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Targeted Regulation of Intracellular Signal Transduction in Regeneration-Competent Cells: A new Direction for Therapy in Regenerative Medicine

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Abstract: A scientific and theoretical justification for developing the original direction for targeted therapy in regenerative medicine - "Strategy of pharmacological regulation of intracellular signal transduction in regeneration-competent cells" is presented. It is proposed to use intracellular signaling molecules, which play an important role in regulating the proliferative and differentiation status of progenitors and microenvironment cells, as targets of drugs with regenerative activity. The selectivity of stimulation of the regeneration of individual tissues is determined by the peculiarities of intracellular signaling in different progenitor cells and/or tissue-specific expression of certain types and isoform signaling molecules. The results of their basic research on the role of some signaling molecules (potential targets) in regulating the cell cycle of the progenitors of different types and the functioning of the tissue microenvironment cells are given. Experimental models of some pathological conditions (CNS, skin, and hematopoietic tissue) show the effectiveness of implementing the proposed concept of pharmacotherapy. The results are fundamental to the creation of novel targeted drugs for the treatment of degenerative diseases.

Keywords: regenerative medicine; targeted therapy; intracellular signal transduction; stem cells.

1. Introduction

The mechanism of action of most created drugs is to modulate the functions of mature cells preserved in the pathology [1, 2]. However, this therapy concept for many diseases, primarily degenerative, is untenable [2-6]. In this regard, the development of fundamentally novel therapeutic approaches and drugs is relevant.

In recent decades, the knowledge gained about the role and functions of poly (multi) potent progenitor cells (stem cells (SC)) opened up the prospect of implementing cell therapy for many diseases [7-9].

Simultaneously, there are insurmountable obstacles to the large-scale introduction of these approaches into practical health care. Moreover, we are not talking about the tumorigenic danger of cellular products [10-12], and not about the lack of technologies at present to make sure of the homing of transplanted cells in organs or tissues in need of intervention and/or specialized techniques that ensure the development of transplanted undifferentiated cells into the required mature cells [2, 13, 14]. Other factors determine the impossibility (at least in the medium term) of the effective implementation of SC transplantation technologies.

2. Challenges of Using Stem Cell Therapy

Transplantation of autologous progenitor cells assumes the presence of the preliminary stage of their cultivation in the vast majority of cases [7-9]. However, almost all types of mutations (from chromosomal aberrations to point mutations, etc.) are well known, even with short-term cultivation of cells with high proliferative activity [15-17]. The resulting genetic changes, of course, do not always carry the risk of malignant transformation. However, their obligate result is almost always a sharp decline in the viability of newly formed cellular elements [2, 16-18].

Allogeneic cell transplants have even more critical drawbacks for their effective large-scale use in practical health care. Multipotent SC (including CD105+CD90+CD73+, etc.) in optimal living conditions do not have on their surface antigens of the major histocompatibility complex (MHC) [19-21]. At the same time, their interaction with immunocompetent cells and products of life of the latter (primarily interferon-gamma) in the recipient's body launches a cascade of biochemical reactions, accompanied by the expression of such [19-23]. Therefore, therapies based on the proliferative and differentiating potential of donor SC must undoubtedly be developed following the requirements of antigenic interoperability of transplants.

Proof of the validity of this postulate is the use (for almost 70 years) in the health care of the only effective, and in some cases non-alternative, method of cell therapy - transplantation of hematopoietic SC (bone marrow) [24-26]. Moreover, in addition to the obligatory compliance with antigenic compatibility requirements, bone marrow transplantation has another essential feature. In the vast majority of cases, they are carried out against the background of immunosuppression, which results from the underlying disease (e.g., leukemia), or iatrogenic (due to cytostatic and/or radiation therapy) [27]. This is a significant factor for the effective engraftment ("implantation") of transplanted cells, as absolute antigenic compatibility is virtually excluded [26, 28]. The intentional formation of an immunosuppressive condition in patients, for example, in treating degenerative diseases, which would allow ignoring antigenic incompatibility, is certainly not possible for obvious objective circumstances.

