Abstract. In this review, we analyzed the results of experimental investigations of the impact of mesenchymal stem cells (MSCs) on tumor cells in vitro and on tumor growth and metastasis in vivo. The discrepancy between available literature data is emphasized, with some investigators finding that MSCs promote tumor growth and others reporting that MSCs inhibit it. Many mechanisms have been found to account for these observations, such as cytokine and/or chemokine signaling, modulation of apoptosis, activation of vessel growth, immune modulation, and others. Here we also present our view on the conditions in which MSCs enhance tumor and metastasis that is essentially important, both for understanding the role of tumor stroma in carcinogenesis and developing MSCs as therapeutic tools to be used in clinic.

Key words: mesenchymal stem cells, tumor growth, metastasis, angiogenesis, tumor microenvironment, stimulation/inhibition of tumor growth

Intensive investigations of the last 10 years have shown that mesenchymal stem cells (MSCs) not only possess pluripotent properties and ability for differentiation to different progenitor types of cells but they also have tropism to tumors, as well as differentiate to tumor-associated fibroblasts and develop fibroblast network within their stroma (1-4).

Presently there are many contradictory literature data showing that MSCs can both promote and inhibit tumor growth. The reasons for such disaccord among research findings remain unclear as yet; they vary greatly. The authors not infrequently mention differences in the variety of tumor models used by the investigators,
MSCs heterogeneity, dosage variability and time of their delivery, animal species specifics and many others. The main reason is still to be established. It is known that MSCs can be derived from fetal tissues and from different organs and tissues of an adult organism. Still they most frequently are derived from the bone marrow (BM) and adipose tissue (AT). Tissue-isolated MSCs differ by a number of characteristics from the BM-derived MSCs, and this may also be one of the reasons for existing discrepancies in the data about biological properties of these cells [1].

The tropism of MSCs to malignances is admitted by almost all the investigators. These cells had been proposed to serve as target-delivery vehicles for various antitumor agents, such as interferons, cytokines, chemical agents, receptor apoptosis inductors and oncolytic viruses [5-7]. The MSC-based preparations undergo preclinical trials on various malignancy models [8]. The number of such trials exceeds significantly the number of works devoted to study of MSC-stimulating tumor growth properties. Mentioning should be made of how it is important to assess conditions under which MSCs can stimulate or induce tumor growth and how MSCs are interrelated with metastasis. In other words, our understanding of the role of stromal cells in the oncogenesis is crucial.

The BM-derived MSCs have been fully investigated; the spectrum of their surface markers has been established and their adhesive properties and capacity to differentiate to other cells of the mesenchymal row (in adipose tissue, muscles, cartilages and bones) under the impact of differentiation factors have been studied thoroughly [1, 5, 8]. Moreover, their tropism to tumors and the transformation of the latter into differentiated fibroblasts has been shown [9, 10]. The MSCs in the organism and in the BM in particular support regeneration and hemopoiesis but the function of native BM MSCs remains still unknown. When some organ is injured, the MSCs are capable to differentiate to tissue elements, support the formation of new vessels and synthesize cytokines and growth factors, stimulating thereby regeneration and recovery of the damaged tissues. The recovery potential of MSCs has been established at many diseases, including such severe diseases as diabetes, stroke and parkinsonism [11]. The MSCs play similar role in malignancies where they perform recovery functions while being differentiated to tumor fibroblasts and pericytes and, probably, into endothelium-like or endothelial cells. Furthermore, MSCs possess immune-suppressive action. Many investigators have proved the immune-suppressive properties of MSCs when using them as a therapeutic tool for suppression of transplant-against-host in BM grafting [12, 13].
MSCs and tumor growth stimulation

