REVIEW ARTICLE

Recent View of Stem Cell Plasticity and Stem Cell Therapy

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SUMMARY

The most controversial problem in biology and medicine at present is the existence of stem cell plasticity. Experimental biology and medicine have been working with stem cells and stem cell therapy for more than twenty years. The term plasticity, as it is understood, is the potential of stem cell phenotypes that is much broader than phenotypes of differentiated cells of their original tissues. Many laboratories have documented the existence of stem cell plasticity; however, the are still many objections to the reported results. Here we present some of these objections questioning the data on stem cell plasticity. We wish to point out some problems associated with plasticity of stem cells, transdifferentiation and cell fusion. Recent experimental results indicate that stem cells may have a key role in stem cell therapy. This review is simply meant as an introduction to the discussion of stem cell plasticity and stem cell therapy.
Key words: stem cells, plasticity, transdifferentiation, stem cell therapy.

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One of the most contentious issues in biology and medicine today concerns the existence of stem cell plasticity. Discussion of "transdifferentiation" or "plasticity" is of considerable interest and evokes ideas which are clearly scientific and also potentially revolutionary.

Plasticity may be also characterized as the mutual substitutability of the organ-specific stem cells. In a certain tissue, organ-specific stem cell produces differentiated elements characteristic for a particular tissue. Under certain circumstances, these stem cells may be forced to create elements not occurring in the original tissue (1). The term plasticity is meant as the phenotype potential of tissue stem cells, which is much broader than phenotypes of differentiated cells of their original tissue. It has been found, for example, that neural stem cells can produce hematopoietic (2) or myogenic cells (3). A further illustration concerns stromal stem cells of bone marrow, which may generate neuronal and glial cells (4), cardiomyocytes (5), pneumocytes, hepatocytes and others (6). At first, the capacity of transformation of stem cells was observed in cases when organ-specific stem cells created the cells which were of a different type but of identical embryonic origin, i. e. organ-specific stem cells and the cells to which they give rise derive from the same embryonic germ layer (*intra-germ layer conversion*).

Later a further phenomenon was found: the transformation of organ-specific stem cells into cells originating from other germ layer than from which the original stem cell is derived (*trans-germ layer conversion*).

Further research indicated that in some cases, instead of apparent reprogramming of the adult stem cells, cellular fusion may develop.

Smith and coworkers documented that during co-cultivation of bone marrow adult stem cells or brain stem cells with ES (embryonic stem) cells, these two types occasionally produced hybrides which looked like ES cells but had abnormal morphology, higher number of chromosomes and were genetically unstable (7). These studies concentrated only on those observations of plasticity that comprised co-cultivation of two cell types. Despite the fact that there were extraordinarily unfavourable cultivation conditions, under which the cells were exposed to various selection agents that contributed to the fusion of two cell types, consternation caused by the fusion motivated the establishment of rigorous standards to provide compelling evidence of plasticity. Anderson, Gage and Weissman - who proposed this set of standards (8, 9) - require that the cells at the beginning of experiment should first be properly identified, because even a single foreign cell in seemingly purified culture might lead to the misleading results. Evidence of production of new proteins is not sufficient; it is necessary to demonstrate that the cells contribute to the host tissue functions, to the transmission of electric signals in nervous system and to elimination of waste products from blood in the liver. This ensures that only the well-characterized donor cell must be capable of creating "robust" population and not only creating several dispersed cells in the new tissue. Plasticity should be a natural phenomenon, which means that the cells must function permanently in the host's tissue, without their change during cultivation (8, 9).

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These conditions have led to a passionate discussion (10), and some scientists agree that cells are to be better characterized and their functionality confirmed. Despite the significant progress that has been achieved, no agreement has been reached over the number of functional steps the cells must go through before plasticity could be proved (10).

In the meantime, none of the studies aimed at plasticity demonstration have met the strict criteria suggested by Weissman, Anderson and Gage (8, 9). Let us recall experiments by Krause and coworkers, who used cells that did not change during cultivation, and who proved that a single blood stem cell may give rise to many cell types (6). Nevertheless, the search for proof of cell fusion still remains problematic. For example, Lassage et al. remain sceptical because they presume that the cells from the first transplant recipient "were not well characterized" (11). Other authors, such as Verfaillie et al., have voiced the opinion that the studies "in fact still do not give evidence about important contribution to any organ" (12). To date there are only small cell groups without any function. In spite of various hypotheses and attempts to establish the truth, this experiment still has not been verified. Weissman et al. report that when he and his team tried to repeat the above-mentioned experiment with carefully selected blood stem cells, they obtained only the expected bone and blood derivatives, six liver cells and one cerebral cell, and this Purkinje cell had twice as high content of DNA, which means that it could be a local cell that had fused with one of the labelled cells (13). Nonetheless, we can say that controversial results of the Krause and Weissman teams raise an important question about how to design a fundamental experiment either to prove or exclude plasticity.

