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АНАЛИЗ МЕХАНИЗМОВ РЕГЕНЕРАЦИИ ПРИ АУТОТРАСНЛАНТАЦИИ

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Поиск эффективных и доступных методов стимуляции регенеративных процессов в восстановительной медицине является приоритетной задачей. Значительный интерес представляют тот вид биостимуляции, за счет которого происходит активация метаболических и репаративных процессов всего организма в целом. ***Цель.*** Обобщение актуальных литературных данных о возможных механизмах биостимуляции при трансплантации собственных тканей организма. На основании результатов обзора литературы показано, что в настоящее время остается множество дискутабельных вопросов, связанных с клеточными и молекулярными механизмами, лежащими в основе межмолекулярного взаимодействия на этапе регенерации. Эффекты стимулирующего действия аутотрансплантата, как в зоне самого трансплантата, так и в организме в целом, могут быть обусловлены медиаторами и сигнальными молекулами, которые выделяются при разрушении тканей аутотрансплантата, его перифокальной области и биологическими активными веществами, продуцируемыми иммунокомпетентными и стволовыми клетками. ***Заключение.*** Тканевые трансплантаты могут выступать в качестве индукторов выработки биологически активных веществ и активаторов иммунных и стволовых и/или стромальных клеток. Последние, в свою очередь, являются продуцентами ряда химических медиаторов, необходимых при полноценной регенерации. Поэтому, одним из перспективных методов стимуляции регенеративных процессов является трансплантация собственной ткани. Этот метод отличается простотой, эффективностью и доступностью, что вызывает повышенный интерес и требует дальнейшего исследования.

Ключевые слова: *биостимуляция; полнослойный кожный лоскут; аутотрансплантация; регенерация.*

ANALYSIS OF REGENERATION MECHANISMS IN AUTO RANSPLANTATION

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Search for effective and available methods of stimulation of regenerative processes is a priority task of restorative medicine. Of high interest is a kind of biostimulation that induces activa-

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tion of metabolic and reparative processes in the whole organism. ***Aim.*** Generalization of the relevant literature data concerning possible mechanisms of biostimulation in transplantation of self tissues of an organism. The results of literature survey showed that there still remain many debatable questions concerning cellular and molecular mechanisms that underlie intermolecular interactions in the stage of regeneration. Stimulating effects of an autotransplant both in the zone of the transplant or in an organism in whole may be caused by mediators and signal molecules released in destruction of the autotransplant tissues and of its perifocal region, and also by bioactive substances produced by immune-competent and stem cells. ***Conclusion***. Tissue transplants may be used as inductors of production of biologically active substances and activators of immune and/or stromal cells. The latter, in turn, are producers of a number of chemical mediators required for large-scale regeneration. Therefore, a promising method of stimulation of regenerative processes is transplantation of self tissue. This method is characterized by simplicity, effectiveness and availability which evokes special interest and requires further study.

Keywords: *biostimulation; full skin graft; autotransplantation; regeneration.*

Modern restorative medicine is characterized by active development of and search for methods of stimulation of regenerative processes of damaged tissue. These methods should possess certain properties such as availability and effectiveness. In this aspect, of a certain interest is a kind of biological stimulation of tissues that activates metabolic and reparative processes in the entire organism in general. Use of these methods opens wide prospects in the modern clinical medicine. From these positions, one of priority tasks may be search, development and introduction of a strategy that could permit elimination of pathological processes in an organism associated with destruction of tissues, and also of pathological disorders induced by such processes, and could also lead to effective full restoration of tissue.

The *aim* of this work was analysis of probable mechanisms of stimulation of tissue associated with use of auto transplantation.

Achievements of the modern science permitted development of some experimental methods based on application of stem cell growth factors obtained from different allotransplants (placental, dermal, amniotic, etc.) [1,2] which are capable of producing biostimulating effect. With this, these methods have a number of serious limitations that prevent their wide clinical use. These limitations arise from the fact that use of growth factor both of allotransplants and of stem cells often leads to severe complications associated with immune conflict, carcinogenesis, and also to different infections [3,4]. At the same time, there exist methods that can prevent development of such severe and unwanted consequences. These methods may include transplantation of self tissues of an organism, in particular, skin. A significant advantage of this method, besides elimination of the mentioned undesirable effects and consequences, is the fact that autotransplantation of skin evokes reparative processes and metabolism. Mechanisms of these processes will be considered and described below.

