Stem cell plasticity and carcinogenesis*

Minireview

S. FILIP[1], J. MOKRÝ[2], D. ENGLISH[3]

[1]Department of Oncology and Radiotherapy, e-mail: filip@fnhk.cz, Faculty of Medicine Charles University and University Hospital, 500 05 Hradec Králové, Czech Republic; [2]Department of Histology and Embryology, Faculty of Medicine, Charles University, 500 38 Hradec Králové, Czech Republic; [3]Center of Excellence for Aging and Brain Repair, University of South Florida College of Medicine, Tampa, FL 33612, USA

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Presently, there is more and more talk about tumors being a disease connected with stem cells. Both stem cells and tumor cells have many similarities, and there is much evidence that microenvironment, cytokines and signal pathways control tissue specificities and have a significant role in the process of carcinogenesis. Recent experimental results show that stem cells and tumor stem cells apparently play a key role in carcinogenesis. Tumors grow up, thanks to the activity of just few stem cells that continuously produce other proliferating progenitor tumor cells. Generally, tumor elements are thought to be either undifferentiated, or dedifferentiated cells. Actually, the truth is that tumors are made of more or less differentiated cells with variable rate of differentiation. We suppose that under certain conditions tumor stem cells may participate in regeneration without giving rise to tumor formation. It is also presumed that we may reprogram tumor stem cells and progenitor cells in a certain period of time and so initiate development of normal tissue. However, till now the real relation between normal and tumor cells is not clear. Finally, we wish to remind that plasticity of tumor and normal cells cannot be separated but should be considered as individual phenomenon expressing certain condition of an organism in time. This communication is only a probe and introduction into a discussion aimed at better understanding of carcinogenesis from the view of processes at the stem cell level. Stimulation of stem cell activation may lead to prophylactic approaches for therapy and prevention in carcinogenesis.

Key words: stem cells, tumor stem cells, plasticity, carcinogenesis

Processes of evolution enhancing complexity of living forms must involve repair mechanisms as an integral part of evolutionary mechanisms for renewal and repair of complicated organisms. The chain of signal pathways, cytokines and other elements is probably not surprising. The formation of tissues and their maintenance mediated by signal pathways suggest a possible connection between normal and tumor stem cells. Signal pathways Hedgehog (Hh) and Wnt are associated with tissue formations, such as skin, muscles, prostate, intestine, and nervous system [1–3]. The role of Hh and Wnt signal pathways in normal tissues and in the pathologic process of initiation and development of malignant tumors is very important [4]. These signal pathways also play a crucial role in regulation of embryonal evolution and postembryonal functions in stem cell renewal, tissue renewal and regeneration [4, 5]. Deviations in activities of these signal pathways may have significant role in initiation of tumor growth, in tumor plasticity, and in reprograming tumor stem cells.

Presently, tumors are more and more discussed as a disease connected with stem cells. We know now that several processes with normal regulation of tissue repair may be associated with carcinogenesis and also with a process called plasticity. In this communication we try to show the relation between plasticity process and carcinogenesis.

Plasticity can be described as mutual substitution of organ specific stem cells. In a given tissue organ specific stem cell produces differentiated elements characteristic for this tissue. Under certain conditions these stem cells can be made produce elements not present in the original tissue [6]. The term

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plasticity means phenotypical potential of tissue stem cells which is broader than phenotypes of differentiated cells of their original tissue.

It has been found that neural stem cells, for instance, may produce hematopoietic [7] or myogenous cells [8]. Another good example, bone marrow stromal stem cells may produce neural and glial cells [9], cardiomyocytes [10], pneumocytes, hepatocytes and others [11]. Hematopoietic stem cells (HSCs) may travel into some tissues and organs and influence their regeneration, such as liver, lung, GIT, vessels, and heart [11, 12]. Mesenchymal stem cells (MSCs) have a capacity to supply blood, lung, liver, and intestines [13]. Stem cell populations found in the brain and fat tissue also show previously unforseen potentiality [14, 15]. A closer relation between somatic cells, such as hematopoietic system and acute myeloid leukemia was demonstrated on a model when isolated leukemic cells obtained from patients with AML (acute myeloid leukemia) were transplanted to NOD/SCID (non-obese diabetic/severe combined immunodeficient) mice and induced real leukemia. Tumor cells with their surface markers, multipotentiality, and hierarchy were similar to normal hematopoietic cells and this led to the view that leukemic cells were either derived from HSCs or from other differentiated cells including HSCs progeny [16–18]. The ability to form many human tumors in NOD/SCID mice indicated also expression of heterogenous surface markers found in original tumors, such as in breast cancer [4]. Only recently, cell lines isolated from brain tumors enhance the regeneration activity and are capable of producing differentiated neurons and glia both *in vitro* and *in vivo* [5, 19].

