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# Triggering effect of "therapeutic MSC"

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The use of MSCs as a therapeutic agent is proven to be highly successful in many cases. However, the effects obtained are often temporary, and not leading to complete recovery. The reasons of such phenomenon are discussed in the article and the concept of "triggering effects" of MSCs is substantiated. The effect consists of the fact, that signal molecules, secreted by MSCs after administration, on one hand reduce the cell damage severity, supports and heals the cells. And on the other hand, MSCs induce mobilization and activation of the own (resident) stem cells, which replace the damaged cells. The realization of the therapeutic effect depends on the presence or absence of genetically determined disorders.

**Keywords:** mesenchymal stem cells, triggering effect, mobilization, activation.

The last fifteen years have witnessed the intense study of mesenchymal stem cells (MSC) as a promising remedy of treating a wide range of human diseases. This trend is based on the extensive fundamental research and technological elaborations [1], evolving into the increasing number of clinical trials [2–4]. It takes a therapeutic preparation a long time to enter the market. However, the first samples of MSC have already become commercial products, although this evident success is accompanied with rather numerous reports about low efficiency of MSC, short duration or absence of the therapeutic effect [5]. The interpretation of even the most successful clinical results of MSC application is complicated due to significant changes in the original ideas about MSC nature [6–8] and the mechanisms of their action [9]. Modern views do not deny the capability of MSC to get differentiated into various specialized cells, but relate their significance in the organism mainly to such signaling-trophic functions as the induction of reprogramming both immune system cells and tissue cells in the damaged zone via signaling molecules released by MSC [7, 10–13]. When the organism is damaged, MSC rebuild their metabolism on their own [14].

Different protocols of applying MSC are reported in the scientific literature [15; 16].

There are differences in doses, terms, frequency, sources, conditions of obtaining, pathologies, recipients, efficiency of obtained results, *etc.* [8]. Currently the available works do not provide specific unambiguous conclusions. Regardless of numerous detailed studies on the mechanisms of MSC action [17], it is yet to be defined why "therapeutic MSC", introduced from outside, have medicinal effect, whereas the inner ones do not. Moreover, many cases prove the efficiency of the inner MSC after they have been extracted and then introduced back.

To find out possible reasons of this phenomenon, we have conducted several series of experiments with laboratory animals. The task was to check our hypothesis that the single-step introduction of a large amount of MSC from outside (regardless of their nature) leads to changing metabolism of the whole organism towards activation, re-programming and mobilization of its own systems of damage restoration, which have been inactive or blocked in a chronically sick organism. These mobilized and re-programmed cells of the mentioned sick organism start restoring it on their own.

The series of experiments on laboratory models of chronic pathologies were conducted to analyze the MSC action. One model simulated well-known in scientific literature liver damage, cirrhosis, in rats caused by carbon tetrachloride. According to histological analyses, these injections during one month resulted in the development of fibrosis, in 12–14 weeks of the experiment – in formation of cirrhosis, thereafter the introduction of $CCl_4$ was stopped. MSC suspension was introduced once into the caudal vein of the experimental group of animals, at the rate of 7 $10^6$/kg of animal's weight. The injection of saline solution was given to the animals of control group. The changes, occurring in the liver of animals, were studied in dynamics for 13 weeks. Gradual restoration of liver was registered in experimental group; with the approximation to the norm for all the defined indices by the end of the experiment. There were no restoration changes in the control group [18].

Another model simulated chronic systemic damage of the organism. The object was the mice, injected twice a week for 12 weeks with carbon tetrachloride in the dose of 1.5 μl of 30 % solution of $CCl_4$ per one gram of the bodyweight. This procedure induced a severe damage of practically the whole organism [19]. 12 weeks later the mice of experimental group were injected with MSC, in dose of $10^5$ per animal. In different schemes of independent experiments, these were either fetal allogenic MSC, obtained from the embryo of the second line animal, or xenogenic MSC from Wharton's jelly of the human umbilical cord. Some animals were taken out of the experiment after 3, 9 and 12 weeks and the state of their organs was evaluated. The restoration of damaged organs was observed in MSC-injected animals. In the mice of control group there were either no positive changes or these were partial. The effect obtained on the models using other animals and other experimental pathologies was practically the same. For instance, the introduction of MSC at rhinitis mucosa damage completely restored damaged tissues of mice and rats whereas there was no self-cure in the control group [20, 21]. The systemic or local introduction of MSC at the simulated allergic encephalomyelitis in rats resulted in clinical recovery of animals, whereas in the control

group the acute phase turned into the recurrent motor impairment [22; 23].

