# Opinion, Discussions, Comments

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## MSCS — CENTRAL ELEMENT OF PRESERVATION-RESTORATION SYSTEM

*The extensive study of MSCs as therapeutic agents has revealed a wide range of different mechanisms of their interaction with other cells. It turned out that MSCs actively interact not only with the cells of immune system, modulating, for example, the inflammatory response, but also with the cells of damaged or altered tissues, supporting them and triggering healing and regeneration processes. Until now, the study and use of MSCs have occurred mainly after their expansion ex vivo. However, due to the high epigenomic plasticity of these cells, dependent on environmental signals, when cultured ex vivo, these cells have time to change so much that this does not allow direct extrapolation of the effects they exhibit to understanding their natural role in vivo. Nevertheless, based on the totality of the data already obtained, we make a provocative assumption about the central place of MSCs in ensuring recovery/regeneration events in the body. In addition, it should be noted that not all effects described to date fit into the established paradigm of cell division by functional features, since the phenomenon of MSCs is rather not a cell type, but a state into which various highly plastic cells surrounding vessels can pass. This indicates a possible need to revise some established concepts and may lead to the allocation of the provision of restoration/reparation processes into a separate system of preservation and restoration of the body.*

***Keywords:*** *MSCs, cells recovery, mesenchymal preservation and restoration cells.*

## Introduction

Currently, science is at the initial stage of yet another radical change of basic concepts. This is especially evident in quantum physics, astronomy, and biology. However, while in physics and astronomy it occurs in a vivid and demonstrative way, the same process in biology is rather unapparent. A good example to illustrate it can be found in the publications about one of the cell therapy compo-

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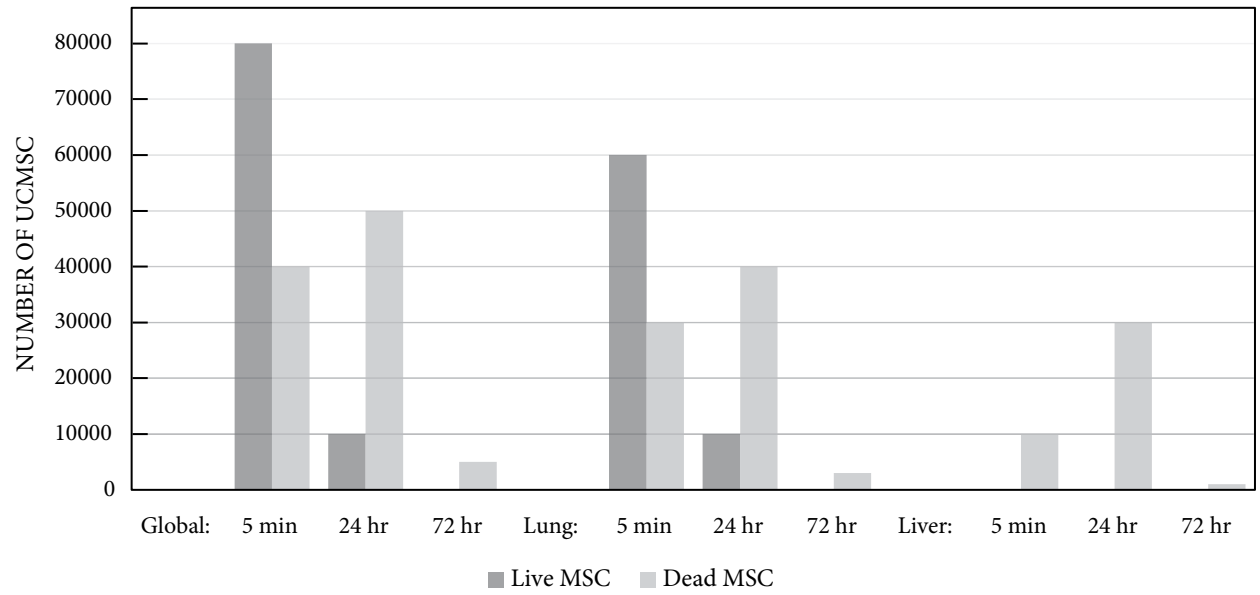


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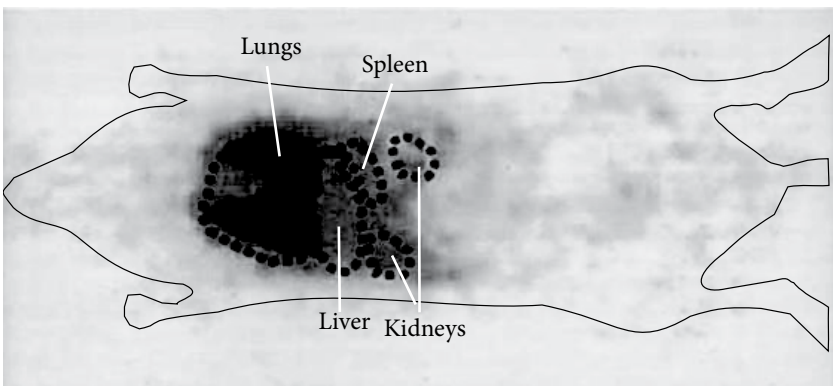


*b*

***Fig. 1.*** The fate of transplanted MSCs. *a* — Rapid death of MSCs introduced into the body according to de Witte SFH. *et al.*, 2018 [7]. *b* — Composite image of whole body scanning immediately after i.v. MSC infusion (Adapted from Gao J., *et al.*, 2001 [8])

nents, usually specified by the abbreviation "MSCs". The traditional basic foundation of notions about MSCs has been well described many times in different variants and combinations (and is still being repeated) in numerous reviews and introductions to experimental articles. In short, it can be summarized as follows.

