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POSSIBILITIES TO CONTROL THE PROLIFERATION OF HEMATOPOIETIC STEM CELLS AFTER IRRADIATION BY NANOSECOND MICROWAVE PULSES

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Annotation. The purpose was to study the possibility to control the proliferation of hematopoietic stem cells in vitro using the nanosecond repetitively pulsed microwave radiation (RPMs). It was found on 9 cultures of hematopoietic cells of the red bone marrow that irradiation with RPMs with a pPFD of 140 W/cm^2 with different pulse repetition rates (8 and 13 Hz) has an effect on proliferative activity. RPM initiates statistically significant stimulation (13 Hz) or inhibition (8 Hz) of proliferation. The data obtained allow us to assume the existence of optimal modes of exposure to RPM, which in specific tasks of regenerative medicine can provide the most effective stimulation of proliferation of stem cells for the rapid production of the required amount or inhibition of cell growth.

Introduction. With an active development and implementation of personalized medicine, and also the direction to develop and create a new, non-invasive technology of health protection for institutes of medical profile, new solutions for sources of electromagnetic radiation with necessary interaction parameters, which are compact and easy to use, are relevant.

New sources of stem cells receiving, technologies of cell differentiation and scaling to different types of progenitor and/or specialized cells and new means of control of these processes are of special interest for cell transplantology and therapy [11, 23, 25, 26]. Currently, certain data were collected, indicating a possibility to

regenerate muscular, nervous, bone and epidermal tissue under the influence of various physical factors, such as electromagnetic waves, optical radiation, ultrasonic oscillations and magnetic fields [3, 19]. It was clearly shown that physiotherapeutic effects by above-mentioned factors are able to change the functional activity of cells [10, 11, 17]. The conducted experimental and clinical studies showed that physical factors impact on processes of regeneration and recovery of physiological functions of tissues indirectly in higher degree, through the impact on metabolism, the state of the nervous and endocrine systems, humoral and tissue regulators, energy processes and the intensity of blood circulation in damaged organs [10, 14]. It is also known, that physical factors of the electromagnetic nature are able to affect the cell regeneration even at very low degrees of impact [1], but results of conducted studies appear contradictory in many aspects. In particular, a possibility of insignificant stimulation (25%) with the extremely high frequency (EHF) radiation on the proliferation of "weakened" stem cells in cell cultures [18], however, "normal, not weakened" multipotent mesenchymal stromal cells (MSC) do not react to the radiation. At the same time, low-intensity laser radiation with the energy flux density of 5-10 J/cm^2 with a wavelength of 410 and 420 nm suppresses significantly the proliferation of fibroblasts in vitro with daily exposure [15]. Nonetheless, the effect of the proliferation stimulation was registered under the impact of the non-stop laser radiation of 635 nm with the power flux density of 32,6 mW/cm^2 and the exposure time of 90 seconds.

Up to the present time, from the viewpoint of the effect on proliferative abilities of cell cultures, the study of biological impact of the nanosecond repetitively pulsed microwave radiation (RPMs) could be of significant scientific interest. It was shown earlier that the RPM with nanosecond pulses effectively affects the functional state of the whole range of cells and tissues [6, 7, 8, 12]. RPM with specific parameters has a stimulating effect on processes of regeneration of damaged tissues, speeds up healing of full-flap skin wounds [9], eliminates peptic ulcer of laboratory rats [13]. Moreover, in the previous study we revealed that the effect of RPM with powerful nanosecond pulses (peak power flux density (pPFD) is 1500 W/cm^2) with specific pulse repetition rate is able to initiate both the stimulation and the inhibition of proliferation of cells of bone marrow of "Wistar" laboratory rats. In particular, single radiation of cell cultures with a pulse repetition rate of 13 Hz increased the cell amount by 30% in relation to the control group [7]. On the contrary, an exposure with 8 Hz frequency was accompanied by the inhibition of cell proliferation by 40% [7]. This being the case, the use of nanosecond microwave pulse for stimulation of stem cells proliferation and their use in the processes of regeneration of damaged tissues and organs is promising. That is why the fundamental research of the effect of RPM with lower values of intensity (10 times lower) could be more relevant from

the viewpoint of standards of safe electromagnetic radiation effect in regenerative medicine. To successfully realize and implement the given physical factor in institutes of medical profile a development of compact and simple in use sources of repetitive nanosecond repetitively pulsed radiation with needed effect parameters.