Noteworthy, in all these experiments, both on rats and mice, only single MSC injection was done after the pathology development. As the introduced cells were non-autologous, their replacement action via differentiation and restoration of damaged organs was almost impossible. The results of PCR analysis, obtained by us on different models, demonstrated the disappearance of the detected material 1–5 days after the MSC introduction [24]. The restoration process without MSC injection lasted for many weeks.

The confirmation of the involvement of exogenous MSC in the mobilization of resident MSC was experimentally obtained. A matrix was implanted under the skin of the animal, and a damaging signal was imitated via the introduction of SDF1 source. Such carrier with chemokine was implanted under the skin of the ICR line mouse, imitating a damage zone. Then bone marrow MSC of GFP-transgenic mice were introduced into the caudal vein of the mice of experimental group. Several days later the explant was removed and analyzed for the presence of MSC. GFP marker was used to differentiate between resident and non-resident MSC. It was established that in the variants with introduced exogenous cells the amount of matrix-attracted MSC was higher compared to the control, which proved the mobilization of resident MSC, mediated by the introduction of the exogenous ones [25].

The analysis of the obtained results, the literature data and current views on MSC status in the organism allows us to draw several key assumptions. One of them is that MSC, introduced from outside (regardless of their nature, including autologous ones), and resident MSC, present in the organism all the time, are different cells by many biological properties. As has already been stated in the literature, MSC cultivated in laboratories on plastic, in nutrient media, in "clean" homogeneous culture outside the organism, are "a phenomenon of *in vitro* cultures" [26]. However, it is not the only problem. Prior to the introduction into the organism, MSC, extracted from it (or from a donor) are reproduced up to the amount of the "therapeutic dose". The number of cells in this "dose" exceeds considerably the number of the resident cells, present at each given moment in the organism. "The dose" is usually calculated taking at least $10^6$ MSC per 1 kg of bodyweight, which is $7 \cdot 10^7$ MSC for an "average" human organism. As for systemic introduction, the minimal single-step introduced doses are usually 5–10 times higher.

It may be stated that MSC in the organism are transitory. Their amount in the normal conditions is not very large, reflecting some kind of "on-duty" state. In normal life of healthy individuals, MSC are massively formed out of their predecessors (progenitors) in the required amounts only in case of emergency needs – wounds, fractures, burns, *etc.* [27]. In such acute states, there is a release of a specific complex of signaling and informational molecules, governing the mobilization and rearrangement of metabolism of different cells of the systems of protection, preservation and restoration, including the stem cells [28]. The same is observed in the experimentally damaged organism. However, on the other hand, it was demonstrated that in case of chronic impairments, stem cells may not be determined in blood at all [29], which may testify to the fact that the signaling

molecules of chronically damaged tissues either switch off or block the response of stem cells to the activation. One of these mechanisms, involving dipeptidyl peptidase-4, which blocks SDF-1, was described by Jixin Zhong and Sanjay Rajagopalan [30]. In this respect, MSC of the chronically sick organism are also "sick" – they are in a "chronically blocked or inactive" state, i.e. unable to function. As for MSC, cultivated *in vitro*, they are not affected by the organism and thus self-tune to the cultivation conditions rather fast. As a result, they differ in terms of status and condition from those still present in the organism. The inner rearrangements in MSC are almost not studied. However, as the conditions in different laboratories are similar, the standardisation of MSC preparation during re-programming seems rather possible.

