 β did not change. Single or serial injections of mitochondria did not show the presence of DAMP in the recipient's tissues [54]. Ramirez-Barbieri G. et al. (2019) investigated the immune response and damage-related molecular patterns (DAMPs) In mice, after single or multiple intraperitoneal injections of allogeneic mitochondria, it was found that serum cytokine and mtDNA levels did not increase either after autologous or after allogeneic mitochondrial injection [55].

Sex-related features of mitochondria

Mitochondria are an almost exclusive legacy of the mother in evolution, and during transplantation therapy, sex differences in the functioning of mitochondria may occur. It was previously reported that the mitochondria of female animals (female mitochondria) are more sensitive to stress and better adapted to combat adverse conditions, therefore, it was assumed that female mitochondria have different activity in antitumor growth compared with the mitochondria of males [56].

A number of reports have described tissue-specific sex differences in mitochondrial morphology and oxidative capacity, while only a few studies have shown functional differences in mitochondria during therapy. At the same time, it has been shown that the mitochondria of women have a higher protein content and the ability to produce ATP than in men [57]. According to the available limited data, female mitochondria have more favorable mitochondrial-nuclear communication in response to stress compared to male mitochondria [58].

Yu Z. et al. (2021) evaluated the activity of mitochondria isolated from female and male mice, and the results showed that female mitochondria showed higher activity and ability to produce ATP than male mitochondria. Subsequently, antitumor mitochondrial effects in a number of experiments, both *in vitro* and *in vivo* models, proved that female mitochondria have a higher efficiency of suppressing tumor cell proliferation than male mitochondria. The study also showed that female mitochondria can induce a more sustained stress response to gene transcription than male mitochondria in tumor cells, suggesting that female mitochondria are more sensitive to the hypoxic microenvironment of the tu-

mor than male mitochondria, and ultimately lead to a stronger antitumor effect. The authors used intact mitochondria to study their antitumor activity when administered intravenously. This study demonstrated a new understanding of mitochondrial function in the development of melanoma and suggests that healthy mitochondria inhibit tumor cell proliferation by preventing transcription of tumor genes. General downregulation of genes leads to cell cycle arrest and stagnation of cell proliferation, as well as activation of autophagy and apoptosis, which ultimately leads to an obvious inhibition of melanoma growth after mitochondrial transplantation therapy [59].

CONCLUSION

Today, mitochondria are much more than just the "powerhouse" of the cells. Mitochondrial transplantation therapy has been an active area of research for the treatment of diseases related to mitochondrial dysfunction, from animal studies to clinical trials. However, the specific mechanism providing antitumor activity of healthy mitochondria has yet to be defined. The mechanism of intercellular mitochondrial transfer is still partially understood and requires further research, while its targeting may provide new opportunities in the treatment of malignant neoplasms. Evidence that mitochondrial transfer can occur in a similar way in solid and hematological tumor cells further increases the importance of this process as a basis for mitochondrial transplantation. In addition, the involvement of mitochondrial transfer in cancer progression and the development of chemoresistance may explain the still unclear mechanisms of action of some anticancer drugs. It has been proven that the therapeutic effect of mitochondrial transplantation is a potential method of treating diseases associated with mitochondria. However, there are several problems that need to be solved so that the treatment of the disease with mitochondrial transplantation can be effectively applied to humans.

Most studies emphasize that the isolation of mitochondria should be completed in a short time at a low temperature, since they are very sensitive, and their activity and survival are rapidly decreasing. In addition, there is currently no method for long-term storage of mitochondria, so they should be used immediately after isolation. Therefore, a protocol for the optimal method of mitochondrial isolation and storage, which maintains the integrity of mitochondria and ensures longer survival, should be developed to enable clinical use.

Since mitochondria are easily obtained from cultured cells, and the technology of mitochondrial isolation and preservation is becoming more mature, it is expected that large-scale mitochondrial donation centers will be established in the future. Thus, when autologous transplantation cannot be performed, it is possible to find a compatible mitochondrial donor just in time.

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Information about authors:

Oleg I. Kit – Academician at the Russian Academy of Sciences, Dr. Sci. (Med.), professor, general director, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-3061-6108, SPIN: 1728-0329, AuthorID: 343182, ResearcherID: U-2241-2017, Scopus Author ID: 55994103100

Elena M. Frantsiyants – Dr. Sci. (Biol.), professor, deputy CEO for science, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-3618-6890, SPIN: 9427-9928, AuthorID: 462868, ResearcherID: Y-1491-2018, Scopus Author ID: 55890047700

Alla I. Shikhlyarova – Dr. Sci. (Biol.), professor, senior researcher, Laboratory of Study of Malignant Tumor Pathogenesis, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-2943-7655, SPIN: 6271-0717, AuthorID: 482103, ResearcherID: Y-6275-2018, Scopus Author ID: 6507723229

Irina V. Neskubina ✉ – Cand. Sci. (Biol.), senior researcher at the Laboratory for the Study of the Pathogenesis of Malignant Tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-7395-3086, SPIN: 3581-8531, AuthorID: 794688, ResearcherID: AAG-8731-2019, Scopus Author ID: 6507509066

Contribution of the authors:

Kit O. I. – scientific editing;
Frantsyants E. M. – text writing, data analysis and interpretation;
Shikhlyarova A. I. – scientific editing;
Neskubina I. V. – technical editing, bibliography design.