The aim of this study is an experimental research of possibility to control the proliferation of hematopoietic stem cells of rats in vitro using the irradiation by repetitive nanosecond microwave pulses.

Methods and organization. The isolation and cultivation of hematopoietic stem cells. The experimental study was conducted on nine cell cultures, isolated from the femur of "Wistar" laboratory rats using the generally accepted standard method [5]. All procedures with animals were conducted according to international regulations and standards [16]. On 12-14th day of the cultivation a 95-100% monolayer of stem cells was formed, which was further exposed to impulse microwaves. Vitality of hematopoietic stem cells of the red bone marrow was at 91,5±2% after the cultivation.

The received cultures were divided into three groups: control group – cell cultures, which were not affected with any exposures and located in the CO_2 incubator; 1 and 2 experimental groups – cell cultures, which were affected with the single exposure of the nanosecond microwave pulses with the pPFD of 140 W/cm^2 with pulse repetition rates of 8 и 13 Hz. In order to study the consequences of irradiation by nanosecond microwave pulses, stem cell cultures were affected by the radiation a day after taking out and counting the monolayer. The cell examination was conducted using the Optika XDS-2SFL microscope (Italy) with a 20-time enhancement. Before the beginning of the experiment, every cell culture contained 595×10^4 to 800×10^4 hematopoietic stem cells of the red bone marrow.

Irradiation of cell cultures by nanosecond RPMs. A laboratory impulse generator based on the MI-505 magnetron was used as a source of RPMs (the device of serial manufacturing by the OJSC "Tantal", Russia). The irradiation of hematopoietic stem cells in culture flask was conducted in the farther zone of the microwave antenna with a cross-section of 40x90 mm, connected to the waveguide at the distance of 20 cm. It supported an exposure with the peak power flux density (pPFD) of 140 W/cm^2 (the standard power flux density is 1,2 mW/cm^2) which is compliant with sanitary and epidemiological standards of approved level of radiation for a human on the workplace (SanRaN 2.2.4/2.1.8.088-96). The intensity of RPMs was measured using the standard method based on antenna measures and calorimetric calibrations [24]. Cells were irradiated single time by 4000 impulses of RPMs (the carrier frequency of the generator was 10 GHz, peak output power – 180

kW, pulse duration on the halved level of power – 100 ns) with pulse repetition rates of 8 and 13 Hz. The explosion time was 8 and 5 minutes. A choice of modes was based on results of previously conducted experiments on the tissue regeneration stimulation.

The obtained data were affected by statistical processing using the Statsoft STATISTICA application software packet for Windows 8.0. During the processing of results, groups were examined for normality of distribution of studied features using the Shapiro-Wilk criteria. The results are presented in the form of median (Me) and quartiles (Q_1 – 25 %; Q_3 –75 %). The significance of differences between indicators of irradiated and control cell cultures was determined using the ANOVA analysis. The level of statistical significance – <5% ($p<0,05$) was set during the testing of statistical hypotheses.

Results and discussion. The evaluation of the state of irradiated cell cultures showed that hematopoietic stem cells of the red bone marrow of "Wistar" laboratory rats are sensitive to the effect of nanosecond RPMs. The proliferative activity in radiated cells was changing depending on the pulse repetition rate. The radiation of cells by RPMs with the pPFD of 140 W/cm^2 with the pulse repetition rate of 8 Hz in a day after the effect was accompanied by the statistically significant suppression of the cell proliferation and growth of culture in relation to the first day of the experiment (Table 1). The inhibition of culture growth was preserved up to the 4th day of observation and was at 67% in relation to the first day of the experiment and at 60% in relation of the control group (Table 1).