There are convincing data about MSC induction and stimulation of tumor processes in the organism. Karnoub et al. [14] have shown that labeled MSCs of the bone marrow origin delivered with lung cancer cells (in ratio 1:3) to immune-deficient mice caused an accelerated growth of the grafted tumors and increased the number of metastases. However, the stimulating effect of MSCs on tumor growth was registered in only one of the four malignant cells of lung cancer. There is no explanation for this phenomenon so far. It was also found that MSCs isolated from bone marrow favor cell growth in other types of malignancy, such as lymphoma, colon cancer and melanomas [15-17]. Bone marrow MSCs (derived from fetal and those derived from adult organism), injected together with colon cancer cells (SW480 and F-6 lines), enhanced not only the growth of tumor nodes but also increased the number of vessels and necrosis sites in them, that evidenced for greater aggressiveness of such tumors. Both types of MSCs (‘adult’ and fetal) produced approximately same impact on the tumor process, although biological activity of ‘adult’ MSCs was somewhat higher [15]. Following injection of melanoma B-16 cells with MSCs versus without MSCs led to the appearance of the greater number of tumor sites in the allogenic mice that indicated the presence of immune-suppressing effect favoring the growth of transplantable model tumors in these experiments [16]. Analogous data were received with human B-cell lymphoma [17] that can be explained by lymphotoxin production and tumor necrosis induced by MSCs capable to delay immune reactions.

MSCs isolated from the gastrointestinal tract are similar in terms of their functional activity to MSCs of the bone-marrow origin [40]. The breast cancer cells injected with adipose tissue MSCs caused growth of tumors of the greater size and promoted their quicker development in the syngeneic mice [18]. Human ‘adipose’ MSCs, injected with cells of human glioma lines (n-460 and U87MG) to immune-competent mice, stimulated a rapid growth of tumors and increased their size [19]. Similar results were obtained with the lung cancer and Kaposi sarcoma cells [20]. Increase of the tumor size is believed to occur for the reason that MSCs in the presence of tumor cells (TCs) are able to proliferate thereby increasing tumor node size [21], whereas MSCs without TCs do not proliferate. Hence the issue about the mechanisms of tumor mass increase still remains unanswered whether it is resultant from increase of the number of TCs or MSCs or both [1]. Neither there is unequivocal answer to the question whether MSCs are capable to transform to TCs. According to the findings of one group of the investigators,
MSCs can spontaneously transform to sarcoma cells when being cultured with HT-1080 sarcoma cells [22, 23] whereas in combination with other cell lines such phenomenon has not been observed. Transformation of MSCs into TCs was also observed in the U-2OS cell line [24, 25]. Notably, direct evidences for MSCs transformation into TCs are few. As has been noted by several authors, not a single case of tumor development from these cells was registered in more than 1000 patients in clinic [1].

**Inhibitory effects of MSCs**

MSCs inhibited the growth of colon carcinoma culture cells *in vitro* and in the cases when animals were injected MSCs/TCs in the ratios 1:1 and 1:10) [26]. In these malignancies the authors registered intensive macrophagal and neutrophyllic infiltration that evidenced for inflammatory reaction in the tumor site. In animal investigations on the model of Kaposi’s sarcoma cells it was showed that injected MSCs (but not other cells, say, endothelial) inhibited the growth of this tumor [27]. When the use was made of thymus-free mice, there were similar observations as regard tumor growth, thus evidencing for the presence of non-immune mechanisms of tumor growth suppression. Human fetal MSCs derived from the skin suppressed the activity of various hepatoma cancer cell lines: decreased their proliferation, colony-formation and expression of oncogenes *in vitro* and *in vivo* [28]. MSCs inhibited growth of breast cancer cells as well and depressed expression of beta-catenin, c-Mus and survivine. It was showed that growth-inhibiting effect was linked with action of soluble inhibitor of Wnt/beta catenin signaling of Dickkopf 1 (DKK-1) protein secreted by MSCs. Neutralization of this protein by antibodies or other factors stopped inhibiting action of MSCs on the tumor [29]. MSCs from adipose tissue (AT) inhibited proliferation of primary culture of leucosis cells by secreting DKK-1 [30]. MSCs inhibited pancreatic cancer via disruption of cell cycle in G-1 phase [31]; the above-said cells inhibited tumor growth when being injected in combination. Bone marrow MSCs injected into subcutaneous tumor inhibited its growth by inducing apoptosis of TCs. If MSCs were placed into a special chamber to prevent their contact with the tumor, the toxic effect of MSCs on TCs was not observed. The supernatants of hypothermia-treated MSCs blocked testiculum cancer cell culture [32].