The transdifferentiation process and the environment of cell residence may be closely related. It appears likely that throughout their lifespan stem cells, which reside predominantly in G_0 phase, retain their loyal relationship to different microenvironments and may have reciprocal influence (6, 9, 13). It seems that hematopoietic stem cells (HSCs) may infiltrate some tissues and organs and may influence their regeneration, e. g. liver, lungs, GIT, vessels and heart (6, 14). Mesenchymal stem cells (MSCs) are capable of replenishing blood cells and pulmonary, liver and intestinal cells (15). The stem cell population found in brain and adipose tissue also shows previously unforeseen potentiality (16, 17). All the same, these studies do not convince many scientists, who insist that there is sufficient reason for scepticism (18, 19).

CELL FUSION

One of the main arguments used in questioning reports about stem cell plasticity is the fact that previous outcomes aimed at evidence of transdifferentiation were in fact evidence of cell fusion (20). The issue came to the fore due to more recent observations proving that tissue-derived stem cells may undergo fusion with other cell types (21). Even though other scientists have admitted that the potential significance of cell fusion is different from the question of stem cell plasticity, the studies dealing with cell fusion are frequently cited to disprove the existence of stem cell transdifferentiation (10). Conclusions have been drawn on the basis of these studies on cell fusion, showing that the phenomenology of cell fusion may explain the previous reports about stem cell plasticity. Moreover, evidence of cell fusion has been described as negating the very concept of stem cell transdifferentiation (20). But it is not clear why cell fusion and transdifferentiation should be antagonistic effects. After all, the development of skeletal muscle includes both effects – cell differentiation and fusion. The latest experimental findings accordingly exclude cell fusion from consideration of the mechanism of stem cell plasticity.

EXPERIMENTAL EVIDENCE OF PLASTICITY

Even though all scientific hypotheses demand rigorous scientific evidence to be fully accepted, there are doubts if the rules suggested by Weissman, Anderson and Gage are always suitable for determination of stem cell plasticity (10). The first rule is stigmatized by exaggerated faith that experiments on living animals are capable of solving problems with potentials of stem cells. While definitive positive results *in vivo* are always the best variant, interpretations of negative results are often questionable. If a population of stem cell reveals itself as incapable of regenerating the target tissue in the animals, does this mean that these cells lack the proper tissue potential? Instead, the negative results may indicate the incapability of donor stem cells to reside or integrate with target tissue, or they may reflect the incapability of the organism or tissue to launch reparative processes. Moreover, in animal experiments it is not always easy to distinguish what is being investigated: the proper phenotypic potential of the donor cells or the supportive microenvironment of the host tissue. Cell cultivation is the useful complement of the animal experiments, because experimental conditions can be much better controlled than in the *in vivo* environment. If the stem cells undergo cultivation manipulations before implantation into the host animal, the cultivation may help accomplish their endogeneous reparative potential. Rather than being misleading for research, the cultivations repeatedly provided important information about the key scientific questions that can be hardly solved in the studies performed on living animals.

At first sight, this proclamation may seem reasonable: "donor cells should be capable of producing a 'robust' and permanent regeneration of the target tissues, so that stem cell plasticity could be exactly determined". Let us inquire the meaning of this criterion in broader sense. It has been assumed for many years that the adult heart muscle is postmitotic, but it is known now that continuous though slow regeneration of adult myocardium does persist (22). This normal rate of replacement of myocytes is far from being robust, even though it is apparently effective to the extent that it maintains normal homeostasis in the myocardium throughout the lifespan. In addition to endogeneous heart stem cells, evidence has been adduced indicating that extracardial cells generate substitutive myocytes in the adult heart (23, 24). It seems that the contribution of extracardial stem cells to myocyte replacement in the adult heart is a physiological reality, but this does not comply with criteria of robustness and thus will be unsatisfactory for the adult myocardium.