In this regard, the introduction to the body of autologous progenitor cells (with reduced vitality) or allogeneic progenitors (excluding immunological compatibility) is accompanied by their death within a few days (maximum a couple of weeks) [20, 29]. Therapeutic effects are implemented solely by the secretion of regulators of physiological functions [30-33]. Thus, transplanted cells are, in fact, only special "delivery systems" pharmacologically active compounds - a complex of endogenous regulators of functions in the biological (cell) membrane.

These include substances that may have undesirable effects, including carcinogenicity (some growth factors) and/or potentiation of tumor growth by action [10, 12]. Besides, the use of this, in fact, pharmacological approach, there is an obvious contradiction with one of the main modern pharmacology and pharmacy requirements - "one drug - one active substance - one target" [2]. The use of "cocktails" of biologically active factors, especially protein nature, always carries high risks of side effects and complications [1, 34].

3. Pharmacological Approaches to Solving the Problems of Regenerative Medicine

3.1. The technology of obtaining cellular or extracellular vesicles and other products of the vitality of progenitor cells.

Evidence of the implementation of therapeutic effects in cell transplantation due to secretion by cells of humoral factors was reflected in the development of one of the approaches of the pharmacological strategy of regenerative medicine [35-37] - "Technology of obtaining cellular or extracellular vesicles and other products of the vitality of progenitor cells" [30-33]. The drugs created under this approach, especially based on certain types of cellular or extracellular vesicles, are potential high-tech pharmaceuticals. At the same time, the complexity of their composition (vesicles also contain a large range of pharmacologically active substances) and the inability to adequately (full) standardization of such "cocktails" do not allow them to be considered devoid of all the above-mentioned shortcomings characteristic of multi-component drugs [2, 34]. Besides, in terms of scientific and technical nature, from the point of view of pharmacology - this is a significant "step backward." Beginning in 1970, several drugs based on extracts of thymus and bone marrow cells («Tactivin», «Thymalin», «Myelopidum», etc.) were created - lyophilized, including standardized supernatants of cell cultures containing the products of the respective cells. These complex drugs are quite effective immunostimulants (immunostimulators) [37, 38]. Some of them concerning several tissues have regenerative activity (due to the content of early-acting growth factors) [2, 37]. However, due to the high risk of complications and side effects, they are not currently used.

3.2. Targeted pharmacological approaches.

The development of highly selective drugs with regenerative activity is relevant. This implies the need for selective action of such drugs against the molecular target and a particular organ or tissue by influencing, in one way or another, specific cellular and/or subcellular structures [1, 2]. Based on the chemical structure, origin, and mechanisms of action of the regulators of regeneration processes, as part of the implementation of the targeted impact approach on endogenous regeneration-competent cells, it is advisable to allocate three main directions [6].

1) The development of drugs based on cytokines by genetically engineered or other regulators of the protein nature's physiological functions, stimulating the realization of progenitor cells' growth potential of different classes.

Receptors for growth factors appear to be the most complained targets of regenerative medicine drugs [34]. This direction is most implemented today in practice. However, all developments are limited solely to the area of hematopoietic drugs and immunostimulants [39]. This is because drugs based on cytokines, cannot fully meet, at least, promising pharmacology requirements, including the selective effects and drug safety. Practically all growth factors, in one way or another, are pleiotropic and multifunctional function regulators [13]. This circumstance makes the selectivity of their actions very relative. Also, the protein nature of growth factors predetermines their immunogenicity and toxicity [2, 40].

In some cases, their pharmacokinetic characteristics are also unacceptable. For example, the inability to ingest, although in regenerative medicine, exactly, oral use of drugs, is the most appropriate, as it is assumed their long, repetitive courses, use [2, 35]. An important drawback is the inability of growth factors to penetrate the "barrier tissues", primarily through the blood-brain barrier (BBB), which makes it impossible to use them for the treatment of

neurodegenerative diseases [3]. Modified cytokines (conjugated with different carriers (PEG, etc.)), which are extended forms of analogs of growth factors, in addition to the above, have other, specific, complexity of the application. In particular, the lack of the possibility of rapid, if necessary (in the development of severe side effects) - the emergency elimination of the substance from the body [35]. In this regard, analogs of growth factors (including genetic engineering) cannot be considered the optimal candidates for regenerative medicine drugs.