Many researchers often describe the results of a single introduction of MSC at chronic pathological processes, which in many cases (although not always) is sufficient for inducing a reliable therapeutic effect. In our experiments we also used a single introduction of allogenic and xenogenic MSC to avoid the effect of engraftment and differentiation. In our experiments a single introduction of MSC was proven to be sufficient for therapeutic effect to start and develop, intensifying over the whole term of observation – up to 13 weeks. However, the allogenic and moreover xenogenic cells introduced from outside were shown in many experiments to be present in the recipient organism only for a few first days. Their main bulk does not enter the damage zone, being stuck in the lungs [30]. Our experiments demonstrated that they were absent

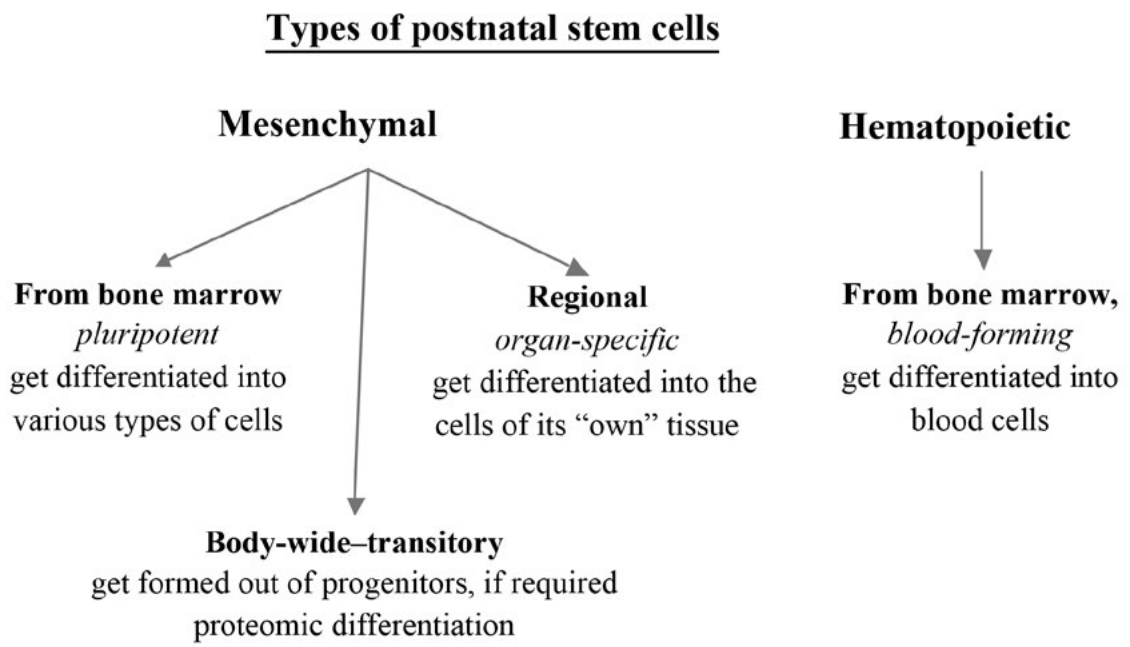


**Fig. 1.**

in the damaged organs as early as after five days whereas the therapeutic effect developed for months, increasing week by week. This takes place at the introduction of any MSC from outside, including the cases when "exogenous", foreign, ones are almost completely eliminated from the recipient organism just a few days after the introduction.

As for the "own" MSC of the organism, they may be formed from progenitors in unlimited amount during any period, required for the restoration of any damage. Noteworthy, three basically different types of MSC are acknowledged in current literature (Fig. 1).

MSC of the first type, localized in the bone marrow, are the closest to the traditional notions about stem cells and the most homogeneous, though they have some subpopulations of different origin [32; 33]. One of subpopulations originates from neural crest in early embryogenesis, the second - from some yet unknown place but not neural crest, and the third one is composed of Schwann cells, marked as a specific subpopulation. There are no clear answers why there are three different MSC types, what their functions are and how they differ by their action in the organism.

