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Mechanisms of Recovery and Regeneration of Thermal Skin Damage Using Nanosecond Microwave Pulses

Samoylova A.V.[1, 4], Zharkova L.P.[1, 3], Bolshakov M.A.[3], Gostyukhina A.A.[2, 3], Zaitsev K.V.[2], Kolobovnikova Yu.V.[4], Rostov V.V.[1], Vykhodtsev P.V.[1]

[1] *Institute of High Current Electronics of the Siberian Branch of the Russian Academy of Sciences*
2/3 Academicheskiy Ave., 634055 Tomsk, Russian Federation

[2] *Federal Research and Clinical Center of Medical Rehabilitation and Balneology (FRCC MRaB) of the Federal Medical and Biological Agency (FMBA) of Russia*
6/1Rodnikovaya St., 141551 Solnechnogorsk, Russian Federation

[3] *National Research Tomsk State University (NR TSU)*
36 Lenin Ave., 634050 Tomsk, Russian Federation

[4] *Siberian State Medical University (SibSMU)*
2 Moskovsky trakt, 634050 Tomsk, Russian Federation

ABSTRACT

The authors of this lecture performed a comprehensive analysis of possible mechanisms for stimulating reparative processes after thermal skin damage using nanosecond repetitive pulsed microwave (RPM) radiation. The study analyzes both thermal and non-thermal mechanisms of the biological action of electromagnetic radiation, with special emphasis on the molecular aspects of the effects of nanosecond microwave pulses. Special attention is paid to the role of membrane proteins, calcium-dependent signaling pathways, and extracellular matrix components in realizing the regenerative potential of low-intensity microwave exposure. The study reveals the complex relationships between the physical parameters of RPM radiation (intensity, frequency, duration of pulses) and the activation of key cellular processes that ensure accelerated healing without scarring. The work uses experimental data obtained on models of burn injuries in laboratory animals (Wistar rats) using spectrophotometric, hematological, and histological methods. RPM radiation is a promising physical factor for stimulating skin regeneration, acting through non-thermal mechanisms. The combination of RPMs with cell therapy and pharmacological agents can become the basis of new protocols for the treatment of burns and other skin injuries. Further research is aimed at developing personalized treatment regimens, taking into account phases of the injury.

Keywords: nanosecond pulses, microwave exposure, burn injury, skin regeneration, stem cells, calcium ions, extracellular matrix

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✉ *Samoylova Anna V.*, kereya21@mail.ru

Механизмы восстановления и регенерации термических повреждений кожи посредством наносекундных микроволновых импульсов

Самойлова А.В.[1, 4], Жаркова Л.П.[1, 3], Большаков М.А.[3], Гостюхина А.А.[2], Зайцев К.В.[2], Колобовникова Ю.В.[4], Ростов В.В.[1], Выходцев П.В.[1]

[1] *Институт сильноточной электроники Сибирского отделения Российской академии наук (ИСЭ СО РАН)*
Россия, 634055, г. Томск, пр. Академический, 2/3

[2] *Федеральный научно-клинический центр медицинской реабилитации и курортологии Федерального медико-биологического агентства (ФНКЦ МРиК ФМБА)*
Россия, 141551, г.о. Солнечногорск, ул. Родниковая, стр. 6, корп. 1

[3] *Национальный исследовательский Томский государственный университет (НИ ТГУ)*
Россия, 634050, г. Томск, пр. Ленина, 36

[4] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Авторы проанализировали возможные механизмы стимуляции репаративных процессов после термических повреждений кожи с помощью действия наносекундного импульсно-периодического микроволнового излучения (ИПМИ). Проведен анализ как тепловых, так и нетепловых механизмов биологического действия электромагнитного излучения, с особым акцентом на возможные молекулярные аспекты взаимодействия ИПМИ с клеточными структурами. Особое внимание уделено роли мембранных белков, кальций-зависимых сигнальных путей и компонентов внеклеточного матрикса в реализации регенеративного потенциала низкоинтенсивного микроволнового воздействия.

В работе раскрываются сложные взаимосвязи между физическими параметрами ИПМИ (интенсивность, частота, длительность импульсов) и активацией ключевых клеточных процессов, обеспечивающих ускоренное заживление без рубцевания. Использованы экспериментальные данные, полученные на моделях ожоговых повреждений у лабораторных животных (крысы линии Вистар), с применением спектрофотометрических, гематологических и гистологических методов.