2) The development of drugs based on synthetic low-molecular substances or individual compounds of plant origin (primarily alkaloids) capable of acting as ligands to cytokines receptors or interacting with other surfaces cellular regulatory structures involved in the regulation of SC functions.

To date, there is only one registered drug that meets all the criteria of this group and can be its benchmark - the target hematopoietic drug Eltrombopag [41]. The specified synthetic low-molecular substance affects the membrane domain of the receptor to thrombopoietin. Even though the eltrombopag binds to the receptor to thrombopoietin, it is deprived of some fundamentally important shortcomings available in cytokine, including that it does not cause platelet aggregation. The results of the V.V. Zakusov Institute of Pharmacology (Moscow, Russia) work on the creation of peptide mimetics NGF and BDNF for the treatment of neurodegenerative diseases may be an example of the successful implementation of this approach in the medium term [42].

This direction has an undoubted perspective. The key factor in its development is developing novel high-yielding methods and technologies target-oriented search and candidates' synthesis.

3) The development of drugs based on the modifiers of activity/expression of intracellular signaling molecules, which play an essential role in regulating progenitors' functions and microenvironment cells of tissues.

In the last couple of decades, the possibility of using key intracellular signal transduction as pharmacological targets has been actively studied [43]. In oncopharmacology, this direction is one of the main trends in the creation of antineoplastic drugs. The world's largest pharmaceutical manufacturers have developed several anti-cancer drugs based on intracellular signaling molecule inhibitors responsible for the growth and development of transformed cells. One of the advantages of these drugs is their selectivity, including not only concerning the type of tissue affected by the pathological process (organ) but also, in some cases - to the type of tumor. For example, Ruxolitinib (JAKs inhibitor) is effective against myelofibrosis, true polycythemia, and essential plateletemia [44], and Imatinib (BCR-ABL tyrosine kinase inhibitor) is effective for chronic myeloid leukemia [45].

Phosphodiesterase (PDE) inhibitors are a clear example of the possibility of selective influence on those or other tissues by modifying the expression/activity of individual signaling molecules. For example, selective PDE3 inhibitors Pentoxyphyllinum, Cilostazol are antiaggregant drugs [46], and the PDE3 inhibitor Milrinone has a cardiotonic effect [47]. PDE4 inhibitors Roflumilast and Cilomylast implement their therapeutic effects through anti-inflammatory action, mainly in the lung tissue [48]. In contrast, the PDE4 inhibitor Apremilast is a treatment for psoriasis [49]. To date, there is no clear answer to the question, what exactly is the reason for the selectivity of the action of various PDE inhibitors. The most acceptable explanation is the assumption that various pharmacological agents have a selective effect on different tissue-specific isoforms of PDE (more than 100 isoforms of PDE are known in total) [2, 50]. The specifics of their expression are often observed even within the same tissue. For

example, PDE4A and PDE4B are found in different regions of mammals' central nervous system. PDE4C is expressed only in the cortex, thalamus, cerebellum of the brain, and PDE4D mainly in the hippocampus [51].

Tissue specificity has also been detected for many isoforms of intracellular protein kinase [52]. For example, JAK3, PI3K-δ, and PI3K-γ are expressed mainly in the blood system cells [53, 54], JNK3 is thought to be characteristic of neural tissue [55]. Therefore, pharmacological agents' selectivity for individual signaling molecules isoforms may be an additional factor ensuring their regenerative activity's selectivity. Thus, there are theoretical grounds and practical examples of the possibility of selective influence on tissues and organs with the help of activity modifiers/expression of intracellular signaling molecules or other secondary messengers.