MSC of the second type are well-described regional MSC, localized in different tissues, e.g. oval hepatocytes, stem cells of eyes, brain, *etc.* They fulfill a replacement function, i.e. if necessary differentiate into highly specialized cells and replace the dying or damaged ones. At first, they were considered as the derivatives of the "real" stem cells and the bone marrow – their central storage. Therefore, the stem cells in the organs were called "regional". However, it is not a common belief, and the origin of stem cells in different tissues is yet to be established.

Most of MSC relate to the third type and actually they exist in the form of their predecessors (progenitors) in the endothelium of small and medium vessels [6]. Vessels permeate all tissues of all organs. Therefore, if required this source of MSC may be almost unlimited. However, this potential is realized mainly in response to the emergency signal, otherwise only an insignificant number of MSC "on duty" circulates. The place of "emergency" is determined in the organism by the gradient of signaling molecules from the damaged zone, where the relevant chemokines are released. MSC are formed, mobilized and enter the affected zone to restore a specific damage in a specific organ [34]. The signaling molecules from the damaged zone cells "license" (commit, prime, polarize, *etc.*) MSC.

In addition to these described and localized sources of MSC there are some MSC, involved in the restoration of tissues and organs, which are formed by the potentially unlimited system of epithelial-mesenchymal/mesenchymal-epithelial transitions [35–40].

Talking about restoration, one should mention another, quite unique, group of self-reproducing differentiated cells (i.e. self-preserving and self-restoring their deficiency in case of pathologies), which is composed of the cells of non-bone-marrow origin, defined as macrophages, originating from the yoke sac (prior to the growth of hematopoietic stem cells) [41–43]. These are Kupffer cells, brain glia, alveolar macrophages, *etc.*, which do not own any SC, reproducing themselves. Additionally, some highly differentiated cells (hepatocytes, for example) are also capable of reproducing without de/re-differentiation, i.e. the differentiated cell divides into the differentiated duplicate.

Summarizing the abovementioned, ***the hypothesis of the mechanism of action of "therapeutic MSC"*** may be formulated.

The restoration of damage, occurring after the introduction of "therapeutic MSC" from outside, is realized via the triggering mechanism. The introduced MSC mobilize and activate the resident stem cells "on-duty" and launch the intense formation of own MSC out of progenitors of the vascular endothelium. When there is acute damage, this accelerates the curing and restoring process in injured tissues (organs). In case of any chronic damage, lasting for a long time due to various reasons, a powerful impulse of signaling, trophic, and other biological molecules from the introduced MSC reprograms, mobilizes resident MSC, which had become insensitive due to chronic impairment, and they ensure their self-formation and restoration of damaged tissues (organs) further on in the self-supporting mode. It has already been described in the literature that endothelial progenitor cells have their receptors of emergency (including SDF1 receptor) and are capable of getting activated and mobilized [44]. It may be assumed that other (hematopoietic, regional) stem cells are activated as well, ensuring the self-cure.

The abovementioned is true for the organism without any additional fundamental impairments. If the latter are present, the mechanism of self-restoration either fails to repair the damage, or is partially blocked. There may be two main types of such impairments.

The first one is conditioned by genetically determined impairments of the functions of a tissue or an organ. In extreme cases, these are clearly manifested hereditary diseases. In a milder (and more wide-spread) variant, these are "hereditary predispositions". When implemented (usually with the individual's aging), there is a constant source of damage which is constitutive by its impact. Here the own cells of the organism are not capable of eliminating this source, no matter how much they are activated or mobilized. However, MSC, introduced from outside, can transfer the organism into a healthy phenotype at least for some time, activating the restoring, compensatory functions of the cells of a chronically sick organ, enhancing their abilities of eliminating the pathological phenotype. Here a single introduction of MSC will have only a temporary effect. Durable return to the functional norm would require the periodic introduction of MSC with the interval depending on the degree of impairment, determined by the "predisposition" gene.