ИПМИ представляет собой перспективный физический фактор для стимуляции регенерации кожи, действующий через нетепловые механизмы. Комбинация ИПМИ с клеточной терапией и фармакологическими агентами может стать основой новых протоколов лечения ожогов и других повреждений кожи. Дальнейшие исследования направлены на разработку персонализированных схем воздействия с учетом фаз раневого процесса.

Ключевые слова: наносекундные импульсы, микроволновое воздействие, ожоговая травма, регенерация кожи, стволовые клетки, ионы кальция, внеклеточный матрикс

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Despite the significant number of studies on developing methods for the treatment of skin injuries (including thermal ones) using pharmacological approaches, surgical methods, and the impact of physical factors (in particular, low-intensity pulsed electromagnetic radiation) [1–6], the problem of effective stimulation of regeneration remains relevant in modern medicine. This necessitates the development of more effective methods that will allow to optimize the time and quality of tissue repair.

The aim of this lecture was to consider possible mechanisms and modern ways to repair damaged tissues, including after thermal injury.

EPIDEMIOLOGY OF BURN INJURIES AND THEIR SOCIAL AND PSYCHOLOGICAL CONSEQUENCES

According to statistical data, burns rank sixth in the profile of injuries in patients admitted to medical institutions of the Russian Federation, with the annual incidence exceeding 300 thousand cases. In about 20% of cases, thermal damage affects open areas of the body, which determines high importance of rehabilitation of post-burn deformities with subsequent prevention to ensure a satisfactory quality of life and psychosocial adaptation.

Clinically significant cosmetic defects following burn injuries can lead to persistent maladaptation, including disability, impaired social functioning, and the development of psycho-emotional disorders, which underscores the need for an integrated approach to rehabilitation of this category of patients [7].

FORMATION OF SCARS AFTER THERMAL INJURIES AND MODERN APPROACHES TO THEIR ELIMINATION

According to the study [8], final burn scar formation ends after an average of two months. The degree of hypertrophic scar severity is determined by a number of factors, including the depth and area of burn injury, individual regenerative abilities of the body, as well as timeliness and adequacy of medical care at early stages of the injury. In case of third-degree burns, the key task of treatment is to prevent the development of gross scar deformities, especially when injuries are localized in aesthetically significant areas (facial region, limbs) or on the joints, where excessive scarring can lead to contractures and limited mobility [7]. In cases of delayed repair or failure of natural epithelialization, surgical treatment is indicated, including autologous skin grafting, aimed at accelerating wound surface closure and minimizing the risks of blood loss and infectious complications.

Modern protocols for prevention of keloid and hypertrophic scars provide for comprehensive conservative therapy, which includes local treatment with silicone gels (*Kelo-Cote*, *Dermatix, Contractubex, Mederma*); intrascar injections of glucocorticoids (*Diprospan*, *Kenalog*), physiotherapy methods (electrophoresis with *Fermencol* or *Lidase*), ultrasound therapy with hydrocortisone, magnetic therapy, and balneotherapy as part of rehabilitation programs. The specified measures are most effective in the first 12–18 months after the injury, during the period of active scar formation. Taking this into account, optimizing duration of medical rehabilitation of patients with burns seems to be the key direction in reducing the risk of disabling consequences and improving the quality of life [8].

MODERN ASPECTS OF THE BIOLOGICAL ACTION OF REPETITIVE PULSED MICROWAVE RADIATION ON REGENERATIVE PROCESSES

Modern research demonstrates a growing interest in the study of the biological activity of various physical factors that are able to modulate regenerative processes. Special attention is drawn to nanosecond repetitive pulsed microwave (RPM) radiation, which has a pronounced impact on various levels of biological organization, from cellular structures to the whole body [9–11]. The conducted experimental studies allowed to reveal the key patterns of the biological action of RPM radiation. It was established that the nature and manifestation of the observed effects are strictly dependent on the impact parameters, including pulse repetition rate, radiation intensity, number of applied pulses, and total exposure duration [12].

The most important achievement of the conducted research was confirmation of the RPM ability to significantly accelerate the reparative processes in full-thickness skin lesions [13]. In addition, a pronounced reparative effect was revealed in experimental models of ulcers of gastric mucosa (ethanol-induced and neurogenic ulcers in laboratory animals), which indicates the prospects for a local application of RPM radiation in regenerative medicine [14].

Modern experimental data indicate a pronounced regenerative ability of RPM radiation in thermal skin lesions in laboratory animals (Wistar rats) [12]. Of particular interest is the combined use of RPM radiation with injection of stem cells from red bone marrow, demonstrating a synergistic effect that manifests itself in accelerated and complete wound healing with absence of keloid transformation of scar tissue with minimal severity of the inflammatory reaction [12].