Other suggested criteria are also inappropriate if they are too widely applied for all experimental situations (10). By way of a hypothetical example of required functionality let us suppose that progeny of transplanted hematopoietic stem cells was fully integrated into contractile myocardium and express numerous muscular proteins. Will determination of functionality be necessary for a reasonable scientist to conclude that "transdifferentiation" took place here? Yes, functional analysis will be necessary for evaluation of clinical usefulness of transplantation, but it will not be necessary to verify the occurrence of transdifferentiation.

Requirement that stem cell plasticity has to be proved in "natural" conditions seems to be especially unsuitable for an understanding of the biological significance of transdifferentiation (25). Since the largest biological regeneration in the adults appears during wound healing, the study of plasticity during tissue and organ reparation will apparently be the proper field for research. However, it seems that this last criterion is inconsistent with many studies in cellular biology, because the traditional models of cell differentiation are based on studies examining the capacity of hematopoietic cells to reconstitute blood system of recipient animals after lethal irradiation (19). Even though calls for greater scientific rigor during

research about stem cell plasticity may seem to be quite reasonable, this requirement of higher level of proofs obscures the nature of the debate. The requirement that each work about transdifferentiation should furnish the most explicit proof is meaningful only if the advocates of stem cell plasticity as a group insist on an alternative to the traditional view of stem cells. But it is not a problem invoked by knowledge of stem cell plasticity. There are innumerable reports on plasticity that have to be confronted, but not every report deals with plasticity. At least some data on plasticity are valid, which led to the experiments trying to integrate these findings into the traditional theory about stem cells (10).

TRANSDIFFERENTIATION

The term transdifferentiation is often used for potential of stem cell plasticity. For example, it can be supposed that stem cells that normally generate blood elements undergo transdifferentiation, if they have produced cardiomyocytes. This understanding of the term transdifferentiation has replaced the older meaning, which described the conversion of one differentiated cell type into another. The most often accepted examples of transdifferentiation are regeneration of limbs in amphibians and conversion of pigment epithelium into the lenses and nervous cells of the retina (26). In these cases the differentiated tissue dedifferentiates itself into cells with clear phenotype of stem cells before their metamorphosis into other differentiated cell phenotypes. Other examples of transdifferentiation include the conversion of pancreatic cells into hepatocytes and vascular endothelium into smooth musculature (27, 28). Moreover, some literary data indicate that macrophages of bone marrow may transdifferentiate into cardiomyocytes if they are cultivated in the presence of myocardium (29).

In adults, the generating of newly differentiated cells is significantly increased during wound healing. It was generally accepted that stem cells feel the tissue damage and migrate from a distance to the site of injury (30, 31). Nevertheless, it has been observed that the activation of immune response increases the regeneration of the cells which occurs during tissue or cell transplantations to the hosts (6, 23, 24). For instance, in a study dealing with heart tissue in males in whom female hearts had been transplanted, there was the largest amount of Y-positive cardiomyocytes in the sites of acute rejection (23). These results are surprising, because the first wave of the cells drawn to the wound are the immune cells – *immune response cells*, which are a necessary first step to the prevention of more serious damage in the site of trauma. If these immune cells may be later the source of the new cells for wound reparation, then their transdifferentiation makes it unnecessary to mobilize the secondary cell population, i. e. stem cells, to the damaged tissue. This hypothesis is in accordance with the results and indicates that macrophages, entering the myocardial tissue, may contribute to the creation of the new heart muscle cells (29).

The next proof that cells may differentiate is provided by studies about properties of monocytes, which are the cells usually considered as immediate progenitors of macrophages. Several studies have established that monocytes may differentiate into endothelial cells (32). A more recent study indicates that the phenotype potential of monocytes may also be extended into other lineages (33). The endothelial potential of monocytes may be considered in the context of one of the oldest controversies in biology of stem cells, pertaining to the connection between lines of blood and endothelial cells. The question was focused on the existence of a multipotent stem cell – *hemangioblast* - which allows the creation of both hematopoietic and endothelial cell lines (34). Even though this debate still goes on, it seems clear now that stem cells with properties of hemangioblasts exist both in the embryo and in adults (35). But finding that this cell as a monocyte, which is supposed to be fully linked with myeloid blood lines, is also capable of generating endothelial cells, has significant consequences for the biology of stem cells. The significance of these observations lies in their deviation from standard hierarchic models of stem cells, which characterize the diversification of lines on the level of multipotent stem cells. If it is possible to redirect the unipotent progenitors to multiple cell profiles, then what is the difference between multipotent and pluripotent stem cells?