In 1966, F. Friedenstein isolated a fibroblast-like population of cells from the bone marrow, which he described as "fibroblast colony-forming units" [1–3]. They did not attract any attention for a long time. However, gradually, with the commencing development of the study on the possibility of applying cells (first, cells from the bone marrow [4], then others as well) as a potential treatment tool, the cells obtained by Friedenstein in the culture were taken notice as well. In the late 1980s, Arnold Caplan named them "mesenchymal stem cells". [*Caplan AI*, 1988.] They turned out to have interesting properties and were used ever wider under the abbreviation of "MSCs". As no special marker was found specifically for MSCs, in 2006, the International Society for Cellular Therapy formalized a set of minimal criteria, meeting which the

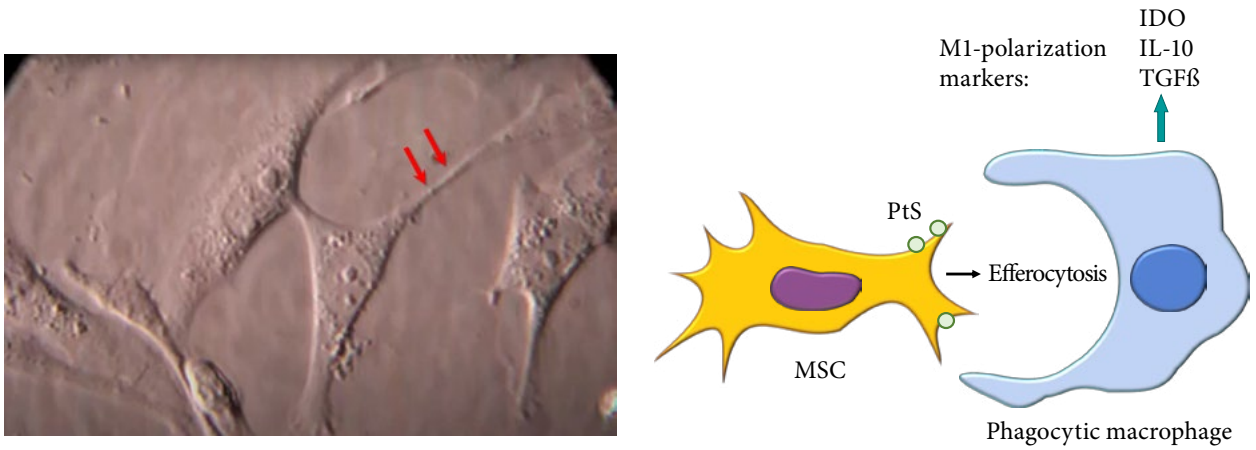


***Fig. 2.*** Examples of direct contact interactions with MSCs. *a* — visualization of the dynamics of intercellular transfer of large cellular elements. (unpublished data) https://youtu.be/Ml1ic9ZLJ_w. *b* — Schematic of phenotypic changes of macrophages — as a result of MSC uptake (efferocytosis). (Based on Galipeau J and Sensébé L. 2018 [15])

cells should be referred to this type [5]. In brief, MSCs should have plastic adhesion, should express CD105, CD73 and CD90 and should not express CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules and should exhibit the ability to differentiate into osteoblasts, adipocytes and chondroblasts *in vitro*.

Considering the unique therapeutic properties found in MSCs, the interest in the study of these cells has been directly or indirectly related to their actual and potential application as the means of treatment. In 1995, the MSCs were applied as a therapeutic agent for the first time [4]. Since then, the spheres of their application and the sources of obtaining them have been constantly expanding. At first, MSCs were isolated only from the bone marrow. With time, the list of the sources of these cells has gotten longer, and now, in addition to the bone marrow, the cells with MSCs properties are actively isolated from the adipose tissue, teeth, hair follicles, *etc.* The prenatal sources of MSCs are the umbilical cord and placenta, where these cells are stored in embryogenesis. With the accumulation of data about the lack of uniformity among the populations of these cells obtained from different sources, the ISCT's MSCs committee has had to expand and clarify the requirements to the nomenclature depending on the method of obtaining them and the tissue they are isolated from [6].

The phenomenon of these cells is that isolated and expanded *ex vivo* MSCs grow well in culture, can survive for a long time and multiply with a large number of passages. However, when such expanded MSCs are introduced into the body, they die quickly in the body and are no longer detectable. [7] (Fig. 1a).

Nonetheless, it does not hinder them from ensuring the therapeutic effects, attracting so much attention. MSCs were found therapeutically effective in treating various diseases. The therapeutic effect of MSCs on such a variety of pathologies is mainly explained by the fact that MSCs impact the immune system multidimensionally, "modify" it, and then the immune system itself conducts those processes which ensure the therapeutic effects.