Main Effects of Tissue Therapy. According to some studies presented in literature, medical preparations obtained from different tissues, can produce antitoxic, hepatoprotective effect [5-9]. Besides, these preparations improve regeneration of damaged tissues and the processes associated with microcirculation. An auto transplant was found to produce a systemic effect on the resident tissues in the zone of its placement, and also to induce alterations associated with the struc-

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tural and functional restructure of the whole organism. Thus, in research of biological activity of transplants, the founder of the first tissue bank in Europe R. Klen discovered (1961) a stimulating effect of the tissue bed on reparative processes [8,10].

On the whole, the choice of self skin for a tissue transplant is determined by simplicity and safety of its obtaining. Besides, skin and subcutaneous tissue are a collection of immune and stem (stromal) cells.

Alteration and Inflammation as Mechanisms of Systemic Stimulating Effects of Regeneration. Transplantation of self tissue is followed by alteration in the zone of transplantation. This process involves both the transplant itself and the zone around its implantation which activates the healing processes. Alteration leads to enhanced production of different signal molecules that travel to the pathological focus. Enhanced production of signal molecules not only causes local changes, but mobilizes the whole organism. It is undoubted that the main components of any process of tissue healing are cells. If the regeneration process is stimulated by a transplant, pathophysiological mechanisms of restoration of the damaged tissue occur with participation of cells of the transplant itself, and cells of the adjacent tissues. Besides, this process is obligatorily participated by cells from remote places of an organism, for instance, by bone marrow cells. It is out of doubt that any damage to tissue is associated with breakage of the integrity of blood vessels of different caliber. Damage to vessels activates coagulation cascade, a role in which is played by platelet aggregation and formation of a thrombus from fibrinogen. Here, fibrin in itself possesses an expressed stimulating effect being a temporary matrix for migrating cells [11].

According to some authors, the stimulating effect owes to the presence in the fibrin clot of significant amounts of platelets producing fibroblastic proliferating factors, cytokines, prostaglandins, thromboxane, chemotactic factors, biogenic amines, collagenase and its inhibitors. Factors that enhance the chemotactic factor [11] and promote activation of the surrounding cells, include platelet (PDGF), epidermal (EGF) and transforming growth factors (TGF-α и TGF-β), fibroblast growth factors (bFGF) and vascular endothelium growth factor (VEGF), cytokines (CXCL4 and RANTES), and stromal factor (SDF-1). It is shown in some research works that in the inflammation focus a therapeutic potential SDF-1/CXCR4 system is activated. It is this system that ‘sends’ immune cells such as neurotrophils, monocytes and lymphocytes, to the damaged zone [11-13].

Stimulating Effects of Macrophages. It is known that any damage of structures of the living system leads to stress reaction. This accounts for the fact that after transplantation, damaged and dead cells of the transplant and of perifocal region produce the so called DAMP (*damage-associated molecular pattern*) and stress-dependent SAMP (*stress-associated molecular pattern*) molecules. These endogenous ‘molecules of danger’ activate signal mechanisms leading to development of inflammatory process [14]. The main cells that determine effectiveness of the inflammatory stage in regeneration process, are macrophage cells. Besides, some researchers [8,15] believe that factors influencing the character of intercellular interactions, are phenotype of macrophages, their activity and maturity. Besides enhancement of phagocytosis, these cells can produce colony-stimulating factor (GM-CSF), which belongs to cytokines and stimulates hematopoietic cells present in the bone marrow. Other most important factors include PDGF, TGF-β, EGF, SDF-1, VEGF produced by macrophages, and insulin-like growth factor (IGF-1). Besides, macrophages participate in secretion of such important cytokines as tumor necrosis

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factor alpha (TNF-α), interleukins 1 and 6 (IL-1/6). These cytokines enhance migration of immune cells to the inflammation focus.

Stimulating Effects of Mastocytes. Resting on the data presented in the modern literature, skin contains a high amount of mast cells. One of their properties is known to be the ability to enhance regenerative processes with the resultant acceleration of wound healing [16-18]. The pathophysiological mechanism of stimulating effect of mast cells present in the transplant and in the surrounding tissues, may be attributed to production of modulators and mediators of inflammation, such as histamine, chymase, tryptase, hydrolase, peptidase, heparin, cytokines. Besides, the processes of proliferation and migration of cells take place [17]. It was shown that in degranulation, mast cells liberate high amounts of growth factors, especially of NGF stimulating growth of the neighboring axons [11].