The obtained results create the theoretical basis for development of innovative reparative therapy methods for skin lesions. The supposed mechanism of observed synergism may include activation of proliferative processes with simultaneous stimulation of cell migration and differentiation, as well as induction of collagen remodeling and proliferation of endogenous fibroblasts. Transformation of granulation tissue into fibrous connective tissue, neogenesis of hair follicles (the appearance of characteristic bulbs), and ultimately complete restoration of the cytoarchitectonics of the dermis are histological confirmation of the effectiveness of the combined impact of stem cells and nanosecond RPM radiation (Fig. 1) [6, 12]. These changes are reliable markers of the completed regenerative process, which confirms the prospects for further study of combined techniques using physical factors and cellular technologies (Fig. 1).

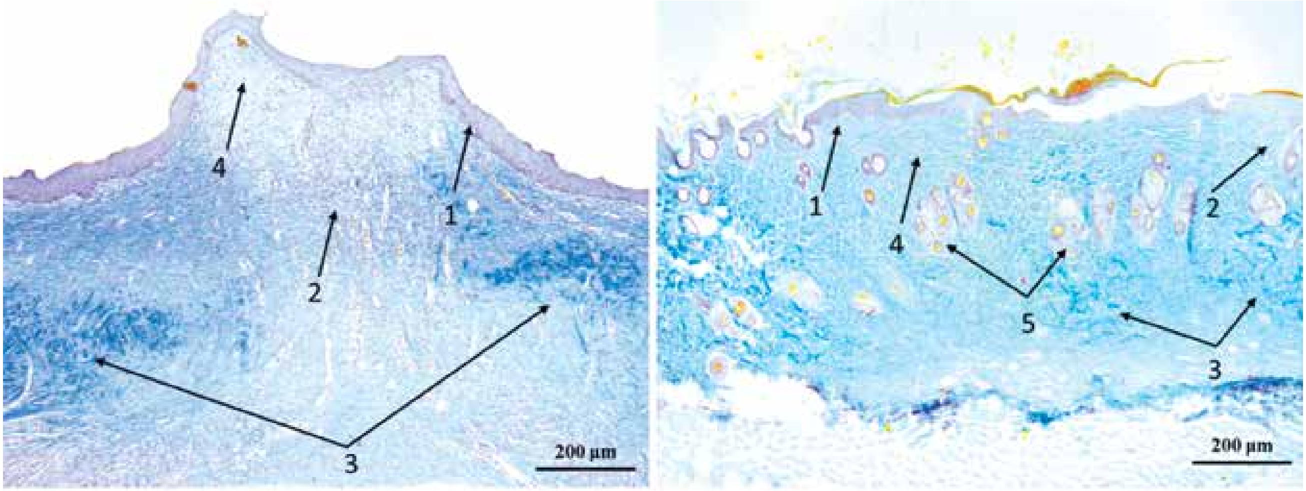

Fig. 1. Histological sections of skin regenerates of the Wistar laboratory rats on day 30 after modeling burn injury in the controls with self-healing without correction (left) [12] and after the combined use of nanosecond RPM radiation and the injection of cultured red bone marrow cells (right). *1* – newly formed epidermis; *2* – young granulation tissue; *3* – reticular dermis, represented by powerful collagen fibers of dense irregular connective tissue; *4* – papillary dermis layer, represented by fibroblasts of loose fibrous irregular connective tissue; *5* – hair follicles. Staining with modified Azan

In spite of the accumulated experimental material demonstrating the stimulating effect of RPM radiation on wound healing, there is still no unified concept explaining the mechanisms of interaction of RPM radiation with the structural components of the skin. Due to bioethical limitations, such studies are possible exclusively on animal models, which determined the aim of this work: to study the primary mechanisms of RPM energy absorption by damaged skin covers and to analyze the stimulating effect of nanosecond microwave pulses on regeneration in the experiment.

PHASE SPECIFICITY OF THE PHYSIOTHERAPY IMPACT DURING SKIN REGENERATION

To optimize therapeutic approaches using RPM radiation, it is necessary to have detailed understanding of the histological and molecular changes occurring in damaged skin at various stages of regenerative process, which sequentially replace one another with partial temporary overlap.

According to literature data, skin is a complex organ consisting of two main layers: epidermis and dermis (Fig. 2) [15]. The epidermal layer is characterized by pronounced structural organization, including pilosebaceous units that combine follicular structures and sebaceous glands associated with them as well as interfollicular epithelium. The dermal layer is morphologically subdivided into a superficial papillary zone and a deeper reticular layer, with the dermal papilla performing regulatory function in relation to the hair follicle cycle and the muscle attached to it ensuring motor activity of the hair.