As the mechanisms of the effects of MSCs on the immune system were studied, it has become clear that these cells are able to modulate the inflammatory response by switching between a pro-inflammatory and anti-inflammatory state [9]. And the corresponding modification (polariza-

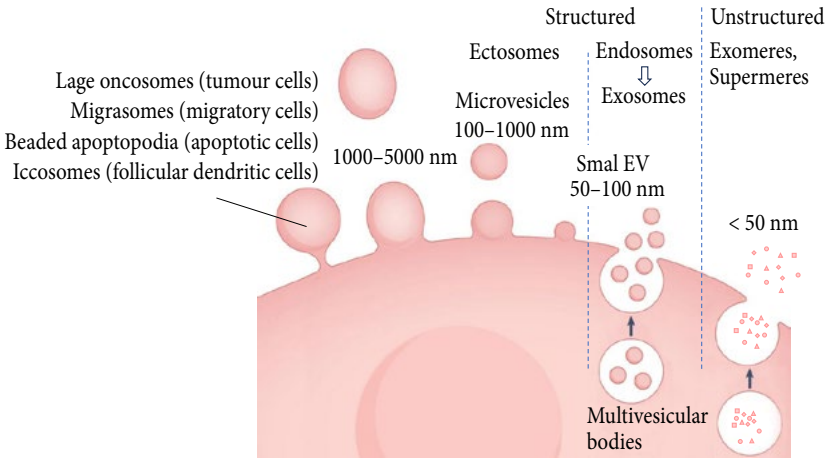


***Fig. 3.*** Classifications of extracellular formations according to Buzas E.I., 2023 and Cappe B, 2023 [16, 17]

tion) of the immune system is implemented due to the effect on the cells comprising it, both via **direct contact interactions** between them and MSCs, and **remotely**, due to the release of different kinds of biologically active products. "**Contact interactions**" should be understood as those that are realized by direct connection of cell surfaces and subsequent 'contact' events. The numerous forms of such contact interactions include gap junctions, tight junctions (TJ; zonulae or fascial adhaerentes), adhesive junctions (AJ), desmosomes (maculae adhaerentes) = (gap junctions (nexuses), [10–12], and microtubules. Not only part of the cytoplasm but also some organelles, including mitochondria, can move along the latter [13, 14]. We captured such organelle movement along the microtubule in dynamics (Fig. 2a). Considering the fact that after uptake of MSCs or their parts macrophages change their phenotype, this process can also be attributed to contact interactions [15] (Fig. 2b).

**The distant interactions** encompass all those that are realized by the escape of various components from the cell in the form of both *unstructured* and *structured constituents*.

*The unstructured constituent* consists of different individual molecules of the entire spectrum of sizes and compositions (peptide and non–peptide hormones, cytokines, lipids, phospholipids, *etc.*) and their aggregates.

*The structured constituent* is presented with different exovesicles, i.e., formations of different origins and compositions with a membrane. At present, they are mainly classified by their size and way of formation (Fig. 3).

The principal difference between exosomes and other exovesicles is that they are specifically formed within the cell, get assembled into special aggregate complexes, and are released from the cell in a targeted way. Exosomes are currently under intense study; they are produced as a standalone and quite promising therapeutic agent, which is independent of MSCs and rather an alternative to the latter. They are believed not to possess those potential dangers which MSCs may carry in themselves, especially in terms of possible acceleration of carcinogenesis. Driven by high hopes, the expectations of huge success and commercial benefits, many forget and do not take into account the fact that exosomes are products, produced by cells in the process of their active metabolism. Thus, whichever MSCs are, that's the kind of exosomes they will produce. In addition, for MSCs themselves, this is only one part of the mechanisms of their active therapeutic effect.

Despite extensive research on MSC over a long period of time, many aspects of phenomenology and its evaluation remain unresolved. Consensus in understanding these aspects has not yet been

reached. These include the questions of diversity, origin, functions performed in the body, mechanisms of therapeutic actions, and the safety limits of their use. The reflection of these conflicting opinions extends even to the nomenclature used to describe and classify these cells:

– fibroblast colony-forming units,
– mesenchymal stem cells,
– mesenchymal stromal cells,
– mesenchymal stromal/stem cells,
– mesenchymal stem/stromal cells,
– vascular stem cells (VSCs)
– MSC-like cells ...

It is important to note that the definition of MSCs encompasses cells that exhibit epigenomic plasticity, which responds to the conditions of cultivation [18]. These cells bear a distinct imprint of differences related to the characteristics of the tissue and donor condition from which they were isolated [19]. In addition, it was discovered not too long ago that the MSC fraction itself, derived from a single tissue from a single donor, may consist of multiple subpopulations [20]. Back in 2017, one of the founders of the study on using MSCs as a therapeutic agent and the author of the term itself, A. Caplan, spoke against calling them "stem cells", "Since the main functionality *in vivo* of MSCs is not multipotency and, thus, not as a stem cell..." [21].