The ability of both differentiated cell and the cells characterized as highly committed progenitors, i. e. monocytes, to transdifferentiate in other cell phenotypes, indicates that the current models of diversification may not adequately represent the increment of cell phenotypes. Even though there are few examples when the existence of transdifferentiation of differentiated cell phenotypes has been clearly proved, the proof is in these cases definitive (26) and creates a precedent that regenerated tissue do not originate always from the stem cells along the pathways of hierarchic differentiation. Despite the definitive proof of transdifferentiation, its existence is usually considered as a special case with little relevance for discussion about biology of stem cell and tissue regeneration. However, a new proof (28) indicates that transdifferentiation may have a broader meaning for comprehension of biology of mammals than it is supposed nowadays. Even though differentiation may be higher than dedifferentiation and transdifferentiation between phenotypes. The significance of transdifferentiation model of cell diversification lies in sum of cell phenotypes in organism as the part of continuity.

CELL THERAPY

Experimental biology and medicine has been working with stem cells for more than twenty years. The discovered method allowing *in vitro* to culture human embryonic stem cells, obtained from abortions or "surplus" embryos from *in vitro* fertilization, immediately evoked ideas about the possibility of directing research and differentiation for the needs of regeneration of damaged tissues (10, 36). Cell therapy faces a difficult task: how to establish an approach to the detection, harvesting and cultivation of stem cells for treatment of some diseases (37). Will it be possible to use adult stem cells for the treatment of broader spectrum of diseases?

The diseases occurring as consequence of destruction or dysfunction of a certain limited number of cell types, such as *diabetes mellitus* (during which selective destruction of beta cells of Langerhans islets occurs) or Parkinson's disease (originating from destruction of dopaminergic neurons in *substantia nigra*), may be treated by transplantation of differentiated derivatives of embryonic stem cells. Animal studies show that transplantation either of pluripotent stem cell or fetal cell derivatives may successfully treat many chronic diseases such as diabetes mellitus, Parkinson's disease, traumatic spinal chord injury, Purkinje cell degeneration, liver failure, heart failure, Duchenne's muscular atrophy, *osteogenesis imperfecta* and other (38-41).

Although substantial progress in transplantation therapy in humans has been achieved during recent years, there are several obstacles limiting the broad application of cell transplantation in routine therapy of these diseases. The main obstacles are the need for massive doses of immunosuppresive drugs to prevent rejection of the transplanted tissue, and the lack of cadaver organs. Despite these set-backs, strategy based on human embryonic stem cells could provide generation of unlimited number of necessary cells and tissues and their sufficient supply from abundant, renewable and quickly accessible source. In addition, embryonic stem cells, due to their adaptability for stable genetic modification, could be treated to avoid or inhibit host immune response.

The first step to the development of successful therapy based on stem cells in humans is to prove that human embryonic stem cells have the ability to differentiate into a cell type that is of interest in this context, and to purify this line from the mixed population. In the second step it would be necessary to critically assess and demonstrate that differentiated cell derivatives function in their normal physiologic way: for example, that secretion of insulin in pancreatic islets is normal and responds to the glucose level. The third and most important milestone on the way to clinical tests would be proof of efficiency in the disease models on big animals. Fourth, it is necessary to rule out the possible creation of tumours derived from derivatives after differentiation of embryonic stem cells and transplanted to the human recipients. Since progress in this direction is very fast, new questions are sure to emerge which may limit the therapeutical use of stem cells. The efforts of scientists to treat diseases that are at present incurable, pressure from patients, their families and also political pressure may complicate the development of new therapeutical approaches (10). It is important to retain one's common sense, to resist emotional pressure and to respect the scientific and ethical rules (36).

The perspective directions of the cell therapy are: therapeutical cloning, embryonic stem cells, fetal treatment, adult stem cells, use of hormones for regulation of behaviour of stem cells and eventually genetic modification of stem cells. Initially it seemed that adult stem cells, for instance, might represent a certain "ethical compromise" towards embryonic cells. Yet we understand now that the single approaches are linked with each other. Scientists have already proved that many cell types, such as neurons and muscle cells, pancreatic beta cells and others, may be obtained by means of embryonic stem cell cultivation (10, 36). The use of stem cells in treatment may come into its own even in such unexpected cases as the therapy of kidney diseases (42) or immunological reparation in patients with AIDS (43).