The dermis contains numerous cellular elements (fibroblasts, immunocompetent cells), vascular and nervous structures, as well as dermal adipose tissue (Fig. 2, *a*). Hypodermis, represented by subcutaneous adipose tissue, is localized directly under the dermal layer. Repair of skin lesions starts immediately after injury and includes successive stages of hemostasis and inflammatory reaction (Fig. 2, *b*). The forming fibrin matrix not only prevents blood loss, but also creates structural basis for migration of various cell populations. During the proliferative phase, it is possible to observe active migration and proliferation of keratinocytes, fibroblasts, and endothelial cells with parallel reorganization of the extracellular matrix (ECM) (Fig. 2, *c*). The remodeling phase is characterized by structural transformation of collagen fibers and elimination of temporary cellular elements (Fig. 2, *c*). It should be noted that, according to experimental data [16] with small excision injuries in laboratory mice, hair follicles do not fully regenerate, and the defect is replaced with scar tissue (Fig. 2, *c*), whereas with extensive injuries, after completion of epithelialization, it is possible to observe the phenomenon of wound-induced hair follicle neogenesis (WIHN).

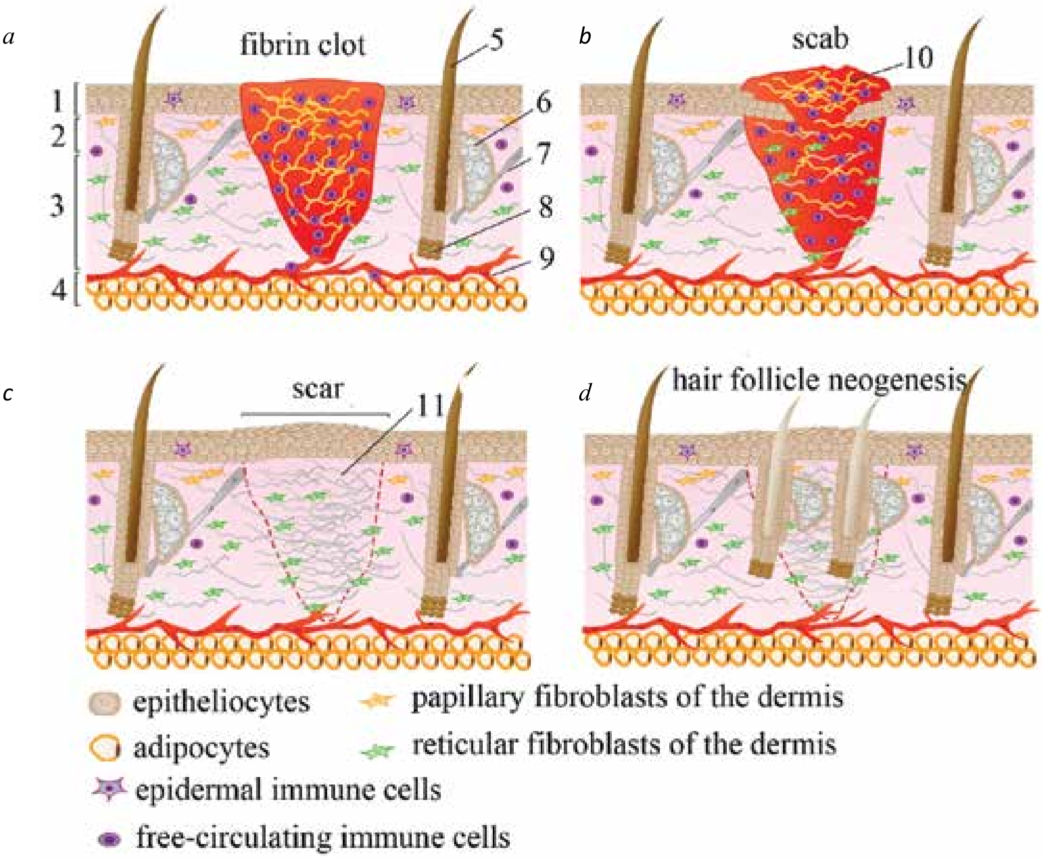

Fig. 2. Structural and functional arrangement of skin covers and dynamics of their repair and regeneration: from homeostatic mechanisms to phases of the wound healing process. The scheme integrates modern concepts of the histological structure of the skin and successive stages of its repair after injury *(a–d),* including the key cellular and molecular events. The dynamics of healing reflects: phases of hemostasis and inflammation (*a*) with formation of a fibrin clot and migration of immune cells; proliferative phase (*b*) with active re-epithelialization, angiogenesis, and formation of granulation tissue; as well as remodeling (*c, d*), demonstrating either scarring of small wounds (*c*) or regeneration with neogenesis of hair follicles and sebaceous glands in cases of extensive damage (*d*). The scheme emphasizes the role of dermal stem cells, the dynamics of ECM remodeling, and critical significance of cell – cell interactions at each stage [15, 16]. *1* – epidermis, *2* – papillary layer of the dermis, *3* – reticular layer of the dermis, *4* – white adipose tissue of the dermis, *5* – hair, *6* – sebaceous gland, *7* – muscle that pulls hair upright, *8* – hair bulb, *9* – blood vessels, *10* – fibrin filaments, *11* – components of ECM (collagen, elastin) [15, 16]

THE MECHANISM OF ABSORPTION OF NANOSECOND MICROWAVE PULSE ENERGY