3.3. The strategy of pharmacological regulation of intracellular signal transduction in regeneration-competent cells.

In 2016, the E.D. Goldberg`s Research Institute proposed a "Strategy of pharmacological regulation of intracellular signal transmission in regeneration-competent cells." This approach involves the use as targets of individual signaling molecules of regenerative-competent cells: progenitor elements and microenvironment cells of tissues, mediated by determining the course of reparative processes in tissues [56]. This concept's implementation requires a detailed understanding of intracellular signaling and the expression of individual forms of signaling molecules in the precursor cells and microenvironment cells of different tissues.

In recent years, in the course of the E.D. Goldberg's Research Institute's research cycle, it has been revealed the significant specificity of the participation and role of individual links of intracellular signal transduction in the implementation of the functions of heterogeneous progenitors (mesenchymal SC, neural SC, neuronal-committed progenitors, hematopoietic, stromal and other progenitors) [57].

For example, JAKs/STAT-, PI3K-, NF-κB-, MAPK-dependent pathways [58-61] have been found to play an important role in the processes of realizing the growth potential of multipotent mesenchymal stem cells (MSC). However, the transduction of the signal via PI3K and NF-κB in them is carried out through alternative secondary messengers - without the participation of protein kinase B, C, and IKK, and from the MAPK-pathways involved only "classic" ERK1/2-mediated signaling, as well as among JAKs - only JAK2 and JAK3 are involved in the signaling process. Also, the bivalent potential of cAMP-mediated signaling was revealed [59], resulting in the absence of the effect of the baseline level of cAMP (when adenylate cyclase is blocked) on the proliferative activity of the ancestors. Simultaneously, the accumulation of cAMP in the cell due to the disruption of its interaction with the blocked PKA stimulates mitotic activity by probably activating Ca2/calmodulin-dependent protein kinase and/or Epac (exchange protein directly activated by cAMP) [62]. The negative effect of JNK on the proliferation of SC has been found, the role of which in several other, including tumor cells, is reduced to the opposite effect [63]. Stimulation of the functions of MSC through the fibroblast growth factor develops due to additional involvement in the process of transmission of the signal PKC, IKK и JAK1 in the corresponding ways [60, 61]. An even more pronounced MSC progression of the cell cycle occurs as a result of the conjugated activation of p38-dependent ("alternative") MAPK-signaling and protein kinase B (when used as a stimulant of semisynthetic alkaloid based on songorine) [58, 59].

Other types of progenitors have been identified as their peculiarities of individual signaling molecules' role in implementing their functions [57, 64-68]. Many fundamentally important differences in intracellular signaling patterns occur in different types of hematopoietic precursors (erythroid and granulocytic) [57, 67], as well as in multipotent neural SC and neuronal-committed progenitors [64, 66-68] (Figure 1).