In summing up there are enough contradicting data about the impact of MSCs on the growth of TCs both in vivo and in vitro; the mechanisms of suppressive and stimulatory effects are unclear.

One of the mechanisms, being realized in vivo, may be the stimulation by MSCs of the angiogenesis in tumor capillaries as well as their differentiation to pericytes.
The pericytes isolated from tumor nodes contain many MSC markers (CD10, CD13 and CD90) which are capable to differentiate to tissues of the mesenchymal row [34-36]. Besides, MSCs secrete different proangiogenic factors: growth of the endothelium vessels (VEGF), fibroblasts (FGF) and thrombocytes (PGF). These factors, as is known, enhance migration of endothelial and smooth muscle cells in the tumor, and stimulate their proliferation, promoting neo-angiogenesis in the tumor [37, 38]. Enhancement of VEGF production has been proved on pancreatic cancer xenotransplants [39]. However recombinant VEGF did not exert any impact on the growth of vessels in the tumor allowing the authors think that other antigenic MSCs-producing factors might play role as well [38]. Synthesis of the angiogenic factors has been found to occur when MSCs were in the form of spheroids rather than monolayer [37]. In contrast to these data, other authors report that MSCs can inhibit vessel growth by releasing nitrogen superoxide which induces apoptosis of endothelial cells [40]. The above phenomena were observed only at the definite endothelial cells/MSCs ratio: 1/1 or 1/3); at as little as 10% of MSCs their influence on endothelial cells was not observe. The antitumor effect of MSCs mediated via their influence on apoptosis of the endotheliocytes was observed in vivo as well: MSCs inhibited the growth of melanoma xenotransplants and decreased vessels thickness in these tumors [40].

Apart from the above, MSCs in the tumor site under impact of tumor microenvironment can be transformed into fibroblasts or interact with the existing tumor-associated fibroblasts and get involved into angiogenesis through enhancement of the synthesis of pro-angiogenic factors [4, 41-43]. Malignancy-associated fibroblasts possess other mechanisms of tumor growth stimulation. Suppression of TCs apoptosis and stimulation of their proliferation have been studied best [1].

Immune-suppressive properties of the MSCs have been studied well enough and it cannot be ruled out that while inhibiting immune reactions and activity of different types of immune cells (including T and B lymphocytes, dendrite and killer cells), they stimulate tumor growth. Probably, in the process of MSCs/TCs interaction the Toll-like receptors (TLRs), which recognize ‘danger signaling’, trigger innate and acquired immunity reactions and induce both pro- and anti-inflammatory cytokines [44-45]. At the same time other investigators have shown that MSCs, while inhibiting ‘graft-versus-host’ reaction observable during BM transplantation, inhibit leukemia progression in the patients, probably, by delaying and suppression of leukemic cells in the ‘niches’ located in the BM [47].
MSCs can influence metastatic potential of TCs: injection of breast cancer cells with MSCs led to a 7-fold increase of the number of metastases in the lung [14]. It is noteworthy that metastasis enhancement occurred at combined injection of these cells and was absent at their separate injection that indicated the paracrine or contact character of interaction. It has been shown that MSCs synthesize CCL5 chemokin for which there is (CCLR-5) receptor on tumor prometastatic cells; and after their interaction there occurs its activation and enhancement of breast cancer metastasis. The capacity of MSCs for synthesis of CCL5 is unique as other mesenchymal cells do not isolate it [4].

MSCs are able to modulate so-called epithelium-mesenchymal transition which, in the opinion of many investigators, promotes tumor turnover into more malignant, more invasive type of growth. Joint culturing of breast cancer cells and MSCs lead to enhancement of expression on TCs of the specific markers of this transition (such as vimentin, N-kadgerin, Twist and Snail) and reduced expression of E-kadgerin [48] that adds to above-described mechanisms of MSCs’ impact on metastasis. There are few papers reporting that MSCs influence metastatasis niches and favor early metastasizing [49].