Tumor stem cells and plasticity

In comparison with other cells, stem cells have relatively long life span. That is why they have more opportunities to accumulate numerous mutations that may lead to increased cell proliferation and formation of tumors. The discovery of multipotent progenitor cells with self-renewal ability out of the hematopoietic system evoked certain ideas how tumor cells might develop from other tissue stem cells and initiate tumor induction. Tissue specific stem cells are candidates and a cell source for tumors as their ability of self-renewal and unlimited proliferating potential are very similar to tumor stem cells [19, 20].

Stem cells and tumor cells share a number of similar features. Both are undifferentiated elements with unlimited proliferating activity and may be considered “immortal”. In certain circumstances, both these cell types are able to migrate through the tissues and settle down in a new niche [21].

It seems that only recently described phenomenon of stem cell plasticity may participate in tumor formation, and several newer experimental studies suggest that tumors may be of other origin than we have thought [22, 23]. It is possible that migration of bone marrow stem cells acts in the body as a supportive system, and in extreme situations, is able to increase organ inner regeneration capacity. In any case, insufficient engraftment even without organ damage, does not challenge the proposition that this really does occur. These conditions are mostly associated with clinically severe organ damage where stem cells with transdifferentiation potential are probably involved. However, in a case contrary to this, tumor formation results. For instance, stromal marrow stem cells may give rise to stomach cancer thought to be of epithelial origin [24]. The latest findings demonstrate that tumors grow thanks to the activity of just few stem cells continuously producing proliferating progenitor cells. The basic conception of what is the real link between tumor stem cells and tissues has not been proved yet. Probably because the number of tumor types for which tumor stem cells are determined is limited [4].

Generally, tumor elements are considered to be undifferentiated, eventually, dedifferentiated cells. Actually, tumors consist of cells more or less differentiated, while the rate and range of differentiation among tumors vary. Nevertheless, stem cells are destined to tumor production. When a certain affection disturbs genetic program of differentiated cells, it does not result in a tumor induction since these cells are not a permanent component in tissues (for example, enterocyte turn-over takes about 4 days). In case of stem cell affection, the situation is different. Stem cell is the permanent component of a tissue and if it comes to its reversal, this cell goes on producing malformed progeny that spreads within the tissue. The behavior of stem cell in tissues under normal conditions is regulated by a tissue niche [25, 26]. If this microenvironment is disturbed, for instance, by a chronic inflammation, this alteration may lead to chronic activation of otherwise normal stem cell and its unrestrained proliferation starts to produce a tumor mass. Apparently, the same situation occurs at that time when the stem cell is lost in an environment where does not belong.

Briefly we will also introduce the current state of knowledge concerning one way of tumor formation from the view of tissue repair. With the tissue damage the number of differentiated cells decreases. Action of signal pathway leads to stem cell activation and later to tissue repair [4]. Another situation, however, develops in chronic tissue damage followed by repeated activation of stem cells. This process may also result in tumor development (Fig. 1). The important phenomenon involved here is the stem cell plasticity. Plasticity is an attribute not only of tissue specific stem cells but tumor stem cells as well [27]. We are the opinion that the plasticity rate decreases with the degree of cell differentiation. Nevertheless, as current experiments show, it would not be full zero, but it seems that highly differentiated cells would nearly not have any plasticity – their plastic ability would be very low, i.e. about the limit needed to follow-up function changes, kinetics, etc. Despite the low plasticity, this phenomenon would not completely disappear. In short, when stem cell number decreases, their ability of plasticity also decreases, that is, the cell population is only little “plastic”, but as plas-

ticity is a generally valid phenomenon for both normal and tumor stem cells, with accrual of tumor stem cell population plasticity, increases plasticity rate of the whole organism increases, too. There is no hierarchic order in plasticity and plasticity is represented by a certain condition of an organism in time. Its rate is given by the total sum of cells with plastic behavior, also tumor cells as they are part of an organism. In certain circumstances, tumor cells may participate in regeneration even without giving rise to tumor growth (Fig. 1). It is also assumed that tumor stem and progenitor cells may be reprogrammed and thus stimulate development of normal tissue. Concluding this section we wish to remind that plasticity of normal cells or tumor cells does not exist but that pasticity is a unified phenomenon expressing condition of an organism in time.