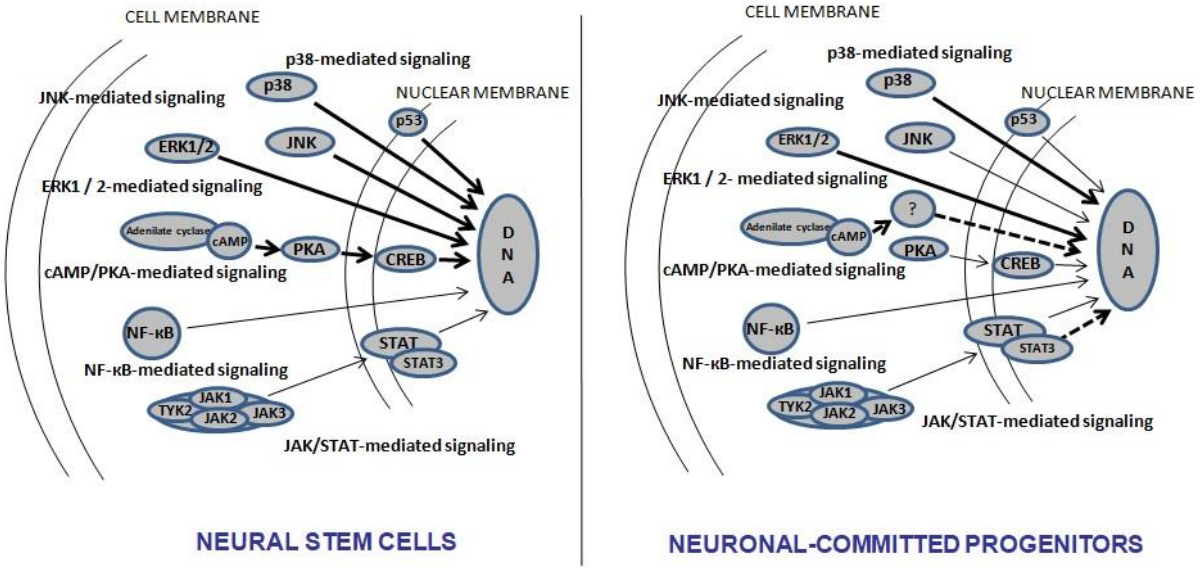

Figure 1. The participation of intracellular signaling pathways in the regulation of proliferative activity of regeneration-competent cells of nerve tissue. NSC - neural stem cells; CPN - neuronal-committed progenitors. Arrows marked by a simple line are not involved in regulating the pathways; arrows marked by a thick line - stimulating pathways; arrows marked by a bar line are inhibitory pathways.

Besides, the influence of pathogenic factors can significantly change (up to the complete inversion) the importance of some parts of signal transduction in the implementation of the functions of regenerative-competent cells. For example, chronic ethanol intoxication leads to the loss of NF-κB-signaling ability to maintain the multipotency of postnatal neural SC [69], to an inversion of the role of cAMP and PKA in the regulation of their cell cycle [66], as well as a change in the role of ERK1/2 concerning the proliferation of the neuronal-committed progenitors [68], etc.

In this regard, when looking for targets for the therapy of alcoholic encephalopathy, it is necessary to take into account not only the importance of individual signaling molecules in the functioning of different types of regeneration-competent cells of nerve tissue (potential targets, at least, should not have the opposite value in the regulation of the functions of NSC and neuronal-committed progenitors) but also the nature of changes in their role in the formation of a pathological state [36]. This is important because, based on the supposed concept of implementing the concept being developed, medical intervention should lead to a "sanogenetic transformation" (normalization) of the pattern of intracellular signaling in regenerative cells formed de novo. Therefore, changes in the activity/expression of these signaling molecules (targets) under the influence of a pharmacological agent should not disrupt the functioning of intact progenitor elements.

Thus, when selecting potential targets among the intracellular molecules involved in the cascade of signal transduction, it is necessary to conduct a detailed analysis of their value in different types of progenitors and microenvironment cells under different conditions their life.

Based on the results of fundamental studies, potential targets of drugs with regenerative activity were identified, some of which should have been activated (or increased expression) to achieve the desired effect. Others, on the contrary, to block (or inhibit their synthesis).

To confirm the validity of the assumptions put forward, some modifiers of individual signaling molecules were studied for their regenerative activity on animal models of pathological conditions. In the conditions of modeling post hypoxic encephalopathy, the pronounced cerebroprotective activity of the JNK inhibitors was detected [64, 70]. Correction of functional disorders of the CNS (exploratory-research behavior, improvement of mnestic functions) and morphology of the brain (reducing the intensity of pericellular and perivascular edema, the number of neurons with vacuole dystrophy and neurons in the state of phagocytosis (especially in the hippocampus)) were associated with an increase in the content and increase of functional activity of neural SC in the subventricular zone of the hemisphere against the background of increasing production of neurotrophic growth factors by neuroglial cells (Figure 2).