By and large it is known that MSCs secrete a number of polypeptide factors capable influence both proliferation and migration of the TCs and tumor angiogenesis. The authors’ [1] review provides information about 30 biologically active compounds secreting MSCs: primarily interleukins 6, 8 and 13; transforming endothelium growth factor beta (TEGF), fibroblast growth factor (FGF), vessel endothelium growth factor (VEGF), insulin-like (IGF) and platelet (PDGF) growth factors; inhibitors of metalloproteinases type 1 and 2; collagens 1, 5, 6 and 12; fibronectin and several chemokins. Such a great number of cytokines, which MSCs are capable to synthesize, is indicative of wide interaction of these cells with the organism’s cells, including the TCs.

Furthermore, MSCs can secrete exosomes or micro particles less 1.0 mm in the diameter composed of lipid layer along with enclosed proteins and RNA, by which MSCs can regulate intracellular signaling pathways in other cells and TCs as well [50, 51]. It is considered that these micro particles contain microRNA in the precursor form which gets activated and thereby produces regulatory influence on the surrounding cells [51].

Summing up, MSCs possess the potential for interaction with TCs via different mechanisms: (a) indirectly or directly via humoral factors; (b) via processes of
angiogenesis in the tumor; and (c) via modification of tumor micro environment. 
MSCs can interact with resident tumor cells - with T- and B-lymphocytes, natural 
killers and macrophages, and endothelial cells of the vessels. It is not ruled out that 
MSCs are not a homogenous but rather heterogenous fraction in their nature. 
Indicative of this are the data about a wide spectrum of the cytokines synthesized 
by them and a variety of phenotypic signs being revealed with the help of 
monoclonal antibodies. Hence, as discussed above, MSCs are able to suppress and 
stimulate malignant processes depending on many circumstances. An important 
issue is the ‘age’ of MSCs: if tumor growth stimulation was initially linked with 
embryonic cells, the scientists are now more inclined to think that MSCs derived 
from the adult organism possess great oncogenic potential. Furthermore it has been 
found that MSCs are able to stimulate and inhibit tumor growth on the same TC 
lineages. Combined and separate injection of MSCs and TCs causes different (in 
its direction) action on tumor progression. And, finally, of no less importance in a 
number of cases has been the MSCs’ dosage, more exactly, the MSCs/TCS ratio: 
large MSCs doses suppressed tumor growth and induced apoptosis of the 
endothelial cells whereas small doses, on the contrary, stimulated angiogenesis and 
fast tumor progression.

CONCLUSIONS:
In conclusion, of today there is no general opinion among investigators regarding 
the mechanism of action of the mesenchymal stromal cells on malignant process. It 
is only conceivable that such mechanism has minimum three key factors: MSCs, 
tumor (including microenvironment) and macroorganism. The third factor is not 
practically taken into account, in particular the availability of viruses in the 
organism, impact of chemical cancerogens on the organism (tobacco smoking for 
instance) that may create conditions for tumor-stimulating action of MSCs [1]. 
Lack of simple paradigm about MSCs/tumor interaction makes be cautious as not 
to stimulate malignancy process in numerous investigations in which MSCs may 
be used as deliverer of various antitumor agents of chemical and biological nature. 
It seems likely that without solution of first (fundamental) problem one cannot 
expect successful solution of the second (practical) problem.

REFERENCES
discrepancy in the literature: do mesenchymal stem cells support or 


38. Kinnaird T, Stabile E, Burnett MS, et al. Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vitro and in vivo arteriogenesis through paracrine mechanisms. Circ Res 2004; 94: 678–85.


50. **Corcoran KE, Trzaska KA, Fernandes H, et al.** Mesenchymal stem cells in early entry of breast cancer into bone marrow. Plos One 2008; **3**: e2563.


52. **Walter MN, Wright KT, Fuller HR, et al.** Mesenchymal stem cell-conditioned medium accelerates skin wound healing: An in vitro

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