Activation of Immune Competent Cells. After autotransplantation of skin, the transplanted tissue starts releasing different biostimulators. Action of biologically active substances leads to inflammation caused by alteration. Inflammation activates immune competent cells, mediators of inflammation, growth factors and different similar substances.

Inflammation is an essential process aimed to elimination of the cause of tissue damage and development of systemic response. One of functions of the innate immunity system is recognition of the damaging agent. This function is realized through PRR receptors on the surface of the innate immunity cells of the transplanted tissues and of the perifocal region: mast cells, macrophages, basophils, neutrophils, natural killers, eosinophils, dendritic cells [14,19]. Innate immunity cells transmit information to the molecular signals of cells associated with adaptive immunity that include T- and B-lymphocytes [20]. The latter produce factors (cytokines and immunoglobulins) which, getting into blood, influence maturation of effector populations and also enhance phagocytizing and migration activity of cells of innate immunity especially of macrophages).

Biostimulating Effect of Stem (Stromal) Cells. In the process of regeneration of damaged tissues, the biostimulating effect may be associated with the action of resident and mobilized stem cells produced both in the tissue of the autotransplant and in surrounding tissues. Besides, the process involves cells from the remote sources of the whole organism that are mobilized in response to inflammation. An important factor for activation of stem cells is hypoxia. Activation of stem cells by hypoxia enhances regeneration potential [5]. The process of tissue replacement directly depends of the antiinflammatory potential of cell. Accordingly, the more these potentials are expressed in cells, the more effective and coordinated the healing process will be. The cells possessing such properties are mesenchyma-derived precursor cells. These cells are indispensable participants of reparative processes of deep reserve adaptation [21].

Mesenchymal stem cells (MSC) are cells having a high differentiation capacity. Besides, they rapidly migrate to the zone of damage. It was found in clinical research that MSC possess paracrine effects manifested by their ability to release factors that act like signals for the surrounding cells and make these cells change their behavior to initiate regeneration process. They may as well reveal immunosuppressive properties. These cells are activated by signal coming from the outside, and restore both the structure and function of the tissue [21,22].

MSC and fibroblasts secrete fibronectin, collagen, glycosaminoglycans and proteoglycans into the extracellular space. They express extracellular proteases which promote remodeling of the architecture of the fibrin skeleton with formation of granulation

tissue which is then gradually replaced with the collage matrix. The analysis of literature sources shows that MSC cooperate with other cells to control the overwhelming majority of mechanisms providing restoration of tissues. In the works with use of dopplerography it was shown that after introduction of MSC from the adipose tissue to an ischemized limb of an immunodeficient mouse of *Nude* line, the condition of the limb improved, and the velocity of the blood flow increased [11]. Some works demonstrated a stimulating effect of transplantation of white adipose tissue associated with the cumulative effect of stem cells contained in it, on regeneration processes in the transplantation zone. This characteristic feature of stem cells of adipose tissue is attributed to its significant endocrine activity associated with secretion of FGF (fibroblast growth factor), VEGF (vascular endothelial growth factor), TGFβ (transforming growth factor β), IGF (insulin-like growth factor), PDGF (platelet growth factor), AP (alkaline phosphomonoesterase). AP being one of stem cell markers, induces morphogenetic processes in an organism, stimulates angiogenesis [14,22].

In connection with the above, degeneration of skin transplant may produce a stimulating effect on the morphogenetic potentials of the regenerative processes through production of a wide range of growth factors and AP [22]. S.K. Kang, et al. (2003) emphasize a high differentiation potential of stem cells of the adipose tissue. These cells may differentiate both to mesenchymal, and non-mesenchymal cells [22,23].

In study of secretory and metabolic functions of stromal cells obtained from fatty tissue in some experiments, a special attention was given to the regenerative function that may be linked with the so called complex of 'stem and progenitor' cells present in the adipose tissue (*adipose-derived stem cells*, ADSCs) [23-30]. These cells were obtained in 2001. They are capable of differentiating in different directions that is their peculiarity [30]. The authors showed that ADSCs can secrete cells of cytokine profile. They may include angiogenic, antioxidant and immunosuppressive factors: vascular endothelial growth factor (VEGF), transforming growth factor (TGF), hepatocyte growth factor (HGF), platelet growth factor (PDGF), placenta growth factor (PIGF) and basic fibroblast growth factor (bFGF) in high concentrations which stimulate migration of endothelial cells of vessels, their proliferation and differentiation [1,17, 22,23,28-29].