Table 1

Proliferative activity of hematopoietic stem cells of the red bone marrow of rats after the radiation by nanosecond RPMs with the pPFD of 140 W/cm^2

Cell groups	Cell amount (abstr. u.), Me (Q_1;Q_3)		
	before radiation	in one day	after four days
Control	595×10^4 (525×10^4; 680×10^4)	600×10^4 (525×10^4; 725×10^4)	625×10^4 (500×10^4; 760×10^4)
8 Hz	800×10^4 (725×10^4; 900×10^4)	750×10^4 (235×10^4; 825×10^4) p_0=0.04	250×10^4 (75×10^4; 300×10^4) p=0.002; p_0=0.001
13 Hz	610×10^4 (400×10^4; 880×10^4)	670×10^4 (490×10^4; 912×10^4)	750×10^4 (400×10^4; 1160×10^4) p_0=0.04 p_1=0.04

Note: the obtained results were presented in the form of median (Me) and quartiles (Q_1 – 25 %; Q_3 – 75 %), p – the level of statistical significance in relation to the control group in the appropriate day of measurement; p_0 – the level of

statistical significance within the appropriate group; p_1 – the level of statistical significance between radiated groups (8 and 13 Hz).

The opposite effect was registered after the exposure of hematopoietic stem cells of the red bone marrow to RPMs with the pPFD of 140 W/cm^2 and pulse repetition rate of 13 Hz. In particular, a day after the irradiation with nanosecond microwave pulses there was a tendency to strengthen the proliferation of stem cells within both the radiated group and the control group (Table 1). Moreover, on the 4th day of after the radiation a statistically significant growth rate of hematopoietic stem cells in relation to the first day of the experiment (before the radiation). That is, the effect of the 13 Hz frequency stimulates the proliferative activity of stem cells in comparison with the inhibition effect, which was caused by the exposure to the 8 Hz frequency. Moreover, it is also important to note that the time of monolayer creation was decreased due to the increase of the proliferation of cell product. In addition, radiated hematopoietic stem cells created 80-85% of the monolayer to the 8-10th day, while in the control group the 95% monolayer of stem cells was formed only to the 12-14 day of cultivating, which approves the fact of stimulation with RPMs with the 13 Hz frequency and the pPFD of 140 W/cm^2.

Those results coincide with earlier received results of the study, in which the exposure to RPMs with the 1500 W/cm^2 with the frequency of 8 Hz and 13 Hz was also accompanied by the inhibition by 40% or stimulation by 30% (13 Hz) of the stem cells proliferation, which could indicate the appropriate manner of cell culture response to RPMs [4].

The literature data, which is available at the current moment, show that the use of various methods of physical exposure (laser radiation of low and moderate intensity, acoustic pulses, generated by laser radiation and EHF-radiation) in vitro and in vivo increases the amount of multipotent stromal cells in the initial bone marrow and also strengthens their proliferative activity in the process of the development of cell strains on vitro [11, 17, 18, 21, 22].

Conclusion. In contrast with data presented in literature, the results of the conducted experiment show that the exposure to nanosecond RPMs has a more complicated manner of response and the mechanism of realization of impact on proliferation of hematopoietic stem cells of the red bone marrow of laboratory rats. The revealed effect could show the balance of two differently directed processes of the proliferation regulation, which support either the stimulation or the inhibition. These processes apparently depend on the presence of the reactive oxygen species (ROS) and are controlled by ferments of the antioxidant defense [4, 8, 20]. Furthermore, the hematopoietic cells of the bone marrow affected with the RPMs

react either by the inhibition or by the proliferation stimulation, depending on pulse repetition rate. Accordingly, the change of oxidation-reduction cell state stimulated by the radiation will support a complicated plan of the realization of impact effects of RPMs [2, 4, 20]. A complicated nature of reaction to the exposure is typical for a wide range of RPM intensities, in particular, the range of intensities that was examined in the study (140 to 1500 W/cm^2) [7]. The RPM effects that formed on low levels of the organism organization (membrane, cell) play the role of physiological mechanisms of impact on higher levels.

According to the received data of the study of the proliferative activity of hematopoietic stem cells of the bone marrow of laboratory rats after radiation with nanosecond impulse microwave pulses, there is a possibility to control of cells' speed rate in vitro using low-intensity (pPFD is 140 W/cm^2) exposure with used pulse repetition rates. The data obtained allow us to assume the existence of optimal modes of exposure to RPM, which in specific tasks of regenerative medicine can provide the most effective stimulation of proliferation of stem cells for the rapid production of the required amount or inhibition of cell growth. Moreover, judging by the results of the conducted study, there is a need to raise an issue about the development of portative hardware based on RPMs for personalized medicine of institutes of medical profile with their further implementation, scaling and active use.

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