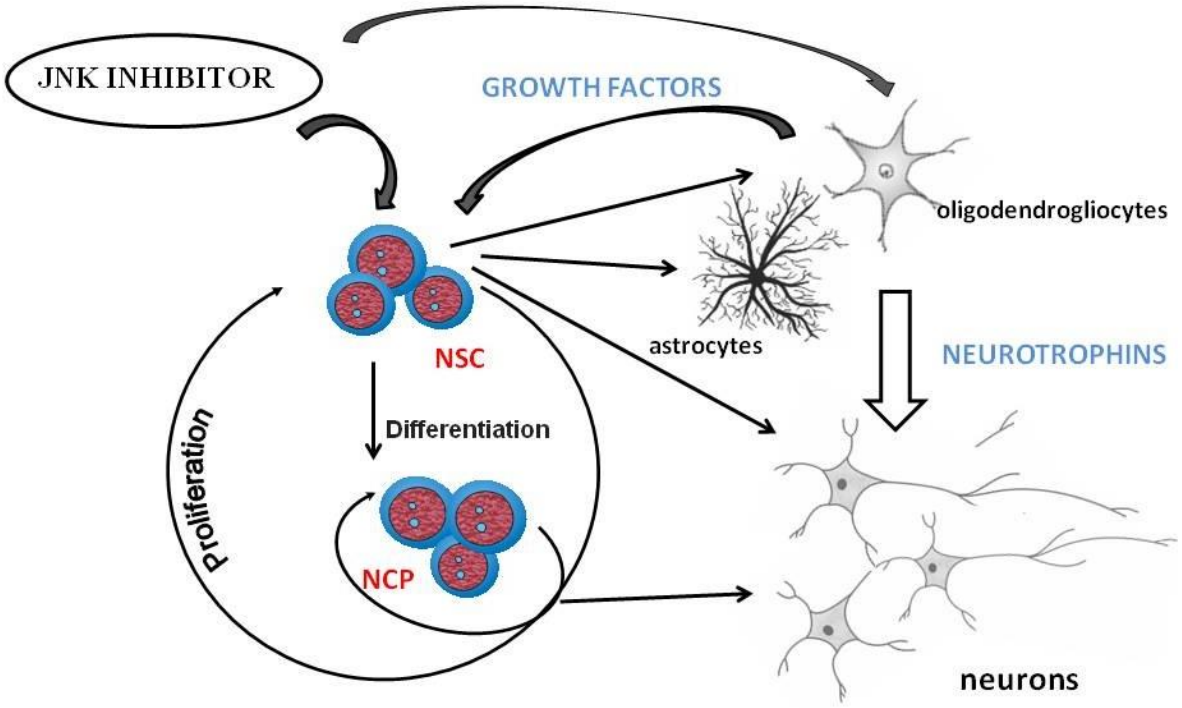

Figure. 2. The neuroprotective and neurodegenerative action of the JNK inhibitor in post hypoxic encephalopathy. NSC - neural stem cells; CPN - neuronal-committed progenitors. Black arrows - the direction of the NSC development; curly gray arrows - the pharmacological agent's effect.

On the model of flat skin wound in mice was found early healing activity of the PKA inhibitor, associated with increasing the realization of the regenerative potential of the stromal precursors of granular tissue [56]. External use of this agent led to a significant reduction in the period of repair of tissue defect (Figure 3).

The principle possibility of applying this approach to correct myelosuppressive conditions of cytostatic genesis is shown [67, 71-73]. At the same time, it was found that the comparison of the role of individual signaling molecules in the regulation of the functions of different types of blood-forming cells and elements of the hematopoietic inducing microenvironment (HIM) in the conditions of influence on the difference in the mechanism of action of cytostatics allows predicting with a high probability the different selectivity of the effects of certain modifiers of

the activity of signaling molecules. For example, the presence of hematoprotective (preventive use of the drug - before cytostatic therapy) and/or hematopoietic (therapeutic use - after the development of cytostatic myelosuppression) properties and potential of specific activity concerning individual growths of blood production (and, taking into account the type of antitumor agent used) [56]. These circumstances in the practical implementation of such developments may be important in specific clinical cases. The creation of such selective drugs is in demand by healthcare and fully consistent with personalized medicine principles.