Immunoregulation and Paracrine Activation of MSC. Resting on some works presented in literature [25,26], one may confidently say that not all stem cells of skin possess equal proliferative potential. As it was shown by research, the highest proliferation potential is possessed by cells of hair follicles, especially in the bulging region. According to literature data [23, 27], 95% of stem cells of hair follicles are concentrated in this region. These cells participate in wound healing after which they disappear from the interfollicular epithelium. The mechanism of restoration of damaged tissue is associated with mitotic division and migration of the progeny of *bulge* stem cells to the wound surface. Besides, it is known at present [31] that the surface of MSC carries expresses *Toll*-like receptors, the main function of which is recognition of molecules of damaged cells and tissues (PAMP and DAMP). Enhancement of the activity of these receptors in triggering the mechanisms of inflammation leads to migration of MSC to the inflammation focus, where the given cells promote secretion of cytokines directed at suppression of inflammation. They include IL-1, IL-6, IL-8, TNF-α, IFN-γ, and also some chemokines, such as CCL2, CXCL9, CXCL10 and CXCL11. These substances act on the immune system in a paracrine manner, in partic-

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ular, on the cells that carry specific receptors for these ligands, and stimulate directed migration of neutrophils, monocytes, and also of cells of immune protection with natural killers being the most important, to the inflammation focus. Thus, MSC create anti-inflammatory microenvironment and attract different immune competent cells to the zone of damage.

Besides the above described cells, such regenerative properties are also present in some progeny of embryonic stem cells residing in the bone marrow. These include pluripotent hematopoietic cells which may further on turn into different forms of leukocytes including endothelial precursor cells) [11,32]. Immune cells activated by alteration and hypoxia of tissues, migrate into the inflammation focus and release high amounts of anti-inflammatory factors including cytokines: TNF-α, IFN-γ and IL-1. Under influence of these cytokines, MSC produce factors that suppress inflammatory reactions, in particular, activation of immune competent cells [11,33, 34]. MSC act on dendritic cells, suppress proliferation of active immune cells of T-lymphocyte class. The mechanism of immunosuppressing effect of MSC may consist in the fact that activation of T-lymphocytes suppresses the function of active T- and B-lymphocytes [33]. The mechanism of the interaction between MSC and cells of immune system may consist in the fact that immune system affects MSC through mediators of immunity (cytokines, chemokines, prostaglandins, etc.), here, MSC also influence immune system.

Besides the mentioned mediators, MSC produce TGF-β and also participate in production of nitric oxide induced by NO synthase (iNOS) [35]. These molecules may act as potential immune suppressors. MSC produce numerous paracrine effects practically at every stage of regeneration process. In *in vivo* conditions the ability of MSC to suppress the immunity is realized through the numeric composition of cells that were attracted to the zone of inflammatory reaction. Besides potential immune suppressors, MSC can also produce factors activating growth of cells, such as VEGF, HGF, IGF, bFGF, GM-CSF, SCF, SDF-1. These molecules can be associated with antiapoptotic, angiogenic and antifibrous effects, and may participate in migration, proliferation and differentiation of fibroblasts recruited into the zone of inflammation of progenitor cells [36]. These factors are assigned an important role in reparation, especially in the initial stages.

A necessary condition for effective regeneration impossible in conditions of hypoxia, is restoration of blood supply to the damaged area. A stimulus to angiogenesis in conditions of reduced saturation of tissues with oxygen in the region of transplant may be a drop in the partial tension of oxygen. The target of this impact is endothelial cells. For example, hypoxia, inflammation and mechanic stretch of damaged tissues activate transcription factor-1 (HIF-1) and induce expression of angiogenic factors that stimulate angiogenesis. Directed migration of circulating endothelial precursors is a key stage in formation of vessels *de novo* in the zone of damage [38,39].

It was demonstrated on a group of white rats that use of autotransplant of a full skin graft (ATFSG) in conditions of frustrated innervation produces an evident biostimulating effect on the microcirculation and provides a more intense structural and functional restoration of nerve fibers after their damage [10]. Regenerative action and distant stimulating effect on the microcirculatory system is realized through stimulation of production of neurotrophin-3 and vascular endothelium growth factors which attract eosinophils, macrophages and lymphocytes to the zone of the autotransplant and to the neighboring tissues [10,40,41].

Activation of Regulatory Peptides in Regeneration. It can be suggested that one of

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mechanisms of biostimulating effect was peptidergic regulation induced by damage to tissues. One of the groups of cell-derived mediators that can be secreted by damaged tissues of the perifocal region and by the skin graft itself is cytomedines which, like cytokines, belong to the group of regulatory peptides.