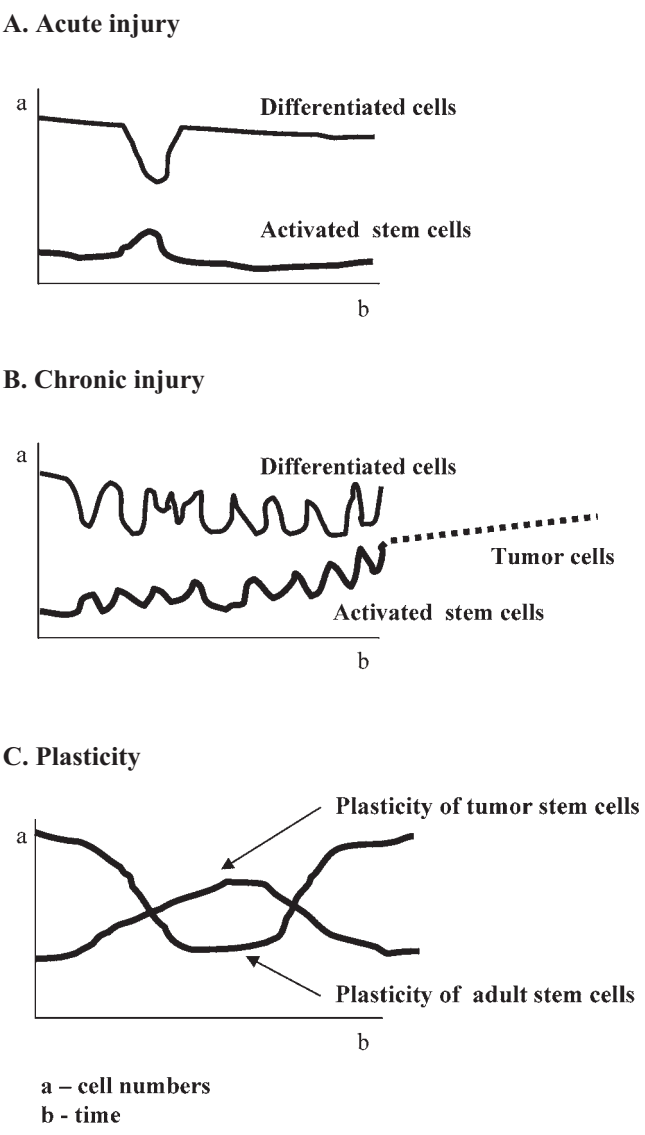

Figure 1. Stem cell plasticity and carcinogenesis. Tissue damage results in reduction of differentiated cell numbers which leads to activation of stem cells and consequently, to tissue repair (A). In chronic tissue damage repeated stem cell activation occurs. This process may cause tumor formation (B). Plasticity is a feature not only of intact stem cells but tumor stem cells, too. The rate of plasticity decreases with decreasing rate of cell differentiation. Fig. (C) suggests the possibility when tumor stem cells take part in tissue regeneration without inducing tumor growth (Corrected according to Beachy et al, Nature 2004; 432: 324–331).

Plasticity, microenvironment, and tumor stem cells

Microenvironment has a significant role in the genome control of both normal and malignant cells. If the genom of differentiated cells would have a complete autonomy, no tissue specificity would exist, and isolated cells would function in a cell culture as in an organ. It is known that isolated cells loose most of functional differentiation if separated and placed in traditional cell cultures. But the cell identity is not lost forever because by regulation of cell microenvironment we can make them "remember" many of their original tissue specific markers [28]. During life span organism of an individual cells acquire many harmful genetic lesions caused by microenvironmental changes. If genetic mutations were the only cause of cancer, then we could expect that every organ might become a tumor. Besides, syndromes of hereditary committed tumors affect mostly one type of tissue even if each cell is of the same mutation. Therefore, except known defensive mechanisms, such as immune reactions, factors from tissue microenvironmen must play the key role in cell decision making and homeostasis maintenance.

Several experiments provided evidence of the balance maintained by normal microenvironment, despite the presence of cells otherwise possibly predisposed to tumor development. One of these experiments is the study of MINTZ and ILLMENSEE where cells of embryonal cancer subcutaneously injected into mice initiated teratocarcinomas, while the same cells injected into blastocysts gave rise to normal chimeric mice instead of tumors [29]. This experiment raised many questions, one of which was nearly futuristic: "May a tumor cell produce a normal descendant?" In compelling elegant experiments of MINTZ and ILLMENSEE, nuclei from malignant tumor cells were inserted into enucleated oocytes and were used first to generate embryonic stem cells and then generated chimeric mice. Although these chimeras were predisposed to malignancy, a vast majority of their tissues was normal, apparently because malignant phenotype was controlled by normal microenvironment [30, 31]. In some cases this phenotype may be the source of mutation and, therefore, the original cause of tumor formation. An example being the interaction between fibroblasts and epithelial cells in intraepithelial prostate neoplasia and in invasive stomach cancer. Experiments have shown that if stromal fibroblasts could not make TGFβ (transforming growth factor beta] to react this leads to unlimited growth of epithelial cells and their invasion. In this case the explanation is that mutated fibroblasts generated HGF (hepatocyte growth factor) and thus abnor-