In general, transferring the results of *ex vivo* studies to *in vivo* phenomenology is not always adequate. And especially in case of high plasticity of MSCs. As it turned out, the presence of even proteins key for MSC determination on the surface of MSCs is not constant. The studies have appeared showing that after entering the culture medium, the composition of surface markers can change rather quickly: some disappear, others appear. A remarkable illustration of this transformation was noted, even with the incorporation of time fixation, when adipose tissue aspirate was transferred to a culture medium (see Figure 4a) [22]. The phenotypic plasticity exhibited by MSCs is not confined to alterations in surface markers alone. Instead, it is indicative of more extensive, systemic reorganization within the cells. A substantial body of research has demonstrated that the properties and, consequently, the phenotype of MSCs are contingent on the method of isolation and the cultivation conditions. A good illustration of such changes was obtained by Wolfgang Wagner *et al.* by simultaneously analyzing BM–MSC proteomes from the same donor in different culture media [23]. For clarity, we only highlighted the areas of greatest change (Fig. 4b).

Even the factors such as culture density [18], surface influence [24, 25] or number of passages lead to significant changes. Such phenotypic plasticity suggests that what cells "look like" *in vitro* may not necessarily correspond to their phenotype and function *in vivo*. For example, the ability to tri-lineage differentiate *in vitro* is not supported by *in vivo* observations [26]. The term "*in vitro* culture phenomenon" has even been formulated to label these discrepancies [27].

What actually happens *in vivo* began to be partially unraveled with the advent of direct RNA sequencing of the individual cell [28] and the development of related bases and methods to analyze the results and predict cellular rearrangements.

There is a sufficient number of studies confirming that apart from a small number (about 0.5% [29]) of "duty" resident MSCs in tissues, the main number of these cells, if necessary, is formed by redifferentiation from other differentiated cells. The main candidates of such precursors are pericytes and adventitial cells of vessel walls. [30, 31]. When transferred to a "flask" these "progenitors" placed in a culture medium also develop into what we see, identify with markers as MSCs, culture and study. The properties of thus obtained expanded (reproduced) MSCs are defined by the very cultivation conditions due to their plasticity and differ from the ones, occurring in the organism under the different states. [32]. When such cells are released back into the body, they rearrange themselves in response to changes, as has been observed as early as the study of proteome changes in implanted MSCs encapsulated in capsules [33].

Transplantation of MSCs into the body results in a variety of therapeutic effects covering a very