Experimental data obtained on a burn injury model in Wistar rats show significant improvement in regenerative processes both with local 4-fold exposure to RPM radiation alone and with its combination with the injection of cultured red bone marrow cells. The effect is manifested through reducing the time of complete epithelialization and, with optimal exposure parameters, through scar-free skin regeneration. It is important to note that the effectiveness of exposure was strictly dependent on radiation parameters, such as the repetition frequency of microwave pulses, their intensity, and total number [6, 12].

Fundamental research would suggest that initiation of reparative processes is related to the features of electromagnetic energy absorption by biological tissues [17]. The physical mechanisms of this phenomenon include generation of conduction currents (caused by the movement of ions under the effect of external radiation) and displacement currents (caused by oscillations of dipole molecules). In this case, the thermal component of the biological effect associated with the heating of tissues during the passage of induced currents is essential [18].

The complex histological organization of skin covers and underlying structures, characterized by pronounced electrophysiological heterogeneity, leads to spatial unevenness in the distribution of the induced electric field and, as a result, to local temperature gradients. The theoretical foundations of this phenomenon were laid in studies on bilayer lipid membrane (BLM) models in the 1980s [19, 20]. It was experimentally established that the difference in dielectric permittivity between the electrolyte (ε of solution) and the Teflon partition (ε of Teflon) leads to concentration of electromagnetic field in the area of the membrane-forming hole, where the specific absorption rate (SAR) can be 2–3 orders of magnitude higher than the values in the surrounding solution (Fig. 3) [19, 20].

A similar mechanism for focusing electromagnetic energy can be implemented in microvessels of the skin, where the heterogeneity of the electrical properties of tissues creates conditions for local thermal effects. It is worth noting that, according to the data [21], the key factor contributing to the acceleration of repair under extremely high-frequency electromagnetic exposure (EMR of EHF) is precisely the improvement of microcirculation in the perifocal area of damage.

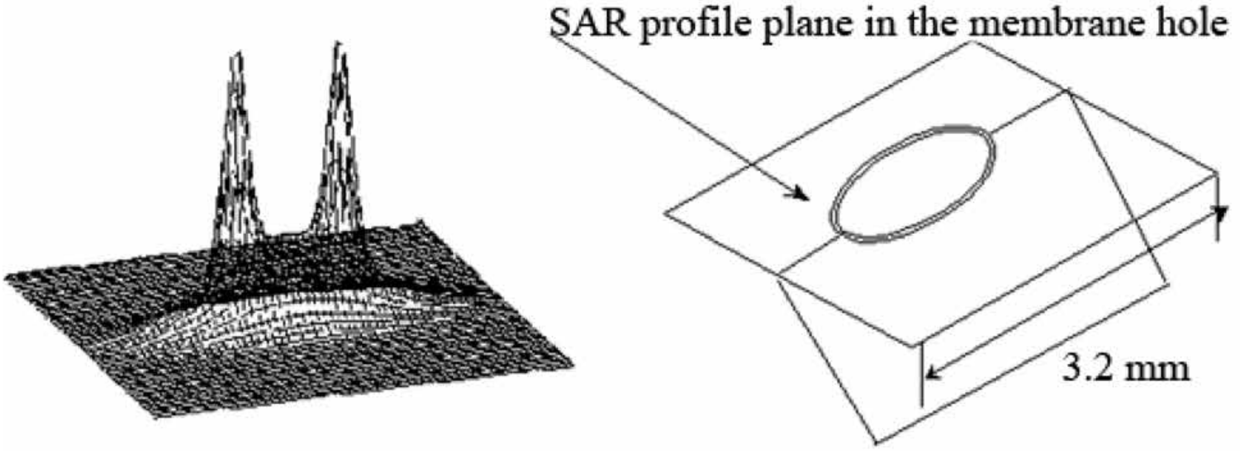

Fig. 3. Specific absorption rate in the solution along the edges of the bilayer lipid membrane. Note: the excess SAR in the solution filling the membrane (on the left) compared to the average overheating in the whole volume [19, 20]