mal paracrinal signal leading to tumors was of epithelial origin [32]. This may be the main principle as it seems that some tumors influence the development of their own supportive environments. Neurofibromatosis may serve as an example affecting 1 of 4000 people born as heterozygots for neurofibromin – NF1 [33]. Also in some breast carcinomas it has been shown that stromal cells acquired a unique new order of chromosomes connected with tumorigenous epithelium [34] and that stromal defects are the cause of some hereditary diseases affecting carriers with higher incidence rate of tumors [35]. Taken together, these examples provide evidence supporting the view that microenvironment may function either as powerful tumor supressor even in the presence of strong oncogene expression or as a tumor promoter for both precancerous and apparently normal cells [36].

Plasticity, as we observe, develops from interaction of cell-microenvironment. These components supplement each other and create a certain condition we perceive as a functional manifestation but also as plastic behavior. So, is plasticity superior to function? In our opinion it is not, plasticity develops in relation of cell-microenvironment, and therefore, function is its part. That is why some experiments aimed at supporting plasticity failed because they did not respect this fact. That might have been one of the problems why no study on plasticity fulfilled rigorous criteria proposed by WEISSMAN, ANDERSON and GAGE [37, 38]. The first rule is based on the idea that studies on living animals are able to solve problems concerning stem cell potential. Positive results *in vivo* are always the best variant while interpretation of negative results is often problematic. For instance, negative results may indicate the inability of donor stem cells to settle down or integrate properly into a target tissue, or eventually, reflect the inability of an organism or a tissue to initiate reparation processes. That is why it is difficult to distinguish in experiment on living animals whether it is the real phenotype potential of donor stem cells or supportive microenvironment of the host tissue currently studied. Addition of cell cultures to experiments on living animals is a useful supplement to studies on living animals because experimental conditions can be better controlled than *in vivo* environment. Other proposed criteria are also insufficient if too widely applied on all experimental situations [37]. The requirement that plasticity must be proved under "natural" conditions seems particularly unsuitable for understanding its biologic importance [39]. The call for higher scientific strictness in studying data on stem cell plasticity may appear quite rational, only demanding higher standard of evidence somewhat blurres the debate. The requirement that every study on plasticity must present the most accurate evidence is sensible only if advocates of plasticity as a group will defend the alternative to traditional view on stem cells. But this is not the problem of stem cell plasticity. There are numerous reports on plasticity that must be confronted but not each of them is about plasticity. At least some data are valid which led to trials to integrate this knowledge into traditional theory on stem cells [22].

Conclusion

Concluding this communication we wish to summarize some important views and questions on stem cell plasticity, tumor cell plasticity and carcinogenesis:

– The phenomenon of stem cell plasticity may participate in tumor formation as some recent experimental studies suggest.

– Plasticity is a common feature not only of tissue specific stem cells but also of tumor stem cells. In our opinion, the rate of plasticity decreases with decreasing rate of differentiation. Generally speaking, reduction of stem cell numbers reduces their plastic ability, i.e. the population is "little" plastic, but considering that plasticity is probably a widely accepted phenomenon for both normal and tumor stem cells, with accrual of tumor stem cells their plasticity increases and thus the plasticity rate of the whole organism increases.

– Tumors grow thanks to the activity of just few stem cells producing other proliferating progenitor cells. Mostly tumor elements are thought to be either undiferentiated or dedifferentiated cells. Actually, even tumors are made of cells more or less differentiated while the rate of differentiation in individual tumors varies.

– Provided that microenvironment is continuously disturbed, this process may lead to tumor formation with participation of stem cell plasticity.

– We suppose that in certain circumstances tumor stem cells may take part in regeneration even without inducing tumor growth.

– It may also be presumed that, in a certain period of time, tumor stem cells and progenitor stem cells may be reprogrammed and so stimulate generation of a normal tissue.

– Finally, we wish to point out that plasticity of normal and tumor cells cannot be separated but take it as a unified phenomenon expressing certain condition of an organism in time.

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