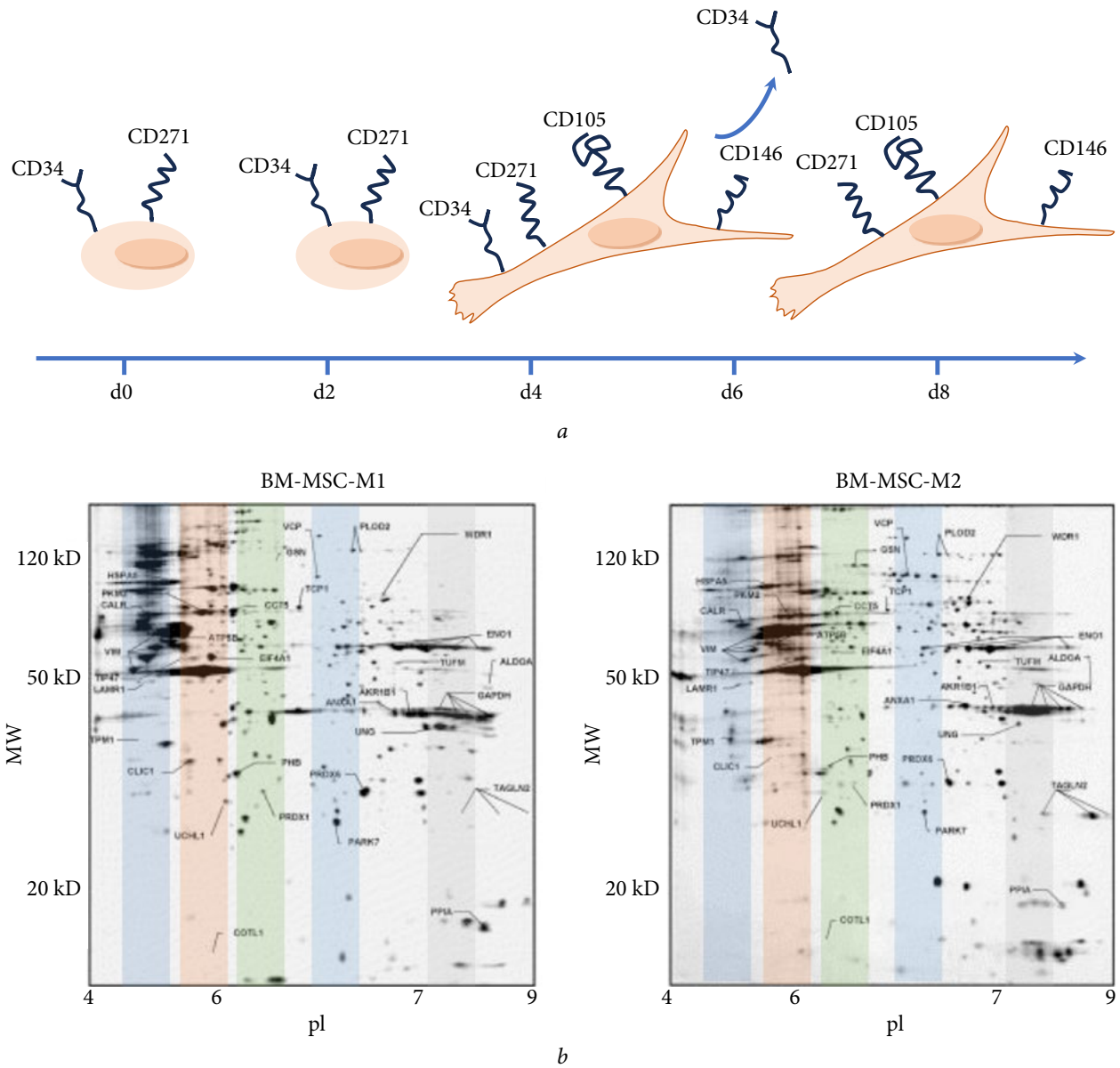


***Fig. 4.*** Profound changes in the MSC proteome under cultured conditions. *a* — Change of surface markers on the surface of MSCs during 8 days of cultivation (based on Braun J., 2013 [22]. *b* — Significant differences in the proteome when cultured in different media (according to Wagner W. *et al.*, 2006 [23])

broad range of pathologies (clinicaltrials.gov/search?intr=MSC). In some cases, just one injection of MSCs into the body after severe trauma or chronic pathology can provide gradual recovery over a relatively long period of time. For example, the biochemical parameters changes in rats with experimental pancreatitis were observed already on the 3rd day after a single administration of MSCs, and restoration of the of the pancreas architectonics was observed on the 14th day [34]

(Fig. 5b). At the same time, the bulk of transplanted MSCs are no longer detectable in the body in a sufficiently short time; at least, fluorescent dyes marking transplanted cells can be transferred to endogenous phagocytes *in vivo* [35] and therefore some markers cannot accurately determine the biodistribution or pharmacokinetics of living MSCs [36]. The paradoxicality of the situation lies in the fact that the healing process starts when the therapeutic agent, which used to be MSCs, is no longer present (or is no longer found) in the sick organism (Fig. 5a) [37]. Consequently, it is not the MSCs themselves, but the recovery mechanisms they launch that lead to such diverse therapeutic effects.

As mentioned before, many therapeutic effects of MSCs can be explained by the effect on immune system cells of signaling factors released by transplanted MSCs (paracrine effect). This is supported by the success of the widespread use of MSC–produced exovesicles and secretome without MSCs themselves [38, 39].

In addition to the reaction of launching the processes of long-term restoration, one can observe the practically instantaneous reaction of macrophages (the universal indicator of inflammation) to the transplanted MSCs in the inflammation zone itself, which was demonstrated using the simulation of acute inflammation caused by non-infectious peritonitis in rats [40] (Fig. 5c). Given the speed and complexity of the chains of paracrine reactions, it is difficult to explain such an "instantaneous" effect due to the release of necessary signaling factors and the subsequent response to them. These rates of reaction probably correspond to the mechanism of receptor-ligand events during which the surface proteins of the MSC membrane act as ligands, and the surface proteins of "the first inflammation line" cells (macrophages and lymphocytes) are receptors, "instantaneously" launching the corresponding processes. It is in agreement with the experimental data, which demonstrate that the killed, dead MSCs that no longer produce or secrete anything outside, yet eliminate acute inflammation just like native live cells, "instantaneously", within the same period of time. The authors of this study observed how "… inactivation of MSCs in which their immunophenotype remained intact while their secretome and active crosstalk with immune cells was disabled, retained the cells' immunomodulatory capacity in a lipopolysaccharide sepsis model. In this model, the therapeutic effect of MSCs appears to be independent of their cellular activity and **depends on a mechanism potentially involving recognition and phagocytosis of MSCs by monocytic cells"** [7, 41]. In some cases, the therapeutic application of the dead MSCs turns out to be even more effective [36, 42].

The above phenomenology allows us to hypothesize that MSCs function as a multi-functional central element of **a complicated comprehensive multi-tier preservation-restoration system.** It was Caplan who was the first to suggest it regarding the MSCs functioning as a therapeutic agent and called for re-naming MSCs into medicinal (treating) signalling cells:

"Since the multipotency of MSCs is not the key aspect for their current therapeutic use, I herein propose a name change: MSCs = Medicinal Signaling Cells» [43].

The same follows from the "commonly accepted" notions about the mechanisms of the therapeutic effect of MSCs [15]. The role of MSCs as rescuers of tissues from damage was pointed out by Rodriguez A.M. with coauthors [44], considering the issues with mitochondrial transport. And later, Manole E. with coauthors paid attention to the tandem of MSCs and macrophages, assigning it an important role in tissue repair processes [45].

MSCs interact "regeneratively" with the damaged cells, directly restoring them with their content, and/or in a "transformative" (or supervisory) way with the cells of the immune system — reformatting them "for the task" [9,15]. To provide a regenerative function in response to damage, MSC restructures its secretome, which contains proteins [46], mRNA [47] and other components. To do this, they can use all types of interaction available to them, from direct contact to distance, through all types of cellular secretome [48], both structured and unstructured [36].