It was shown by numerous research that these chemical regulatory compounds are responsible for maintenance of homeostasis in a multicellular organism. Cytomedines were found to be multifunctional and pleiotropic complexes of alkaline polypeptides with a relatively low molecular mass. They were identified in all organs and tissues. Experimental research showed their ability to induce differentiation of pluripotent cells. Thus, addition of regulatory peptides to pluripotent cells of the ectoderm in an experimental model led to emergence of different tissues [43,44]. Besides, these bioregulators, also called true transmitters, directly act on receptors, and the triggered reaction may involve secondary and tertiary mediators into the process with increase in the quantity of probable different effects in geometric progression, [45]. A study of these group of compounds showed that they are peptidergic regulators: they determine the status of intercellular interactions in the immune system by regulating proportion of T- and B-lymphocytes, can influence the humoral immunity, suppress peroxide oxidation of lipids (POL), stimulate reparative and metabolic processes. Besides, they 'wake up' regional stem cells, activate processes of cell regeneration, produce effect on the process of transmission of genetic information, etc. [46]. Biological effect of cytamins can be explained by acceleration of differentiation of stem cells in tissues and activation of their transition into a more mature form. Simultaneously, they participate in regulation of metabolic processes. In result, physiologically normal cell populations appear with optimal metabolism [47,48].

Thus, these substances of peptide nature released by cells of transplant and surrounding tissues, can produce both local, and distant effects on tissues (through chemical processing, circulating with blood stream) in an organism [43]. One more probable mechanism of biostimulating effect was change in the immune response through balancing the inflammatory cascade of reactions in the zones of transplantation and of neurrhoraphy of the peripheral nerve which restricted excessive activity of the immune cells which could lead to destruction of the extracellular matrix and to suppression of regenerative processes.

Phenomenon of Preconditioning of Tissues. One of effects that promotes stimulation, and, consequently, leads to improvement of regeneration of the damaged tissue after a severe trauma, is a phenomenon of preconditioning of tissues. The effect of this phenomenon can be compared to that of stress [49]. In transplantation of the self skin graft a distant preconditioning of tissue takes place, with the underlying neurrhoraphy.

This phenomenon consists in creation of short episodes of ischemization of tissue not associated with the main organ. This leads to enhanced entry of different biologically active substances from the ischemized tissue and stimulates processes of tissue regeneration [41,49-54].

In literature an experiment was reported with two wound channels (the zone of transplantation and neurrhoraphy of a peripheral nerve) each having its own resident cells including macrophages with the potential directed at full regeneration. The immune response in this experiment was modified – accelerated restriction of the zone of inflammatory process, accelerated activation of biomechanical and molecular signals between cells and extracellular matrix, active differentiation of cells, rapid restoration of the blood flow which, in general, permitted to improve angio-

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genesis and microcirculation. It was shown in the experiment that the mechanism of reparative effect of ATFSG was expressed in reduction of the quantity of nerve fibers with degenerative alterations proximally to the place of suturing. At the same time, there was an increase in the amount of nerve fibers that grow from the proximal to distal region. Besides, the reinnervation rate of muscle tissue increased, excitability of muscle tissue increased and transmission of impulse accelerated.

Stimulation of microcirculation may be associated with maintenance of a high level of perfusion of tissue, reduction of hypersensitivity of the vessel wall (due to its deinnervation) [41,42].

Conclusion

Regeneration of tissues may be referred to one of the most complicated processes in a living organism. Its complexity is due to the fact that it involves activation of numerous processes, mechanisms and different types of cells. As a result, many disputable and unsolved questions arise in this context.

One of such questions is mechanisms providing the basis for intermolecular interactions in regeneration of tissue. The stimulating effect of autotransplant (both in the zone of the transplant itself, and in an organism in general) is known to be associated with some biologically active substances released in destruction of the transplanted self tissue, and also with the products of stem and immune competent cells.

Resting on this, it may be concluded that autotransplant may act as a stimulator of production of different biologically active substances and may activate both immune, and stem and/or stromal cells. As it is known stromal cells are produced under the influence of a number of chemical mediators and are required for full regeneration of tissue.

The next important problem is a study of possibilities of the influence of different molecules and signaling systems on the processes of regeneration of tissue. Understanding of these processes will permit to control behavior of cells and to regulate intracellular cascade reactions. One of such promising methods is transplantation of self tissues. Application of autotransplantation has a number of indisputable advantages: simplicity of use, availability and effectiveness. All this causes increased interest and require further investigation.

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