Abbreviations

DNA - deoxyribonucleic acid
ES cells - embryonic stem cells
GIT - gastrointestinal tract
HSCs - hematopoietic stem cells
MSCs - mesenchymal stem cells

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COMMENTARY

Commentary on Paper by Filip S., Mokrý J., Pudil R.: "Recent View of Stem Cell Plasticity and Stem Cell Therapy"

The authors present recent ideas about the plasticity of tissue-specific stem cells, and in the last part of the review they discuss applications of embryonic stem cells in regenerative medicine. Some parts are difficult to understand for educated nonspecialists, and the text does not always flow well. There are definitely basic schemes missing that would help reader to orient himself in a relatively complex field. On the other hand, one has to point out that the authors present and discuss many publications based on *in vivo* experiments that put the theory of stem cell plasticity in doubt. This is certainly a valuable contribution, since every piece of news about adult stem cell potential tends to be accepted with uncritical enthusiasm within the clinical community. Therefore it is important to set strict rules for plasticity, since there is a danger that clinicians in the Czech Republic and all over the world may treat patients using very "sophisticated" approaches based on inadequately designed experiments or misinterpretation of results - which actually have little chance of success.

In discussing the plasticity of stem cells and the processes of transdifferentiation and dedifferentiation we are dealing with the transition of the stem cell of one specific cell lineage into a cell of a different lineage that is characterized by the change of expression profile of tissue-specific markers and functional parameters (1, 2). These terms were used earlier rather in the context of more differentiated cells, e. g. hematopoietic cells, where these processes were extensively studied and described (3).

Recently, several alternative explanations of this phenomenon have appeared. Some of them are schematically depicted in Fig. 1. Transdifferentiation and dedifferentiation (Fig. 1A, B) have not been proved reliably (1). Multiple types of adult stem cells are frequently present (Fig. 1C) that come from non-homogenous or incompletely purified cells used for the experiment (1, 4). This applies to cells isolated from the bone marrow, which, in addition to hematopoietic stem cells, also contains mesenchymal and even pluripotent stem cells

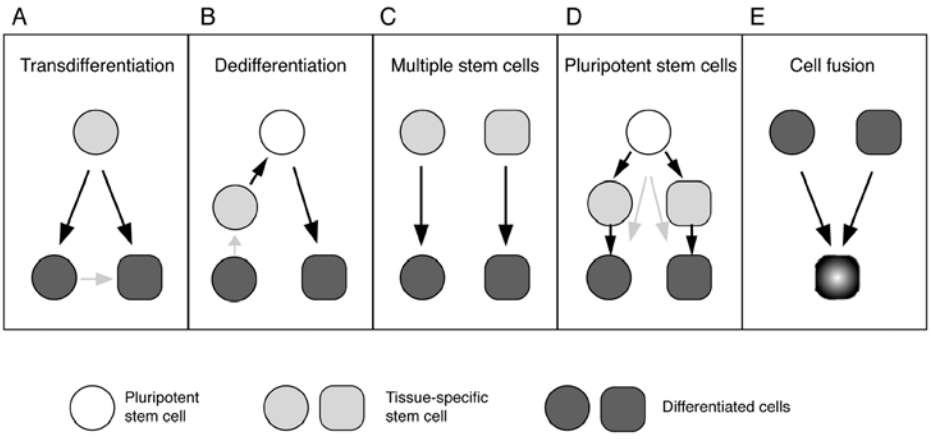

Fig. 1. Scheme depicting potential mechanisms and explanations for observations of adult stem cell plasticity. Modified from (1).

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(Fig. 1D). In addition, this applies for example to neuronal and muscle stem cells that are contaminated with hematopoietic stem cells. Cell fusion (Fig. 1E) is therefore not the only argument against the theory of adult stem cell plasticity. Other problems considering plasticity are technical artifacts coming from the analysis of experimental results. One of the examples is use of beta-galactosidase or chromosome Y for detection of donor bone marrow cells in the tissue of the recipient (5).

The question of increased efficiency in stem cell transplantation has also not been completely solved. Few cells present in the target tissue of the recipient seem not to be satisfactory for real application in the regenerative medicine. The expansion of pluripotent stem cells derived from bone marrow *ex vivo* and their subsequent application, pharmacological mobilization of pluripotent stem cell potential in situ (by small molecules, growth factors and chemokines) seem to be right approaches for the future.

Despite the many questions that remain unanswered, cell therapy based on embryonic and adult stem cells holds great promise (6, 7). Updated information and links to the articles on stem cell topic can be found on the homepage of The International Society for Stem Cell Research (http://www.isscr.org).

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