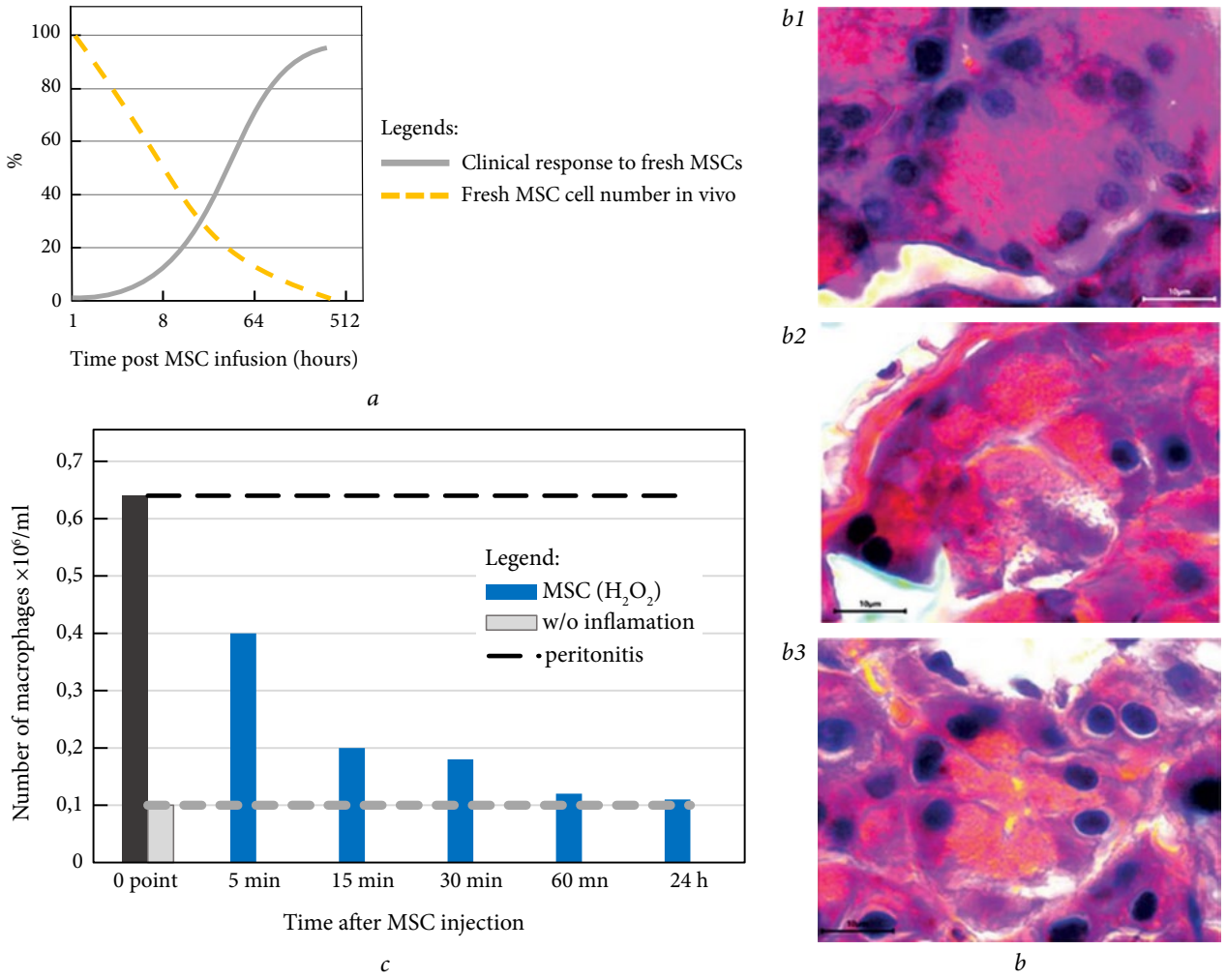


***Fig. 5.*** Almost instantaneous response of MSCs to MSC transplantation leads to long-term development of a noticeable therapeutic effect.

*a* — The healing process starts when the therapeutic agent, which used to be MSCs, is no longer present (according to the Moll G. et al., 2016, [37].

*b* — The restoring of the pancreas histological architectonics after a single administration of MSCs. *b1* — Normal morphology of the pancreatic acinus of a healthy rat, *b2* — Morphology of rat pancreatic acinus 3 days after induction of pancreatitis, *b3* — Morphology of the rat pancreas acinus with pancreatitis 14 days after the transplantation of native or preconditioned hUC-MMSCs (according to the Pikus, P. et al., 2023 [34])

*c* — Dynamics of anti-inflammatory action of MSCs — decreased concentration of macrophages in peritoneum in non-infectious peritonitis (by Pikus P. et al., 2022 [40])