A legitimate question arises about the applicability of the thermal effect model to RPM radiation. Experimental studies on the epididymal adipose tissue model in laboratory mice [22] demonstrated that exposure to 4,000 nanosecond pulses with peak power flux density of 1,500 W/cm^2 caused a temperature increase of no more than 0.08 °C. Taking into account electrophysiological heterogeneity of biological tissues, it can be assumed that even local overheating of blood in microvessels unlikely exceeds 10 times the value of the baseline temperature effect, which limits the maximum local temperature increase to about 0.2 °C. Such insignificant temperature gradient is physiologically incapable of inducing significant vasodilation and, as a result, cannot explain the observed improvement in the trophism of regenerating tissues.

These data allow to exclude with a high degree of probability the thermal mechanism as the main factor responsible for stimulation of reparative processes under the effect of RPM radiation and suggest existence of alternative, non-thermal mechanisms of biological action. One of the possible non-thermal mechanisms may be indirect activation of skin mast cells, leading to the release of histamine, which was demonstrated in experiments with low-intensity (up to 50 μW/cm^2) EMR of EHF [23].

It is known that histamine is able to modulate expression of heat shock proteins, which, in turn, activates endothelial nitric oxide synthase (eNOS) contributing to an increase in NO production [24]. The combination of these processes ensures the development of a vasodilator effect and improvement of the microcirculatory channel in the perifocal area of the injury. The obtained data suggest that the mechanism of the stimulating effect of low-intensity nanosecond RPM on wound healing is a complex, multilevel process involving both intracellular signaling cascades and intercellular interactions, which requires further detailed research.

ANALYSIS OF NON-THERMAL MECHANISMS OF SKIN REGENERATION BY LOW-INTENSITY RPM

In the process of skin injury repair, the crucial role is attributed to the ECM and stem cells, which is a complex dynamic system ensuring the structural and functional integrity of tissue components (Fig. 4) [25]. The ECM performs multiple functions: it serves as a mechanical framework of connective tissue, mediates intercellular interactions, regulates transport of substances and cell migration, and also acts as a depot for growth factors, ensuring their controlled release in accordance with the phases of regeneration. The most important mechanism of stem cell regulation on the part of the ECM is realized through the maintenance of cellular polarity, orientation of the mitotic spindle, and control of the asymmetry of cell division [26]. By binding growth factors and interacting with cellular surface receptors, the ECM modulates the transmission of molecular signals and regulation of transcriptional activity, thereby determining the morphofunctional characteristics of regenerating tissue [27].

Fibroblasts, as the main effector cells, exercise strict control over synthesis and proteolytic degradation of the ECM components, which directly affects the processes of self-renewal, proliferation, and differentiation of stem cells. Involvement of the ECM in the formation of specialized stem cell niches, unique microenvironments that support the pool of progenitor cells, is of particular importance [28]. In these niches, transmembrane integrin receptors mediate transmission of signals from the ECM to stem cells, regulating their proliferative activity and mobility (Fig. 4) [28]. Integrins specifically interact with the key ECM ligands, including fibroblast growth factor (FGF), tumor necrosis factor (TNF α), interleukin (IL) 1, IL-6, and fibronectin fibers. Activation of integrin receptors initiates a cascade of intracellular signals, in particular through the PI3K/AKT pathway, that stimulates migration and endothelial differentiation of mesenchymal stem cells, significantly enhancing their reparative potential [29]. Thus, modulation of the dynamics of ECM remodeling and activation of components of stem cell niches can be considered as some of the key mechanisms of stimulation of wound healing under the impact of RPM radiation.