The efficiency of multiple introduction of MSC was demonstrated by us in the experiments using mice with a severe degree of systemic chronic damage. Single introduction of allogenic or xenogenic MSC is insufficient for restoration and some animals still perish, a larger number in the control, and a smaller in the experiment. When allogenic MSC were introduced three times, all the animals survived and restored the damaged organs. This is expected in case of various "predispositions", affecting the restoration systems. A single introduction of MSC induced the mobilization and activation of the resident SC. With no predisposition, such induction was sufficient for re-programming for further self-support of the restoring status of SC and the organism was cured. With predisposition, the induction diminished and the initially weaker animals, which had more severe pathology, died.

However, the three-time introduction of MSC resulted in 3-time periodical induction of the restoration systems and the restoration process was going on. There are some communications in the literature, stating that standard systems of treatment cannot be of the same efficacy for different individuals. Thus, an individualized analytical base should be developed] [45].

The second extreme type of impairments is related to the source of stable or increasing impairment, which cannot be eliminated by the organism itself. In this variant, the introduced MSC cannot adjust the metabolism of a constitutively self-supported impairment. In case of allogenic origin, they are transitory in the organism, while the source of impairment works constantly. Even if syngen or autologous MSC are introduced into such an organism, the signaling and informational products of the constitutive source of damage will reconstruct the metabolism of the introduced MSC, making them either inactive, or "acting on the contrary", supporting the pathology. Tumors are the most vivid [46; 47], although not the only example of the second type of impairments. The chronic infections, leading to the death of all or most key differentiated cells of different organs (kidneys, glands of internal secretion, mucosa, *etc.*), such as hepatitis B virus, hepatitis C virus, HIV and others, will act in the same way. The scheme of MSC application should be modified depending on the reasons of chronic disease. With no fundamental impairments, a stable effect may be expected from a single introduction of MSC in the restoring status. In case of impairments, caused by a constitutively acting damaging factor, MSC may be in another state (in another polarization, as they now say) and serve merely as an additional mean. Another promising method is the transfection using a target gene, the product of which promotes the elimination of a constitutively acting damaging factor of non-autogenetic nature. At genetically determined predispositions, the introduction of MSC will be highly effective only in case of periodic application or in the variant of replacement action. However, regular multiple introduction of allogenic MSC may cause the avalanche of autoimmune diseases. So, it is necessary to use either only autologous, genetically modified MSC, or the allogenic ones, along with the procedures, eliminating the development of immune impairments. At present this is only a perspective at the level of rare laboratory investigations.

The fundamental and technological basis of the next level of replacement cell therapy is being developed now, and chronic pathologies will be the main target of its application.

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**Пусковий ефект «терапевтичних МСК»**

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Використання МСК як терапевтичного препарату не завжди виявляється високоефективним. У статті аналізуються можливі причини такої дії МСК і обґрунтовується концепція їх «пускового ефекту». Він полягає в тому, що сигнальні молекули, що виділяються МСК, що вводяться в організм, з одного боку зменшують ступінь ураження клітин, підтримуючи і відновлюючи пошкоджені клітини, а з іншого – призводять до мобілізації і активації власних (резидентних) СК, що в подальшому реалізують заміщення уражених клітин. Реалізація власне терапевтичного ефекту залежить від наявності або відсутності генетично детермінованих порушень.

**Ключові слова:** мезинхімальні стовбурові клітини, пусковий ефект, мобілізація, активація.

**Пусковой эффект «терапевтических МСК»**

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Использование МСК в качестве терапевтического препарата не всегда оказывается высокоэффективным. В статье анализируются возможные причины такого действия МСК и обосновывается концепция их «пускового эффекта». Он заключается в том, что сигнальные молекулы, выделяемые введенными в организм терапевтическими МСК (имеют двойное действие), с одной стороны уменьшают степень поражения клеток, поддерживая и восстанавливая поврежденные клетки, а с другой – приводят к мобилизации и активации собственных (резидентных) СК, которые в дальнейшем и реализуют замещение пораженных клеток. Реализация собственно терапевтического эффекта зависит от наличия или отсутствия генетически детерминированных нарушений.

**Ключевые слова:** мезенхимальные стволовые клетки, пусковой эффект, мобилизация, активация.

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