The integral understanding of the general principle of MSCs action as a central element of the protection-restoration system of the organism requires the clarification of the term "action" as applied to MSCs, by which we mean changes in a significant indicator — the therapeutic effect, changes, modification in the spectrum of immune system indices, the mobility of cells, *etc.* In this

context, such an action has a unidirectional character from the MSC to "something". But to have an effect "on something" and to change this "something", MSCs should receive "a signal about the need" from this "something" and/or whatever precedes it or is related to it. In conformity with the occurring damage or a threat of a damage, MSCs should change their metabolism, get re-formatted to eliminate this damage (an absolutely specific one), to prevent damage, disorders, *etc.* And such feedback is found. For example, in chronic inflammatory conditions, such as rheumatoid arthritis, NR4A nuclear receptors have been shown to modify the activity of MSC and fibroblast-like stromal cells to regulate synovial tissue hyperplasia, pathological angiogenesis, and cartilage turnover *in vivo* [49], and in MSCs transplanted into the body as part of alginate capsules, epigenetic changes were recorded under the influence of the inflammatory microenvironment compared to the state at the time of transplantation [33]. It means that initially, while still in the organism, prior to the transfer into the flask in the form of aspirate or a tissue fragment, "the MSCs actions" were bilateral — receiving the information about the things MSCs were required to do, and re-formatting and "acting" adequately according to this information. This bilaterality is incessant because in the "action" process, the zone of the action changes; thus, MSCs should change accordingly, constantly, and adequately to a new state, too. Similar changes were demonstrated by the *in situ* proteome changes of implanted MSCs in ischemic heart tissue by labeling newly synthesized proteins with azidonorleucine [50], as well as the mutual modulation of MSCs and macrophages, where TNF-α secreted by M1 macrophages was shown to be critical for MSC recruitment during bone regeneration [51]. The results of single cell RNA sequencing in normal paradontium and chronic paradontitis may also provide indirect evidence of changes in MSCs *in vivo* depending on microenvironmental conditions [29]. For better understanding the mechanism of therapeutic action of MSCs *in vivo*, we will await new research results on the changes of the transcriptome and metabolome in MSCs under *in vivo* conditions that correspond to the specific needs of tissues, during their damage or pathology.

The mechanisms of ensuring this bilaterality can be conveniently divided into three groups: some **indirectly "remote-direct" contacts** and two "polar" **remotely dispersed signalling molecules** and **immediate direct contacts**.

**The remotely dispersed** signalling molecules may comprise the entire spectrum of non-structural products of cells, released from MSCs and

*Table 1.* **Trophic and immunomodulatory factors secreted by cultured MSCs known by early 2009, structured by categories of action. (according to Meirelles Lda S, 2009)** [52])

| | |
|---|---|
| Immunomodulation | Cell mDC ← PGE-2 |
| | Cell CD8,CD4 ← HLA-G5, HGF, iNOS, PGE-2, TGFb1, IDO |
| | Cell NK ← IDO, PGE-2, TGFb |
| | Cell Treg ← LIF |
| Anti-apoptosis | VEGF, HGF, IGF-1, Stanniocalcin-1, TGFb, FGFb, GM-CSF |
| Angiogenesis | VEGF, IGF1, PIGF, MCP1, FGFb, IL6 |
| Support of growth and differentiation of stem and progenitor cells | SCF, LIF, M-CSF, SDF1, Angiopoietin1 |
| Anti-scarring (anti-fibrosis) | HGF, FGFb, Adrenomedullin(?) |
| Chemoattraction | CCL2-6, -20, -26, CX3CL1, CSCL1, -2, -5, -8, 10–12 |

leading to paracrine effects, thus promoting the required changes (metabolism modification, activation or inhibition of some processes, repair of damaged target cell systems, *etc.*), all the systems and tissues of the organism (Table 1).

All this undergoes qualitative and quantitative changes along with the MSCs re-formatting according to the information they receive about the "current state" of the need. These changes vary in the widest range, reaching differences to the magnitude of several orders (Table 2).

We have considered the diversity of **direct contact interactions** above, and here we would like to draw attention to the fact that after the exchange of substances, recipient cells change their physiological characteristics [55,56]. To describe changes in immune cells after such contacts, different authors use the terms either "learning" [57] or "adaptation" [7].

This "education" has long eluded the researchers because the studies on the migration of transplanted MSCs have used different stable markers for a long time, the presence of which in different parts of the organism has been interpreted as the presence of transplanted cells. After the discovery of efferocytosis, it became clear that the registered signals may demonstrate both the whole cells and the absorbed particles of transplanted cells. Yet, numerous experiments show that the transplanted MSCs spread in all the organs and tissues "instantaneously", though the main part is initially concentrated in the lungs (Fig. 1b). Then, MSCs are concentrated in lymphoid tissues, and, as can be extrapolated from the *in vitro* experiments, adjust the cells of the immune system "to the task".