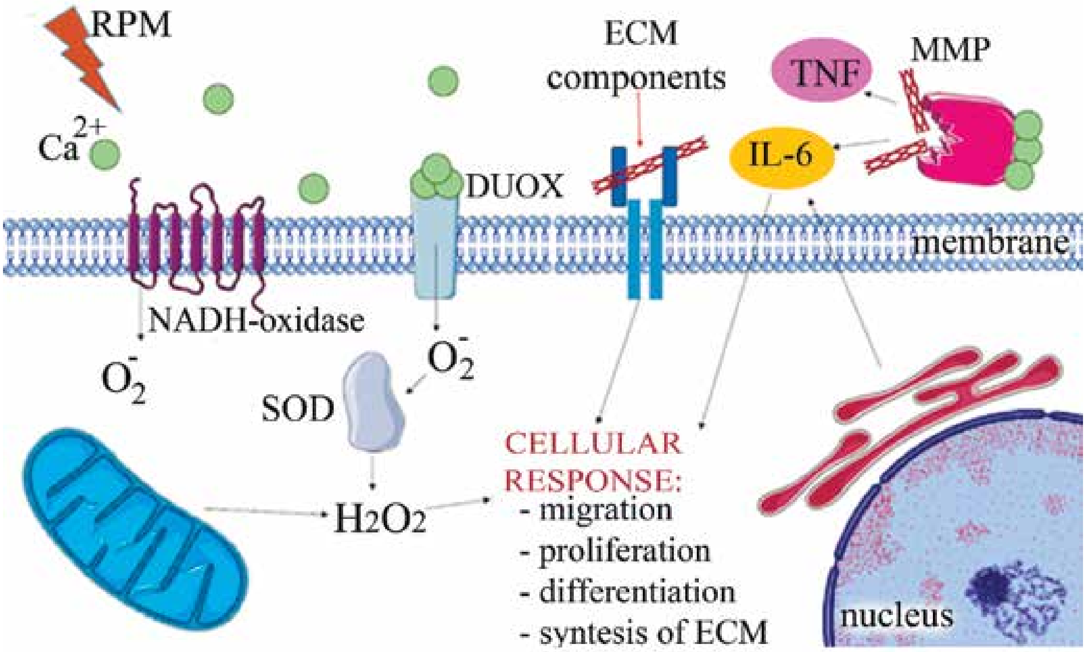

Fig. 4. Possible targets for the impact of nanosecond RPM, providing stimulation of skin lesion regeneration. Explanations are contained in the text

The impact of nanosecond RPM radiation is potentially able to modulate affinity of interaction of the ligands with integrin receptors, changing efficiency of signal transmission and functional activity of corresponding proteins. The similar mechanism can be realized through Ca^{2+}-dependent processes in accordance with the Adey model [30], which explains the frequency dependence of biological effects of electromagnetic actions. Under certain RPM parameters, calcium ions that stabilize the liquid crystal structure of cell membranes can dissociate from surface receptors, increasing fluidity of the membrane bilayer and conformational mobility of integrins. Microwave pulse energy is sufficient to transfer the key molecular components in the active state, that leads to a change in the efficiency of the total signal cascade.

Electromagnetic radiation of non-thermal intensity, which includes nanosecond RPM radiation, is able to influence intracellular signaling pathways through several interrelated mechanisms: changes in membrane permeability for Ca^{2+} ions; modulation of calcium binding to surface polyanionic structures; regulation of calcium interaction with calcium-binding proteins (calbindin, calretinin) [31] and matrix metalloproteinases (MMP) [32]. MMPs play the key role in ECM remodeling by controlling processes of cell adhesion, differentiation, and proliferation in the wound zone, which promotes minimization of scarring changes [28, 32]. Nanosecond RPM radiation can alter calcium-dependent activity of MMP, inducing controlled degradation of ECM components (collagen, elastin). This process leads to a decrease in the volume of scar tissue and creation of space for migration and differentiation of stem cells, which ultimately promotes full-fledged regeneration of all skin layers.

Calcium-activated dual oxidase (DUOX), a membrane enzyme involved in the generation of reactive oxygen species (ROS), may be an important molecular target of RPM radiation [33]. It can be assumed that the impact of RPM can modulate catalytic activity of DUOX, changing the kinetics of conversion of molecular oxygen in hydrogen peroxide, which acts as an important paracrine messenger in cellular signaling pathways. An increase in the local concentration of hydrogen peroxide in wound area initiates a cascade of physiological reactions: increased leukocyte recruitment, activated proinflammatory M1 macrophages, responsible for cytokine production, and anti-inflammatory M2 macrophages, promoting resolution of inflammation and re-epithelialization [33].

The ability of DUOX to take part in realization of "respiratory explosion" of immunocompetent cells, the key mechanism of antimicrobial protection in the wound, is of particular interest [33]. This assumption is consistent with the results of previous studies, which recorded changes in the levels of peroxides, lipid peroxidation products, and oxidative modification of proteins in the liver and blood of the laboratory animals (outbred mice) after the impact of RPM [34, 35].