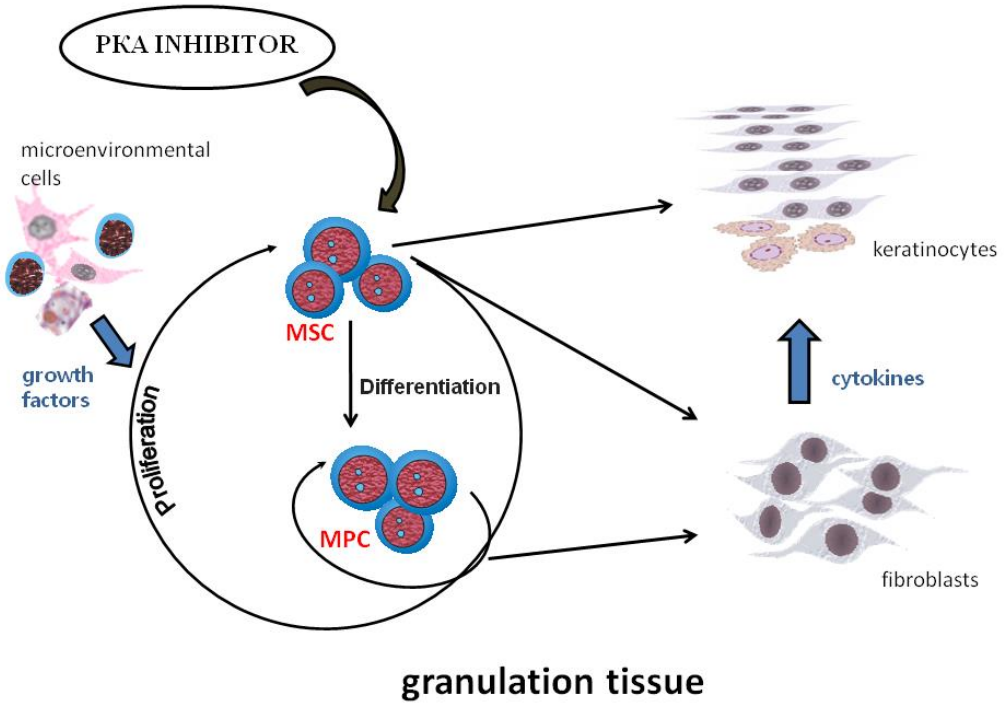

Figure 3. The wound healing action of the PKA inhibitor. MSC - mesenchymal stem cells; MCP - mesenchymal committed progenitors; curly gray arrows - the pharmacological agent's effect.

Of particular interest among the results in the field of hematology are data on the fundamental possibility and effectiveness of use: JNK inhibitors as both hematopoietic and hematoprotective drugs in the conditions of chemotherapy by antimetabolite (5-fluorouracil) [67, 71]; and PKA activators to prevent the development of myelosuppression caused by alkylating cytostatic Cyclophosphamide [72] (Figure 4). It is known that JNK inhibitors [74] and 8-Cl-cAMP, used as the PKA activator [75], in some cases, have self-sustaining anti-cancer activity. Therefore, when creating on their basis hematopoietic drugs, in addition to preventing the development of side effects of chemotherapy, theoretically, it is possible to increase the effectiveness of treatment of the underlying disease (tumor) (by summing up the anti-cancer action of a cytostatic and hematopoietic drug). For cytokines-based hematopoietic drug, this combination of pharmacological properties is virtually impossible. The development of many drugs based on growth factors (stem cell factor, fibroblast growth factor, etc.) was discontinued, on the contrary, due to their potentiation of tumor growth and/or carcinogenic effects [2].