The remote-contact interactions are implemented by special structurally organized fragments of cells with the common name — "exovesicles". Exovesicles can be produced by any cell and are released into the cell environment by various mechanisms. They are organized as spherical bodies ranging in size from 20 to 1000 nm, surrounded by a lipid membrane with embedded proteins that act as receptors or ligands, which enables recognition of target cells, thus providing "targeted delivery," while still being able to move around the body. A great number of various signaling agents, directly related to exosomes, have already been described. Varderidou-Minasian S. and Lorenowicz M.J. identify sixteen groups of molecules present in EV-MSCs based on their molecular and cellular functions. These groups together comprise about 200 elements, of which 20 have already been proven to have a therapeutic effect. These are:

– transcription factors,
– extracellular matrix proteins,
– chemokines, cytokines,
– enzymes,
– growth factors, RNA binding molecules,
– miRNAs,
– molecules involved in angionenesis,
– cell adhesion,
– development,
– degradation,
– protein folding,
– immunomodulation,

*Table 2.* **Quantitative changes in the expression of some genes between proinflammatory and antiinflammatory cell states (according to Waterman RS., 2010** [53] **and Tomchuck SL., 2008** [54])

| | k=MSC2/MSC1 | MSC1 (pro-inflammatory) | MSC2 (anti-inflammatory) |
|---|---|---|---|
| **iL6** | 5,5 | 7–287 | 39987 |
| **iL8** | 10,1 | 6–998 | 71233 |
| **CCL10** | 540 | 337 | 181777 |
| **CCL5** | >121 | 297 | >36000 |
| **CCL2** | 12,3 | 259 | 3191 |
| **IFN1β** | 0,045 | 807 | 37 |

– regulation of apoptosis and survival,
– adipogenesis [58].

The diversity of exovesicle cargo indicates the diversity of possibilities, goals and functions of intercellular transfer. Together with the direct close contacts described for MSCs, this provides a "material base" for a two-way exchange of not only control (signal) but also structural cellular elements, and in both directions [13].

In terms of MSCs, "stromality" is not a mechanic maintenance of the tissue structure but an implementation of the preservation function of differentiated cells of all tissues. This is convincingly demonstrated by the experiments of Hui E.E., Bhatia S.N., in 2007 [59].

Essentially, the same task — preservation and restoration — is fulfilled by MSCs regarding the "real" stem cells in niches [60,61]. "These include the fact that each separate tissue-specific stem cell is both in communication with its underlying vascular endothelial cells and neighboring specific pericyte/MSC (Universal Stem Cell Niche). These pMSCs are specific to each stem cell, including a chemically different pMSC next to the active versus quiescent HSC in marrow" [21].

And now that all the known facts are brought together, a full-scale function of MSCs takes its shape.

**MSCs are a special type of cells, whose role is to support the functions of all the cells in the organism, preserve and restore them.**

What we see in the flask and call MSCs is the central link in a special system of the organism, the "relay" comprehensive preservation-restoration system of the organism, consisting of MSC progenitors → formed MSCs → target cells which need to be immediately preserved (restored), and fulfilling the long-term restoration function.

All the properties of MSCs, their types of action, their biological and therapeutic effects are external manifestations of the mechanisms of a unified, comprehensive preservation-restoration system of the organism. And the name for MSCs should correspond to their place and relevance in the organism: **mesenchymal preservation and restoration cells — MPRC**, the central element of this system.

Gauging by the properties, place, and functions of MSCs in the organism, a new direction is being formed — a restoring the body using its own capabilities. Tissue engineering and regenerative medicine, based thereon, aim to restore the organism from the outside by constructing and growing tissues and organs to use them for subsequent replacement of sick, damaged, destroyed residential ones. Cellular engineering and cellular therapy, based thereon, undertake the task of preserving full-scale functioning and restoration of damaged, sick, destroyed cells of the organism from the inside, within the organism itself. Thus, we are getting one step closer to activating and using the mechanisms of self-maintenance, self-preservation, self-replacement and self-healing of the body.

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МСК — ЦЕНТРАЛЬНИЙ ЕЛЕМЕНТ СИСТЕМИ ЗБЕРЕЖЕННЯ-РЕСТАВРАЦІЇ

Широке вивчення МСК як терапевтичних агентів виявило широкий спектр різноманітних механізмів їх взаємодії з іншими клітинами. Виявилося, що МСК активно взаємодіють не тільки з клітинами імунної системи, модулюючи, наприклад, запальну реакцію, але і з клітинами пошкоджених або змінених тканин, підтримуючи їх і запускаючи процеси загоєння і регенерації. До цього часу вивчення та використання МСК відбувалося в основному після їх розширення *ex vivo*. Однак через високу епігеномну пластичність цих клітин, залежну від сигналів навколишнього середовища, при культивуванні *ex vivo* ці клітини мають час змінитися настільки, що це не дозволяє прямої екстраполяції ефектів, які вони демонструють, для розуміння їхньої природної ролі в природних умовах. Тим не менш, на основі сукупності вже отриманих даних, ми робимо провокативне припущення про центральне місце МСК у забезпеченні процесів відновлення/регенерації в організмі. Крім того, слід зазначити, що не всі описані на сьогоднішній день ефекти вписуються в усталену парадигму клітинного поділу за функціональною ознакою, оскільки феномен МСК — це скоріше не тип клітини, а стан, в який можуть переходити різні високопластичні клітини, що оточують судини. Це свідчить про можливу необхідність перегляду деяких усталених концепцій і може призвести до виділення забезпечення реставраційних/репараційних процесів в окрему систему збереження та реставрації організму.