Thus, it is possible to assume the existence of a DUOX-mediated mechanism in which RPM radiation, through activation of this enzyme and subsequent generation of hydrogen peroxide and other ROS, triggers a complex network of signaling pathways regulating key processes of wound healing: cell migration and proliferation, differentiation of cellular elements, neoangiogenesis, and mobilization of the stem cell pool. This mechanism may explain the observed acceleration of reparative processes under the impact of RPM radiation, although additional experimental studies are required to definitively confirm this hypothesis.

CONCLUSION

The performed analysis of possible molecular mechanisms of stimulation of reparative processes in burn injuries of the skin under the effect of RPM radiation of non-thermal intensity allows us to form comprehensive understanding of the multilevel regulation of regeneration processes. However, it is necessary to take into account that existing data do not exclude the presence of additional, yet unexplored, pathways of biological action of RPM, which can significantly contribute to the observed therapeutic effect of accelerated and high-quality healing without cicatricial complications.

Systematic study of correlation dependences between impact parameters (radiation intensity, pulse repetition rate, number of pulses per session, and total number of procedures) and dynamics of reparative processes, that would allow to optimize treatment protocols and maximize clinical effectiveness, acquires particular importance. Deep understanding of fundamental mechanisms stimulating regeneration of thermally damaged skin opens up prospects for the development of combined therapeutic approaches combining the effect of RPM radiation with cellular technologies (injection of mesenchymal stem cells) or pharmacological agents (cytokines, growth factors).

Early initiation of comprehensive treatment aimed at preventing functionally significant complications of burn injury, in particular hypertrophic scarring, using rational combinations of medical therapy, surgical methods (dermotension, autologous skin grafting), and physiotherapy procedures is of particular importance. Such a multimodal approach makes it possible not only to improve the quality of the regenerated skin, but also to significantly reduce rehabilitation time in patients with burn injuries.

Accumulated experimental data create the theoretical basis for the development of innovative methods to stimulate healing of superficial skin defects of various origins that can be widely used both in burn medicine and in the treatment of trophic ulcers, diabetic skin lesions, and other pathological conditions accompanied by violation of skin integrity. A promising direction of further research is detailed decoding of molecular and cellular mechanisms of synergistic action of RPM in combination with biologically active substances and cellular preparations, which will make it possible to create personalized treatment protocols taking into account features of pathological process in a particular patient.

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Author Information

Samoylova Anna V. – Cand. Sci. (Biology), Senior Researcher, Department of Physical Electronics, Institute of High Current Electronics SB RAS; Associate Professor, Division of Normal Physiology, SibSMU, Tomsk, kereya21@mail.ru, http://orcid.org/0000-0003-4857-935X

Zharkova Lubov P. – Cand. Sci. (Biology), Senior Researcher, Department of Physical Electronics, Institute of High Current Electronics SB RAS; Associate Professor, Department of Human and Animal Physiology, NR TSU, Tomsk, zharkova_lubov@mail.ru, http://orcid.org/0000-0003-0293-3077

Bolshakov Michael A. – Dr. Sci. (Biology), Professor of the Department of Human and Animal Physiology, NR TSU, Tomsk, mbol@yandex.ru, http://orcid.org/0000-0001-7955-1478

Gostyukhina Alena A. – Cand. Sci. (Biology), Senior Researcher, Experimental Laboratory for Biomedical Technologies, FRCC MRaB of FMBA of Russia, Tomsk; Associate Professor, Department of Vertebrate Zoology and Ecology, NR TSU, Tomsk, antariks-tomsk2015@yandex.ru, http://orcid.org/0000-0003-3655-6505

Zaitsev Konstantin V. – Cand. Sci. (Med.), Head of Experimental Laboratory for Biomedical Technologies, FRCC MRaB of FMBA of Russia, Tomsk, limdff@yandex.ru

Kolobovnikova Yulia V. – Dr. Sci. (Med.), Associate Professor, Dean of the Department of Medical Biology, SibSMU, Tomsk, kolobovnikova.julia@mail.ru, http://orcid.org/0000-0001-7156-2471

Rostov Vladislav V. – Dr. Sci. (Phys – Tech.), Professor, Chief Researcher, Department of Physical Electronics, Institute of High Current Electronics SB RAS, Tomsk, rostov@lfe.hcei.tsc.ru, http://orcid.org/0000-0002-1718-0111

Vykhodtsev Pavel V. – Researcher, Head of the Department of Physical Electronics, Institute of High Current Electronics SB RAS, Tomsk, pasha@lfe.hcei.tsc.ru, http://orcid.org/0000-0003-2569-7919

(✉) **Samoylova Anna V.,** kereya21@mail.ru

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