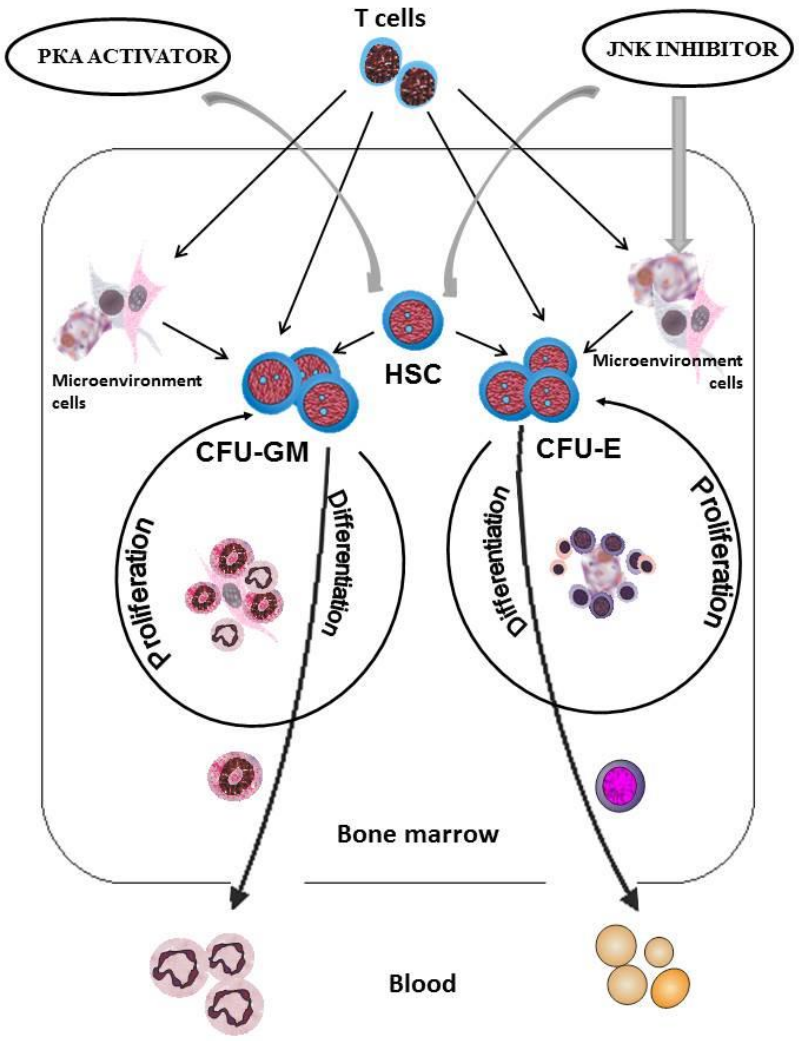

Figure 4. The mechanisms of hematoprotective and hematopoietic action of the PKA activator and JNK inhibitor in myelosuppression caused by cyclophosphamide and 5-fluorouracil, respectively. HSC - hematopoietic stem cells; CFU-GM - granulocyte-committed progenitors; CFU-E – erythroid-neuronal-committed progenitors; gray arrows - cell targets of the pharmacological agent's action.

4. Conclusions

The presented data show the prospect of developing "Strategy of pharmacological regulation of intracellular signal transduction in regeneration-competent cells." It should be taken into account that in the case of the use of highly selective concerning tissue-specific isoform molecules of pharmacological agents, the selectivity of regenerative activity of drugs on their basis will be as pronounced as possible. Therefore, the fundamental importance of implementing this direction is an in-depth study of the specifics of intracellular signaling and expression of individual isoform signaling molecules in progenitors and microenvironment cells of different tissues. These studies can create an appropriate scientific and theoretical platform for the development of fundamentally novel targeted drugs with regenerative activity. The selectivity of these innovative drugs will allow them to meet modern and promising pharmacology requirements (including carcinogenic safety) and the criteria of personalized medicine [1, 2, 34]. The novelty of the proposed pharmacotherapy strategy determines the possibilities of achieving practical implementation leadership positions in the promising sector of the world pharmaceutical market - drugs for regenerative medicine.

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Conflicts of Interest

The author declares no conflict of interest.

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